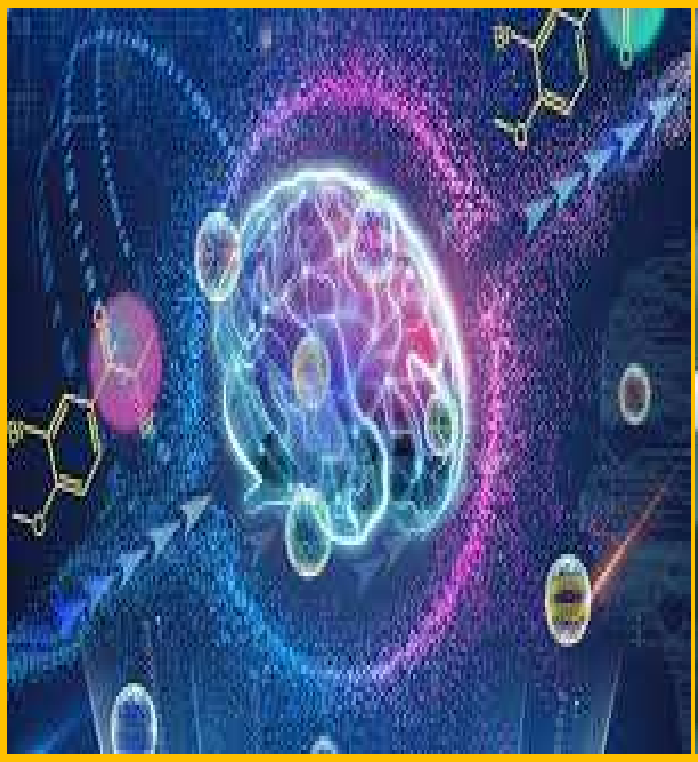
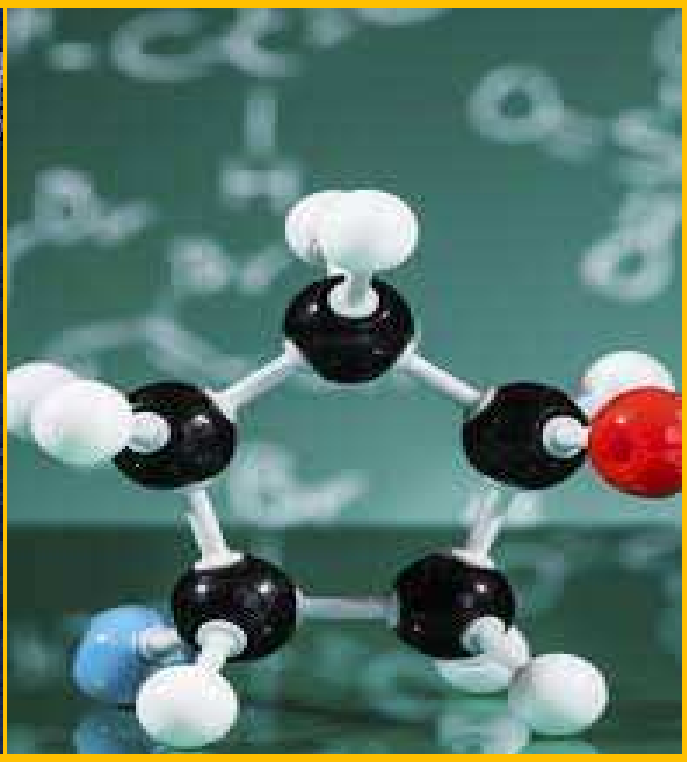
MSCCH-507

M. Sc. II Semester

ORGANIC CHEMISTRY-II





SCHOOL OF SCIENCES
DEPARTMENT OF CHEMISTRY
UTTARAKHAND OPEN UNIVERSITY

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CONTENTS

Block I: Nucleophilic Substitution

Unit 1 Aliphatic Nucleophilic Substitution 1-60

Unit 2 Aromatic Nucleophilic Substitution 61-86

Block II: Electrophilic Substitution

Unit 3 Aliphatic Electrophilic Substitution 87-112

Unit 4 Aromatic Electrophilic Substitution 113-135

Unit 5 Elimination Reactions 136- 156

Block III: Addition and free Radical Reactions

Unit 6 Addition to Carbon-Carbon Multiple Bonds 157- 200

Unit 7 Addition to Carbon-Hetero Atom Multiple Bonds 201-236

Unit 8 Free Radical Reactions 237-261

Block IV Pericyclic Reactions

Unit 9 Electrocyclic Reactions 262-294

Unit 10 Cycloadditions and Sigmatropic Reaction 295-344

UNIT-1 ALIPHATIC NUCLEOPHILIC SUBSTITUTION

CONTENTS:

1. Objectives

1.1 Introductions

1.1.1 Leaving groups as (or leaving) nucleophiles or nucleofuge

1.1.2 Incoming nucleophile

1.2 Mechanism S_N2 reactions

1.2.1 Evidence for the S_N2 mechanism

1.3. The S_N1 mechanism (carbocation process)

1.3.1 Evidence for the S_N1 mechanism

1.4. Mixed S_N1 and S_N2 mechanism

1.5. S_Ni mechanism

1.6. SET mechanism

1.6.1 Evidence for SET mechanism:

1.7. Neighbouring Group Participation (Intramolecular Nucleophilic Displacement)

1.8. Classical and Non- Cassical Carbocation (bridged carbocations)

1.9. Carbocation Rearrangements

1.10: Norbornyl systems

1.11: Norbornyl cation

1.12. Nucleophilic substitution at an allylic carbon

1.13. Nucleophilic substitution at an aliphatic trigonal carbon

1.14. Nucleophilic substitution at vinylic carbon

1.15. Structure & Reactivity Analysis of Nucleophilic Substitution Reactions

1.16. HSAB principle

1.16.1 HSAB Principle

1.16.2. HSAB & FMO Analysis

1.16.3 Characteristics of Hard, Soft & Borderline Acids & Bases

1.16.4 Applications of HSAB Principle

1.17. Ambident Nucleophiles

1.18. Summary

1.19 Terminal questions

1.20. Answer to terminal questions

1.21. References

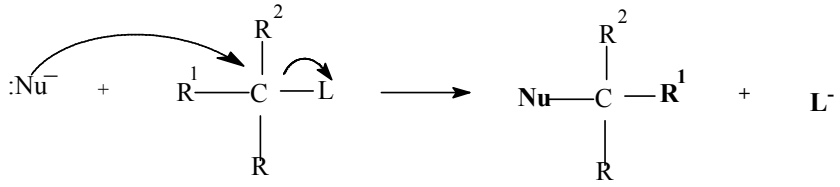
1. OBJECTIVES

Objective of this unit is to make students aware about the S_N2, S_N1, mixed S_N1 and S_N2, S_Ni and SET mechanism. This chapter will also provide knowledge of neighboring group participation by π and σ bonds, anchimeric assistance, classical and non-classical carbocations, arenium ions, norbornyl systems and common carbocation rearrangements. This chapter will also provide useful information about the S_Ni mechanism, nucleophilic substitution at an allylic, aliphatic trigonal and a vinylic carbon. The other objectives of this chapter are reactivity effects of substrate structure, attacking nucleophile, leaving group, reaction medium, HSAB principle and ambident nucleophiles.

1.1 INTRODUCTION

Replacement of an atom or group by any other atom or group is known as substitution reaction. Attack of nucleophile at saturated carbon atom bearing a substituent, known as leaving group, result in substitution reaction. The group that is displaced (leaving group) carries it's bonded pair of electrons. The new bond is formed between nucleophile and the carbon using the electron supplied by the nucleophilic reactant. In general, an aliphatic substitution reaction may be depicted as follows:

Substrate + Nucleophile ⟶ Product + Leaving Group



Nucleophile may be neutral or negatively charged, whereas substrate undergoing nucleophilic substitution may be neutral or positively charged. Four possibilities in nucleophilic substitution reaction may thus be visualised as below:

(i) $\bar{O}H + CH_3Br \longrightarrow CH_3OH + Br^-$

(ii) $NH_3 + CH_3Br \longrightarrow CH_3\overset{+}{N}H_3 + Br^-$

(iii) $Cl^- + CH_3\overset{+}{O}H_2 \longrightarrow CH_3Cl + H_2O$

(iv) $H_2S + R\overset{+}{N}(CH_3)_3 \longrightarrow R\overset{+}{S}H_2 + N(CH_3)_3$

1.1.1 Leaving groups as nucleophiles or nucleofuge

The leaving group is the part of the substrate that is missing at the end of the reaction. The leaving group must have following characteristics:

(i) A leaving group is electron-withdrawing so that it creates a partial positive on the carbon atom.

$$R^{\delta+}\text{----}L^{\delta-}$$

(ii) The leaving group should be stable after leaving with the bonding pair of electrons. In general good leaving group should be weak bases, and therefore, they are conjugate bases of the strong acids. Thus

Leaving power of the group $\propto$ 1/ Basicity of the group

For example:

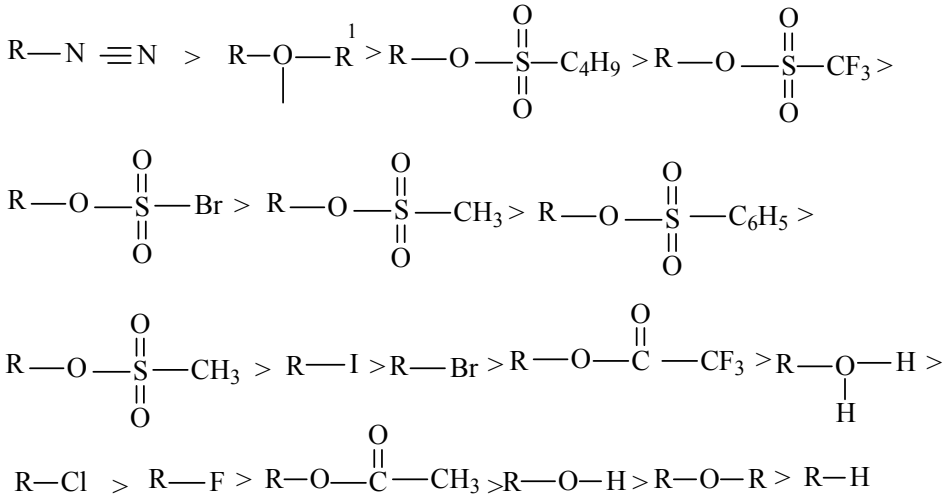
Acid	Conjugate base
HF	$F^\ominus$
HCl	$Cl^\ominus$
HBr	$Br^\ominus$
HI	$I^\ominus$

Acidity in increasing order Basicity in decreasing order (leaving group nucleophilicity in increasing order)

Thus, the stronger the conjugate acid of the leaving group, the better is its ability

(iii)The ability of a species to act as a good leaving depends on its polarisability.

Decreasing order of leaving ability of some group is as follows:



1.1.2 Incoming nucleophile:

An incoming nucleophile may either be negatively charged or it may be an uncharged species with lone pair of electrons. Examples of some incoming nucleophiles given as followes:

$\overset{\ominus}{NO_2}$, $\overset{\ominus}{N_3}$, $RCOO^{\ominus}$, $\overset{\ominus}{CN}$, $\overset{\ominus}{I}$, $\overset{\ominus}{Br}$, $\overset{\ominus}{Cl}$, $\overset{\ominus}{OH}$, $\overset{\ominus}{RO}$, HOH, ROH, NH_3, RNH_2, $\overset{\ominus}{SH}$, RSH

The reactivity of nucleiophile is known its nucleophilicity. The nucleophilicity increases with increasing polarisability. Nucleophilicity can be explained as given below:

(i) A negative charge species is a stronger nucleophile than a smilar species without a negative charge (a base is a stronger nucleophile than its conjugated acid). For example- OH^- is a stronger nucleophile than HOH.

(ii) Nucleophilicity decreases on going from left to right in the periodic table. Therefore-

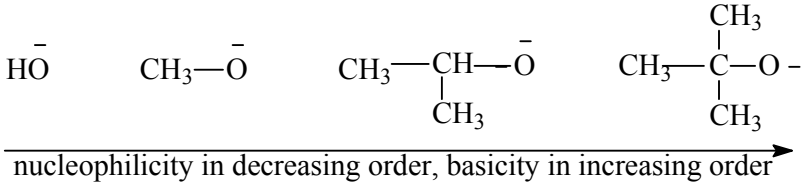
$\overset{\ominus}{CH_3} > \overset{\ominus}{NH_2} > \overset{\ominus}{OH} > \overset{\ominus}{F}$

Similarly, NH_3 is more nucleophilic than HOH.

(iii) Nucleophilicity increases on going down in the group of the periodic table. Therefore:

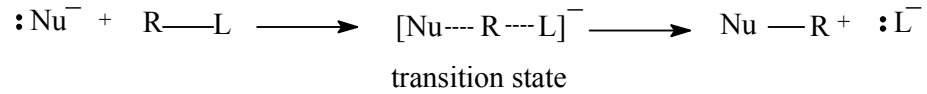
$I^- > Br^- > Cl^- > F^-$, Similarly $\overset{\ominus}{SeH} > \overset{\ominus}{SH} > \overset{\ominus}{OH}$ and $R_3\ddot{P} > R_3N:$

(iv) Bulky group present on nucleophile centre decreases nucleophilicity and increase basicity of the negatively charged species.

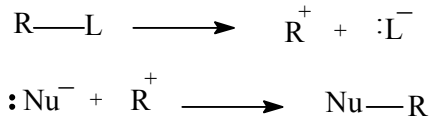


Depending on nuleophile, substrate, leaving group and reaction conditions, several mechanism are possible for aliphatic nucleophilic substitution reaction but most proceed either by a direct displacement mechanism in which bond making and bond breaking simultaneous, or by a two-step mechanism in which C-L bond is broken first, followed by a reaction between the resultant carbocation and nucleophile.

Direct Displacement Process



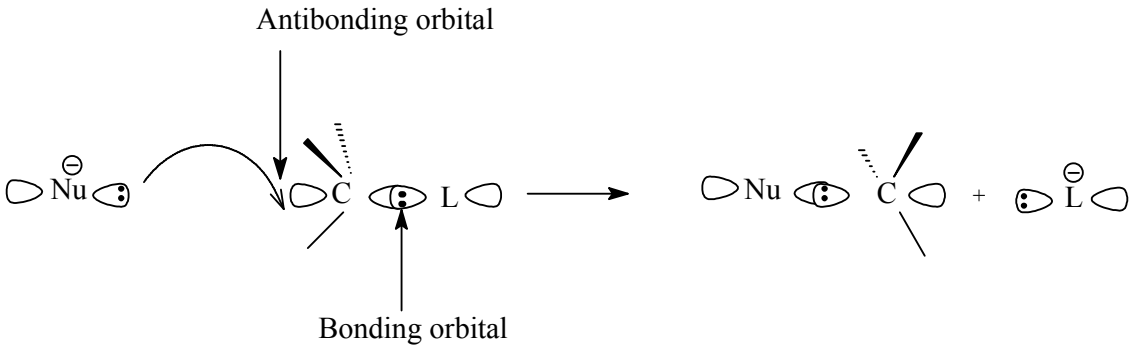
Carbocation Process



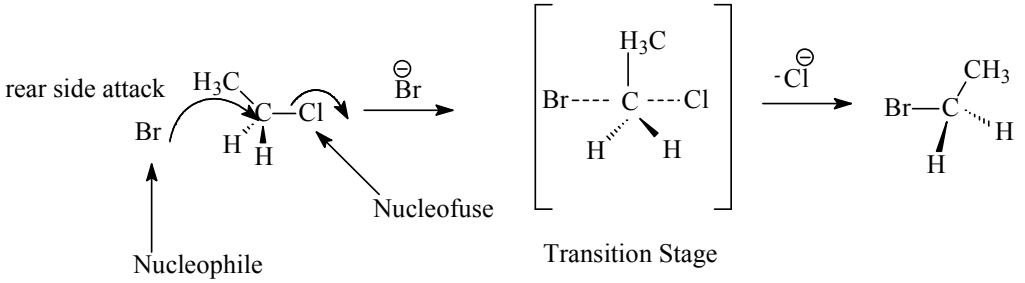
1.2 THE SN^2 MECHANISM (DIRECT DISPLACEMENT PROCESS)

The designation S_N2 stands for substitution nucleophilic bimolecular. The IUPAC designation is A_ND_N. The letter A represents formation of a bond (association), D the breaking of a bond (dissociation). In any process, the subscript is N if a core atom is forming a bond to a nucleophile (A_N) or breaking a bond to a nucleofuge (D_N). The direct displacement mechanism is concerted (single step), without an intermediate and with a single rate determining transition step. In S_N2 reaction, the substrate is attacked by the nucleophile from the side opposite the nucleofase (180^0).

The direct displacement reaction generally occurs at an aliphatic sp^3 carbon center with an electronegative, stable leaving group attached to it (X), which is frequently a halide atom. The breaking of the C–X bond and the formation of the new bond (C–Y or C–Nu) occur simultaneously through a transition state in which a carbon under nucleophilic attack is penta coordinate, and approximately sp^2 hybridised. The nucleophile attacks the carbon at 180° to the leaving group, since this provides the best overlap between the nucleophile's lone pair and the C–X σ* antibonding orbital. The leaving group is then pushed off the opposite side and the product is formed with inversion of the tetrahedral geometry at the central atom.



Let us consider an example: the attack of Br^- (the nucleophile) on an ethyl chloride (the electrophile) results in ethyl bromide, with chloride ejected as the leaving group.



S_N2 reaction of chloroethane with bromide ion

S_N^2 attack occurs if the backside route of attack is not satirically hindered by substituents on the substrate. Therefore, this mechanism usually occurs at unhindered primary and secondary carbon centres. If there is steric crowding on the substrate near the leaving group, such as at a tertiary carbon centre, the substitution will involve an S_N^1 rather than an S_N^2 mechanism. Figure represents the free energy vs reaction coordinate diagram for S_N^2 reaction.

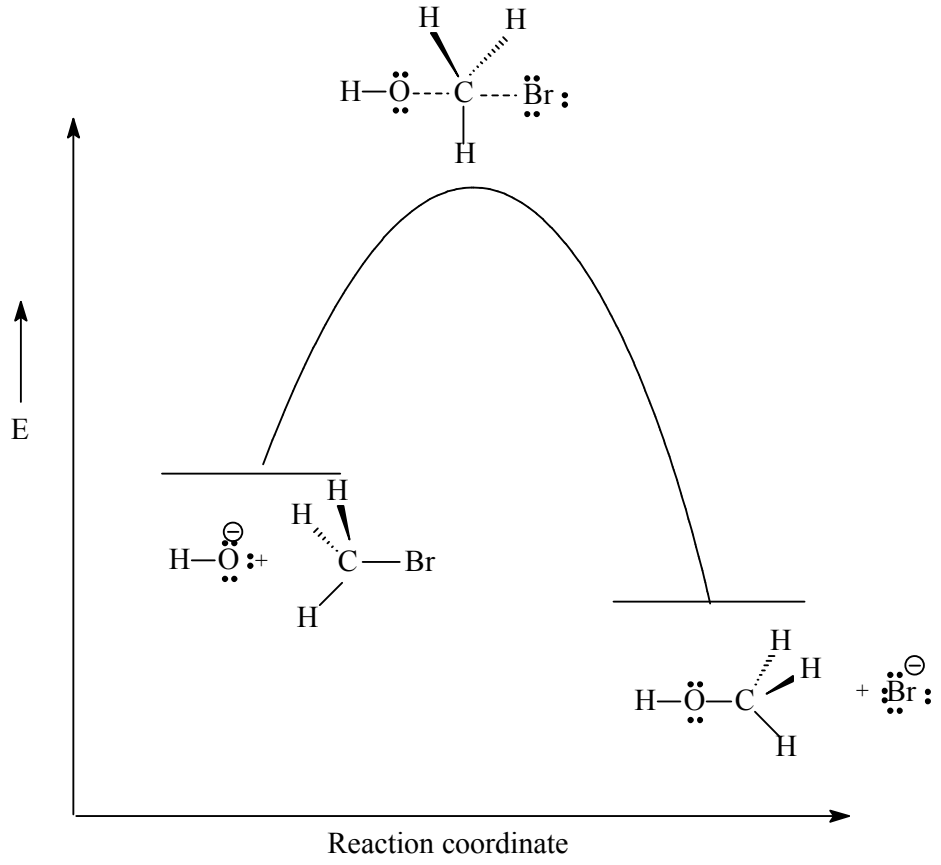


Fig:1 Potential energy diagram for the reaction of methyl bromide with hydroxide ion by the S_N2 mechanism

1.2.1 Evidence for the S_N2 Mechanism

1. **Kinetics:** Both the substrate and the nucleophile take part in the rate determining step (the only step), the reaction should be first order in each component, second order overall and satisfy the below mentioned rate expression. Thus the reaction follows second order kinetics. Hence, the rate equation is:

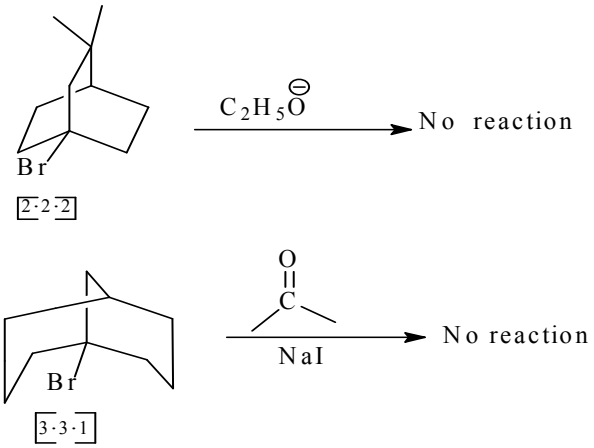
   Rate = k [substrate] [nucleophile]

   This law was found to apply for many reactions in chemistry. But for reactions involving excess of nucleophile (solvent), even though the mechanism is bimolecular, experimentally determined rate will be first order. This is because the rate is dependent on the concentration of the substrate molecule, the kinetics involved in this reaction is referred as pseudo first order:

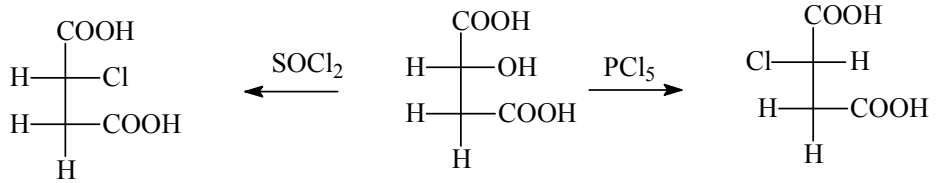
   Rate = k [substrate]

   The unfortunate part is that the reaction mechanism can't be operated for the substrate containing the leaving group at bridgehead carbon atom of any polycyclic systems.

The reason is that the back side of this carbon can't be free to allow the nucleophile from that side during the formation of transition state. For example: The reaction between [2.2.2] system with ethoxide ion and [3.3.1] system with NaI, where acetone is used as a solvent does not result in product formation. But their open chain analogues underwent the reactions gradually.



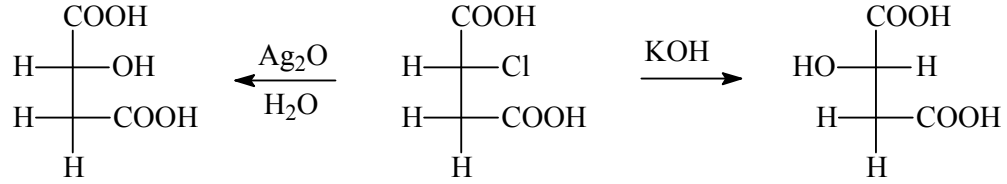
2. **Stereochemistry:** The S_N^2 reaction proceeds with inversion of configuration at the carbon at which the substitution has taken place. The S_N^2 reaction is a stereospecific reaction. When a substitution takes place in a chiral carbon, inversion of configuration occurs and this is known as Walden inversion (Paul Walden 1863-1957) and was observed long before the SN^2 mechanism was formulated by Hughes and Ingold. In S_N2 reaction an ethyl chloride converted into ethyl bromide in presence of strong base results inversion of configuration. The change of configuration can be established by observing the directions of optical rotation. Examples for Walden inversion:
   1. **Chlorination of (+)-malic acid:** When (+)-malic acid is treated with $SOCl_2$, it results in (+) - chlorosuccinic acid, where retention in configuration is there. On the other hand, when (+)-malic acid is treated with PCl_5, it results in (-)-chlorosuccinic acid, i.e inversion in configuration is there.



(+)-chlorosuccinic acid (+)-malic acid (–)-chlorosuccinic acid

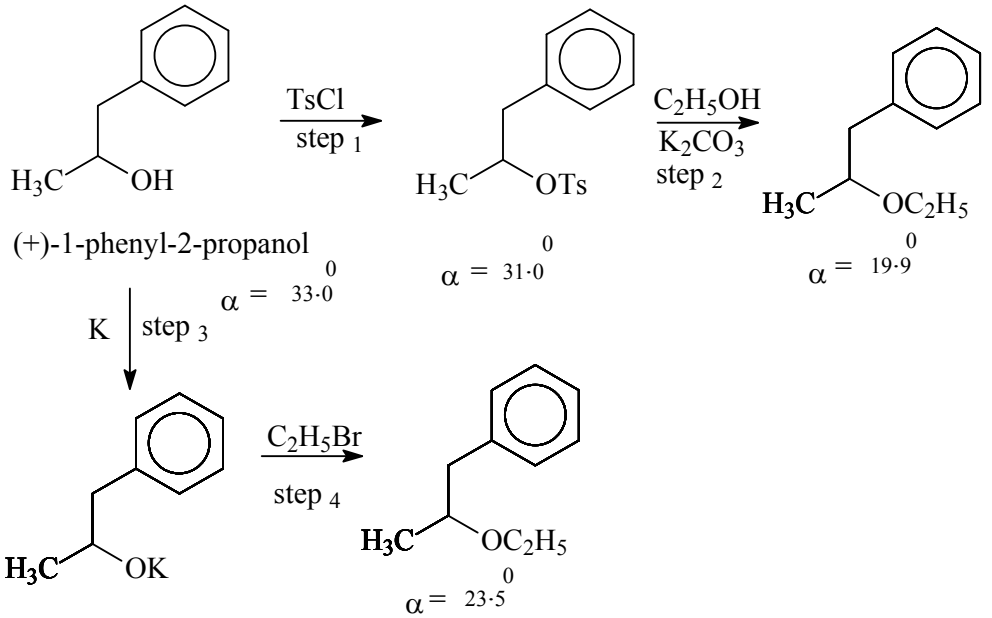
   2. **Hydrolysis of (+)-chlorosuccinic acid:** When (+)-chlorosuccinic acid is hydrolyzed with silver hydroxide or aqueous silver oxide, it results in (+)-malic

acid, where retention in configuration is there. On the other hand, when (+)-chlorosuccinic acid is hydrolysed with KOH, it results in (-) malic acid, i.e inversion in configuration is there.



(+)-malic acid (+)- chlorosuccinic acid (-)- malic acid

Philips & co-workers (1923) reported about the prediction of exact position of inversion by using (+)-1-phenyl-2-propanol as a starting material. In this reaction, two routes are possible, first (step 1 and 2) and second- (step 3 and 4). In the step 1, 3 and 4, C-O bond is not broken at all, which creates no possibility of inversion. Thus there is high probability of retention of configuration. But in step 2 the C-O bond is broken and the new C-O bond is formed which must come from the reagent ethanol in presence of base, thus the step 2 should follow the inversion of configuration.



(+)-1-phenyl-2-propanol $\alpha^0 = 33{\cdot}0$

$\alpha^0 = 31{\cdot}0$

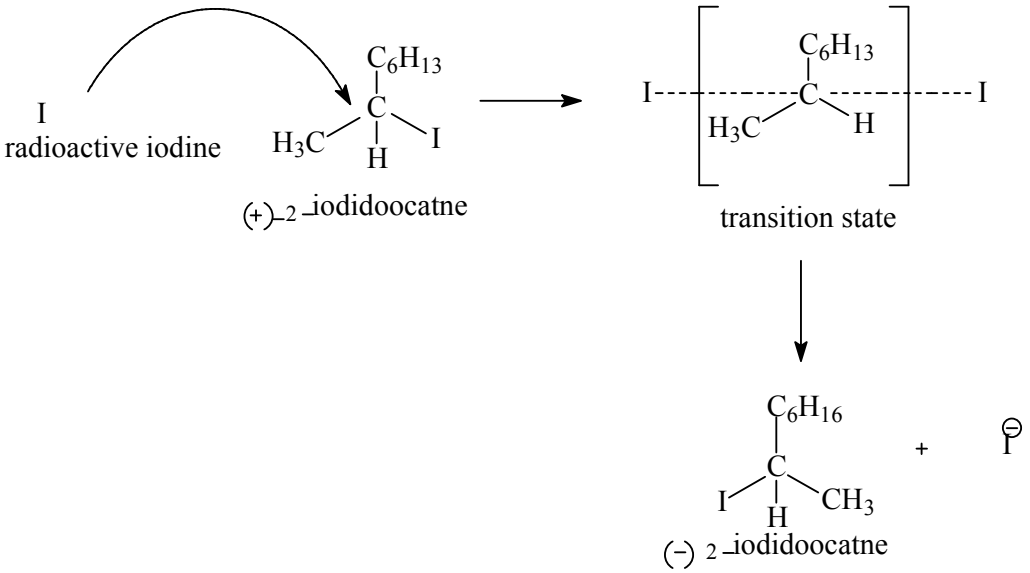
$\alpha^0 = 19{\cdot}9$

$\alpha^0 = 23{\cdot}5$

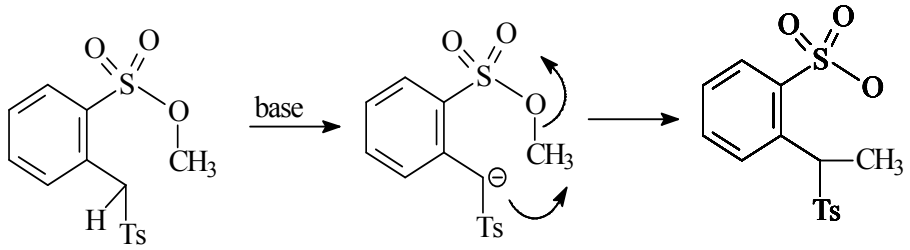
Hughes & Ingold did fabulous work to establish the inversion of configuration in S_N2 reaction. For example, reaction of (+)-2-iodooctane with KI* (radioactive iodide) results in (-)-iodooctane. The rate of this reaction is as follows:

$$\text{Rate } \alpha\ [C_6H_{13}CHICH_3]\ [I^-]^*$$

Thus the exchange of actual iodide with the radioactive iodide results the loss of optical activity, which indicates the formation of (-) isomer from (+) isomer. Thus, inversion of configuration indicates the S_N2 reaction.



3. **Linearity of Transition State**: Eschenmoser and co-workers postulated that the transition state in S_N2 reactions should be linear. The base treatment of methyl-α-tosyl-o-toluene sulfonate (1) results in o-(1-tosylethyl) benzene sulphonate (2). In this reaction base is used to remove α-proton which results in the formation of an anion. Thus this reaction may undergo an internal nucleophilic substitution reaction.



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The carbanion produced was believed to act as an internal nucleophile and attacks the methyl carbon of sulfonate ester by intramolecular mechanism. If it is linear the transition state cannot be achieved. But later, the cross over experiments of this reaction showed that the negatively charged carbon attacks the methyl group of another molecule rather than the nearby one in the same molecule i.e. this is an

intermolecular reaction and not intramolecular reaction which confirms the linear transition state. In intra molecular reactions linearity of transition state can be very difficult.

1.3 THE SN[1] MECHANISM (CARBOCATION PROCESS)

The ionization mechanism for nucleophilic substitution proceeds by rate determining heterolytic dissociation of the reactant to a tricoordinate carbocation and the leaving group. This dissociation is followed by rapid combination of the electrophilic carbocation with a Lewis base (nucleophile) present in the medium. A potential energy diagram representing this process for a neutral reactant and anionic nucleophile is shown in **Fig.** 2 The ionization mechanism has several distinguishing features. The ionization step is rate determining and the reaction exhibits first-order kinetics, with the rate of decomposition of the reactant being independent of the concentration and identity of the nucleophile. The symbol assigned to this mechanism is S_N1, for substitution, nucleophilic, unimolecular (IUPAC: D_N+A_N).

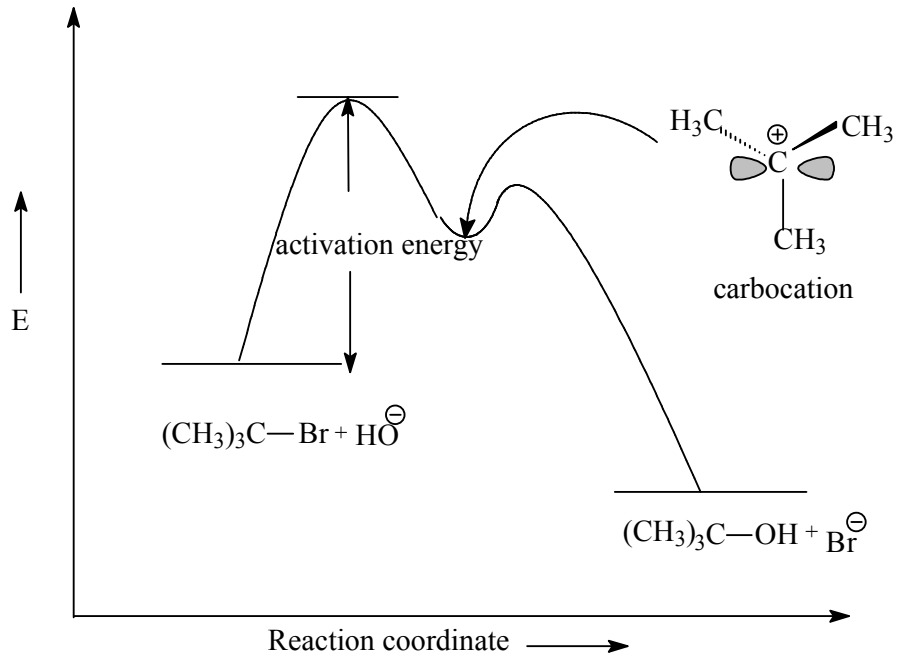
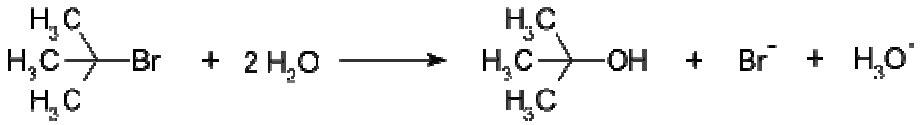


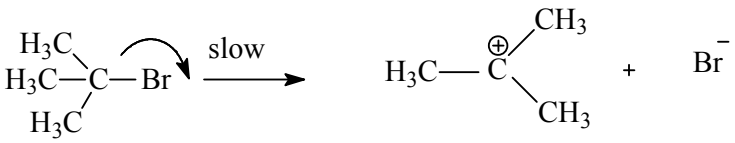
Fig: 2 Energy diagram for S_N1 mechanism

Let us take the example of of a reaction taking place with an S_N1 reaction mechanism is the hydrolysis of tert-butyl bromide with water forming *tert*-butanol.

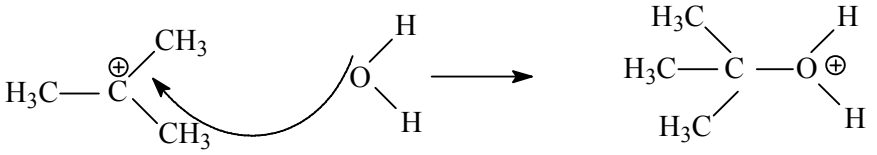


This S_N1 reaction takes place in three steps:

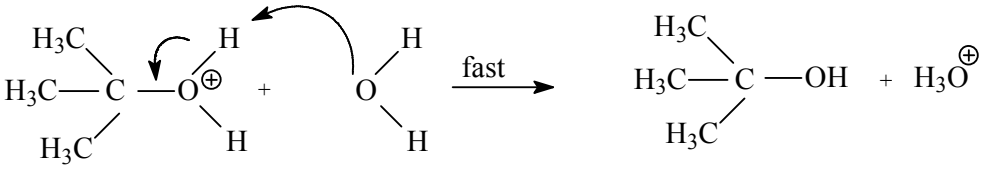
Step 1 (Formation of a *tert*-butyl carbocation by separation of a leaving group (a bromide anion) from the carbon atom): This step is slow and reversible.



Step 2 (Nucleophilic attack): The carbocation reacts with the nucleophile. If the nucleophile is a neutral molecule (i.e. a solvent) a third step is required to complete the reaction. When the solvent is water, the intermediate is an oxonium ion. This reaction step is fast.



Step 3 (Deprotonation): Removal of a proton on the protonated nucleophile by water acting as a base forming the alcohol and a hydronium ion. This reaction step is fast.



1.3.1 Evidence for the S_N1 mechanism

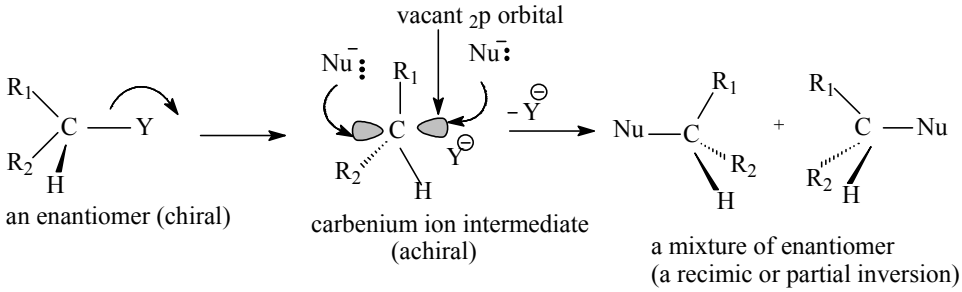
1. **Kinetics:** The S_N1 reaction is initiated by the dissociation of the leaving group and formation of the carbocation intermediate in the first step. After formation of the carbocation intermediate, the nucleophile takes part in the second step. Increasing or decreasing the concentration of the nucleophile has no measurable effect on the rate.

The nucleophile is not involved in the initial step of rate-determination, thus the concentration does not affect the overall reaction rate. This reaction follows first order kinetics. The reaction is first order with respect to alkyl halide while zero order with respect to the nucleophile.

$$\text{Rate} = k\,[\text{Substrate}]$$

2. **Stereochemistry:** If the S_N1 reaction proceeds *via* a carbenium ion, the stereochemical outcome must quite different from that the S_N2 reaction because the central carbon of the intermediate is sp^2 hybridised and planar. The lobes of the vacant 2p orbital (LUMO) are perpendicular to the plane of the carbenium ion and the HOMO of the nucleophile may interact with either of the lobes. If the reaction site of substrate (RY) is a chiral centre, and the nucleophilic attack at the carbenium ion is equally possible from both sides, the outcome must be the formation of the racemic product regardless of the enantiomeric purity of the substrate (RY).

   Racemization is usually only partial (experimentally) because the leaving group is still present as counter-ion on the side of the carbenium ion from which it departed. In another way we can say that the carbenium ion initially exists as an ion pair and its counter ion Y^- (leaving group) inhibits nucleophilic capture from the side leading to product with retention of the configuration. The result is partial inversion of the configuration, the degree of which depends on the stability (lifetime) of the ion pair and the nature of the solvent.



1.4 MIXED SN[1] AND SN[2] MECHANISM

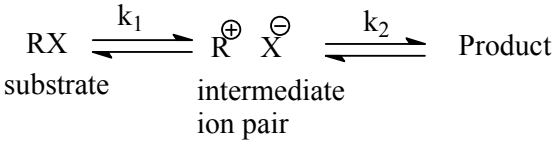
In a Nucleophilic substitution reaction a nucleophile (electron rich species) bonds with a positive/partially positively charged centre in a substrate expelling the leaving group. The two factors i.e. molecularity and reaction kinetics, classifies nucleophilic substitution mechanisms as substitution nucleophilic unimolecular (S_N1) and substitution nucleophilic bimolecular (S_N^2). Where the S_N^1 mechanism is a two step mechanism, involving carbocation

intermediate whereby the product of the reaction is a racemic mixture and the SN^2 mechanisms proceed in a single step through a transition state whereby the reaction leads to inversion of configuration.

There is only difference in the timing of the steps between S_N1 and S_N2 mechanisms. On one hand in the S_N1 mechanism, first the leaving group leaves followed by the nucleophile attack whereas, in the S_N2 mechanism, the two things happen simultaneously. But sometimes under a given set of conditions there are reactions that are known to proceed with a mechanistic ''borderline'' region i.e. mixed S_N1 and S_N2. At least two broad theories have been devised to explain mixed S_N1 and S_N2 mechanism.

1. One theory explain that One theory holds that intermediate behavior is caused by a mechanism that is neither ''pure'' S_N1 nor ''pure'' S_N2, but some ''in-between'' type **(given by Sneen et al, 1973).**
2. According to second theory, there is no intermediate mechanism at all and borderline behavior is caused by simultaneous operation, in the same flask, of both the S_N1 and S_N2 mechanisms; that is, some molecules react by the S_N1, while others react by the S_N2 mechanism.

According to Seen, all S_N1 and S_N2 reactions can be accommodated by the ion-pair mechanism. Firstly, the substrate ionizes in to an intermediate ion pair then an intermediate ion pair converted in to products:

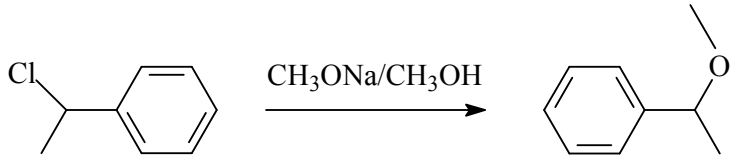


The difference between the S_N1 and S_N2 mechanisms is that in the former case the formation of the ion pair (k_1) is rate determining, while in the S_N2 mechanism its destruction (k_2) is rate determining. Borderline behavior is found where the rates of formation and destruction of the ion pair are of the same order of magnitude.

The Experimental evidence suggests that the borderline mechanism or mixed SN_1/SN_2 mechanism were shown by benzyl chloride hydrolyses in aqueous solvents. The substitution proceeds with a clear S_N2 mechanism. However, upon p-substitution, p-methoxybenzyl chloride solvolysis takes place by the S_N1 route. As the para substituent changes from the order of electron withdrawing to electron donating functional groups (NO_2, Cl, H, CH_3,

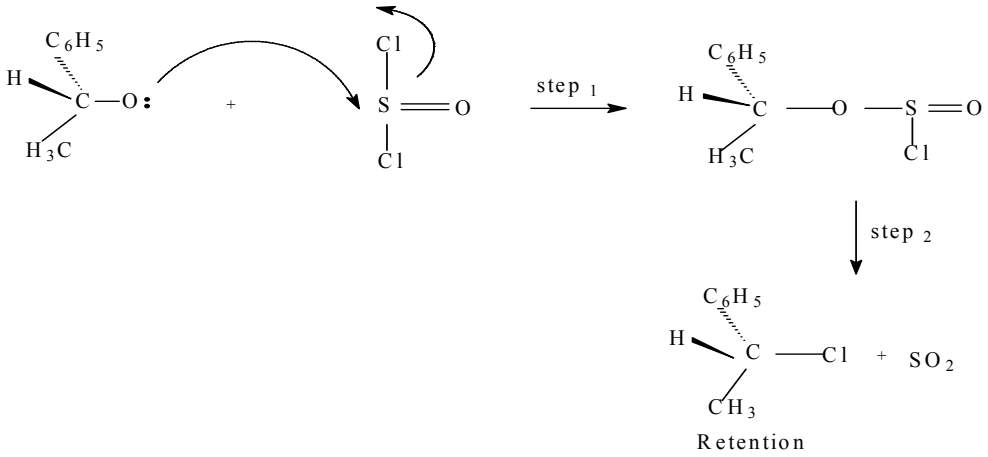
OCH_3), a progressive change from the bimolecular mechanism to the unimolecular pathway is observed. The intermediate situation for p-methylbenzyl chlorides was found to be border line where it was argued that S_N1 and S_N2 processes occur side by side. With the addition of azide ions (good nucleophile) to the reaction, the alcohol is still there as a product, but 4-methoxybenzyl azide comes out to be another product. The role of additional nucleophile azide ions is thus to increase in the rate of ionization (by the salt effect) but decreases the rate of hydrolysis. Thus, both S_N1 and S_N2 mechanisms were shown to be operative simultaneously.

Example of mixed SN1 and SN2 mechanism:



1.5 SN^i MECHANISM

The label SN^i stands for substitution, nucleophilic internal. The IUPAC designation is $D_N + A_NDe$. A typical representative organic reaction displaying this mechanism is the chlorination of alcohols with thionyl chloride, or the decomposition of alkyl chloroformates, the main feature is retention of stereochemical configuration. Thionyl chloride first reacts with the alcohol to form an alkyl chloro sulfite, actually forming an intimate ion pair. The second step is the concerted loss of a sulfur dioxide molecule and its replacement by the chloride, which was attached to the sulphite group. In S_Ni reaction both the reactants are the crucial component and both are playing crucial role in completion of reaction. Thus the rate will be directly proportional to the reactant and catalyst therefore; we can say the reaction follows a second order rate equation.



Rate= k [ROH] [$SOCl_2$]

In the SN^i reaction the sulphite reacts with a chlorine ion in a standard S_N2 reaction with inversion of configuration. When the solvent is also a nucleophile such as dioxane two successive SN^2 reactions take place and the stereochemistry is again retention. With standard S_N1 reaction conditions the reaction outcome is retention via a competing SN^i mechanism and not racemization and with pyridine added the result is again *inversion.*

1.6 SET MECHANISM

Involvement of free radicals has been shown in many aliphatic substitution reactions. Following steps are involved in SET mechanism.

Step 1: Transfer of an electron from the nucleophile to the substrate to form a radical anion.

$$R—X + Y^- \longrightarrow R—X^{\bullet -} + Y^{\bullet}$$

substrate nucleophile a radical anion

Mechanisms that begin this way are called single electron transfer mechanisms.

Step 2: The radical ion cleaves.

$$R—X^{\bullet -} \longrightarrow R^{\bullet} + X^-$$

The radicals formed in this way can go on to product by reacting with the $Y^{\bullet}$ produced in Step 1 or with the original nucleophilic ion Y^-.

Step 3: The radicals formed in step 2 can go on to product by reacting with the $Y^{\bullet}$ produced in Step 1.

$$R^{\bullet} + Y^{\bullet} \longrightarrow R—Y$$

Or

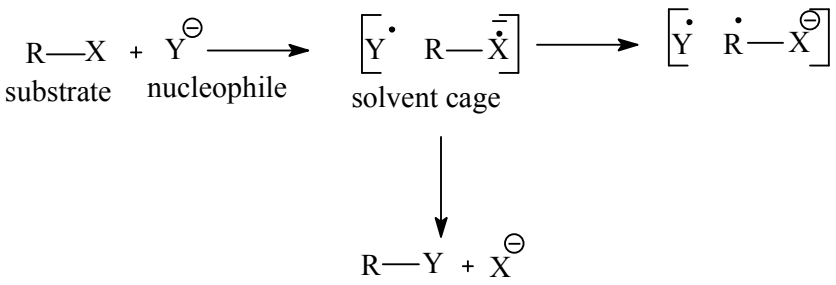
Step 3: The radicals formed in step 2, reacting with the the original nucleophilic ion Y^{-} and formed a radical anion.

$$R^{\bullet} + Y^{-} \longrightarrow R—Y^{\bullet -}$$

Step 4: A radical ion coming from step 3 react with substrate and formed a radical ion like in step 1 (chain reaction).

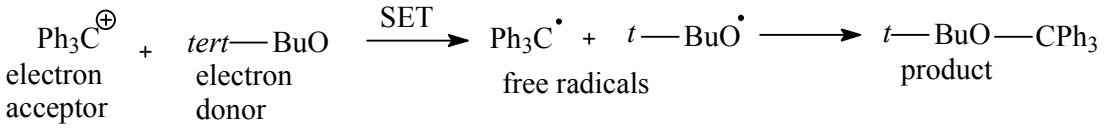
$$R—Y^{\bullet -} + R—X \longrightarrow R—Y + R—X^{\bullet -}$$

1.6.1 Evidence for SET Mechanism: Above reactions show inversion of configuration, but in many reactions some racemization has also been determined. In case of racemization, involves intermediacy of a simple free radical and a completely racemized product (R-Y) would have been formed. Explanation- it has been suggested that nucleophile approaches substrate from the backside and the radical is tied up in solvent cage having the nucleophile on the back side.



Another example of substitution reaction in which S_N1 mechanism is highly probable and free radicals involved in the reaction (intermediates detected by ESR). In such cases, a carbocation is a good electron acceptor and the nucleophile is an electron donor. The reaction

between the triphenylmethyl cation and tert-butoxide ion can be explained by SET mechanism.

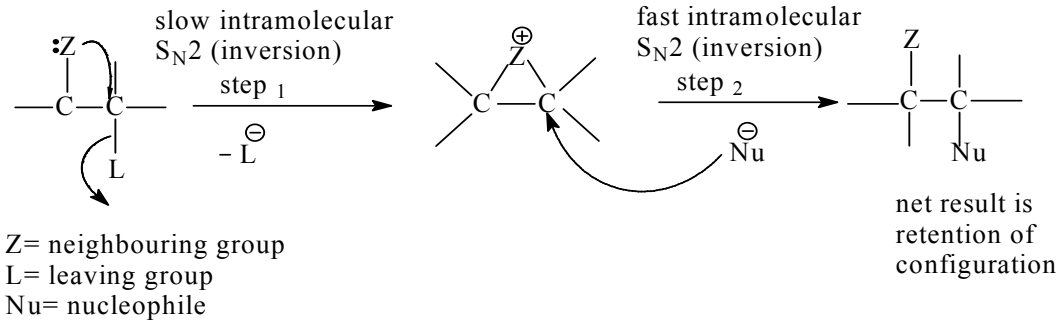


1.7 NEIGHBOURING GROUP PARTICIPATION (INTRAMOLECULAR NUCLEOPHILIC DISPLACEMENT)

Neighbouring Group Participation (NGP) is observed in nucleophilic substitution reactions, where a neighbouring group helps in the removal of the leaving group to form a reactive intermediate that leads to the formation of the product. Increase in the reaction rate (anchimeric assistance) and unexpected stereo chemical outcomes (retention of configuration) are associated in reactions involving NGP.

An atom having an unshared pair of electrons and also present at least β to the leaving group can act as a neighbouring group. Also, NGP is mostly observed on solvolysis reactions where the solvent acts as the nucleophile.

A typical reaction involving NGP is shown below.



During NGP, the neighbouring group (G) attacks the electrophilic centre to eliminate the leaving group (L). This leads to the formation of a cyclic intermediate which is very reactive. This is called anchimeric assistance from the neighbouring group. The nucleophile (Nu^-) then attacks this intermediate to form the product. If the attack happens of the carbon that was having the leaving group the configuration will be retained because the configuration at that carbon will be inverted twice.

The neighbouring group mechanism follows the first order rate law shown below:

Rate = K [substrate]

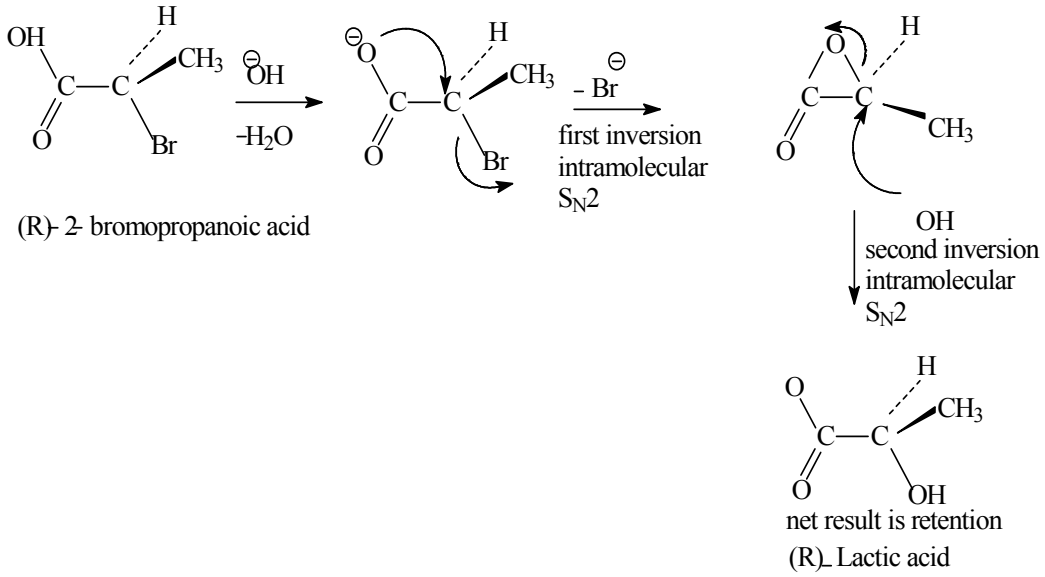
That is, the external nucleophile does not take part in the rate determining step.

Groups like halides, hydroxides, ethers, thio ethers, amino groups, carboxylates, phenyl group, pi-bonds etc. have been indentified to act as neighbouring groups in many reactions.

Some more examples of reaction involving NGP are shown below.

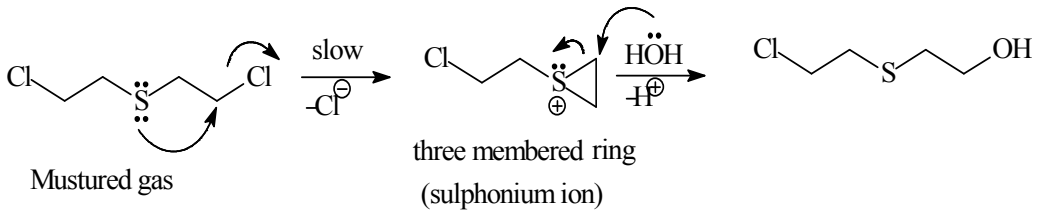
1. **Lone pair as Neighboring group**

   Example 1: alkaline hydrolysis of 2-bromopropanoate anion to lactate anion in which the carboxylate anion participates as a neighbouring group. When 2-bromopropanoic acid is treated with dilute alkali, it gives lactate anion with complete retention of configuration. However, with concentrated sodium hydroxide (*R*)-2-bromopropanoic acid gives (*L*)-lactic anion. This reaction proceeds with inversion of configuration and is a typical S_N2 reaction.

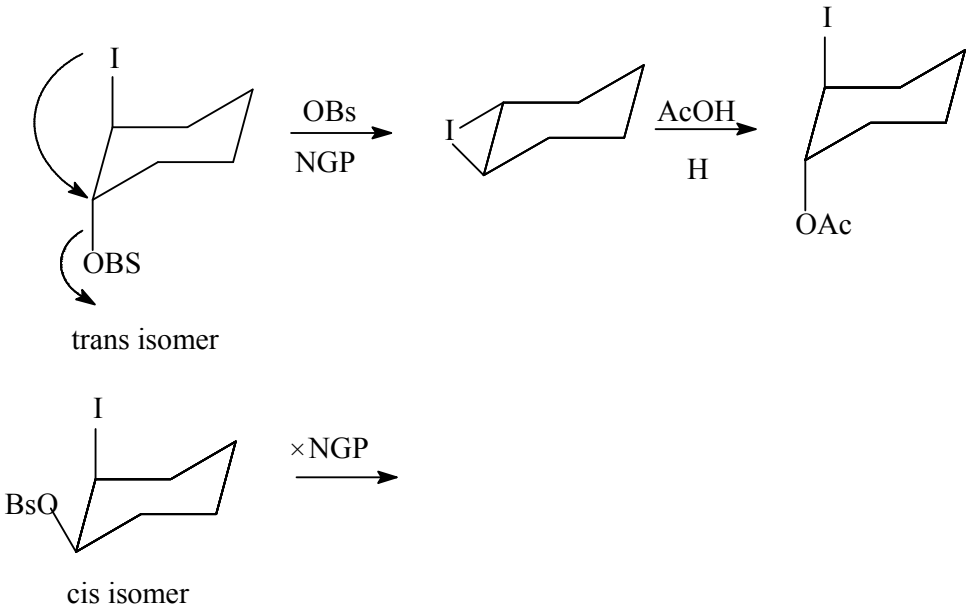


(R)- 2- bromopropanoic acid

   Example 2: The base catalysed hydrolysis of mustard gas is an example of neighbouring group participation by sulphur. The toxicity of mustard gas is because of neighbouring group participation by sulphur, which accelerates its alkylation reactions.

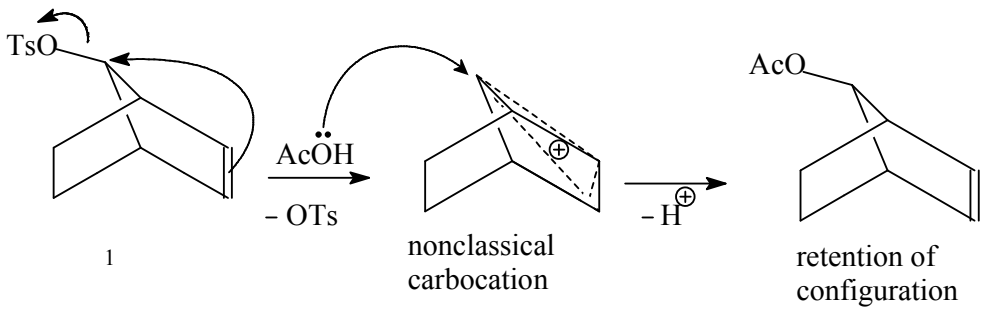


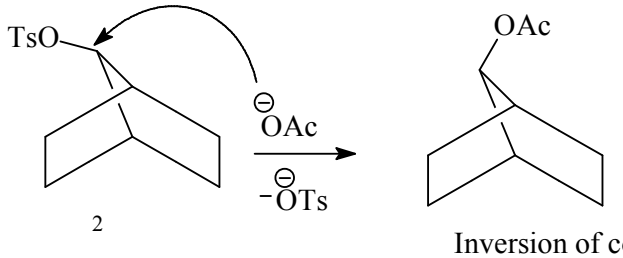
Example 3: A very good example of neighbouring group participation by iodo group is the acetolysis of trans-2-iodocyclohexyl brosylate which is 1.7×10^6 times faster than the acetolysis of the cis isomer in which the iodo group cannot attack from the backside, thus, there is no neighbouring group participation.



2. Double bond as Neighbouring group

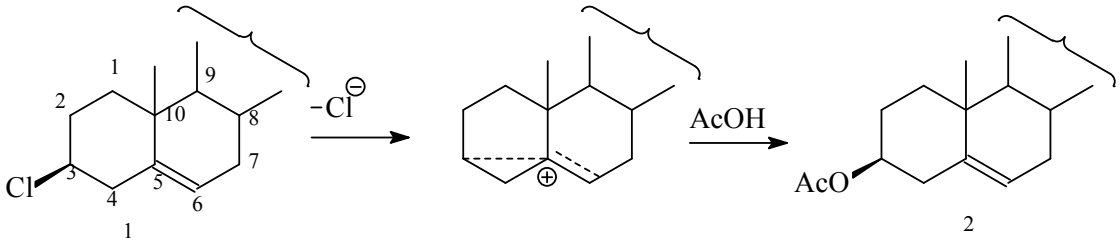
Example 1: The acetolysis of 7-norbornenyl tosylate (1) is 10^{11} times faster than that of the saturated analogue, 7-norbornyl tosylate (2) and process with retention of configuration, which gives a very strong evidence that C=C π bond can act as a neighbouring group. In the case (2) of the saturated analogue, no such anchimeric assistance is available, thus, its acetolysis proceeds through simple SN^2 reaction with inversion of configuration and at a normal rate which is very low (10^{11} times) as compared to that in the (1).



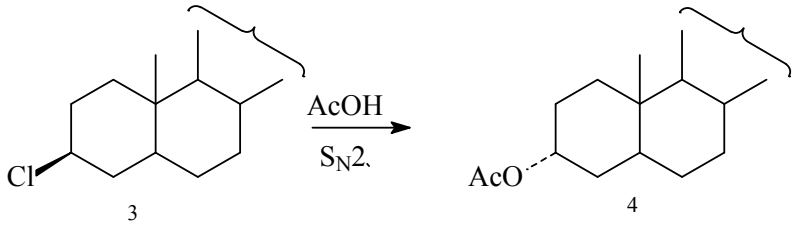


Inversion of configuration

Example 2: The acetolysis of cholesteryl chloride (1) to give cholesteryl acetate (2) with retention of configuration, while its dihydro derivative cholestanyl chloride (3) undergoes normal S_N2 reaction with inversion of configuration (4).



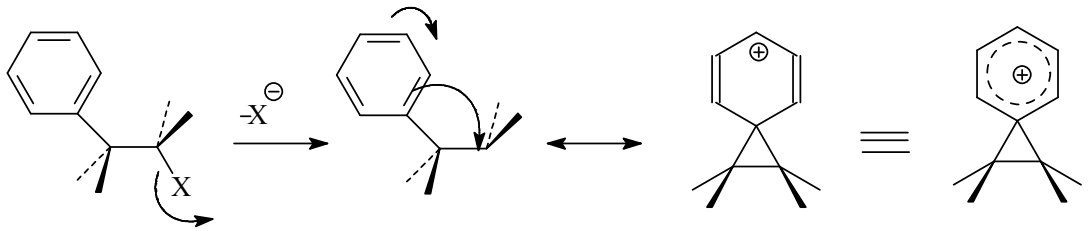
(retention)



(inversion)

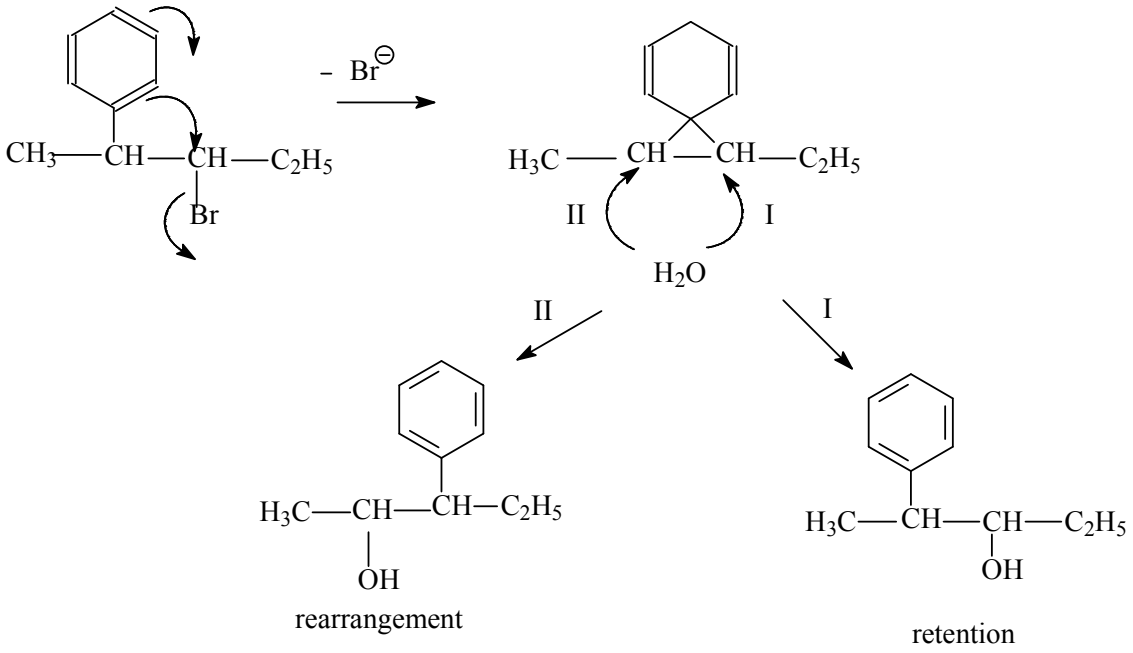
3. Phenyl group as Neighbouring group

The neighbouring group participation by an aryl group is indicated by retention of configuration and occurs through the formation of resonance stabilized phenonium ion.



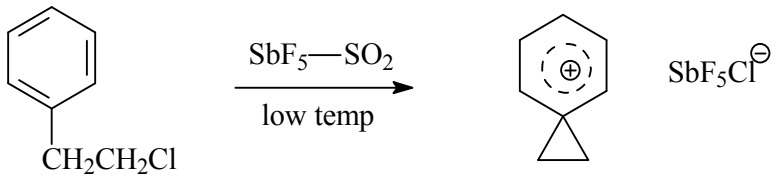
phenonium ion

As shown in the following example, the substitution takes place with retention of configuration (path I) and is accompanied by a rearranged product (path II).

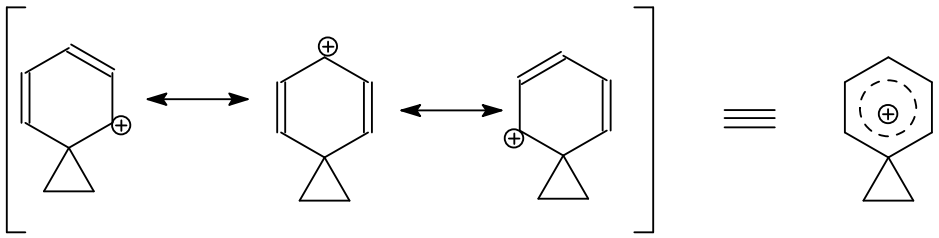


rearrangement retention

Evidence for the existence of the phenonium ion was provided by Olah in 1970s, who prepared many phenonium ions and investigated their structures using NMR spectroscopy. Treatment of β-phenylethyl chloride, for instance, with SbF_5-SO_2 at low temperature generated the corresponding phenonium ion, which has been adequately characterized by NMR spectroscopy.

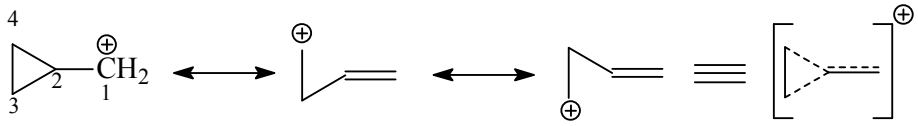


Resonance in the phenyl ring has been demonstrated by a combined application of ^{1}H and ^{13}C NMR spectroscopy. Overlapping of the cyclopropyl orbitals with π-orbitals of the phenyl ring helps in the delocalization of the electron-deficiency and the resultant positive charge in to the cycloprapane ring.



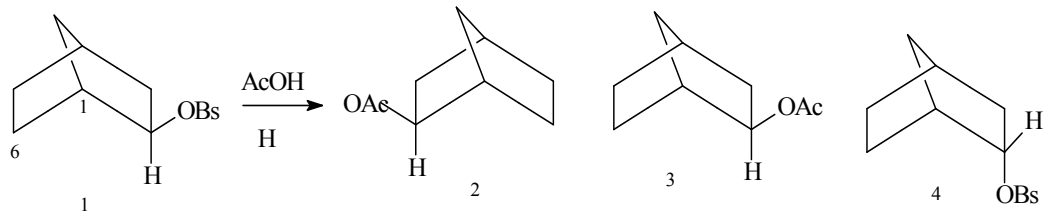
3. Sigma bond (σ) as Neighbouring group

(1) Participation by C-C single (σ) bond (the cyclopropylmethyl system): In solvolysis of primary cyclopropylmethyl systems the rate is high because of the participation by sigma (σ) bond of the ring. The ion which forms initially is an unrearranged cyclopropylmethyl cation which is symmetrically stabilized i.e. sigma (σ) bond at the position 2,3 and the 2,4 help to stabilized the positive charge (The evidence for cyclopropylmethyl cation is symmetrical is that substitutation of one or more methyl groups in the 3 and 4 positions increases the rate of solvolysis of cyclopropylcarbinyl 3,5-dinitrobenzoates by approximately a factor of 10 for each methyl group). The cation may be represented as follows:

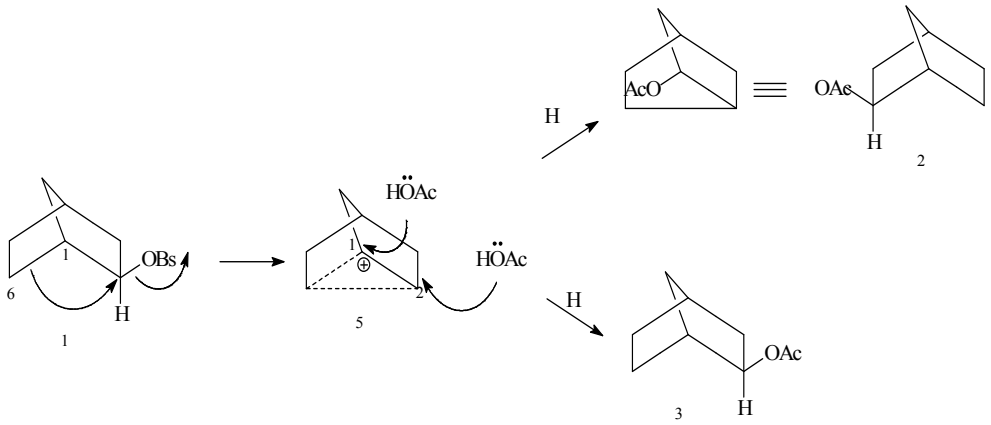


Unrearranged cyclopropylmethyl cation

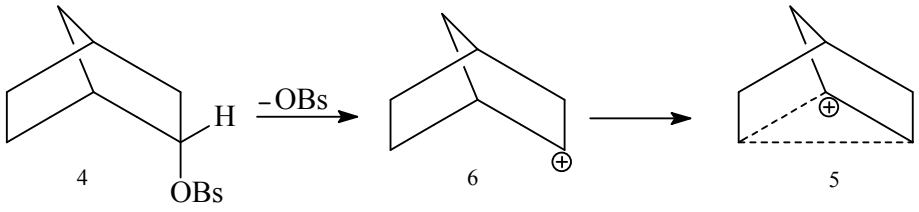
(2) Participation by C-C single (σ) bond (the 2-norbornyl system): The acetolysis of optically active exo-2-norbornyl brosylate **(1)** which gave a racemic mixture of two exo acetates **(2, 3)**, no endo imomer was formed. Furthermore **(1)** solvolysed about 350 times faster than its endo isomer **(4).** These two results (A) that solvolyis of an exo isomer gave only racemic exo isomers and (B) the high exo/endo rate ratio, were interpreted by Winstein and Trifan (1952) as indication that the 1,6 bond assists in the departure of the leaving group and that a nonclassical intermediate (**5**) is involved.



Solvolysis of the endo isomer (**4**) is not assisted by the 1,6 bond because it is not in a favourable position for the backside attack. Consequently, solvolysis of (**4**) takes place at a normal rate. Therefore, much faster rate for the solvolysis of (**1**) must be caused by anchimeric assistance. The stereochemistry of the product is also explained by the intermediacy of the nonclassical carbocation (**5**), since in (**5**) the 1,2 positions are equivalent and would be attaked by the nucleophile with equal facility but from the exo direction in either case.

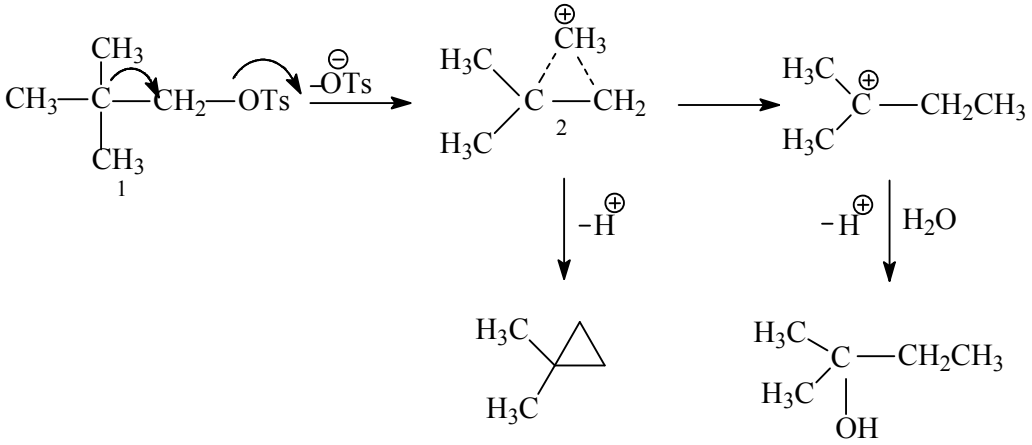


Acetolysis of (**4**) also leads exclusively to the exo acetetes (**2**) and (**3**). In this case it has been postulated that a classical ion (**6**) is first formed and then converted to more stable (**5**). Evidence for this interpretation is that the product from solvolysis of (**4**) is not racemic but contains somewhat more (**3**) than (**2**), suggesting that when (**6**) is formed; some of it goes to give (**3**) before it is converted to (**5**).



(3) Methyl as a neighbouring group: Neopentyl tosylate (1) undergoes almost exclusive rearrangement on solvolysis and (2) lie in the reaction path. Evidence

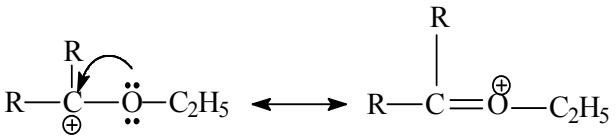
has been presented that under some conditions the methyl group in the neopentyl system does indeed participate. Evidence that (2) is an intermediate is that small amounts of cyclopropanes (10-15%) can be isolated in these reactions. (2) is protonated cyclopropane and would give a cyclopropane on loss of a proton.

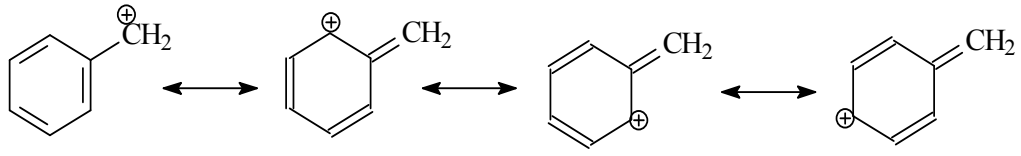


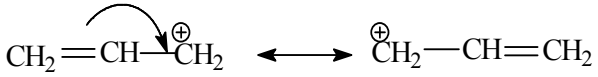
Rearranged product

1.8 CLASSICAL AND NON CLASSICAL CARBOCATION (BRIDGED CARBOCATIONS)

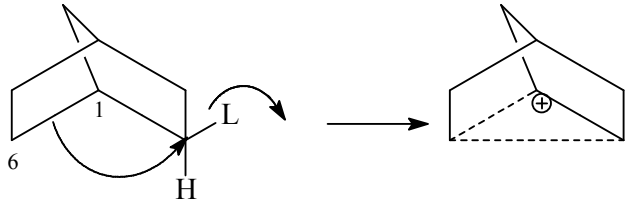
The carbocations so far studied are called classical carbocations in which the positive charge is localized on one carbon atom or delocalized by resonance involving an unshared pair of electrons or a double or triple bond in the allylic positions (resonance in phenols or aniline).

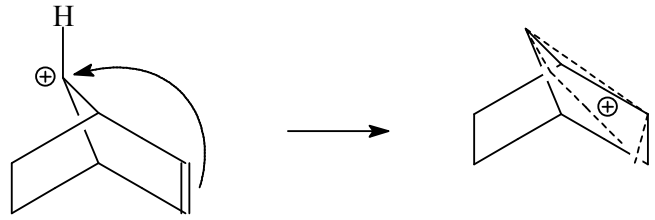


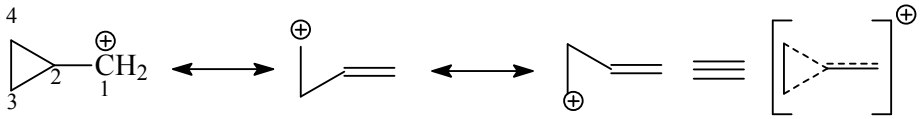




In a non-classical carbocation the positive charged is delocalized by double or triple bond that is not in the allylic position or by a single bond. These carbocations are cyclic, bridged ions and possess a three centre bond in which three atoms share two electrons. The examples are 7-norbornenyl cation, norbornyl cation and cyclopropylmethyl cation.



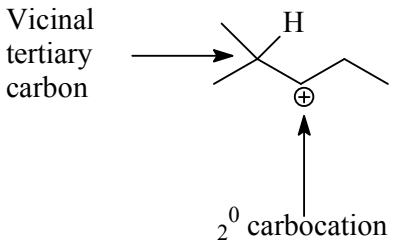




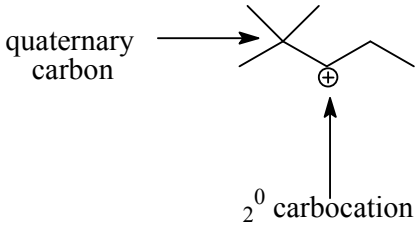
1.9 COMMON CARBOCATION REARRANGEMENTS

In a rearrangement a group moves from one atom to another in the same molecule. Most are migrations between adjacent atoms and are called 1,2-shifts. Carbocation rearrangements occur more frequently on secondary carbocations to form tertiary which are more stable and energetically more favourable. Simple alkyl primary carbocations are too high in energy to form so you don't tend to see a primary carbocation. There are some exceptions to this general rule for primary carbocations. Certain structural conditions such as being benzylic or allylic, due to resonance, allows for the formation of primary carbocations. Tertiary carbocations do not need to rearrange as they are already the most stable. In general, the bonding electrons of a carbocation may shift between adjacent atoms to form a more stable carbocation.

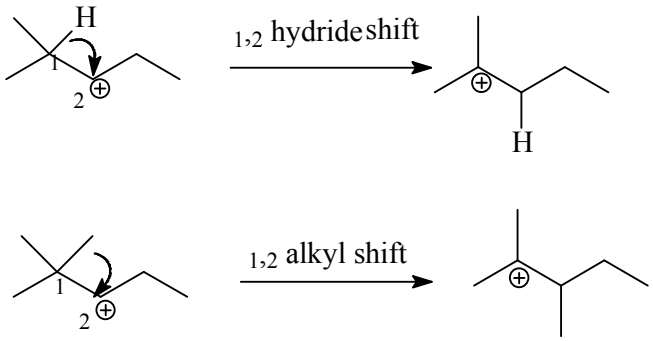
If a secondary carbocation is vicinal to a tertiary carbon bearing a hydrogen, a 1,2- hydride shift should occur.



If a secondary carbocation is vicinal to a quaternary carbon, a 1,2-alkyl shift should occur. The general rule in alkyl shifts is: the smaller alkyl substituent tends to be the substituent that shifts. Therefore, the most common 1,2-alkyl shift is a 1,2-methyl shift.



The mechanism of a 1,2-hydride shift and 1,2-alkyl shift: The mechanism for a 1,2-hydride and a 1,2-alkyl shift are the same. The arrow (electron movement) starts at the bond of the substituent moving and point's right at the carbocation. This shows that the atom/atoms in the substituent with the electrons moved to the carbocation. The shift (moving the electrons) results in a new carbocation where the substituent moved from.



The following "rules" hold for carbocation rearrangements:

i. Carbocation rearrangements are equilibrium processes.
ii. Usually lead to more stable carbocations.
iii. Sometimes lead to carbocations of equal stability (not so common).
iv. Sometimes lead to less stable carbocations (very unusual but does happen).

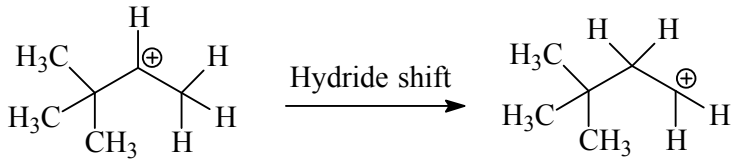
v. Hydride shift is more common, favorable, than alkyl shift.

vi. The least bulky alkyl substituent shifts (usually CH_3).

vii. Only groups adjacent to C^+ can migrate.

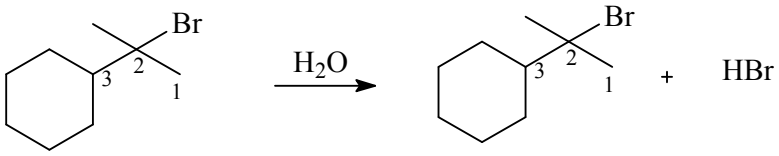
viii. Only carbon groups and H atoms can shift (1, 2-OH shift is forbidden)

1, 2-Hydride Shift: If a carbocation is vicinal to a tertiary carbon bearing a H atom, a 1,2-Hydride shift should occur. Hydride shift leads to a 3^o carbocation which is more stable than a 2^o.

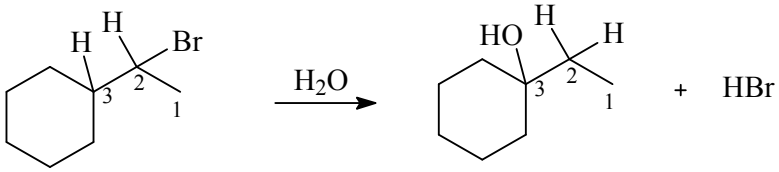


Secondary carbocation — Primary carbocation (less stable)

The hydride shift would occur more readily than the alkyl shift. For nucleophilic substitution, the pattern of bonds that form and break is pretty straightforward. You break C-(leaving group) and you form C-(nucleophile), a straight swap. But you might see a "weird" substitution reaction. If you look closely at the pattern of bonds formed and bonds broken in the second reaction below, there's an extra set.



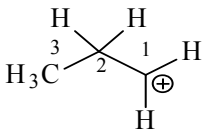
A normal Substitution Reaction



Substitution with Rearrangement

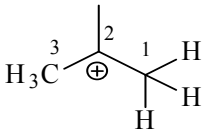
In other words it's a substitution reaction where the hydrogen has moved or rearranged. As it turns out, reactions that go through carbocations can sometimes undergo rearrangements. And looking back at substitution reactions, recall that the SN1 reaction goes through a carbocation intermediate. Carbocations contains six electrons bearing a positive charge. In

other words, they are electron deficient (–2 electrons short of a full octet). So, it would make sense that carbocations become more stable as you increase the number of electron donating groups attached to them. Alkyl groups are a perfect example. That's why carbocation stability increases as you go from primary to secondary to tertiary. Carbocation with the same substitution pattern can rearrange if it result in a resonance stabilized carbocation.

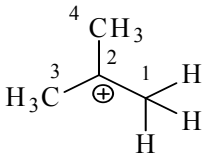


primary carbocation

(least stable)

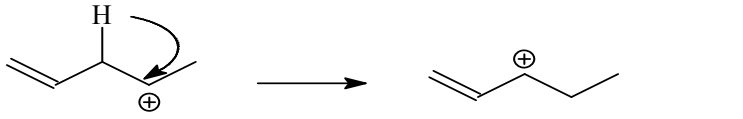


Secondary carbocation



Tertiary carbocation

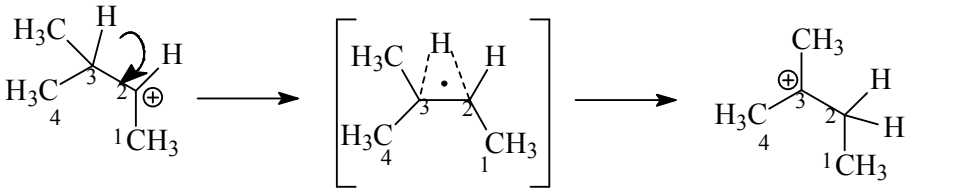
(most stable)



Secondary

Secondary
(resonance stabilized)

Carbocations are also stabilized by resonance, which allows the positive charge to be delocalized or "spread out" over a greater area on the molecule. One rearrangement pathway where an unstable carbocation can be transformed into a more stable carbocation is called a hydride shift.



Secondary carbocation

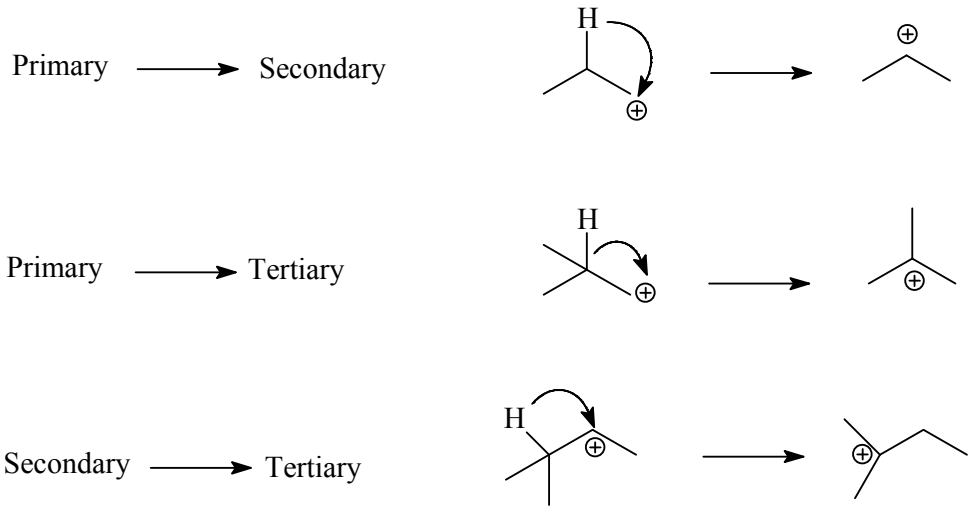
Transition state

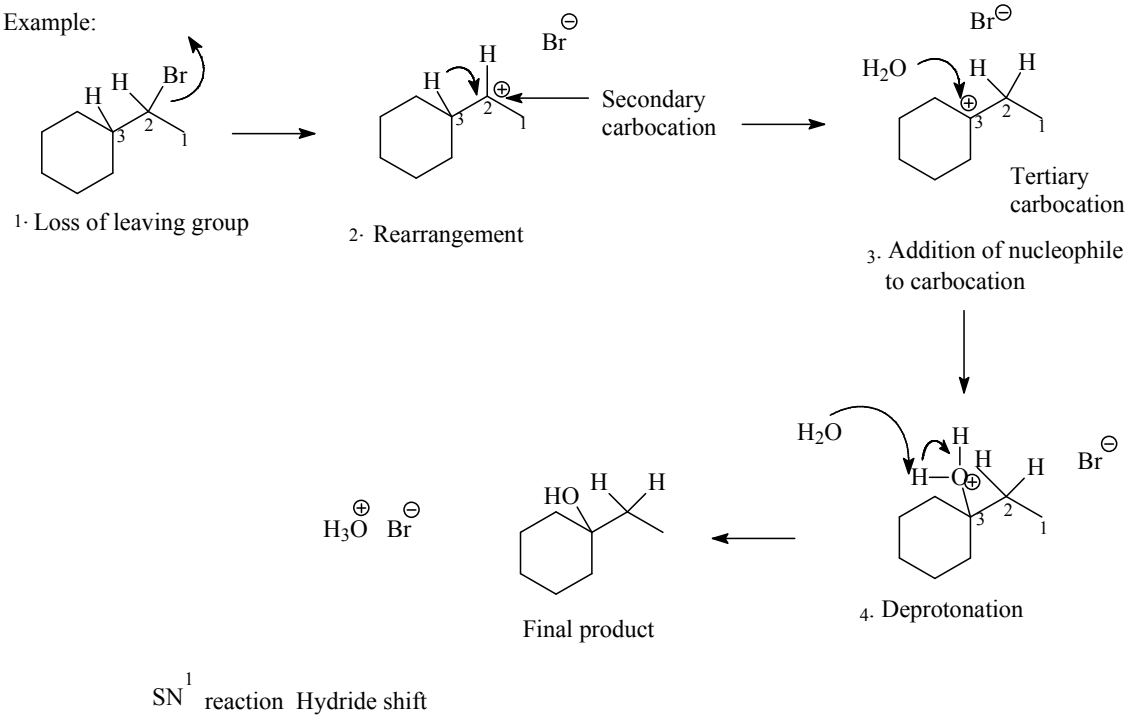
Tertiary carbocation

Hydride shift pathway

In this rearrangement reaction, the pair of electrons in the C-H bond is transferred to the empty p orbital on the carbocation. In the transition state (or called non classical carbocation) of this reaction, there's a partial C-H bond on C3 and a partial C-H bond on C2. The transition state here is kind of like that split second in a relay race where one sprinter is passing the baton to another sprinter and they both have their hands on it. Then, as the C2-H

bond shortens and the C3-H bond weakens, we end up with a carbocation on C3 (3o carbocation) in the product which is more stable. Here are some examples of "allowed" rearrangement reactions. Notice how we are always going from a less substituted carbocation to a more substituted carbocation. One exception is at the very bottom; the rearrangement is favorable because the new carbocation has increased stabilization. Some example of "allowed" H rearrangements to make more stable carbocation:

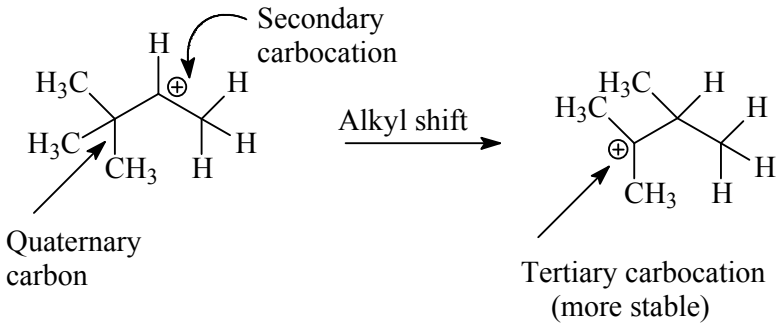




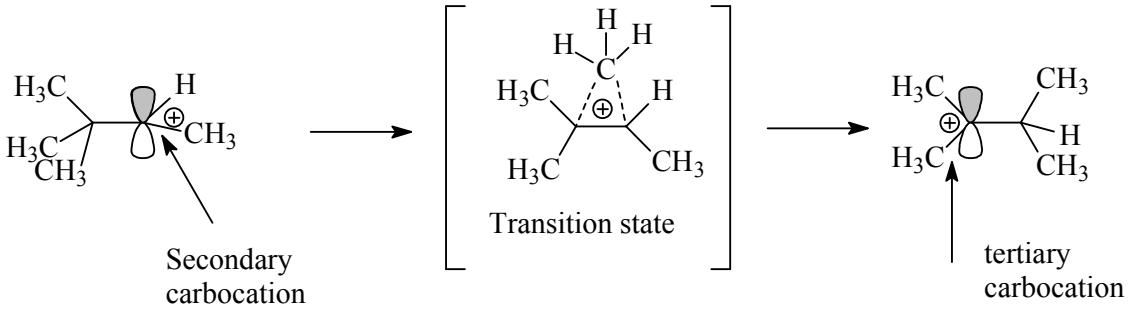
SN^1 reaction Hydride shift

1, 2-Alkyl Shifts

If a carbocation is vicinal to a 3° carbon, a 1,2-alkyl shift should occur. You might note something with this example, however: There is only possibility to form more stable 3° carbocation if an alkyl group migrates. The most common situation where alkyl shifts can occur is when a quaternary carbon is adjacent to a 2° carbocation.

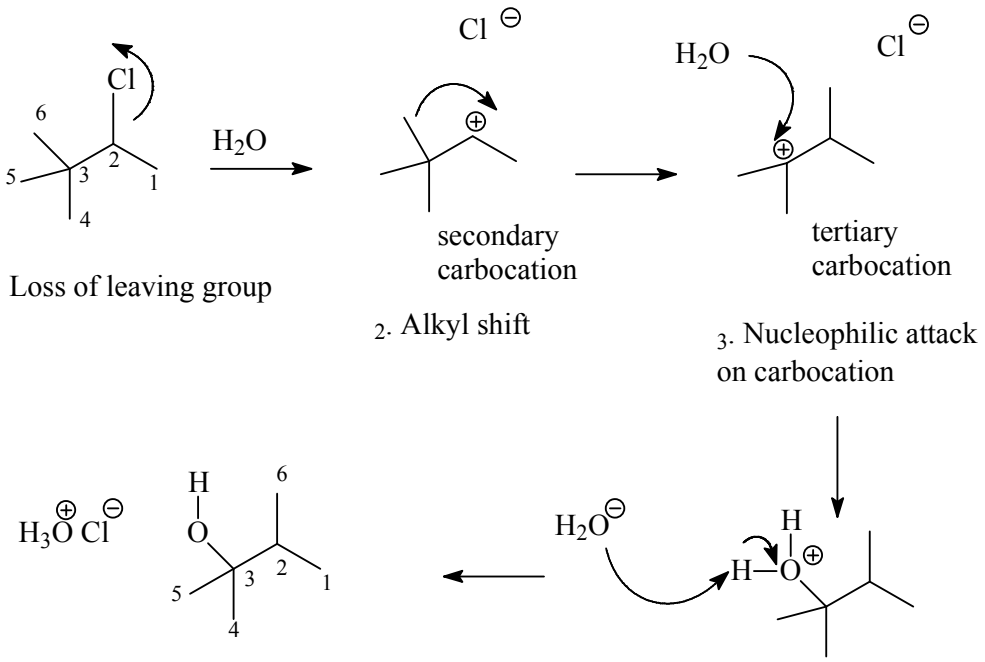


The pair of electrons from the C-C bond can be donated into the empty p-orbital on the carbocation (this means they have to be aligned in the same plane). In the transition state, there are partial bonds between the carbon being transferred and each of the two adjacent C-atoms. Then, as one bond shortens and the other lengthens, we end up with a (more stable) 3o carbocation.



Alkyl shift pathway

Once a carbocation is formed, rearrangements can potentially occur at any time. That includes SN1 reactions. Here's an example of an SN1 with an alkyl shift.



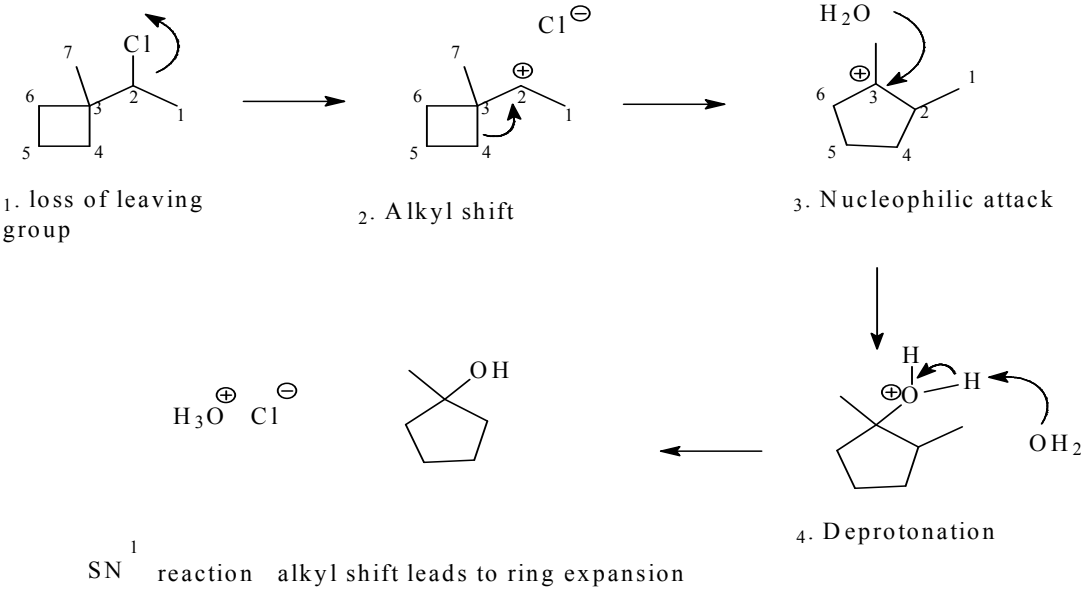
1. Loss of leaving group

2. Alkyl shift

3. Nucleophilic attack on carbocation

SN_1 reaction Alkyl shift

It doesn't always have to be a methyl group that moves. One interesting example is when a carbocation is formed adjacent to a strained ring, such as a cyclobutane. Even though the CH_3 could potentially migrate in this case, it's favorable to shift one of the alkyl groups in the ring, which leads to ring expansion and the formation of a less strained, 5-membered ring.



1. loss of leaving group

2. Alkyl shift

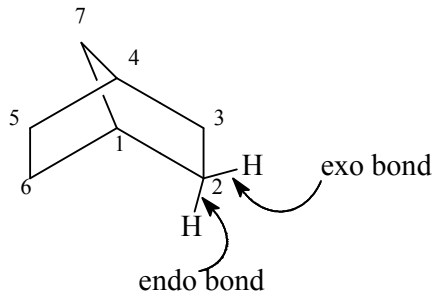
3. Nucleophilic attack

4. Deprotonation

SN^1 reaction alkyl shift leads to ring expansion

1.10 NORBORNYL SYSTEMS

Norbornane is an organic compound and its chemical formula C_7H_{12}. Its IUPAC name is [2.2.1] heptane. It is a 1, 4 bridged bicyclohydrocarbon. The norbornane molecule possesses a rigid structure with uncommon steric characteristics. Carbon atoms 1-6 constitute a cyclohexane structure in the higher-energy boat conformation. Moreover, the 7-methylene group not only locks this ring system into a rigid boat conformation, but the constraint so produced accentuates the steric crowding within the boat structure. Much of the chemistry of norbornane is dominated by the far greater steric accessibility of the exo as compared to the endo position. For example, in many free radical substitution reactions the exo product is produced preferentially.



Norbornane

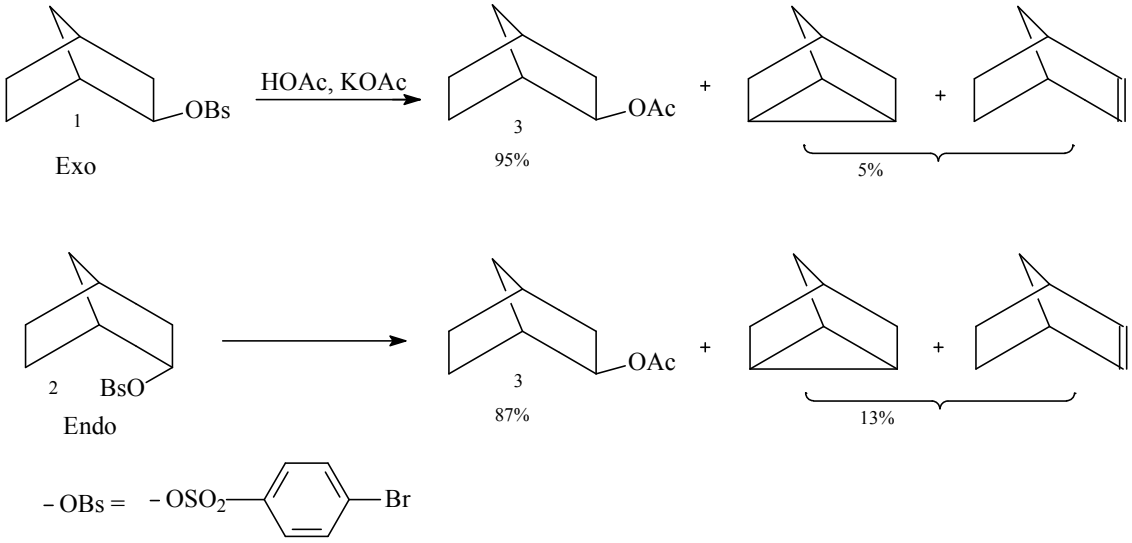
1.11 NORBORNYL CATION

Many naturally occurring terpenes are derivatives of Norbornane. Molecular rearrangements are common among these bicyclic terpenes. Winstein and roberts (1950) actively pursued the mechanism of the rearrangemts and the associated stereochemical problems using the basic norbornyl system.

Acetolysis of 2-norbornyl brosylates: Each of the isomeric brosylates (1 and 2) is prepared and subjected to acetolysis. (Solvolysis using acetic acid as solvent and nucleophile).

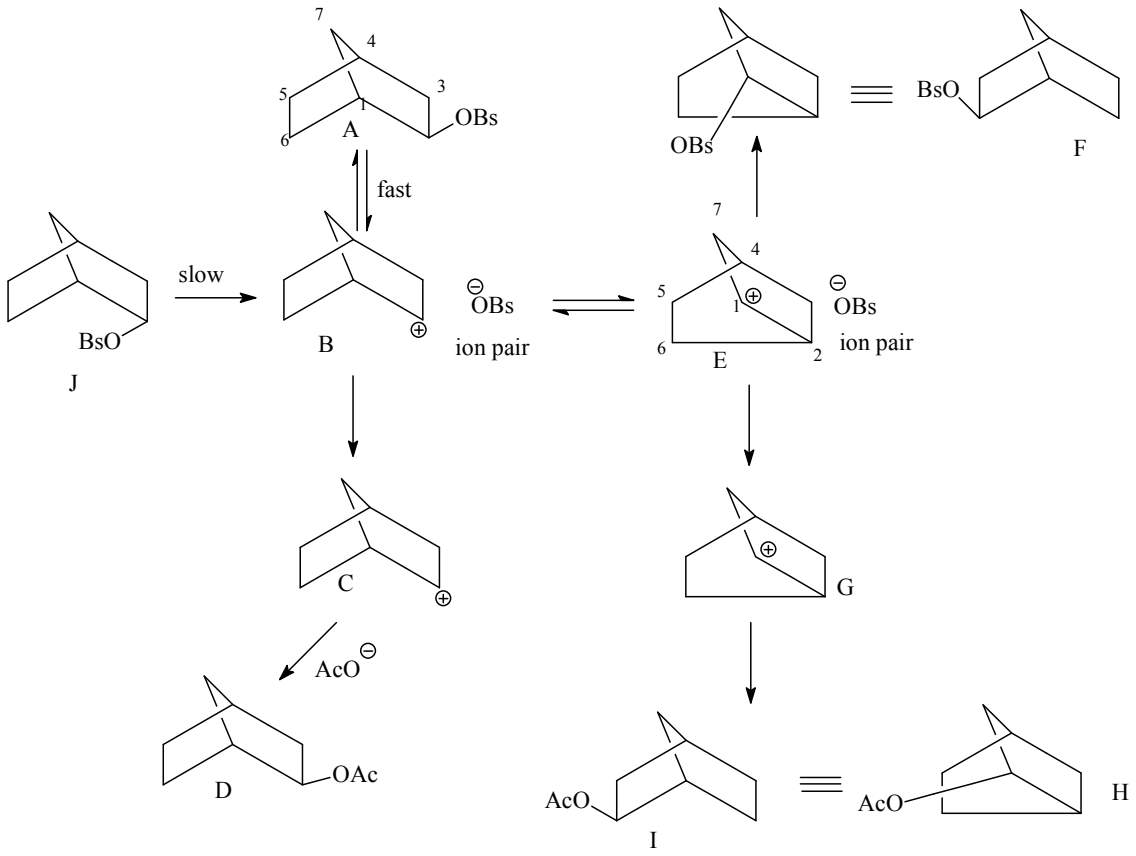
Observations regarding following reactions: (i) Rate of solvolysis of 1 to 2 is about 400 (ii) Both 1 and 2 give 3, the exo-acetate (iii) Optically active exo-brosylate (1) gives 3 which is racemic (±) (iv) The recovered brosylate (1) is also racemic (v) The rate of racemisation (measured from specific Rotation) is greater than solvolysis in the case of the exo-isomer (vi) The rate of racemization is equal to the rate of solvolysis in the case of endoisomer.

Following are for comparison: (i) Solvolysis rate of endo-brosylate is nearly equal to cyclohexyl brosylate (ii) Relative rate of 1 to cyclopentyl brosylate is 13.

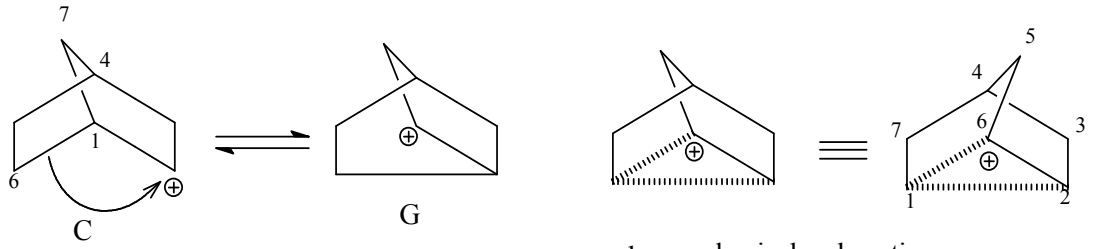


Satisfactory explanation for these observations is needed and also identifies the nature of the intermediate norbornyl carbocation and its reactivity. Beginning 1950 and till 1980, the topic became one of the very important area in theoretical organic chemistry. A new concept has been evolved, namely non-classical carbocation, nonclassical resonance, the sigma (σ) bridged norbornyl cation. The researches have raised healthy debates and also great controversies.

Acetolysis of 2-exo and 2-endo-norbornyl brosylate: (i) A → B → C → D is acetolysis with retention of configuration. The norbornyl cation C is attached by actetate ion from the exo face (preferred) (ii) B→E is ion pair rearranging to another ($C_1 – C_6$ bond migration to C_2) (ii) A → B →E →G (H) is acetolysis of A with rearrangement. D and I are (+),(-) forms of the acetate (mirror images) (iv) J → B is a slow ionization of endo–brosylate (the C_1- H and $C_1 – C_6$ bonds hinder ionisation) No such hindrance exist with A. B→A is ion pair return and E→F is the rearranged ion pair (E) return. A and F are enantiomers and hence racemic.



There are two proposals to represent the intermediate carbocation (1) Two rapidly equilibrating carbocations (C) and (G). (2) Sigma bridged non –classical norbornyl cation.



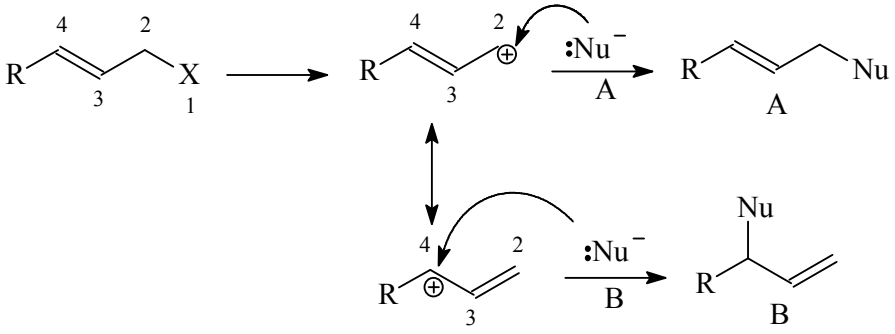
a. classical carbocations b. non classical carbocations

The carbocation (b) is unconventional and unusual therefore called non–classical as against (a) which is localized carbocation. The cation (b) is also spoken as split – sigma bond (C_1 – C_6), bridged cation. Some call these delocalized structures as non – classical resonance. We will not enter into any discussion at this stage but sum-up the main points.

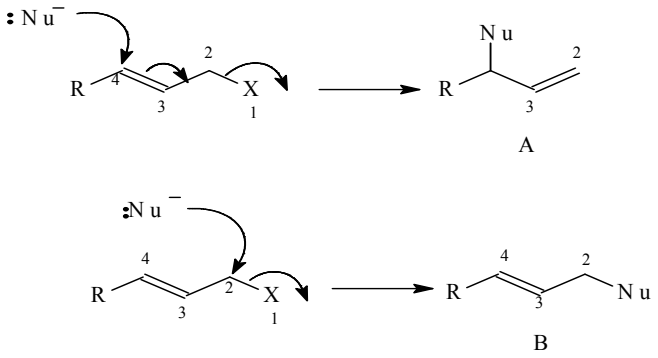
There appears to be small anchimeric assistance to solvolyis of A – from C1 – C6 bond at the T.S. This bond is just located at the back of the 2 – exo position. The intermediate derived from this Transition State is stabilized in comparison with localized carbonium ion by about 3kcal / mole (calculated from rates of acetolysis of A and J) this energy difference is too small to think of major reorganization of bonds. The non–classical norbornyl carbocation has a plane of symmetry (passing through C4, C5 and C6 and the midpoint of C1 - C2 and therefore achiral. The achiral carbocation is expected to give racemic acetate (product).

1.12 NUCLEOPHILIC SUBSTITUTION AT AN ALLYLIC CARBON

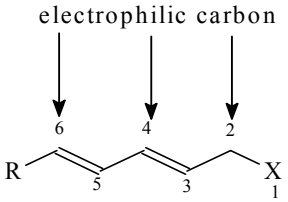
Generally nucleophilic substitution reactions are involved in direct displacement at a carbon center: the carbon that is bonded directly to the leaving group is the target for the attacking nucleophile. This process also known as S_N2 substitution. Generally primary alkyl halides undergo substitution by the S_N2 mechanism and do not undergo S_N1 reaction. However, a primary allyl halide is very reactive in an S_N1 reaction, for example allyl halides are more than 30 times reactive than an ethyl halide. Allylic substrates are usually accompanied by a rearrangement known as allylic rearrangement. In an S_N1 mechanism, the carbocation intermediate would have two possible resonance forms. This is likely in cases when the allyl compound is unhindered, and a strong nucleophile is used and the products will be similar to those seen with S_N1 substitution. Thus reaction of 1-halo-2-butene system with nucleophile (viz. NaOH) gives a mixture of 2- buten-1-ol and 1-buten-3-ol, as:



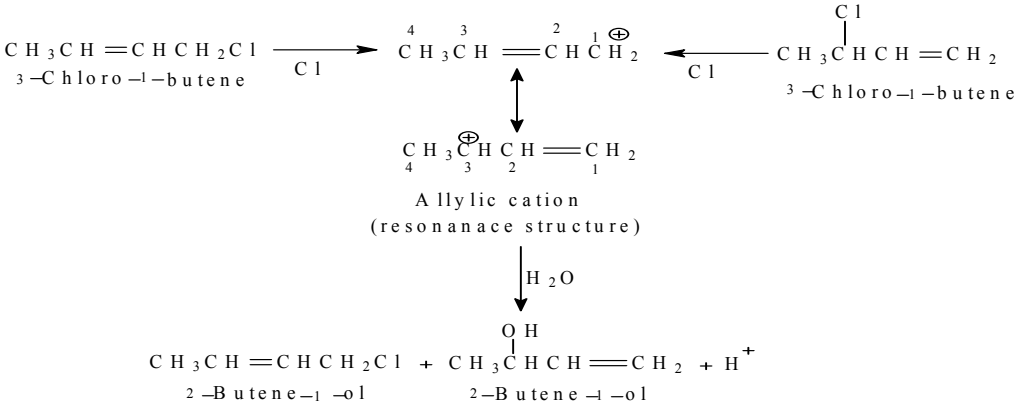
The incoming nucleophile, therefore, could attack either C2 (the carbon originally bonded to the leaving group), or alternatively at C4. These two events would lead to two different substitution products B and A, respectively:



The mechanisms leading to product A are referred to as nucleophilic allylic substitution. They are also sometimes referred to as 1,4 substitutions, according to a numbering system where the leaving group is designated atom. If the conjugated π-orbital system extends further, more allylic substitution products can result: in the following example, 1,6 as well as 1,4 and 1,2 substitutions are possible.



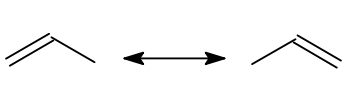
For example: Hydrolysis of **1-Chloro-2-butene**

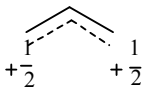


Two distinct mechanisms for aliphatic nucleophilic substitution (SN) are S_N1 and S_N2. In terms of stereochemistry, the S_N2 process is attended with inversion of configuration where substitution occurs at a chiral carbon. The S_N1 mechanism involves inversion and retention of configuration (racemization). The question is that arise is whether there are cases where is

retention of configuration in SN reactions. The answer is yes. Besides NGP in SN reactions, there is another important mechanism labelled S_Ni.

Allylic System: The positions adjacent to C=C often show enhanced reactivity compared to simple alkanes due to the proximity of the adjacent p system. Such positions are referred as "allylic". Recall that the term "vinylic" is used to described the atoms directly associated with the C=C unit.

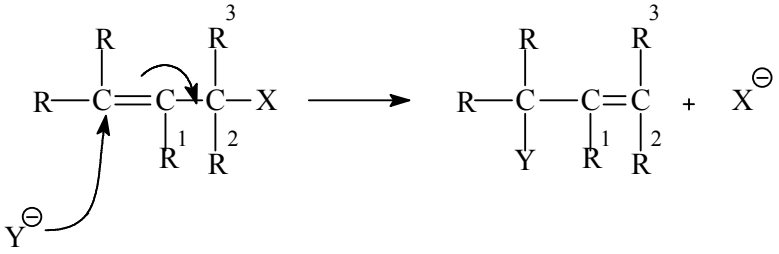




resonance hybrid

Thus in allylic systems C1 and C3, each carry a partial positive charge and both were attacked by a nucleophile which lead to the formation of two products.

The resonance stabilization of the allylic carbocation is presented as above in the orbital picture. The positive charge is delocalized over two C-atoms by overlap of the filled p-orbital of the π bond with the vacant p-orbital of the carbocation. Nucleophilic substitution at an allylic carbon can also take place by an S_N2 mechanism in which no allylic rearrangement usually takes place. However, allylic rearrangements can also take place under S_N2 conditions through the following mechanism in which the nucleophile attacks at the γ carbon rather than the usual position. This mechanism is called S_N2' mechanism. The S_N2' rearrangement normally occurs exclusively when the SN2 process is sterically hindered.

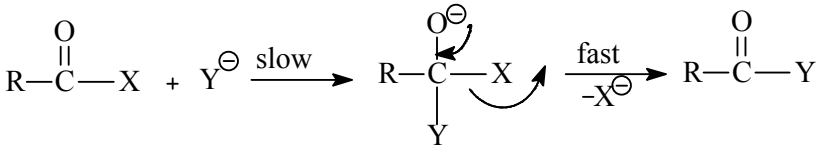


Thus, the p orbital system of a double bond can stabilize an adjacent carbocation by donating electron density through resonance. Due to the stability of these allylic cations, they are readily formed as intermediates during chemical reactions, for example S_N1 reactions of allylic halides.

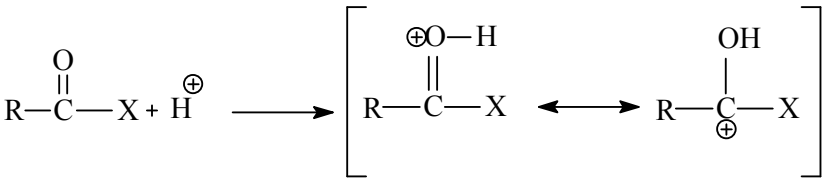
1. Allyl chlorides, bromides and iodides are good substrates for substitution reactions.
2. A variety of nucleophiles can be used to generate a range of new functional groups.
3. The process can be complicated by the allylic rearrangement where the nucleophile can attack either of the deficient sites.

1.13 NUCLEOPHILIC SUBSTITUTION AT AN ALIPHATIC TRIGONAL CARBON

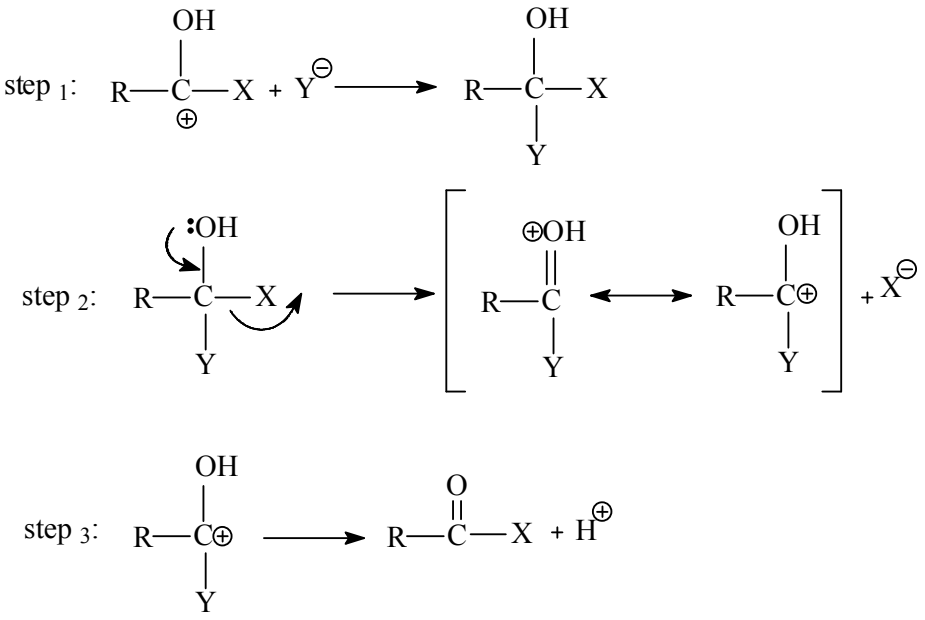
Nucleophilic substitution is also important at trigonal carbons, especially when the carbon is double bonded to oxygen, sulphur or nitrogen. The nucleophilic substitution occurs through tetrahedral mechanism, often called as addition-elimination. Although this mechanism displays second order kinetics, it is not the same as the S_N2 mechanism.



In tetrahedral mechanism first the nucleophile (Y) attacks to give a tetrahedral intermediate containing both X (leaving group) and Y and then the leaving group (X) departs. The tetrahedral mechanism is supported by the second order kinetics and isotopic labelling. In some cases, tetrahedral intermediates have been isolated or detected spectrally. When the reaction is carried out in acid solution the hydrogen ion acts as a catalyst. The reaction rate is increased as it is easier for the nucleophile to attack the carbon when the electron density of it has decreased.

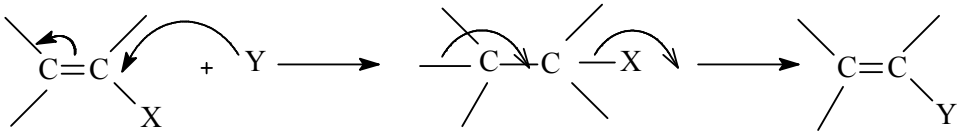


Mechanism:



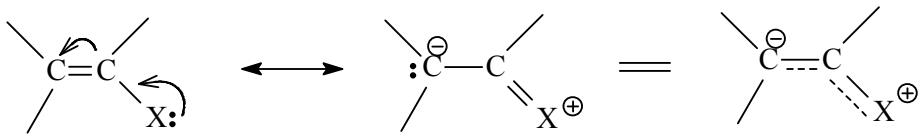
1.14 NUCLEOPHILIC SUBSTITUTION AT VINYLIC CARBON

The subject matter under the title is concerned with nucleophilic substitution at unsaturated carbon such as vinylchloride (CH_2=CHCl).

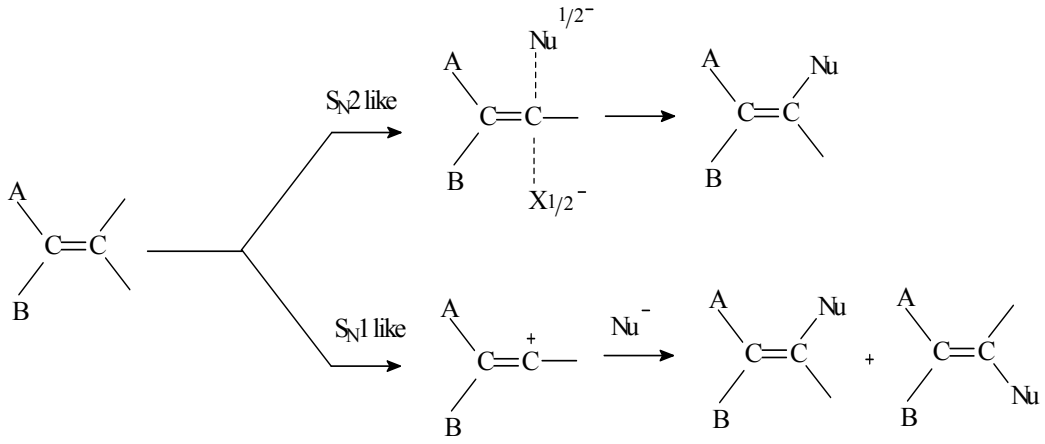


Under normal conditions, nucleophilic substitution at vinylic carbon is extremely slow compared to substitution at saturated carbon. Vinyl substrates are essentially inert towards nucleophiles. There are two reasons for this lack of reactivity. The first one is vinyl C-X bond (X- halogens). This is clearly depicted in the above reaction.

In fact most of contexts, vinyl halides and related compounds can be considered essentially inert towards nucleophiles. There are two reasons for this, first, a vinyl C–X bond (X = halogen, oxygen, or nitrogen) is stronger than and alkyl C–X bond because of a resonance interaction between the double bond and an unshared pair on X. This interaction also weakens and polarizes the π-bond, which is why such compounds are reactive towards electrophilic addition.



The second reason for low reactivity of vinyl substrate towards nucleophilic substitution is that the S_N2 transition state as well as the S_N1 intermediate (a vinyl cation), are too high in energy to be readily accessible



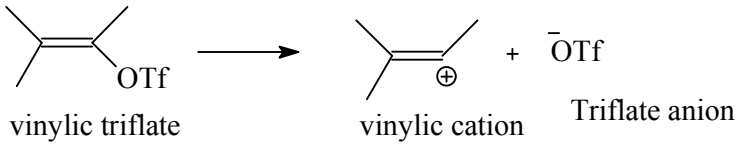
Example: The heterolytic bond dissociation energy for vinyl chloride is 207 kcal as compared with 191 kcal for EtCl and 227 kcal for MeCl. Values for the fluorides, bromides and iodides show the similar differences. It takes 16-18 kcal more energy to break the C–X bond in a vinyl halide than in the corresponding EtCl. Except for the bond in methyl halides, this is the strongest C–X bond we have so far encountered. The bond length for vinylic C-Cl is 1.73 Å compared with 1.78 Å for the saturated C-Cl bond. A shorter bond is, in general, a stronger bond. Thus the rate determining step involves breaking of the C–X bond. The bond in vinyl halides is harder to break, and reaction is slower.

Not surprisingly, the difficulty of generating vinylic cations by heterolysis has been taken as a challenge by the organic chemist, and, in work done mostly since about 1970's, vinylic cations have emerged as accessible intermediates with fascinating properties. Many people from many countries have been involved in this research. The vinylic cations can readily be made through solvolysis of the S_N1 kind if two conditions are met:

a) The leaving group is extremely good one, and

b) The vinylic group contains electron releasing substituents.

Most commonly used for this purpose is the super leaving group, viz. trifluoro methanesulfonate, ($–OSO_2CF_3$) which is also known as triflate. The powerful electron withdrawing F-atom (through dispersal of the negative charge) help to stabilize the triflate anion, and make the parent acid CF_3SO_2OH one of the strongest Lowry Bronsted acids known, much stronger than the familiar H_2SO_4 or $HClO_4$. The triflate anion is correspondingly an extremely weak base, and one of the best leaving group in organic chemistry.



vinylic triflate vinylic cation Triflate anion

1.15 STRUCTURE REACTIVITY ANALYSIS OF ATTACKING NUCLEOPHILE, LEAVING GROUP AND REACTION MEDIUM

1.15.1 Factors Influencing S_N2 Reaction:

a. Solvent: Nucleophiles are more stabilized than the transition state in polar protic solvents due to solvation where the ground state energy of nucleophile is reduced in comparison to the transition state's energy. Due to this, reaction progress leads to a higher activation energy and thus to a lower reaction rate. The nucleophiles are less solvated in polar aprotic solvents (DMSO, DMF and HMPT) which results in the less stabilized ground state when compared to the polar protic solvents. Thus, the nucleophile is more reactive which leads to the lowering of activation energy, and a higher rate of the reaction. Thus, for SN2 mechanism, increasing solvent polarity usually decreases the rate of reaction.

b. Nucleophile: In S_N2 reaction, the nucleophile is involved in the rate determining step, so the nature and concentration of nucleophile affect the rate of S_N2 reaction. The stronger the nucleophile, the faster is the S_N2 reaction. In S_N2 reaction the high energy transition is required. Therefore, a high concentration of strong nucleophile is required for S_N2 reaction. Good nucleophiles having higher energy in the ground state, and are less stable than the poor nucleophiles. Thus, the activation energy in S_N2 reaction is lower and the reaction rate is

consequently higher than in S_N1 reaction with a comparatively stable nucleophile. The reactivity of small nucleophiles is rapid than the sterically demanding nucleophiles. Basic and negatively charged nucleophiles are more reactive as compared to uncharged nucleophiles.

c. Substrate: Activation energy of the transition state in S_N2 reaction increases as the steric hindrance in the substrate increases, while at the same time reaction rate is decreased. The reaction rate of S_N2 reactions will be in the order of $1^o > 2^o > 3^o$ alkyl halide ($CH_3–X > RCH_2–X >> R_2CH–X >>> R_3C–X$). In the cases of secondary and tertiary alkyl compounds, SN2 reaction is largely superseded by an SN1 reaction or elimination. Rates of S_N2 reactions for allylic and benzylic systems are also increased because of resonance in the transition state.

d. Leaving Group: A leaving group which becomes a more stable species after it departs is a better leaving group. The best leaving groups are the weakest bases. Stable anions are good leaving groups which results in the lowering of activation energy while reaction rate is higher. For example, iodide anions are better leaving groups than chloride anions. Hydroxide anions, alkoxides, fluoride anions, and amide anions are poor leaving groups thus SN2 reactions with fluoroalkanes, alcohols, ethers, or amines virtually never occur. However, acid-catalysed SN2 reactions with alcohols or amines can take place, as the leaving group does not consist of the hydroxide anion. Thus the leaving groups can be arranged in the order:

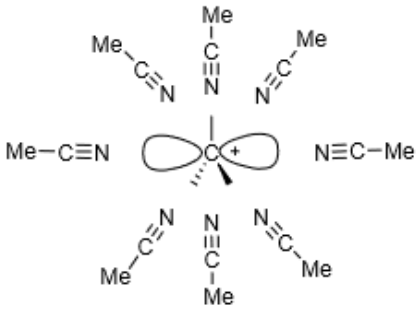
$$MsO^-, TsO^- > I^- > Br^- > Cl^- > F^- > (^-OH, ^-NH2)$$

Where, MsO– and TsO– are extremely good leaving groups due to resonance stabilization. Thus, the nature of leaving group not only affects the rate of reaction but may also change the reaction mechanism.

1.16.2 Factors Influencing S_N1 Reaction:

a. Solvent: The rate of the reaction can be affected by the energy level of the reagents. Solvation of the carbocation allows the carbocation to be surrounded by more electron density, making the positive charge more stable (see below). The solvent can be protic or aprotic, but it must be polar solvent. Polar protic solvents have a H-atom attached to an electronegative atom so the hydrogen is highly polarized. Polar aprotic solvents have a dipole moment, but their hydrogen is not highly polarized. Polar aprotic solvents are not used in SN1 reactions because some of them can react with the carbocation intermediate and lead to unwanted product. Thus, polar protic solvents are preferred in S_N1 reaction which helps to

speed up the rate of reaction due to large dipole moment of the solvent which helps to stabilize the transition state. The highly positive and highly negative parts interact with the substrate to lower the energy of the transition state. Since the carbocation is unstable, anything that can stabilize this even a little will speed up the reaction.

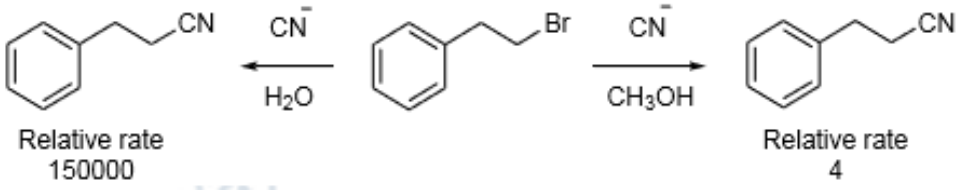


Sometimes in an SN1 reaction the solvent acts as the nucleophile known as solvolysis reaction. The polarity and the ability of the solvent to stabilize the intermediate carbocation, is very important as shown by the relative rate data for the solvolysis (in table). The dielectric constant of a solvent provides a measure of the solvent's polarity. A dielectric constant below 15 is usually considered non-polar. Thus, higher the dielectric constant more polar will be substance and in the case of SN1 reactions the faster the rate.

Table

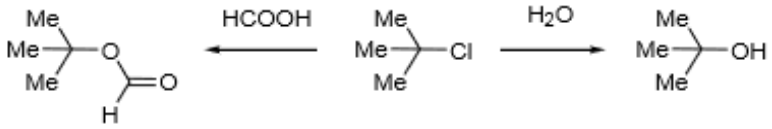
Solvent	Dielectric Constant	Relative rate
Acetic acid	6	1
Methanol	33	4
Water	78	150000

The example given here illustrates this concept.



b. Nucleophile: Nucleophiles involved in the SN1 mechanism are mostly weak and neutral molecules (viz. H_2O, ROH). The strength of the nucleophile does not affect the reaction rate of SN1 because; the nucleophile is involved in the rate-determining step. However, if you

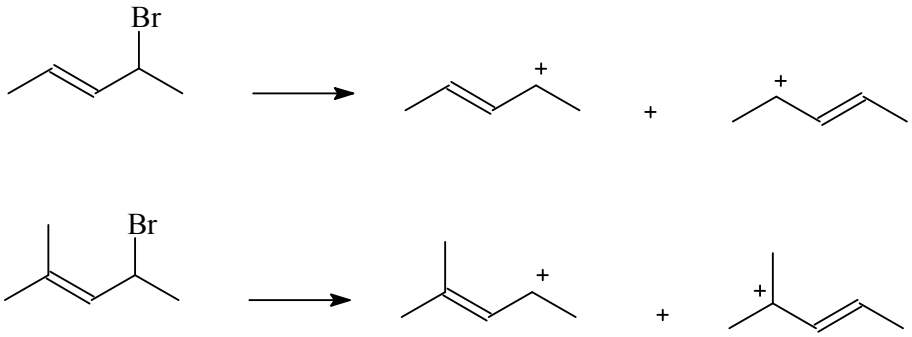
have more than one nucleophile competing to bond to the carbocation, the strengths and concentrations of those nucleophiles affect the distribution of products. For example, if you have $(CH_3)_3CCl$ reacting in water and formic acid where the water and formic acid are competing nucleophiles, you will get two different products: $(CH_3)_3COH$ and $(CH_3)_3COCOH$. The relative yields of these products depend on the concentrations and relative reactivities of the nucleophiles.



c. Substrate: The hyperconjugation and the inductive effect allow alkyl groups to stabilize carbocations. The more stable carbocation intermediate has a lower activation barrier, so the S_N1 reaction occurs faster. In general, the SN1 reaction is favored in the order is-

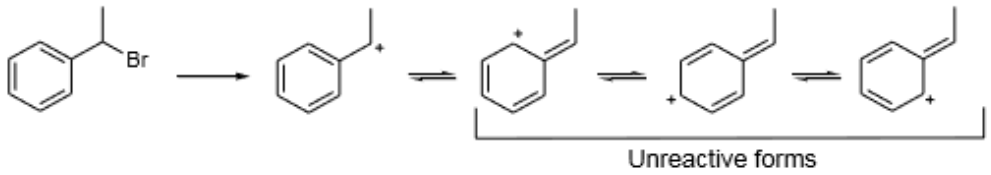
$$\text{Benzylic} > \text{Allylic} > 3° > 2° > 1° >> Me^+$$

Substrates wherein the leaving group (LG) is on a 3° carbon will lead to a reaction in the presence of a good nucleophile (Nu). Since, 1° carbocations are highly energetically unfavorable, as a rule of thumb they generally do not form. The rate for hydrolysis of alkyl halide is in the order of halides, $3^o > 2^o > 1^o >$ MeX. Thus, we can say the electronic factor is more important than the steric factor. The Eact for the carbocation intermediate will be highest for MeX (1^o), while least for the 3^o. The molecules in which carbon next to the site of substitution contains a double bond, the S_N1 reaction is possible. The reason is that the positive charge on the carbocation can be delocalized among multiple possible resonance structures (resonance and delocalization) making the carbocation dramatically stable. This effect can occur when the carbon atom of interest is next to one double bond (allylic) or a benzene ring (benzylic). In allylic case the delocalization of the positive charge, the nucleophile can attack at multiple sites while this effect is absent in the benzylic system due to the need to preserve aromaticity. For example, the allylic carbocation can form two different resonance structure, both are available for reaction (see below). In the first example we end up with similar carbocation intermediate but we have different situation in the second example where we have 2^o and 3^o carbocation intermediates. Thus, second reaction will lead to 3^o product through stable 3^o carbocation intermediate.



Delocalized and resonance

If there is a benzylic carbocation, it is also resonance stabilized but only the carbocation on the benzylic position is reactive (retains the aromatic ring) as follows:



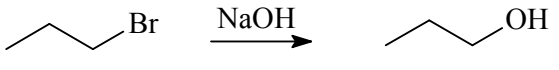
d. Leaving Group: The leaving group is almost always expelled with a full negative charge. The best leaving groups are those that can best stabilize an anion (i.e. a weak base). S_N1 reaction speeds up with a good leaving group. This is because the leaving group is involved in the rate-determining step. A good leaving group wants to leave so it breaks the C-leaving group bond faster. Examples of LG:

(Good…….) -OMs, -OTos, Triflate ion, NH3 > H2O ≈ I- , Br- > Cl- > F- (-OH, -NH2) (…….poor)

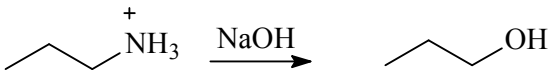
As you go from left to right on the periodic table, electron donating ability decreases and thus ability to be a good leaving group increases. Halides are an example of a good leaving group whose leaving-group ability increases as you go down the column. Other examples of good leaving group viz. methyl sulfate ion and other sulfonate ions.

(Good)….. I- > Br- > Cl- > F- …..(poor)

For example: The two reactions below is the same reaction done with two different leaving groups. One is significantly faster than the other. This is because the better leaving group leaves faster and thus the reaction can proceed faster.



faster



slower

1.16 HSAB PRINCIPLE

Hard and Soft Acids and Bases (HSAB) Theory is a qualitative concept introduced by **Ralph Pearson** to explain the stability of metal complexes and the mechanisms of their reactions. However it is possible to quantify this concept based on **Klopman's FMO analysis** using interactions between HOMO and LUMO. According to this theory, the Lewis acids and bases can be further divided into hard or soft or border line types. Hard Lewis acids are characterized by small ionic radii, high positive charge, strongly solvated, and empty orbital's in the valence shell and with high energy LUMOs. Soft Lewis acids are characterized by large ionic radii, low positive charge, and completely filled atomic orbital's and with low energy LUMOs. Hard Lewis bases are characterized by small ionic radii, strongly solvated, highly electronegative, weakly polarizable and with high energy HOMOs. Soft Lewis bases are characterized by large ionic radii, intermediate electro negativity, highly polarizable and with low energy HOMOs. The Border line Lewis acids and bases have intermediate properties. Remember that it is not necessary for Lewis acid or base to possess all the properties to be classified as hard or soft or borderline. In short, hard acids and bases are small and non-polarisable, whereas soft acids and bases are larger and more polarisable.

1.16.1 HSAB Principle: According to HSAB concept, hard acids prefer binding to the hard bases to give ionic complexes, whereas the soft acids prefer binding to soft bases to give covalent complexes. It is sometimes referred to as Hard-Soft Interaction Principle (HSIP). The large electro negativity differences between hard acids and hard bases give rise to strong ionic interactions. The electro negativities of soft acids and soft bases are almost same and hence have less ionic interactions. i.e., the interactions between them are more covalent. The

interactions between hard acid - soft base or soft acid - hard base are mostly polar covalent and tend to be more reactive or less stable. The polar covalent compounds readily form either more ionic or more covalent compounds if they are allowed to react.

1.16.2. HSAB & FMO Analysis: According to FMO analysis, the interactions between acids and bases are controlled by the relative energies of the participating frontier molecular orbitals (FMO) i.e., HOMO and LUMO. Greater the energy gap between the HOMO & LUMO, harder is the species. Quantitatively the absolute hardness of a species is determined by following equations.

$$\text{hardness} = n = \frac{\text{Ionization energy (I) - Electron Affinity(EA)}}{2}$$

or

$$n = \frac{E_{LUMO} - E_{HOMO}}{2}$$

Here, it's better to conclude with the Soft Bases as good nucleophile and a comprehensive comparison between Basicity & Nucleophilicity ….

Section 1.16.3 and 1.16.4 are academic overflows can be avoided to have a space in Organic Chemistry domains.

1.16.3: Characteristics of Hard, Soft & Borderline Acids & Bases

Type of Acid/Base	Characteristics	Examples
Hard acids	**a.** Atomic centres of small ionic radii (<90 pm). **b.** High positive charge. **c.** Empty orbitals in their valence shells. **d.** Low electronegativity (0.7-1.6) and low electron affinity. **e.** Likely to be strongly solvated. **f.** High energy LUMO.	H^+, Li^+, Na^+, K^+, Be^{2+}, Mg^{2+}, Ca^{2+}, Sr^{2+}, Sn^{2+} Al^{3+}, Ga^{3+}, In^{3+}, Cr^{3+}, Co^{3+}, Fe^{3+}, Ir^{3+}, La^{3+}, Si^{4+}, Ti^{4+}, Zr^{4+}, Th^{4+},U^{4+}, VO^{2+} , UO_2^{2+} $BeMe_2$, BF_3, BCl_3, $B(OR)_3$, $AlMe_3$

Soft acids	**a.** Large radii (>90 pm). **b.** Low or partial positive charge. **c.** Completely filled orbitals in their valence shells. **d.** Intermediate electronegativities (1.9-2.5) **e.** Low energy LUMO's with large magnitude of LUMO coefficients.	Cu^+, Ag^+, Au^+, Hg^+ , Cs^+ , Tl^+ , Hg^{2+} , Pd^{2+}, Cd^{2+} , Pt^{2+} Metal atoms in zero oxidation states BH_3
Border line acids		Fe^{2+} , Co^{2+} , Ni^{2+} , Cu^{2+} , Zn^{2+} , Pb^{2+} , $B(CH_3)_3$, SO_2, NO^+
Hard bases	**a.** Small radii (around 120pm) & highly solvated. **b.** electronegative atomic centres (3.0-4.0). **c.** Weakly polarizable. **d.** Difficult to be oxidized. **e.** High energy HOMO.	H_2O, OH^-, F^-, Cl^-, CH_3CO_2-, PO_4^{3-}, SO_4^{2-}, CO_3^{2-}, NO_3^-, ClO_4^-, ROH, RO^-, R_2O, NH_3, RNH_2, N_2H_4
Soft bases	**a.** Large atoms (>170 pm) with intermediate electronegativity (2.5-3.0). **b.** High polarizability **c.** Easily undergoes oxidation. **d.** Low energy HOMO's but large magnitude HOMO coefficients.	S^{2-}, RSH, RS^-, R_2S, I^-, CN^-, SCN^-, $S_2O_3^-$, R_3P, R_3As, $(RO)_3P$, RNC, CO, C_2H_4, C_6H_6, R^-, H^-
Border line bases		Aniline, pyridine, N_3^-, Br^-, NO_2^-, SO_3^{2-}, N_2

1.16.4 Applications of HSAB Principle

a. In hydrogen bonding: The strong hydrogen bond is possible in cases of H_2O, NH_3 and HF, since the donor atoms (F, O & N) are hard Lewis bases and their interactions with partially positively charged H, which is a hard acid, are stronger.

b. Linkage of ambidentate ligands to metal atoms:

The SCN^- ligand is an ambidentate ligand and can be S-bound to metal (M-SCN) and referred to as thiocyanate or can be N-bound to metal (M-NCS) and is referred to as isothiocyanate. The choice among S-bound or N-bound is decided by soft or hard acid base behaviour. S is comparatively soft base than N atom. Hence soft metal ions are S-bound while hard metal ions are N-bound.

1) SCN^- bonds through sulfur atom (soft base) when bonded to Pt^{2+}, a soft acid.

2) It bonds through nitrogen atom (a hard base) when linked to Cr^{3+}, a hard acid.

3) When Fe^{2+} reacts with SCN^- a bright red $[Fe(SCN)]^+$ ion is formed, whereas Cr^{3+} forms $[Cr(NCS)]^{2+}$. Fe^{2+} is a border line acid and is S-bound. Whereas Cr^{3+} is hard acid and prefers to be N-bound.

4) The molecule $(CH_3)_2NCH_2PF_2$ would bond to BF_3 through N whereas it would bond to BH_3 through P. BF_3 is a hard acid and prefers to bind with N atom - a hard base. Whereas, BH_3 is a soft acid and preferentially bonded to soft base, P atom.

Symbiotic effect: The hard-soft character of the metal ion is altered by the other groups attached. It is referred to as a symbiotic effect. For example, the isolated Co^{3+} is a hard acid and is expected to make bond with SCN^- ion through N atom as observed in $[Co(NH_3)_5(NCS)]^{3-}$. However, when bound to five soft base ligands like CN^- ions, the hardness of cobalt ion (Co^{3+}) is reduced. Thus $[Co(CN)_5]^{2-}$ behaves as a soft acid and prefers to bind with SCN^- ion through S atom to form $[Co(CN)_5(SCN)]^{3-}$.

c. HSAB to predict direction of Inorganic reactions:

HSAB principle is used to predict the outcome of few of the reactions. We can predict whether a reaction proceeds to the right or left based on soft or hard acid/base interactions.

1) The following reaction is possible and proceeds to the right since As^{3+} is softer than P^{3+} and I^- is softer than F^-. Remember that both As^{3+} and P^{3+} are soft but relatively As^{3+} is softer due to larger size.

$$AsF_3 + PI_3 \longrightarrow AsI_3 + PF_3$$

2) The following reaction is possible since Mg^{2+} is harder acid than Ba^{2+} and O^{2-} is harder base than S^{2-}.

$$MgS + BaO \longrightarrow MgO + BaS$$

3) P_2F_4 is prepared by treating PF_2I with mercury as shown below.

$$2PF_2I + 2Hg \text{ ------> } Hg_2I_2 + P_2F_4$$

In this reaction, it is iodine rather than fluorine that is removed from PF_2I. Hg_2^{2+} ion is a soft acid that prefers soft base I^- rather than hard base F^-.

d. Hard Soft interactions - Types of ores:

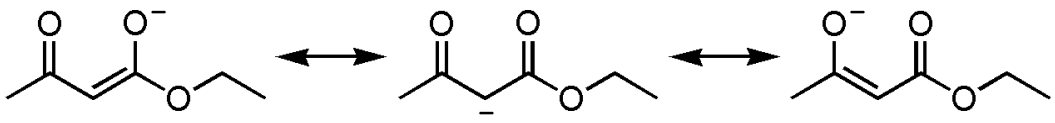
We know that the hard metals prefer to bind with hard anions and thus they are available as oxides or fluorides or carbonates or silicates in the nature. Whereas, the soft metals prefer to bind with soft anions and hence are found in the nature as sulfides or phosphides or selenides. E.g. Aluminium is mostly found in nature as alumina, Al_2O_3 - an oxide ore, since Al^{3+} is a hard metal which prefers to combine with hard oxide anion rather than the soft sulfide ion. Silver & copper metals exist as sulfide ores since both Ag^+ and Cu^{2+} are soft metals. The f-block elements are found in nature as silicate minerals since the trivalent lanthanides are actinides are hard acids and tend to bind with hard oxygen bases as in silicates.

e. Precipitation reactions & Qualitative analysis:

The softer acids like Ag^+, Hg^+, Hg^{2+} etc., and border line acids like Fe^{2+}, Ni^{2+}, Cu^{2+}, Zn^{2+}, Pb^{2+} etc., can be precipitated as sulfides from their aqueous solutions since S^{2-} ion is a softer base. Following table illustrates the separation of cations based on their hardness or softness.

1.17. AMBIDENT NUCLEOPHILES

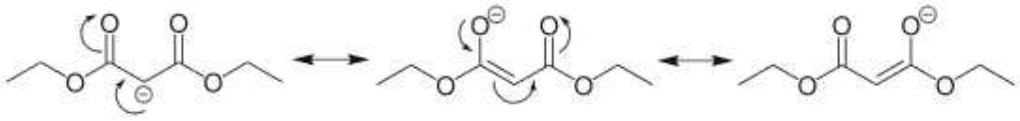
Many nucleophiles may be represented by two or more resonance forms in which the unshared pair of electrons may residue on two or more atoms. In these cases, the nucleophiles may attack in two or more different ways to give different products. E.g. removal of a proton from ethyl acetoacetate (i), for instance, gives an ion which is a resonance hybrid of ii (Carbanion) and iii (Enolate).



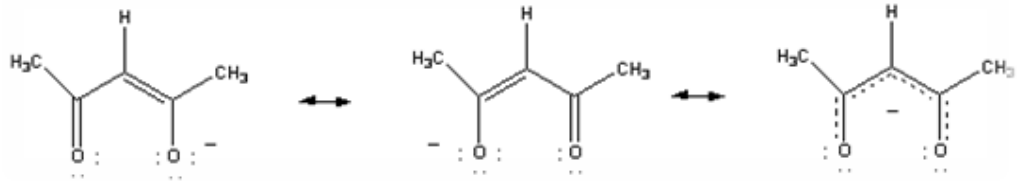
i **ii** **iii**

Such ions are called ambident anions, since they have two possible attacking atoms leading to the formation of two compounds. Similar types of anions are derived from compounds such as diethyl malonate DEM (a) and acetylacetone (b).

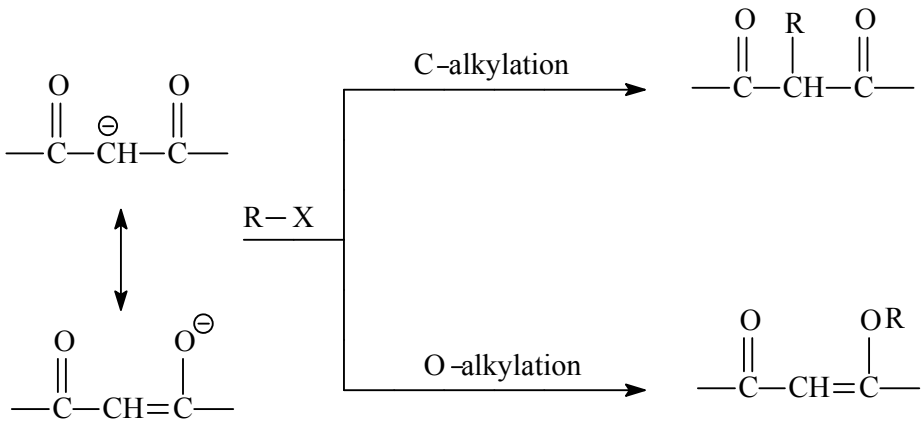
a.



b.

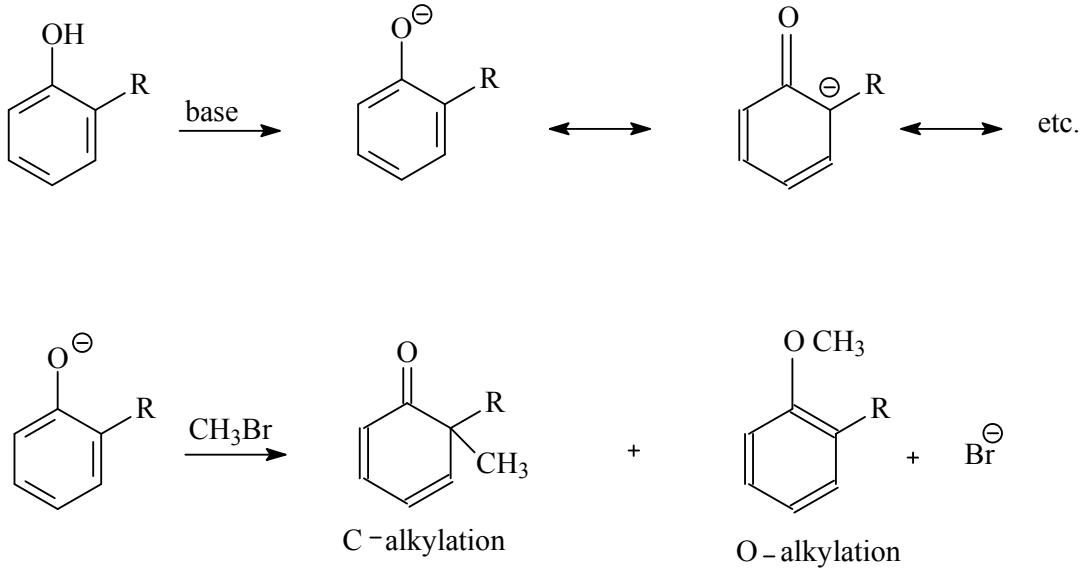


On treatment with alkyl halides, these ions attack the carbon (leading to C-alkylation) or oxygen (leading to O-alkylation).



Mention Chemoselectivity Reaction conditions ?????

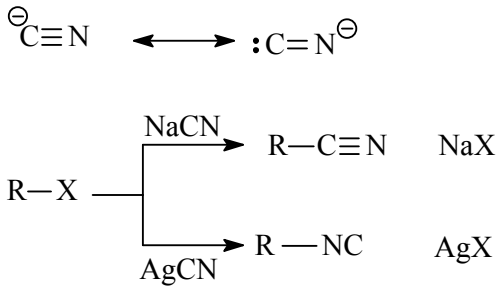
Similarly, phenoxide ions, generated by the treatment of phenols with base, may undergo C-alkylation (a) or O- alkylation (b) on treatment with alkyl halides.



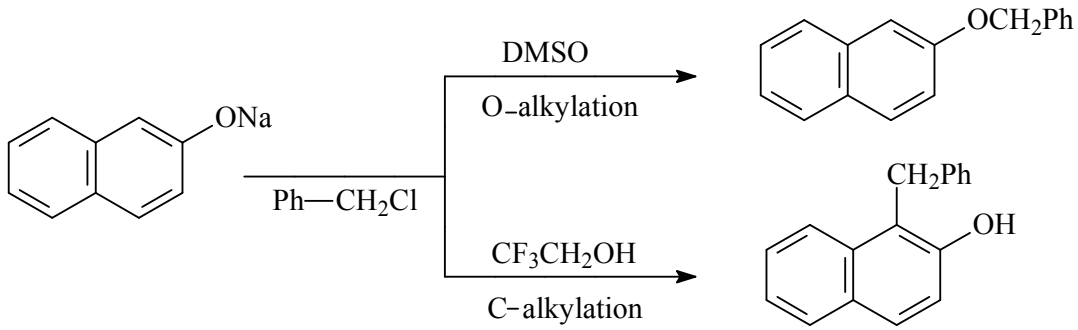
The positive counter ion plays an important role in deciding the atom which act as a nucleophile. For example, in case of NaCN, the attack of cyanide ion takes place from the carbon atom, whereas in AgCN, attack takes place from the nitrogen atom.

NaCN- Kinetically controlled product and the more nucleophilic C-atom is approached

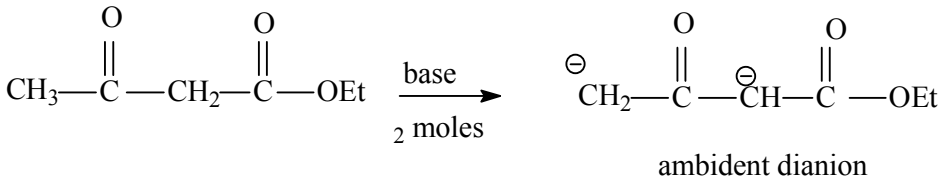
AgCN- Thermodynamically controlled and more electronegative N-atom is approached as K_{sp} of AgX is quite large in organic medium



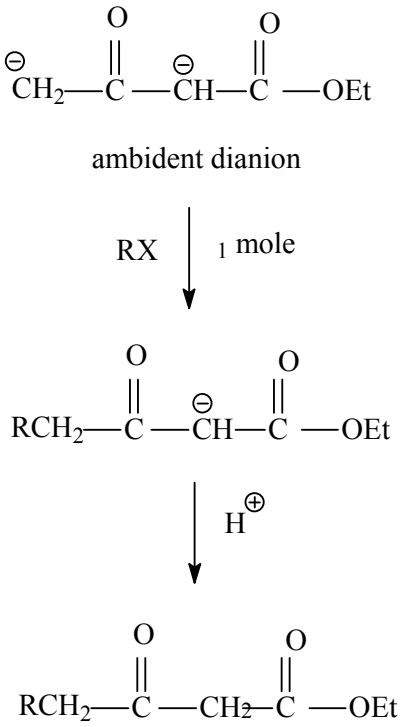
In many cases, it has been observed that the nature of solvent influence the course of reaction. When a nucleophile is relatively free, it normally attacks with its more electronegative atom. However, when the atom is solvated or located close to the positive counterion, attack takes place through the less electronegative atom. An illustrative example is that of sodium naphthoxide which gives the product of O-alkylation, on treatment with benzoyl bromide in DMSO, in 95% yield. However, when the same reaction is performed in 2,2,2-trifluoroethanol, the major product is obtained by C-alkylation.



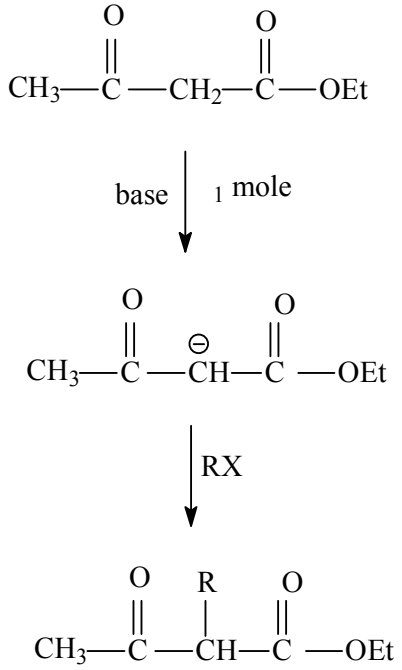
Ambident dianions can be generated by treating compounds such as ethyl acetoacetate with two moles of a strong base.



Hydrogen atom attached to the middle carbon atom of compound such as ethyl acetoacetate, being flanked by two carbonyl group, would be more acidic than those on the end carbon being attached to a single group.



In case one mole of base is used, the alkylation at methylene can be carried out as methine Carbanion is more stabilized through delocalization.

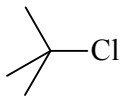


1.18. SUMMARY

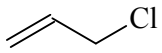
In this unit we have provided a brief knowledge about the S_N2, S_N1, mixed S_N1 and S_N2, S_Ni and SET mechanism. This chapter will also provide knowledge of neighboring group participation by π and σ bonds, anchimeric assistance, classical and non-classical carbocations, arenium ions, norbornyl systems and common carbocation rearrangements. We also learned about the the S_Ni mechanism, nucleophilic substitution at an allylic, aliphatic trigonal and a vinylic carbon. We learned reactivity effects of substrate structure, attacking nucleophile, leaving group, reaction medium, HSAB principle and ambident nucleophiles.

1.19. TERMINAL QUESTIONS

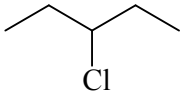
1. Using the given codes, arrange the following compounds in decreasing order the rate of solvolysis by S_N1 mechanism:



A



B

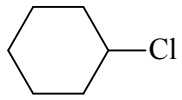
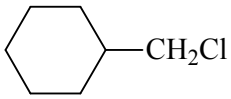


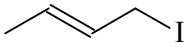
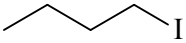
C

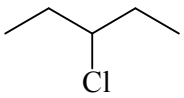
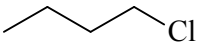
Codes:

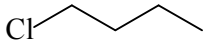
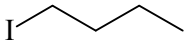
A. A > C > B
B. C > B > A
C. A > B > C
D. B > A > C

2. Which one of the following statements is correct for the reactivity in S_N2 reaction?

A.  is more reactive than 

B.  is more reactive than 

C.  is more reactive than 

D.  is more reactive than 

3. Which of the following statements are correct?

A. Vinyl chloride does not give SN reaction but allyl chloride gives.

B. $CH_3CH=CHCH_2Cl$ react with KCN to give a mixture of isomeric products.

C. Displacement of H^- is easier than that of Cl^-.

D. CH_3CH_2-O-CH_2Cl is much more reactive in S_N1 reaction than $CH_3CHClCH_3$

4. Using the following codes, arrange the given halides in order of decreasing reactivity towards NaI in acetone:

MeCl	Me_2CHCl	Me_2CHF
1	2	3

A. 1 > 2 > 3

B. 2 > 3 > 1

C. 2 > 1 > 3

D. 3 > 2 > 1

5. Which among the following anions is the best nucleofuse?

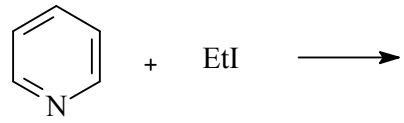
A. AcO^-

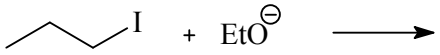
B. ^-OH

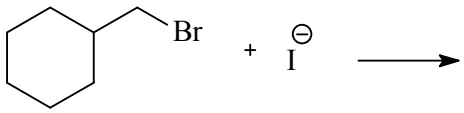
C. TsO^-

D. EtO-

6. Predict the products of the following S_N2 reactions?

1. 

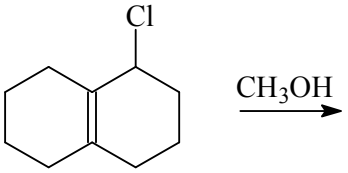
2. 

3. 

7. Complete the following reaction:

1. $CH_3CH{=}CHCH_2Cl + H_2O \longrightarrow$

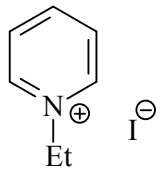
2. $CH_3CH{=}CHCH_2Cl + \text{aq. NaOH} \longrightarrow$

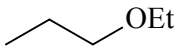
3. 

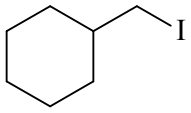
8. Most nucleophiles are anions but some anions are not nucleophiles. A particular example is $BF4^-$. Explain the inertness of $BF4^-$ as a nucleophile.
9. Thiocynate (SCN^-) and cynate (OCN^-) each give two products when allowed to react with allyl bromide. In the former case, one product predominates highly. Show the products in each reaction and account for this predominance.
10. 3-Bromo-3-methyl-1-butene forms two substitution products when it is added to a solution of sidium acetate in acetic acid.
    a. Give the structures of the substitution products.
    b. Which are the kinetically controlled products?
    c. Which is the thermodynamically controlled product?

1.20. ANSWER TO TERMINAL QUESTIONS

1. C
2. B
3. A, B & D
4. A
5. C
6.

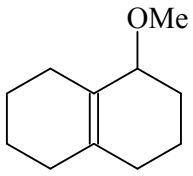
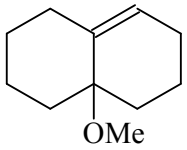
1. 

2. 

3. 

1. $CH_3CH{=}CHCH_2OH$ and $CH_3{-}\underset{\displaystyle OH}{\underset{|}{CH}}{-}CH{=}CH_2$

2. $CH_3CH{=}CHCH_2OH$ and $CH_3{-}\underset{\displaystyle OH}{\underset{|}{CH}}{-}CH{=}CH_2$

3.  and 

1.21. REFERENCES

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UNIT-2 AROMATIC NUCLEOPHILIC SUBSTITUTION REACTION

CONTENTS:

2. 0. Objectives

2.1 Introductions

2.2 The S_NAr mechanism

2.2.1 Evidence for Nucleophilic Aromatic Substitution (S_NAr) mechanism:

2.3 The SN^1 mechanism

2.3.1 Evidence for a unimolecular s_N1 mechanism

2.4 The benzyne (arynes) mechanism

2.4.1 Benzyme (aryne) mechanism:

2.5 The $S_{RN}1$ mechanism

2.5.1 Evidence for the $S_{RN}1$ mechanism:

2.6 Effects of Reactivity & Structure, leaving group and attacking nucleophile

2.6.1 The effect of substrate structure:

2.6.2 The effect of the leaving group:

2.6.3 The effect of the attacking nucleophile:

2.7 Von Richter rearrangements

2.8 Sommelet-Hauser rearrangement

2.9 Smiles rearrangement

2.10 Summary

2.11 Terminal questions

2.12 Answers to terminal questions

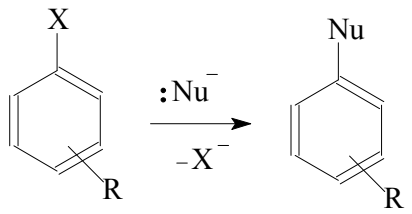
2.13 References

2.0 OBJECTIVES

Objective of this unit, Aromatic Nucleophilic Substitution reaction is to make students aware about the SNAr, S_N1, benzyne and SNR^1 mechanism. This chapter will also provide knowledge of reactivity effect of substrate structure, leaving group and attacking nucleophile. Besides important name reactions of synthetic utility alongwith the von Richter, Sommelet-Hauser and Smiles rearrangements.

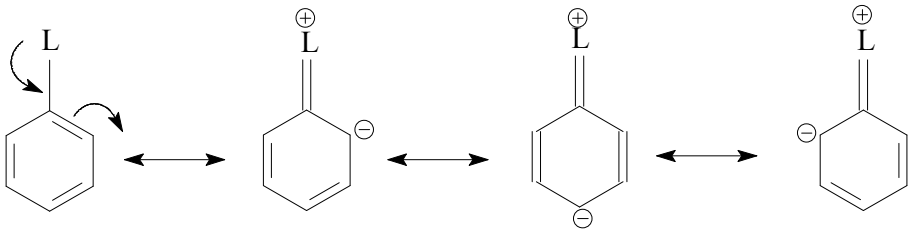
2.1 INTRODUCTION

A Nucleophilic Aromatic Substitution reaction is a reaction in which one of the substituent's in an aromatic ring is replaced by a nucleophile (Ipso Substitution).



X= halogen etc.
Nu= nucleophile

Unlike aliphatic compounds having a nucleophilic group as a leaving group, aromatic compound having the same group bonded directly to the aromatic rings, which do not undergo nucleophilic substitution under ordinary conditions. This unusual reactivity of aromatic compounds arises due to the presence of a lone pair of electrons/π-bond on the leaving group/key atom. As a result result of delocalization of this lone pair of e^- / π-bond through conjugation with the π e^- of the ring, there is partial double bond character between the carbon of the ring and the key atom. Thus, the key atom/leaving group become soundly bonded to the aromatic ring and cannot be replaced by easily.



Another reason for the low reactivity is the aromatic rings behave like a nucleophile due to the presence of electron cloud above and below the plane of aromatic rings. This shields the ring carbon from the attack of a nucleophile.

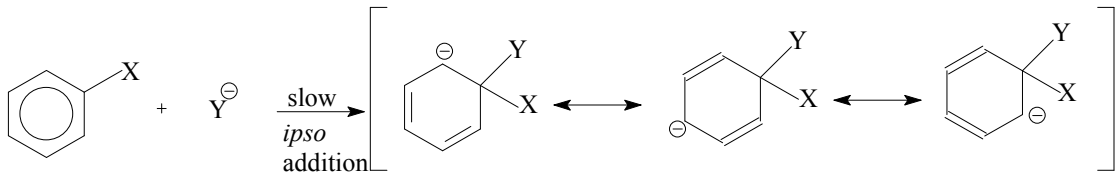
Aromatic nucleophilic substitution may take place in extreme conditions like high pressure or high temperature or both, catalyst etc. Aromatic nucleophilic substitution reactions undergoes with less difficulties by proper substitution of aromatic rings with –R or –I group at ortho or para or both the positions and aromatic nucleus having electronegative heteroatom (O, N, S etc.) because –R or –I group are the activating groups for aromatic nucleophilic substitution. These groups decrease electron density on the aromatic ring and activate it for nucleophilic substitution. There are four principal mechanisms for aromatic nucleophilic substitution. Each of the four is similar to one of the aliphatic nucleophilic substitution mechanisms.

1. The S_NAr Mechanism
2. The S_N1 Mechanism
3. The Benzyne Mechanism
4. The $S_{RN}1$ Mechanism

2.2 THE S_NAr MECHANISM

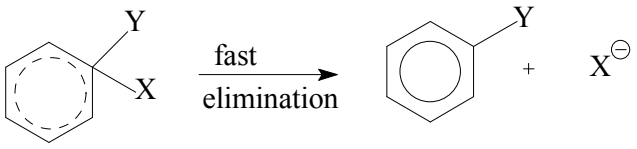
The IUPAC designation is A_N+D_N (the same as for the tetrahedral mechanism). This mechanism is generally found where activating groups are present on the ring. Nucleophilic aromatic substitution (S_NAr) mechanism consists of following two main steps:

Step 1: Attack of the nucleophilic species at the ipso carbon (the carbon bearing the leaving group) of the aromatic ring. It is a rate determining step (not always).



Meisenheimer complex

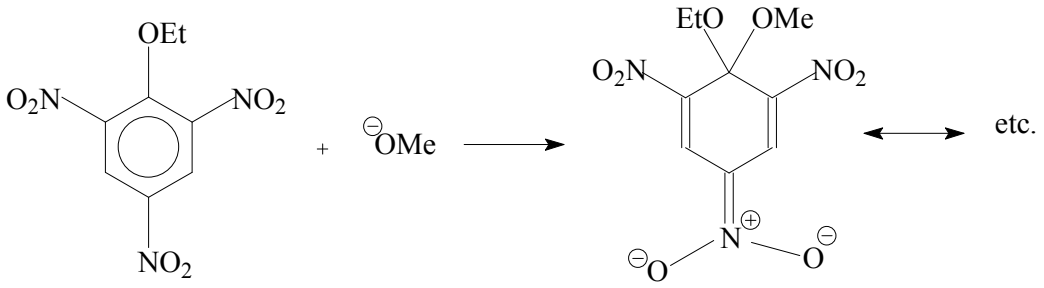
Step 2: Elimination of the leaving group and regeneration of the aromatic ring.



It resembles the arenium ion mechanism of aromatic electrophilic substitution. In both the cases (aromatic nucleophilic substitution & aromatic electrophilic substitution), the attacking species form a bond with the substrate, giving an intermediate and then the leaving group depart, i.e., both involve an addition elimination process.

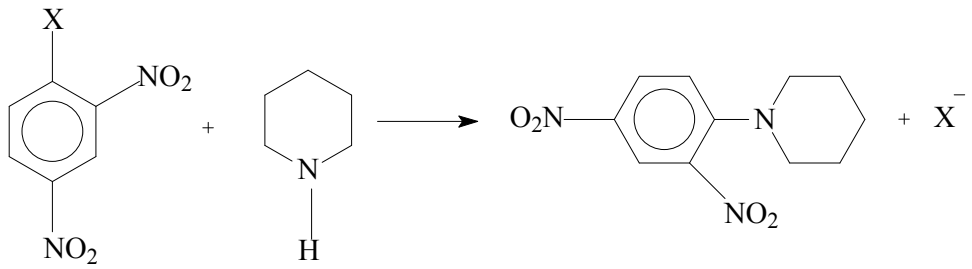
2.2.1 Evidence for Nucleophilic aromatic substitution (S_NAr) mechanism:

1. Probably the most convincing evidence for nucleophilic aromatic substitution mechanism was the isolation of Meisenheimer or Meisenheimer–Jackson salts intermediate, prepapred by the reaction between 2,4,6-trinitrophenetole and methoxide ion. The structures have been proved by NMR and by X-ray crystallography.



Meisenheimer-Jackson salts intermediate

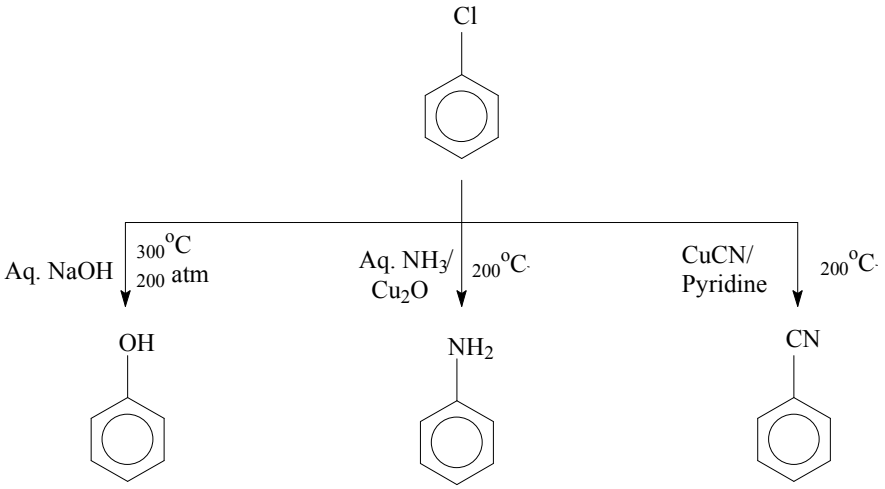
2. Studies of the effect of the leaving group on the nucleophilic aromatic substitution reaction. If the nucleophilic aromatic substitution mechanism were similar to either the S_N1 or S_N2 mechanisms, the Ar–X bond would be broken in the rate-determining step. In the nucleophilic aromatic substitution mechanism, this bond is not broken until after the rate-determining step (i.e. if step 1 is rate determining). There is some evidence that electron transfer may be operative during this process. We would predict from this that if the S_NAr mechanism is operating, a change in leaving group should not have much effect on the reaction rate. In the reaction of dinitro compound with piperidine, when X was Cl, Br, I, SOPh, SO_2Ph, or p-nitrophenoxy, the rates differed only by a factor of 5.



This behavior would not be expected in a reaction in which the Ar–X bond is broken in the rate-determining step. We do not expect the rates to be identical, because the nature of X affects the rate at which Y attacks. An increase in the electronegativity of X causes a decrease in the electron density at the site of attack, resulting in a faster attack by a nucleophile. The very fact that fluoro is the best leaving group among the halogens in most aromatic nucleophilic substitutions is good evidence that the mechanism is different from the $S_N1$and the S_N2 mechanisms, where fluoro is by far the poorest leaving group of the halogens.

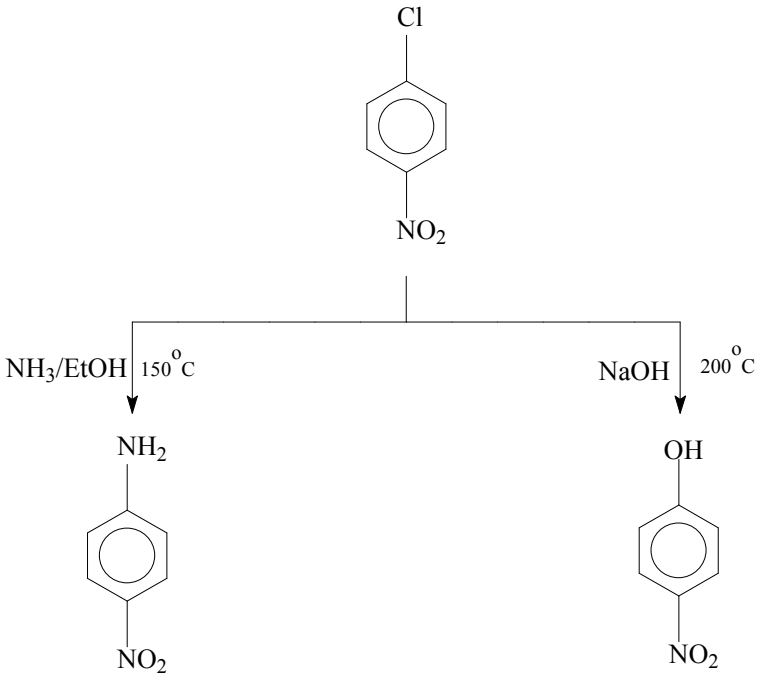
Some examples of nucleophilic aromatic substitution (S_NAr) reaction:

a. With substrate having no activating group.

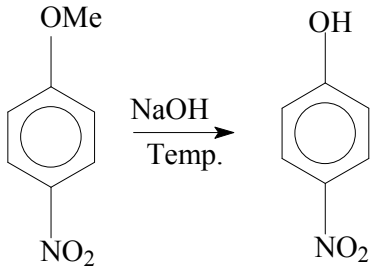


b. With substrates having activating group (s)

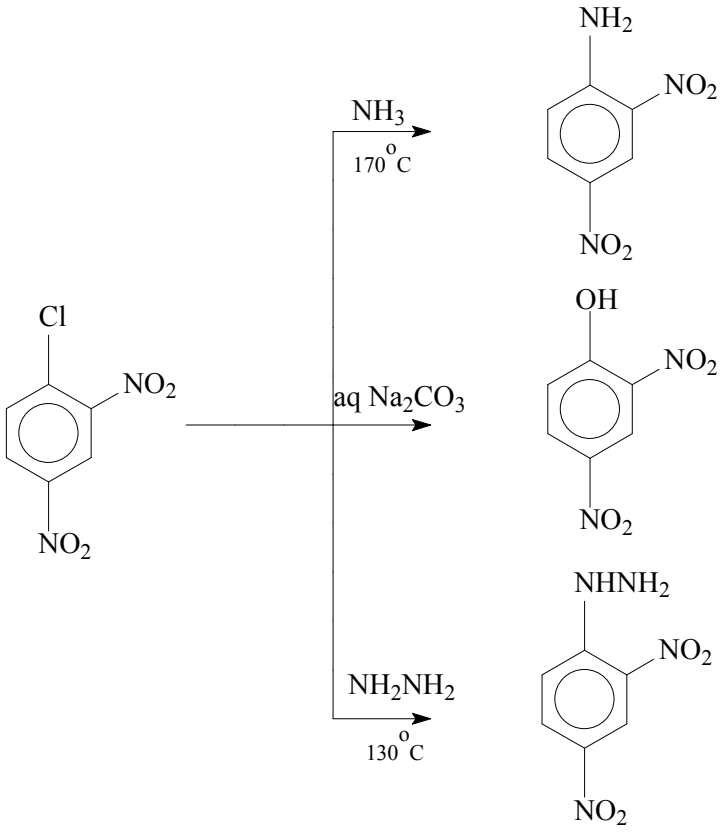
1.


Cl
NO2
NH3/EtOH 150°C
NaOH 200°C
NH2
NO2
OH
NO2

2.


OMe
NaOH
Temp.
NO2
OH
NO2

3.

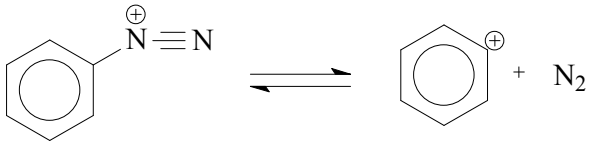


2.3 THE S_N1 MECHANISM

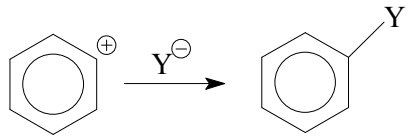
A unimolecular S_N1 mechanism (IUPAC: D_N+A_N) is very rare; it has only been observed for aryl triflates in which both ortho positions contain bulky groups (tert-butyl or SiR_3). A unimolecular S_N1 mechanism are mainly given by aromatic diazonium salts.

Mechanism:

Step 1:



Step2:



Aryl cation is highly unstable but nitrogen is highly stable. Hence nitrogen is very good leaving group, this makes the generation of aryl cation extremely easy.

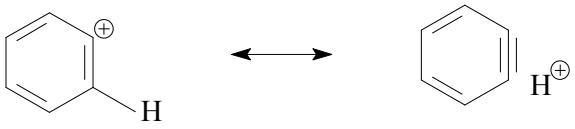
2.3.1 Evidence for a unimolecular S_N1 mechanism

1. The reaction rate is first order in diazonium salt and independent of the concentration of nucleophile.

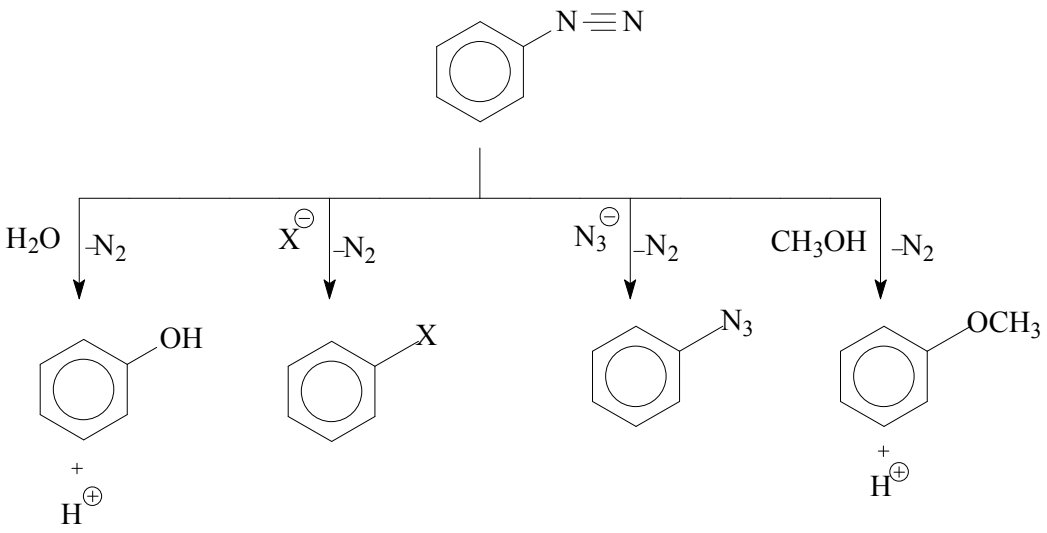
2. When high concentrations of halide salts are added, the product is an aryl halide but the rate is independent of the concentration of the added salts.

3. The effects of ring substituents on the rate are consistent with a unimolecular rate-determining cleavage e.g., electron releasing m substituents (OH, OMe, Me, etc.) increase the rate and electron withdrawing m substituents (COOH, NO_2, Cl, etc.) decrease the rate of reaction.

4. When reactions were run with substrate deuterated in the ortho position, isotope effects of 1.22 were obtained. It is difficult to account for such high secondary isotope effects in any other way except that an incipient phenyl cation is stabilized by hyperconjugation, which is reduced when hydrogen is replaced by deuterium.



Some examples of unimolecular SN1 reactions of aromatic diazonium cation are given below:



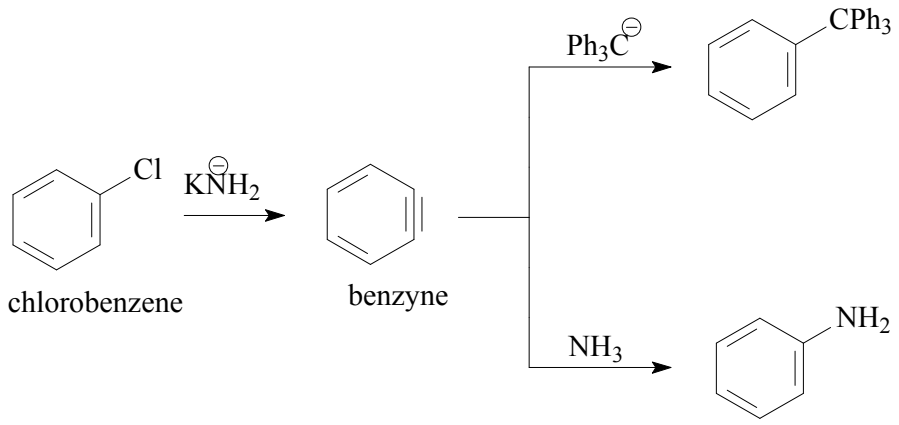
2.4 THE BENZYNE (ARYNES) MECHANISM

Some aromatic nucleophilic substitutions are clearly different in character from those that occur by the S_NAr mechanism or the S_N1 mechanism. Unactivated aryl halides having at lest one hydrogen in ortho position undergo nucleophile substitution with a very strong base like potassium amide or sodium amide in liquid ammonia. The reaction also occurs with bases such as PhLi and BuLi. This reaction proceeds through benzyne (aryne) intermediate and the mechanism is called benzyne (aryne) mechanism.

Some important facts involve in the benzyne (arynes) mechanism are:

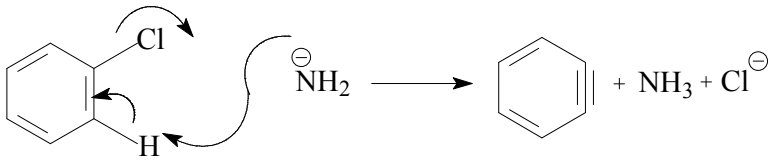
i. Substitutions occur on aryl halides that have no activating groups.
ii. Bases are required that are stronger than those normally used.
iii. The incoming group does not always take the position vacated by the leaving group (*Cine substitution*).

Example of aromatic nucleophilic substation via benzyne:

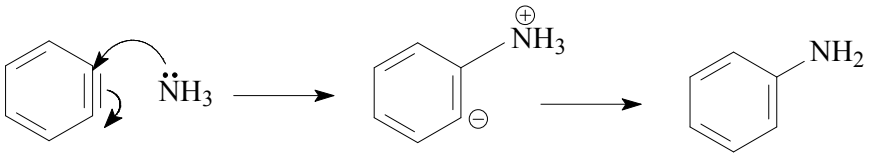


2.4.1 Benzyme (Aryne) Mechanism: This mechanism involves elimination followed by addition. Hence, it is called elimination-addition mechanism of aromatic nucleophilic substitution.

Step 1: a suitable base removes the ortho hydrogen, with subsequent (or concomitant) loss of the chlorine (leaving group) to generate symmetrical intermediate is called benzyne.

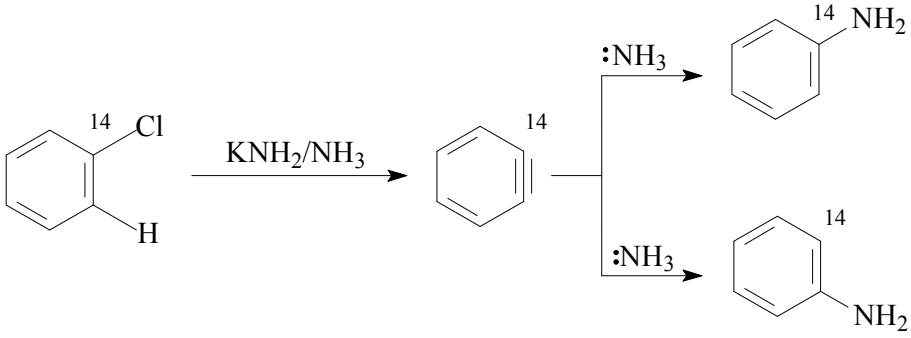


Step 2: benzyne is attacked by the NH_3

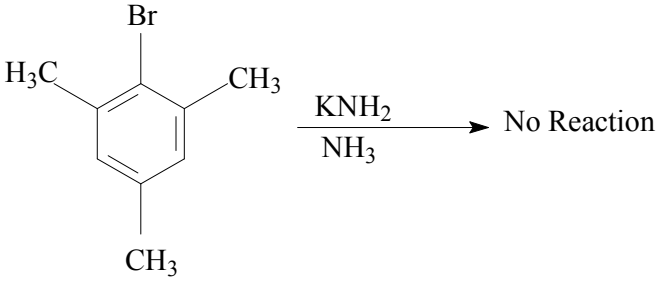


Evidence in support of the benzyne (aryne) mechanism:

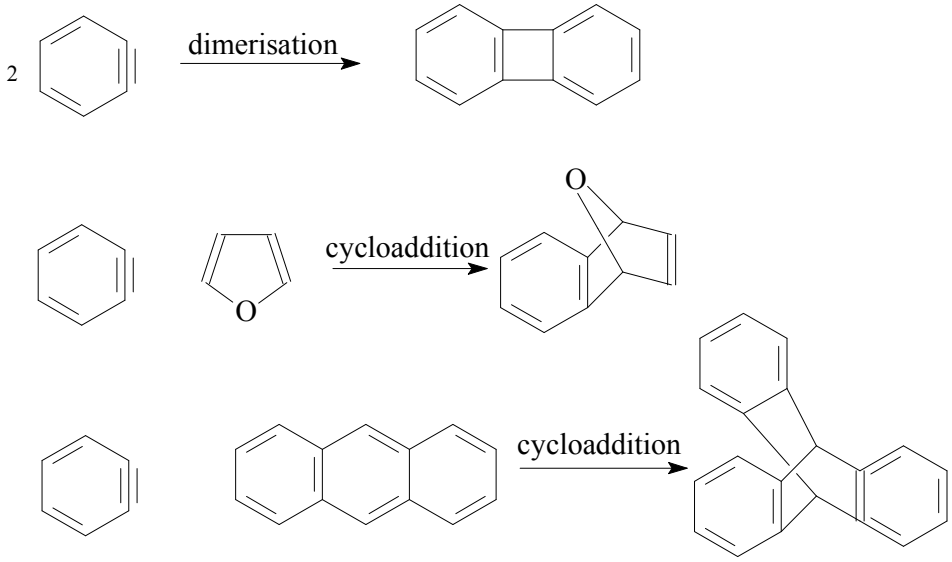
i. 1-^{14}C-chlorobenzene reacts with potassium or sodium amide in liquid ammonia gives almost equal amounts of 1-^{14}C-aniline and 2-^{14}c-aniline, due to the formation of symmetrical intermediate benzyne.



ii. Aryl halides having no hydrogen, ortho to the halogen do not react under the same conditions.

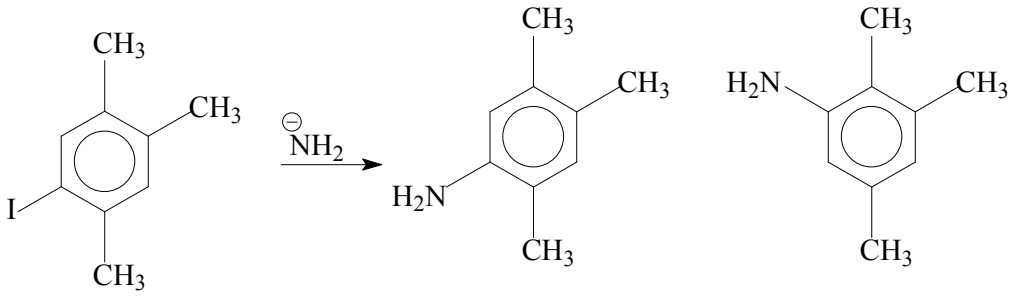


iii. Benzynes are usually detected by spectroscopy or by their participation in dimerisation and trapping through cycloaddition.



2.5 THE $S_{RN}1$ MECHANISM

When 5-iodo-1,2,4-trimethylbenzene treated with KNH_2 in NH_3, gives A and B in the ratio 0.63:1. The presence of an unactivated substrate and a strong base, the cine substitution occur along with normal substitution product indicate that the reaction proceeds through the benzyne mechanism. However the 6-iodo isomer of 5-iodo-1,2,4-trimethylbenzene should have given A and B in the same ratio (because the same aryne intermediate would be formed in both cases), but in this case the ratio of A–B was 5.9:1 (the chloro and bromo analogs did give the same ratio, 1.46:1, showing that the benzyne mechanism may be taking place there).



5–Iodo –1,2,4–trimethylbenzene A B

To explain the result of iodo analogue of 5-iodo-1,2,4-trimethylbenzene, it has been proposed that besides the benzyne mechanism, this free-radical mechanism is also operating here:

$$ArI \xrightarrow[donor]{electron} ArI^{-\bullet} \longrightarrow Ar + I^-$$

$$Ar^{\bullet} + NH_2^- \longrightarrow ArNH_2^{-\bullet} \xrightarrow{ArI} ArNH_2 + ArI^{-\bullet}$$

This is called the $S_{RN}1$ mechanism (The IUPAC designation is $T+D_N+A_N$). The above reaction involves a chain mechanism. An electron donor is required to initiate the reaction and solvated electrons from KNH_2 in NH_3.

2.5.1 Evidence for the $S_{RN}1$ mechanism:

1. The addition of potassium metal (a good producer of solvated electrons in ammonia) completely suppressed the cine substitution.
2. Addition of radical scavengers (which would suppress a freeradical mechanism) led to A:B ratios much closer to 1.46:1.
3. Some 1,2,4-trimethylbenzene was found among the products. This could be easily formed by abstraction of H by Ar from the solvent NH_3.
4. Besides initiation by solvated electrons, $S_{RN}1$ reactions have been initiated photochemically, electrochemically, and even thermally.

The $S_{RN}1$ reactions have a fairly wide scope. The efficiency of the reaction has been traced to the energy level of the radical anion of the substitution product. There is no requirement for

activating groups or strong bases, but in DMSO haloarenes are less reactive as the stability of the anion increases. The reaction has also been done in liquid ammonia, promoted by ultrasound and ferrous ion has been used as a catalyst. Alkyl, alkoxy, aryl, and COO^- groups do not interfere, although Me_2N, O^-, and NO_2 groups do not interfere.

2.6 EFFECTS OF REACTIVITY & STRUCTURE, LEAVING GROUP AND ATTACKING NUCLEOPHILE

2.6.1 The Effect of Substrate Structure:

Generally, $Ar_{SN}2$ reactions are accelerated by electron withdrawing groups, especially in the ortho and para positions to the leaving group and retarded by electron donating groups. Heteroatoms of the ring are also strongly activating e.g., nitrogen which is more activating when quaternized. The decreasing order of activating power of some groups in $Ar_{SN}2$ reaction is given below:

$$NH_3>NO_2>CF_3>CN>SO_3H>CHO>CO>COOH>COOR>CONH_2>F>Cl>Br>I$$

2.6.2 The Effect of the Leaving Group:

The common leaving groups in aliphatic nucleophilic substitution (halide, sulfate, sulfonate, NR_3^+, etc.) are also common leaving groups in aromatic nucleophilic substitutions, but the groups NO_2, OR, OAr, SO_2R and SR, which are not generally lost in aliphatic systems, are leaving groups when attached to aromatic rings. Surprisingly, NO_2 is a particularly good leaving group. An approximate order of leaving-group ability is F > NO_2 > OTs > SOPh > Cl, Br, I > N_3 > NR_3^+> OAr, OR, SR, NH_2. However, this depends greatly on the nature of the nucleophile, as illustrated by the fact that $C_6Cl_5OCH_3$ treated with NH_2^- gives mostly $C_6Cl_5NH_2$; that is, one methoxy group is replaced in preference to five chlorines. As usual, OH can be a leaving group if it is converted to an inorganic ester. Among the halogens, fluoro is generally a much better leaving group than the other halogens, which have reactivities fairly close together. The order is usually Cl > Br > I, but not always. The leaving-group order is quite different from that for the S_N1 or S_N2 mechanisms. The most likely explanation is that the first step of the S_NAr mechanism is usually rate determining, and this step is promoted by groups with strong –I effects. This would explain why fluoro and nitro are such good leaving groups when this mechanism is operating. Fluoro is the poorest leaving group of the halogens when the second step of the S_NAr mechanism is rate determining or when the

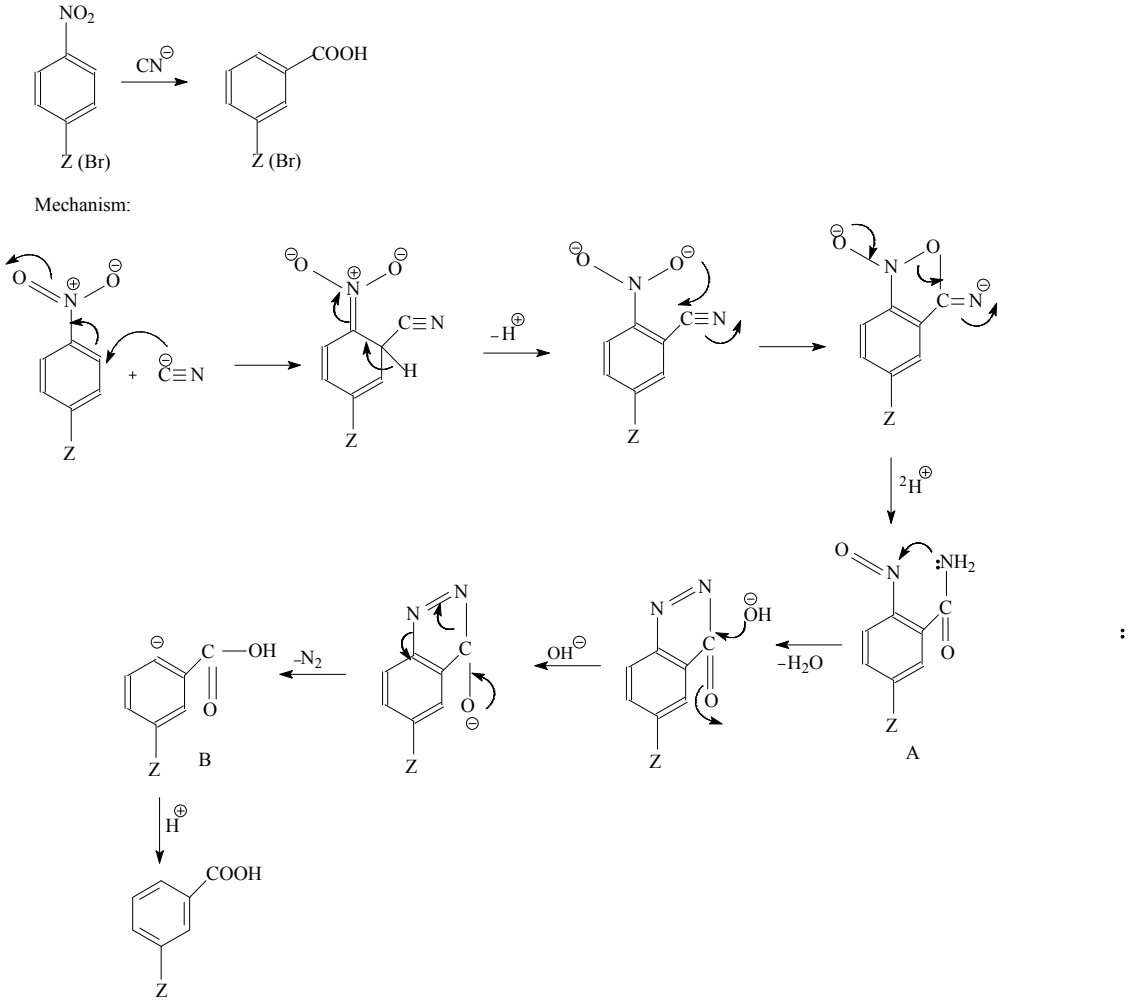
benzyne mechanism is operating. The four halogens, as well as SPh, NMe_3^-, and $OPO(OEt)_2$, have been shown to be leaving groups in the $S_{RN}1$ mechanism. The only important leaving group in the SN_1 mechanism is N_2^+.

2.6.3 The effect of the attacking nucleophile:

It is not possible to construct an invariant nucleophilicity order because different substrates and different conditions lead to different orders of nucleophilicity, but an overall approximate order is $^-NH_2 > Ph_3C^- > PhNH^-$ (aryne mechanism) $> ArS^- > RO^- > R_2NH > ArO^- > ^-OH > ArNH_2 > NH_3 > I^- > Br^- > Cl^- > H_2O >$ ROH. As with aliphatic nucleophilic substitution, nucleophilicity is generally dependent on base strength and nucleophilicity increases as the attacking atom moves down a column of the periodic table, but there are some surprising exceptions, for example, ^-OH, a stronger base than ArO^-, is a poorer nucleophile. In a series of similar nucleophiles, such as substituted anilines, nucleophilicity is correlated with base strength. Oddly, the cyanide ion is not a nucleophile for aromatic systems, except for sulfonic acid salts and in the von Richter and Rosenmund-von Braun reactions, which are special cases.

2.7 VON RICHTER REARRANGEMENT

The Von-Richter reaction, also named Von-Richter rearrangement & it is named after Victor von Richter, who discovered this reaction in year 1871. In this reaction, aromatic nitro compounds with potassium cyanide giving carboxylation ortho to the position of the former nitro group. As with other aromatic nucleophilic substitutions, the reaction gives best results when an electron-withdrawing group (Z) is present in ortho and/or para positions. For example-conversion of bromonitrobenzene into bromobenzoic acid in the presence of cyanide ion.



First, the cyanide attacks the carbon-atom in *ortho*-position to the nitro-group. After this the compound is aromatic again. In the next step, the negative charged oxygen-atom attacks the neighbor carbon-atom and a five-membered ring is build. It opens under building a carconlylic-grou. Next, another five-membered ring is built. After a condensation, a double bond is build between the two nitrogen-atoms. Elemental nitrogen is cut off for opening the ring. In the last step, the compound is protonated and the 3-halogenbenzoic acid is built.

Evidence support of the Von-Richter rearrangement:

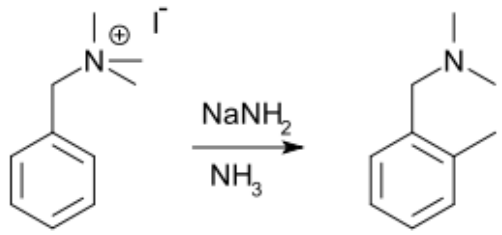
1. N_2 is a major product of the reaction. This indicates that nitrogen-nitrogen bond must be formed during the course of the reaction.
2. A is stable compound which has been prepared independently, and gives the product of Von-Richter rearrangement when subjected to the condition of this reaction.

3. When the reaction was performed in $H_2{}^{18}O$ with CN^-, the half oxygen in the product was labeled, showing that one of the oxygen of the carbonyl group came from the NO_2 group and one from the solvent as required by the above mechanism.
4. When the reaction is carried out in the presence of D_2O/C_2H_5OD, the carboxylic acid formed contains the deuterium at the position originally occupied by the NO_2 group. This confirms the formation of the species B.

2.8 SOMMELET-HAUSER REARRANGEMENT

The **Sommelet–Hauser rearrangement** (named after M. Sommeletand Charles R. Hauser) is a rearrangement reaction of certain benzyl quaternary ammonium salts. The reagent is sodium amide or another alkali metal amide and the reaction product a *N*, *N*-dialkylbenzylamine with a new alkyl group in the aromatic ortho position.

For example, benzyl trimethyl ammonium iodide, $[(C_6H_5CH_2)\ N(CH_3)_3]I$, rearranges in the presence of sodium amide to yield the *o*-methyl derivative of *N*,*N*-dimethylbenzylamin.

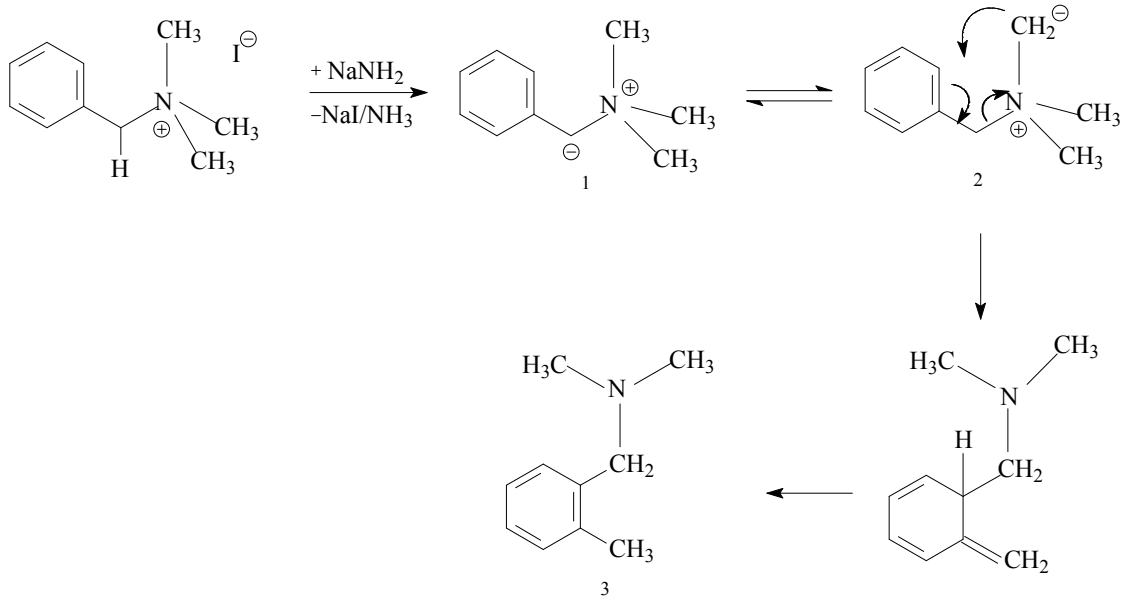


Mechanism:

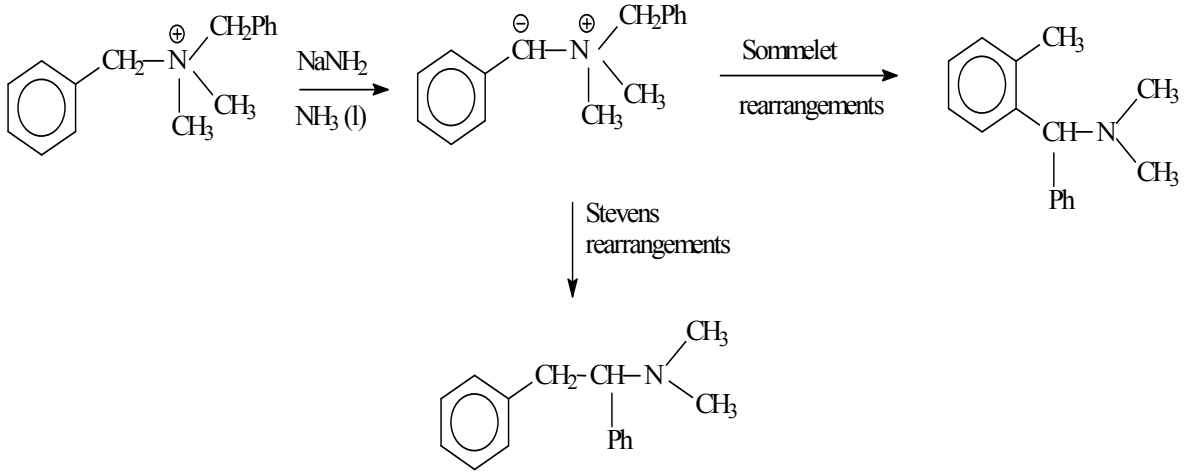
The benzylic methylene proton is acidic and deprotonation takes place to produce the benzylic ylide (**1**). This ylide is in equilibrium with a second ylide that is formed by deprotonation of one of the ammonium methyl groups (**2**). Though the second ylide is present in much smaller amounts, it undergoes a 2,3-sigmatropic rearrangement and subsequent aromatization to form the final product (**3**).

The Sommelet–Hauser rearrangement is most often carried out with three methyl groups on nitrogen, but other groups can also be used. However, if beta-hyhydrogen is

present, Hofmann elimination often competes. This mechanism is an example of [2,3] sigmatropic rearrangement.

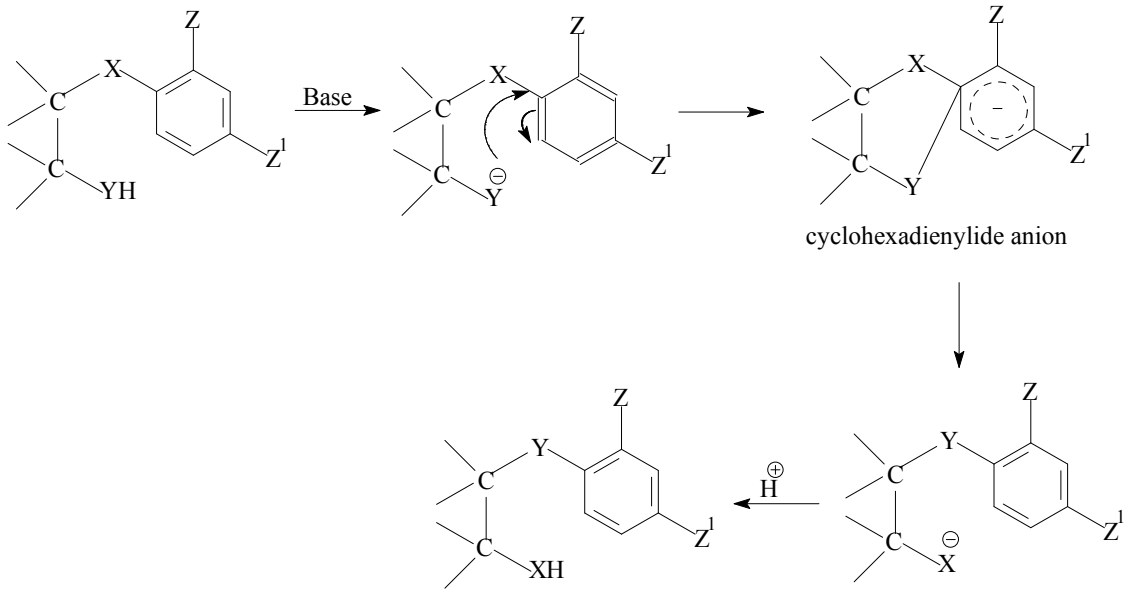


The main drawback of Sommelet rearrangement is that it is accoupanied by Stevens rearrangement.



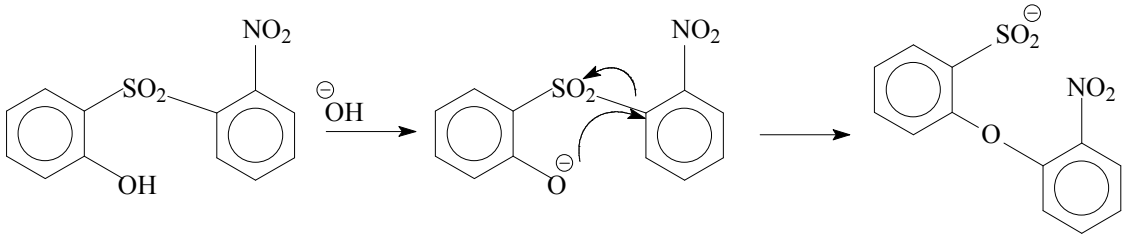
2.9 SMILES REARRANGEMENT

Smiles rearrangements are simply intramolecular nucleophilic substitution as shown in the following reaction.



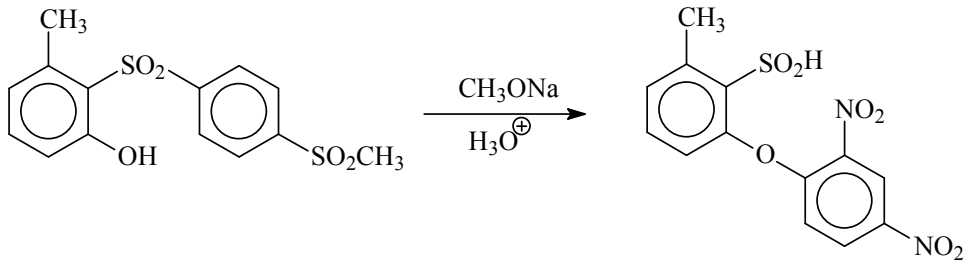
Z and Z^1 are the activating groups for a nucleophilic aromatic substitution reaction, which are electron-withdrawing substituent's, to stabilize the cyclohexadienlide anion generated in the reaction. In this rearrangement, X in the arene compound can be a sulfone, a sulfide, an ether or any substituent capable of dislodging from the arene carrying a negative charge. The terminal functional group in the chain end Y is able to act as a strong nucleophile for instance an alcohol, amine or thiol.

For example, o-(o-nitrosulphonyl) phenol undergoes Smiles rearrangement to o-(o-nitrophenoxy) sulphinic acid in the presence of hydroxide ions.



In this case, SO_2Ar is the leaving group, and ArO- the nucleophile. The nitro group serves to activate the ortho position of the ring. In this rearrangement the chain linking X and Y can be aromatic as well as aliphatic. The rearrangement also takes place in heterocyclic aromatic systems. Examples of Smiles rearrangement:

a.



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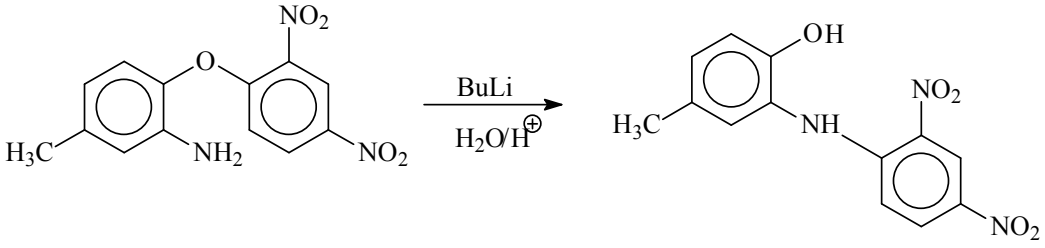
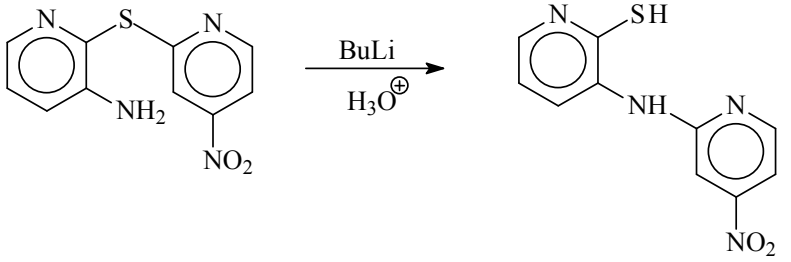


c.

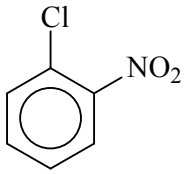


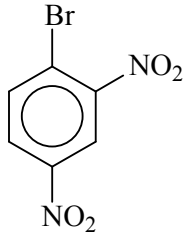
2.10 SUMMARY

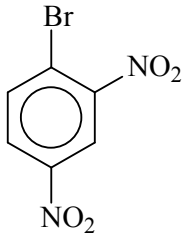
This unit provided us concise knowledge about the S_NAr, S_N1, benzyne and $S_{NR}1$ mechanism. This chapter also provides the knowledge of reactivity effect of substrate structure, leaving group and attacking nucleophile. We learned also about the von Richter, Sommelet-Hauser and Smiles rearrangements.

2.11 TERMINAL QUESTIONS

1. Which among the following compounds will undergo ArSN2 reaction?

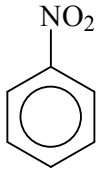
A. 

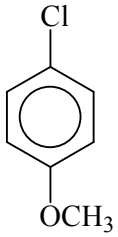
B. 

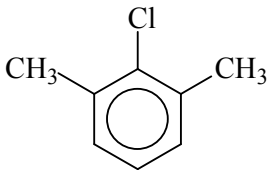
C. 

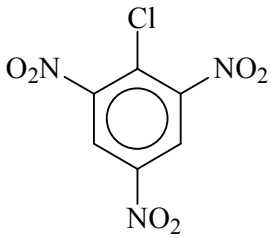
D. All of these

2. Which of the following compounds will undergo aromatic nucleophilic substitution through benzyne intermediate?

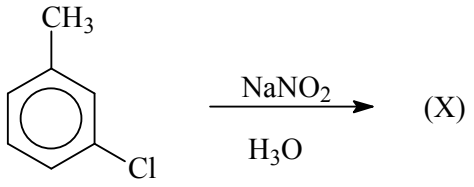
A. 

B. 

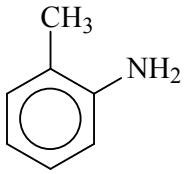
C. 

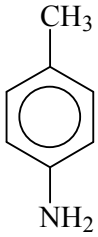
D. 

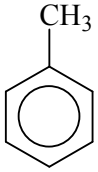
3. Consider the following reaction:

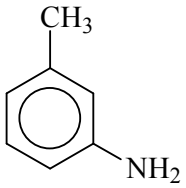


(X) Will be:

A. 

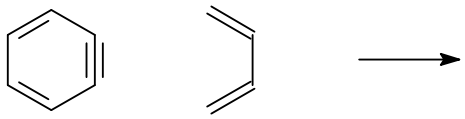
B. 

C. 

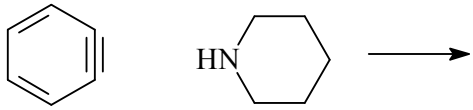
D. 

4. Complete the following reactions:

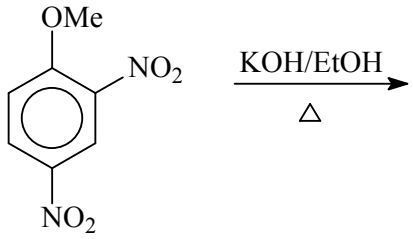
a.



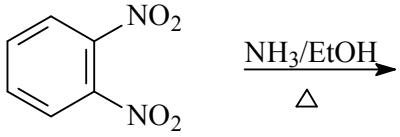
b.



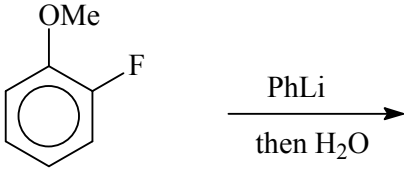
c.



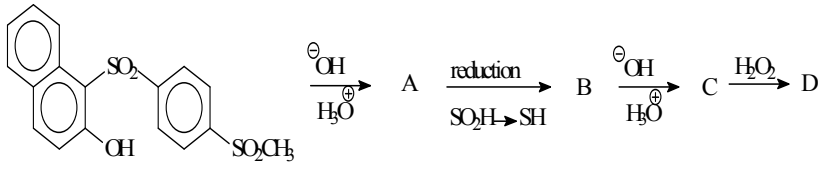
d.



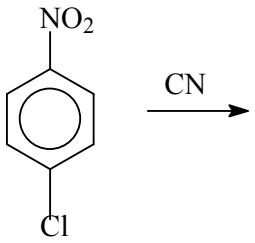
5. The reaction of *o*-bromoanisole with $NaNH_2$ in liquid NH_3 gives only *m*-aminoanisole. Explain the regioselectivity in this reaction.
6. Both *m*-bromoanisole and *o*-bromoanisole tield the same product m-anisidine. Explain why?
7. Complete the following reaction with mechanism.

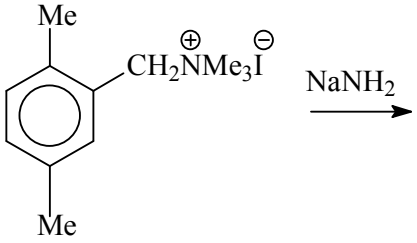


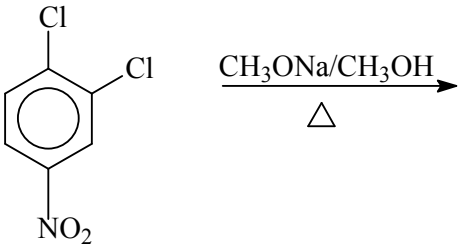
8. After the reaction of fluorobenzene with deuterated amide ion (ND_2^-) in deuterated ammonia (ND_3). The unreacted starting material contains deuterium. Explain.
9. Complete the following sequences of reactions:



10. Predict the product in the following reactions:

a. 

b. 

c. 

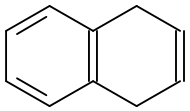
2.12 ANSWER TO TERMINAL QUESTIONS

1. D

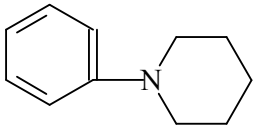
2. B

3. D

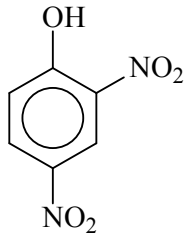
a.



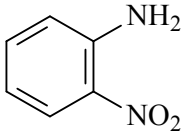
b.



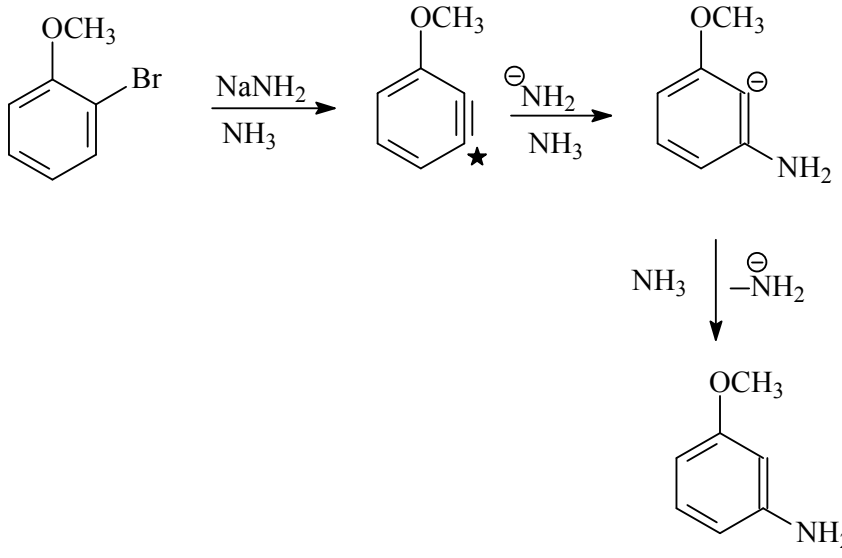
c.



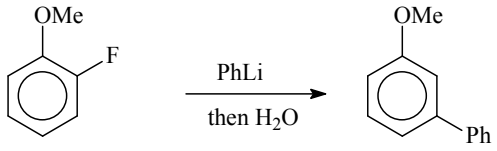
d.



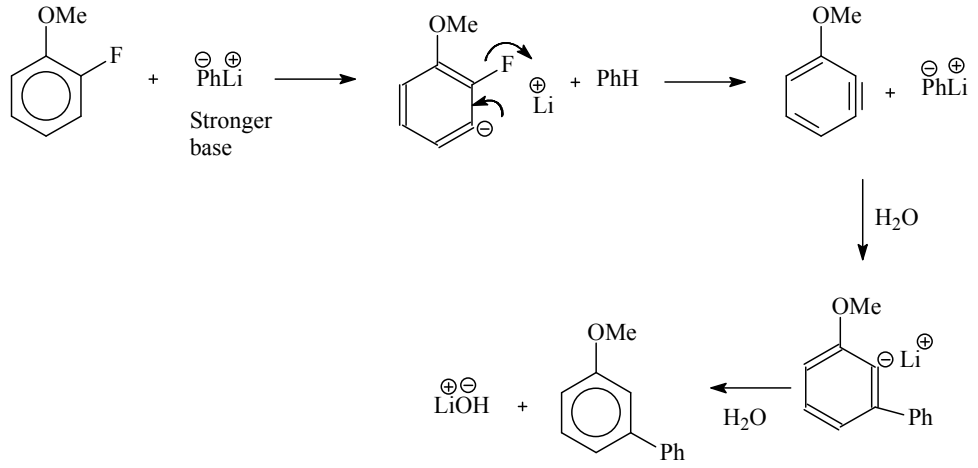
5. The attack of nucleophile at the carbon shown by star in the benzyne intermediate will lead to more stable carbanion where the negative charge is closer to the *–I* group.



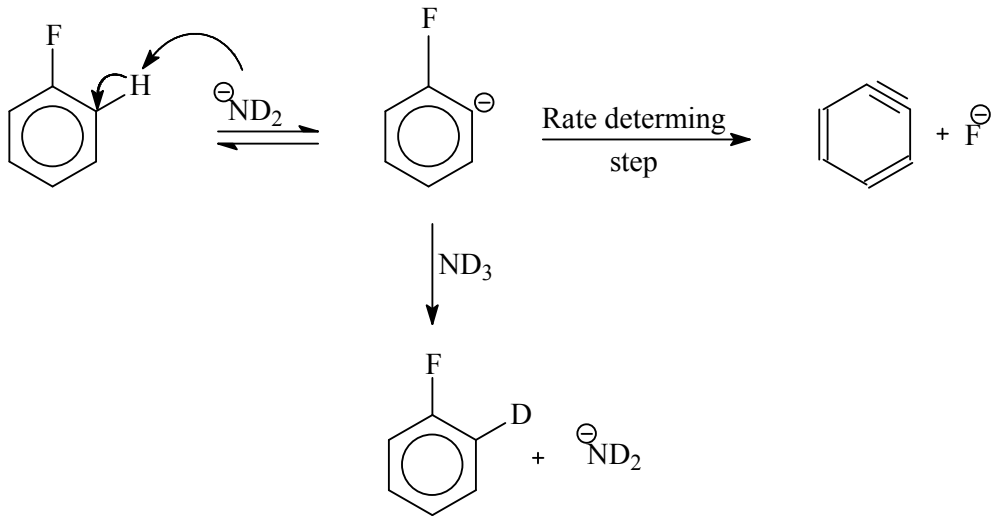
6. The yield the same product because they form the same benzyne intermediate.



Mechanism:



7. The reaction indicates that the hydrogen ortho to florine is replaced in a rapid reversible reaction. These data also support that the rate-determining step in benzyne formation from flourobenzene is loss of fluoride ion.



2.13 REFERENCES

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UNIT-3 ALIPHATIC ELECTROPHILIC SUBSTITUTION

CONTENTS:

3.1 Objectives

3.2 Introduction

3.3 Unimolecular Substitution Reactions (S_E1)

3.3.1 Evidence for the S_E1 mechanism

3.3.2 Stereochemistry of S_E1 reaction

3.4 Bimolecular Substitution Reaction (S_E2)

3.4.1 S_E2 (Front) and S_E2 (Back): Evidence and Stereochemistry

3.4.2 S_Ei mechanism: Evidence and Stereochemistry

3.5 Electrophilic substitution accompanied by double bond shift

3.6 Effect of various factors on aliphatic electrophilic substitution

3.6.1 Effect of substrate

3.6.2 Effect of leaving group

3.6.3 Effect of solvent

3.7 Migration of double bond

3.7.1 Base catalysed double bond migration

3.7.2 Acid catalysed double bond migration

3.8 Some examples of aliphatic electrophilic substitution reactions

3.8.1 Halogenations of aldehydes and ketones

3.8.1a Mechanism of base catalysed halogenations

3.8.1b Mechanism of acid- catalysed halogenations

3.8.2 Halogenations of carboxylic acids and acyl halides

3.8.3 Halogenation of sulphoxide and sulphones

3.8.4 Aliphatic Diazonium coupling

3.8.5 Diazo transfer reaction

3.8.6 Nitrosation at Carbon (C-Nitrosation)

3.8.7 Nitrosation at Nitrogen (N-Nitrosation)

3.8.8 Addition – Elimination mechanism

3.8.8.1 Acylation at an aliphatic carbon

3.9 Some Naming Reaction of Aliphatic Substitution

3.9.1 Hell-Volhard-Zelinskii reaction

3.9.2 The Stork- Enamine reaction

3.9.3 Haloform reaction

3.10 Summary

3.11 Terminal questions with answers.

3.12 References

3.1 OBJECTIVES

In this unit learner will be able to

► Learn various types of aliphatic electrophilic substitution reactions like unimolecular S_E1 and bimolecular S_E2 (front), S_E2 (back) and S_Ei.

► Learn comparative mechanism and stereochemistry of S_E1, S_E2 (front), S_E2 (back) and S_Ei reactions.

► Learn Effect of various factors on aliphatic electrophilic substitution like effect of substrate,effect of leaving group and effect of solvent.

► Learn Migration of double bond as base catalysed double bond migration and acid catalysed double bond migration

► Learn about Some aliphatic electrophilic substitution reactions like Halogenations of carboxylic acids and acyl halides, halogenation of sulphoxide and sulphones, aliphatic diazonium coupling, diazo transfer reaction, nitrosation at carbon (C- Nitrosation), nitrosation at Nitrogen (N-Nitrosation), addition-elimination reaction.

► Learn about Mechanisms of some naming Reaction of Aliphatic Substitution Hell-Volhard-Zelinskii reaction, Stork- Enamine reaction and haloform reaction

3.2 INTRODUCTION

Aliphatic electrophilic substitution reactions are related to carbanions. The mechanism of electrophilic substitution is less clear than the aliphatic nucleophilic substitution and aromatic electrophilic substitution reactions. In electrophilic substitution reactions, the entering and the leaving group (electrofuse) are the electrophiles, i.e. Lewis acid. Aliphatic substitution reactions also proceed through unimolecular or bimolecular (direct displacement) mechanism. The four possible electrophilic aliphatic reaction mechanisms are S_E1, S_E2 (front), S_E2 (back) and S_Ei types. In the S_E1 mechanism, the substrate first ionizes into the carbanion or a positively charged organic residue then quickly recombines with the electrophile. The S_E2 reaction mechanism has a single transition state in which the old bond and the newly formed bond are both present.

3.3 UNIMOLECULAR ELECTROPHILIC SUBSTITUTION (S_E1) MECHANISM

S_E1 reaction involves two steps, i.e. a slow heterolysis following carbanion formation and fast combination of the resulting carbanion with electrophile.

Step 1. $R—X \rightleftharpoons R^{\ominus} + X^{\oplus}$

Step 2. $R^{\ominus} + Y^{\oplus} \longrightarrow R—Y$

Electrophilic substitution can occur when the leaving group is more electro positive with respect to carbon i.e. metal atom and hydrogen.

Example of S_E1 reaction

- **Hydrogen-deuterium or hydrogen-tritium exchanges**

$$R—H + B—D \xrightleftharpoons{:\bar{B}} R—D + B—H$$

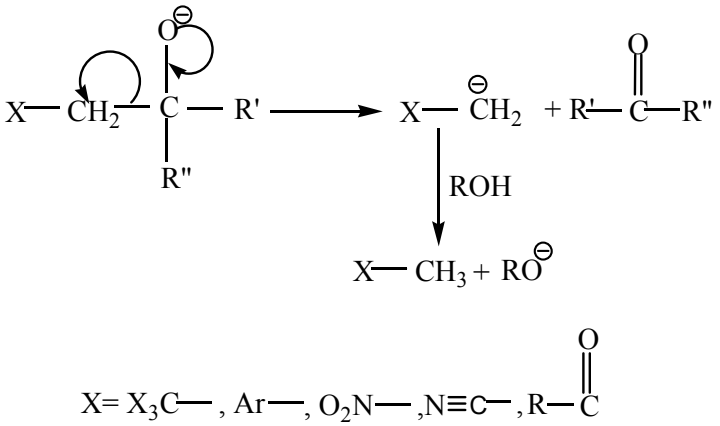
$:\bar{B}$ = base

Such exchange occurs with relatively acidic protons, e.g. alpha position to a carbonyl group. However, even weakly acidic protons can exchange bases which are strong enough.

- **Decarboxylation**

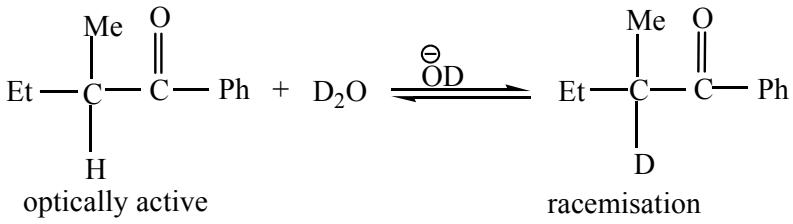
$$X—CH_2—\overset{\overset{O}{\|}}{C}—O^{\ominus} \xrightarrow[-CO_2]{} X—CH_2^{\ominus} \xrightarrow{ROH} X—CH_3 + RO^{\ominus}$$

- **Anionic fragmentation**



3.3.1 Evidence for the S_E1 mechanism

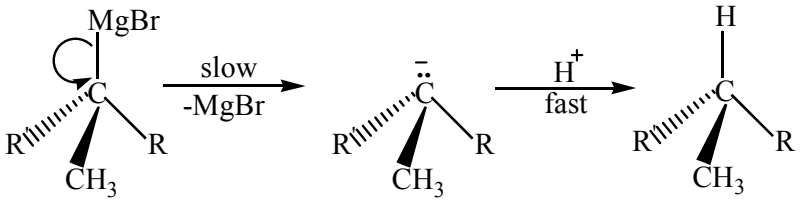
- The reaction follows first order kinetics.
- In the following base catalysed tautomerisation



The rate of deuterium exchange was found to be the same as the rate of racemisation and there was an isotope effect. S_N1 reaction do not occur at bridgehead carbons in [2, 2, 1] bicyclic systems because planer carbocations cannot form at these carbons. Carbanions not stabilised by resonance need not be planar, hence S_E1 reaction should readily occur at bridgeheads and this is found to be the case also.

3.3.2 Stereochemistry of S_E1 reaction

The carbanion formed as an intermediate in S_E1 reactions retains its tetrahedral configuration and hence will be attack only from one side retaining the original configuration. For ex. Replacement of the metal in an organometallic compound by hydrogen proceeds with retention of configuration.



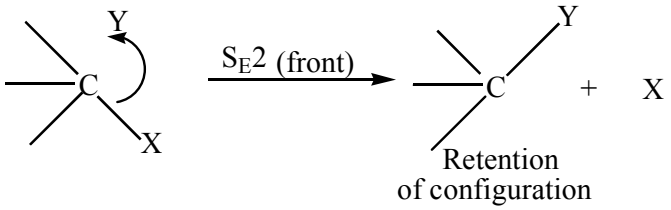
3.4 BIMOLECULAR ELECTROPHILIC SUBSTITUTION REACTION

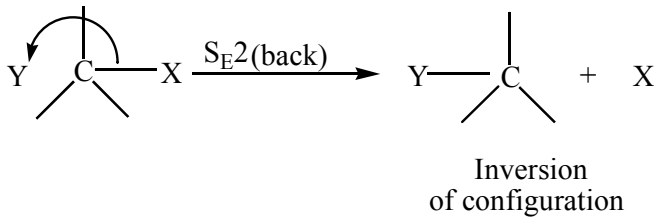
S_E2 reactions occur with organometallics that have a considerable degree of covalent character or with C—H bonds under conditions not sufficiently basic for proton removal. They have been extensively studied with organomercury compounds, but have been observed with a number of other metals as leaving group, e.g., Li, Cr, Sn, Fe, and Co. Aliphatic bimolecular substitution reactions are of two types: S_E2 and S_Ei.

3.4.1 S_E2 and S_Ei Mechanisms

Both S_E2 and S_Ei mechanisms are bimolecular and are analogous to S_N2 mechanism. i.e. the new bond forms and at the same time, the old bond breaks. In the S_N2 mechanism, the attacking group brings with it a pair of electrons and the leaving group takes away its electrons. These things are happening simultaneously. Therefore the incoming attacking group attacks backside at a position 180^0 away from the leaving group, resulting in inversion of configuration.

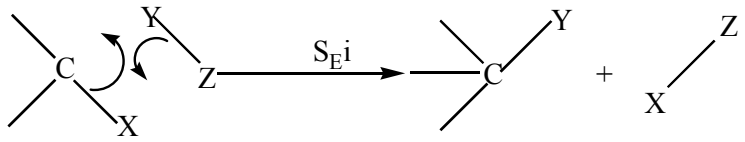
But in S_E2 mechanism the attacking group is an electrophile. This brings to the substrate only a vacant orbital. Therefore we cannot predict from which direction the attack must come. We can imagine two main possibilities. They are attack from the front, i.e. S_E2 (front) and attack from rear, i.e., S_E2 (back). These can be represented as follows.





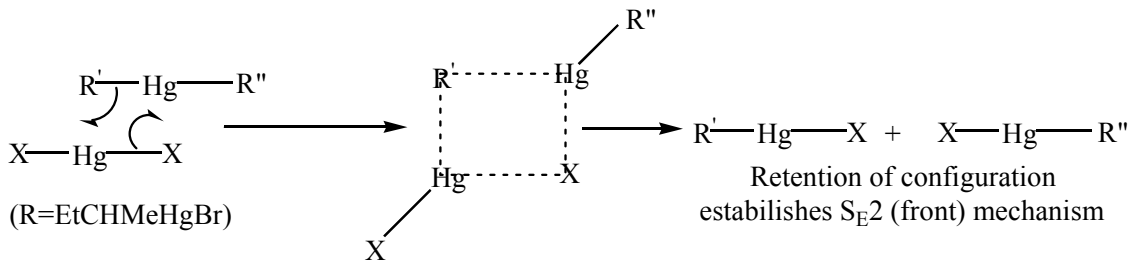
3.4.2 The S_Ei Mechanism

When an electrophile attacks from the front, there is a possibility for a portion of the electrophile to assist in the removal of leaving group, forming a bond with it at the same time a new C-Y bond is formed.



This mechanism also results in retention of configuration, where a second order kinetics involves internal assistance that prevents the backside attack of an electrophile.

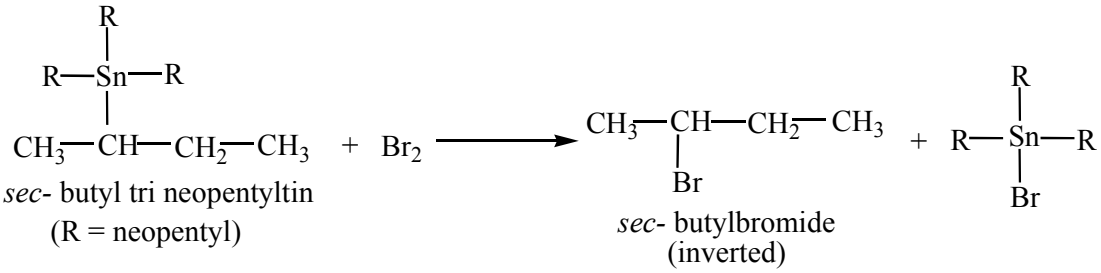
The S_E2 (front), S_E2 (back) and S_Ei mechanism are not easy to distinguish. All these three types of mechanisms give second order kinetics in which S_E2 (front) and S_Ei result in retention of configuration. The study of stereochemistry can distinguish between S_E2 (front), S_E2 (back) and S_Ei in such a way that S_E2 (back) results in inversion of configuration on the one hand and S_E2 (front) and S_Ei on the other. In the majority of second order electrophilic substitution reaction, the results have been retention of configuration due to the front side of electrophile following either S_E2 (front) or S_Ei mechanism.



This indicate the bonds between the Hg atom and the ring on the one side, and the carbon (Hg-C) on the other side have be broken , electrophile which facilitate the front side attack of the electrophile on the substrate carbon to produce the cis isomer. Another

indication of front side attack is that the second order electrophilic substitutions proceed very easily at bridgehead carbons, where back side attack is impossible.

However, inversion of configuration has been found in certain case indicating that S_E2(back) mechanism can also takes place for example, the reaction of optically active sec-butyl tri-neopentyl tin with bromine gives inverted *sec*-butyl bromide.

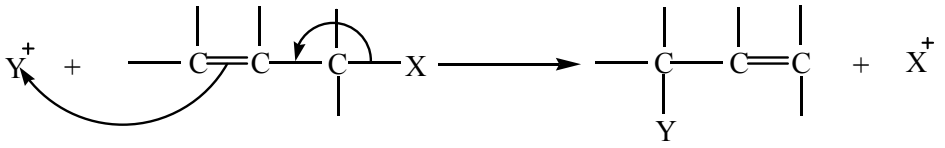


sec- butyl tri neopentyltin (R = neopentyl)

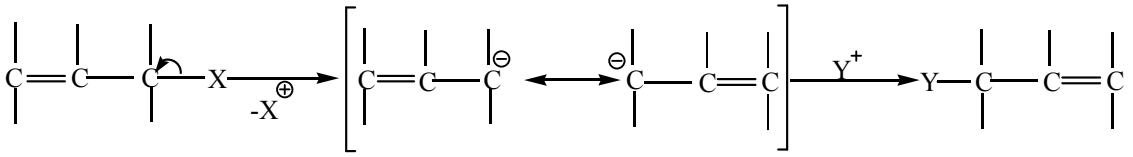
sec- butylbromide (inverted)

3.5 ELECTROPHILIC SUBSTITUTION ACCOMPANIED BY DOUBLE BOND SHIFTS

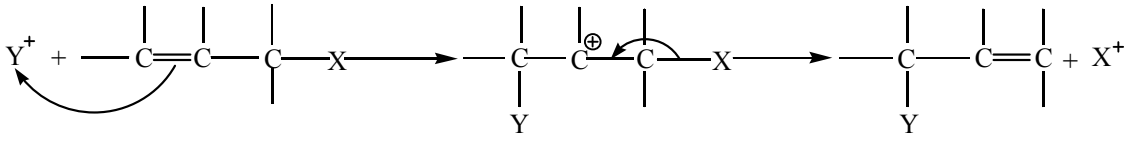
When electropilic substitution is carried out at an allylic substrate, the product may be rearranged:



This type of process is analogous to the the nucleophilic allylic rearrangements. There are two principal pathways. The first of these is analogous to the S_E1 mechanism in that the leaving group is first removed, giving a resonance stabilised allylic carbanion and then the electrophile attacks.



In the other pathway the Y group first attacks, giving a carbocation, which then loses X.



Most electrophilic allylic rearrangements involve hydrogen as the leaving group, but they have also been observed with metallic leaving groups. The crotyl mercuric bromide reacted with HCl about 10^7 times faster than n-butyl mercuric bromide and the product was more than 99% 1-butene. These facts point to a S_Ei mechanism.

3.6 EFFECT OF FACTORS ON ALIPHATIC ELECTROPHILIC SUBSTITUTION

3.6.1 Effect of substrate:

For S_E1 reaction, electron–donating group decreases while electron withdrawing group increases the rate of reaction. This is as would be expected from a reaction in which the rate determining step is analogous to the cleavage of a proton from an acid.

For the S_E2 (back) reaction, it is shown that the reactivity of the alkyl group is similar to that for the S_N2 reaction (i.e. Me.> Et > Pr > iso-Pr > t-Bu> Neo pentyl), as would be expected, since both involve backside attack and both are equally affected by steric hindrance. In fact, this pattern of reactivity can be regarded as evidence for the occurrence of the S_E2 (back) reaction in cases where stereo chemical investigation is not feasible. For S_E2 reactions that proceed with retention. α- branching of alkyl group increases, while the β-branching decreased the rate of reaction. The decreased rates to steric hindrance, through attack here was definitely front side, and the increased rates to the electron-donating effect of the alkyl groups, which stabilized the electron-deficient transitions state. Of course, steric hindrance should also be present with the branched groups.

3.6.2 Effect of leaving group:

For both S_E1 and second order mechanisms, the more polar the C-X bond, the easier it is for the electrofuge to cleave. For metallic leaving groups in which the metal has a valence greater than 1, the nature of the other groups attached to the metal thus has an effect

on the reaction. For example, consider a series of organo mercurials RHgW. Because a more electronegative decreases the polarity of the C-Hg bond and furthermore results in a less stable HgW^+, the electrofugal ability of HgW decreases with increasing electronegativity of W. Thus, HgR'(from RHgR') is a better leaving group than HgC (from RHgCl). Also in accord with this is the leaving group order Hg-*tert*-Bu>Hg-*Iso*-Pr >HgEt >HgMe, reported for acetolysis of R_2Hg, since the more highly branched alkyl groups better help to spread the positive charge. It might be expected that, when metals are the leaving group, S_E1 mechanism would be favoured, while with the carbon leaving groups, second order mechanism would be found. However the results so far reported have been just about the reverse of this. For carbon leaving groups the mechanism is usually S_E1, while for metallic leaving groups the mechanism is almost always S_E2 or S_Ei.

3.6.3 Effect of solvent:

In addition to the solvent effects on certain S_E1 reactions, solvent can influence the mechanism that is preferred. As with nucleophilic substitution, an increase in solvent polarity increases the possibility of an ionising mechanism, in this case S_E1, in comparison with the second order mechanisms, which do not involve ions. The solvent can exert an influence between the S_E2 (front or back) and S_Ei mechanism in that the rates of S_E2 mechanisms should be increased by an increase in solvent polarity, while S_Ei mechanisms is much less affected.

3.7 MIGRATION OF DOUBLE BOND

The double bonds of many unsaturated compounds are shifted on treatment with strong bases. In many cases equilibrium mixtures are obtained and the thermodynamically most stable isomer predominates. Thus if the new double bond can be in conjugation or with an aromatic ring, it goes that way. If the choice is between an exocyclic and an endocyclic double bond (in a six membered ring), it chooses the latter. In the absence of consideration like Zaitsev rule* applies and the double bond goes to the carbon with the fewest hydrogens. All these considerations lead us to predict that terminal olefins can be isomerized to internal ones, non conjugated olefins to conjugated, exo six membered-ring olefins to endo etc., and not the other way around. This is usually indeed the case.

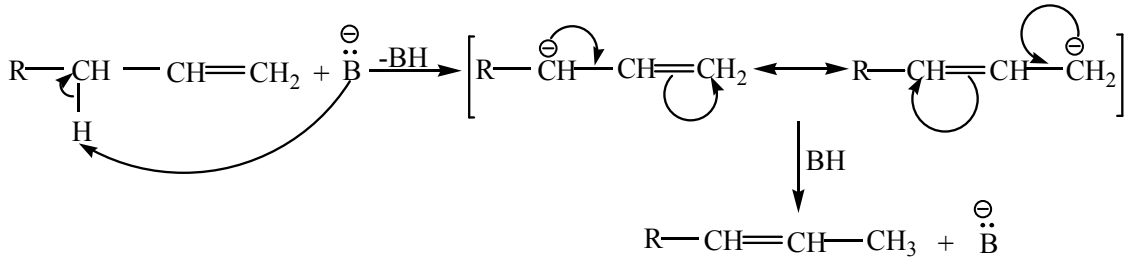
This reaction, for which the term prototropic rearrangement is sometimes used, is an example of electrophilic substitution with accompanying allylic rearrangement. The mechanism

involves abstraction by the base to give a resonance – stabilized carbanion, which then combines with a proton at the position that will give the more stable olefins.

**Zaitsev rule (*also known as *Saytzeff rule): This rule implies that an elimination reaction will predominantly to lead to the highly substituted olefin formation.*

3.7.1 Base catalysed double bond migration:

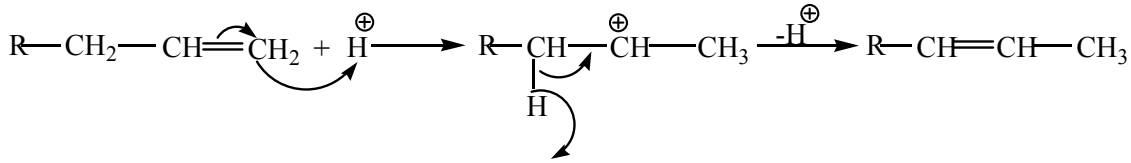
The double bonds of many unsaturated compounds are shifted (rearranged) on treatment with strong bases. Usually this results in equilibrium mixtures in which the thermodynamically most stable isomer predominates, thus terminal olefins can be isomerised to internal olefins; as the double bond has a tendency to become internal, non-conjugated olefins to conjugated, exo six member-ring olefins to endo, etc. This reaction is an example of electrophilic substitution accompanied by allylic rearrangement and sometimes it is also called prototropic rearrangement. The mechanism is as follows:



In the first step the base abstract a proton to give a resonance-stabilised carbanion, which then combines with a proton (electrophile) to give the more stable product. The mechanism is exactly analogous to the allylic rearrangement mechanism for nucleophilic substitution.

3.7.2 Acid catalysed double bond migration:

Both proton and Lewis acids can also bring about double bond rearrangement. As in the base catalysed .as in the case of base-catalysed double bond migration, thermodynamically most stable olefin is predominantly formed. The mechanism is as follows:

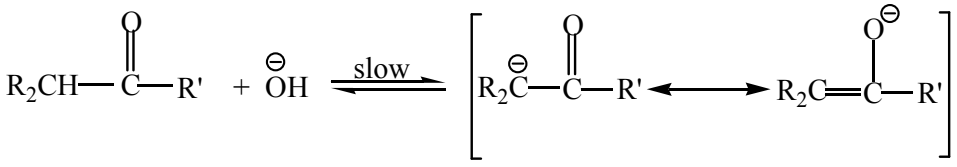


3.8 Some Electrophilic substitution reactions:

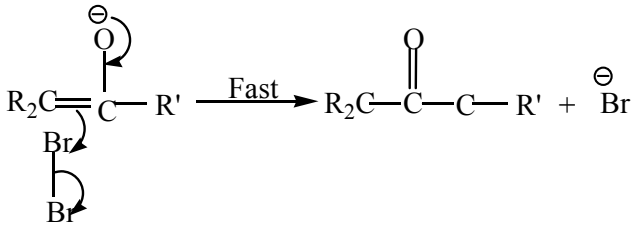
3.8.1 Halogenation of aldehydes and ketones

Aldehydes and ketones undergo α-helogenation with chlorine, bromine or iodine. Aldehyde or Ketone itself is not halogenated but the corresponding enol or enolate ion is halogenated. A base is used acid is used as a catalyst to generate a small amount of enol or enolate ion. When basic catalyst are used, one α position of a ketone is completely halogenated before the other is attacked, and the reaction cannot be stopped until all the hydrogens of the first carbon has been replaced. If one of the groups is methyl group them Haloform reaction takes place. In the case of acid catalyst it is easy to stop the reaction at mono substitution stage, though the second halogen can be introduced by using excess reagents.

Step 1.



Step 2.



3.8.1a. Mechanism of base catalysed halogenations:

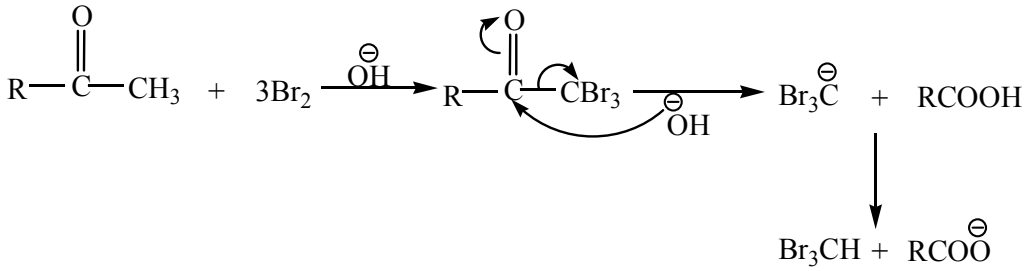
The above mechanism is supported by the kinetics

$$\text{Rate} = K [\text{ ketone }] [\text{base}]$$

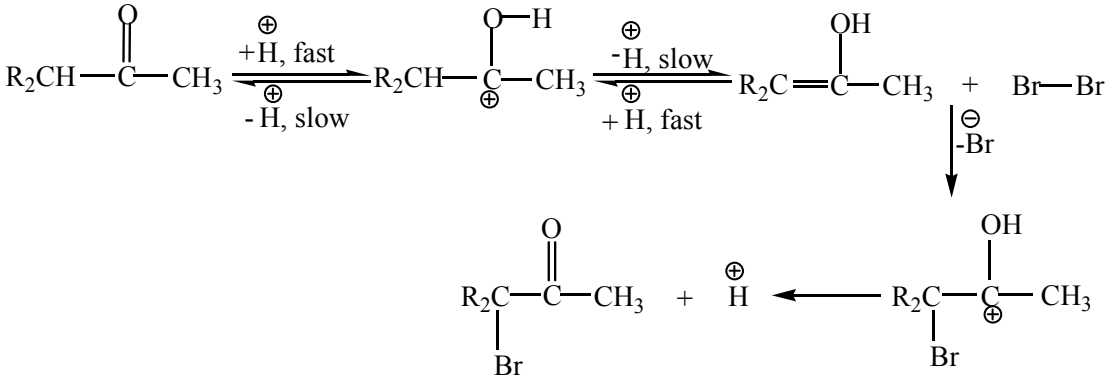
The rate of the reaction depends on the concentration of the ketone and that of base but is independent of the concentration of the halogen. Another evidence for the carbanion mechanism is provided by the base catalysed racemisation of (+)-phenyl *sec*- butyl ketone. The rate of racemisation and the rate of bromination are found to be the same. The rate of racemisation is also found to be the same as the rate of deuteriation when the reaction is carried out in the presence of a base in D_2O.

The electron–withdrawing effect of the first halogen increases the acidity of the remaining hydrogen's on the same carbon, e.g. a CHX group is more acidic than a CH_2 group, and the more acidic hydrogen is replaced by halogen more easily because the greater the acidity of the α-hydrogen, the more rapid is the enolization of the carbonyl compound. Thus base catalysed halogenation of an unsymmetrical ketone preferably takes place on that α carbon which bears fewer alkyl groups because the +I effect of alkyl group decreases the acidity of α-hydrogen, and so the rate of enolization.

Base catalysed halogenation of a carbonyl compound cannot be stopped until all the α-hydrogens are replaced. For example, a methyl ketone thus results in the formation of a trihaloketone through the mechanism (shown in *3.8.1*). Because of the combined –I effect of the three halogen atoms, the carbonyl carbon of the trihaloketone is highly positive, hence it is attacked by a base with cleavage of the C C bond to give a haloform and salt of a carboxylic acid. This reaction is known as haloform reaction. Methyl ketones, acetaldehyde, the primary and secondary methyl alcohols (which are first oxidised to the carbonyl compounds and then produce haloform under the reaction conditions) give haloform reaction* with Cl_2, Br_2 or I_2 in the presence of a base.



3.8.1b Mechanism of acid- catalysed halogenations:

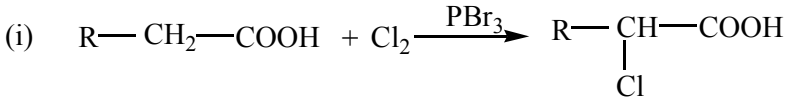


Haloform reaction is given by those compounds which have R —C O— CH_3 or $RCH(OH)CH_3$ group.

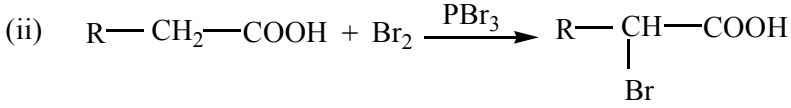
3.8.2 Halogenations of carboxylic acids and acyl halides:

Carboxylic acid undergoes α-halogenations with bromine or chlorine in the presence of phosphorus halide as catalyst. The reaction is known as Hell-Volhard-Zelinskii reaction (HVZ reaction). The reaction actually takes place on the acyl halide formed from the carboxylic acid and phosphorus halide, as it has higher enol content than the acid itself.

For example, the use of Cl_2 and PBr_3 gives α-chlorination but not α-bromination. The halogen from the catalyst does not enter the α-position. It can be explained by the following mechanism:



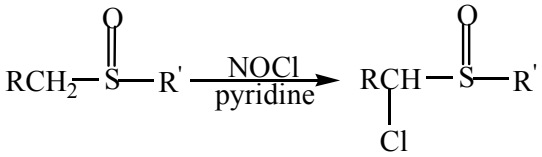
(i) $R—CH_2—COOH + Cl_2 \xrightarrow{PBr_3} R—\underset{Cl}{CH}—COOH$



(ii) $R—CH_2—COOH + Br_2 \xrightarrow{PBr_3} R—\underset{Br}{CH}—COOH$

3.8.3 Halogenation of sulphoxide and sulphones:

Sulphoxide can be chlorinated in the α position by treatment with NOCl, Cl_2, TsCl*, or N- Chlorosuccinimide, all in the presence of pyridine,



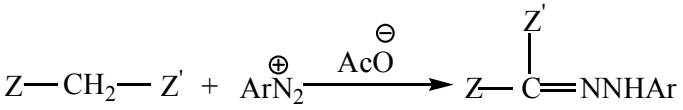
$RCH_2—\overset{\overset{O}{\|}}{S}—R' \xrightarrow[\text{pyridine}]{NOCl} RCH(Cl)—\overset{\overset{O}{\|}}{S}—R'$

The chlorination can also be brought about in the absence of base, e.g., with SO_2Cl_2 in CH_2Cl_2. The bromination of sulphoxide can be brought about with Br_2 with N-bromosuccinimide-bromine. Sulphones have been chlorinated by treatment of their conjugate base RSO_2CHR' with SO_2Cl_2, CCl_4, N- Chloro succinimide, and hexachloroethane.

TsCl is 4- Toluene Sulphonyl Chloride having molecular formula $C_7H_7ClO_2S$

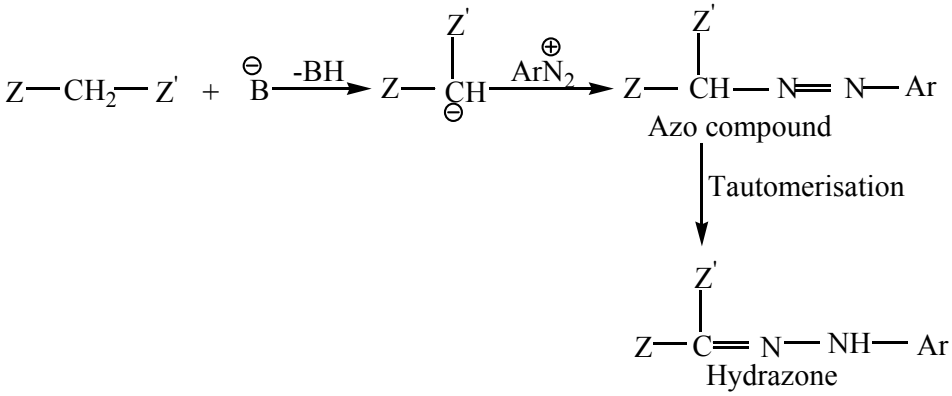
3.8.4 Aliphatic Diazonium coupling:

Compounds containing active hydrogen (acidic C-H bond) couple with diazonium salts in the presence of a base, usually aqueous sodium acetate, e.g.

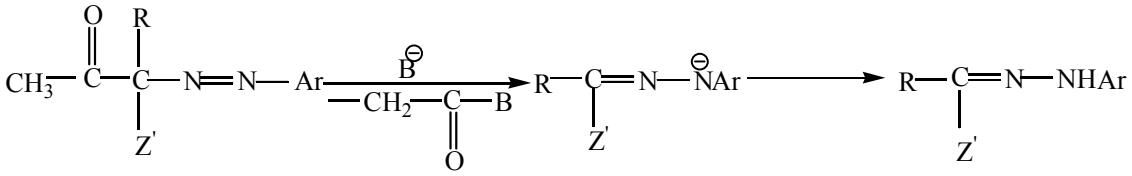


(Z, Z'= electron –withdrawing groups such as NO_2, CN, COOR, SO_2R, COR, etc.)

The reaction proceeds through simple S_E1 mechanism as follows:



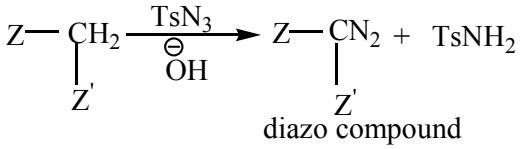
If the carbon containing the azo group has hydrogen then it tautomerises to more stable hydrazone. When the azo compound does not have a tautomerisable group, and at least one Z is acyl or carboxyl, this group cleaves to give a hydrazone, e.g.



If there no acyl or carboxyl group present then the aliphatic azo compound is stable.

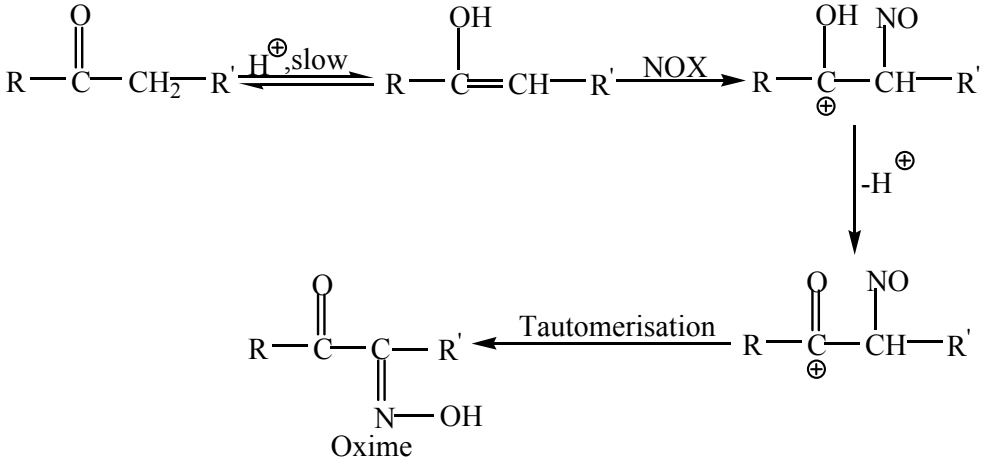
3.8.5 Diazo transfer reaction:

Compound containing a CH_2 group bonded to two electron –withdrawing groups (Z, Z') can be directly converted into diazo compounds on treatment with tosyl azide in the presence of a base. This reaction is called diazo transfer reaction. It can also be applied to other reactive positions, e.g., 5-position of cyclopentadiene.

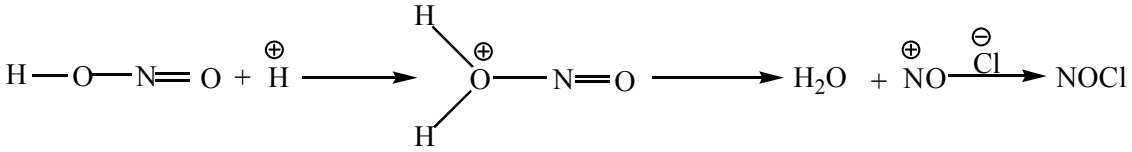


3.8.6 Nitrosation at carbon (C- nitrosation):

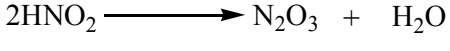
Carbons containing an active hydrogen can be nitrosated with HNO_2 or alkyl nitrites to give the C-nitroso compounds which tautomerises to more stable oximes if a tautomerisable hydrogen is available, e.g.,



The attacking species is NO or a carrier of it which is formed as follows, e.g. when $NaNO_2$ and HCl are used.

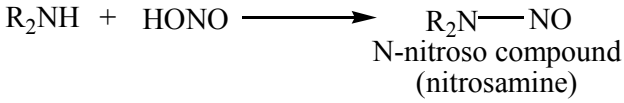


In dilute acids the actual attacking species is N_2O_3 formed as:

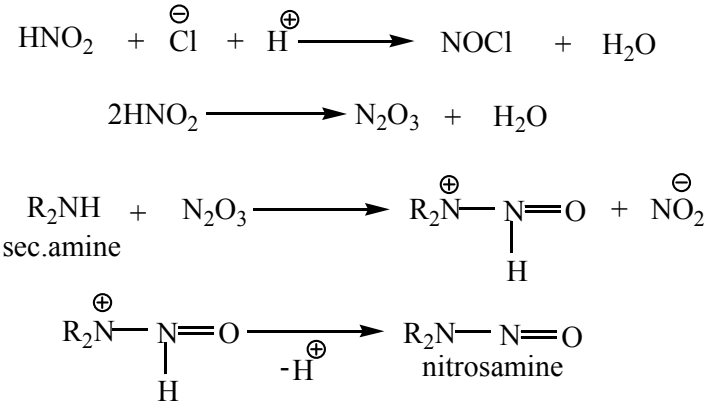


3.8.7 Nitrosation at Nitrogen (N-Nitrosation):

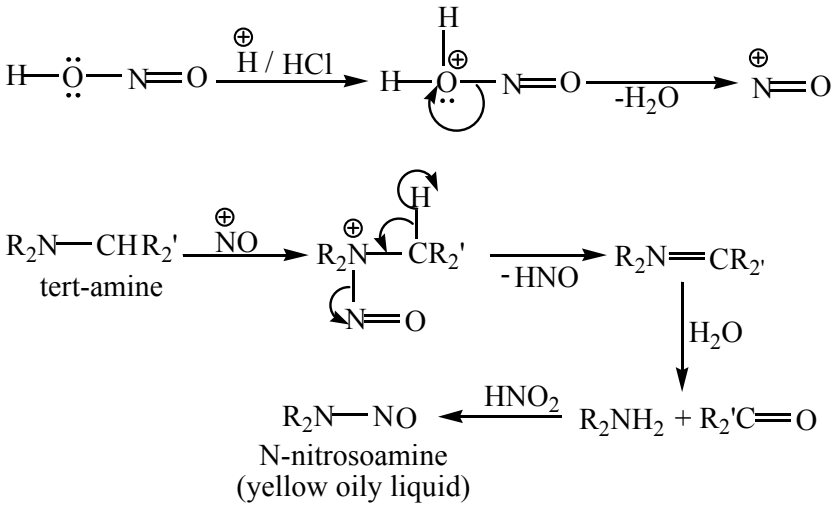
Secondary amines and mono-N-substituted amides (RCONHR') undergo N-nitrosation when treated with nitrous acid.



Tertiary amines have also been N-nitrosated but in this case one group cleaves to give the nitroso derivative of a secondary amine and an| aldehyde or ketone. The mechanism is as follows and the attacking species is N_2O_3, NOCl, $\overset{+}{N}O$, $H_2\overset{+}{N}O_2$ Nucleophiles Cl-, SCN- and thiourea catalyse the reaction by converting HNO_2 to a better nucleophile, e.g.



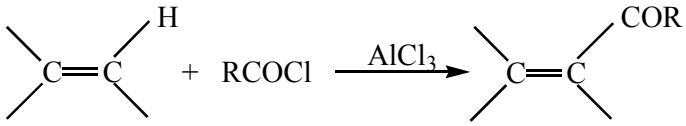
The following is the mechanism for the reaction with tertiary amines:



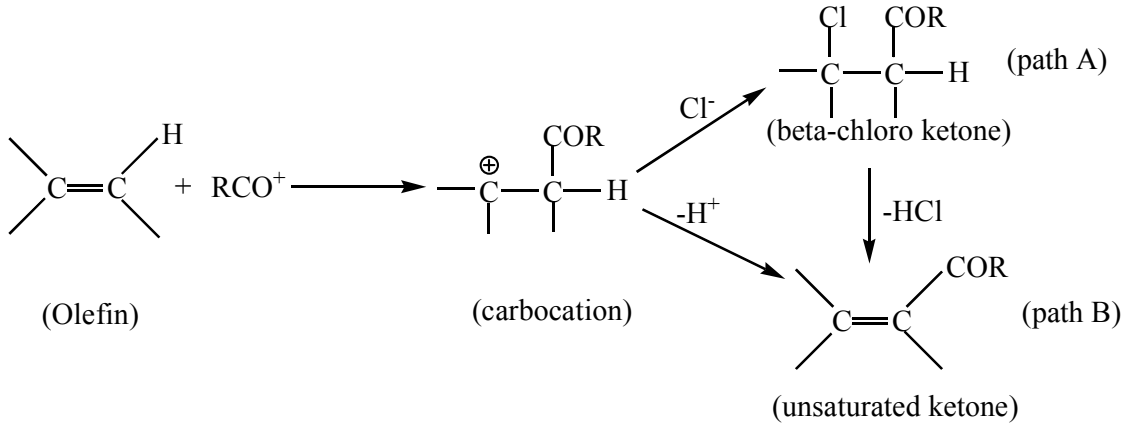
3.8.8 Carbon Electrophiles (Addition–Elimination Mechanism):

Addition- Elimination mechanism is also known. Less work has been done on aliphatic substitution mechanisms than nucleophilic substitution mechanisms, so the exact mechanisms of many of the reactions are in doubt.

3.8.8.1 Acylation at an aliphatic carbon

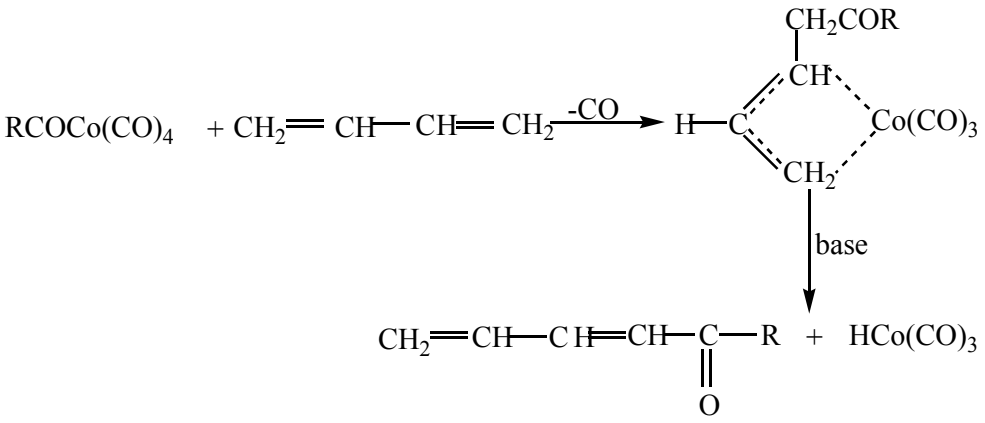


Olefins can be acetylated with an acyl halide and Lewis-acid catalyst in what is essentially a Friedal-Crafts reaction at an aliphatic carbon. The product can arise by two paths (*path A and path B*). The initial attack is by the acyl cation RCO^+ at the double bonded carbon atom to give a carbocation.

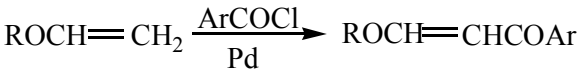


Carbocation can either lose a proton or combine with chloride ion. If it loses a proton, the product is an unsaturated ketone. If it combines with chloride ion, the product is a β- halo-ketone, which can be isolated. On the other hand, the β- halo-ketone may under the condition of the reaction, lose HCl to give the unsaturated ketone, this time by an addition–elimination mechanism. In the case of unsymmetrical olefins, the attacking ion prefers the position at which there are more hydrogens, following Markovnikov's rule. Anhydrides and carboxylic acids are sometimes used instead of acyl halides. With some substrates and catalysts double-bond migrations are occasionally encountered so that, for example, when

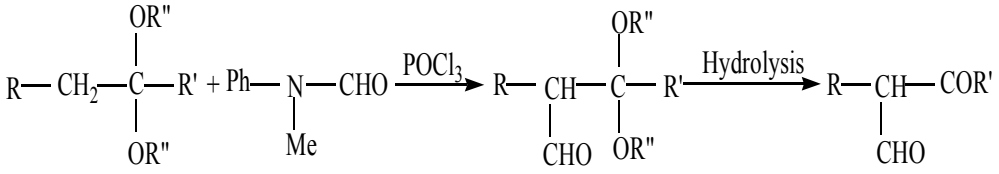
1-methylcyclohexene was acetylated with acetic anhydride and zinc chloride, the major product was 6-acetyl-1-methylcyclohexene. Conjugated dienes can be acetylated by treatment with acyl-or alkylcobalt tetracarbonyls, followed by base-catalysed cleavage of the resulting π- allyl carbonyl derivatives.



The reaction is very general with unsymmetrical dienes, the acyl group generally substitutes most readily at a *cis* double bond, next at a terminal olefinic group, the least readily at a *trans* double bond. The most useful bases are strongly basic, hindered amines such as dicylohexylethylamine. The use of an alkyl cobalt tetracarbonyl $RCo(CO)_4$ gives the same product as that shown above. Acylation of vinylic ethers has been accomplished with aromatic acyl chloride, a base, and a palladium catalyst.



Formylation of olefins can be accomplished with N di-substituted formamides and $POCl_3$. This is a Vilsmeier reaction. Vilsmeier formylation can also be performed on the α-position of the acetals and ketals, so that hydrolysis of the products gives keto aldehydes or dialdehydes.

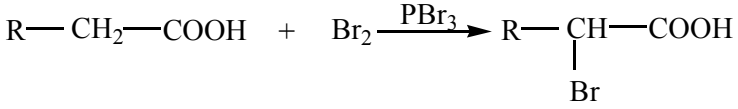


Acetylation of acetal or ketals can be accomplished with acetic anhydride and BF_3-etherate. The mechanism with acetals or ketals also involves attack at an olefinic carbon, since enol ethers are intermediates. Ketones can be formylated in the α- position by treatment with CO and a strong base.

3.9 SOME NAMING REACTION OF ELECTROPHILIC ALIPHATIC SUBSTITUTION

3.9.1 Hell-Volhard-Zelinskii Reaction:

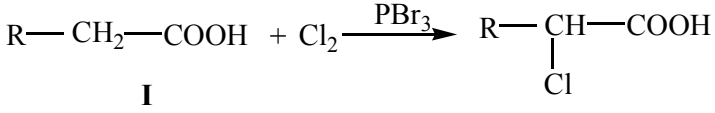
The α-hydrogen atoms of carboxylic acids can be replaced by bromine or chlorine with a phosphorus halide as catalyst. This reaction is known as Hell–Volhard-Zelinskii (HVZ) reaction. This is not applicable to iodine or fluorine*.



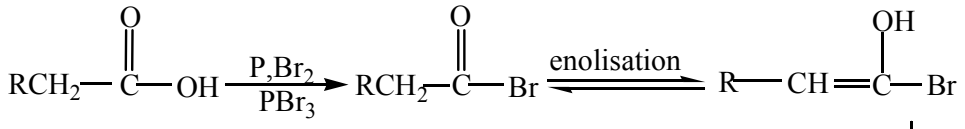
The reaction actually takes place on the acyl halide formed from the acid and the catalyst.

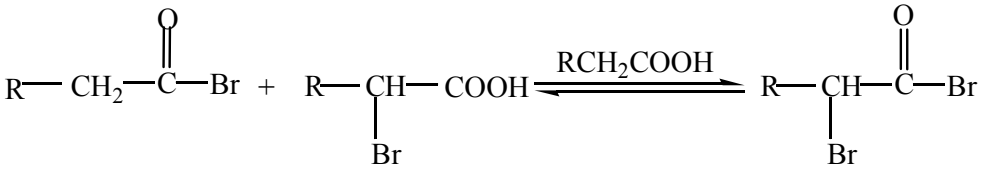
**Iodine is large; therefore, it cannot undergo substitution in presence of COOH group due to steric hindrance while Fluorine is reactive enough to replace all hydrogen atoms.*

(i)



I





II

Enolisation of the acyl bromide is far more rapid than the bromine exchange between **II)** and the parent acid **(I)**, thus the equilibrium is shifted in the forward direction. Since HVZ reaction with bromine is specific for α-hydrogen, it can be used to detect the presence of α-hydrogen in a carboxylic acid. When there is more than one α-hydrogen, all may be replaced; it is often difficult to stop the reaction at the mono substitution stage.

3.9.2 The Stork-Enamine reaction:

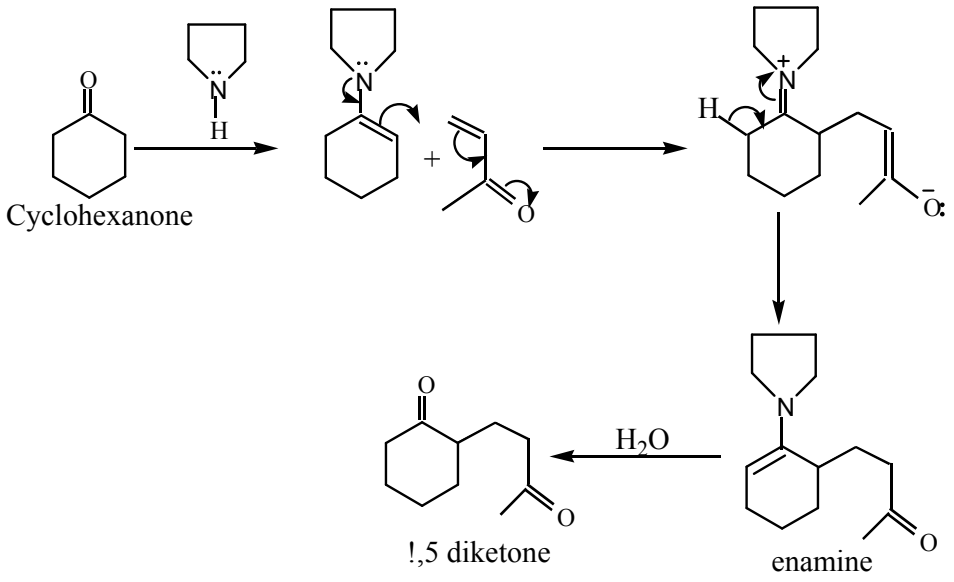
This reaction involves the addition of an enamine to an α, β – unsaturated carbonyl acceptor. The product is then hydrolysed by an aqueous acid to produce a 1, 5- dicarbonyl compound. While if the electrophile is an acylhalide, a 1, 3- diketones is formed (Stork acylation)

The process follows the following steps:

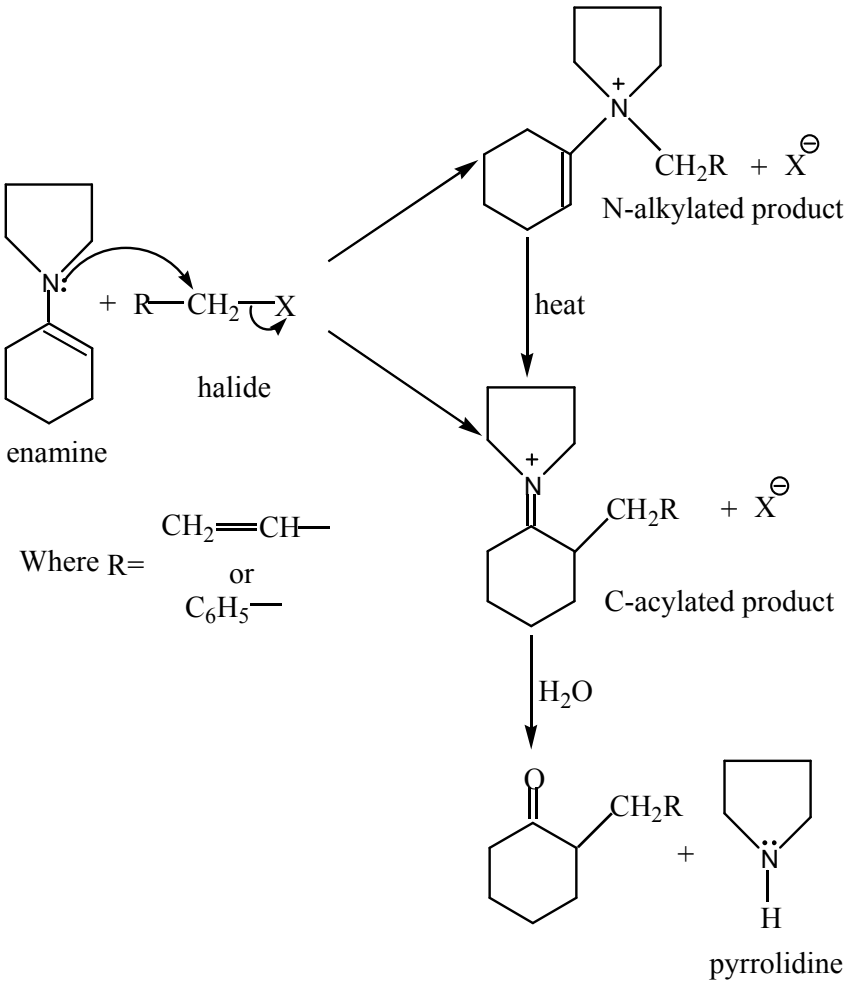
Step I - Formation of an enamine from a ketone.

Step II - Addition of the enamine to α, β – unsaturated aldehyde or ketone.

Step III – Hydrolysis of an enamine results in the formation of a ketone.



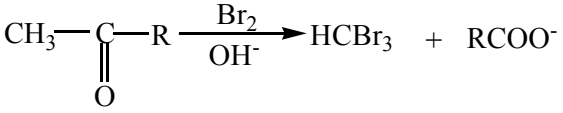
When enamine is treated with acyl halides, an alkylation occurs. This is analogous to the first step of Freidel Craft acylation at an aliphatic carbon and the hydrolysis of the resultant imine salt gives a ketone.



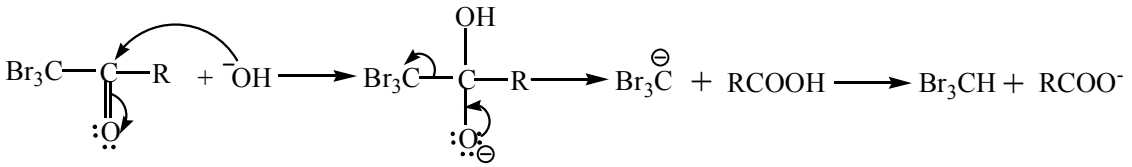
The net result is the alkylation of ketone at the α-position since the enamine is formed from a ketone. This method is known as Stork Enamine reaction. This method is alternative to the alkylation of ketone by the aliphatic nucleophilic substitution method. The stork method has an advantage that the reaction can be brought to an end with the introduction of just one alkyl group. Alkylation usually takes place on the less substituted side of original ketone.

The most commonly used amines are the cyclic amines such as piperidine, morpholine and pyrrolidine. This method is quite useful for active alkyl halides such as allyl, benzyl and propargyl halides and also for alpha–halo ether and esters. This is not applicable for ordinary primary, secondry and tertiary halides.

3.9.3 Haloform reaction:



In the Haloform reaction, methyl ketones (and the only methyl aldehyde, acetaldehyde) are cleaved with halogen and a base. The halogen can be bromine, chlorine or iodine. It takes place is actually a combination of two reactions. The first is an example in which, under the basic conditions employed, the methyl group is tri-halogenated. Then the resulting tri halo ketone is attacked by hydroxide ion.



Primary or secondary methyl carbinols also give the reaction, because they are oxidised to the carbonyl compounds under the conditions employed. A side reaction is α-halogenation of the non methyl R group. Sometimes these groups are also cleaved. The reaction cannot be applied to F_2, but ketones of $RCOCF_3$(R=alkyl or aryl) give fluoroform and $RCOO^-$ when treated with base. The haloform reaction is often used as a test for methyl carbinols and methyl ketones. Iodine is most often used as the reagent, since idoform is an easily identifiable yellow solid. The reaction is also frequently used for synthetic purposes. Methyl ketones $RCOCH_3$ can be converted directly to methyl esters $RCOOCH_3$ by an electrochemical reaction.

3.10 SUMMARY

In electrophilic substitution in aliphatic compounds, an electrophile displaces a functional group. This reaction is similar to nucleophilic aliphatic substitution.

In electrophilic substitution reactions, the entering and the leaving group are the electrophile, i.e. Lewis acid. The electron pair of the breaking bond remains with the substrate and is used to form the new bond to the entering electrophile.

Aliphatic substitution reactions proceed through unimolecular or bimolecular (direct displacement) mechanism. The four possible electrophilic aliphatic reaction mechanisms are S_E1, S_E2 (front), S_E2 (back) and S_Ei.

In the S_E1 reaction the substrate first to ionizes into carbanion and a positively charged organic residue. The carbanion then quickly recombines with the electrophile.

The S_E2 reaction mechanism has a single transition state in which the old bond and the newly formed bond are both present. In S_E2 mechanism the attacking group is an

electrophile. It attacks to the substrate only a vacant orbital. Therefore we cannot predict from which direction the attack must come. We can imagine two main possibilities. This can attack from the front, i.e. S_E2 (front) and attack from rear, i.e., S_E2 (back).

In S_Ei reaction an electrophile attacks from the front, there is a possibility for a portion of the electrophile to assist in the removal of leaving group, forming a bond with it at the same time a new bond is formed. All these three types of mechanisms give second order kinetics in which S_E2 (front) and S_Ei result in retention of configuration but S_E2 (back) results in inversion of configuration.

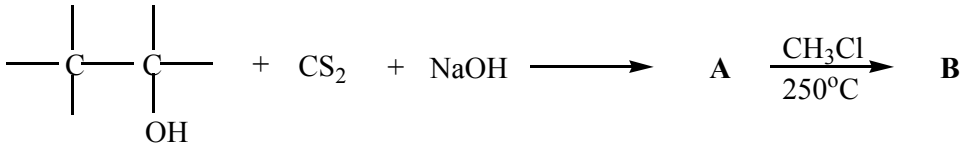
For both S_E1 and S_E2, the more polar the C-X bond, the easier it is for the electrofuge to cleave. For metallic leaving groups in which the metal has a valence greater than 1, the nature of the other groups attached to the metal thus has an effect on the reaction. An increase in solvent polarity increases the possibility of an ionising mechanism of S_E1 reaction. The solvent can exert an influence between the S_E2 (front or back) and S_Ei mechanism in that the rates of S_E2 mechanisms should be increased by an increase in solvent polarity, while S_Ei mechanisms are much less affected.

3.11 TERMINAL QUESTIONS

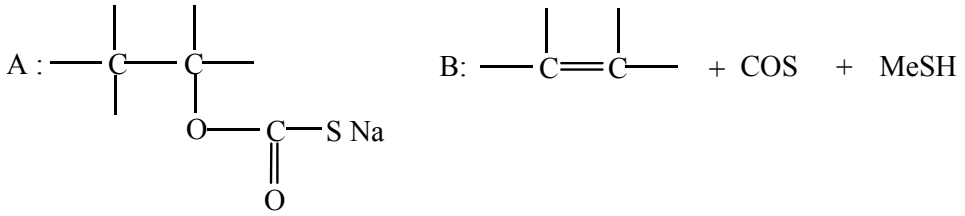
Ques.1. what do you mean by electrophilic substitution reaction?

Answer: Electrophilic substitution reaction is chemical reaction in which an electrophile displaces a functional group in a compound which is typically, but not always, a hydrogen atom.

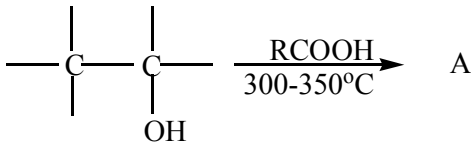
Ques.2. Complete the following reaction:

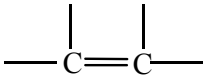


Answer :

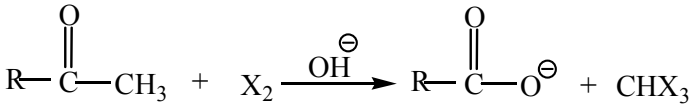


Ques.3. Complete the following reaction:



Answer : A :  + H_2O

Ques.4. Can you explain Haloform test.

Answer : 

$X_2 = Cl_2$, Br_2 or I_2

Ques.5. Which of the following does not give HVZ reaction:

(a) CH_3CH_2COOH

(b) CH_3COOH

(c) HCOOH

(d) $(CH_3)_2CHOH$

Answer: C

Ques.6. S_E1 results in inversion in configuration. (True/False)

Answer: False

Ques.7. Increase in polarity in solvent can increase the rate of reaction of S_E2. (True/False)

Answer: True

Ques.8. Compare the mechanism between S_E1 and S_E2 reaction.

Ques.9. Write a short note on S_Ei reaction and its mechanism.

Ques.10. Discuss the stereochemistry of aliphatic electrophilic substitution reaction with reference to S_E1 and S_Ei reaction.

Ques11. What is an aliphatic electrophilic substitution reaction. Discuss various types of aliphatic electrophilic substitution?

Ques.12. Write a short note of the following reaction.

(A) Haloform reaction

(B) Stork- Enamine reaction

(C) Hell-Volhard-Zelinskii reaction

Ques.13. Explain the effect of substrate in aliphatic substitution reaction.

3.12 REFERENCES

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UNIT-4 AROMATIC ELECTROPHILIC SUBSTITUTION

CONTENTS:

4. Objectives

4.0 Introduction

4.1 The arenium ion mechanism

- 4.1.1 Energy profile diagrams of Aromatic Electrophilic Substitution eaction:
- 4.1.2 Nitration
- 4.1.3 Sulphonation
- 4.1.4 Halogenation
- 4.1.5 Alkylation
- 4.1.6 Acylation

4.2 Orientation and reactivity

- 4.2.1 Electrophilic substitution in other poly-substituted benzene rings:

4.3 Some name reactions involving aromatic electrophilic substitution mechanism:

- 4.3.1 Vilsmeir reaction
- 4.3.2 Gatterman –Koch Reaction
- 4.3.3 Diazonium compounds coupling
- 4.3.3 .1 Diazonium coupling

4.4 Summary

4.5 Terminal questions

4.6 Answers to terminal questions

4.7 References

4. OBJECTIVES

The Objective of this chapter is to aware students about the electrophilic substitution reactions in aromatic compounds. The nature of the electrophile, its attack on electron rich aromatic ring, formation of σ and π complexes, formation of arenium ion and its stability, the energy profile diagram of electrophilic substitution reactions. How electron rich aromatic ring direct the attacking electrophile in presence of substituents or without substituents. Mechanism of some important name reactions involving electrophilic substitution reactions

4. 0 INTRODUCTION

The marked reactivity of aromatic compounds towards the electron deficient species, electrophiles arises mainly from two factors: the presence of π electron cloud above and below the plane of the ring, which shield it from the attack on electron rich nucleophiles, at the same time the electron cloud of π electrons are loosely held as compared to σ electrons. These loosely bound π electrons are available for easy attack of electrophiles. In contrast the olefinic compound with π electrons cloud undergo addition reactions because of their localized nature

4.1 THE ARENIUM ION MECHANISM

A arenium ion in organic chemistry is a non-classical cyclohexadienyl cation and formed as a reactive intermediate during aromatic electrophilic substitution reaction. So far the mechanism is concerned, it is a bimolecular reaction and also designated as SE_2 (electrophilic substitution bimolecular) reaction. It is a two-step reaction;

Step 1. The electrophile attack to the substrate in this step and produce a resonance establized reactive intermediate known as benzonium ion or cyclohexadienyl cation or σ-complex. This step is rate determining step.

Step 2.The leaving group from benzene ring (H or substituent) depart in this step. The attacking electrophile may be positive ion or a dipole. Fig. 1

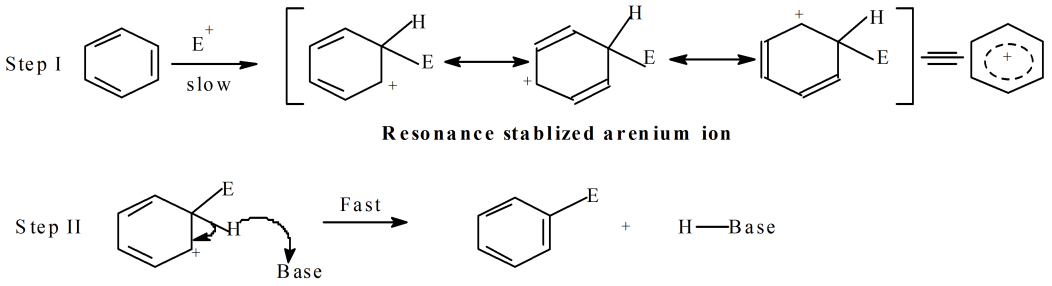
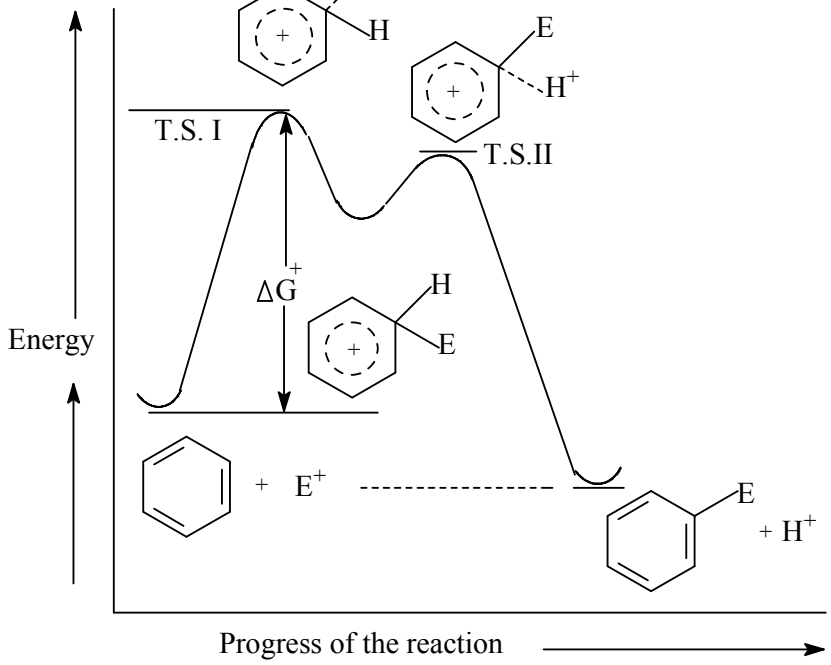


Fig.1 Mechanism of aromatic electrophilic substitution reaction

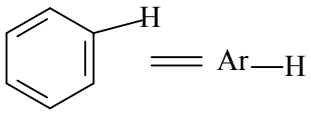
4.1.1 Energy profile diagrams of E^+ substitution reaction:

As discussed in above reactions the attacking reagent produce a reactive arenium ion (Wheland Intermediate) through transition state I followed by the removal of departing group through transition state II, which ultimately gives the thermodynamically stable product. The entire mechanism can be presented through energy profile diagram as in fig.2. Similar energy profile diagram can be drawn for substituted aromatic rings. However the rate of substitution and the regioselectivity of the reaction at *ipso, ortho, para* or *meta* positions depends on the height of the energy barrier (E^+ (ΔG^+) between the reactant and the T.S.



Some common electrophilic substitution reactions are:

Electrophilic Aromatic Substitution (Aromatic compounds)



1. Nitration

   $Ar\text{-}H + HNO_3, H_2SO_4 \rightarrow Ar\text{-}NO_2 + H_2O$

2. Sulfonation

$Ar\text{-}H + H_2SO_4, SO_3 \rightarrow Ar\text{-}SO_3H + H_2O$

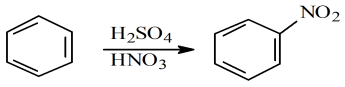
3. Halogenation

   $Ar\text{-}H + X_2, Fe \rightarrow Ar\text{-}X + HX$

4. Friedel-Crafts alkylation and acylation

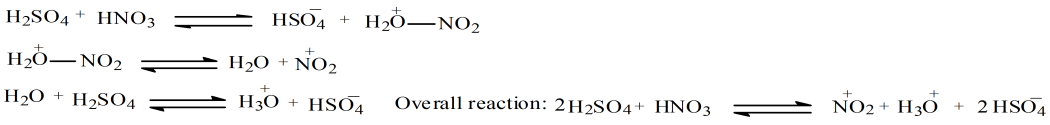
   $Ar\text{-}H + R\text{-}X, AlCl_3 \rightarrow Ar\text{-}R + HX$

4.1.2 Nitration: H is substituted by NO_2 group while the aromatic compound is treatied with nitrating mixture at elevated temperature.

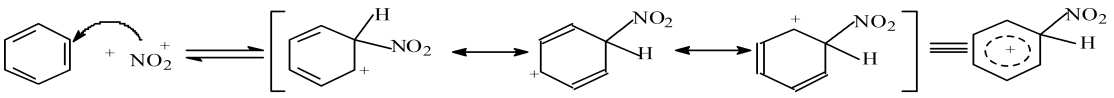


Mechanism:

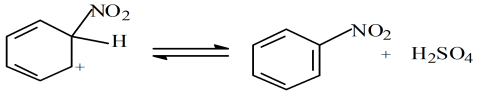
Generation of electrophile



Attack of electrophile and formation of final product

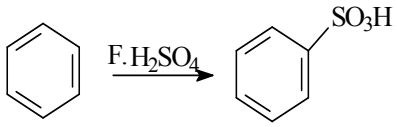


Finally deprotonation by base lead the formation of final product



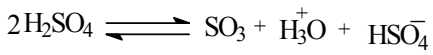
4.1.3 Sulphonation:

Sulphonation is done usually in presence of fuming sulphuric acid or con. H_2SO_4. The reaction takes place as under:

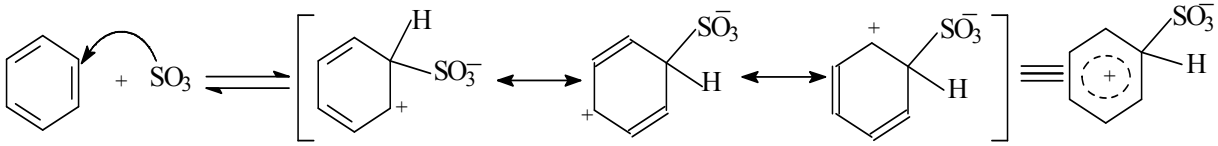


Mechanism:

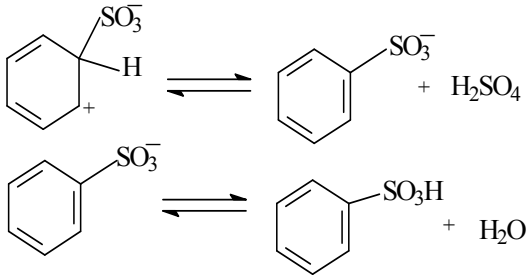
Generation of electrophile



Electrophile



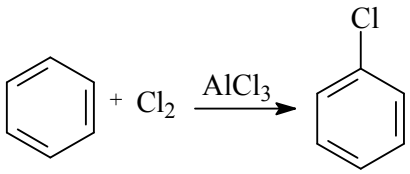
Finally deprotonation by base lead the formation of final product

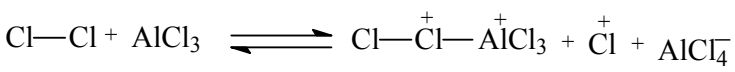


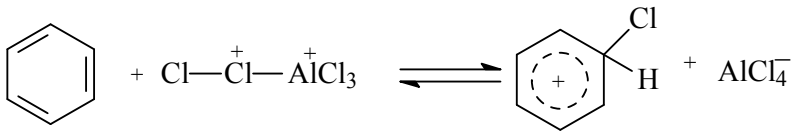
Sulphonation is a reversible reaction at higher temperature

4.1.4 Halogenation:

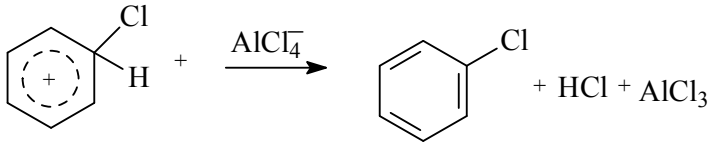
Aromatic compounds can be halogenated through chlorination or bromination particularly in presence of Lewis acids viz; BF_3, $AlCl_3$, $FeCl_3$, $FeBr_3$, $AlBr_3$ etc. The electrophile in such reactions is either halogen-Lewis acid complex or positive halogen. As per the mechanism predicted in fig. 1 the halogenated product is/are formed as under:







Finally the conjugate base of Lewis acid depronate the arenium ion to give halogenated product

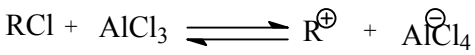


A similar mechanism is operated with HOCl and HOBr in presence of strong acid. The electrophile in that case is H_2O^+- X or positive halogen where X= Cl or Br

***4.1.5 Alkylation*:**

Introduction of alkyl group on benzene ring is known as alkylation. The most common method for alylation is Friedel-Craft alkylation. The reaction is carried out in presence of Lewis acids Viz; BF_3, $AlCl_3$, $FeCl_3$, $FeBr_3$, $AlBr_3$ etc. Since alkyl substituents activate the arene substrate, polyalkylation may occur. The active E^+ in Friedel – Craft alkylation is either an alkyl halide- Lewis acid complex or an alkyl carbocation.

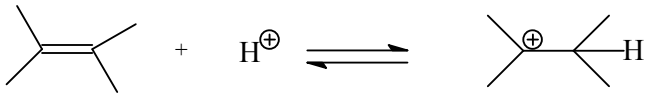
E^+ from alkyl halides:



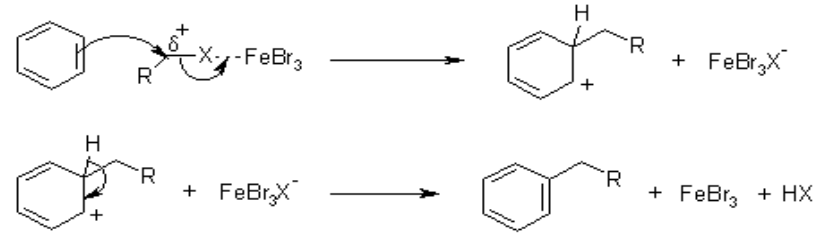
E^+ from alcohol and Lewis acid:

E^+ from alcohol and proton acid:

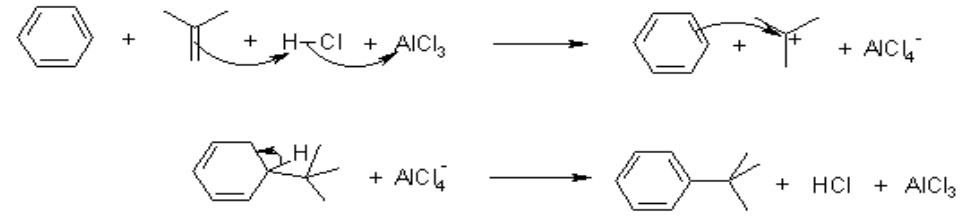
E^+ from olefins: (proton is always required)



The active E^+ generated as above attack the aromatic molecule and lead to the formation of



Using alkenes :



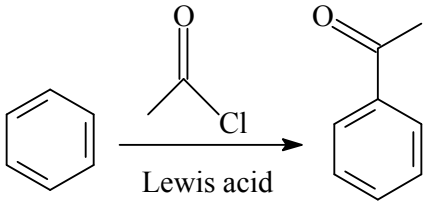
product:

Limitations of Friedel –Craft alkylation:

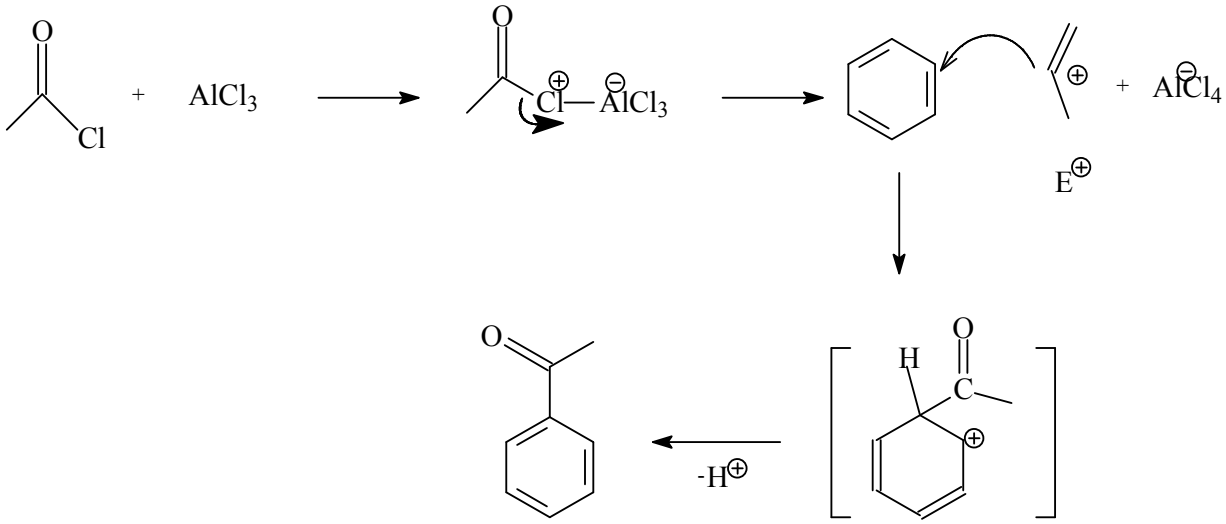
1. Generally it is not possible to introduce a 1^0 alkyl group (except $–CH_3$ and $–CH_2CH_3$) into an aromatic ring as the alkyl substituent obtained undergo rearrangement viz; alkylation of benzene by n-propyl chloride gives a mixture of n and isopropylbenzene
2. The entering group in alkylation is ring activation hence di and polyalkylation occur frequently
3. Aromatic molecules containing m-directing groups do not undergo Fridel-Craft alkylation.
4. Aryl halids cannot be used in place of alkylhalides,
5. Rearrangement can also occur after the formation of product through isomerization

4.1.6 Acylation:

Introduction of acyl group into an aromatic ring is called acylation. This reaction can also be frequently Carried out through Fridel-Craft reaction using Lewis acid catalysts.



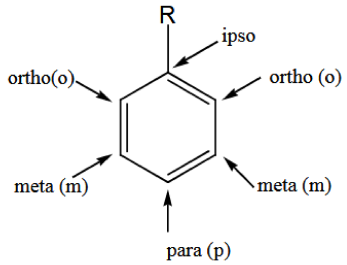
Mechanism:



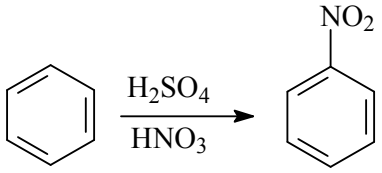
4.2 ORIENTATION AND REACTIVITY

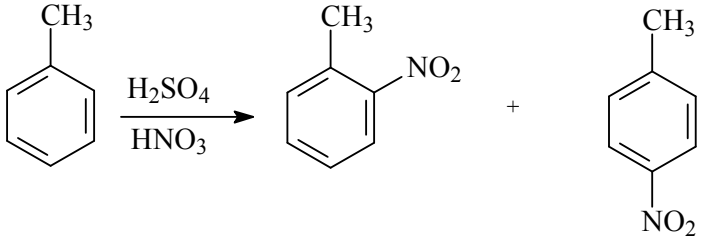
What do we mean by these terms? If we have mono substituted benzene instead of benzene itself then attack by the electrophile can occur in four possible positions (ipso, ortho, meta and para): Which of these possible sites will be attacked by a reactive E^+ is called orientation effect.

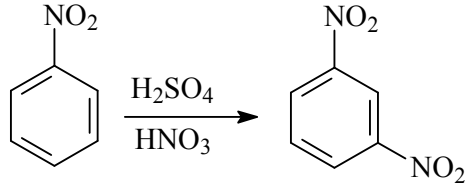
(Note: The electron density calculations based on partial rate factor can be included from Bruckner's book)



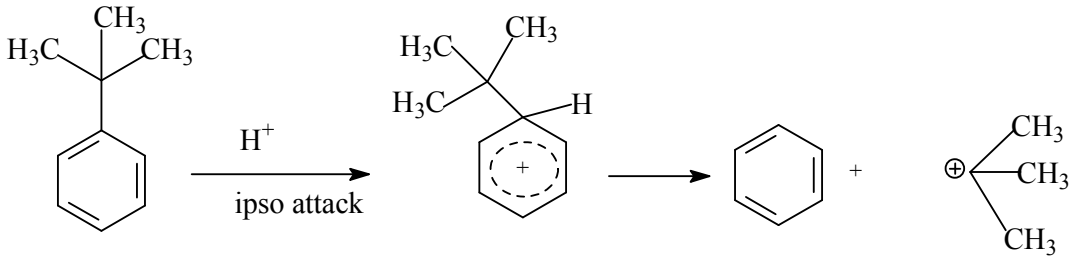
The rate of the reaction of mono-substituted benzene may be slower or faster than benzene. This is the Reactivity of the reaction. If the reaction is slower the substituent is said to deactivate the ring; if faster than it is said to be activating the ring.

I 

II 

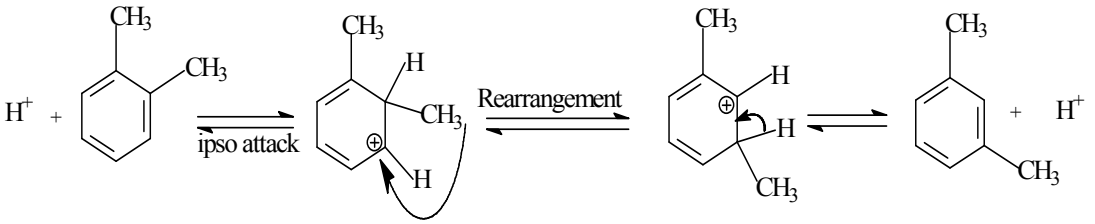
III 

In above reactions toluene II react faster and produce *ortho* and *para* product than benzene I, while nitrobenzene III is very much less reactive and give only meta product. In ipso attack a position already occupied by a non-hydrogen substituent in aromatic is replaced by attacking substituent is called ipso attack, while the position is called ipso position ipso (Latin: *ipso*, on itself)

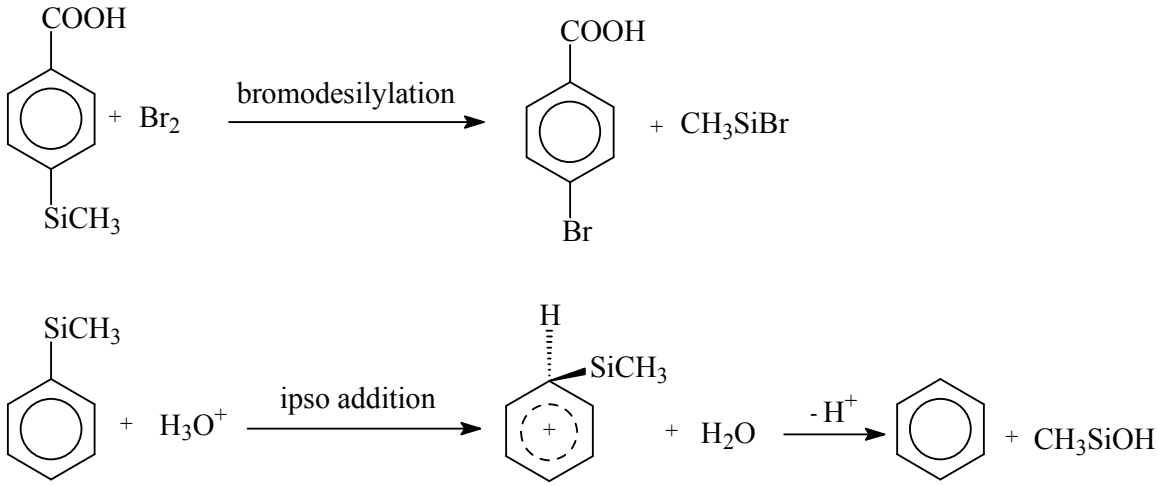


In above ipso attack the tertiary alkyl group is most easily removed, because it departs as stable 3^0 carbocation. The t-butyl group is generally used to protect the most reactive position in a compound to effect reaction at other position.

Rearrangement of alkylbenzenes leading to their isomerism also involve ipso attack viz isomerization of o-xylene to m-xylene



Other examples of ipso attack are bromodesilylation and protodesylylation as under:



In electrophilic substitution reactions of benzene derivatives, a substituent directs the incoming group either to the *ortho* and *para* positions or the *meta* positions. The *otho para* directing group increase electron density at o and p positions and decrease activation energy between T.S and substrate while the energy gap is more in meta position viz; electrophilic substitution reaction of toluene (Fig.3). The o,p director group activate the aromatic ring for further substitution(X=Cl, Br,I are exception, because in case of them -I effect of halogen atoms). The directions of uncoming electrophile in benzene ring generally depend upon the nature of key atom (the atom directly attached with benzene ring). If the key atom has loan pair of electron, it will direct the incoming electrophile to attack at ortho or para positions (-CH_3 is exception. –CH_3 is o,p director in spite of having no loan pair of electron. The reason is hyperconjugation as a result it increases electron density at *otho* and *para* positions). The orientation of attacking electrophile is also influenced by inductive and steric effect. These

effects lead to the positional and reactivity preferences as summarized in table 1-2. The activating and diacticating effect of groups have been presented in fig.4

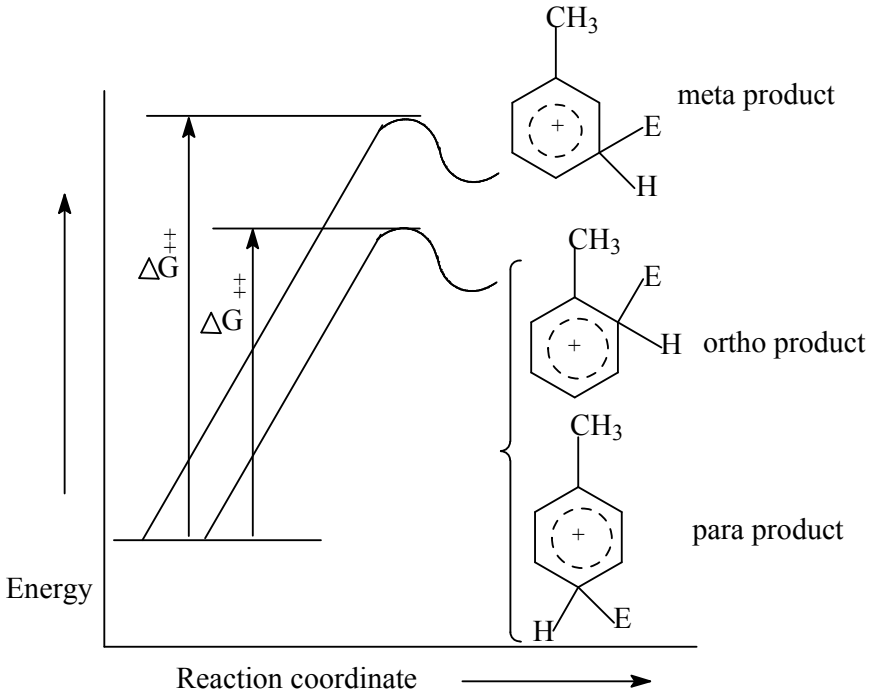
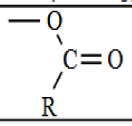
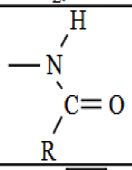
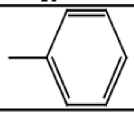


Fig 3. Energy profile activity for electrophilic substitution reaction of toluene

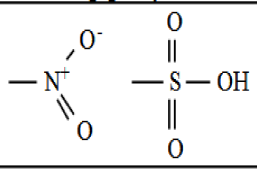
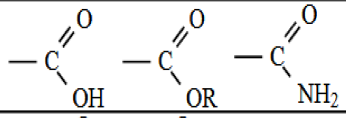
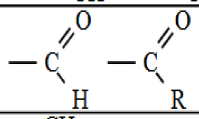
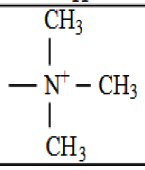
Table 1: Orientation (*ortho* and *para)* effect of groups attached in aromatic system

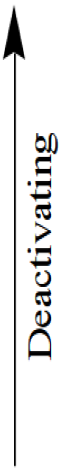
Ortho, para directing groups:	
–OH, –OCH_3, –OR	Alcohols, ethers
	Esters
–NH_2, –NHR, –NR_2	Amines
	Amides
	Phenyl rings (aromatic compounds)
–CH_3, –CH_2CH_3, –R	Alkyl groups
–F, –Cl, –Br, –I	Halides

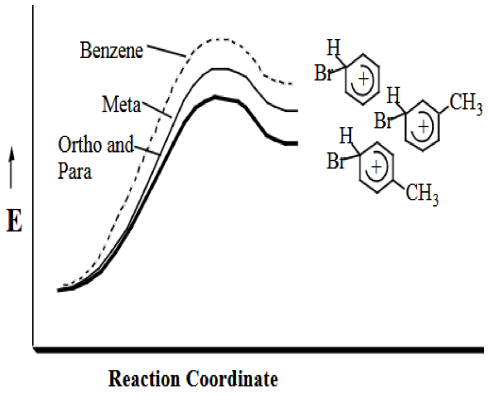
Activating

Table 2: Orientation (*ortho* and *para)* effect of groups attached in aromatic system

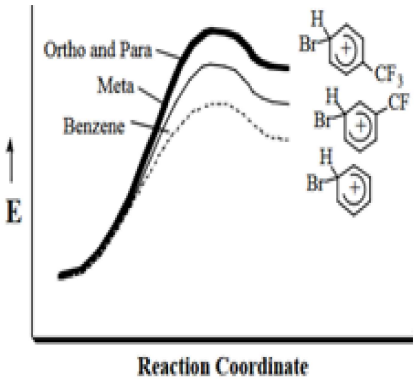
Meta directing groups

	Nitro group, sulfonic acid
	Carboxylic acid, ester, and amide
	Aldehyde, ketone
	Quaternary ammonium

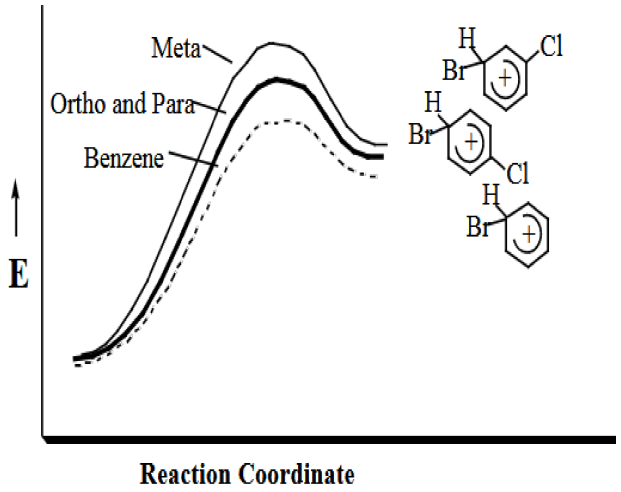




(A)



(B)



(C)

Fig.4 Energy profile diagram: (A) ortho, para director, activator (B): Meta director, deactivator: (C): Ortho, para director, deactivator

4.2.1 Electrophilic substitution in other poly-substituted benzene rings:

If two or more groups are attached to a ring, electrophilic substitution is influenced by a combination three factors

1. He position to which the attacking E^+ will be oriented by each substituent (o/p vs m)
2. He relative activating and deactivating strength of each substituent teric effect

The general orientation and activating properties of various substituents have been summarized above in tables1-2. With regard to activation and deactivation, substituents can be more precisely classified according to their relative strengths, as in table 3.

A. Whent two meta directing substituents are attached to a ring, E^+ substitution occurs with difficulty because the ring is too deactivated.

B. Feiedel-Craft alkylation and acylation do not occur if ring has only m-directing substituent.

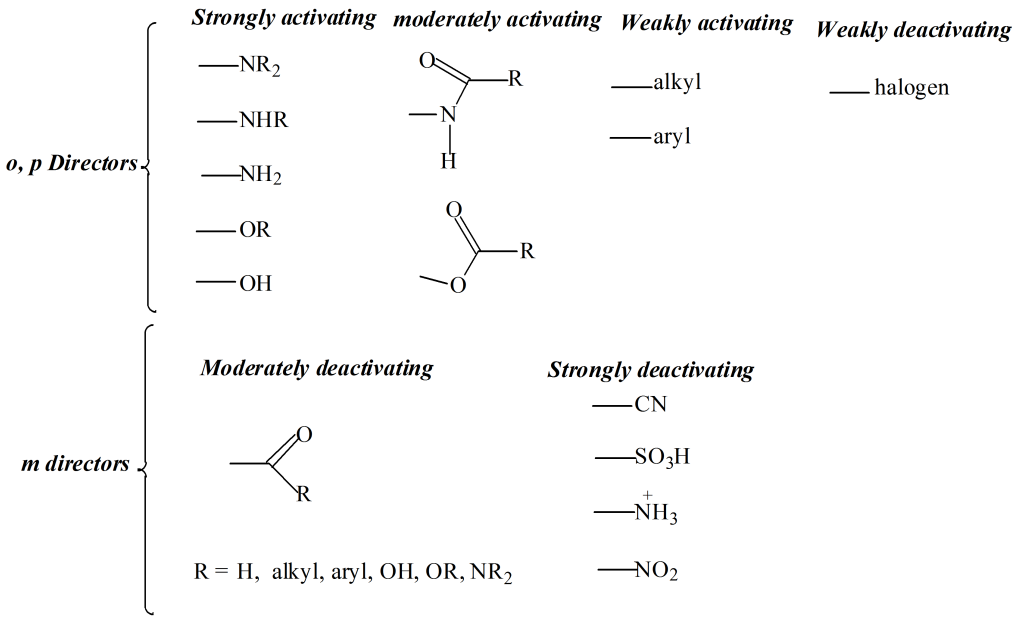
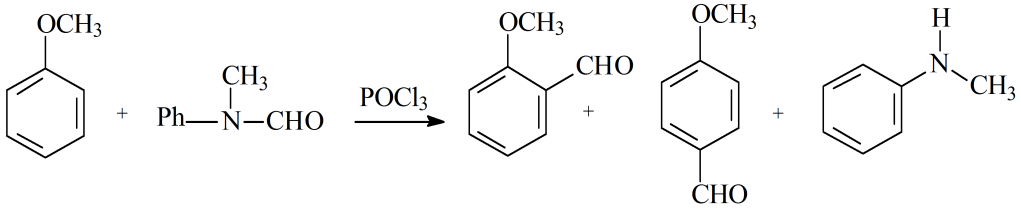


Table 3 Relative effect of activation on benzene ring by o, p-directing substituents and of deactivation by m- directing substituents

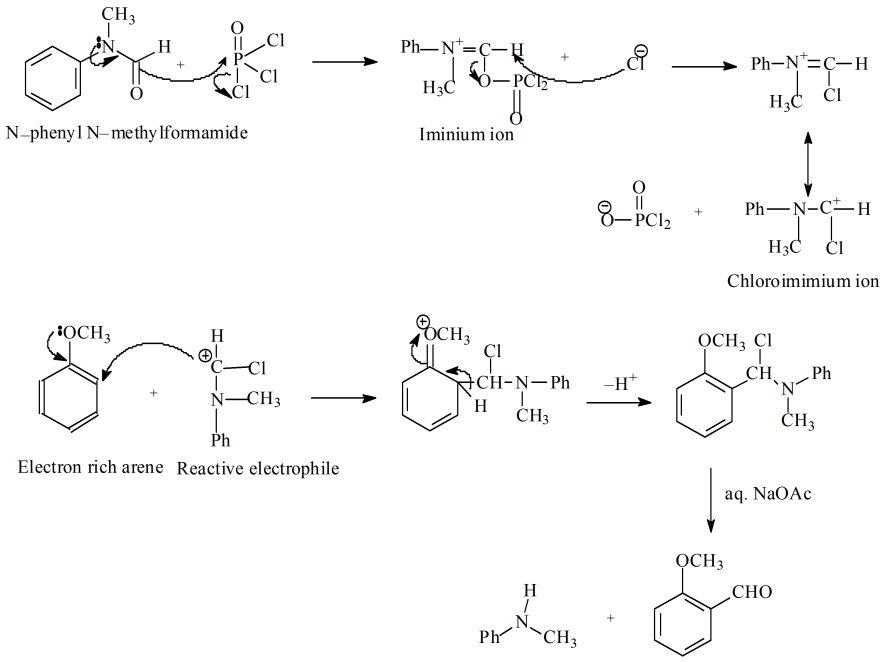
4.3 SOME NAME REACTIONS INVOLVING AROMATIC ELECTROPHILIC SUBSTITUTION MECHANISM

4.3.1 Vilsmeir reaction:

The chemical reaction of asubstituted amide with $POCl_3$ and an electron rich arene to produce an aryl aldehyde or ketone is known as Vilsmeir reaction.



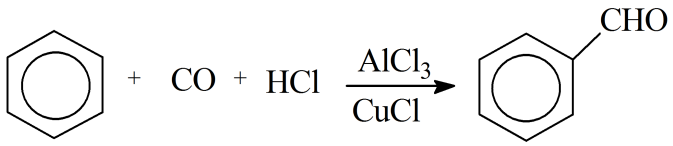
The reaction follows following mechanism:



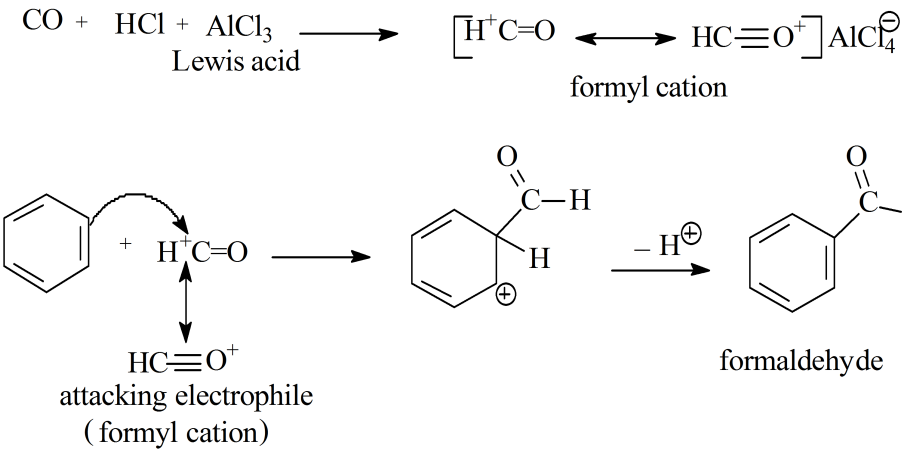
N-phenyl N- methylformamide is the most common reagent in this reaction, however substituted amides are also used. In place of $POCl_3$, other halides like $SOCl_2$, and $COCl_2$ have also been used.In all the case the reacting electrophile is always chloroiminium ion.

4.3.2 Gatterman –Koch Reaction:

The formylation of aromatic compound with CO and HCI in presence of Lewis acid is known as Gatterman-Koch reaction.The reaction require out either under pressure or using copper(I) chloride whose role may be to aid the reaction between CO and HCl via the complex which it forms with CO

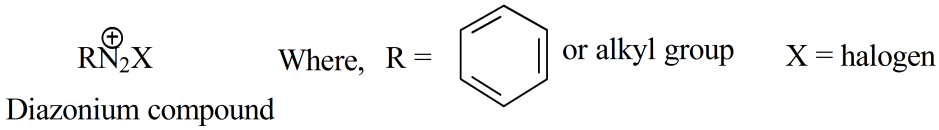


Though the mechanism of this reaction is uncertain, however probably the formyl cation is the active electrophile. The reaction takes place as follow:



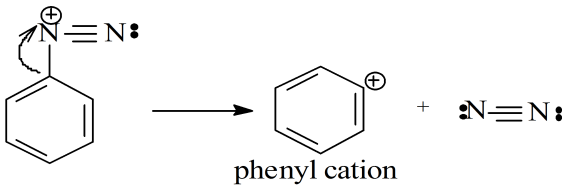
4.3.3 Diazonium compounds coupling:

Diazonium compounds are nitrogencontaining organic compounds with following functionality. Where R can be any organic group such as alkyl or aryl, while X is an inorganic or organic anion like halogen.

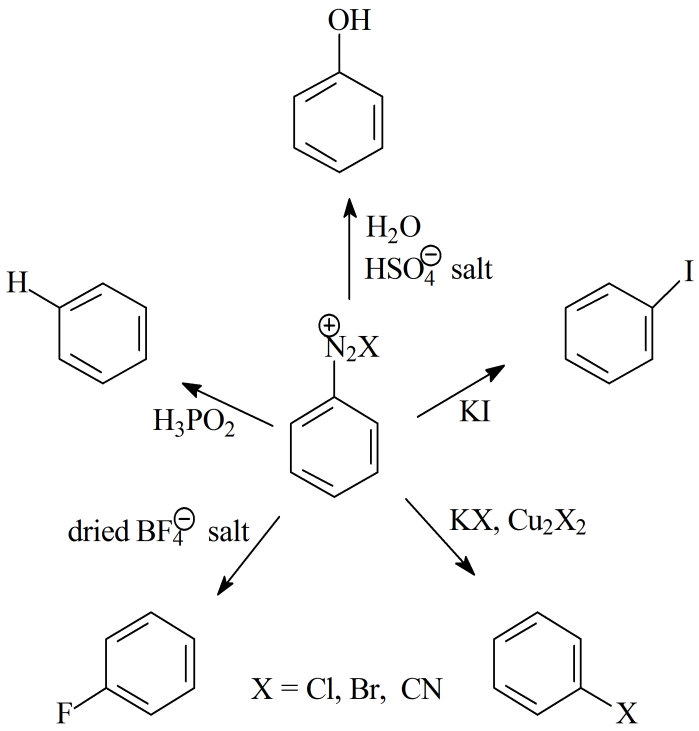


Diazonium salts especially where R is aryl group have synthetic utility as they play important role as reaction intermediate in organic synthesis.

Molecular nitrogen is the vest possible leaving group that exists, so it is dissociated as N_2 and a reactive phenyl cation is formed.

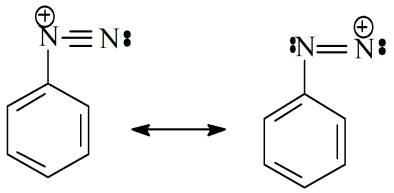


Some of the compounds synthesized by using diazonium compounds are summerised as under.



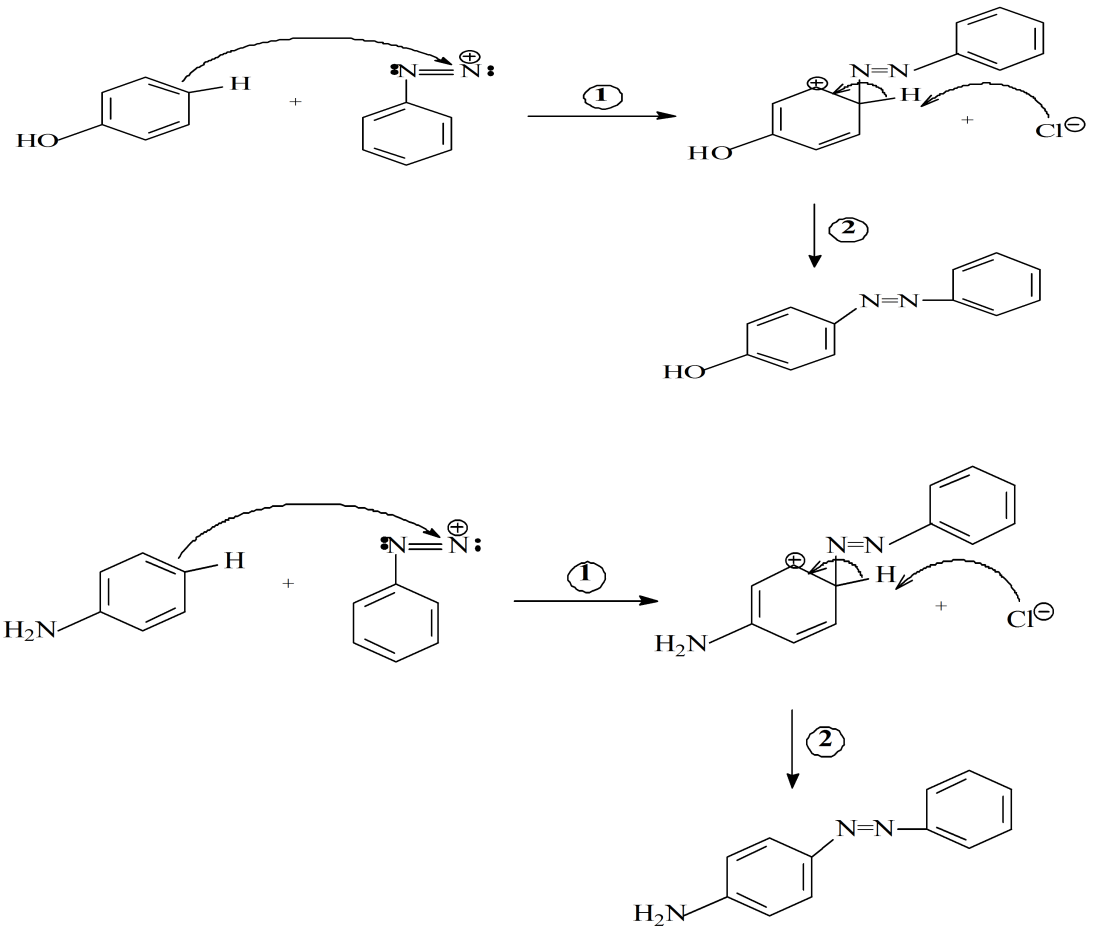
4.3.3.1 Diazonium coupling:

The diazonium ion has two resonance forms, one of which place the positive charge on the terminal nitrogen atom



If activated aromatic compounds are added to the solution of diazonium salt, then electrophilic substitution can occur. Only the most activated substrates derivatives of aniline and phenol can be employed in this reaction, because the diazonium ion is a weak electrophile.

The mechanism of coupling reaction takes place as follow:



Besides these reactions the diazo coupling reactions are used for the synthesis of organic dyes in textile industry.

4.4 SUMMARY

This chapter provides us concise knowledge about electrophile, electrophilic reactions in arene system. We studied about formation of arenium ion as aresult of attack of electrophile. We learned about how thermodynamically different orientation are possible in substituted and unsubstituted arenes. We also studied about the mechanism of important name reactions with possible products.

4.5 TERMINAL QUESTIONS

Q.1. which of the following can act as electrophile

A. $AlCl_3$

B. NH_3

C. H_2O

D. All are electrophile

Q.2. Which one of the following cannot easily undergo Friedel-Craft reaction?

A. Anisol

B. Nitro benzene

C. Toluene

D. Xylene

Q.3.Which among the following undergoes nitration readly?

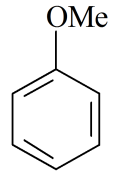
A. Benzene

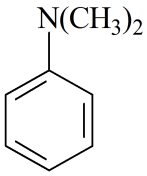
B.Acetamide

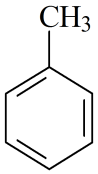
C. Acetophenone

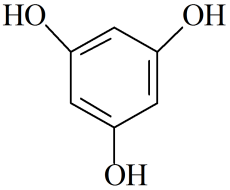
D. Chlorobenzene

Q.4. Which among the following will undergo Gatterman-Koch formylation?

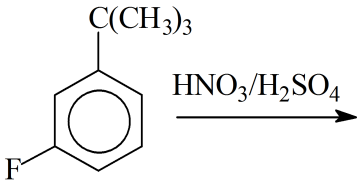
A. 

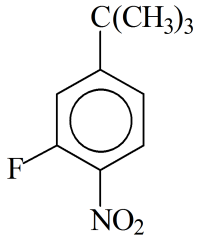
B 

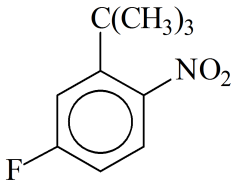
C 

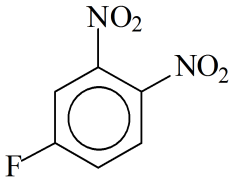
D 

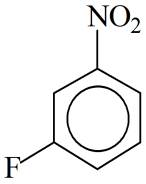
Q.5.Which in the following product is formed due to ipso substitution?



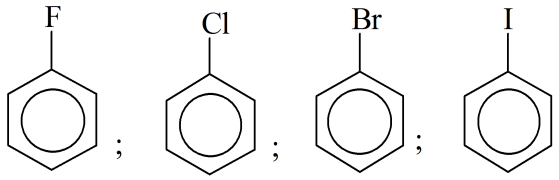
A. 

B. 

C. 

D. 

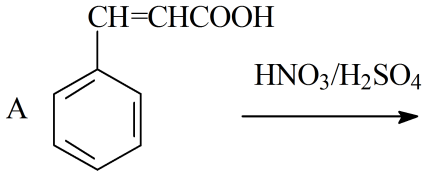
Q.6. Increasing amount of *ortho* isomers is obtained on nitration in the series:

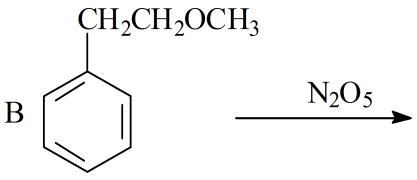


explain.

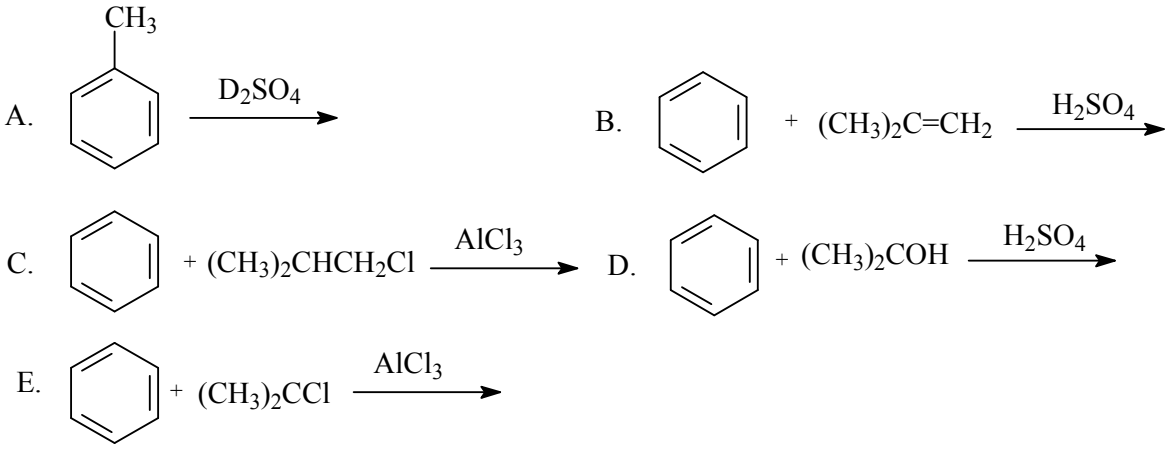
Q.7. Why nitration of anisol with fuming HNO_3 in Ac_2O gives mainly *ortho* product, while with mixed acid *para* isomer is chief product?

Q.8. what are the major products in following reactions?





Q.9. Predict the product (s) and indicate the active electrophile in each of the following reactions:



Q. 10. Explain why aniline is more reactive than actanilide in electrophilic substitution reaction?

4.6 ANSWERS TO THE TERMINAL QUESTIONS

1. A

2. B

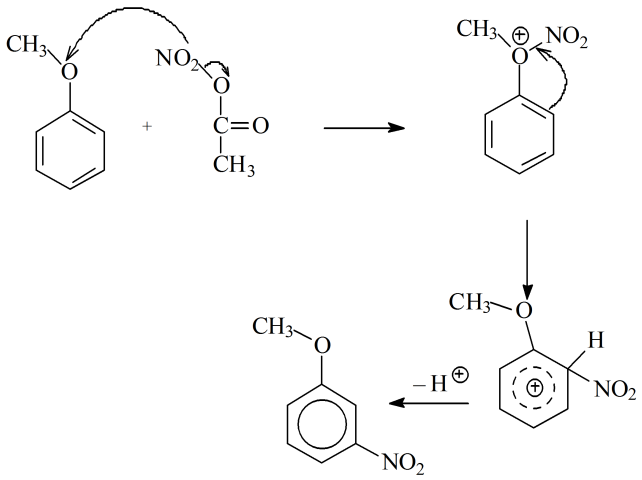
3. B

4. C

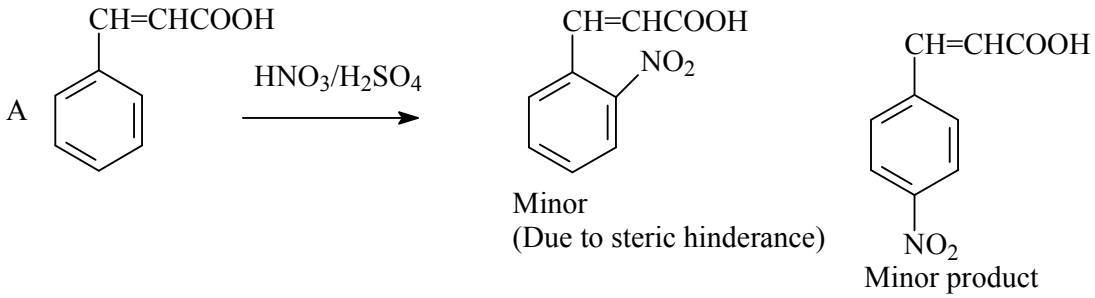
5. D

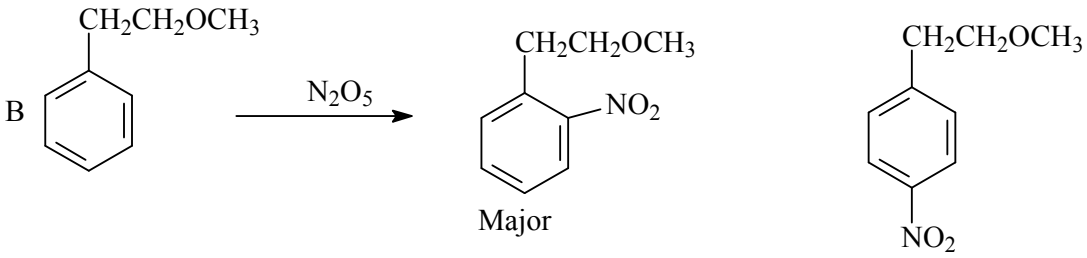
Q.6 this is because the deactivation effect at the *ortho* position decreases with the decreasing electro negativity from F to I.

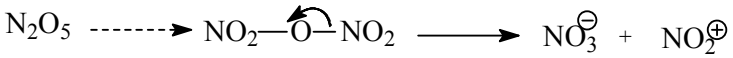
Q.7 In the case of fuming HNO_3 in Ac_2O the nitrating agent is acetyl nitrate which intrects with the methoxy group resulting in predominant formation of the ortho isomer as shown in the reaction. On the other hand, in the case of mixed acid the nitrating agent as NO_2 this is free to attack at the less hindered para position to give para isomer predominantly. See following reactions



Q.8 Ans.

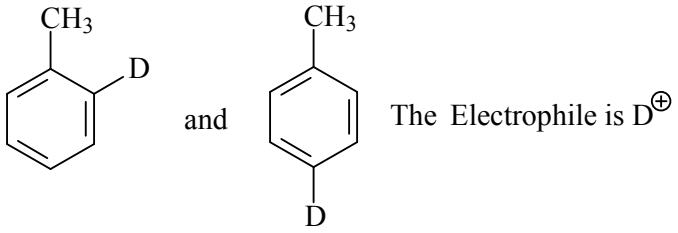






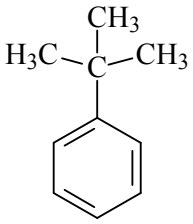
Intrect with methoxy group

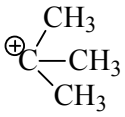
Q.9. The product for A is:



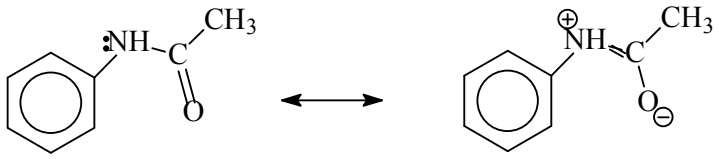
The Electrophile is $D^{\oplus}$

For B. C D and E the product and electrophile is:



The active electrophile is 

Q.10 In case of aniline the nitrogen contains loan pair of electron and participate in resonance with benzene ring as a result increase electron density at *ortho* and *para* position hence more reactive for electrophilic substitution. In acetanilide the electrons on nitrogen are involved in resonance with adjacent carobyl group and are less available for donation towards benzene ring at the same due to resonance with carbonyl group the nitrogen acquire partial positive charge which further exert great electron withdrawl from benzene than aniline.



4.7 REFERENCES

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UNIT-5 ELIMINATION REACTIONS

CONTENTS:

5.0 Objectives

5.1 Introduction

5.2 E2 Elimination Reaction

5.3 E1 Elimination Reaction

5.4 E1CB Elimination reaction

5.5 E2C Elimination reaction

5.6 Orientation of the double bond

5.7 Reactivity effects of substrate, attacking base, leaving group and solvent medium

5.7.1 Factors effecting E2 Elimination

5.8 Mechanism of pyrolytic elimination reaction:

5.9 Cope elimination

5.11 Saytzeff elimination

5.12 Hofmann Elimination

5.12 Summary

5.13 Terminal Question

5.14 Answers (MCQ) terminal questions

5.15 References

5.0 OBJECTIVES

Objective of this chapter is to provide students with a concise detail on the elimination reactions. The topics covered in this chapter will be types of elimination reactions like E1, E2, E1CB etc. Mechanism of elimination reaction and direction of double bond formed as aresult of elimination. Discussions of Pyrolitic elimination and Satyzeffs elimination besides Hoffman and Cope eliminations. The chapter is developed to stimulate interest of the reader into the elimination reactions and to build the deep understanding of the fundamental mechanisms. To offer students an easy and interesting learning experience, each of the topics is covered with struct

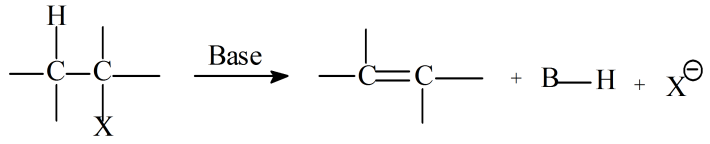
5.1 INTRODUCTION

The elimination reactions are the organic reaction in with two substituents from a molecule are eliminated in asingle or two steps. These reactions are carried out inpresence of acid or base or some time throufg pyrolysis. During elimination reactions two sigma bonds are broken and a pi bond is formed. In most organic elimination reactions, at least one hydrogen is lost to form the double bond. An important class of elimination reactions is those involving alkyl halides, and alcohols. The halogens are considered to be good leaving group.The elimination reactions are reverse of addition reactions.When the substrate molecule is asymmetric; the regioselective products are formed in elimination reaction. The elimination reactions occur via three distinct mechanisms, viz; E_1, E_2, E_{1CB}

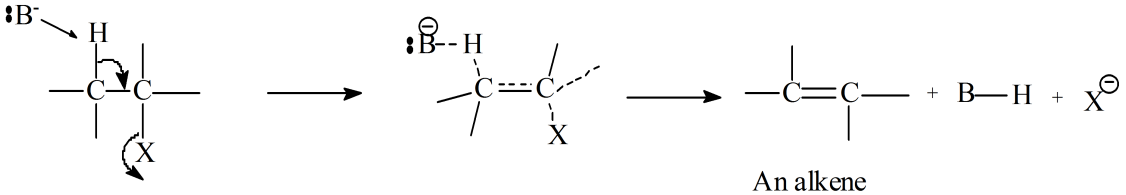
5.2 E2 ELIMINATION REACTION

E_2 elimination reaction is a single step reaction and facilitated through a transtition state. 1^0 alky halides generally undergo E_2 elimination but some time are possible in 2^0 halides and other compounds.Since it is a biomolecular reaction and rate of reaction depends upon the concentration of both substrate and reagent (base) hence follow second order kinetics. The E2 mechanism results in the formation of a π bond, the two leaving groups (often a hydrogen / halogen) should be in antiperiplanar (staggered) orientation. Because this orientation has minium energy and are thermodynamically stable than syn- periplanar (eclipsed) therefore the reaction mechanism involving staggered conformation is more favorable for E2 reactions (unlike E1 reactions). The elimination reaction to occur E_2

typically uses a strong base which can remove the weakly acidic hydrogen.The hybridization stae of carbon should be lowered from sp^3 to sp^2 in order to form π- bond. E_2 elimination reactions compete with the mechanism, if the base can also act as a nucleophile.



Mechanism:



Antiperiplanar orientation

Intermediate transition state

An alkene elimination product

Rate = k [RX] [B-]

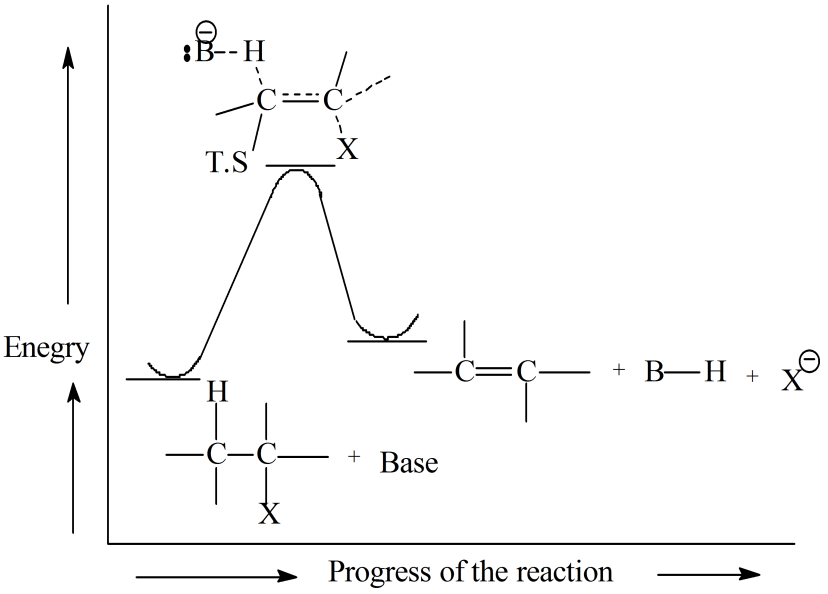


Fig1 Enerrgy profile diagram of E_2 reaction

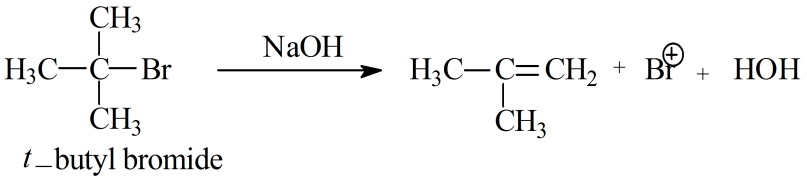
5.3 E1 ELIMINATION REACTION

- It is a two step reaction. The first step is a unimolecular ionization of the substrate to form carbocation. It is a slow and rate determing step.

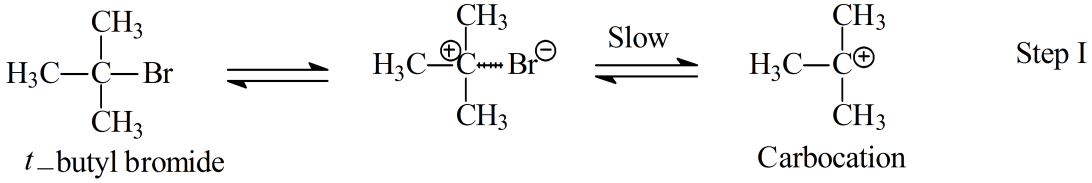
- In second steps the base abstract proton on the adjacent carbon atom to form a double bond. It is fast step
- In first step ionization is favourd by electron releasing group
- The composition of product (alkene) in E1 elimination generally follow the Saytzeff orientation
- During E1 elimination the carbocation intermediate is expected to two competeting reactions: S_N1 or proton removal E1. A strong base favor E1 path over S_N1.

E1 Mechanism:

The hydrolysis of t-butyl bromide in presence of NaOH is an example of E1 elimination



t–butyl bromide



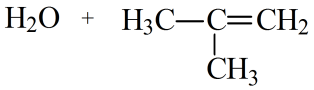
t–butyl bromide

T.S I

Carbocation

T.S. II

Fast



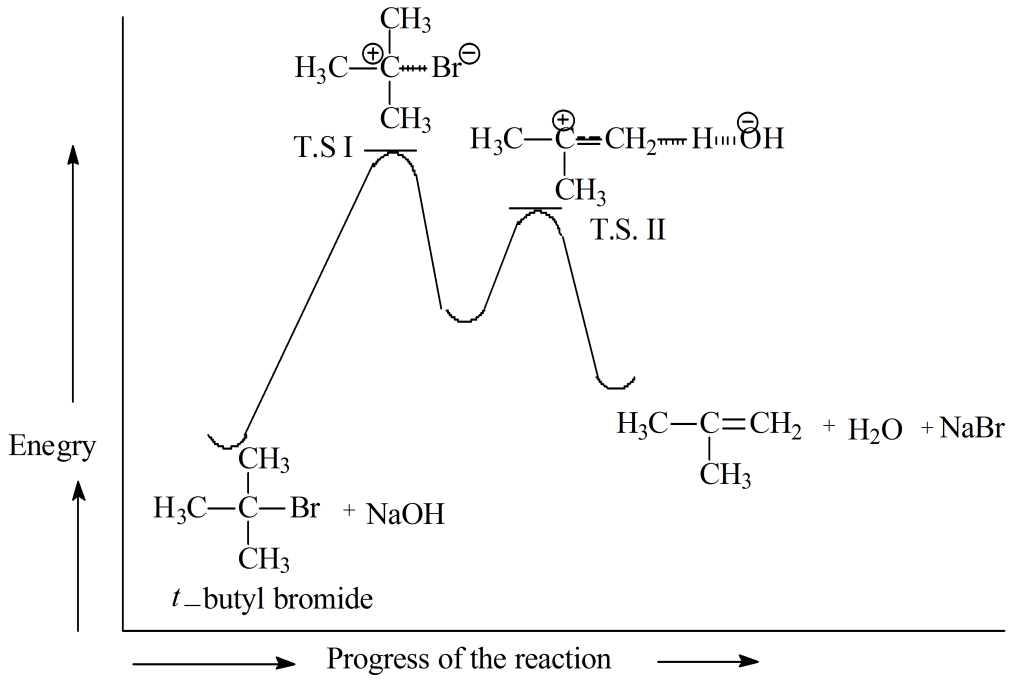


Fig.2 Enerrgy profile diagram of E_2 reaction

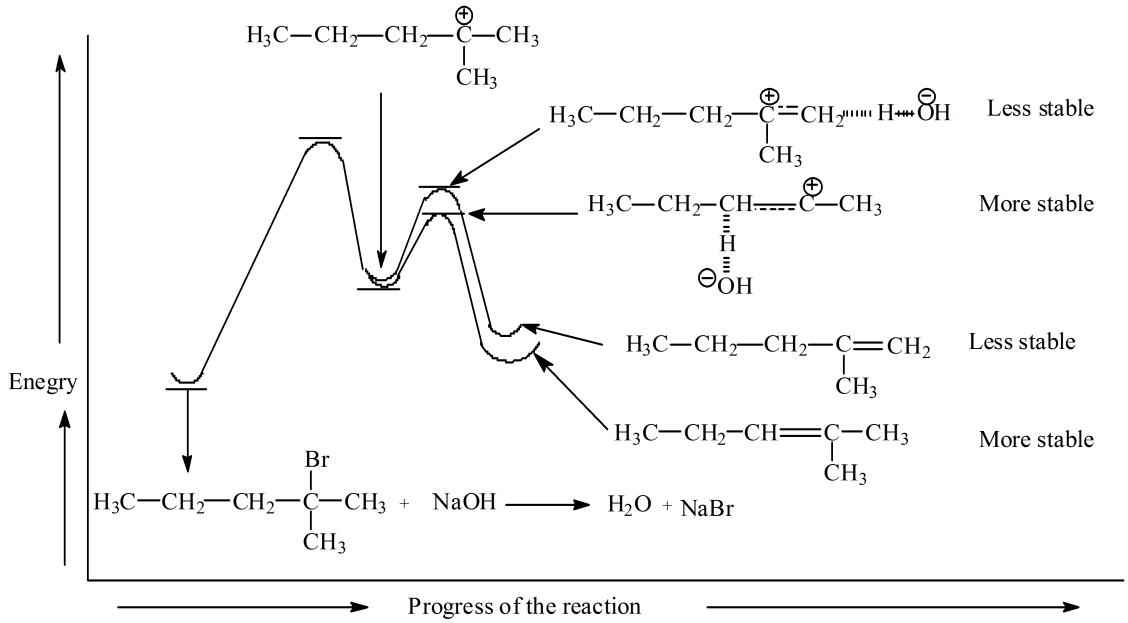
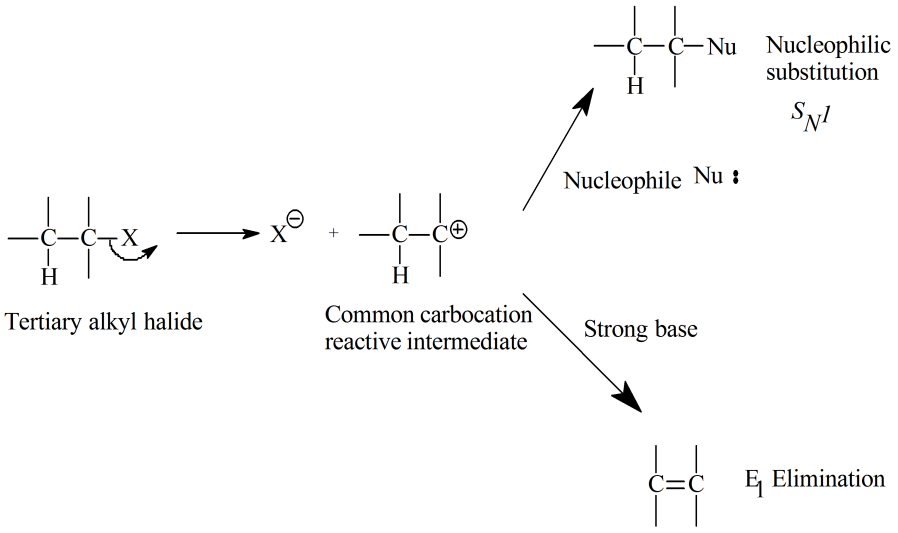


Fig: 3 Orientation of double in E_1 elimation follow Saytzeff's orientation

There is always a competetive reaction between Elimination and Substitution reactions. Depending upon the availability of a strong nuleophile or a strong base the common carbocation undergo substitution or elimination reaction as follow.



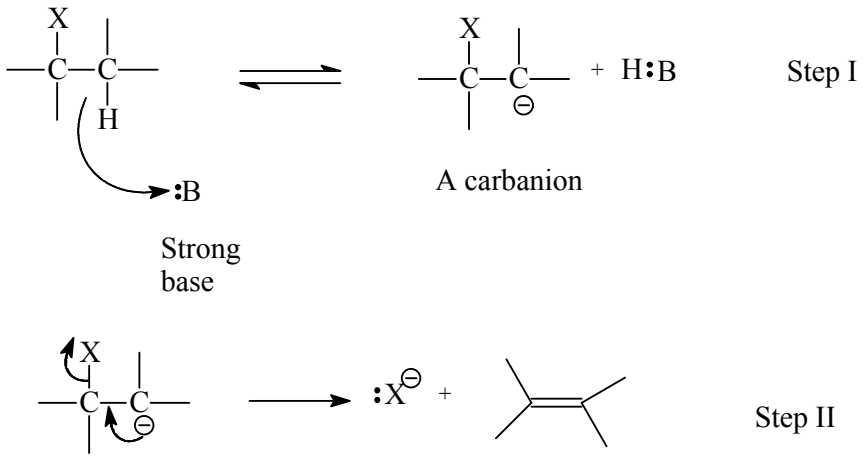
5.4 E_1cB ELIMINAYION REACTION

This reaction stands for elimination, unimolecular of the conjugate base. It is a two step reaction and occur via carbanions in first step.E_1cB mechanism is limited to substrates with substituents which can stabilize the carbanion intermediate i. e. the leaving group is β to a carbonyl, nitro, cyano,sulphonyl or other carbanion stabilizing group.

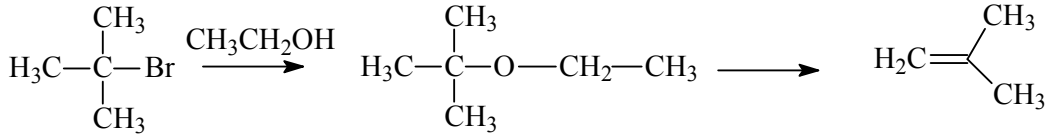
The reaction is second order in kinetics like E_2 reaction

Rate=K[alkyl halide(substrate)][Base]

The leaving group in E_{1cB} reaction is generally poor, while the β-hydrogen should be highly acidic so that carbanion mau form eaisy.since the reaction takes place through conjugate base of the starting material hence designated as E_1cB reaction. The E_1cB reactions generally compete with E_2 elimination, however E_1cB are less common than E_2 reactions. Indeed very small percentage of elimination follow this path.The mechanism of E_1cB is as follow.



Example: reaction of t-butylbromide with ethanol:



periods

ethyl t - butyl ether

nucleophilic product

2 –methylpropene

elimination product

5.6 ORIENTATION OF THE DOUBLE BOND

During elimination reactions when two β-hudrogen atoms can be eliminated, an alkene mixture is formed. The formation of an alkene with more substituted alkene us considered to be most stable and called Saytzeff's orientation while in the formation of less substituted alkene product is said ti be Hoffmann's orientation.

The preferred direction of double bond in E_2- elimination may be because of intermediate transition state.The two T.S. in the case of E_2 elimination resemble E_1 and E_{1cB} mechanism in their orientational effect.

The leaving group also also effects the orientation of double bond. Poorer is the leacing group the more E_{1cB} like is the transition state (Hoffmann orientation). The positively charged leaving group may also favor E_{1cB} reactionsince their field and inductive effect increase the acidity of the β-proton. Besids this direction of elimination is also determined by stearic hinderance. The orientation of double bond in detail is being described in following sections;

5.7 REACTIVITY EFFECTS OF SUBSTRATE, ATTACKING BASE, LEAVING GROUP AND SOLVENT MEDIUM

As discussed above in section 5.6 the orientation of double dependes upon various factors like substrate, reagent, leaving group, medium etc.

5.7.1 Factors effecting E2 Elimination:

1. Substrate: It has been found that branchin at α and β- carbon increases the rate of E_2 reaction. The reason is as the number of substituents increases on carbon atoms of the developing double bond, the stabilitu of T.S. increases. The presence of electron withdrawing

group at β-carbon enhances E2 elimination because of –I effect, which increase the acidity of β-hydrogens and stablise the carbanion chacter of the T.S.

The rate of S_{N2} reaction is slowed down because of steric strain at α and β carbon, while it is branching at α and β carbon increase the rate of elimination reaction.

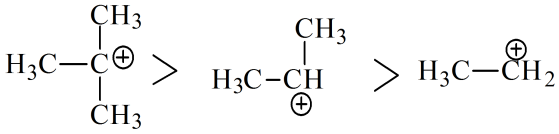
The table-1 as follow show the rate and yield of elimination reactions because os substrate in E2 elimination

Table 1: Structure of substrate and E_2 reactions

Substrate	**Yield (%)**	**Rate of reaction at 25^0C**
$H_3C—CH_2—Br$	0.9	1.0×10^5
$H_3C-\underset{\displaystyle CH_3}{\underset{\vert}{CH}}-Br$ branching at alpha	80.3	2.3×10^5
$H_3C—\underset{\displaystyle CH_3}{\underset{\vert}{\overset{\displaystyle CH_3}{\overset{\vert}{C}}}}—Br$ branching at alpha	97	4.7×10^5
$H_3C—CH_2—CH_2—Br$ branching at beta	8.9	5.3×10^5
$H_3C-\underset{\displaystyle CH_3}{\underset{\vert}{CH}}-CH_2-Br$ branching at beta	59.5	4.5×10^5

The table also predicts that the order of reaction in alkyl halides is: $3^0 > 2^0 > 1^0$

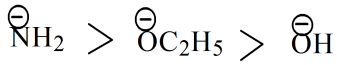
E_1 reactions takes place by the formation of carbocation as reaction intermediate.The rate of E_1 reaction thus depends upon stability of carbocation. Because +I effect and hyperconjugation effect stabilize the carbocation in following order



Further steric strain around leaving group also favours the formation of carbocation. Thus the alkyl or aryl group on α and β –carbons with respect to leaving group increase E_1 reactions.

2. Strength of base:

With the increasing basicity of the base being used in elimination reaction, the rate of E2 reactions have been found to increase for eample the basic strength and order of rate of E2 elimination among three bases is as under

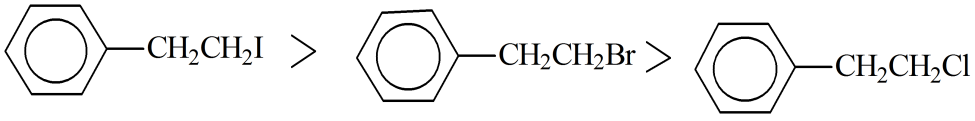


However, when the base is weak and stron nucleophilic towards carbon then the ratio E_2/S_{N2} decreases while if it is strong then the ratio is increased.

In E1 elimination the reactions generally do not require any base because of first order reaction kinetics and the purpose is also served by solvent in rate determining step which themselves hehave as base. The con and strength has nothing to do with E_1 reactions.

3. The nature of leaving group:

Better the leaving group, the higher the rate of the E_2 elimination. Thus when β-phenyl halids are treated with $NaOC_2H_5$ in C_2H_5OH the rate of E_2 reaction increasese with leaving power off halogenatoms as under



It has also been found that increasing size of halogen atom increases the ratio of E_2/S_{N2} but to a minimum extent.

In E_1 reactions the reactivity of the substrate depends mainly on the nature of the departing group. The best leaving groups are those which are **least basic and more polarizable.** Thus the decreasing oreder of leaving group reactivity is:

4. Nature of solvent: $I^{\ominus} > Br^{\ominus} > Cl^{\ominus} > F^{\ominus}$

The E_2 elimination reactions are favoured in less polar or aprotic solvents.Because the less polarsolvents favour the formation of the transition state of the reaction.The ratio of E_2/S_{N2} increase as the solvent polarity decreases

Comparasion between E_2 and S_{N2} reactions is as under in table-2

Table 2: comparasion between E_2 and S_{N2} reactions

S.N.	Reaction parameters	S_N2	E2
1	Step	Single	Single
2	Reagent	Strong bucleophile	Stron base
3.	Solvent	Aprotic solvent favour this reaction	Aprotic solvent favour this reaction
4.	Phse transfer catalyst	Favour	Favour
5.	Substrate	$1^0 > 2^0 > 3^0$	$3^0 > 2^0 > 1^0$
6.	Kinetics	II^{nd} order	II^{nd} order
7.	Stereochemistry	Inversion of configuration	Anti elimination (in pyrolytic reactions syn-elimination)

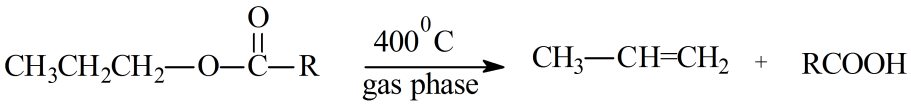
Since E1 elimination reactions involve ionic reaction intermediate, the carbocation. Thus the rate of reaction increases with increasing polarity of the solvent .i.e. E1 elimination reactions are favoured in protic solvents. Since E_1 reactions enerally competye with S_{N1} reaction ,then the comparasion between with respect to various reaction parameters becomes essential. The comparasion is as follow in table 3.

Table 3: comparasion between E_2 and S_{N2} reactions

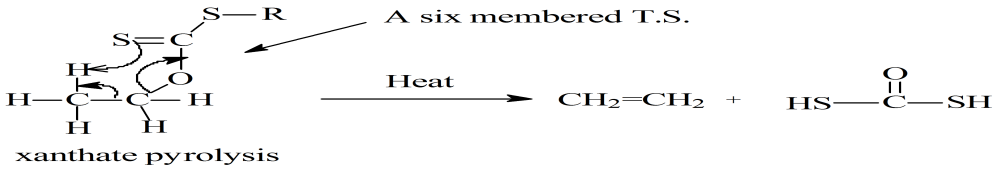
S.N.	Reaction parameters	S_N1	E1
1	Step	Two	Two
2	Reagent	Favoured by weakly basic reagent of low con.	Favoured by weak base
3.	Solvent	Polar protic	Polar protic solvents
5.	Substrate	$3^0 > 2^0 > 1^0$	$3^0 > 2^0 > 1^0$
6.	Kinetics	I^{st} order	I^{st} order
7.	Stereochemistry	Racemeic mixture	Non streospecific

5.8 MECHANISM OF PYROLYTIC ELIMINATION REACTION

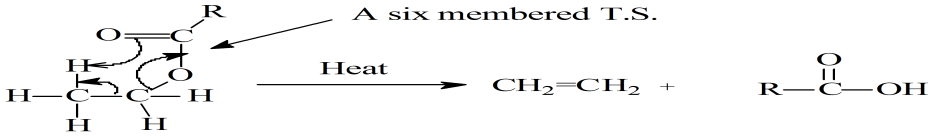
The elimination reactions which do not require any reagent like base for elimination but are facilitated through acyclic transition by involving one molecule of the substrate in presence of heat is known as pyrolytic elimination.Esters and amine oxides are the examples of two substrate which do not require base to promote elimination. In these compounds heating provides sufficient energy for the leaving group to function as a nitermolecular base.The thermal cleavage of molecules are termed pyrolysis (E_i –elimination internal). The organoselenium analoge of amine –oxide and sulfoxides provide good alkene precursors, which require room temperature conditions and give good yield of alkenes.



Mechanism:



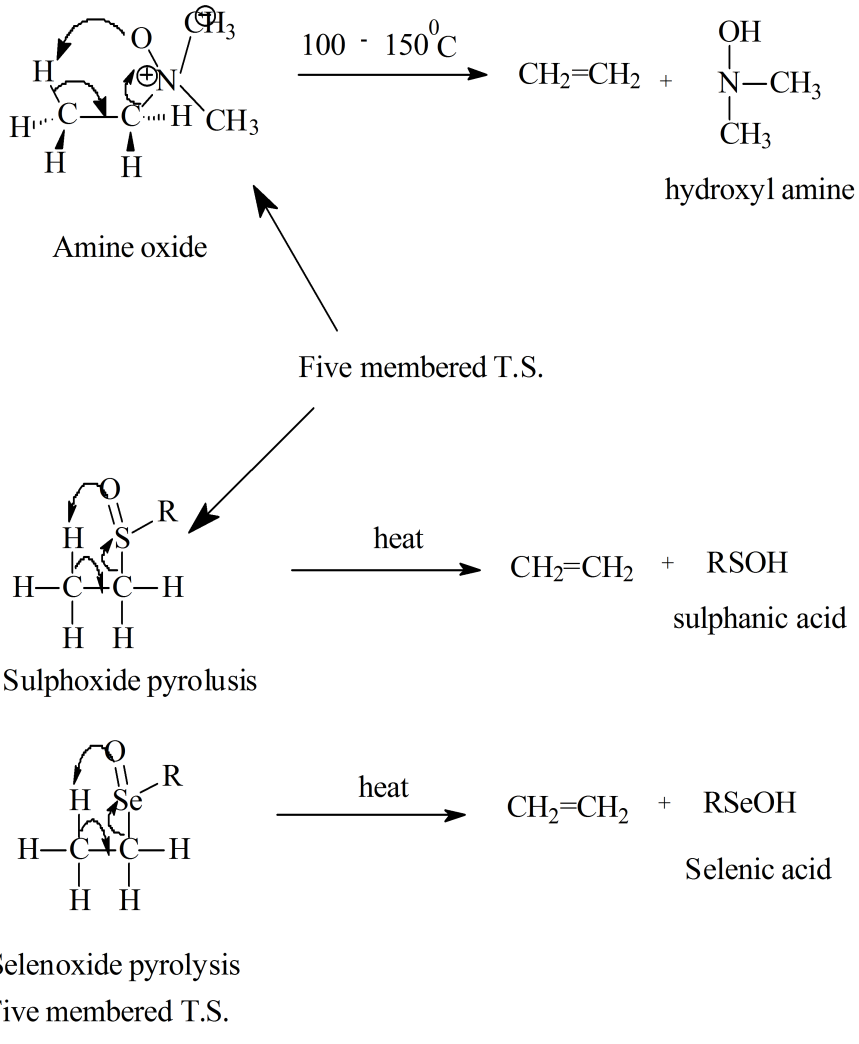
xanthate pyrolysis



Ester pyrolysis

5.9 COPE ELIMINATION

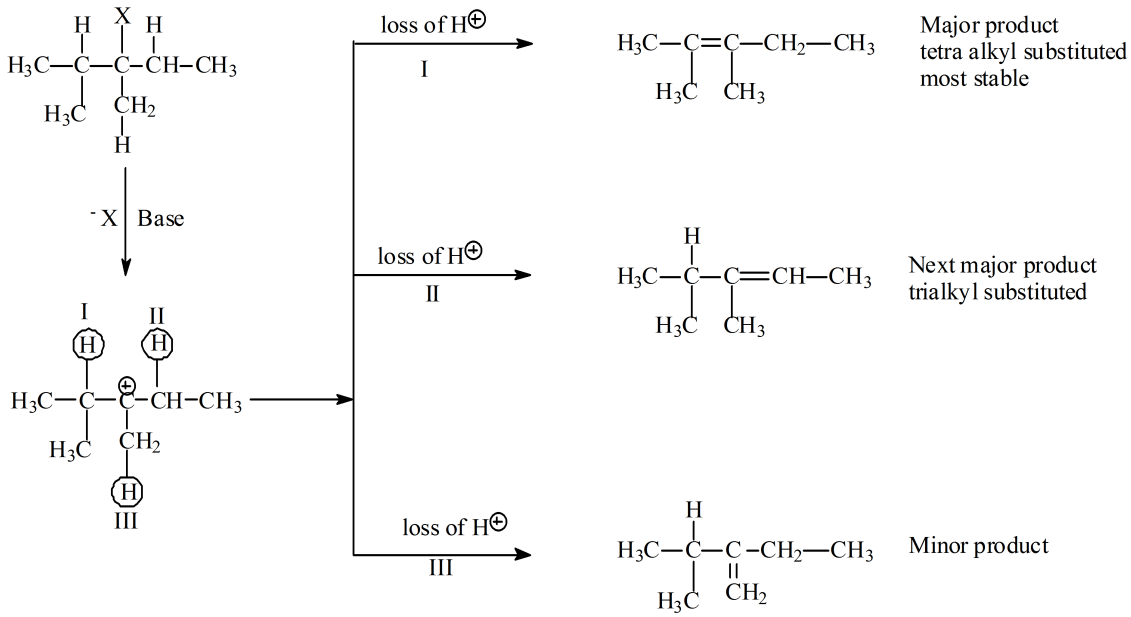
The cope elimination involves the cleavage of amine oxide, sulfoxide or selenoxide to give alkene through five membered cyclic T.S. when heated. In this reaction the elimination takes place on the same face i.e. syn elimination. And the substrate must be planar in geometry. During this elimination reaction The amine oxiode sulfoxide and or selenoxide act as its own base and facilitate the elimination of neural molecules like hydroxylamine, sulfenic acid and selenic acid and result the formation of an alkene as follow.



5.10 SAYTZEFF'S ELIMINATION

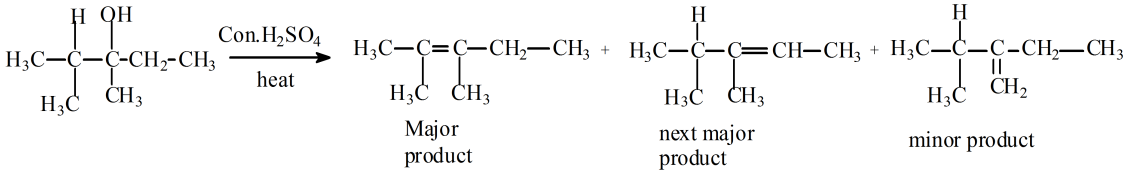
Elimination reactions which decides regeoslectivity i.e. orientation of double bond is called Saytzeff's rule and the orientation is called Saytzeff's orientation. According to this rule the in mixture of eliminated product the major product is that which contain maximum no of alkyl substituted double bonded carbon atom because of thermodynamic stbility as shown in fig 2.

The mechanism of Saytzeff's elimination is as follow:



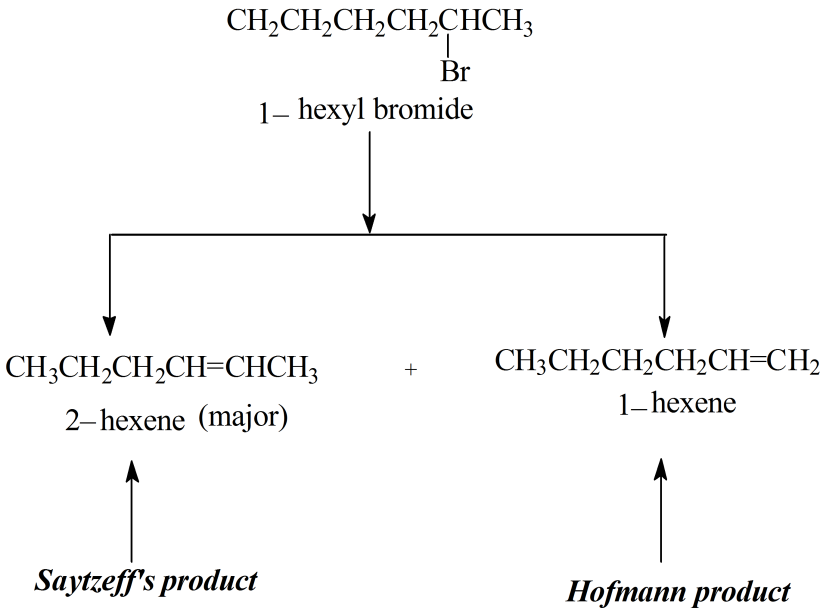
So far stability order of the product is concerned as in above case it is I>II>III because as the number of substituent α to the double bonded carbon will increase, the number of hyperconjugative structures will increase that provides stability to the molecule.

The alcohols also undergo Saytzeff's reactions when dehydrated in presence of con H_2SO_4 and than heated.

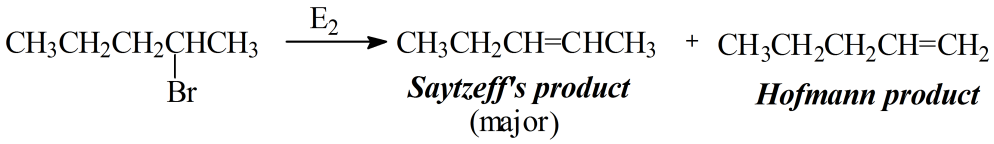


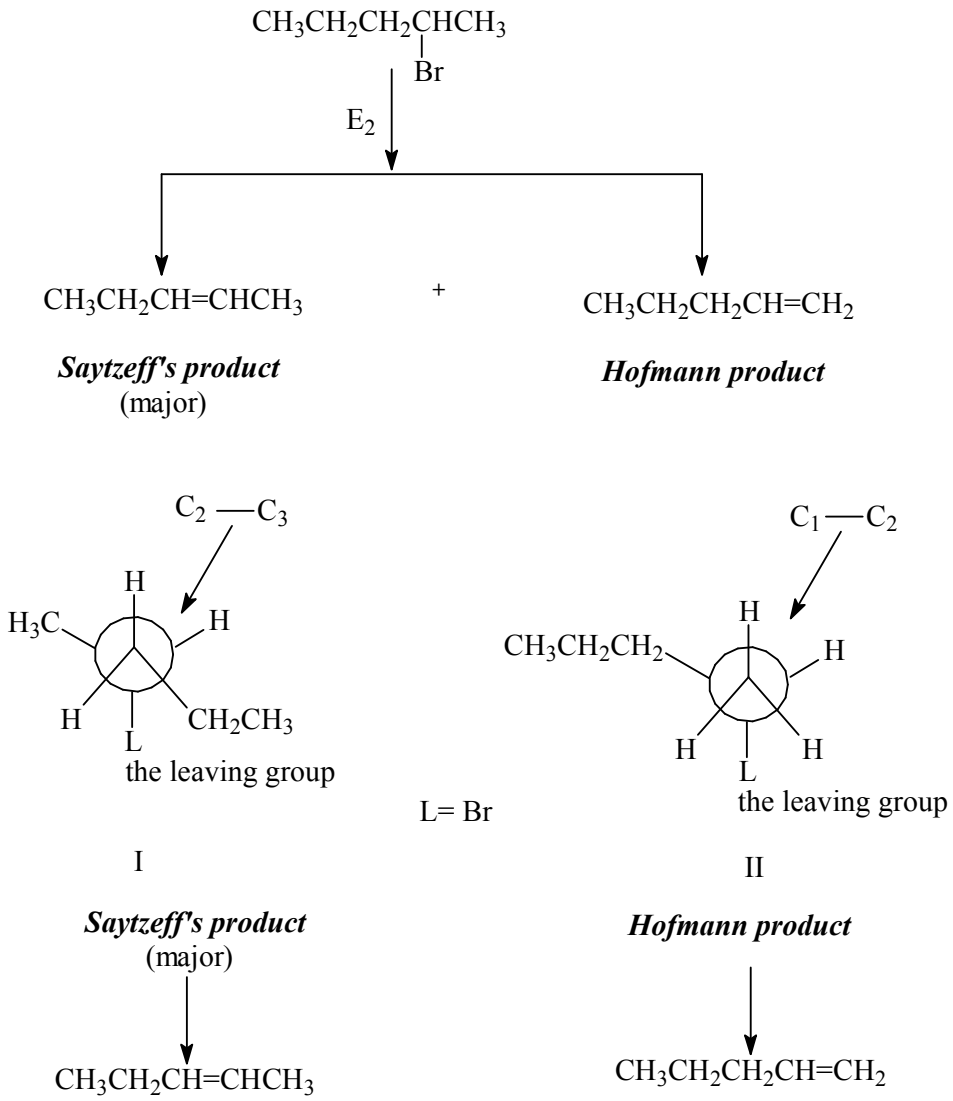
5.11 HOFMANN ELIMINATION

When the least substituted alkene is favoured product in elimination, than it is called Hofmann's orientation and the elimination is called Hofmann's elimination.



Similarly debromination of 2-bromo pentane gives 2-pantene and 1-pantene respectively upon elimination of HBr from 2-bromo pentane. In this reaction regioslecetively the double bond is oriented either to give Saytzeff's elimination or Hofmann's elimination to give less substituted alkene. Conformationally it can be explained that the steric effect is the important factor to give two different products. The anti elimination of 2-bromopentane could occur via two most stable conformations (staggered) I and II as follow (L= leaving group, -Br). Bothe the conformation are present in solution and the major elimination occurs through conformation I to give the thermodynamically more stable product, which is the more highly substituted alkene i.e. 2.pentene.





(Note: Discussion of E1 reactions are not proportionate further SN/Elimination reaction competition needs more space).

5.12 SUMMARY

This chapter was aimed to enhance the knowledge of students about elimination reactions. In this unit the mechanism of various types of elimination reactions was discussed alongwith their energy profile diagrams. The orientation of double bond in product which is resulted by the loss of two sigma bond was discussed. The factors like nature of substrate undergoing elimination reaction, base, and solvent medium has been discussed with suitable example. Most of the organic reactions undergo elimination without external base generally by heating known as pyrolytic eliminations have also been discussed. The unit is also helpful to understanding the Cope, Saytzeff's and Hofmann's elimination processes. Last but not least the there is a competition between nucleophilic substitution and elimination reactions.This chapter provide the feasibility and possibility of nucleophilic or elimination reactions.

5.13 TERMINAL QUESTIONS:

Q.1 Tick the correct options.

i Which of vthe following compounds undergo thermal elimination reaction

A. Acetate

B. Chlorides

C. Bromides

D. Alcohols

ii Reaction intermediate in E_{1cB} reaction is:

A. Carbocation

B. Carbanion

C. Cyclic T.S.

D. Carbene

iii Reaction intermediate in E_1 reaction is

A.Carbocation

B.Carbene

C. Cyclic T.S.

D. Carbanion

iv Which one of the following is correctly matched

A. Saytzeff's rule, least substituted alkene

B. Hofmann rule, most substituted alkene

C. E_{1cB} reaction, Hofmann elimination

D. E_1 reaction, Hofmann product

v Which one of the following alcohol will give E_1 elimination reaction ?

A. CH_3CH_2OH

B. $CH_3CH_2CH_2OH$

C. $C(CH_3)_3CH_2CH_2CH_2OH$

D. $C(CH_3)_3CH_2OH$

vi. In which reaction product formation takes place by Hofmann rule?

A. $CH_3CH_2CHBrCH_3 \xrightarrow[\text{heat}]{(CH_3)_3COK}$

B. $CH_3CH_2\underset{\displaystyle OAc}{\underset{|}{C}}HCH_3 \xrightarrow{\text{heat}}$

C. $CH_3CH_2\underset{\displaystyle \overset{\oplus}{N}(CH_3)_3}{\underset{|}{C}}HCH_3 \xrightarrow{\text{heat}}$

D. $CH_3CH_2\underset{\displaystyle Br}{\underset{|}{C}}HCH_3 \xrightarrow[\text{heat}]{CH_3ONa}$

vii. Pyrolytic elimination is

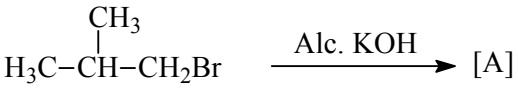
A. Carried out at elevated temperature in amine oxides

B. Carried out in presence of strong base and temperature

C. Carried by using acid and catalyst

D. Carried out in alkanes by using strong base and elevated temperature

viii. In the following reaction [A] will be:



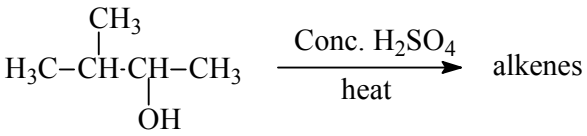
A. 3-methyl-1- butane

B. 2-methyl-2-butene

C. 2-butene

D. 2-butene

ix. In the following proposed reaction how many alkene molecules will be formed?



A.One

B. Two

C.Three

D. Four

x. Cope elimination is related to

A. Six membered cyclic T.S.

B. Five membered cyclic T.S.

C. T.S. not involved

D. None of them

Q.2. What are eliminationreactions?

Q.3. How will you define elimination reaction? Discuss various types of elimination reactions

Q.4. What is pyrolytic elimination? Discuss your answer with example. Why the reactions undergoing pyrolytic elimination does not require base?

Q.5. Write note on

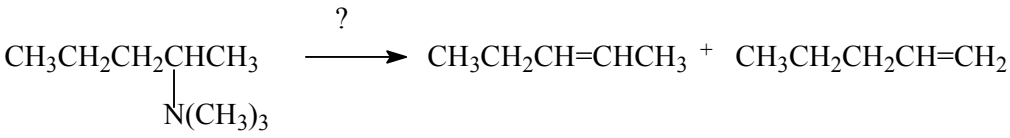
a. Saytzeff,s orientation

b. Regeoselectivity

c. Hofmann orientation

d. Cope rearrangement

Q.6. Sketch out mechanism of following reaction with justification.



5.14 ANSWER (MCQ) TERMINAL QUESTIONS

i A

ii C

iii A

iv C

v D

vi A

vii A

viii B

ix C

x. B

5.14 ANSWER (MCQ) TERMINAL QUESTIONS

1. Singh, J and Yadav, L.D.S, Advanced organic chemistry 2004, Pragati Prakashan, Meerut. 336-379.
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UNIT-6 ADDITION TO CARBON-CARBON MULTIPLE BOND

CONTENTS:

6. 0. Objective

6.1. Introduction

6.2. Electrophilic addition

- 6.2.1 Halogen addition reaction
- 6.2.2 Hydrohalogenation
- 6.2.2.1 Anti-Markovnikov addition
- 6.2.3 Oxymercuration reaction
- 6.2.3.1 Regioselectivity and stereochemistry of oxymercuration

6.3 Nucleophilic addition

6.3.1 Cyanoethylation

6.3.2 Hydro-cyano-addition

6.3.4. Epoxidation of α,β-unsaturated carbonyls

6.4 Free radical addition

- 6.4.1 Stereochemistry of Free radical addition of HBr
- 6.4.2 Free Radical Addition of Halomethanes
- 6.4.3 Other Free Radical Additions of Alkenes

6.5 Addition to cyclopropane ring

- 6.5.1 Structure and bonding in the cyclopropane ring
- 6.5.2 Addition reactions of cyclopropane ring
- 6.5.3 Mechanism of electrophilic addition to cyclopropane
- 6.5.4 Nucleophilic addition to cyclopropane
- 6.5.5 Addition of Free radicals to cyclopropane

6.6 Hydrogenation of double and triple bonds

6.7 Hydrogenation of aromatic rings

6.8 Hydroboration and related reactions

- 6.8.1 Properties of Borane
- 6.8.2 Concerted mechanism of hydroboration
- 6.8.3 Steric-effects also explain regiochemistry and stereochemistry of hydroboration

6.9 Michael addition

6.10 The Sharpless asymmetric epoxidation

6.10.1 Selectivity of Sharpless epoxidation

6.10.2. Mechanism of Sharpless epoxidation

6.10.3 Application of Sharpless epoxidation

6.11 Summary

6.12 Terminal questions

6.13 Answers to terminal questions

6.14 References

6.0. OBJECTIVES

Objective of this chapter is to make students aware about electrophilic addition, nucleophilic addition and free radical addition reaction. This unit will also provide knowledge of addition to cyclopropane ring hydroboration and Michael addition. Besides this many important name reactions of synthetic utility alongwith the Sharpless asymmetric epoxidation, selectivity of Sharpless epoxidation, mechanism of Sharpless epoxidation and their applications have been provided.

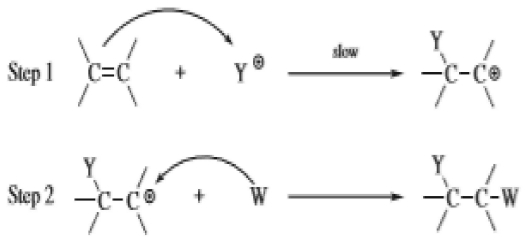
6.1 INTRODUCTION

There are four basic ways in which addition to carbon-carbon multiple bond can take place. Three of these are two-step processes, with initial attack by a nucleophile, or attack upon an electrophile or a free radical. The second step consists of combination of the resulting intermediate with, respectively, a positive species, a negative species, or a neutral entity (a free radical). In the fourth type of mechanism, attack at the two carbon atoms of the double or triple bond is simultaneous (concerted). Which of the four mechanisms is operating in any given case is determined by the nature of the substrate, the reagent, and the reaction conditions.

6.2 ELECTROPHILIC ADDITION

In this mechanism, a positive species approaches the double or triple bond and in the first step forms a bond by donation of the p pair of (extending π) electrons to the electrophilic species to form a s pair (Carbocation):

Better first discuss the π-complex formation



In step 2 of an electrophilic addition, the positively charged intermediate combines with (W) that is electron-rich and usually an anion to form the second covalent bond. Step 2 is the same

nucleophilic attack process found in an S_N1 reaction. The exact nature of the electrophile and the nature of the positively charged intermediate are not always clear and depend on reactants and reaction conditions. In all asymmetric addition reactions to carbon, regioselectivity is important and often determined by Markovnikov's rule. Organoborane compounds give anti-Markovnikov additions. Electrophilic attack to an aromatic system results in electrophilic aromatic substitution rather than an addition reaction.

Typical electrophilic additions to alkenes with reagents are:

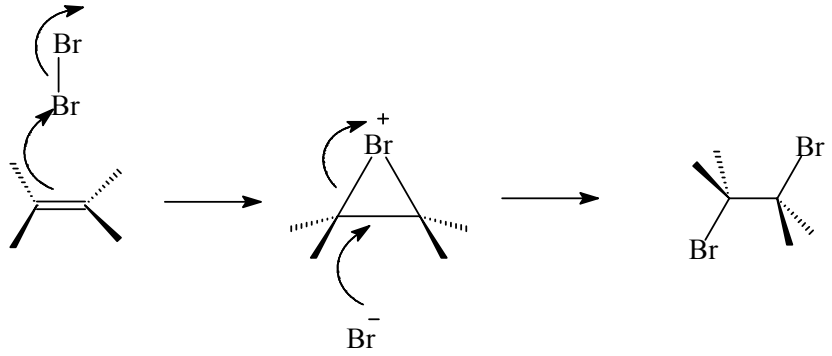
6.2.1 Halogen addition reaction

A halogen addition reaction is a simple organic reaction where a halogen molecule is added to the carbon–carbon double bond of an alkene functional group. The general chemical formula of the halogen addition reaction is:

$$C{=}C + X_2 \rightarrow X{-}C{-}C{-}X$$

(X represents the halogens bromine or chlorine, and in this case, a solvent could be CH_2Cl_2 or CCl_4). The product is a vicinal dihalide. This type of reaction is a halogenation and an electrophilic addition. The reaction mechanism for an alkene bromination can be described as follows-

In the first step of the reaction, a bromine molecule approaches the electron-rich alkene carbon–carbon double bond. The bromine atom closer to the bond takes on a partial positive charge as its electrons are repelled by the electrons of the double bond.



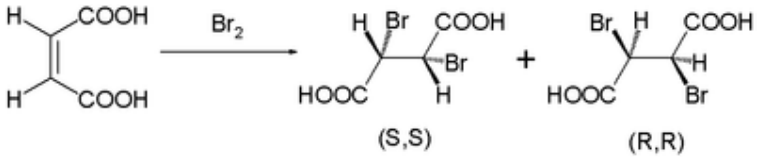
The atom is electrophilic at this time and is attacked by the pi electrons of the alkene (carbon–carbon double bond). It forms for an instant a single sigma bond to *both* of the carbon atoms involved. The bonding of bromine is special in this intermediate, due to its relatively large size compared to carbon, the bromide ion is capable of interacting with both carbons which once shared the π-bond, making a three-membered ring. The bromide ion

acquires a positive formal charge. At this moment the halogen ion is called a "bromonium ion" or "chloronium ion", respectively.

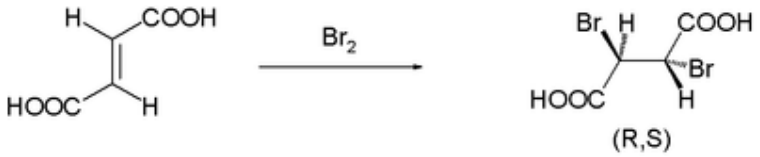
When the first bromine atom attacks the carbon–carbon π-bond, it leaves behind one of its electrons with the other bromine that it was bonded to in Br_2. That other atom is now a negative bromide anion and is attracted to the slight positive charge on the carbon atoms. It is blocked from nucleophilic attack on one side of the carbon chain by the first bromine atom and can only attack from the other side. As it attacks and forms a bond with one of the carbons, the bond between the first bromine atom and the other carbon atoms breaks, leaving each carbon atom with a halogen substituent.

In this way the two halogens add in an *anti* addition fashion, and when the alkene is part of a cycle the dibromide adopts the *trans* configuration. For maximum overlap of the C–Br σ* antibonding molecular orbital (the LUMO, shown to the right in red) and the nucleophile (X^-) lone pair (the HOMO, shown to the right below in green), X^- must attack the bromonium ion from behind, at carbon.

This reaction mechanism was proposed by Roberts and Kimball in 1937. With it they explained the observed stereospecific *trans*-additions in brominations of maleic acid and fumaric acid. Maleic acid with a *cis*-double bond forms the dibromide as a mixture of enantiomers:



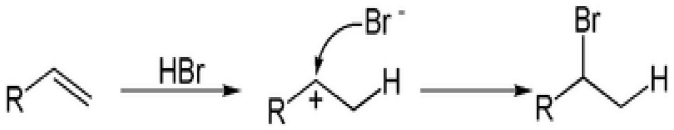
While the *trans*-isomer fumaric acid forms a single *meso* compound:



The reaction is even stereospecific in alkenes with two bulky *tert*-butyl groups in a *cis* position as in the compound *cis*-di-*tert*-butylethylene. Despite the steric repulsion present in the chloronium ion, the only product formed is the *anti*-adduct.

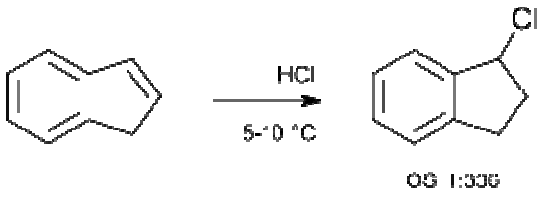
6.2.2 Hydrohalogenation

A hydrohalogenation reaction is the electrophilic addition of hydrohalic acids like hydrogen chloride or hydrogen bromide to alkenes to yield the corresponding haloalkanes.



If the two carbon atoms at the double bond are linked to a different number of hydrogen atoms, the halogen is found preferentially at the carbon with fewer hydrogen substituents, an observation known as Markovnikov's rule. This is due to the abstraction of a hydrogen atom by the alkene from the acid (HX) to form the most stable carbocation (relative stability: 3°>2°>1°>methyl), as well as generating a halogen anion.

A simple example of a hydrochlorination is that of indene with hydrochloric acid gas (no solvent):

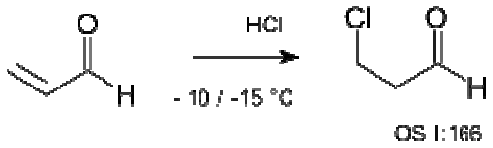


6.2.2.1 Anti-Markovnikov addition

In the presence of peroxides, HBr adds to a given alkene in an anti-Markovnikov addition fashion. This regiochemistry follows from the reaction mechanism, which favors formation of the most stable carbon radical intermediate (relative stability: 3° > 2° > 1°> methyl). The mechanism for this reaction is similar to a chain reaction such as free radical halogenation in which the peroxide promotes the formation of the bromide radical. Therefore, in the presence of peroxides, HBr adds so that the bromine atom is added to the carbon bearing the most numerous hydrogen substituents and hydrogen atoms will add to carbons bearing fewest hydrogen substituents. However, this process is restricted to addition of HBr.

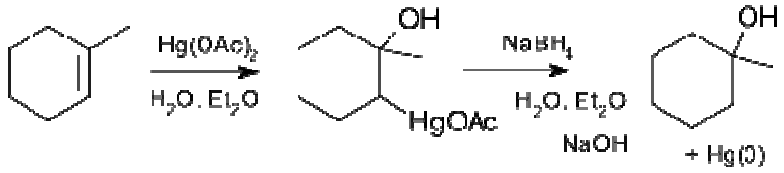
Other hydrogen halide (HF, HCl, HI) do not behaves in the manner described above. The resulting 1-bromoalkanes are versatile alkylating agents. By reaction with dimethyl amine, they are precursors to fatty tertiary amines. By reaction with tertiary amines, long-chain alkyl bromides such as 1-bromododecane, give quaternary ammonium salts, which are used as phase transfer catalysts.

With Michael acceptors the addition is also anti-Markovnikov because now a nucleophilic X^- reacts in a nucleophilic conjugate addition for example in the reaction of HCl with acrolein.



6.2.3 Oxymercuration reaction

The **oxymercuration reaction** is an electrophilic addition organic reaction that transforms an alkene into a neutral alcohol. In oxymercuration, the alkene reacts with mercuric acetate (AcO–Hg–OAc) in aqueous solution to yield the addition of an acetoxymercury (HgOAc) group and a hydroxy (OH) group across the double bond. Carbocations are not formed in this process and thus rearrangements are not observed. The reaction follows Markovnikov's rule (the hydroxy group will always be added to the more substituted carbon) and it is an anti addition (the two groups will be trans to each other). Oxymercuration followed by reductive demercuration is called an oxymercuration–reduction reaction or oxymercuration–demercuration reaction.



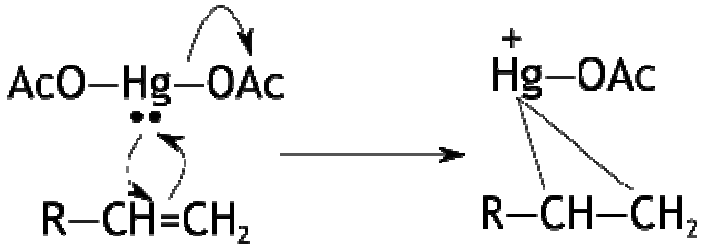
Oxymercuration can be fully described in three steps (the whole process is sometimes called *deoxymercuration*), which is illustrated in stepwise fashion to the right. In the first step, the nucleophilic double bond attacks the mercury ion, ejecting an acetoxy group. The electron pair on the mercury ion in turn attacks a carbon on the double bond, forming a *mercuronium ion* in which the mercury atom bears a positive charge. The electrons in the highest occupied

molecular orbital of the double bond are donated to mercury's empty dz^2 orbital and the electrons in mercury's dxz orbital are donated in the lowest unoccupied molecular orbital of the double bond.

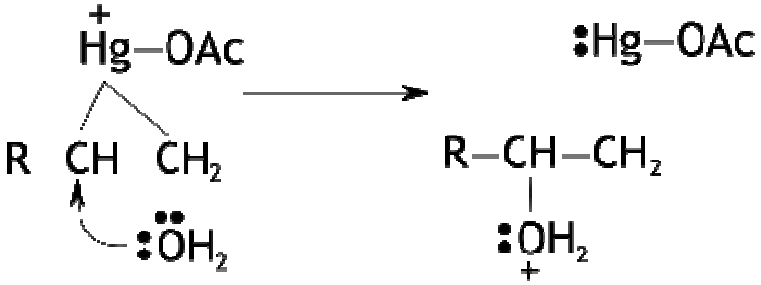
In the second step, the nucleophilic water molecule attacks the more substituted carbon, liberating the electrons participating in its bond with mercury. The electrons collapse to the mercury ion and neutralize it. The oxygen in the water molecule now bears a positive charge.

In the third step, the negatively charged acetoxy ion that was expelled in the first step attacks hydrogen of the water group, forming the waste product HOAc. The two electrons participating in the bond between oxygen and the attacked hydrogen collapse into the oxygen, neutralizing its charge and creating the final alcohol product.

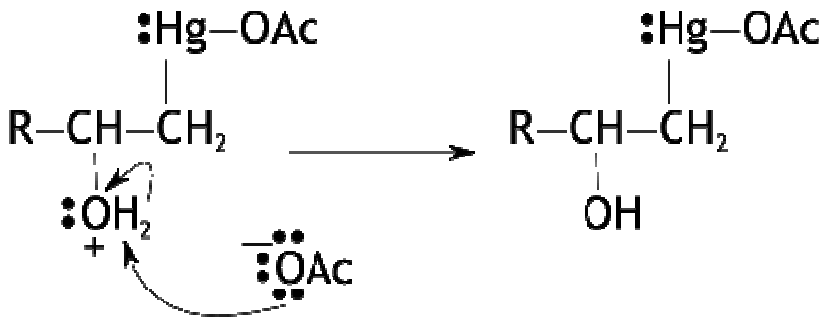
Step1:



Step2:



Step3:



6.2.3.1 Regioselectivity and stereochemistry of Oxymercuration

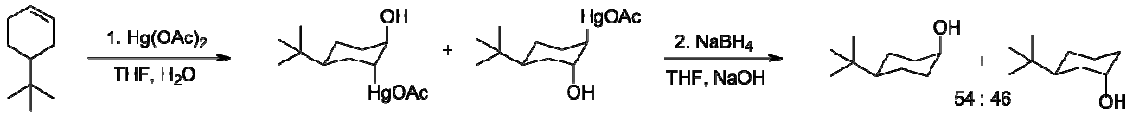
Oxymercuration is very regioselective and is a textbook Markovnikov reaction; ruling out extreme cases, the water nucleophile will always preferentially attack the more substituted carbon, depositing the resultant hydroxy group there. This phenomenon is explained by examining the three resonance structures of the mercuronium ion formed at the end of the step one.

By inspection of these structures, it is seen that the positive charge of the mercury atom will sometimes reside on the more substituted carbon (approximately 4% of the time). This forms a temporary tertiary carbocation, which is a very reactive electrophile. The nucleophile will attack the mercuronium ion at this time. Therefore, the nucleophile attacks the more substituted carbon because it retains a more *positive character* than the lesser substituted carbon.

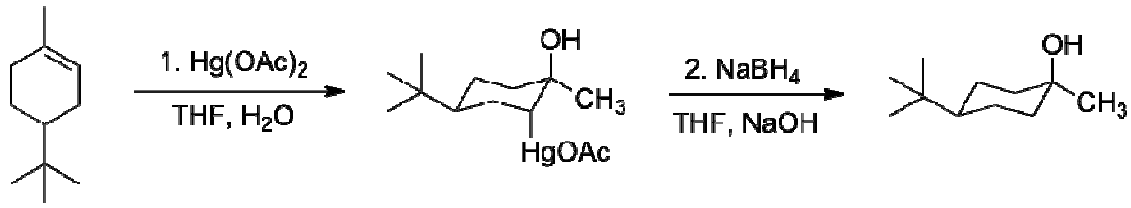
Stereochemically, oxymercuration is an *anti* addition. As illustrated by the second step, the nucleophile cannot attack the carbon from the same face as the mercury ion because of steric hindrance. There is simply insufficient room on that face of the molecule to accommodate both a mercury ion and the attacking nucleophile. Therefore, when free rotation is impossible, the hydroxy and acetoxymercuri groups will always be *trans* to each other.

Shown below is an example of regioselectivity and stereospecificity of the oxymercuration reaction with substituted cyclohexenes. A bulky group like *t*-butyl locks the ring in a chair conformation and prevents ring flips. With 4-*t*-butylcyclohexene, oxymercuration yields two products – where addition across the double bond is always *anti* – with slight preference towards acetoxymercury group *trans* to the *t*-butyl group, resulting in slightly more *cis* product. With 1-methyl-4-*t*-butylcyclohexene, oxymercuration yields only one product – still

anti addition across the double bond – where water only attacks the more substituted carbon. The reason for *anti* addition across the double bond is to maximize orbital overlap of the lone pair of water and the empty orbital of the mercuronium ion on the opposite side of the acetoxymercury group. Regioselectivity is observed to favor water attacking the more substituted carbon, but water does not add *syn* across the double bond which implies that the transition state favors water attacking from the opposite side of the acetomercury group.



Oxymercuration stereospecificity

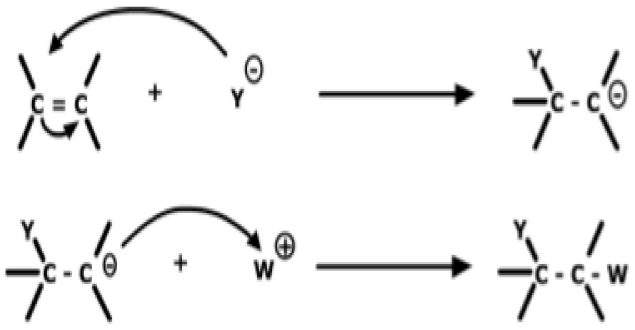


Oxymercuration regioselectivity

6.3 NUCLEOPHILIC ADDITION

The steps of nucleophilic addition to alkenes are just the reverse of electrophilic addition. Thus, the nucleophile first attacks the alkene double bond and adds up to form a carbanion. In the second step, the carbanion combines with the electropositive species.

This is illustrated in the following figure.

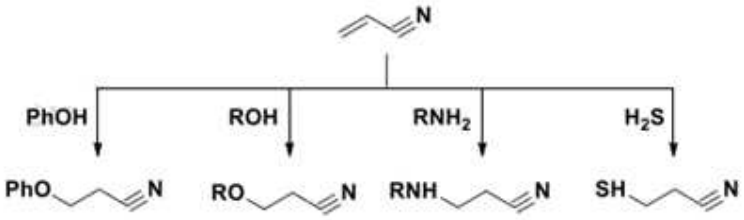


Because of the conjugation, the α, β-unsaturated carbonyls have two electrophilic sites: the carbonyl carbon and the β-carbon. Thus, the nucleophile may possibly attack both sites leading to either a 1,2-addition or a 1,4-addition respectively. The latter is also known as conjugate addition as addition occurs to the double bond conjugated with the carbonyl functionality. The conjugate addition results initially to an enol which tautomerizes to the keto form. The addition to the 3- position never occurs since the resulting carbanion would have no resonance stabilization. These scenarios are illustrated in the following figure.

The regiochemistry of nucleophilic addtions is dependent upon the type of nucleophile employed. Stronger the nucleophile, the more chance is for 1,2-addition. Thus strong nucleophiles such as Grignard reagents (RMgX) or RLi or hydride ion favour 1,2-addition. Whereas weaker nucleophiles such as enolate ions favour 1,4-addition. Actually, a 1,2-addition occurs first (kinetically favoured) and it may be reversible or irreversible (again depending upon the nature of nucleophile; stronger nucleophiles are poor leaving groups and hence difficult to eliminate from a 1,2-addition product). If irreversible, then 1,2-addition predominates. If reversible and allowed to run for more time, then 1,4-addition product will predominate as it is more stable and thermodynamically favoured. Also if perfomed at lower temperatures, kinetic product i.e. 1, 2-addition product predominates while at higher temperatures thermodynamic product i.e. 1,4-addirion product prevails. Important nucleophilic addition reactions of alkenes are discussed as follows:

6.3.1 Cyanoethylation

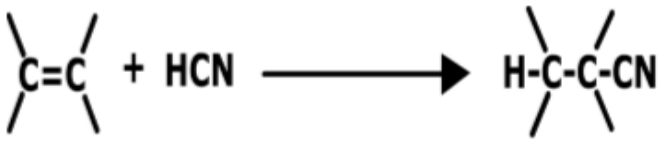
With alkenes containing a -CN substituent, the most common being acrylonitrile, a variety of nucleophiles such as phenols, alcohols, amines or sulfides may easily add to the unsubstituted carbon of the double bond. Thus, on abstraction of a proton from the solvent, the original nucleophile now has an attached 2-cyanoethyl group and this process is termed as cyanoethylation.



Thus, incorporation of a 3-carbon unit takes place in which the terminal cyano group can be transformed via reduction, hydrolysis etc. for further synthetic manipulations. The cyanoethylation procedure is performed in presence of a base which can convert the HNu to the more powerful nucleophile Nu^{-}.

6.3.2 Hydro-cyano-addition

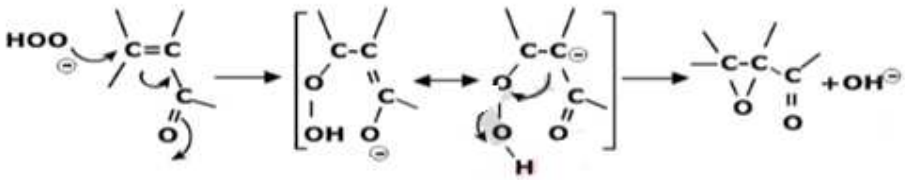
Alkenes having electron-withdrawing groups and also poly haloalkenes undergo base catalysed addition with HCN to give nitriles.



HCN in presence of base gives –CN which is a good nucleophile and adds to the activated alkene. Proton abstraction then results in the formation of the nitrile product. When the reaction is performed with α,β-unstaurated carbonyls, then the 1,2-addition may be the competing reaction an sometimes is the major reaction.

6.3.4. Epoxidation of α,β-unsaturated Carbonyls

The epoxidation of α,β-unsaturated ketones with hydrogen peroxide under basic conditions is essentially a nucleophilic addition reaction. These conjugated alkenes usually do not give epoxides when treated with peroxyacids. But this method is quite good for prepartaion of epoxides from α,β-unsaturated ketones, aldehydes and even sulfones. The reaction involves 1,4addition of the nucleophile HOO– (generated by reaction of H2O2 and NaOH) to the conjugated alkene and subsequent internal attack of the carbanion to the O—O bond to form an epoxide ring via liberation of an OH– ion as depicted below



6.4 FREE RADICAL ADDITION

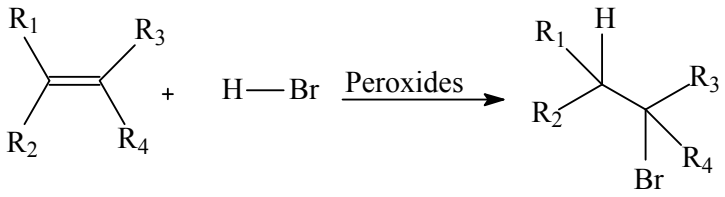
It was observed that in presence of peroxide, the addition of HBr to alkenes takes place in an anti-Markovnikov manner. This was discovered by famous chemist Kharasch and this effect came to be known as peroxide effect or Kharasch effect. Thus, 1-butene gave 1-bromobutane (anti Markovnikov product) with HBr/H_2O_2, while 2-bromobutane was formed when no peroxide was used.

$$H_2C{=}CHCH_2CH_3 + HBr \xrightarrow{\text{Peroxides}} BrCH_2CH_2CH_2CH_3$$

$$H_2C{=}CHCH_2CH_3 + HBr \xrightarrow{\text{no Peroxides}} CH_3\underset{\displaystyle Br}{\underset{|}{C}}HCH_2CH_3$$

This anomaly was explained by the involvement of a free radical mechanism in the addition reaction of HBr in presence of peroxide. Subsequently it was also demonstrated that the reaction could occur even if peroxides were not deliberately added to the reaction mixture. Alkenes can be oxidised by atmospheric oxygen and become contaminated with small amounts of alkyl hydroperoxides (ROOH) which can cause the same effect.

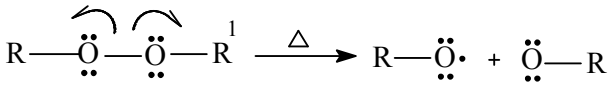
For examples-

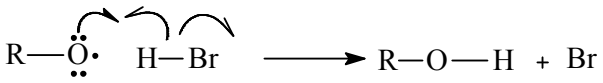


The steps involved in the mechanism are:

1. Initiation

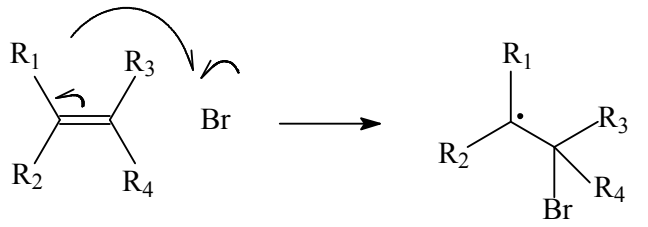
Peroxides contain a weak oxygen-oxygen bond (bond energy~35 kcal/mol). Homolytic dissociation of the peroxide into two hydroxyl (or alkoxy) radicals by heat or light occurs and the subsequent abstraction of Hydrogen atom from hydrogen bromide by this radical results in a Bromine radical.

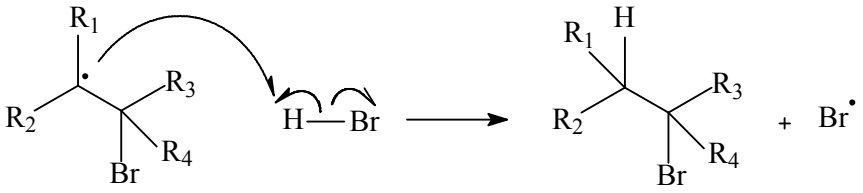




2. Propagation

The bromine radical is electron deficient and adds to the double bond, generating a carbon centered radical. This radical, in turn, abstracts hydrogen from a molecule of H-Br, giving the desired product, and another bromine radical which may gain add up to the alkene leading to a chain process.

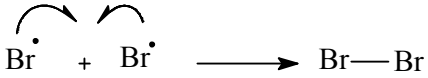




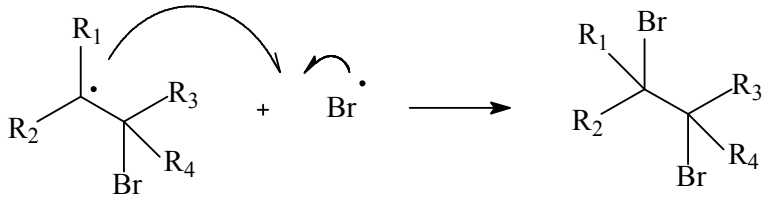
3. Termination

The termination of the reaction can occur via 3-ways:

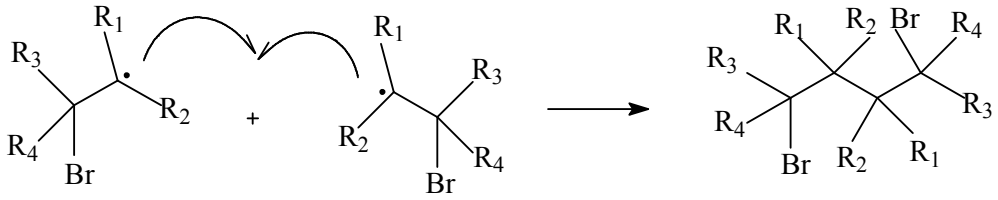
i. Two bromine radicals may combine



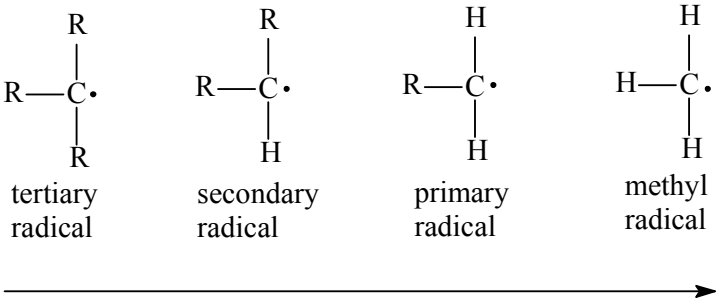
ii. An alkyl free radical may combine with a bromine free radical



iii. Two alkyl radicals may combine with each other to terminate the reaction.



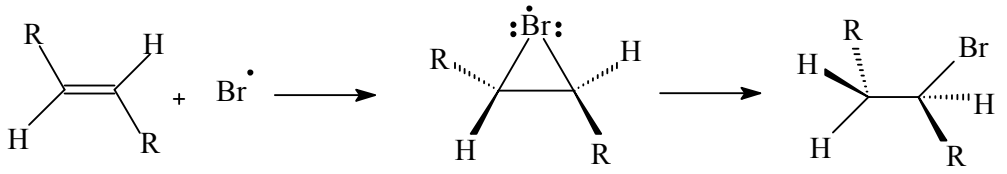
Under free-radical conditions the regioselectivity is governed by addition of the bromine radical to give the more stable alkyl radical. Also, addition of bromine radical to the alkene is governed by steric factors. Thus, bromine radical adds to the less substituted carbon of the double bond (resulting in lesser steric strain) which in turn leads to a more stable alkyl radical and hence the observed orientation is anti-Markovnikov. The stability order for alkyl radicals is



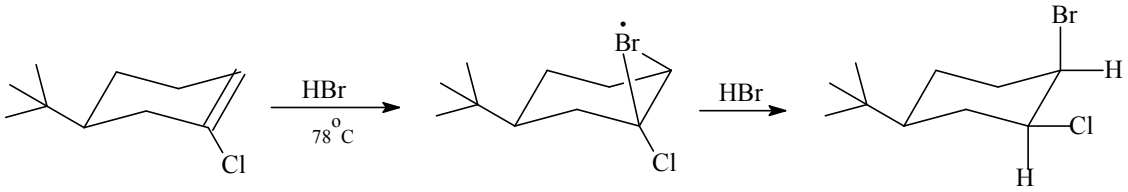
It must be noted that while HBr in presence of peroxides can undergo free radical addition with alkenes, no such mechanism has been observed ever with HF or HI or rarely with HCl owing to the greater bond energies of these hydrogen halides. HI has lower bond energy than HBr, but the alkyl radical that forms by addition of iodine radical to the alkene is unstable and quickly loses the iodine radical to regenerate the alkene.

6.4.1 Stereochemistry of Free radical addition of HBr: The free radical addition of HBr to alkenes favours anti addition. This is contrary to the concept that the alkyl free radical generated can also rotate about the C-C bond having the radical sp^2 carbon to give a mixture of both syn and anti-products. At very low temperatures (–80 0C), HBr adds by overall anti

addition but at higher temperatures the reaction is not stereospecific. This was attributed to the involvement of a bridged intermediate.



For example, HBr addition to cylohexenes is strictly trans-diaxial at lower temperatures owing to the formation of a bridged intermediate.

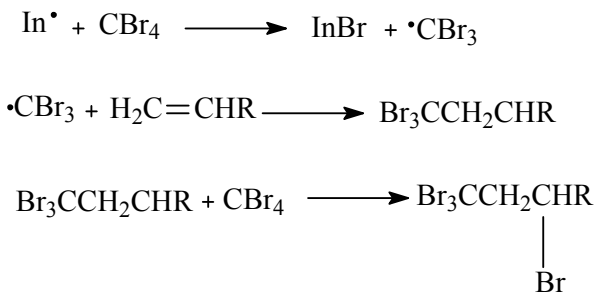


At higher temperatures, however, rotation at C—C* bond can take place resulting in loss in stereo-specificity of the reaction.

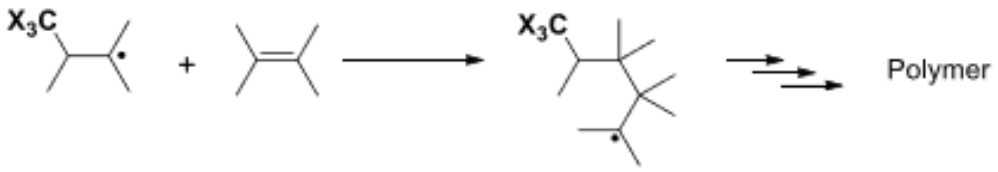
6.4.2 Free Radical Addition of Halomethanes

Various polyhalomethanes such as CCl_4, CBr_4, and $CHBr_3$ etc. have been found to add to alkenes via a free radical mechanism. The reactivity order of the halomethanes is CBr_4 > $CBrCl_3$ > CCl_4 > CH_2Cl_2 >$CHCl_3$.

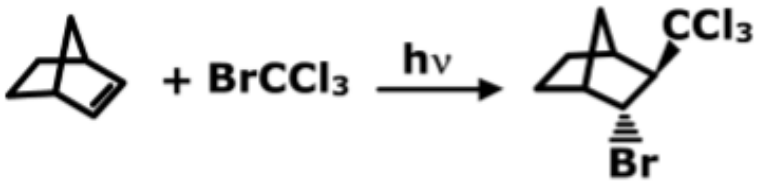
Addition of CBr_4 to an alkene via use of an initiator (In) is shown as an example:



Chain polymerization can compete with the halogen atom abstraction step. For substituted terminal alkenes having phenyl or ester substituents, the polymerization reaction is more rapid.

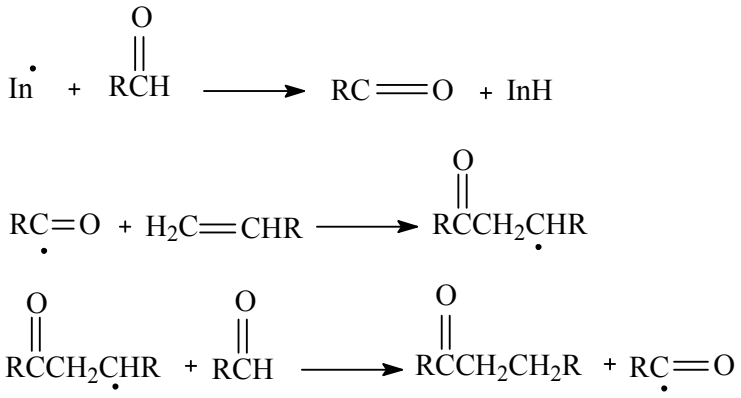


The stereo-chemistry of this free radical addition is governed by the steric bulk of the substituents present in the alkene. This effect is more pronounced in sterically congestedused skeletons such as in decalin or in norbornene where the addition is anti due to blocking of one side by the trihalomethyl group as shown for addition of $BrCCl_3$ to norbornene.

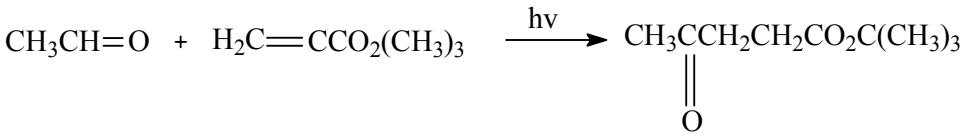


6.4.3 Other Free Radical Additions of Alkenes

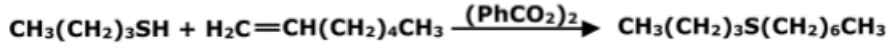
Acyl radicals can be formed by abstraction of the aldehydic hydrogen by a free radical initiator and can add to the alkenes.



An example is shown below:



Also, free radical addition of thiols and thiocarboxylic acids also occurs efficiently and the mechanism is similar to the peroxide initiated HBr addition to alkenes. The stereo-chemistry is anti but the reactions have less stereoselectivity than HBr addition. An example is illustrated below:



6.5 ADDITION TO CYCLOPROPANE RING

6.5.1 Structure and bonding in the cyclopropane ring:

Cyclopropane has a triangular planar structure due to which, the bond angles between C-C bonds are expected to be 60°. This is far less than the thermodynamically stable angle of 109.5° as per the sp^3 hybridisation of the carbon atoms. Due to this there is a considerable amount of ring strain in the cyclopropane molecule. In addition to this angular strain, cyclopropane also suffers additional torsional-strain. The torsional strain is due to the coplanar arrangement of the carbon atoms wherein leading to the eclipsed arrangement of the C-H bonds. Important characteristics of cyclopropane ring are as given below:

- **i.** C—C bonds are shorter than in alkanes (1.51 Å vs. 1.54 Å).
- **ii.** H—C—H angle opened up (115 Å vs. 106 Å in propane)
- **iii.** C—H bonds are more acidic (pKa=46, vs. 51 in propane
- **iv.** Strain energy = 27.5 kcal/mol.
- **v.** The C-C bond strength in cyclopropane is considerably weaker (65 kcal/mol) than for a typical C-C bond (80-85 kcal/mol).

It has been suggested that significant re-hybridization occurs in cyclopropane and bonding between the carbon centres occurs in terms of 'bent' bonds (Coulson-Moffitt model) wherein the carbon-carbon bonds are bent outwards so that the inter-orbital angle is 104° which consequently reduces the level of bond strain. So it is intermediate between σ and π bonding. These bonds are also sometimes called "banana bonds" (Fig). Thus, the C—C bonds have more p-character than normal while C—H bonds have more s character. Thus, it can be seen that ring strain substantially weakens the C-C bonds of the cyclopropane ring. Hence, cyclopropane is much more reactive than alkanes or other higher ring systems. Another

model viz. Walsh model based on M.O. considerations, envisions cyclopropane as being constructed from three sp^2-hybridized methylenes (CH_2), (Fig 1). Two of these sp^2 orbitals are used for C−H-bonds (not shown) and one forms an inner two-electron-three-centre σ bond, leaving p-orbitals to form some kind of degenerate π-like orbitals. Thus, Walsh cyclopropane has considerable sp^2 character and should react in analogy to olefins. Fig 1 shows the Molecular Orbital diagram for cyclopropane as formed up of 3 methylenes, in inceasing order of energy.

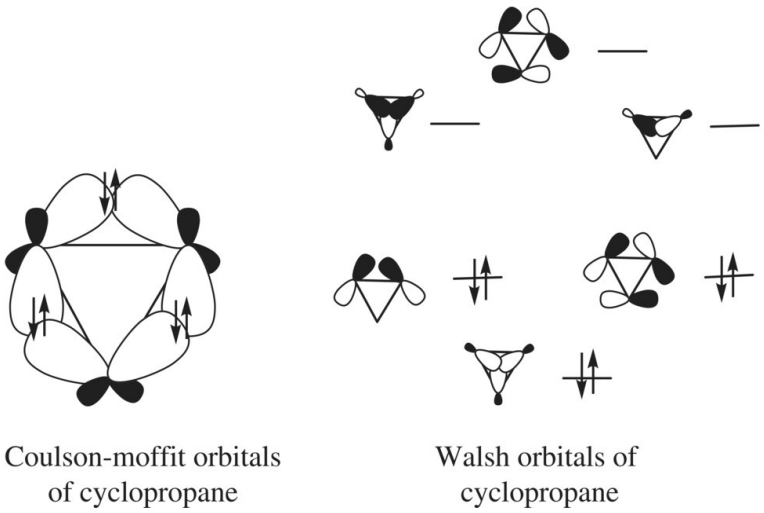
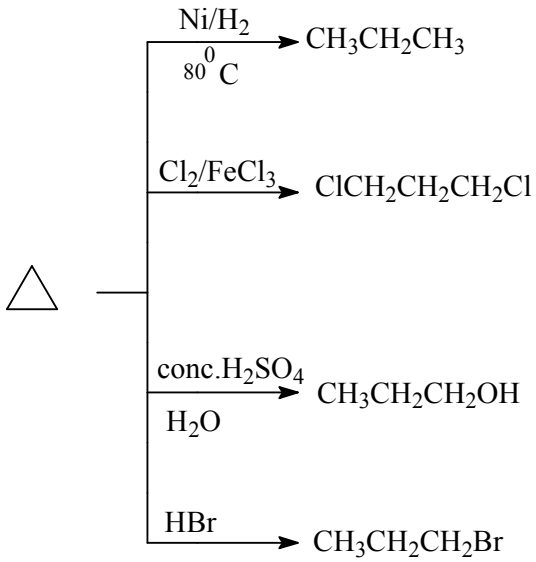


Fig. 1 : Models for bonding in cyclopropane

6.5.2 Addition Reactions of Cyclopropane Ring:

Cyclopropane ring system suffers from a large ring strain (which is a combination of angle strain and torsional strain) which leads to a significant weakening of the C—C bond. Thus, C—C bonds show a greater p-character, while C—H bonds have more s character. Thus, in effect, the cyclopropane ring undergoes any such reaction which can subsequently help in relieving the ring strain. Most of these reactions are similar to those of alkenes and most common of these are addition reactions (electrophilic nucleophilic or free-radical) which lead to opening of the ring. For example:

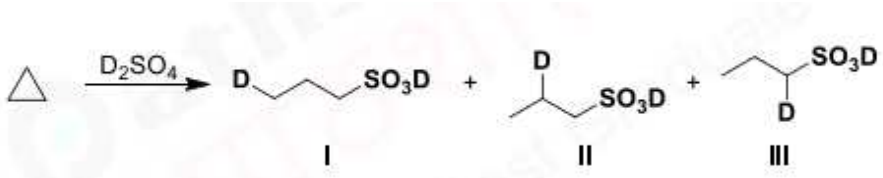


In each of these reactions, a C—C bond is broken leading to ring fission and the atoms of the reagent attach at two terminals of the resulting propane chain. Depending upon the substitution of cyclopropane ring, which can be electron donors or acceptors, any of its three bonds are likely to undergo cleavage. The reagent must be able to polarize itself into nucleophilic and electrophilic centres for the subsequent addition to occur. Thus, propylene reacts more readily with Br_2 or Cl_2 while for reaction with cyclopropane a Lewis acid is required ($FeCl_3$ or $FeBr_3$) to effect sufficient polarization of the Cl_2 or Br_2 molecule.

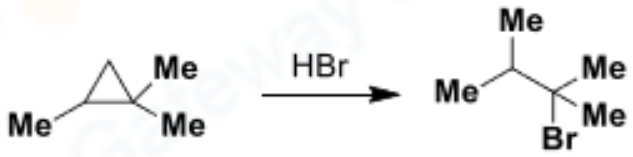
6.5.3 Mechanism of Electrophilic Addition to Cyclopropane:

Before discussing the mechanism, there are two important points to be noted for addition reaction of cyclopropane:

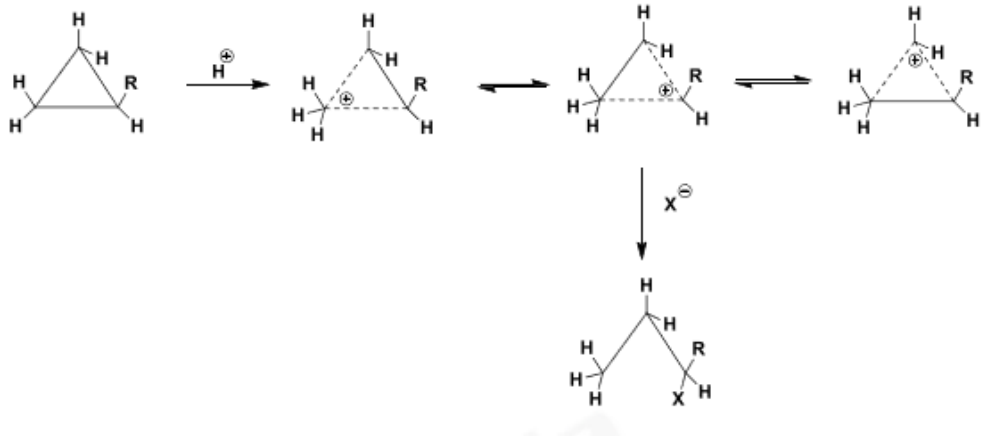
1. The mechanism must be stepwise as reaction of D_2SO_4 with cyclopropane yields along with the expected product (I), minor amounts of 2 more products (II and III) as shown below:



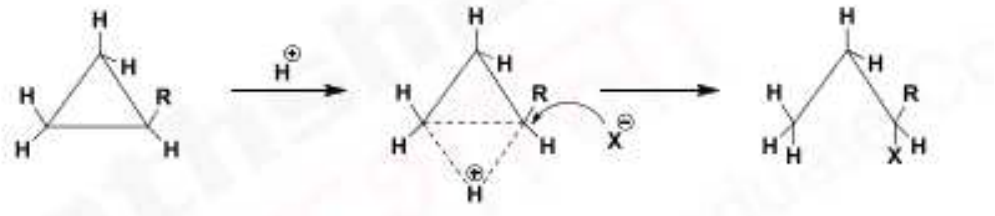
2. The electrophilic addition in substituted cyclopropanes generally follows Markovnikov's rule wherein hydrogen adds to the carbon which already contains more hydrogens.



This suggests that the mechanism comprises of an initial attack by the electrophile (e.g. H^+) on the ring carbon with the most hydrogens, generating a positive charge on the carbon (carbocation). This positive charge may be transferred on to the other carbons of the ring and the most favourable intermediate would be the one in which the positive charge is on the most substituted carbon (most stable carbocation). This cation is subsequently trapped by its reaction with the nucleophile as shown below.

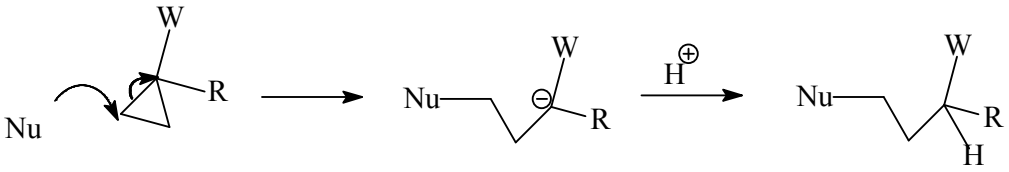


Another type of mechanism has been suggested which depicts an edge-protonated cyclopropane:

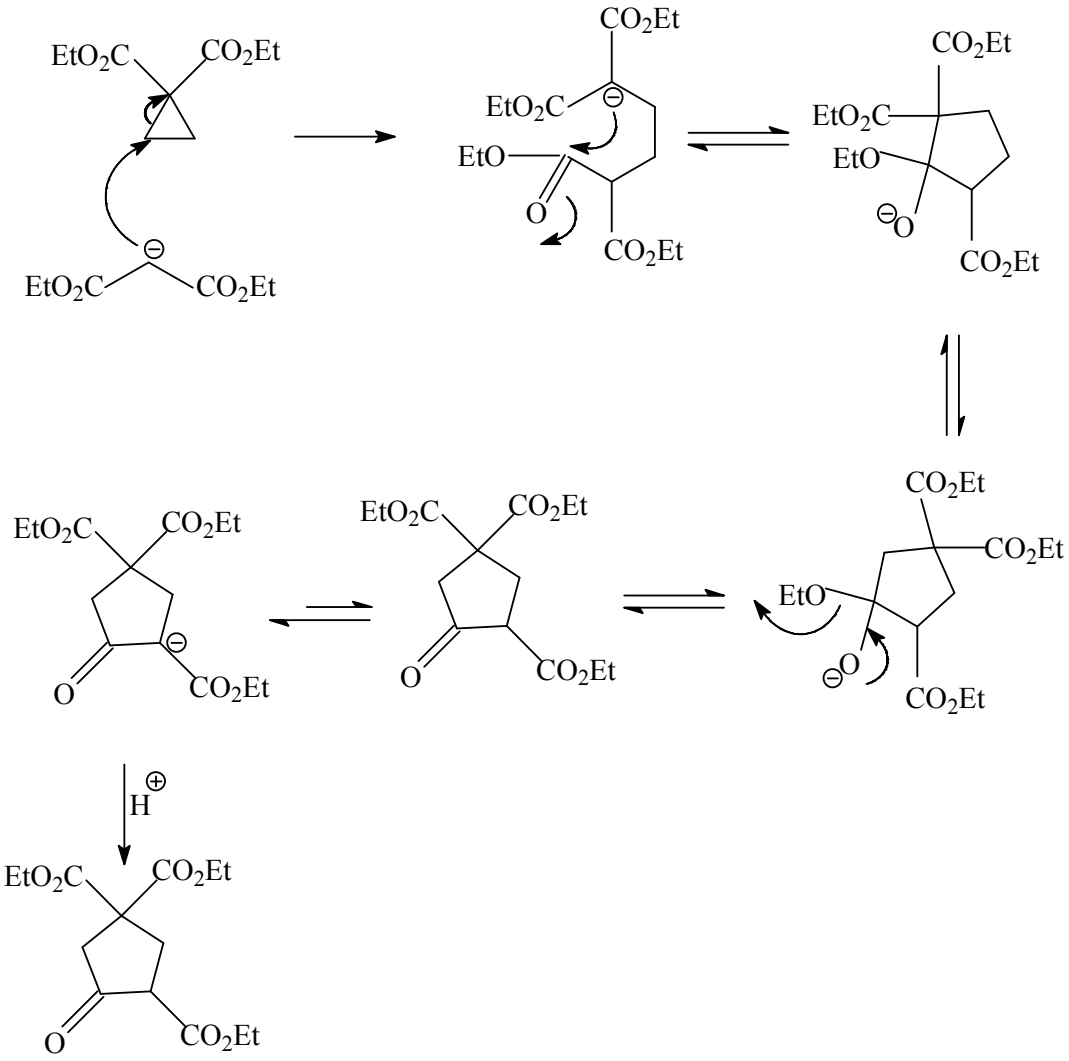


6.5.4 Nucleophilic Addition to Cyclopropane:

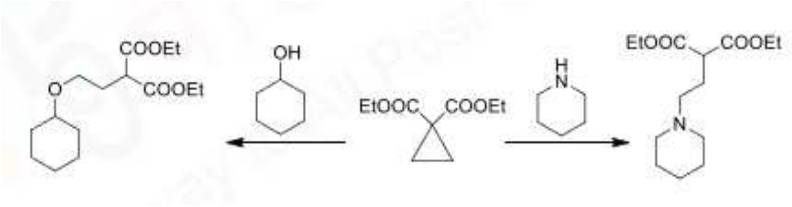
Ring-fission of cyclopropane by nucleophiles is possible only when an electron-withdrawing group (W) is present on the ring.



This reaction has been used widely in organic synthesis and can be used as a homologous variant to a Michael-type addition to generate a 5-membered ring as shown.

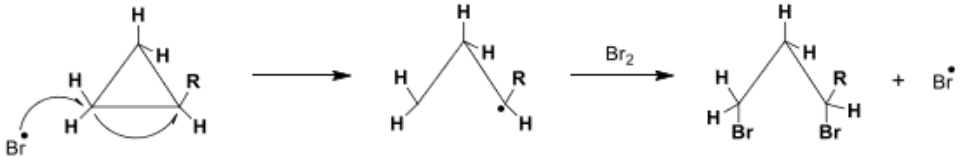


Similarly, secondary amines or alcohols can also effect the opening of the cyclopropane ring as shown below.



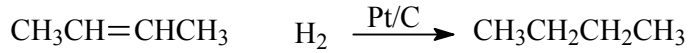
6.5.5. Addition of Free radicals to Cyclopropane

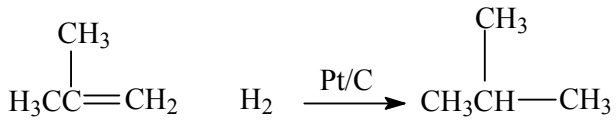
Free radicals also add to the cyclopropane ring system. Thus, Br_2 can add to a cyclopropane ring in presence of UV light via a free radical mechanism. Initially, $Br^{\bullet}$ attacks the least hindered carbon, to yield the most stable radical, and the second one goes to the most substituted carbon.

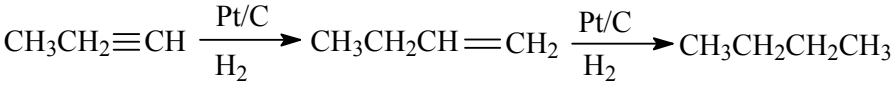


6.6 HYDROGENATION OF DOUBLE AND TRIPLE BONDS

In the incidence of a metal catalyst such as Pt, Pd, or Ni, H_2 adds to the double and triple bonds of alkenes and alkynes, respectively to form an alkene. Hydrogen adds to an alkyne in the same manner that it adds to an alkene. It is complicated to stop the reaction at the alkene stage because hydrogen readily adds to alkene in the presence of these catalysts. Ultimately, the product of the hydrogenation reaction of alkynes is an alkane. For example-





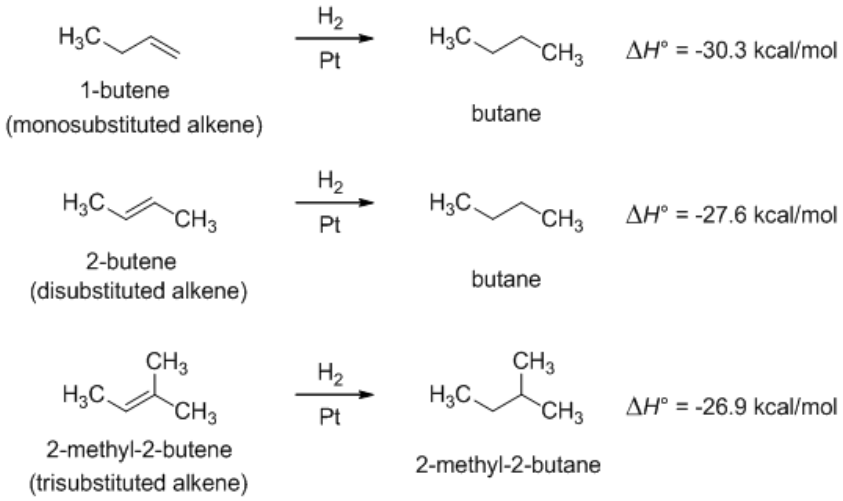


Withuot catalyst the energy barrier to the reaction would be massive because of the strength of the H-H bond. The catalyst decreases the energy of the activation by breaking the H-H bond. Platinum and palladium are used in a finely divide state adsorbed on charcoal (Pt/C, Pd/C). The platinum catalyst is commonly used in the form of PtO_2, which is known as Adam's catalyst. Due to existence of a catalyst in these reactions, the process is called catalytic hydrogenation. The metal catalysts are insoluble in the reaction mixture, and are consequently, classified as heterogenous catalysts. A heterogenous catalyst can easily be separated from the reaction mixture by filteration. It can then be recycled, which is an important property, since metal catalysts are expensive. The reaction can be stopped at the alkene stage if partially deactivated metal catalyst is used.the most commonly used partially deactivated metal catalyst is Lindler catalyst, which is prepared by precipitating palladium on calcium carbonate and treating it with lead (II) acetate and quinoline. This modifies the surface of palladium, making it much more effective at catalyzing the addition of hydrogen to a triple bond than to a double bond.

6.6.1 Heat of hydrogenation and relative stability of alkene:

The stability of an alkene depends on its structure. The heat released in a hydrogenation reaction is called the heat of hydrogenation. When an alkene is treated with hydrogen in the presence of a platinum catalyst, hydrogen adds to the double bond, reducing the alkene to an alkane. Hydrogenation is exothermic, evolving about 20 to 30 kcal of heat per mole of hydrogen consumed.

The difference in the stabilities of alkenes is the difference in their heats of hydrogenation. While considering the hydrogenation of 1-butene (a monosubstituted alkene), 2-butene (a disubstituted alkene) and 2-methyl-2-butene (a trisubstituted alkene), 2-methyl-2-butene is more stable by 3.4 kcal/mol and 2-butene is stable by 2.7 kcal/mol (Scheme 1). More substituted double bonds are usually more stable. In other words, the alkyl groups attached to the double bonded carbons stabilize the alkene.

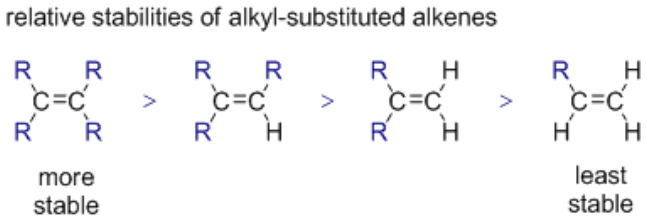


$\Delta H°$ = 30.3 kcal/mol - 27.6 kcal/mol = 2.7 kcal/mol

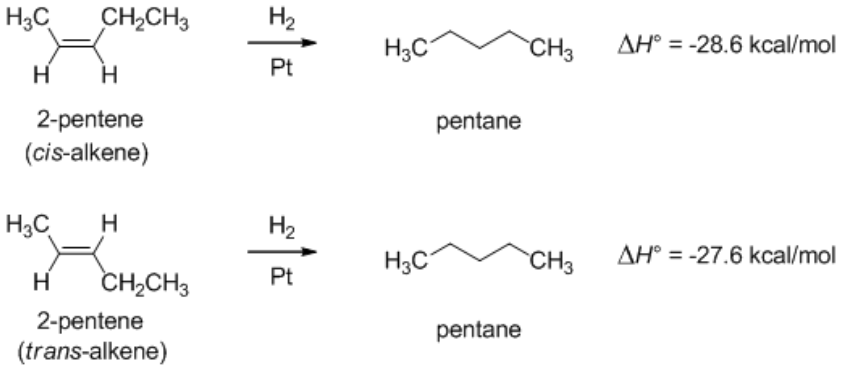
$\Delta H°$ = 30.3 kcal/mol - 26.9 kcal/mol = 3.4 kcal/mol

Scheme 1

Alkene, which releases the most heat, must be the least stable. In contrast, the alkene, whichreleases the least heat, must be the most stable.



The heats of hydrogenation show that *trans*- isomers are generally more stable than the corresponding *cis*- isomers. Because the alkyl substituents are separated farther in *trans*-isomers than they are in *cis*- isomers. The greater stability of the *trans*- isomer is evident in the following example, which shows that the *trans* -isomer is stable by 1.0 kcal/mol (Scheme 2).

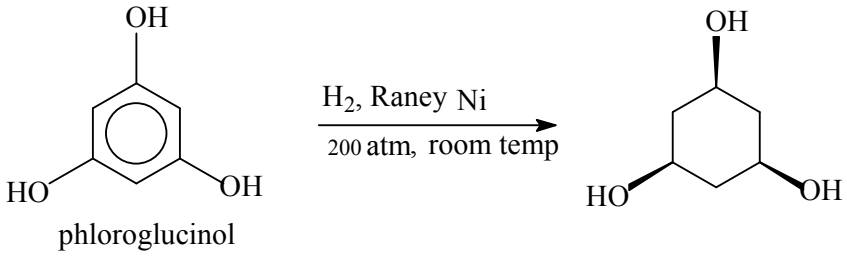


$\Delta H°$ = 28.6 kcal/mol - 27.6 kcal/mol = 1.0 kcal/mol

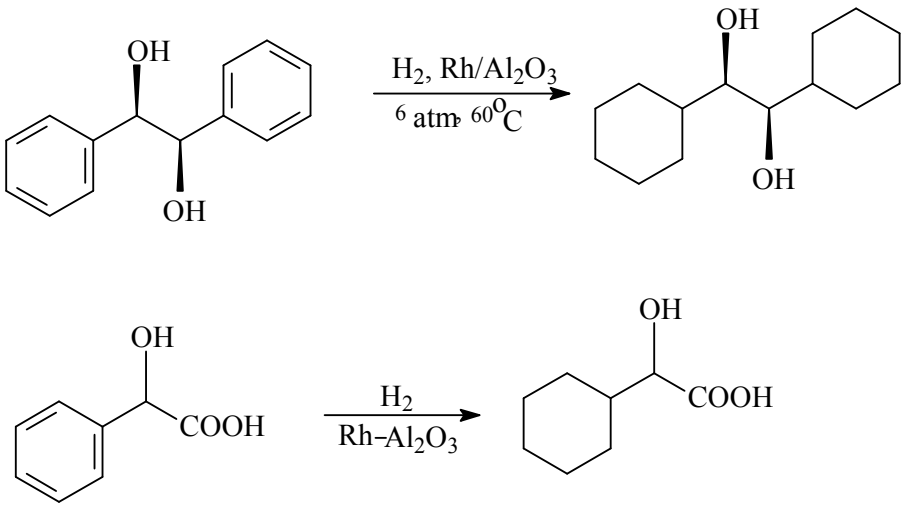
Scheme 2

6.7 HYDROGENATION OF AROMATIC RINGS

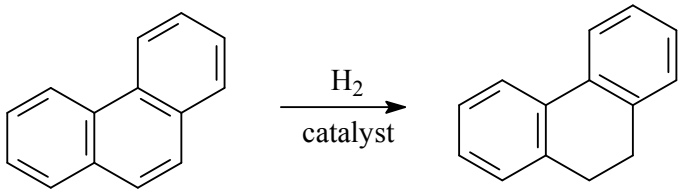
Aromatic rings are among the hardest to be hydrogenated and even with precious metal catalysts, require higher temperatures and pressures. But, once a benzene ring starts to hydrogenate, there is nothing like partial hydrogenation, and it hydrogenates to cyclohexane. This is because when benzene has been converted to cyclohexadiene (the first hydrogenation and the hardest, endothermic step), it is associated with the loss of resonance energy and the subsequent hydrogenations are exothermic and faster than the first one.



Pt and Rh catalysts are common and used at ordinary temperatures whereas Raney-Nickel or Ru catalysts require higher temperatures and pressures and Raney-Nickel is used for large scale hydrogenations involving heating at 150^{o}C at high pressures (100-200 atm). Rh over Alumina is another prominent catalyst used and requires milder conditions than others. Also, it does not cause hydrogenolysis of the sensitive C—O bonds present in the molecule.

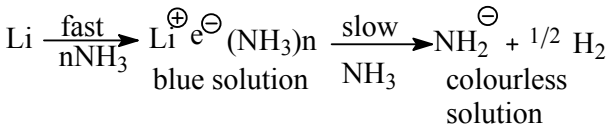


Hydrogenation of polycyclic aromatic rings such as naphthalenes and phenanthrenes are also performed and by varying the reaction conditions, partially hydrogenated or fully hydrogenated products may be obtained. For example, Raney-Nickel may be used to obtain tetrahydro or decahydro-naphthalene by varying the reaction conditions. Similarly, 9, 10-dihydro phenathrenes or anthracenes can be obtained by reduction over copper-chromite and to fully reduce them, more active catalysts are required.

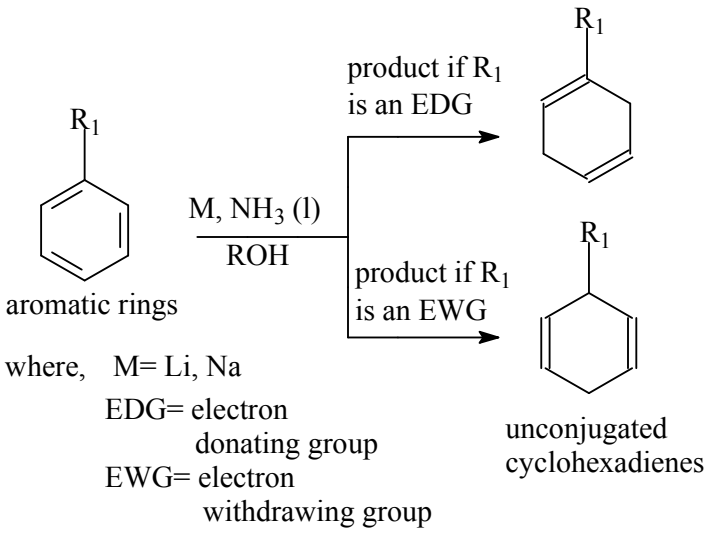


When aromatic rings are reduced by Li/K/Na in liquid ammonia (such reductions are known as dissolving metal reductions), usually in the prersence of an alcohol (eg. EtOH, 2-propanol, or t-BuOH), 1,4-addition takes place and nonconjugated cyclohexadienes are produced. This reaction is known as Birch reduction. According to this reaction an aromatic ring is more readily reduced than an alkene.

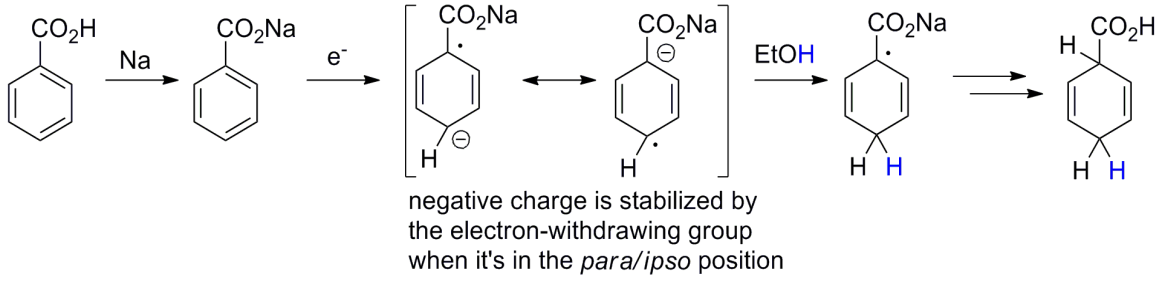
When lithium (or potassium or sodium) dissolved in ammonia an intense blue solution is obtained. Blue is colour of the solvent electrons: $e^-(NH_3)n$. In Birch reductions there blue solutions with solvated electrons. Are used as reducing agent. The reaction NH_3 to NH_2 and H_2 is quite slow and a better electron-acceptor is preferentially gets reduced.



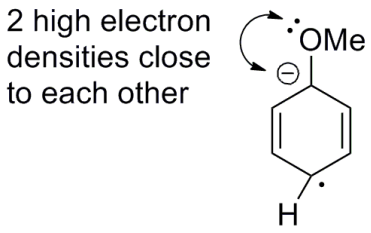
The mechanism begins with a single electron transfer (SET) from the metal to the aromatic ring, forming a radical anion. The anion then picks up a proton from the alcohol which results in a neutral radical intermediate. Another SET, and abstraction of a proton from the alcohol results in the final cyclohexadiene product and two equivalents of metal alkoxide salt as a byproduct. In the case of substituted aromatic rings, the regiochemistry can be predicted using Birch's empirical rules.



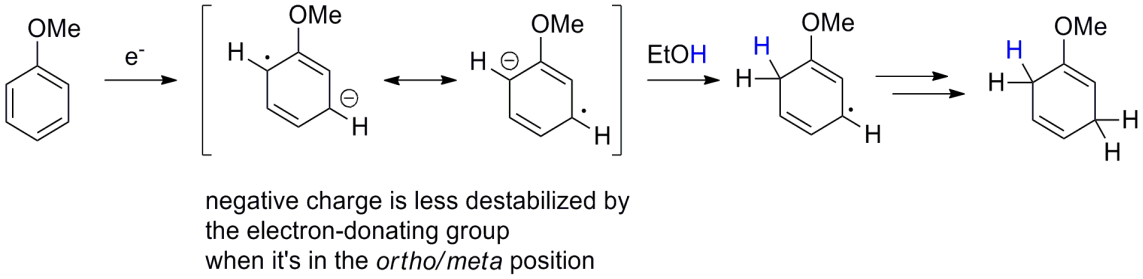
Electron-withdrawing groups stabilize electron density at the *ipso* and *para* positions through conjugation and so the negative charge will mainly be found in these positions; subsequent protonation occurs *para*.



Electron-donating groups destabilize a negative charge (when compared to simple benzene) through conjugation and this effect would be strongest at the *ipso* and *para* positions.

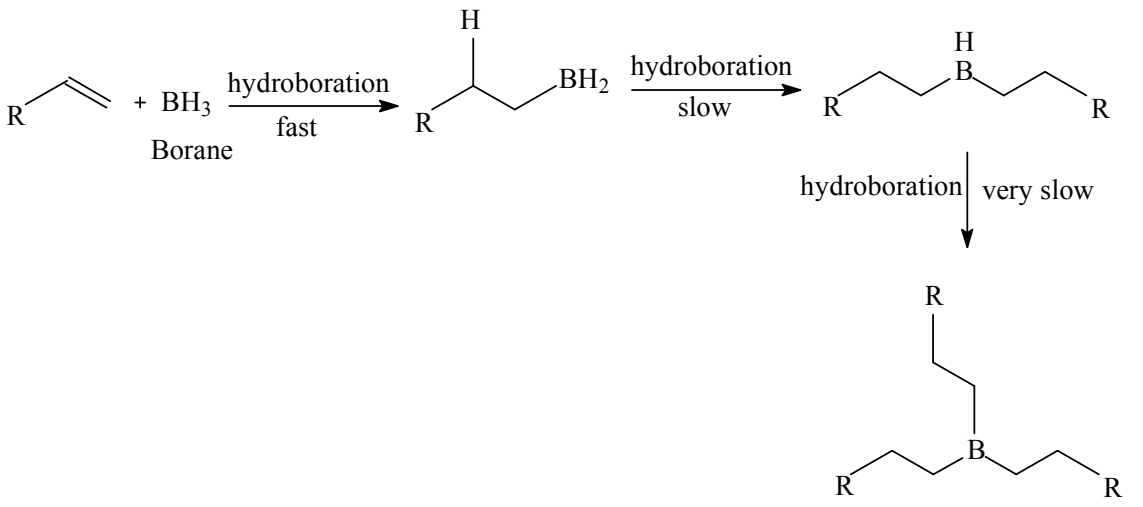


Thus the negative charge will mainly be found at the *ortho* and *meta* position.

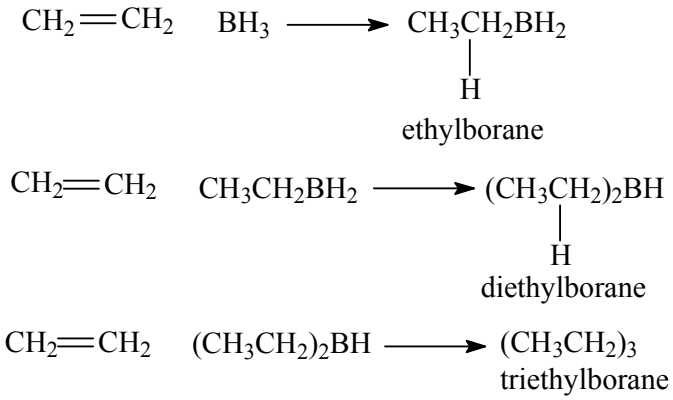


6.8 HYDROBORATION AND RELATED REACTIONS

Hydroboration refers to the addition of a hydrogen-boron bond to an unsaturated system such as alkene or alkyne resulting in the formation of organoboranes which can be converted to other products via subsequent transformations. This reaction was first explored by H. C. Brown and coworkers during 1950s. Alkenes react with borane, BH_3, and a number of its derivatives to give synthetically useful alkylboranes. The reaction is an electrophilic addition to alkene, but unlike others, this addition is a concerted one. The initially formed monoalkylborane product may undergo addition with another molecule of alkene to produce a dialkyl borane which in turn may undergo further reaction to produce a trialkyl borane.



Thus, ethylene will yield triethyl borane on hydroboration.



However, trisubstituted alkenes usually yield a dialkylborane and tetrasubstituted alkenes form only the monoalkylboranes. The extent of hydroboration may also be controlled by the stoichiometry of alkene and borane. This reaction is often combined with subsequent oxidation reaction to produce an alcohol and is commonly known as hydroboration-oxidation reaction.

6.8.1 Properties of Borane

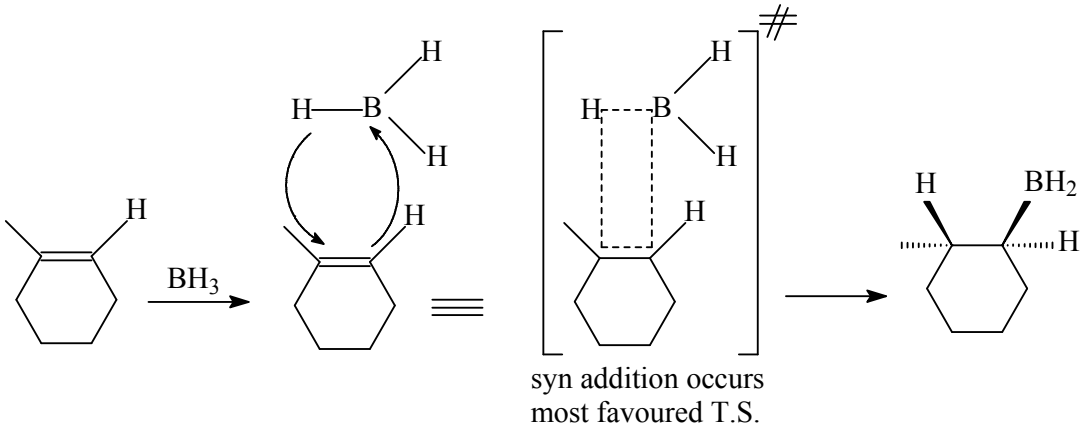
Borane (BH_3) is a very reactive electrophile since it has only a sextet of electrons Borane (BH_3) exists primarily as a colourless gas called diborane (B_2H_6) which is actually its dimeric form. This is because, Boron is a highly electron-deficient element and thus, two B-atoms share the electrons in the two B-H bonds in an unusual manner. Diborane gas may be generated in situ by the reaction of $NaBH_4$ with BF_3 in laboratory. But, the diborane gas is highly toxic, flammable and explosive gas and is more conveniently handled by making it's adduct with an electron-donor such as tetrahydrofuran (THF), dimethylsulfide (DMS) etc. and are available in solution form in an ethereal solvent, commonly THF. The dimethylsulfide complex ($BH_3.Me_2S$) is more stable than BH_3·THF and is soluble in a variety of organic solvents, such as diethyl ether and hexane. Borane is very reactive and is also used for reduction of a host of carbonyl compounds including aldehydes, ketones, carboxylic acids and other functional groups such as epoxides, lactones and nitriles. Thus, on treatment with borane of alkene substrates which contain these functionalities may also cause their reduction in addition with the hydroboration reaction. Thus, easily reducablefunctional groups like aldehydes must be protected as their acetal. Carboxylic esters are usually tolerated. Sometimes mono- or di-alkyl borane reagents are used for hydroboration which are less

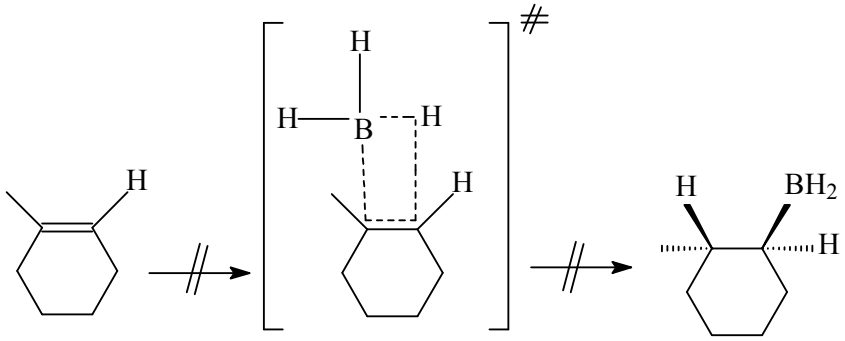
reactive and more selective than diborane and can be used for hydroboration of less-hindered alkenes. Common examples of such alkylborane reagents include disiamylborane, thexylborane and 9-borabicyclo [3.3.1] nonane (9-BBN).

6.8.2 Concerted Mechanism of Hydroboration

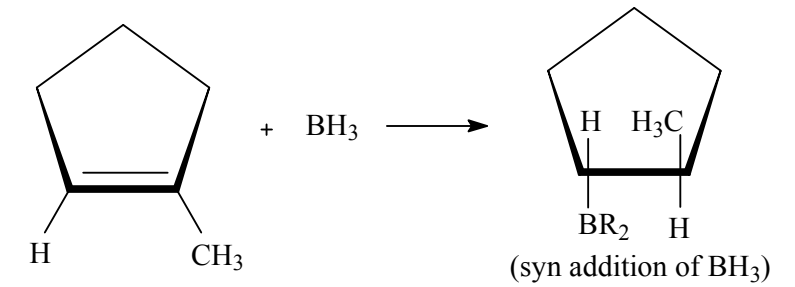
The boron atom is highly electrophilic because of its empty p orbital and the π-electrons of the alkene act as a nucleophile to attack the electrophilic B-atom. However, the reaction is a concerted process and no carbocation-type intermediate has ever been isolated. A four-membered transition state is thought to involve in which breaking of B—H bonds and making of C—H bonds all take place simultaneously as shown below for the hydroboration of methylcyclohexene.

The reaction results in anti-Markovnikov product i.e. the hydrogen adds to the more substituted carbon of the double bond. This regio-chemistry is reverse of a typical HX addition to the alkene which is a result of the polarity of the B—H bonds. The B—H bond in diborane is polarized ($B^{\delta+}$—$H^{\delta-}$) due to electronegativity difference between the B and H-atoms. As the addition of the empty p orbital to the less substituted end of the alkene gets under way, a hydrogen atom from the boron adds, with its pair of electrons, to the carbon atom, which is becoming positively charged. Thus, the addition is a syn addition. The formation of the C–B bond is slightly faster than that of the C–H bond (but still concerted) so that boron and carbon are partially charged in the fourcentred transition state. The developing positive charge is present on the more substituted carbon (analogous to a stable carbocation) and hence the reaction proceeds via anti-Markovnikov regiochemistry.





Due to the syn-addition of the boron and hydrogen atom, the reaction can also be stereoselective, with hydroboration taking place preferentially on the less hindered side of the double bond as shown for 1-methylcyclopentene.



1–Methylcyclopentene

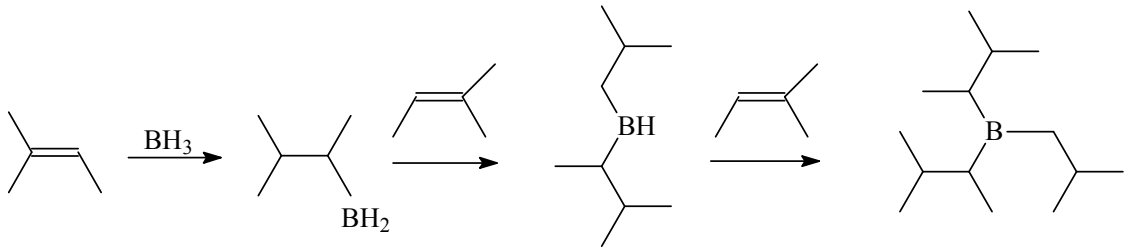
(syn addition of BH_3)

(R= 2–methylcyclopentyl)

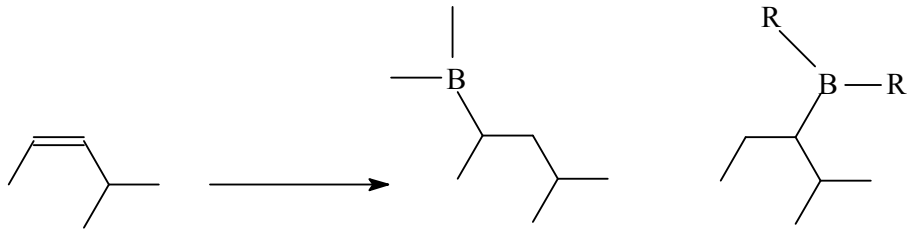
6.8.3 Steric-effects also explain regiochemistry and stereochemistry of hydroboration

Another explanation for the anti-Markovnikov regiochemistry of hydroboration is the steric effect of Boron containing group which is much bulkier than H-atom and hence boron gets attached to the less hindered end of the double bond. The selectivity of the first addition of borane is relatively low but the steric effect is more pronounced in the second or third successive hydroboration and anti-Markovnikov selectivity may predominate in the end.

With most substituted alkenes, the reaction stops at second hydroboration as third hydroboration becomes quite difficult due to increased steric strain.



However, it must be noted that borane itself may not give good regioselectivity as it is highly reactive and does not have enough steric bulk. The steric effect is more pronounced in sterically-congested alkylborane reagents like 9-BBN, which are also less reactive than borane and lead to enhanced regioselectivity. This is exemplified by the case of hydroboration of 4methylpent-2-ene by various boron reagents.



BH_3	57	:	43
disamylborane	97	:	3
9–BBN	99·8	:	0·2

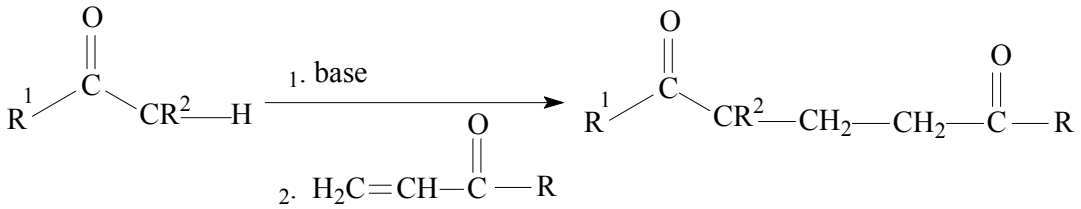
The sterically-congested alkyl boranes (9-BBN etc.) show extremely good stereoselectivities in bicyclic systems where the attack of 9-BBN occurs from the less hindered side as exemplified by the norbornyl systems as shown below.

Haloboranes like BH_2Cl, BH_2Br, $BHCl_2$, and $BHBr_2$ are also useful hydroborating reagents. These compounds show similar reactivity as borane but are somewhat more regioselective than borane. Also, after hydroboration, the halogen-atom can be replaced by hydride and subsequent hydroboration can be carried out and thereby preparation of unsymmetrical alkyl boranes can be carried out.

6.9 MICHAEL ADDITION

The Michael addition is an organic reaction used to convert an activated methylene and a conjugated olefin to the corresponding addition product using a base catalyst followed by an acid work-up. The activated methylene is essentially a methylene bonded to electron withdrawing groups that would stabilize the negative change that forms after deprotonation by the base. This deprotonation results in an enolate which in turn does a 1, 4 additions to the conjugated olefin. An acid work-up then provides the final Michael addition product

The substrates of the Michael reaction are compounds, esters, cyanides, quinines, α, β-unsaturated nitro compounds. Reagents of the reaction are those compounds which have at least one acidic hydrogen and convert into nucleophile in the presence of a base. Such compounds are compouns having active methylene group, nitroalkanes, sulphones, indene, fluoenes, alcohols, and thioalcohols and terminal alkynes. For example

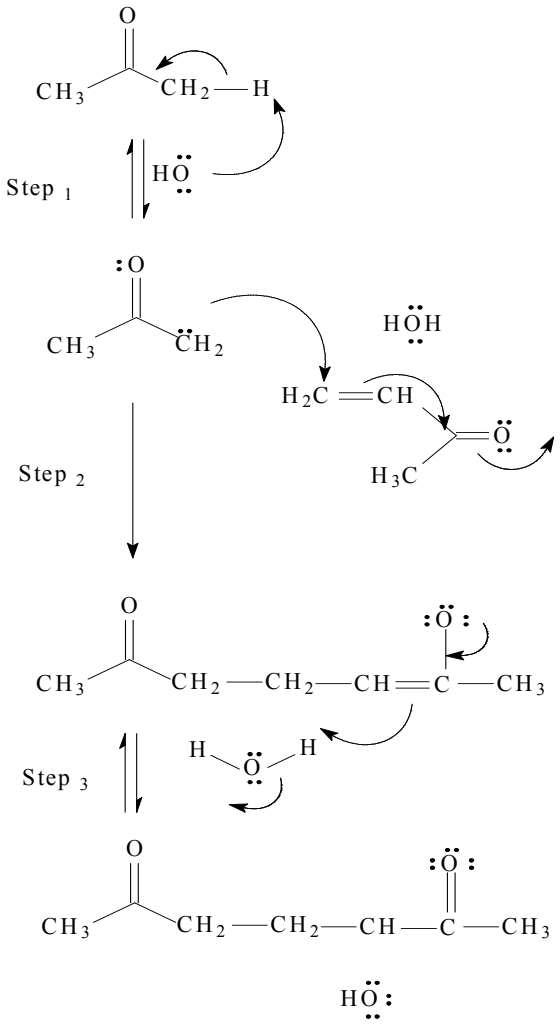


Mechanism:

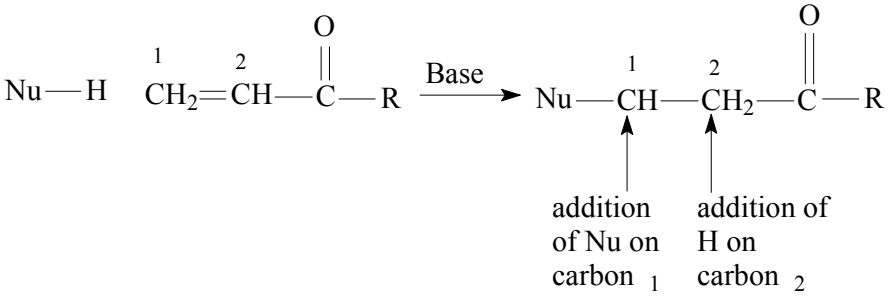
Step 1: First, an acid-base reaction. Hydroxide functions as a base and removes the acidic α-hydrogen giving the reactive enolate.

Step 2: The nucleophilic enolate attacks the conjugated ketone at the electrophilic alkene C in a nucleophilic addition type process with the electrons being pushed through to the electronegative O, giving an intermediate enolate.

Step 3: An acid-base reaction. The enolate deprotonates a water molecule recreating hydroxide and the more favourable carbonyl group.



Thus the net reaction can be written as followes

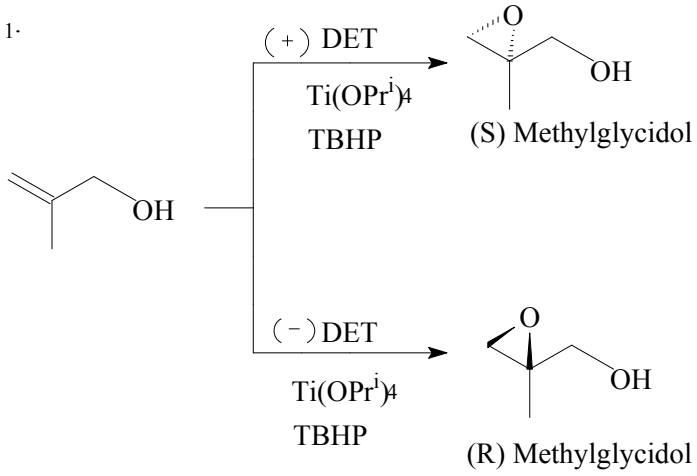


Michael addition is conjugate addition, i.e., 1,4-addition reaction but overall product of the reaction is 1,2-addition product which takes place on carbon-carbon double bond due to the tautomerisation.

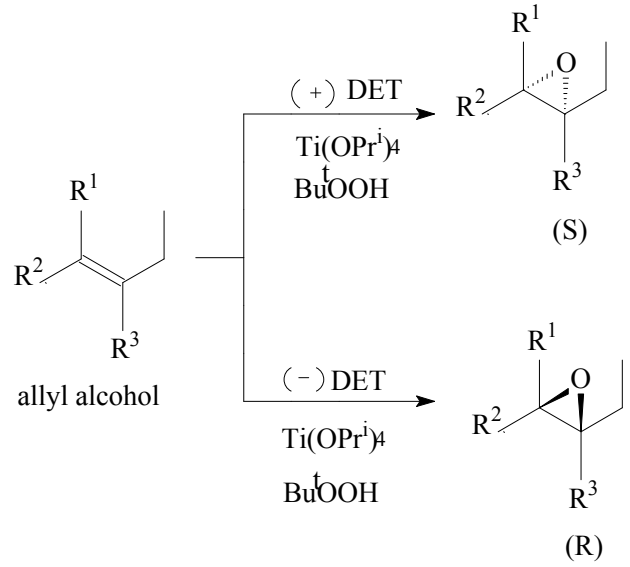
6.10 THE SHARPLESS ASYMMETRIC EPOXIDATION

The Sharpless and co-workers reported a method that has since become one of the most valuable tools for chiral synthesis. The Sharpless epoxidation is an organic reaction used to steroselectively (with preference for one enatiomer rather than formation of a racemic mixture) convert an allylic alcohol to an epoxy alcohol using a titanium isopropoxide catalyst, t-butyl hydroperoxide (TBHP), and a chiral diethyl tartrate (DET). The esters most commonly used are (+) or (-) diethyl or diisopropyl tartrate (DET and DIPT). The tartrate stereisomer that is chosen depends on the specific enantiomer of the epoxide desired. The main attraction of the Sharpless epoxidation procedure is that it effords a single enantiomer of the epoxide in high enantiomeric excess and in a predictable manner. For example

1.

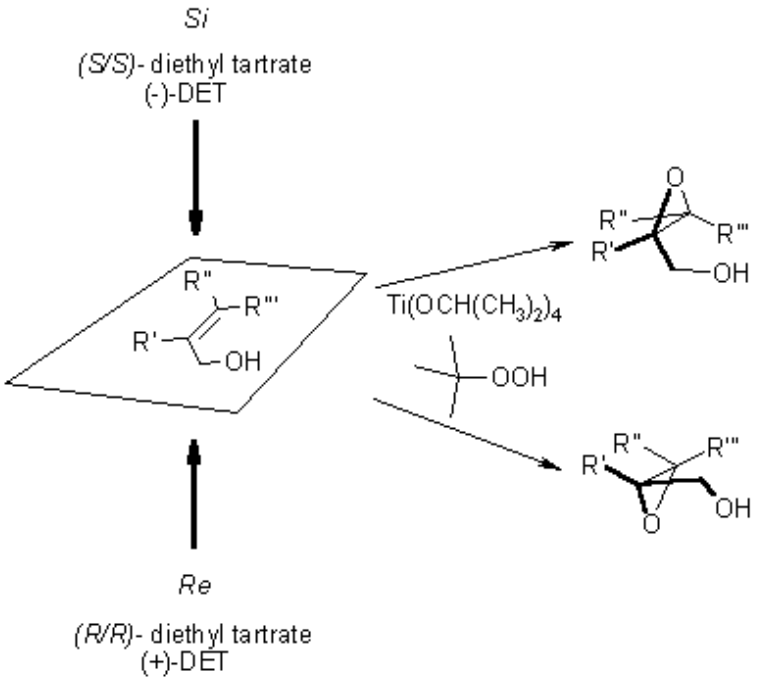


2.



6.10.1 Selectivity of Sharpless epoxidation

The chirality of the product of a Sharpless epoxidation is sometimes predicted with the following mnemonic. A rectangle is drawn around the double bond in the same plane as the carbons of the double bond (the *xy-plane*), with the allylic alcohol in the bottom right corner and the other substituents in their appropriate corners. In this orientation, the (−) diester tartrate preferentially interacts with the top half of the molecule, and the (+) diester tartrate preferentially interacts with the bottom half of the molecule. This model seems to be valid despite substitution on the olefin. Selectivity decreases with larger R^1, but increases with larger R^2 and R^3.



6.10.2. Mechanism of Sharpless epoxidation

As discussed, there are four main elements required for Sharpless epoxidation: the allyl alcohol, t-butylhydroperoxide (TBHP), the transition metal catalyst $Ti(O^iPr)_4$ and the chiral ligand (dialkyltartrate). Initially, the reaction involved use of stoichiometric amounts of the $Ti(O^iPr)_4$ catalyst but use of molecular sieves improved the scope of the reaction requiring only about 5-10 mol% Ti(IV) catalyst. However, no reaction takes place in the absence of the Ti-catalyst. $Ti(O^iPr)_4$ is added so that the oxidizing agent, the chiral ligand, and the substrate can assemble to form an enantiomerically pure chiral complex. The actual mechanism is not

known, but DFT and kinetic studies along with experimental results have led to a most plausible mechanism for this reaction (Fig.):

1. The coordination of the tartrate ligand to the Titanium catalyst occurs with displacement of two isopropoxide ligands (attributed to higher binding constant of the bidentate tartrateligand).

2. Then, the tert-butyl peroxide displaces one more isopropoxide followed by another isopropoxide displacement by the allyl alcohol to coordinate with the metal.

3. This Titanium complex is the active catalyst species and is believed to exist as a dimer. It has many features conducive for the successful epoxidation to occur:

(a) Instead of a planar arrangement, the peroxide-titanium interaction has a spiro arrangement in the TS for oxygen transfer.

(b) The O—O bond of peroxide is approximately perpendicular to the plane of the¬ alkene bond, facilitating the latter's attack.

(c) The steric effects of the bulky peroxide and the chiral tartrate ligand lead to such a¬ conformation of the TS that blocks one side of attack by the alkene and play an important role in deciding the enantioselectivity of the reaction.

4. Oxidation of the olefin with TBHP then occurs. The alkene acts as a nucleophile to attack the equatorial oxygen atom of the peroxide. Studies have shown that the dimeric complex has ester groups of the tartrate in axial positions which blocks one mode of approach. Thus, the chiral diiethyltartrate dictates the face of attack and leads to a steroselective epoxide alcohol.

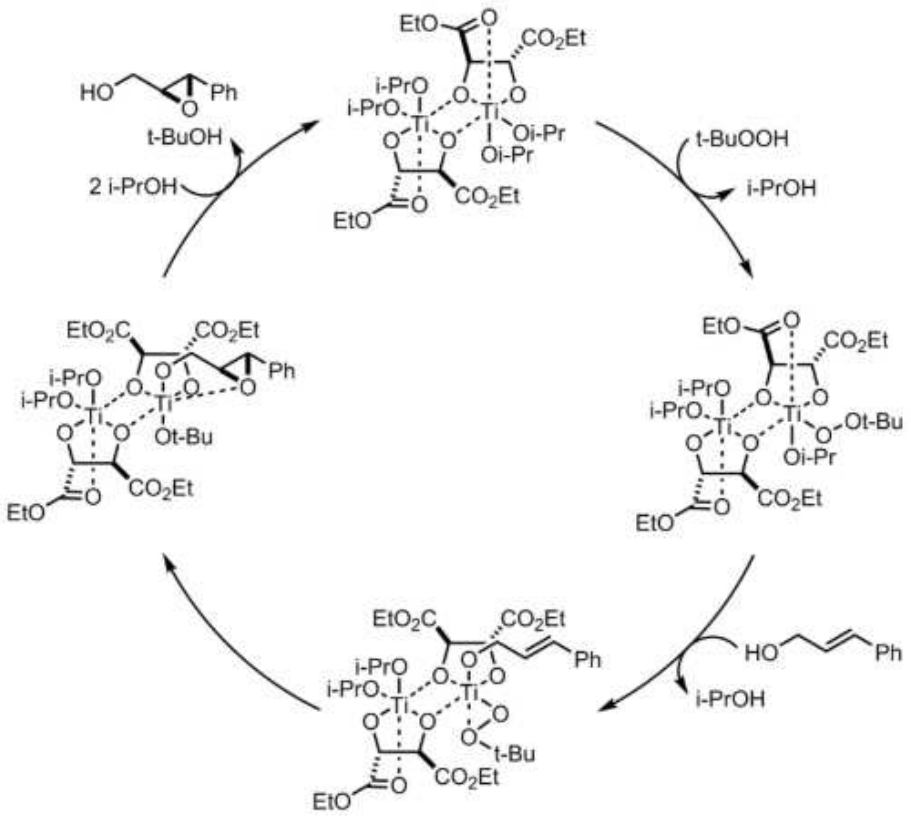
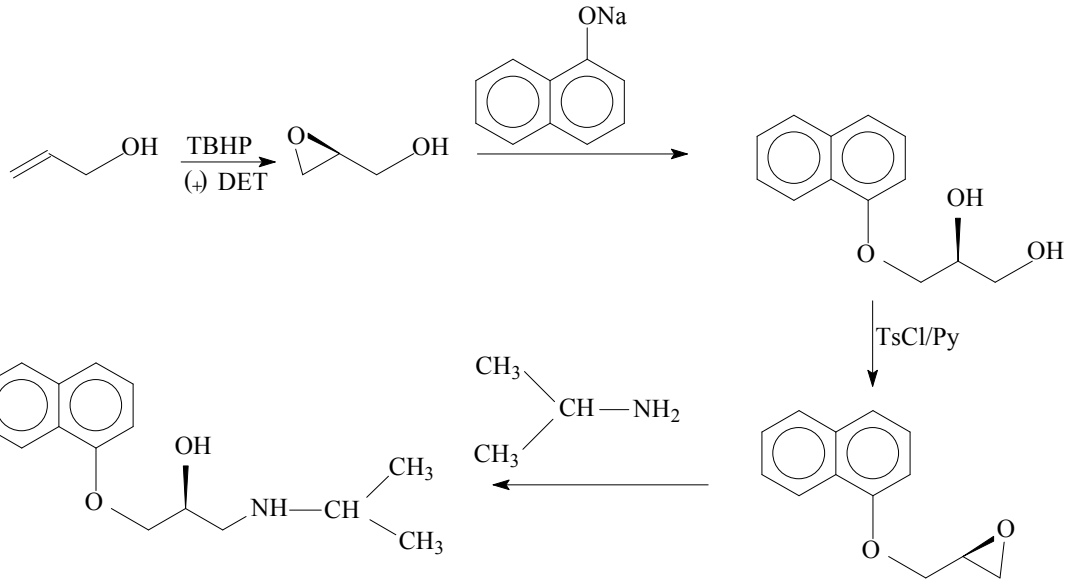


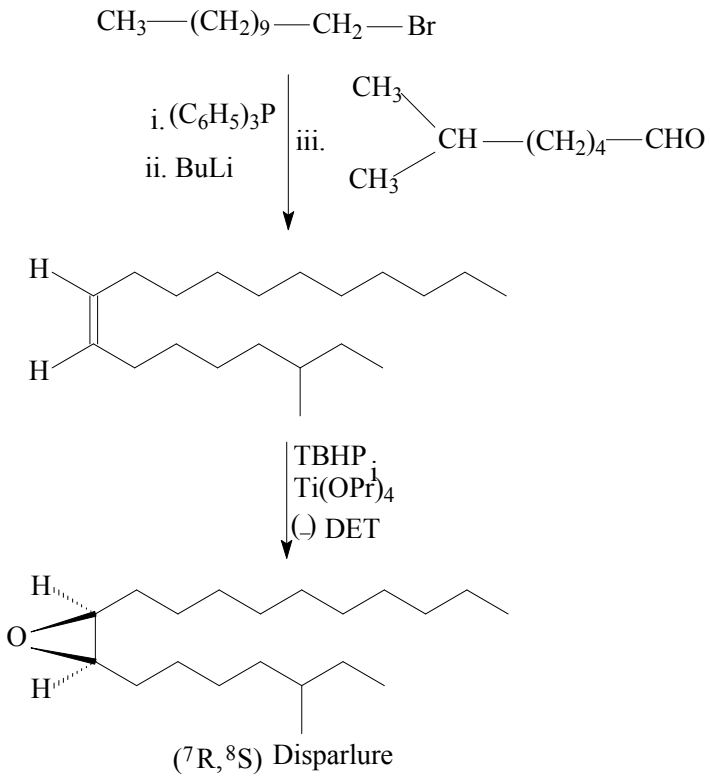
Fig.: 2 Catalytic cycle showing the Sharpless Asymmetric epoxidation

6.10.3 Application of Sharpless epoxidation

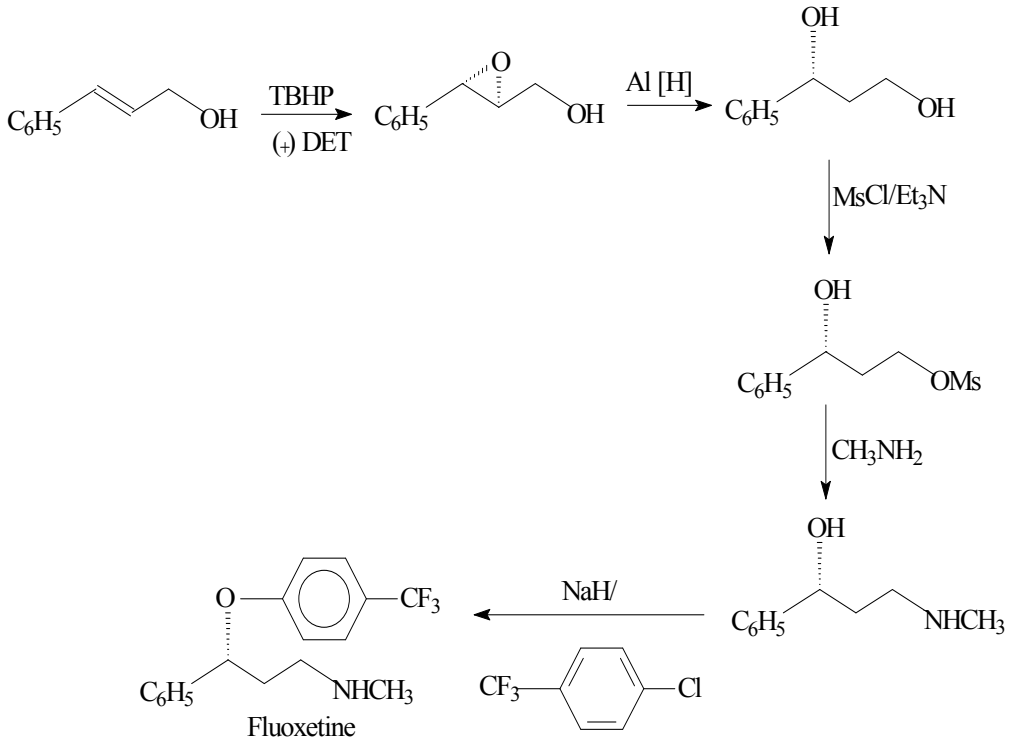
1. Synthesis of the β-blocker (S)-propranolol



2. Synthesis of gypsy moth pheromone (*7R, 8S*)-disparlure



2. Synthesis the anti-depressant drug fluoxetine



6.11 SYMMARY

In this chapter provided us concise knowledge about electrophile, nucleophilic and free radical addition reaction to carbon-carbon multiple bond. We also studied about addition to cyclopropane ring, hydrogenation of double, triple bonds and aromatic rings. We learned about hydroboration, Michael addition and the Sharpless asymmetric epoxidation reactions. We also studied about the stereoselectivity, mechanism of important name reactions with possible products.

6.12 TERMINAL QUESTIONS

1. Which one of the following alkenes will give optically active product with Br_2/CCl_4?

A. 1-Butene

B. Propene

C. *trans*-2-butene

D. *cis*-2-butene

2. Which one of the following alkenes will give optically active product with Bayer's reagent?

A. 1-Butene

B. Propene

C. *trans*-2-butene

D. *cis*-2-butene

3. In which compound electrophilic addition takes place according to *anti*-Markovnikov rule?

1. CH_2=CH-NO_2
2. CH_2=CH-CHO
3. CH_2=CH-CN
4. CH_3-CH=CH_2

Select the answer on the basis of given code:

Code:

A. 1, 2 and 3

B. 1, 2, 3 and 4

C. Only 4

D. Only 1

4. Consider the following statements:

1. Alkene is more reactive than alkyne for electrophilic addition
2. Alkyne is more reactive than alkene for nucleophilic addition
3. Alkyne is more reactive than alkene for electrophilic addition
4. Alkene having CF_3 at vinylic carbon is more reactive than alkene having CH_3

Of these, correct statements are:

A. 3 and 4
B. 1, 2 and 3
C. 1, 2 and 4
D. 1 and 2

5. Which among the following reagents gives syn-addition with alkenes.

1. Br_2
2. Dil $KMnO_4/OH^-$
3. OsO4 | NaSO3H | HOH
4. H2 | Ni | Δ

Select the answer on the basis of given code:

Code:

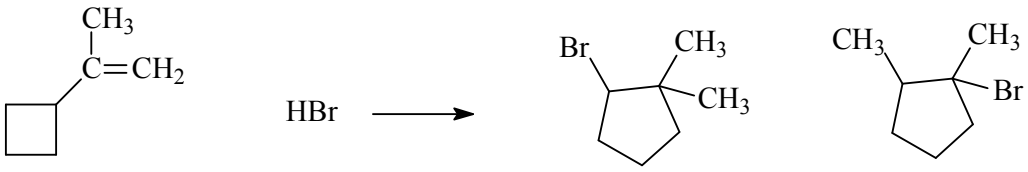
A. Only 1
B. 2 and 3
C. 2, 3 and 4
D. Only 4

6. Give the mechanism of and application of Sharpless asymmetric epoxidation.

7. Addition of HX on alkenes is regioselective. Why?

8. What is meant by iodolactonisation? Give mechanism of this reaction.

9. Propose the mechanism for the following reaction.



10. Predict the product of the following reactions:

1. $CH_3CH=CH_2 \xrightarrow{HBr}$

2. $RCH=CHR \xrightarrow[OH]{KMnO_4}$

3. $^3CH_3CH=CH_2 \xrightarrow{BH_3}$

4. $CH_2=C=CH_2 \xrightarrow{HCl}$

5. $CH_2=CH—CH=CH_2 \xrightarrow{Br_2}$

6.13 ANSWERS TO TERMINAL QUESTIONS

1. D

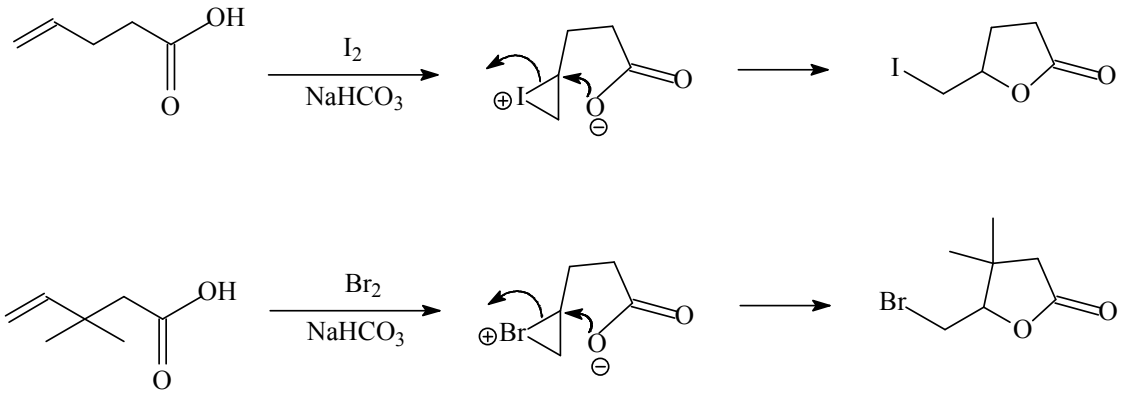
2. C

3. A

4. D

5. C

8. 4- Pentanoic acids from iodonium ion with iodine in the presence of $NaHCO_3$. This reaction is an example of electrophilic addition reaction in which electrophile is I^-. In the presence of $NaHCO_3$, carboxylic group convert in to carboxylate ion. Thus thus nucleophile of the reaction is carboxylate ion. The carboxylate ion attacks intramolecularly to form iodolactone. This type of reaction: the cyclization of 4-pentenoic acids in to lactone is known as iodolactonisation. This reaction is also given by bromine and in this case reaction is known as bromolactonisation. Intermolecular attack on the bromonium ion by bromide ion (or by I^-) does not complete with the intramolecular cyclization step.



6.14 REFERENCES

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2. Jerry March. 2007. Advanced Organic Chemistry-Reactions, Mechanism and Structure, John Wiley. 4th edition. 734-878.

3. Mukherji S. M. and Singh S. P. 2015. Reactions Mechanism in Organic Chemistry. Trinity Press. 328-364.

UNIT-7 ADDITION TO CARBON-HETERO ATOM MULTIPLE BONDS

CONTENTS:

7.0 Objectives

7.1 Introduction

7.2 Mechanism of metal hydride reductions in saturated and unsaturated carbonyl compounds

7.3 Addition of Grignard reagent with carbonyl groups

7.4 Reformatsky and related reactions.

7.5 Wittig reaction and its mechanism

7.5.1 Modified Wittig Reaction (Horner-Wadsworth-Emmons reaction)

7.5Knoevenagel reaction

7.6 Claisen condensation

7.7 Mannich reaction

7.8 Stobbe reactions

7.9 Stork enamine reaction

7.10. Concept and applications of Reaction Umpolung

7.11 Sulfur ylides

7.12 Summary

7.13 Terminal questions

7.14 Answers(MCQ) terminal questions

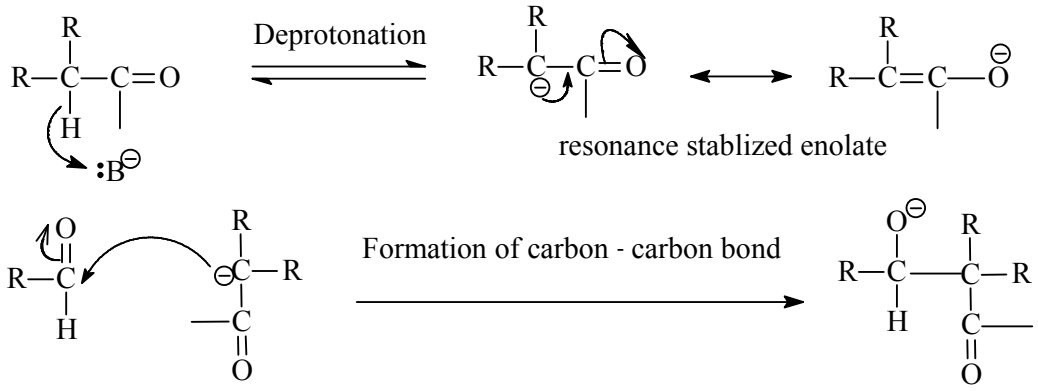
7.15 References

7. OBJECTIVES

Objective of this chapter is to make students aware about metal hydrides, their synthetic application particularly to remove the funcationality and introduction of stereocenters by gaining protons. This unit will also provide knowledge of addition of reagents to pi-bonds in a carbon-hetero atom multible bonds.Besides many important name reactions of synthetic utility alongwith the concepts of umpouling and sulfur yelides and their applications.

7.1 INTRODUCTION

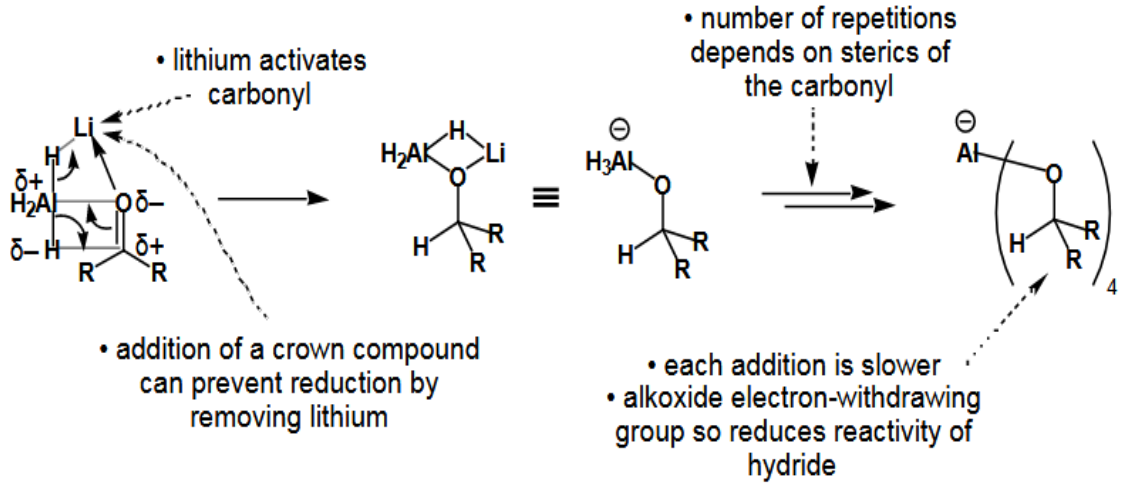
The carbon carbon hetero atom containing multiple bonds is very indespensible group of compounds for synthesis point of view. One of the important processes for carbon-caron bond formation is reaction between nucleophilic carbons with an electrophile. A very crusial mean to generate a carbon nucleophile is to remove proton from a carbon which generate carbanion. The rate of deprotonation for the generation of nucleophilic carbon and its stability are enhanced by the substituent groups attached.The negatively charged carbon attached with carbonyl or multiply bonded hetero atom gets stabilized by resonance through delocaiztion of electrons.The carbanions formed by deprotonation of α-hydrogen bear negative charge on hetero atom like oxygen and are termed as enolates.The enolates are highly reactive and resonance stabilized, react with electron deficient carbonyl compound and form carbon-carbon bond.



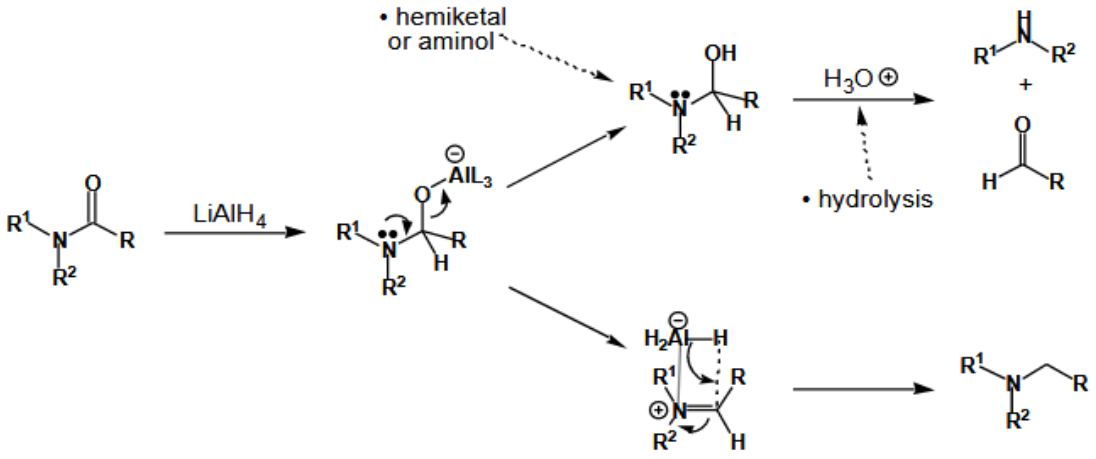
7.2 MECHANISM OF METAL HYDRIDE REDUCTIONS IN SATURATED AND UNSATURATED CARBONYL COMPOUNDS

Metal hydrides play very important role in the reduction of carbonyl groups. They play a versatile method for introducing stereocentres. Formally reduction is the gain of electrons but it is more easy to visualise it as the gain of hydrogen (although this far from mechanistically correct).The most common metal hydrides are lithium aluminium hydride ($LiAlH_4$) and sodium borohydride ($NaBH_4$) There are differences mechanistically In many cases the lithium cation is vital for reaction.

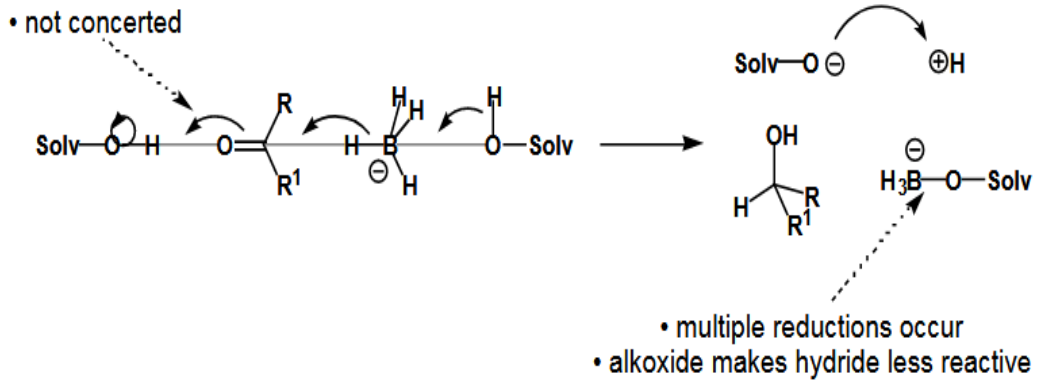
Reduction of ketone to alcohol



Reduction of amide to amine:-



In $NaBH_4$ reactions cation is not important but solvent can be not concentrated

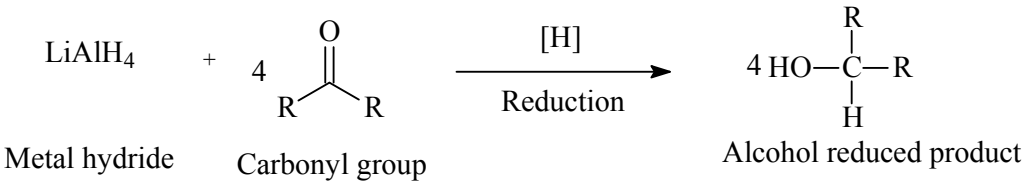


Lithium aluminium hydride $LiAlH_4$

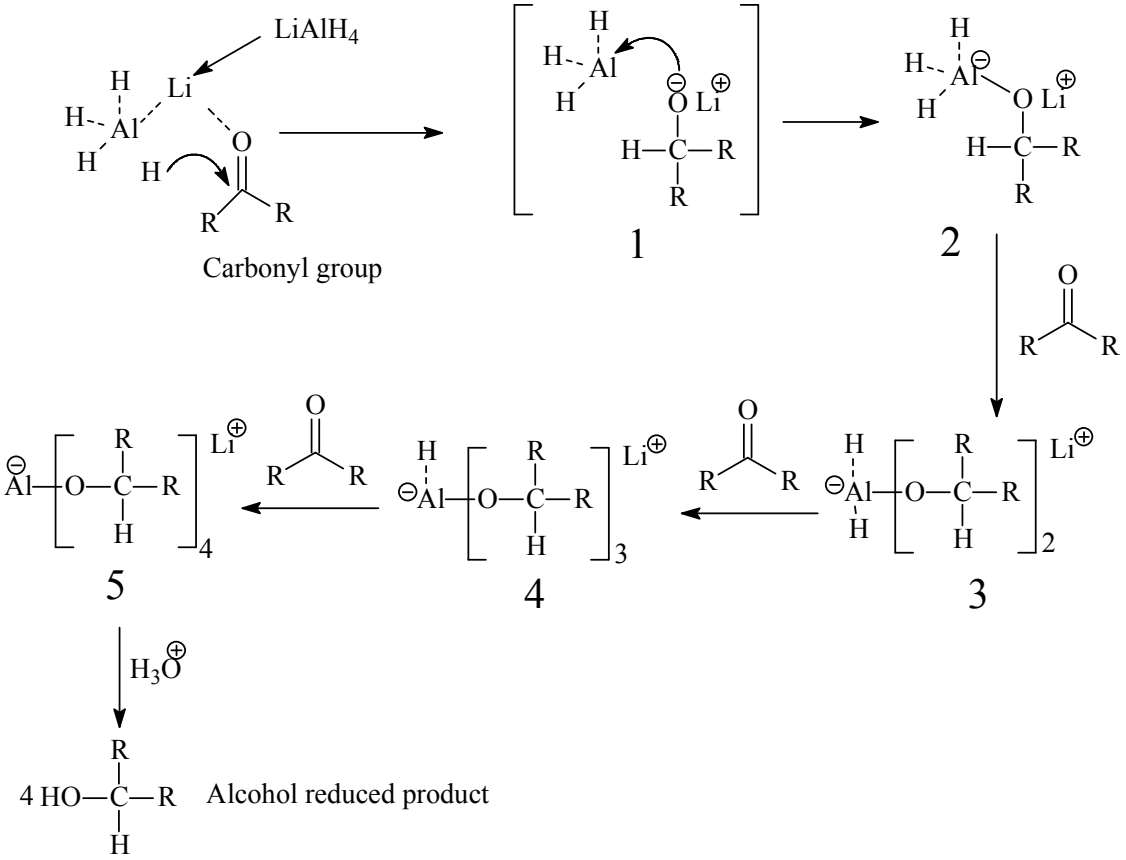
This metal hydride reduce all types of carbonyl groups.It also reduce other functional groups.Reaction of $LiAlH_4$ with acidic protons generate H_2

$$3LiAlH_4 + 4RCO_2H = LiAl(OCH_2R)_4 + 2\ LiAlO_2 + 4H_2$$

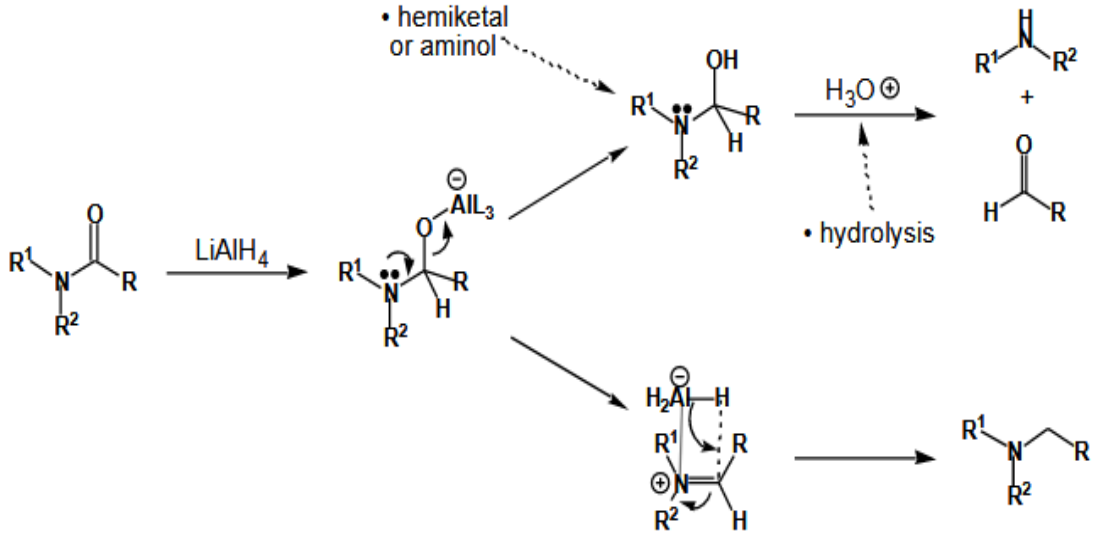
During carbonyl group reduction by $LiAlH_4$ there is a initial transfer of hydride to the carbonyl generates 2, possibly via direct coordination of aluminum to oxygen and transfer of hydride to the carbonyl carbon. Complex 1 has also been proposed as an intermediate.Alkoxide 2contains three additional active hydrides, so a second equivalent of carbonyl can react to give bis(alkoxide) 3. Similarly, a third equivalent gives 4 and a fourth gives 5.



Mechanism:



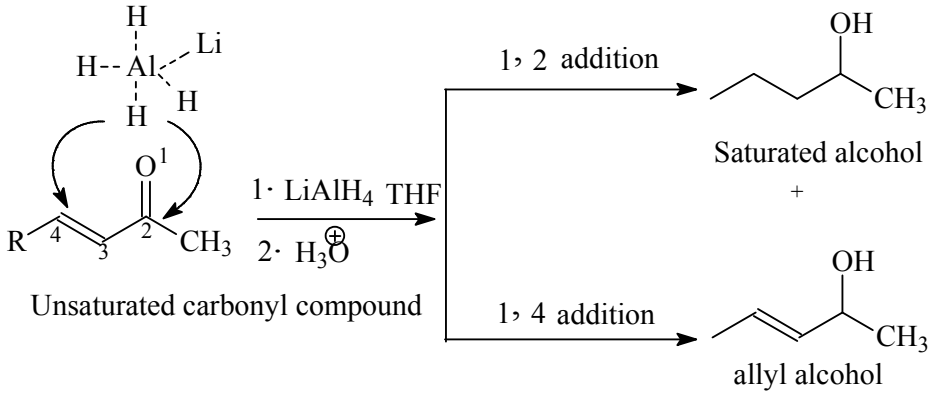
Mechanism of carbonyl group reduction by metal hydride like $LiAlH_4$



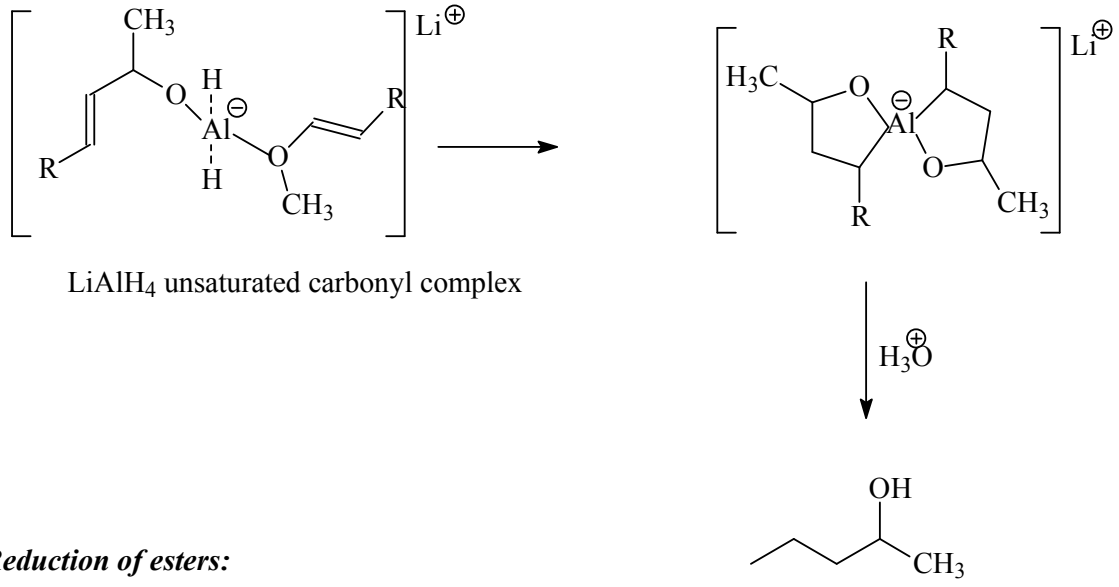
Reduction of amides to amine:

Which path is followed is a result of electronics around the amine

Similarly it reduces the unsaturated carbonyl group as in case of enones (α,β- unsaturated ketone The metal hydride react with unsaturated carbonyl compounds with same mechanism and yield a mixture of saturated and unsaturated alcohols as discussed follow.The metal hydride react with different way through 1,4-addition or 1,2 addition. Addition via normal 1,2 additon gives a saturated alcohol while via 1,4- addition gives allylic alcohol(unsaturated alcohol).

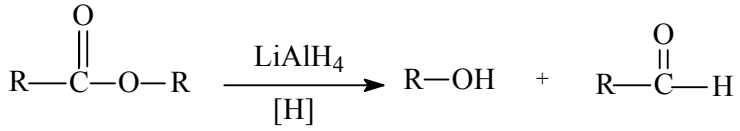


Mechanism: 1، 2 addition

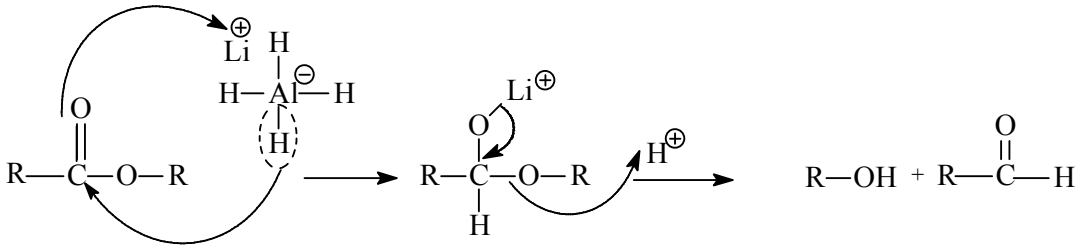


Reduction of esters:

The reaction mechanism of esters by metal hydride like $LiAlH_4$ is based on nucleophilic addition of hydride to the carbonyl carbon. In some cases, the alkali metal cation, especially Li^+, activates the carbonyl group by coordinating to the carbonyl oxygen, thereby enhancing the electrophilicity of the carbonyl.

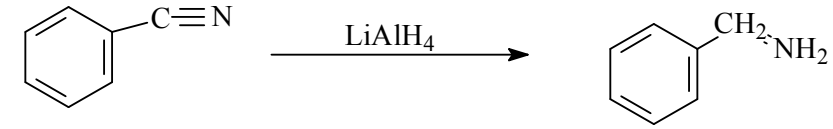


Mechanism



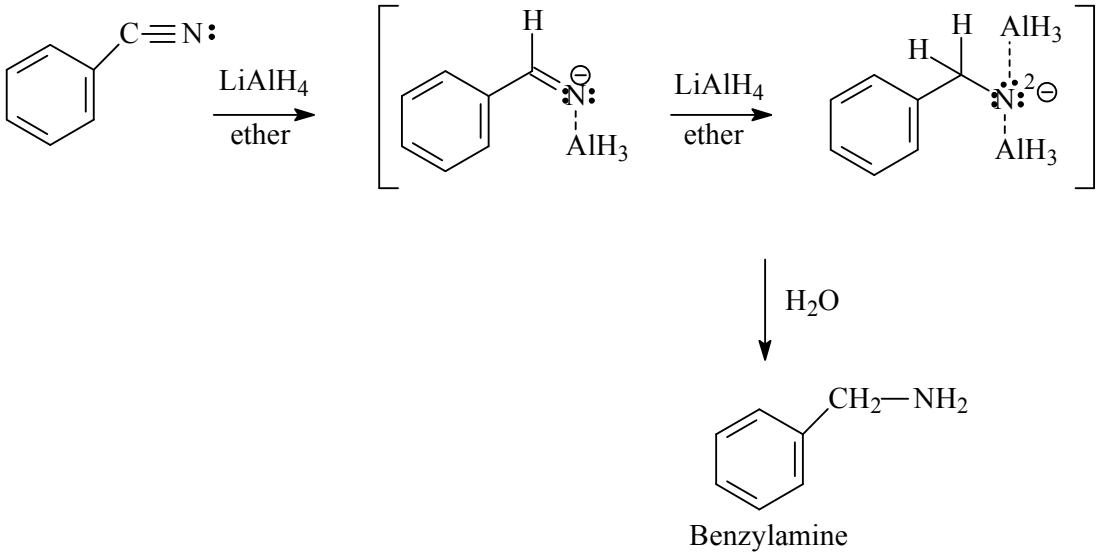
Reduction of acids:

Reduction of nitriles gives an amine via two successive hydride additions



Benzonitrile Benzylamine

Mechanism:

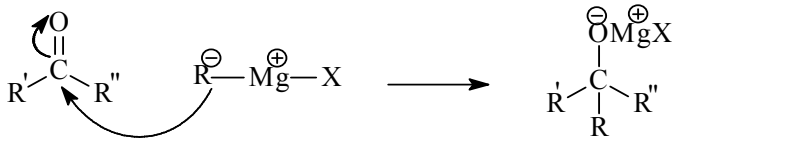


Benzylamine

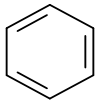
7.3 ADDITION OF GRIGNARD REAGENT WITH CARBONYL GROUPS

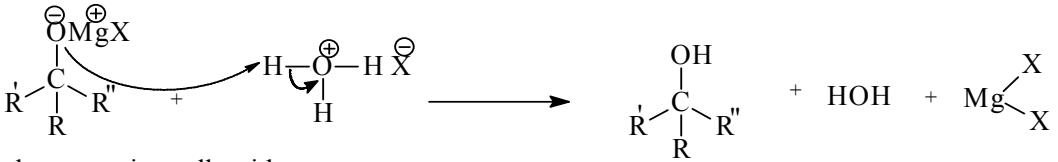
The Grignard reagent is an organometallic reagent like alkyl/aryl magnesium halide. Grignard reagents are prepared by the reaction of an alkyl or aryl halide with magnesium metal. The reaction is conducted by adding the organic halide to a suspension of magnesium in an etherial solvent, which provides ligands, required to stabilize the organomagnesium compound. The reaction of an organic halide with magnesium is *not* a Grignard reaction, but provides a Grignard reagent. This reagent is an important tool for the formation of carbon–carbon bonds. Some of the reactions of Grignard reagents with carbonyl groups are being explained herewith:

The carbonyl compound react with Grignard reagent to form halomagnesium alkoxide, which in susquent step react with water in presence of mineral acid (HX) to give alcohol. If the product is 3^0 alcohol than a solution of NH_4Cl in H_2O is preferred because 3^0 alcohols are pron to acid catalysed dehydration. Hence to avoid dehydration the ammonium chloride solution in water is used which convert the halomagnesium alkoxide to ROH(3^0 alcohol) without causing dehydration.



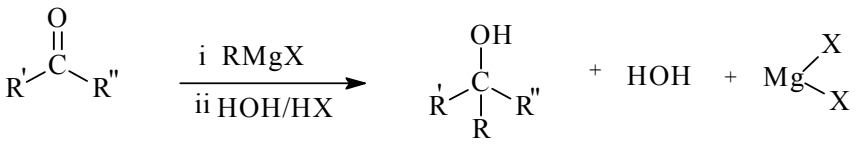
halomagnesium alkoxide

R= alkyl, or  X= halide, Cl,Br I etc

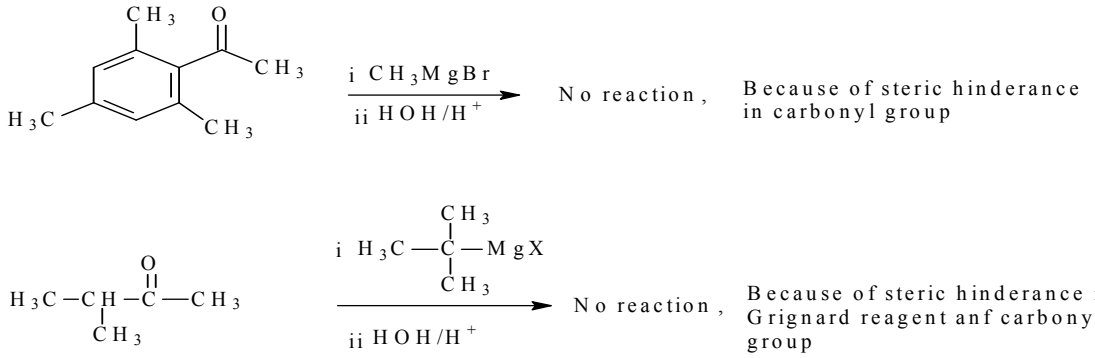


halomagnesium alkoxide

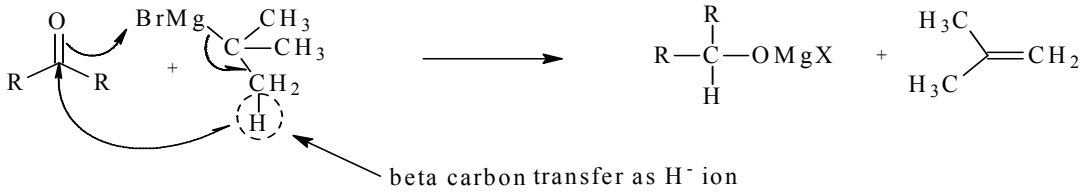
The oveeall reaction is:



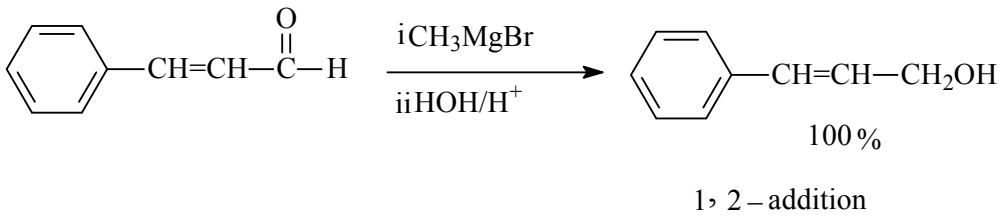
The addition of Grignadrd reagent is influenced by steric hinderance by the presence of groups around the carbonyl funcationality or in itself in Grignard reagent both. In such cases either the reaction does not take place or takeplace in reduced extent or sometime some abnormal different products have been reported.

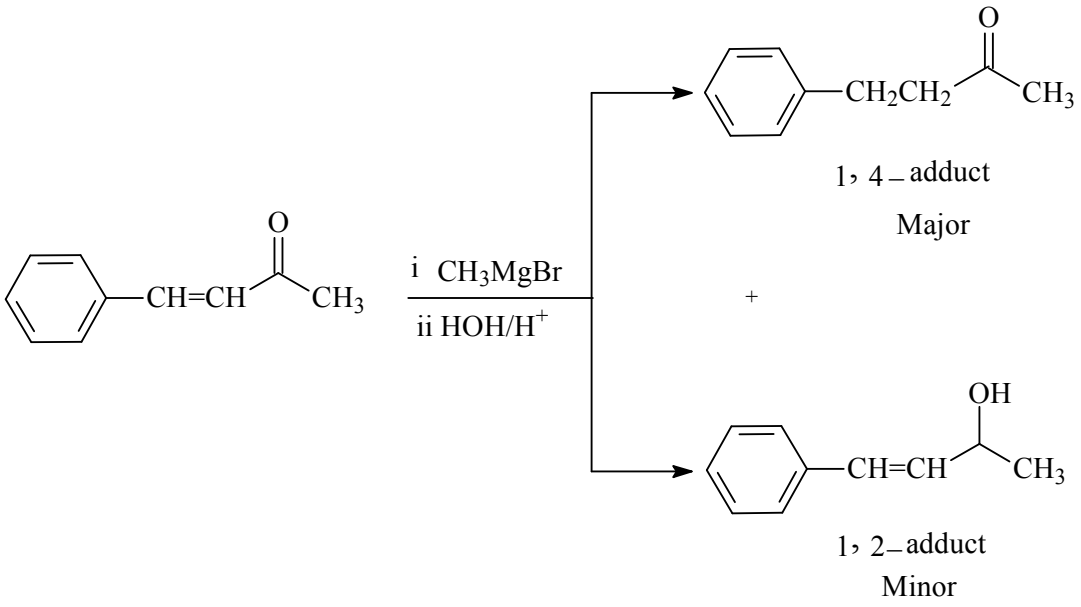


If bulky group of Grignard reagent has β- hydrogen which is abstractable then reduction of carbonyl group via hydride ion transfer is observed

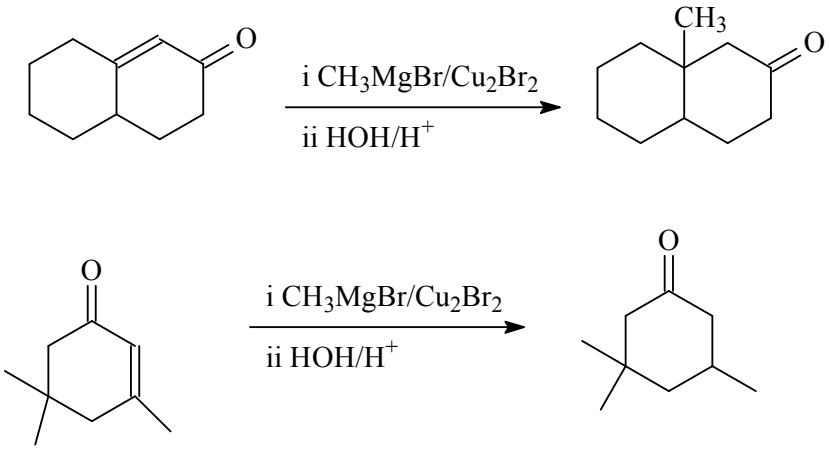


Grignard reagent adds to α, β –unsaturated aldehyde and ketones. In these reactions 1, 2 and 1, 4 addition products are formed. Generally α, β –unsaturated aldehyde gives dominantly 1, 2- addition product while ketones give 1, 4- addition product as the major one.

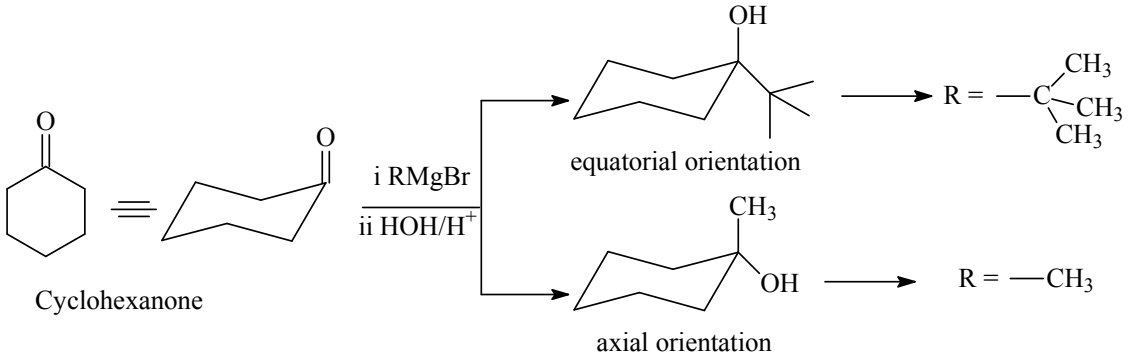




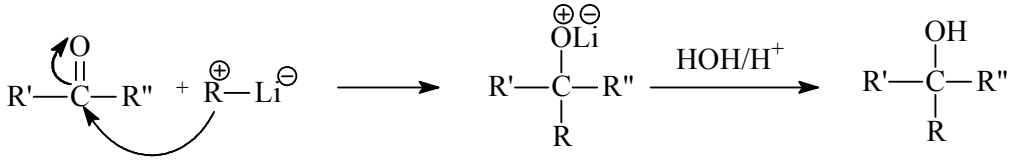
In presence of Cu_2Br_2 during addition of Grignard reagent in α, β –unsaturated ketones only 1, 4 –addition adduct is formed



Orientation of group in cyclic system like cyclohexanone depends upon bulky nature of ra group in Grignard reagent. If bulkier the group ,-OH orient in axial position, while in less bulkier group the position lies in equatorial side, because the reagent always attack to the keto group from less hindered side due to steric repulsion.



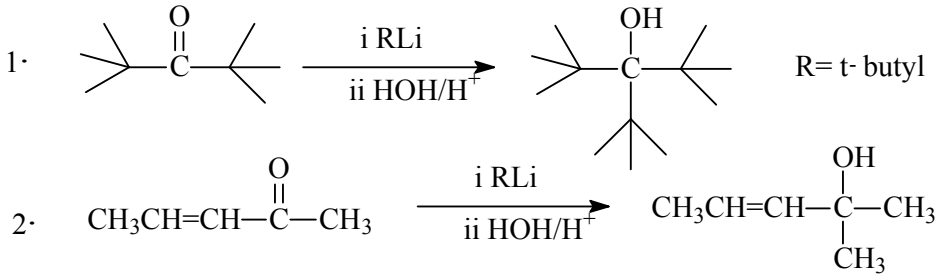
Similarly R-Li, the organolithium compound react with carbonyl and yields hydroxyl compound as a result of hydrolysis of RCOLi (lithium alkoxide). But in some case elimination as result of deprotonation because of strong basic nature of RLi has been observed.



There are few advantages of RLi compound over RMgX.-

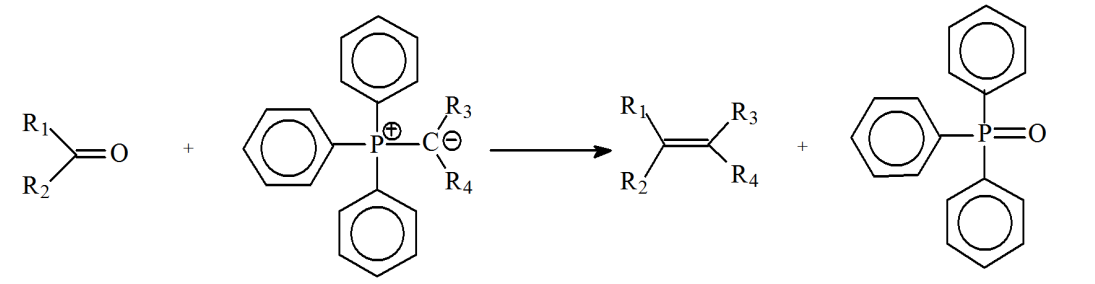
1. RLi react with hindered side and gives normal product, while RMgX fails to react with highly hindered side.

2. RLi compounds do not give conjugate addition products, they only give 1, 2 –addition reactions

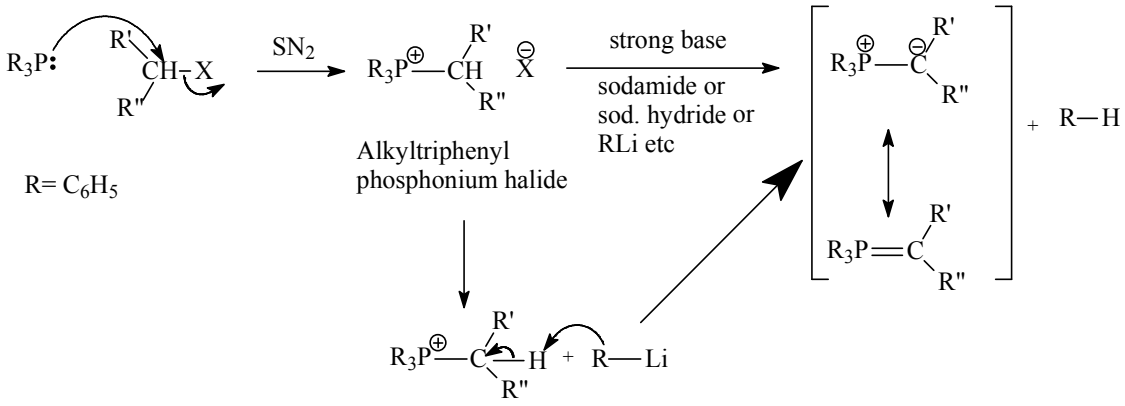


7.5 WITTIG REACTION AND ITS MECHANISM

The reaction of aldehyde with phosphorane or phosphonium ylide (tre Wittig's reagent) to produce an olefinic compound is dessignated as Wittig reaction. The Wittig reaction was discovered in 1954 by Georg Wittig, for which he was awarded the Nobel Prize in Chemistry in 1979. It is widely used in organic synthesis for the preparation of alkenes

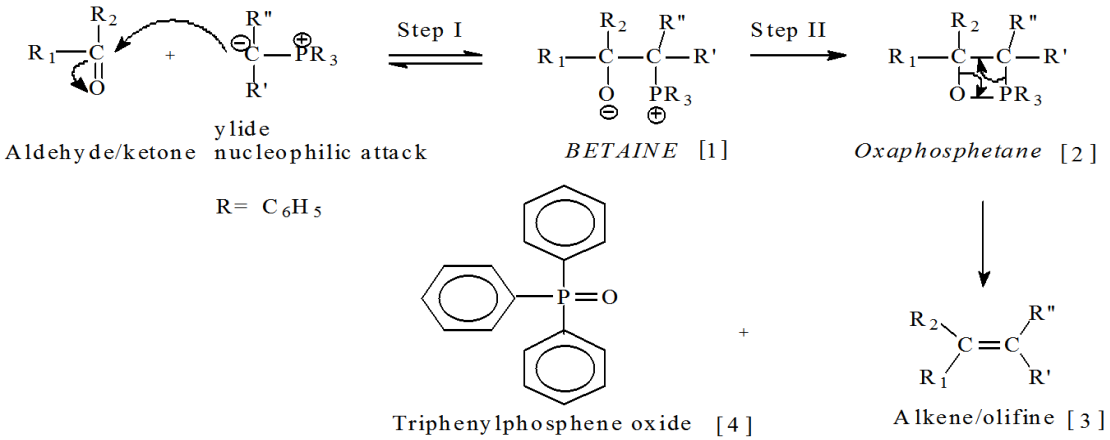


The Wittig reagent in this reaction is prepared from triphenylphosphine and alkyl halides with at least one α- hydrogen.(1^0 or 2^0 alkyl halides) in presence of astrong base usually alkyllithium, sodium hydride or sodamide which abstract hydrogen from carbon which is attached with phosphorus to give oppositely charged adjacent group known as yelide.



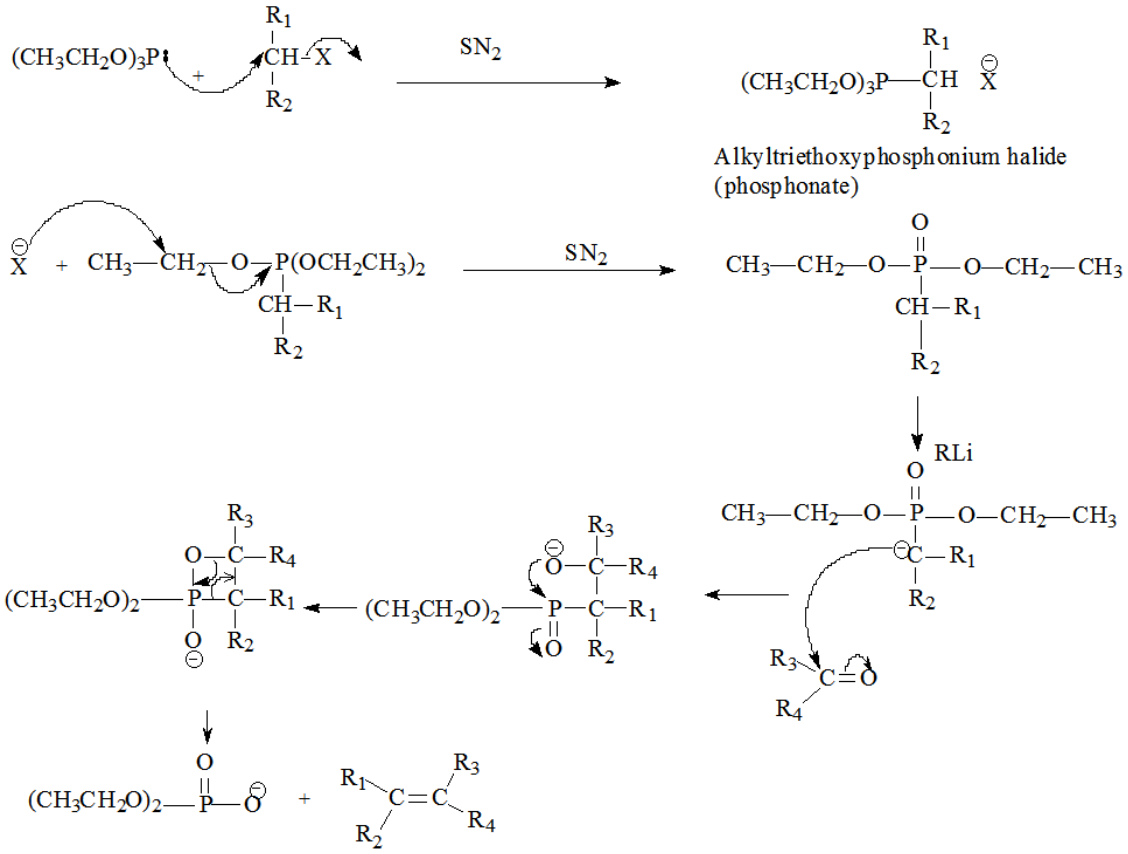
Mechanism:

The carbon of ylide with negative charge is a nucleophile and attack to carbonyl group to give addition product BETAINE [1]. Betaine further leads the formation of four membered ring oxaphosphetane [2].The four membered oxaphospetane intermediate is formed because of strong phosphorus oxygen bond. The ring is strained and unstable, which ultimately gives an alkene (olifine) [3] and triphenylphosphene oxide [4]. The complete mechanism is as under:-



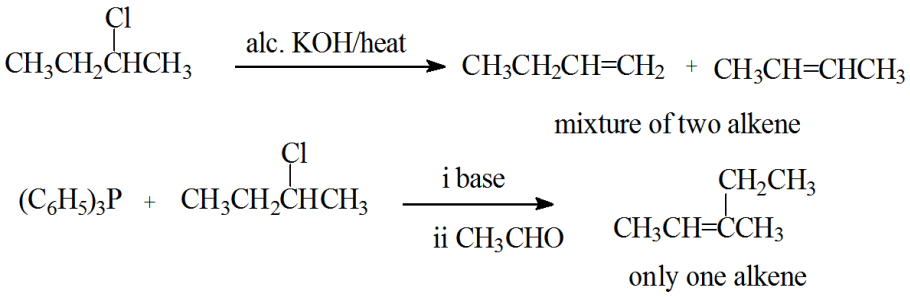
7.5.1 Modified Wittig Reaction (Horner-Wadsworth-Emmons reaction:

A variation in Wittig reaction was done by Horner-Wadsworth-Emmons and known as Horner- Wadsworth-Emmons modification. In this modification a phosphanate ester instead of triphenyl phosphonium salt was used. Formation of phosphonate in this reaction is known as Arbuzov reaction.The base used in this reaction were NaH, potassium tert-butoxide and phenyllithium.The entire reaction sequence can be understand as follow:-

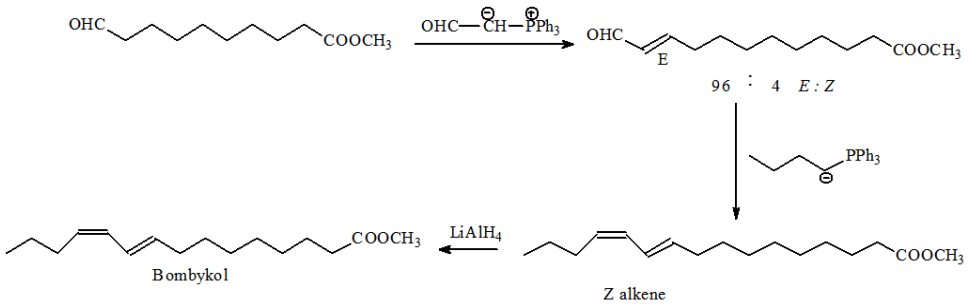


Application of Wittig reaction:

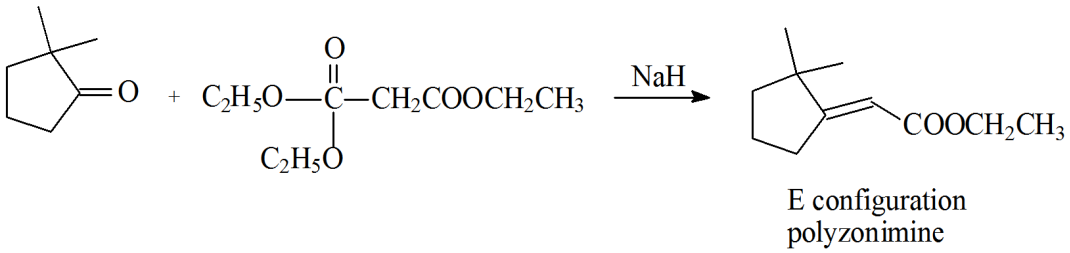
This reaction is widely applicable for the synthesis of alkenes from aldehydes and ketones.A Wittig reaction gives advantage over most other alkene synthesis in that no ambiguity exists as to the location of double bond in the product. This is incontrast to β- elimination reaction of alkyl halides which gives multiple alkene products either by rearrangement or by β- carbon as under.



One of the applications of Wittig reaction is synthesis of pheromone known bombukol in two consecutive steps

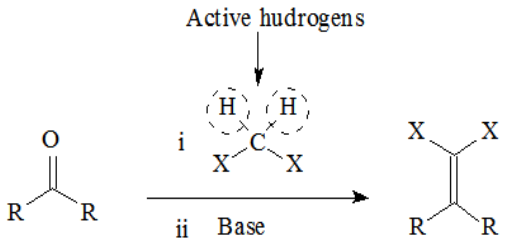


Polyzonimine a natural insect repellent produced by millipedes having E- geometry can also be synthesized by Wittig reaction.

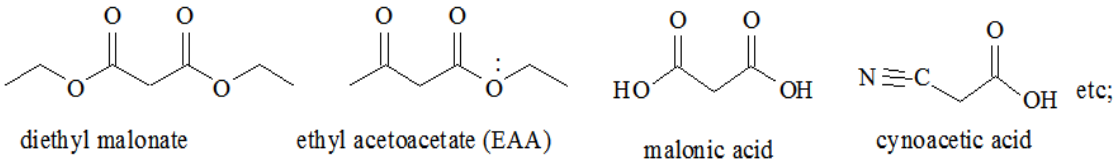


7.5 Knoevenagel reaction

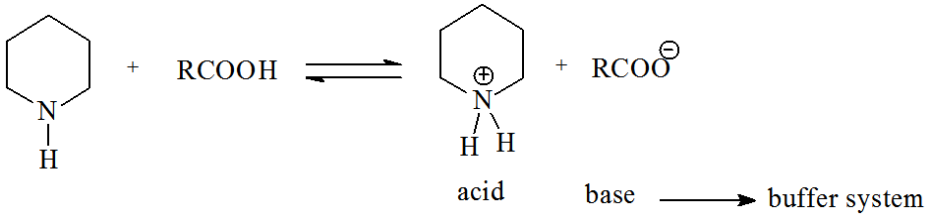
It is a modified aldol condensation. In is simply a nucleophilic addition of active hydrogen to the carbonyl group which finally undero dehydration with the formation of α, β- unsaturated product.This reaction is catalysed by amines generally piperidine/buffer system containing an amine and acid. A base is required to generate carbanion while acid is for activation carbonyl group.



X = electron withdrawing group, XCH_2X may be



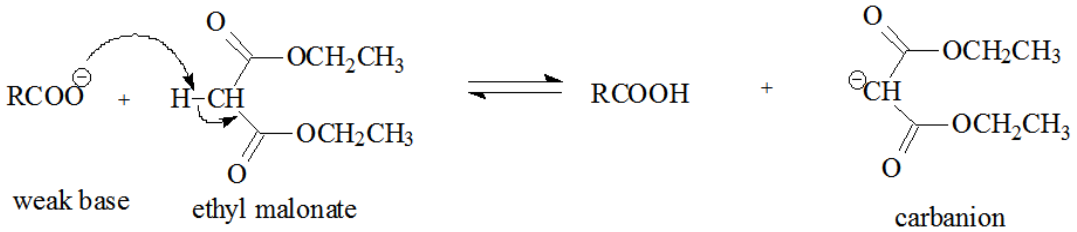
diethyl malonate ethyl acetoacetate (EAA) malonic acid cynoacetic acid



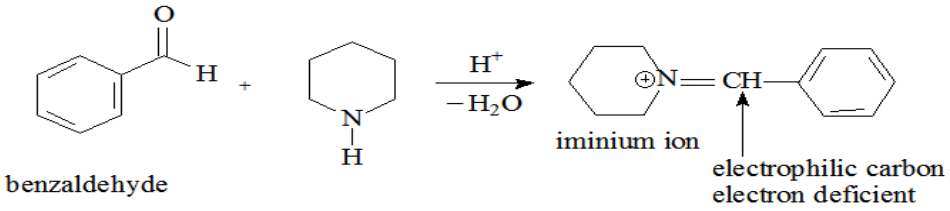
Mechanism of the reaction:

The sequencewise mechanism of Knoevenagel reaction is as follow:-

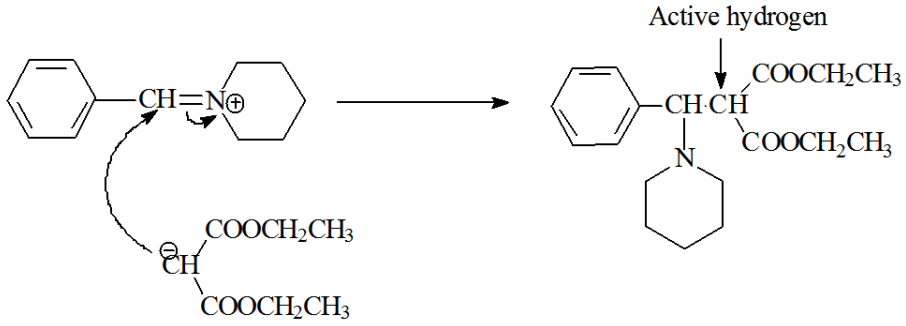
Step-I The weak base $RCOO^-$ abstract the hydrogen from active methylene group and provide aresonance stabilized enolate/ crabanion.



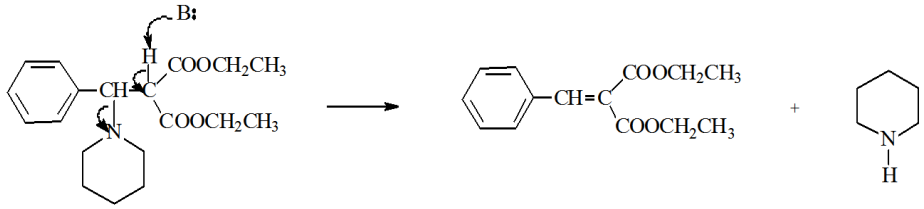
Step II. This step involve the formation of reactive electrophile from pyridine by reaction with aldehyde viz; benzaldehyde to form iminium ion. This intermediate is more reactive than carbonyl group.



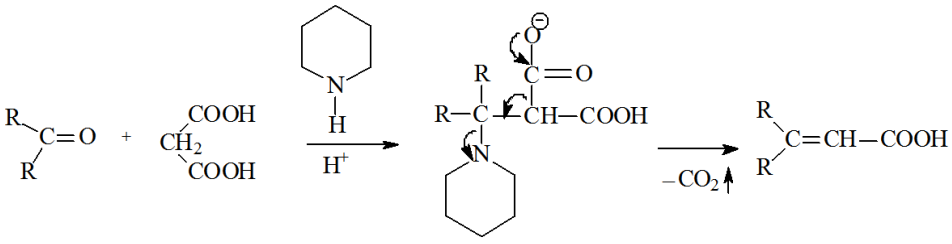
Step III In this step the electron-deficient carbon of iminium ion is attacked by carbanion



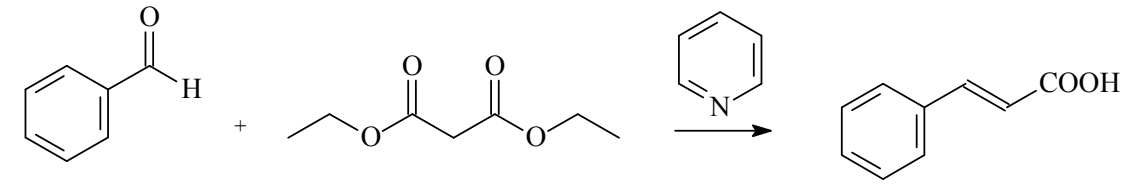
Step IV The weak base depronates acidic hydrogen followed by elimination of NR_2 group to give α, β- unsaturated derivative of the adduct



With malonic acid or cynoacetic acid as reactant, the products usually undergo decarboxylation, which occurs as a concerted decomposition.



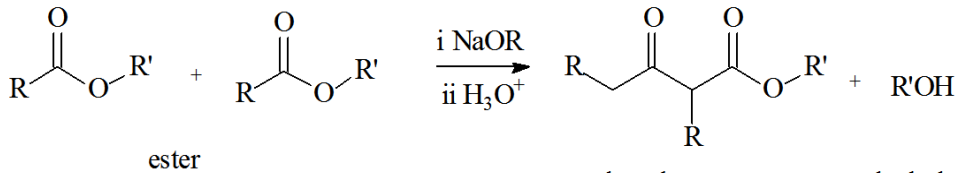
Decarboxylation is also carried out in presence of pyridine.



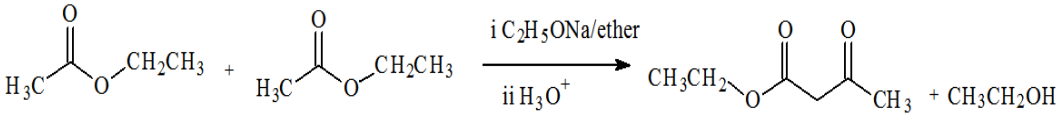
benzaldehyde

7.6 CLAISEN CONDENSATION

The Claisen condensation is a reaction between two esters or one ester and another carbonyl compound in the presence of a strong base like alkosixd to form carbon–carbon bond. As aresult of Claisen reaction a β-keto ester or a β-diketone is formrd.



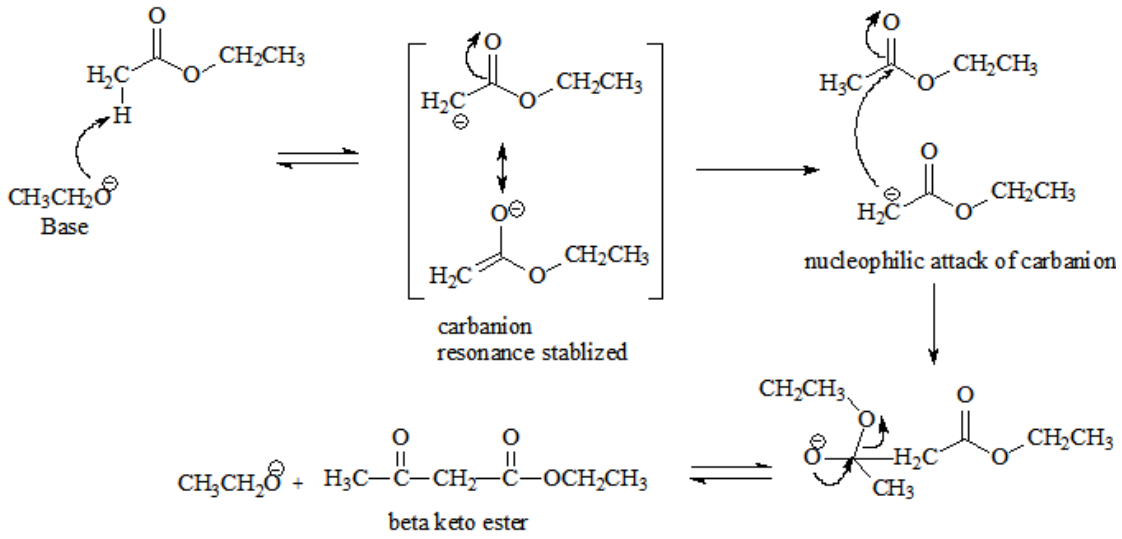
ester beta keto ester alcohol



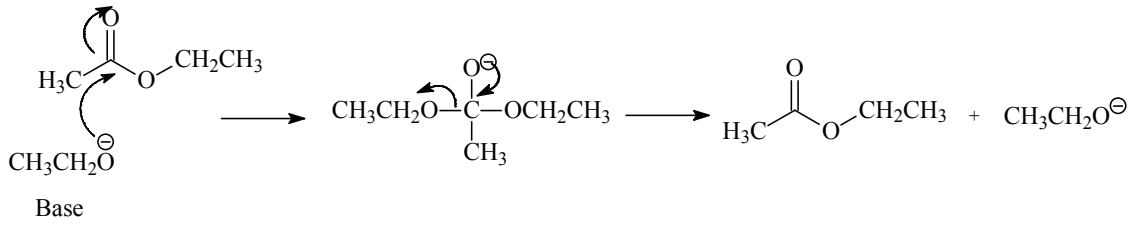
ethylacetoacetate beta keto ester alcohol

Mechanism:

The ester in first step reacts with alkoxide to form enolate or cabanion by the removal of hydrogen due to base. The enolate/carbanion so formed is resonance stabilized and reacts nucleophilically with another molecule of ester which finally gives β-keto ester as end product. The entire mechanism is as follow

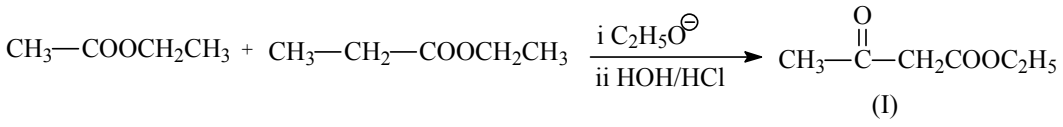


As ethoxide ion is anucleophile, it can attack the carbonyl group of the ester to give usual carbonyl substitution reaction but the product are same as the reactant.This is the reason why ethoxide ion is used as a base in the Claisen condensation.

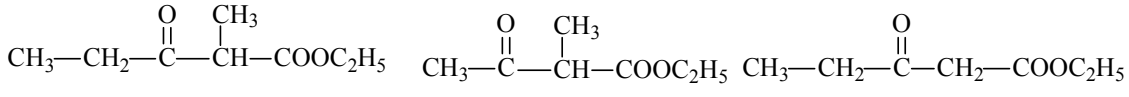


Crossed Claisen Condensation:

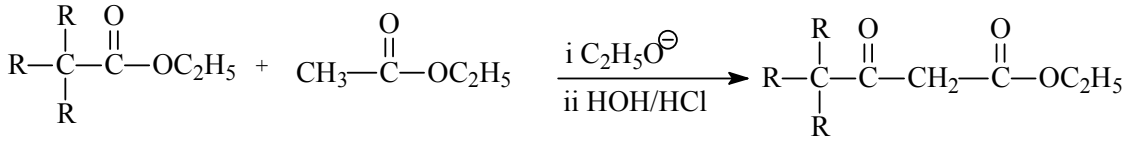
In crossed Claisen condensation two reactin esters are of different types.The reactions are synthetically not so useful if both the ester contain α- hydrogens with comparable acidity. Such esters give mixiture of all of the four possible products. However successful crossed Claisen condensation makes use of one ester which lacks any α- hydrogens. Such esters are known as reactive esters and do not undergo enolization.such esters serve as a carbanion acceptor



(I)

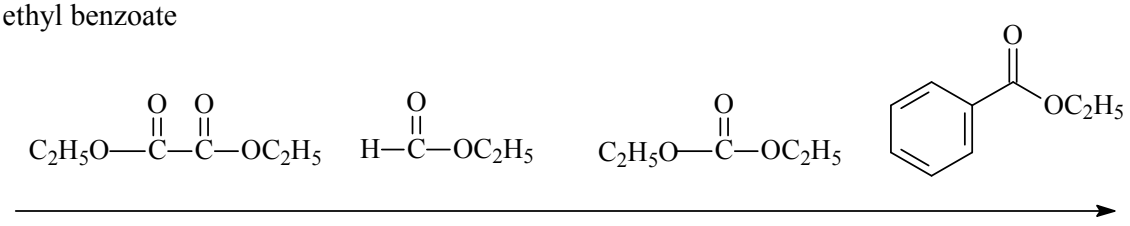


(II) (III) (IV)



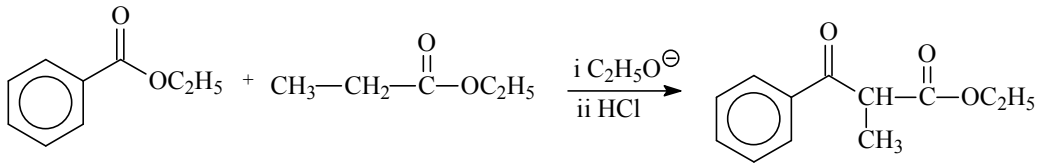
As the only cross product

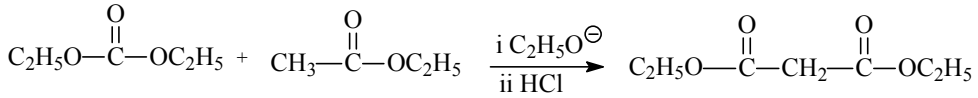
Reactive esters that cannot enolise are diethyl oxalate, ethyl formate, diethyl carbonate and ethyl benzoate



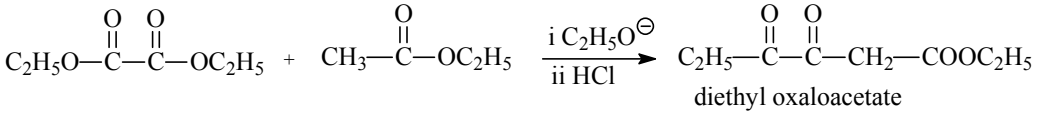
Eletrophilic character of carbonyl carbon in decreasing order

Some examples of crossed Claisen condensation are as follow:-

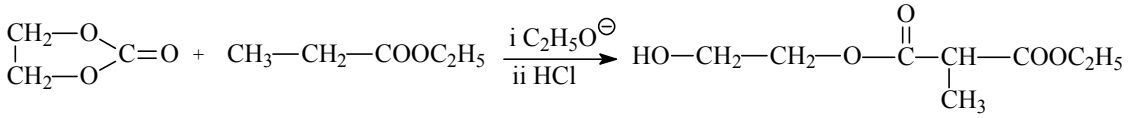




diethyl malonate



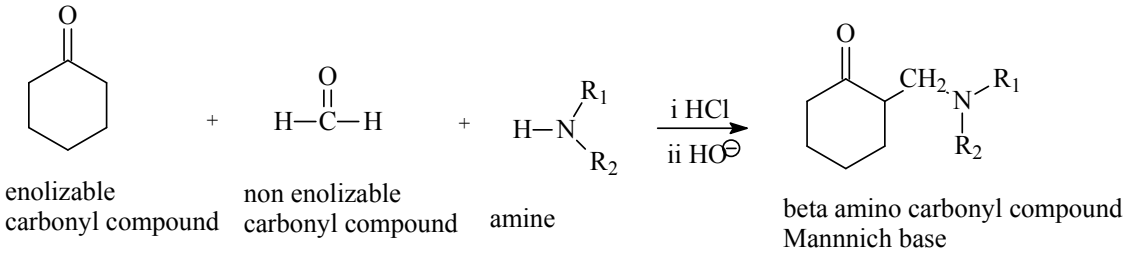
diethyl oxaloacetate



7.7. MANNICH REACTION

A Mannich Reaction is a formation of a β - amino carbonyl compound. The Mannich base is an endproduct in the Mannich reaction, which is formed through nucleophilic addition reaction of a non-enolizable aldehyde (formaldehyde) and any primary or secondary amine to produce resonance stabilized imine salt. Finally the addition of a carbanion from compound

(any enolizable carbonyl compound, amide, carbamate etc.) to the imine gives the Mannich base.

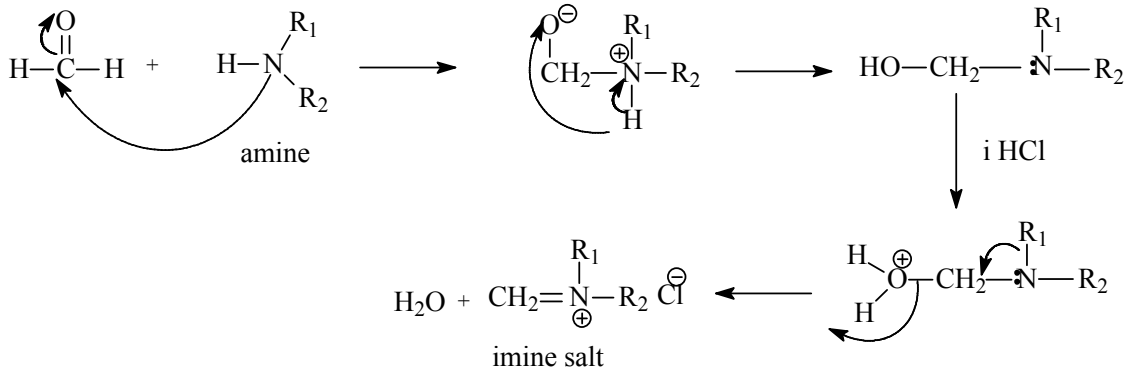


enolizable carbonyl compound | non enolizable carbonyl compound | amine

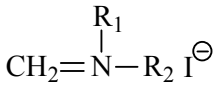
beta amino carbonyl compound
Mannnich base

Mechanism:

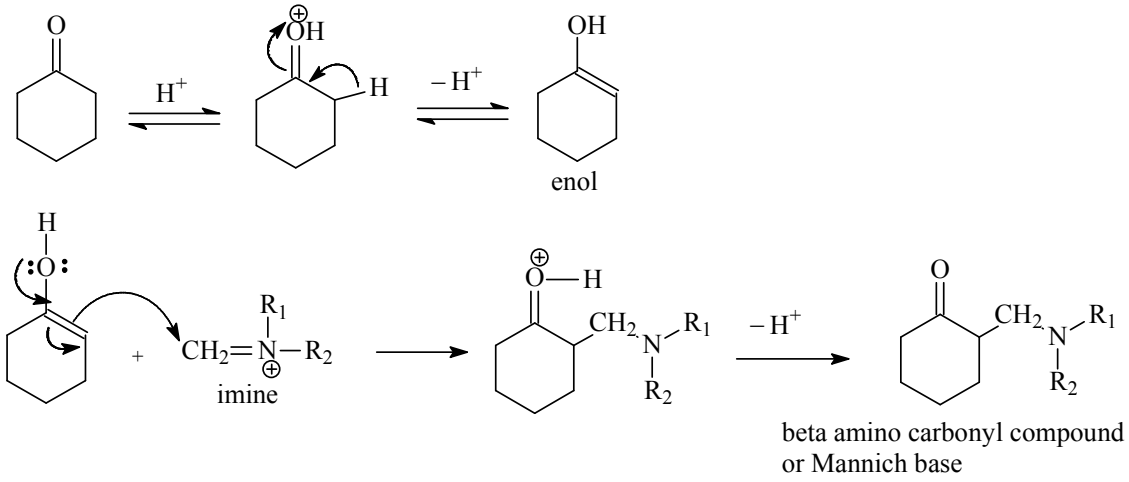
The mechanism involve the formation of imine salt first from formaldehyde and amine. In this reaction being nucleophilic nature of amine it attacks the carbonyl group of formaldehyde. No acid is required for that, however the acid-catalysed dehydration of the addition product reveals the imine salt as follow.



The imine salt is a just intermediate but quite stable. The iodide salt is solid in nature and known as **Ecchenmoser salt**.

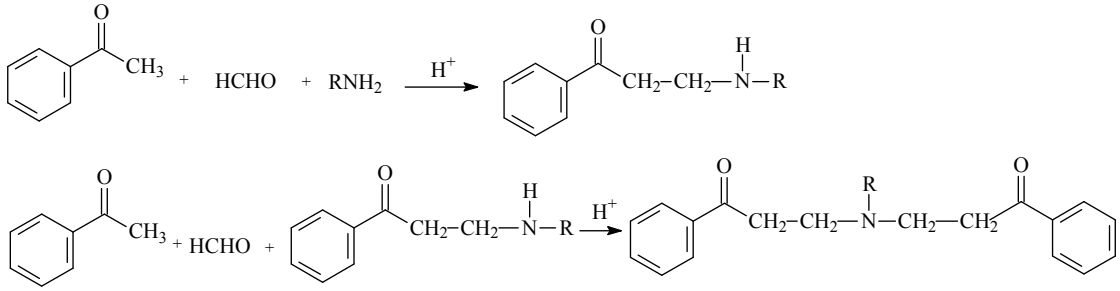


The electrophile imine salt now add to the enol form of carbonyl compound to give the product of the reaction, β- amino carbonyl compound or Mannich base

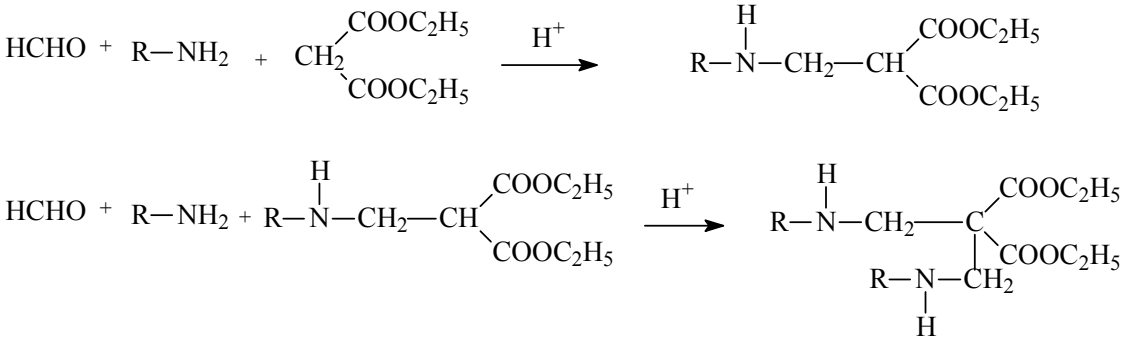


The reaction can further react by there different way provided that:

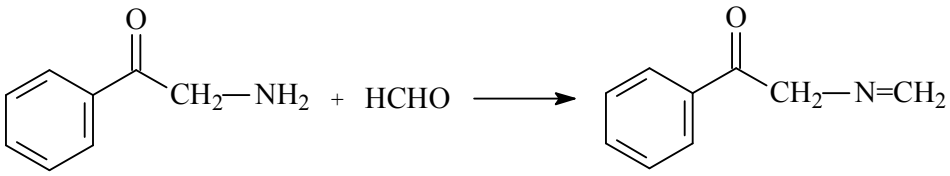
1. The Mannich base is 1^0 or 2^0 amine, in such cases it condense further with two or one additional HCHO and enolizable carbonyl compound.



2. The enolizable carbonyl compound has active methylene group, stepwise condensation of two or more molecules of HCHO and amine with one molecule of the compound with active methylene group will take place.

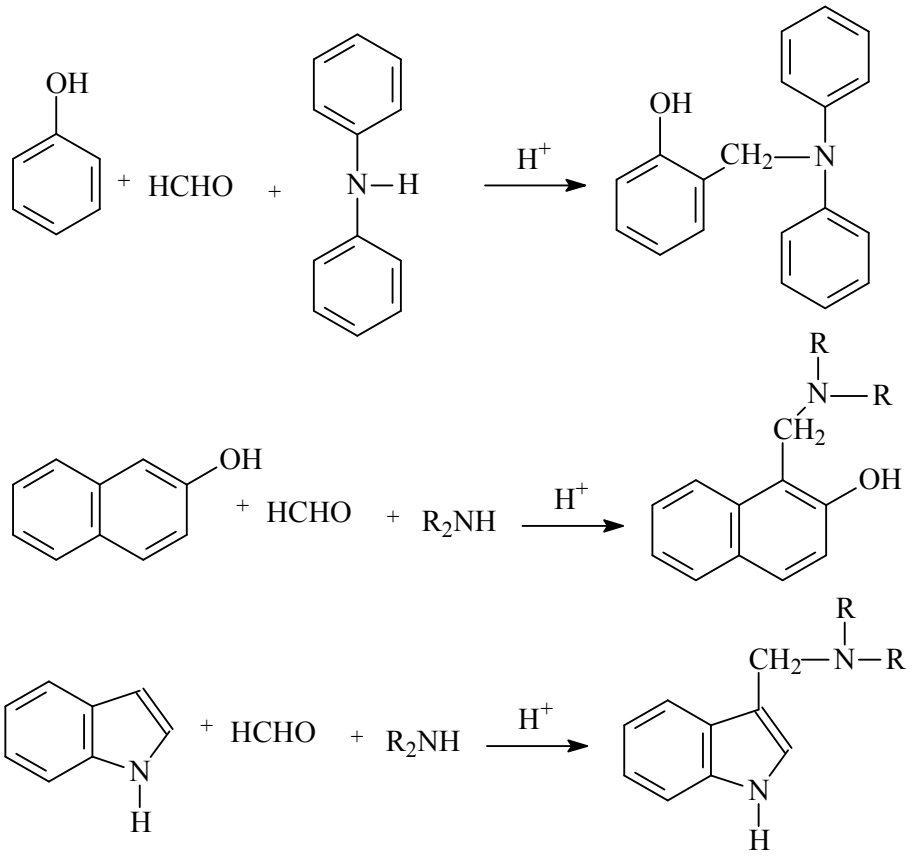


3. The Mannich base obtained may condense with excess HCHO



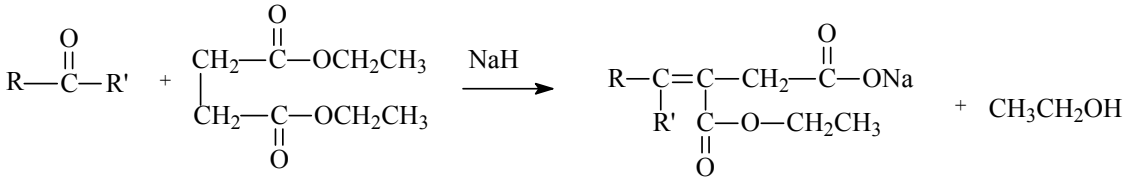
Mannich reaction is very important reaction for the synthesis of reaction intermediate imine salt. The mannich product can be converted to enones which can be used in Mannich addition.

Phenols, furan, pyrrole, indole also give this reaction because intermediate of the reaction is iminium salt which is a strong electrophile and these compounds give aromatic electrophilic substitution (ArSE) reaction.



7.8 STOBBE REACTIONS

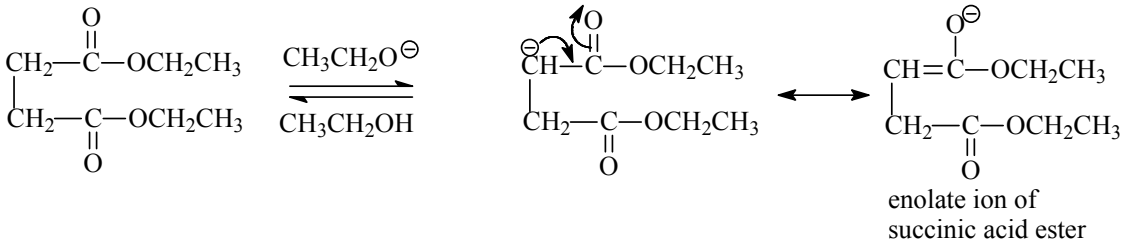
The reaction of aldehydes or ketones with an ester of succinic acid to form alkylidenesuceinic acids (substituted itaconic acids), or isomers formed by a tautomeric shift of hydrogen, is known as the Stobbe condensation.



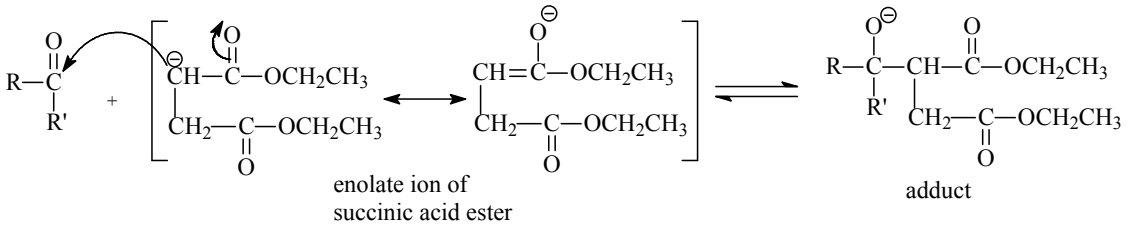
Mechanism:

The mechanism of Stobbe condensation follows the following consecutive steps.

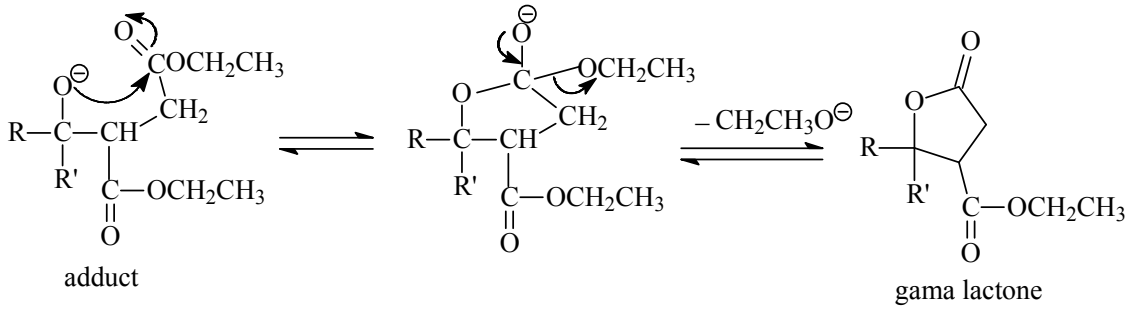
Step I formation of enolate of succinic acid ester in the presence of base



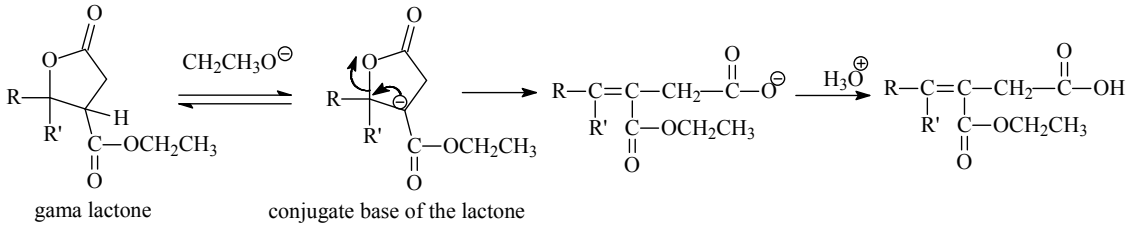
Step II Enolate ion as generated in step I give nucleophilic addition reaction with aldehyde or ketone reversibly.



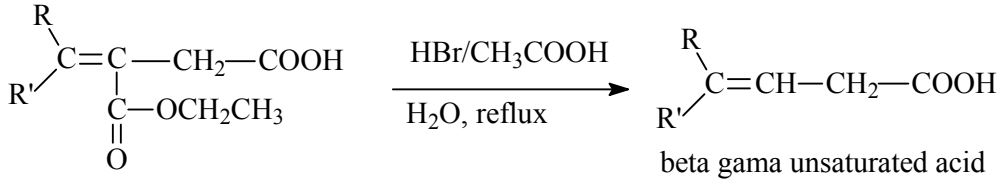
Step III The resulting adducts as in step II cyclise to γ-lactone. This process is also reversible



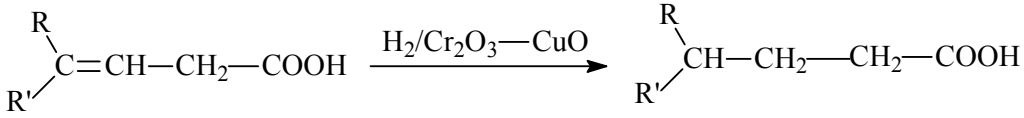
Step IV Irreversible ring –opening of the conjugate base of the lactone –ester to give the anion of the unsaturated ester- acid



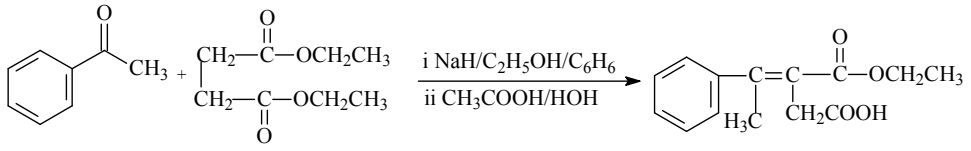
The prime synthetic application of the Stobb condensation arises from the fact that the final condensation product, the unsaturated acid ester, may be decarboxylated with HBr/CH_3COOH. The product obtained is β, γ- unsaturated acid.



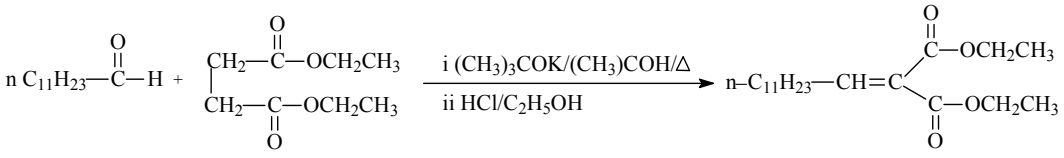
The β, γ- unsaturated acid can be hydrogenated to saturated acid as follow



I



II



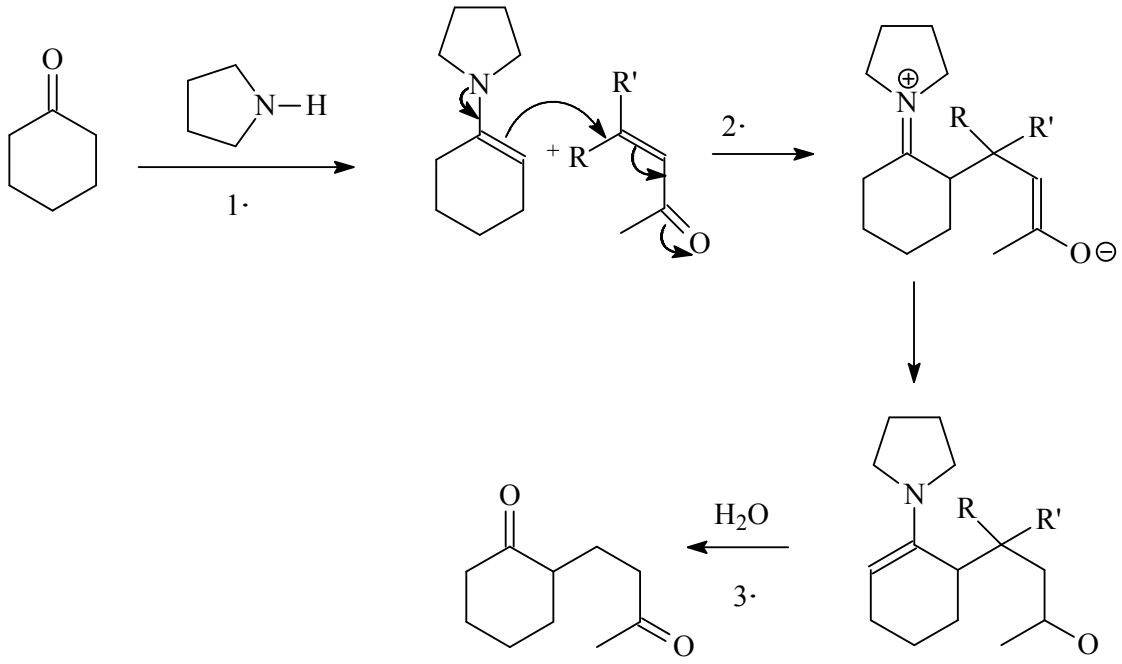
7.9 STORK ENAMINE REACTION

The Stork enamine reacton is a addition of an enamine to α, β- unsaturated carbonyl compound. The process is similar to the Michael reaction. The product of the reaction upon hydrolysis by an aqueous acid to produce a 1, 5-dicarbonyl compound.

The mechanism involve the

1. formation of an enamine from a ketone
2. addition of the enamine to an alpha, beta-unsaturated aldehyde or ketone
3. hydrolysis of the enamine back to a ketone

The entire sequence of the reaction can be mentioned as follow.



7.10 CONCEPT AND APPLICATIONS OF UMPOLUNG

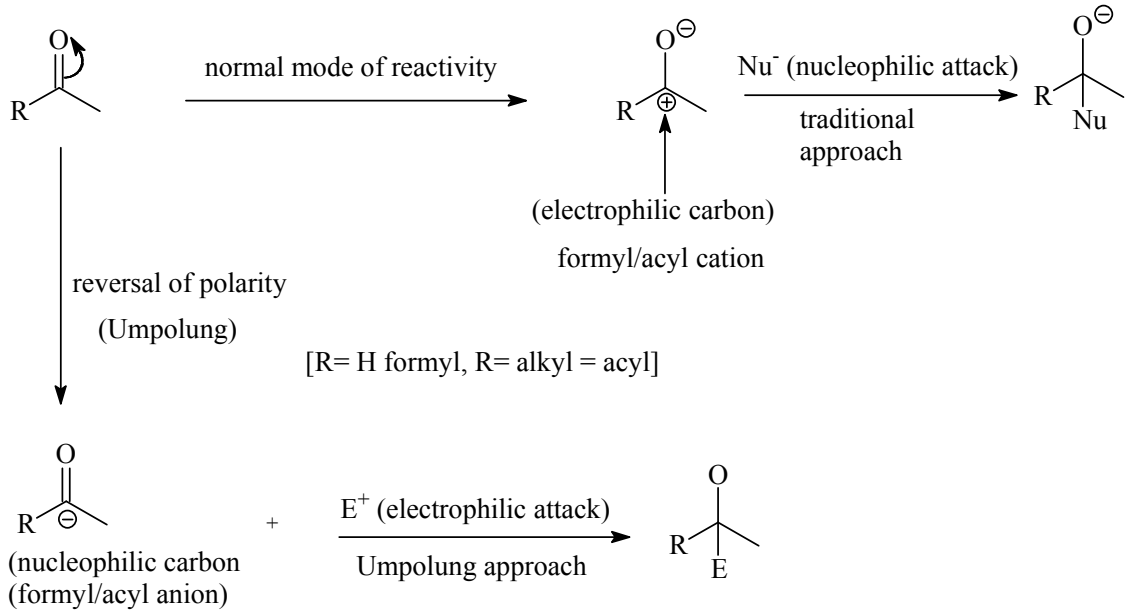
Majority of organic molecules containing heteroatoms, polarize carbon skeletons by virtue of their electronegativity. Therefore, in reactions, the new bonds are formed between atoms of opposite polarity, which we call the "normal" mode of organic reactions. In umpolung means reversal of polarity/pole inversion in organic reactions is the modification of functionality in

order to reverse the polarity in synthones. The umpolung allows the secondary type of reactions in the functional groups which otherwise difficult or not possible.

Example:

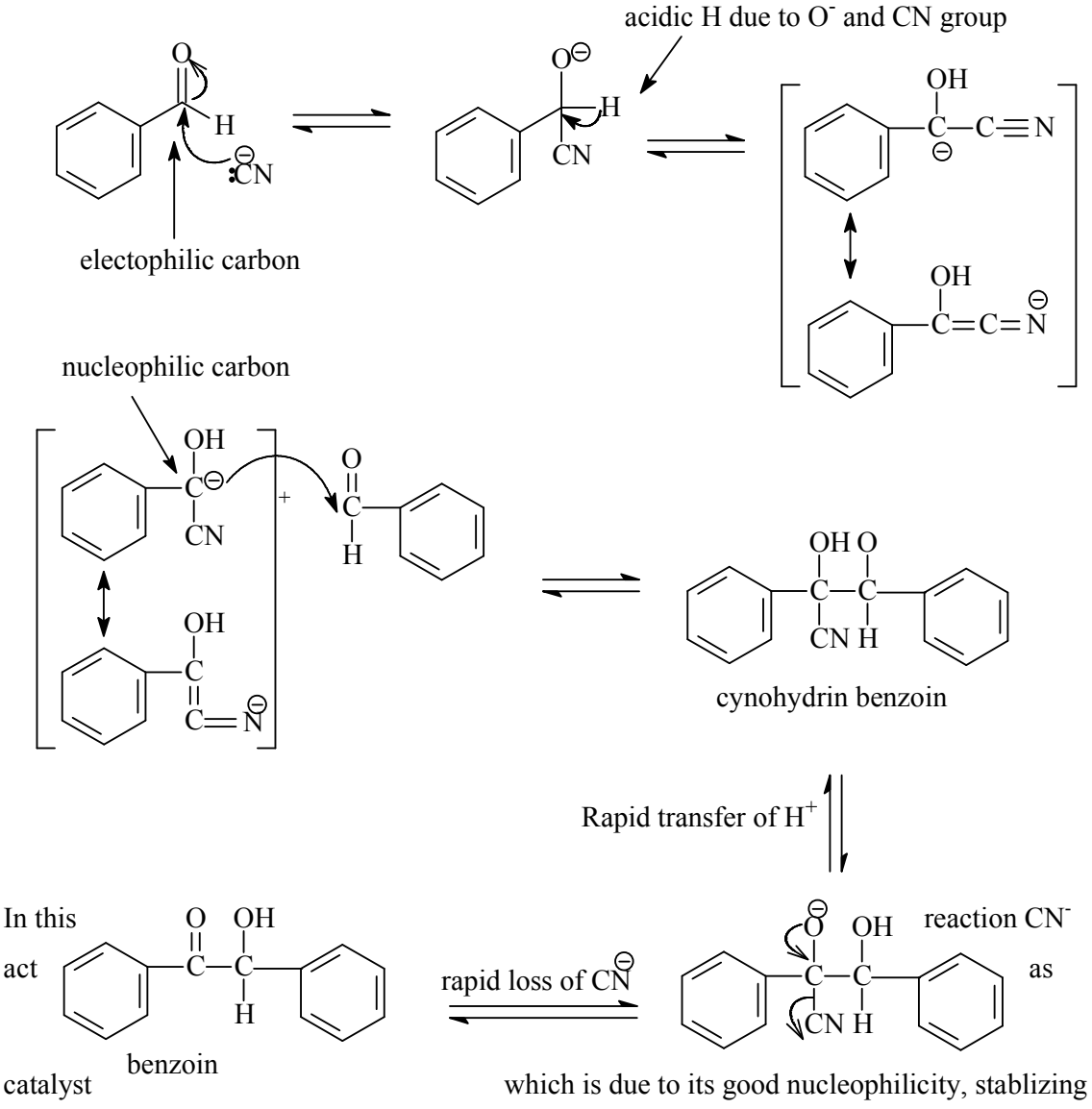
The carbonyl group is electrophilic at the carbon atom and hence is susceptible to attack by nucleophilic reagents. Thus, the carbonyl group reacts as a **formyl cation** or as an **acyl cation**. A reversal of the positive polarity of the carbonyl group so it acts as a **formyl or acyl anion** would be synthetically very attractive. Umpolung in a synthesis usually requires extra steps. Thus, one should strive to take maximum advantage of the functionality already present in a molecule

Reversal of carbonyl group polarity (Umpolung) :-



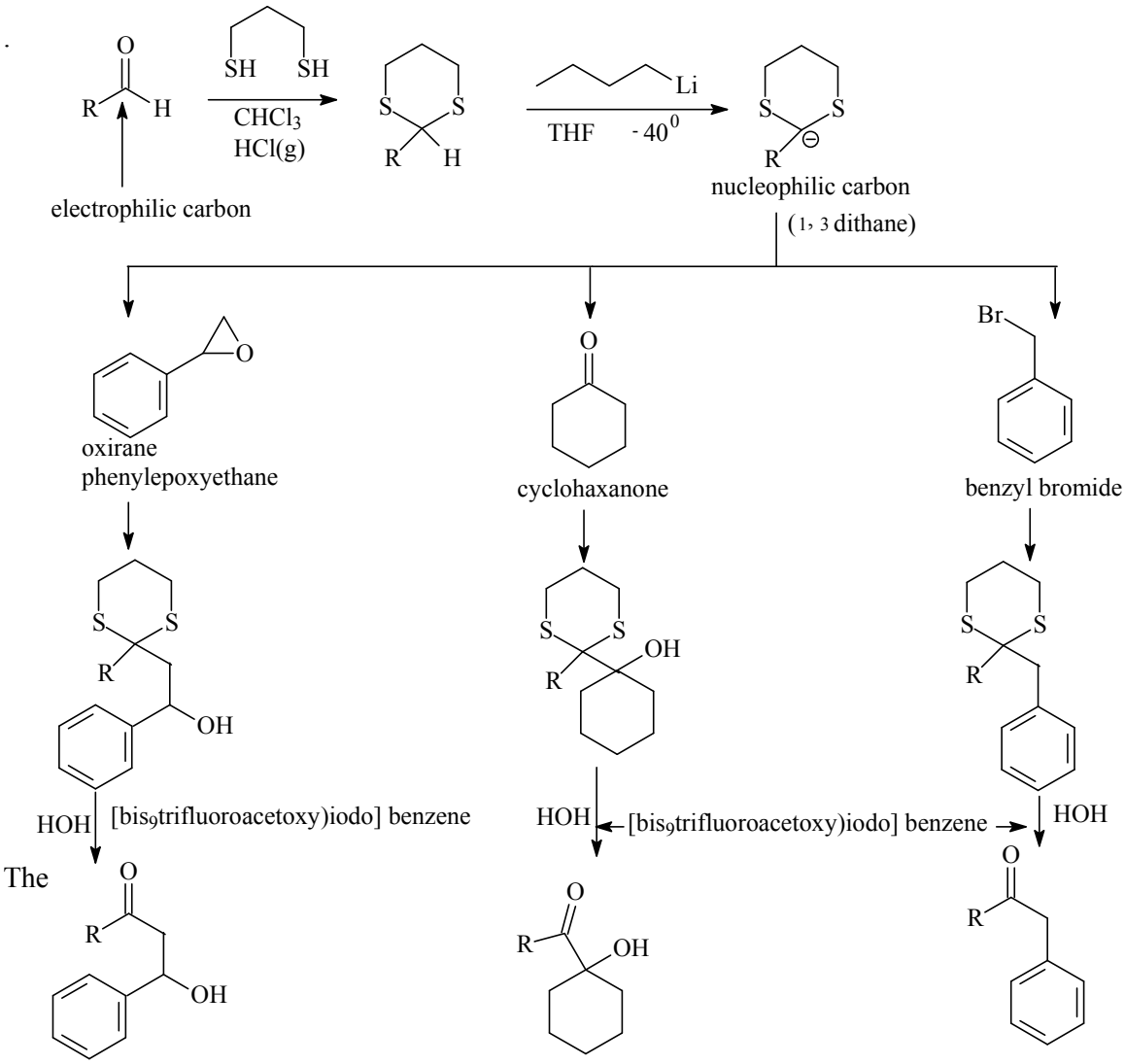
Cyanide type Umpolung:

In this umpolung reaction CN^- play key role as catalyst the well known example is Benzoin condensation in which the net result is that a bond is formed between two carbons that are normally electrophiles, because of umpolung.

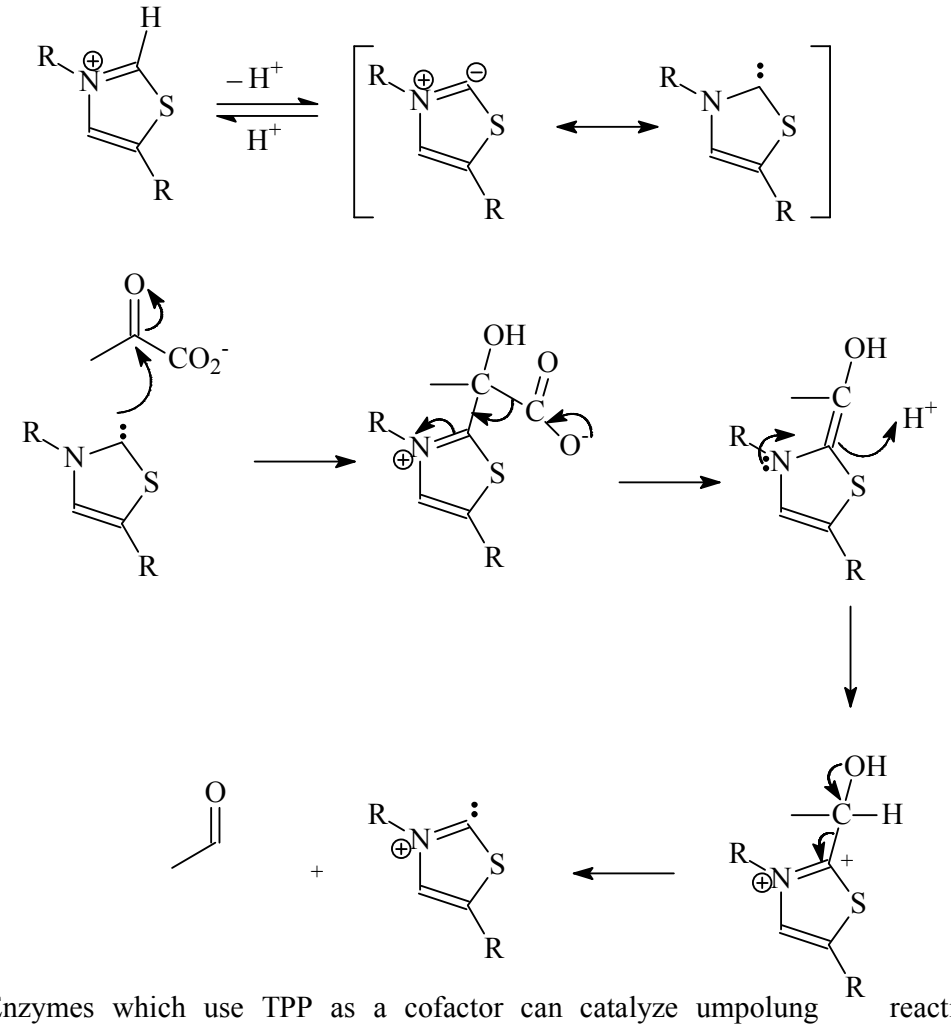


Carbonyl umpolung

The polarity can be reversed when the carbonyl group is converted into a dithiane or a thioacetal. In synthon terminology the ordinary carbonyl group is an acyl cation and the dithiane from carbonyl group reversed to acyl anion by treating with *n*-butyllithium in THF at low temperatures, which then reacts as a nucleophile in nucleophilic displacement with alkyl halides such as benzyl bromide, with other carbonyl compounds such as cyclohexanone or oxiranes such as phenyl-epoxyethane. After hydrolysis of the dithiane group the final reaction products are α-alkyl-ketones or α-hydroxy-ketones. A common reagent for dithiane hydrolysis is (bis (trifluoroacetoxy) iodo) benzene



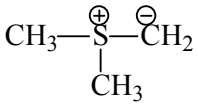
umpolung reactions are veru useful for synthetic and biological point of view. Viz; The human body can employ cyanide-like umpolung reactivity without having to rely on the toxic cyanide ion. Thiamine (which itself is a N-heterocyclic carbenes) pyrophosphate (TPP) serves a functionally identical role. The thiazolium ring in TPP is deprotonated within the hydrophobic core of the enzyme, resulting in a carbene which is capable of umpolung.



Enzymes which use TPP as a cofactor can catalyze umpolung reactivity, such as the decarboxylation of pyruvate. In the absence of TPP, the decarboxylation of pyruvate would result in the placement of a negative charge on the carbonyl carbon, which would run counter to the normal polarization of the carbon-oxygen double bond.

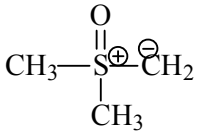
7.11 SULFUR YLIDES

Sulfur ylides are oppositely charged sulpher and carbon with positive charge on sulfur and negative on adjacent carbon. The most important sulphur ylides are dimethylsulfonium methylide and dimethylsulfoxonium methylide (Corey -Chaykovskyreagent).



dimethylsulphonium methylide

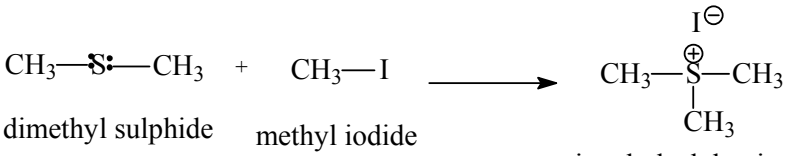
sulphonium ylide



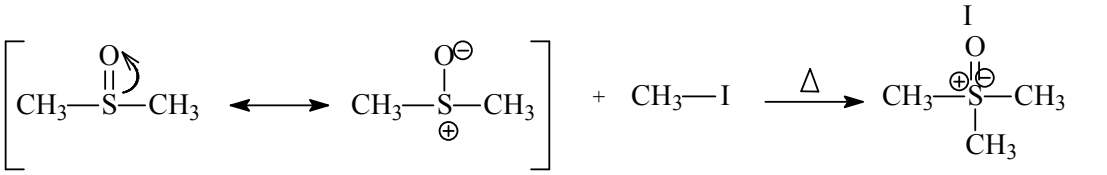
dimethylsulfoxonium methylide

sulphoxonium ylide

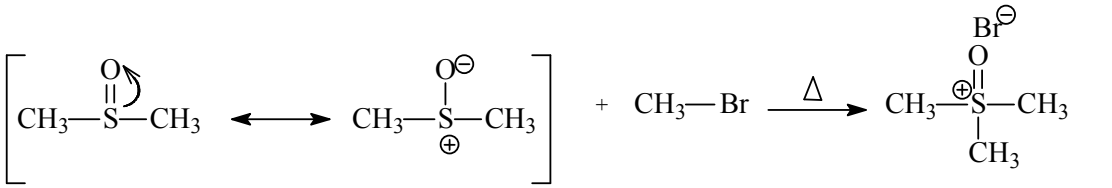
These ylides are prepared by deprotonation of the corresponding sulfonium salts, which can be Prepared from the reaction of either dimethylsulphide or dimethylsulphoxide with methyl iodide/methyl bromide.



dimethyl sulphide methyl iodide trimethylsulphonium iodide



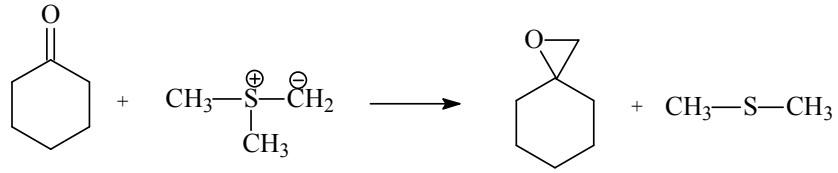
dimethyl sulphide trimethylsulphoxonium iodide

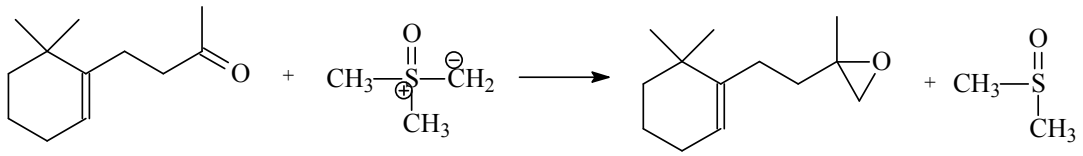


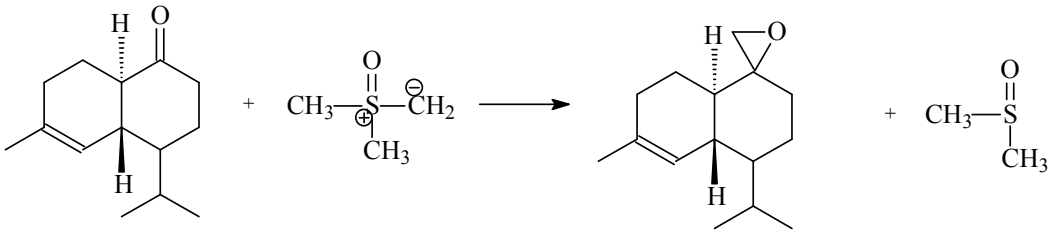
dimethyl sulphide trimethylsulphoxonium bromide

Synthetic utility of sulfur ylides

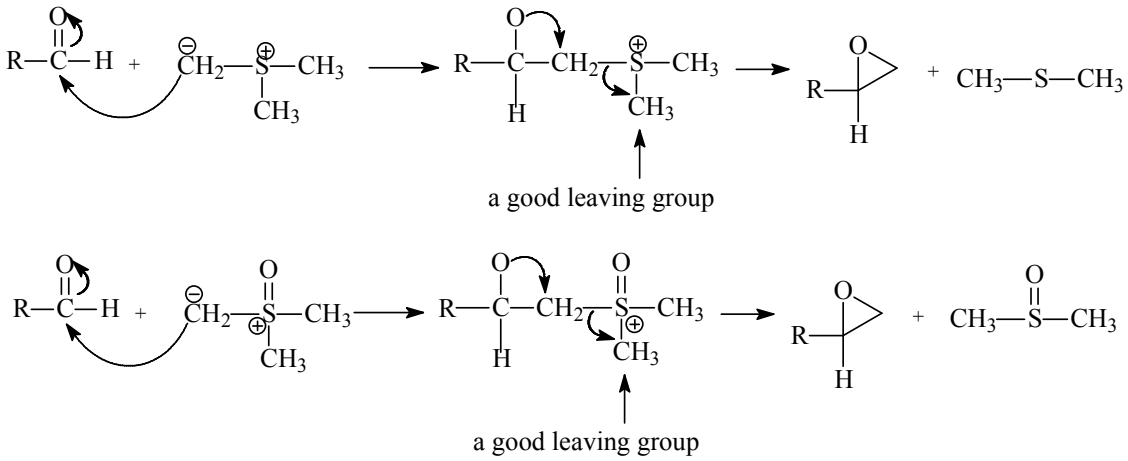
To synthesise epoxides from carbonyl compounds



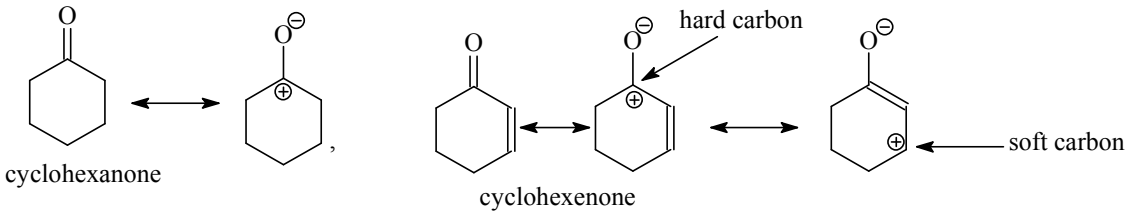




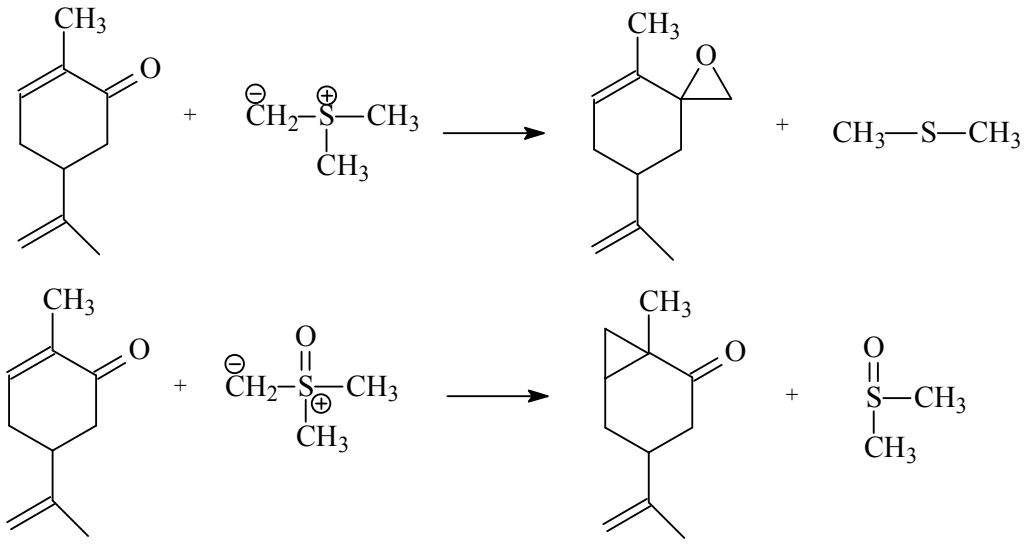
Aldehydes and ketone form epoxide with sulfur ylides while phosphorus ylide gives alkenes

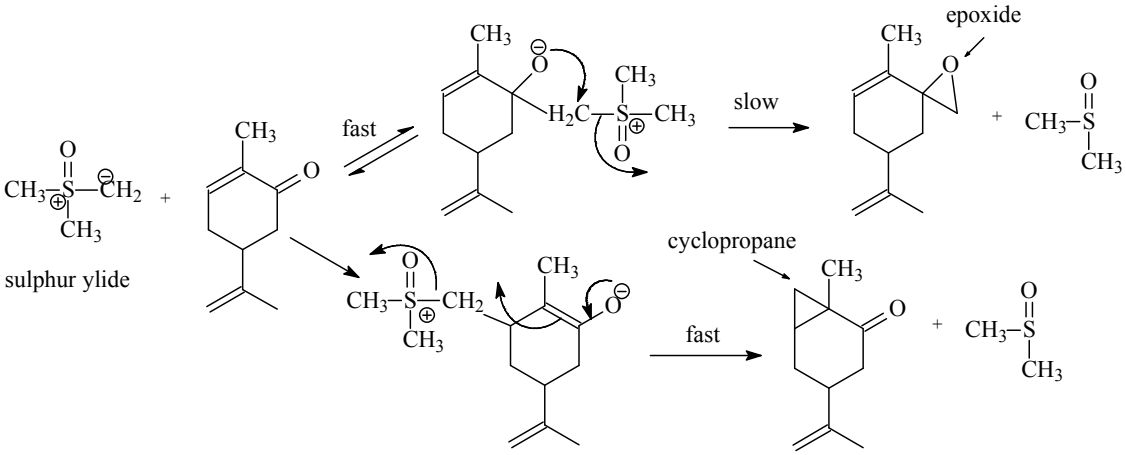


Reaction of Sulphur Ylides with α,β-unsaturated Aldehydes and Ketones



Whereas the harder nucleophile dimethylsulfonium methylide reacts with α,β-unsaturated carbonyl compounds to provide epoxides, the softer reagent dimethylsulfoxonium methylide reacts by conjugate addition to give cyclopropanes**.**





epoxide Vs cylopropane from sulphur ylide

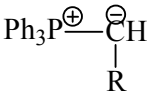
7.12 SUMMARY

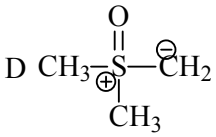
This unit reveals the knowledge about the mechanism of reduction of carbonyl groups and unsaturated molecules by metal hydrides to form many beneficial products which otherwise are difficult to synthesise from carbonyl functionalities. The important reactive reagent, named Grignard reagent with wide synthetic ultility has been incorporated with mechanism.In this unit we also learn about the transformation of carbonyl functionalities to other many beneficial synthetic compounds by using different mechanistic pathways along with specific reagent and reaction conditions. These transformations include Reformatsky reaction, Wittig reaction, Knoevenagel, Claisen, Mannich, Stobbe reactions and enamine reactions. The carbonyl compounds generally contain electrophilic carbon because of polarization by hetero atoms, hence only nucleophile can attack to this carbon in traditional mode, however this unit gives an idea how the electrophilic nature of carbonyl carbon is reversed by using the concept of umpolung. This process of polarity reversal has much synthetic application in synthesis and biological system. The formation and applications of sulphur ylides along with their comparision with phosphorus ylide has also been given in this unit.

7.13 TERMINAL QUESTION

Q1. Tick the correct option (MCQ)**:**

i. Which of the following compound givs epoxide while reacting with aldehydes?

A  B ArMgI

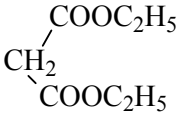
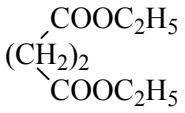
C $LiAlH_4$ D 

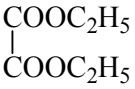
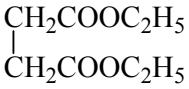
ii The catalyst in Benzoin condensation is:

A. K^+ B. CN^-

C. KCN D. C_2H_5/OH

iii Stobbe reaction is given by

A.  B. 

C.  D. 

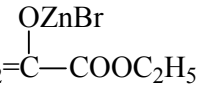
iv Which of the following compounds will form enolate anoin ?

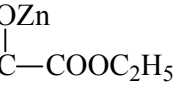
1· CH_3COCH_3 2· $CH_3COCH_2COCH_3$ 3· $CH_3COCH_2COOC_2H_5$ 4· $CH_3COOC_2H_5$

A. Onle A B. 2 and 3

C. Only 4 D. All 1, 2, 3 and 4

v. Reformatsky reagent is

A. $BrZnCH_2COOC_2H_5$ B. 

C.  D. $CH_3COOZnBr$ vi. Which of the following reactions vi.

can be used for the formation of C-C bond in organic synthesis?

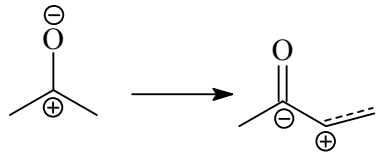
1. Reformatsky reaction 2. Claisen condensation

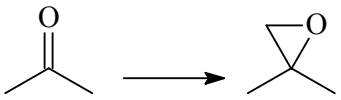
3. Wittig reaction 4. Knoevenagel reaction

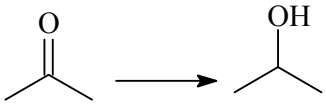
A. Only 4 B. 1,2 and 3

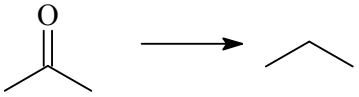
C. 2,3 and 4 D. All 1,2,3 and 4

vii Which of the following represent umpolung?

A. 

B. 

C. 

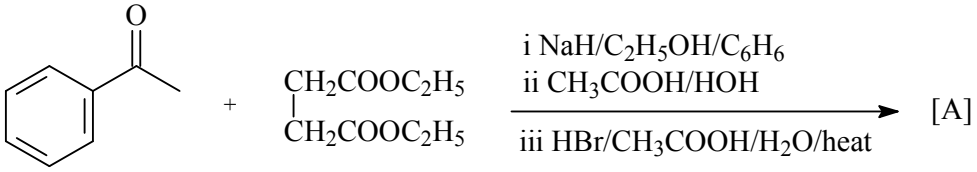
D. 

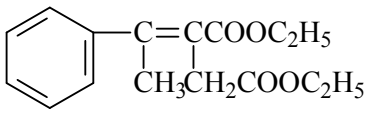
viii Which gives epoxide with sulphur ylide?

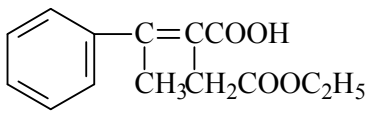
A. Aldehyde B. cyclohexene

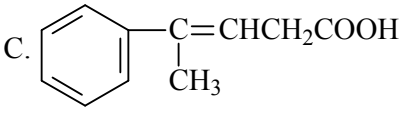
C. Ester D. Amide

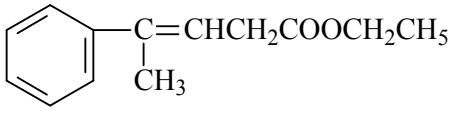
ix. In the given reaction sequence what will be the final product A ?



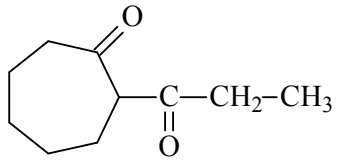
A. 

B. 

C. 

D. 

x. Consider the following compound [X] and tick the correct answer which can be best used for its synthesis



[X]

A. Crossed-claisen- ester condensation

B. Wittig reaction

C. Benzoin condensation

D. All A, B and C

Q.2 Discuss the mechanism of:

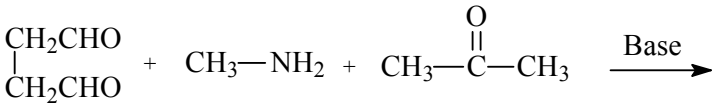
1. Wittig reaction

2. Stobbe reaction

3. Mannich reaction

4. Benzoin condensation

Q.3Complete the following reaction with mechanismand give name of the product



Q.4.What is sulphur ylides? Discuss their importance

Q.5 what do you understand by umpolung? Discuss mechanism of carbonyl group umpolung. Write applications of umpolung

7.14 ANSWERS (MCQ) TERMINAL QUESTIONS

i D

ii B

iii D

iv D

v. B

vi. D

vii A

viii A

ix. C

x. A

7.15 REFERENCES

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UNIT-8 FREE RADICAL REACTIONS

CONTENTS:

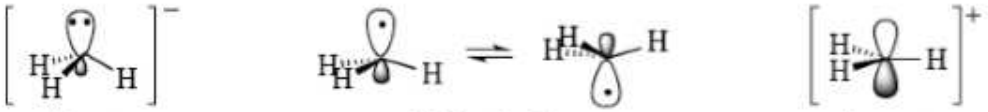
8.0 Objectives
8.1 Introduction
8.2 Mechanism of free radical substitution
8.2.1 Free-radical substitution of alkanes
8.2.2 Free-radical halogenation is most commonly applied to allylic or benzylic halogenations
8.3 Neighbouring group assistance in free radical reactions
8.4 Reactivity
8.4.1 Reactivity for aliphatic substrates:
8.4.2 Reactivity in aromatic substrate:
8.4.3 Reactivity in the attacking radicals:
8.4.4 The effect of solvent on reactivity:
8.4.5 Reactivity at a bridgehead:
8.5 Oxidation of aldehydes to carboxylic acids
8.6 Autooxidation
8.7 Coupling of alkynes
8.7.1 Modifications: Eglinton Reaction
8.8 Arylation of aromatic compounds by diazonium salts
8.8.1 Gomberg or Gomberg-Bachmann reaction
8.8.2 Sandmeyer reaction:
8.9 Hunsdiecker reaction
8.10 Sandmeyer reaction
8.11 Free radical rearrangement
8.12 Summary
8.13 Terminal questions
8.14 Answers to terminal questions
8.15 References

8. OBJECTIVES

Objective of this chapter is to let students aware about types of free radical reactions, mechanism of free radical substitution, reactions on aromatic substrates and neighboring group assistance. This unit will also provide knowledge of reactivity for aliphatic and aromatic substrates at a bridgehead carbon, reactivity of the attacking radicals, the effect of solvents on reactivity and allelic halogenations (NBS). This chapter also aware about oxidation of aldehydes to carboxylic acids, auto-oxidation, coupling of alkynes and arylation of aromatic compounds by diazonium salts. Besides many important name reactions of synthetic utility alongwith Sandmeyer reaction, free radical rearrangement and Hunsdiecker reaction.

8.1 INTRODUCTION

A free radical is a species containing one or more unpaired electrons. Free radicals are electron-deficient species, but they are usually uncharged, so their chemistry is very different from the chemistry of even-electron electron-deficient species such as carbocations and carbenes. The alkyl radical (·CR3) is a seven-electron, electron-deficient species. The geometry of the alkyl radical is considered to be a shallow pyramid, somewhere between sp2 and sp3 hybridization, and the energy required to invert the pyramid is very small. In practice, one can usually think of alkyl radicals as if they were sp2-hybridized.



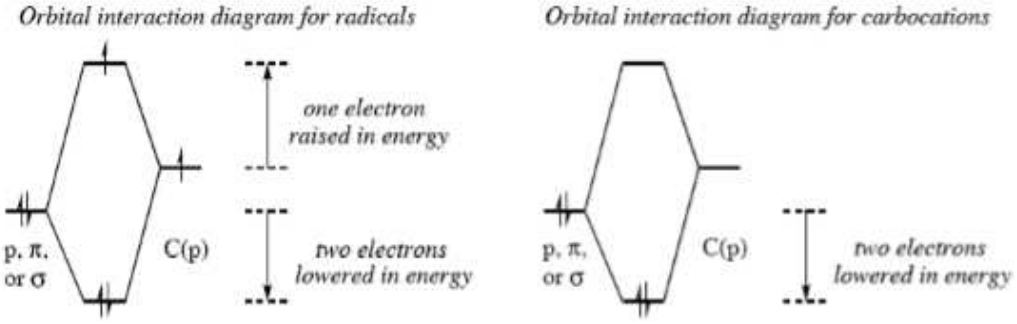
carbanion pyramidal *alkyl radical shallow pyramid* *carbocation trigonal planar*

Both alkyl radicals and carbocations are electron-deficient species, and structural features that stabilize carbocations also stabilize radicals. Alkyl radicals are stabilized by adjacent lone-pair-bearing heteroatoms and by π bonds, just as carbocations are, and the order of stability of alkyl radicals is 3° > 2° > 1°. However, there are two major differences between the energy trends in carbocations and alkyl radicals.

1. A C atom surrounded by seven electrons is not as electron-deficient as a C atom surrounded by six electrons, so alkyl radicals are generally not as high in energy as

the corresponding carbocations. Thus, the very unstable aryl and 1° alkyl carbocations are almost never seen, whereas aryl and 1° alkyl radicals are reasonably common.

2. The amount of extra stabilization that adjacent lone pairs, π bonds, and σ bonds provide to radicals is not as great as that which they provide to carbocations. The reason is that the interaction of a filled AO or MO with an empty AO (as in carbocations) puts two electrons in an MO of reduced energy, whereas the interaction of a filled AO or MO with a half-filled AO (free radicals) puts two electrons in an MO of reduced energy and one electron in an MO of increased energy.



Even though adjacent lone pairs, π bonds, and σ bonds do not stabilize radicals as much as they stabilize carbocations, the cumulative stabilizing effect of several such groups on a radical can be considerable. Benzylic radicals (those with the radical on a C atom next to a benzene ring, but not in a benzene ring) are particularly low in energy, as the radical center is stabilized by resonance with three π bonds.

The most important reaction types involving free radicals are:

i. Free-radical substitution, for instance free-radical halogenation and autoxidation.
ii. Free-radical addition reactions
iii. Intramolecular free radical reactions (substitution or addition) such as the Hofmann–Löffler reaction or the Barton reaction
iv. Free radical rearrangement reactions are rare compared to rearrangements involving carbocations and restricted to aryl migrations.
v. Fragmentation reactions or homolysis, for instance the Norrish reaction, the Hunsdiecker reaction and certain decarboxylations. For fragmentations taking place in mass spectrometry see mass spectrum analysis.

vi. Electron transfer. An example is the decomposition of certain peresters by Cu(I) which is a one-electron reduction reaction forming Cu(II), an alkoxy oxygen radical and a carboxylate. Another example is Kolbe electrolysis.

vii. Radical-nucleophilic aromatic substitution is a special case of nucleophilic aromatic substitution.

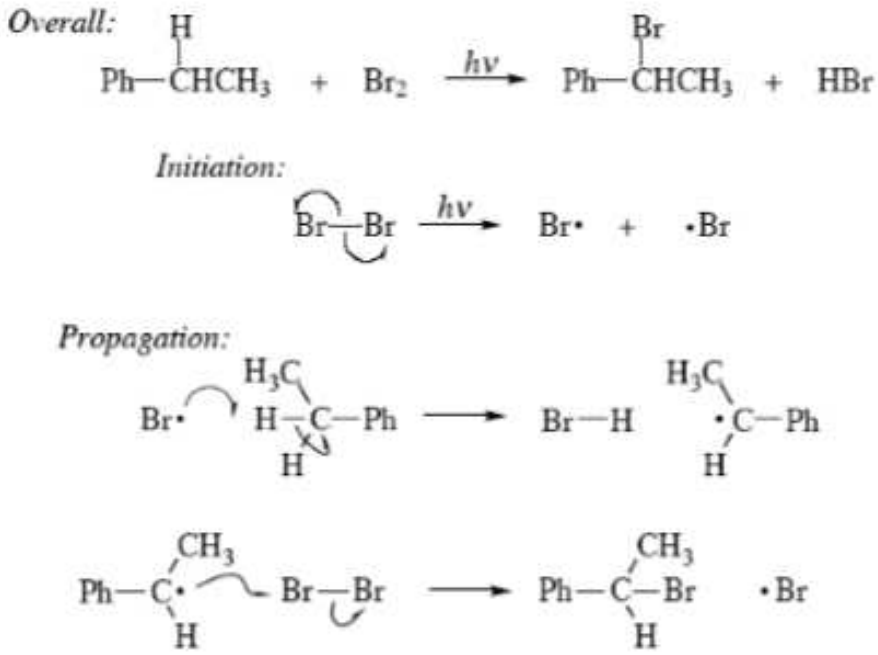
viii. Carbon–carbon coupling reactions, for example manganese-mediated coupling reactions.

ix. Elimination reactions

8.2 MECHANISM OF FREE RADICAL SUBSTITUTION

8.2.1 Free-Radical Substitution of Alkanes

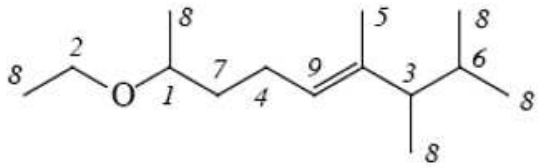
Probably the best-known example of a free-radical reaction is the halogenation of alkanes with Br_2 or NBS (N-Bromosuccinimide). This chain reaction is initiated by homolytic cleavage of Br_2 induced by light or heat. The propagation step consists of two atom abstraction reactions.



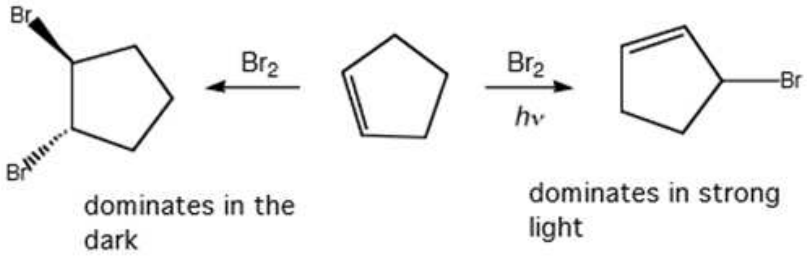
When more than one kind of H atom is present, the H atom that is removed is usually the one that will leave behind the lowest energy radical. H atoms are never removed from C(sp) or C(sp2), only from C(sp3). Among C(sp3)–H bonds, it is easiest to remove a H if a heteroatom such as N or O is attached to the C. If no such H atom is present, then the H

atom that is removed is best allylic or benzylic (the C is attached to a C=C π bond or to a benzene ring). If there are no allylic or benzylic H atoms, then the order of reactivity of H atoms is 3° > 2° > 1°.

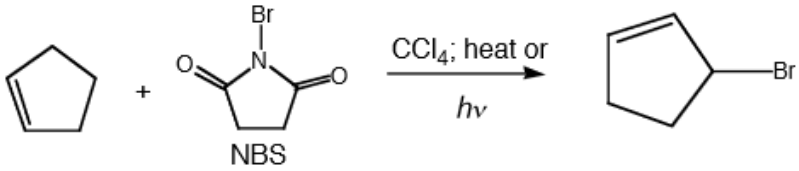
Ease of removal of H (1 easiest, 9 hardest)



8.2.2 Free-radical halogenation is most commonly applied to allylic or benzylic halogenation because the radicals formed at these positions are most stable. Note that alkenes can react with Br_2 by either an electrophilic addition reaction, to give 1,2-dibromoalkanes, or by a free-radical substitution reaction, giving 3-bromoalkenes. The former pathway predominates in the dark, whereas the latter pathway predominates in the presence of strong light.

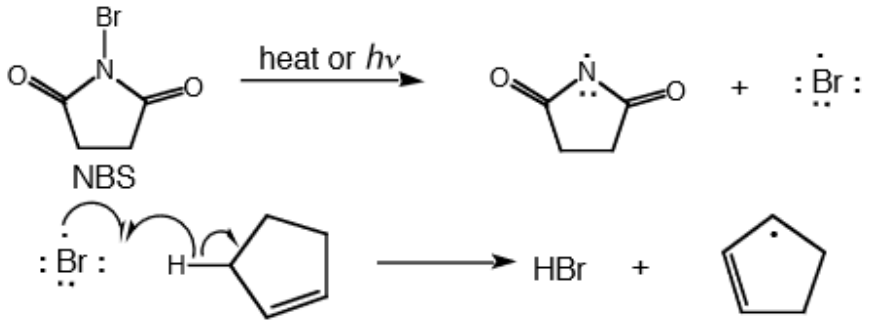


NBS (N-bromosuccinimide) is often used as the Br source in freeradical brominations. This is to keep the concentration of bromine low and hence reduce competition by electrophilic addition of Br_2 to give 1,2-dibromoalkane. In these reactions using NBS in CCl_4, it is thought that Br_2 is the actual halogenating agent.

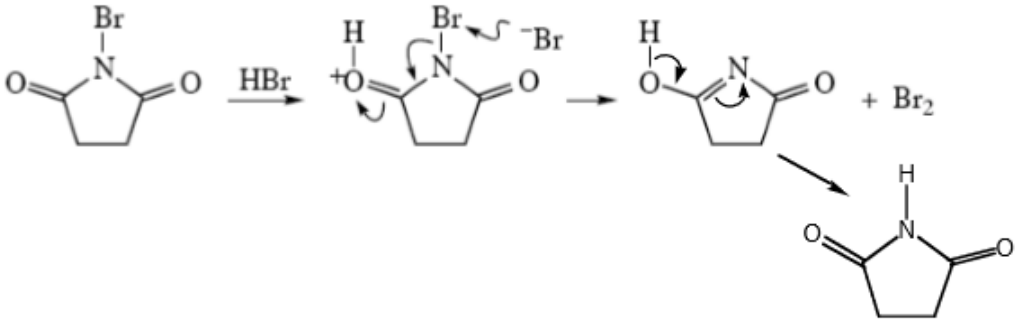


Br_2 is generated as follows:

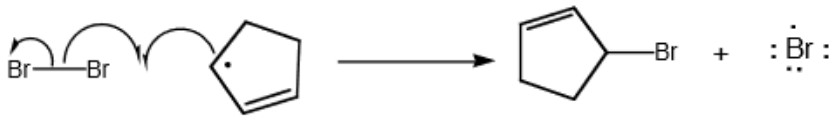
i. Homolytic cleavage of the N-Br bond of NBS generates a Br atom, which abstracts an allylic hydrogen from the alkene (cyclopentene).



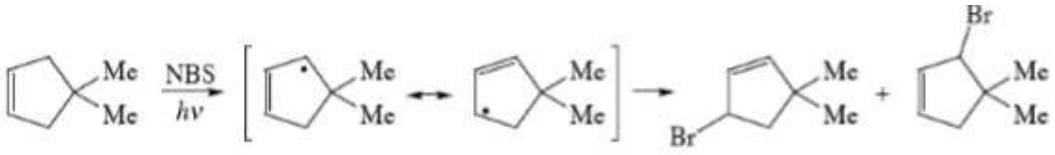
ii. The HBr thus formed reacts with NBS to produce a Br2 molecule.



iii. This Br_2 molecule reacts with the allylic radical formed earlier and a new bromine atom is produced that can begin the cycle a new.



Of course, in allylic halogenation, transposition of the double bond can easily occur. For example, in 4,4-dimethylcyclopentene:

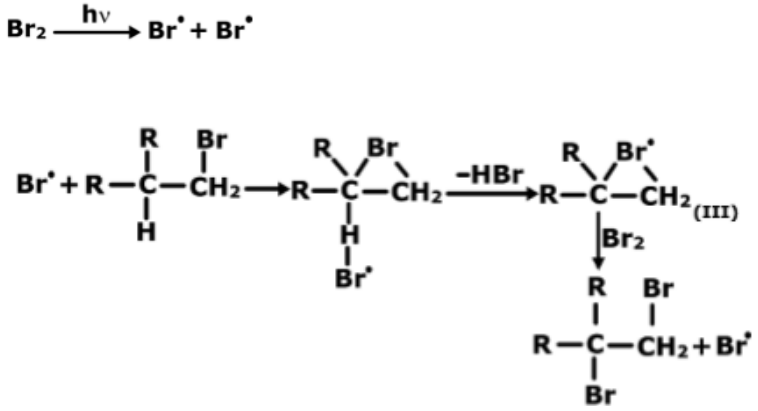


Elemental chlorine can be used in free-radical halogenation reactions, too, but these reactions are less easily controlled, because the Cl· radical is more reactive than the Br· radical and hence less selective. The reagents t-BuOCl and SO_2Cl^2 are used as alternative chlorinating agents. The F· radical is so reactive, and the reaction F–F + C–H → H–F + C–F is so exothermic, that free-radical fluorinations result in violent and uncontrollable exotherms

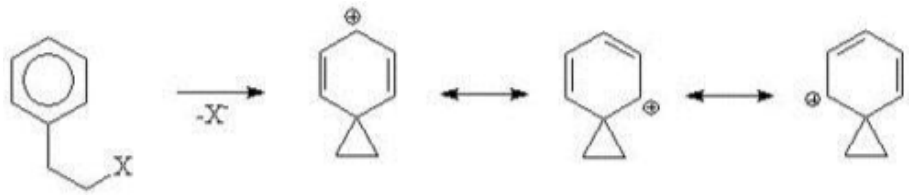
(explosions). At the other extreme, free-radical iodinations of alkanes do not work well at all, as the H· abstraction step is too endothermic.

8.3 NEIGHBOURING GROUP ASSISTANCE IN FREE RADICAL REACTIONS

In a few cases it has been shown that the free radical reactions are accelerated by the presence of neighbouring groups. Bromination of carbon chains containing a bromine atom occurs with high regioselectivity. Bromination of alkyl bromides gave 84 to 94% substitution at the carbon adjacent to the bromine already in the molecule. This is especially as positions close to a –I group such as bromine should actually be deactivated by the electron-withdrawing effect of bromine. The unusual regioselectivity is explained by a mechanism in which abstraction of hydrogen is assisted by a neighbouring bromine atom as shown below:



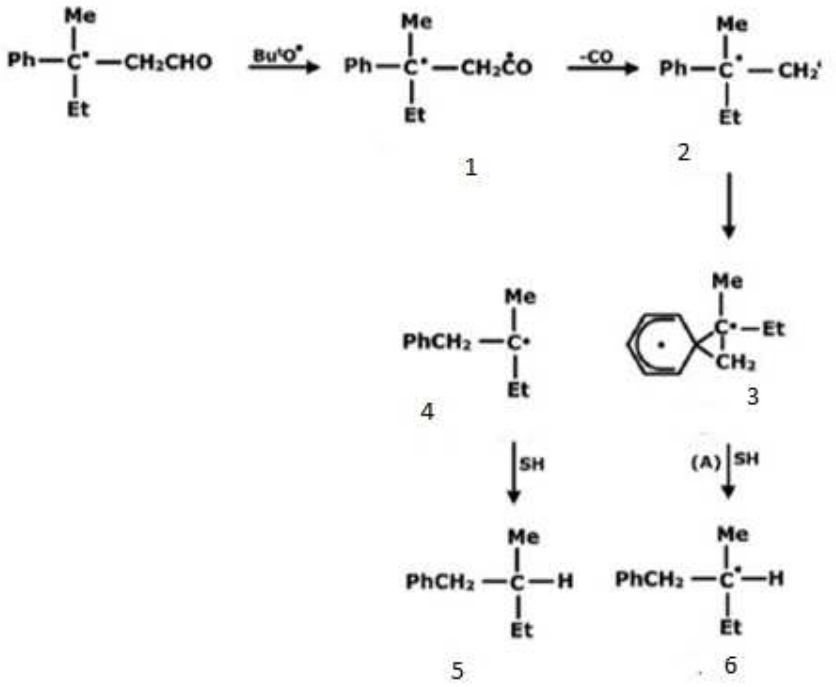
In the normal mechanism, Br• abstracts a hydrogen from RH, leaving R•. When bromine is present in the proper position, it assists this process, giving a cyclic intermediate (a bridged free radical, III). In the final step, this bridgehead free radical is attacked by another Br• to give the dibromoalkane. The above mechanism is supported by the fact that it proceeds with retention of configuration. Photolytic bromination of optically active 1-bromo-2-methylbutane gave 1, 2-dibromo-2-methylbutane with the retention of configuration. You already know that an aromatic ring can assist in the formation of a carbocationic intermediate called a phenonium ion by delocalising the positive charge.



Let us now study about the NGP by aromatic rings involving free radicals.

NGP by an aromatic ring involving free radicals:

Taking an example of free radical NGP, Ruchardt has successfully distinguished between these pathways in the given reaction by showing that the optically active aldehyde undergoes decarbonylation to from the product (5) with at least 98% racemization.

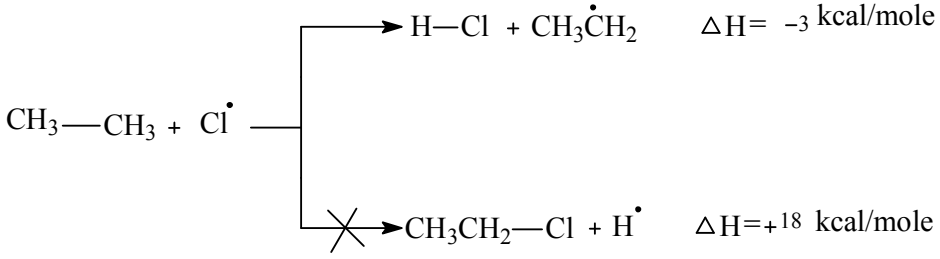


If the reaction involved attack by a bridged radical intermediate on a second molecule of aldehyde, then retention of configuration would have been observed, as with the analogous carbonium ion rearrangement (Route A). Racemization indicates that the bridged radical (3) rearranges to the acyclic radical (4) before reaction with a second molecule of aldehyde.

8.4 REACTIVITY

8.4.1 Reactivity for aliphatic substrates:

It is the abstraction step that determines which product will be formed in a chain reaction. A free radical almost always abstracts a univalent (hydrogen or halogen) and never a tetra- or tercovalent atom, and seldom a divalent one. For example, a reaction between a chloride free radical and ethane gives an ethyl radical, not a hydrogen free radical:



The main reason for this is steric. A univalent atom is much more exposed to attack by the incoming radical than an atom with a higher valency. Another reason is that in many cases abstraction of a univalent atom is energetically more favoured.

In the case of alkanes, the following is the decreasing order of the ease of abstraction of different kinds of hydrogens:

Tertiary H > secondary H > primary H > methane

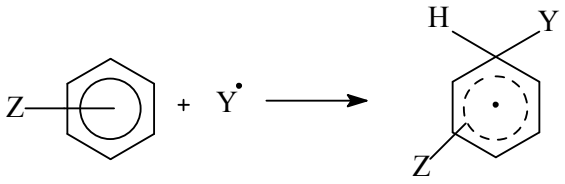
This is according to the relative stabilities of the free radicals formed after the abstraction of hydrogen.

In the case of alkyl chains of aromatic rings the preferential position of attack on a side chain is usually the position alpha to the ring. Aromatic hydrogens are seldom abstracted if there are aliphatic hydrogen present.

In the case of compounds containing electron withdrawing substituents e.g., Z-CH_2CH_3 (Z=COOH, COCl, COOR, SO_2Cl or CX_3) the β-position is attacked predominantly or exclusively in free radical halogenations. This is because electron-withdrawing group highly deactivate adjacent alpha position. Compounds like acetic acid and acetyl chloride are not attacked at all. This is because halogen atoms are electrophilic radical and look for positions of high electron density. Hydrogens on carbon atom next to the electron-withdrawing groups have low electron densities; therefore, the attack is avoided at this position. The radicals that are not electrophilic do not show this behavior e.g., the methyl radical does not avoid the attack at the alpha position. Some radicals, e.g., t-butyl, benzyl, cyclopropyl and phenyl are nucleophilic and tend to abstract electron poor hydrogens.

8.4.2 Reactivity in aromatic substrate:

Free radical substitution at an aromatic carbon seldom takes place by a mechanism in which ring hydrogen is abstracted to give an aryl radical. Usually, the mechanism is similar to that of aromatic electrophilic and nucleophilic substitution.



The following generalizations have been made regarding the reactivity in aromatic substitution:

1. All substituents increase reactivity at ortho and para positions as compared to that of benzene. There is no great difference between electron-donating and electron withdrawing group. This is because radicals are neutral species and are not influenced by the polar properties of the substrate to any significant extent. Furthermore, it has been shown that both electron donating and electron withdrawing group stabilize a free radical.
2. Reactivity at *meta* positions almost equal to that of benzene. This fact, coupled with preceding one, means that all substituents are activating and ortho-para directing, none are deactivating or mainly *meta* directing.
3. Reactivity at ortho positions is greater than at para positions, except where a large group decreases ortho reactivity due to steric reasons.
4. Electron withdrawing group exert a greater *ortho-para* directing and activating effect than electron donating groups.
5. Substituents have a much smaller effect than in electrophilic and nucleophilic substitution.
6. Although hydrogen is the leaving group in most free radical aromatic substitutions, *ipso* attack and *ipso* substitution (e.g., with Br, NO_2, or CH_3CHO as the leaving group) have been found in certain cases.

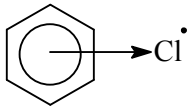
8.4.3 Reactivity in the attacking radicals: The greater the reactivity of a species the less is the selectivity. The bromine atom is so selective that when only primary hydrogen are available, as in neopentane or t-butylbenzene, the reaction is slow or nonexistent. Isobutene

can be selectively brominatede to give t-bromide and toluene reacts with bromine instantly. Other alkylbenzenes e.g., ethylbenzene and cumine are brominated exclusively at the alpha position emphasizing the selectivity of bromine free radical.

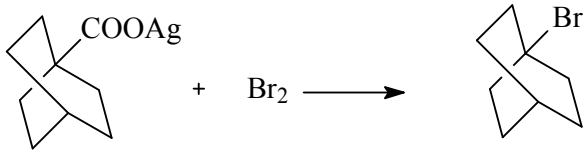
Some radicals e.g., triphenylmethyl are so unreactive that they abstract hydrogen very slowly. As mentioned earlier, some free radicals e.g., chloro are electrophilic and some eg., t-butyl are nucleophilic. However, the predominant character of a free radical is neutral, whether it has slight electrophilic or nucleophilic tendency.

8.4.4 The effect of solvent on reactivity: Unlike ionic substitutions, the solvent usually has little effect on free radical substitutions. Free radical reactions in solution are quite similar in character to those in the gas phase, where there is no solvent. However, in certain cases the solvent can make an appreciable difference.

For example, chlorination of 2, 3-dimethylbutane in aliphatic solvents gave about 60% $(CH_3)_2CHCH(CH_3)CH_2Cl$ and 40% $(CH_3)_2CHCCl(CH_3)_2$, while in aromatic solvents the ratio become 10:90. This is due to complex formation between the aromatic solvent and the chlorine free radical which makes the chlorine less reactive and thus more selective.



8.4.5 Reactivity at a Bridgehead: Many free radical reactions have been observed at bridgehead carbons. For example, in the following reaction a free radical is formed at the bridgehead carbon.

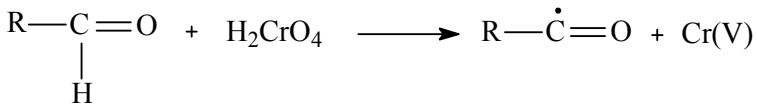


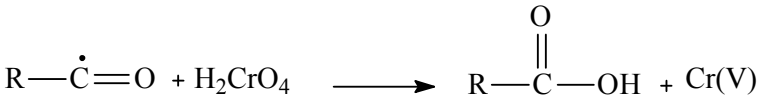
This demonstrates that the free radical need not be planner. Although bridgehead free radical substitution is possible, it is not preferred because of the straine involved.

8.5 OXIDATION OF ALDEHYDES TO CARBOXYLIC ACIDS

Oxidation of aldehyde to carboxylic acids has been carried out with various oxidizing agents, the most well-liked of which is acidic, basic or neutral solution of permanganate, chromic acid, silver oxide, bromine, Benedict's solution and Fehling's solution. The mechanism of

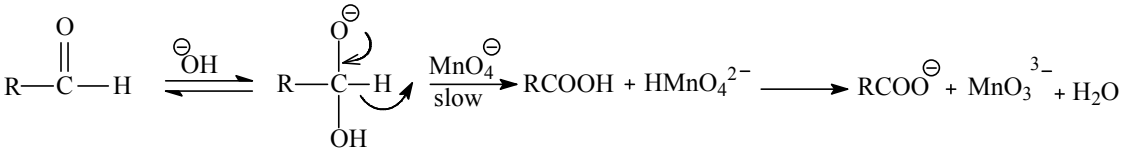
aldehyde oxidation may be free radical or ionic. Both the mechanism may take place simultaneously. In the free radical mechanism, the aldehyde hydrogen is abstracted to give an acyl radical, which obtains OH from the oxidizing agent. For example-



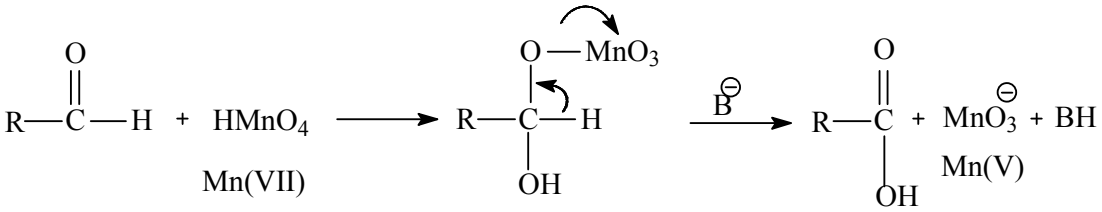


The above mechanism is also similar with $KMnO_4$

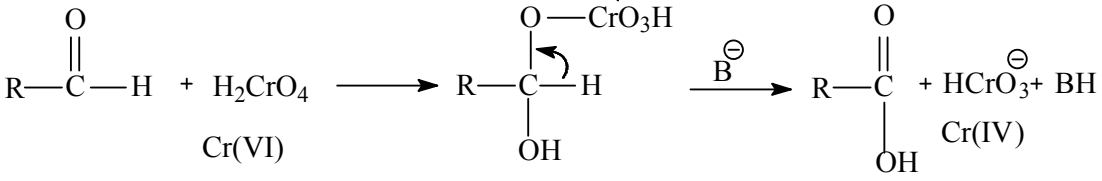
For alkaline permanganate, the ionic mechanism is as follows:



For neutral and acidic permanganate, the following ionic mechanism has been proposed:



Similarly, with H_2CrO_4 the ionic mechanism is as follows:



8.6 AUTOOXIDATION

Oxidation reaction takes place by atmoshpheric oxygen without combustion is called autooxidation. This type of reaction occurs when compounds are stand in air. Autoxidation catalysed by light and and initiators and inhibited by antioxidants (like hydoquinone).

According to observation it is suggested that a free radical mechanism is involved. By the autooxidation process foods, rubber, paint, lubricating oils etc. deteriorate on exposure to the atmoshphere for a long time. A important application of autooxidation is the drying of paints and varnishes in atmospheric conditions.

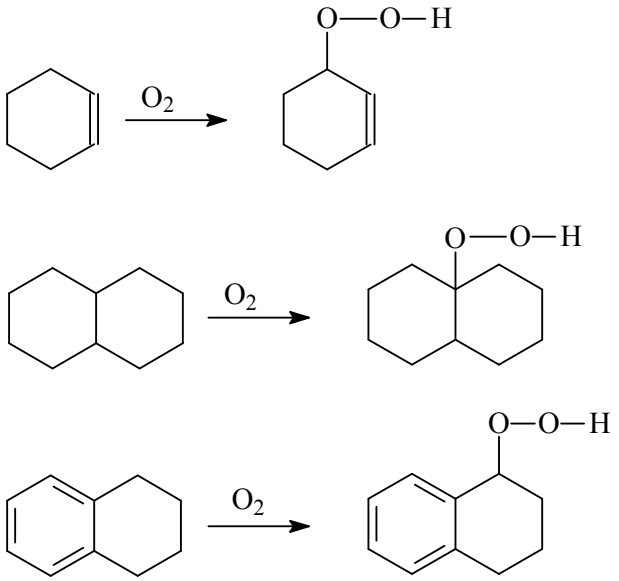
Oxygen itself (a diradical) is not reactive enough to abstract the hydrogen. But if a trace of free radical ($R^{\cdot}$) is produced by some initiating step, it reacts with oxygen to give R-O-O· Which abstract hydrogen. The following reraction is the reaction chain-

$$R'^{\bullet} + O_2 \longrightarrow R'—O—O^{\bullet} \xrightarrow{R—H} R^{\bullet} + R'—O—O—H$$

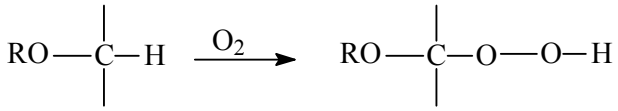
$$R^{\bullet} + O_2 \longrightarrow R'—O—O^{\bullet} \xrightarrow{R—H} R—O—O—H + R^{\bullet}$$

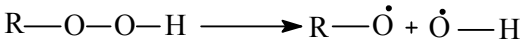
hydroperoxide

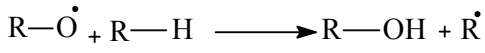
As with other free radical reaction, resonance stabilization of tertiary, benzylic, and allylic free radicals, the abstraction of these hydrogens is greatly facilitated. Example-



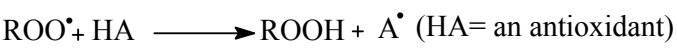
The alpha positions of ethers are also easily attacked by oxygen. This reaction is responsible for a hazard in the storage of ethers because solutions of these hydroperoxides and their rearrangement products in ethers are potential spontaneous explosive. Hydroperoxides decompose further to generate radicals which start new chain reaction.



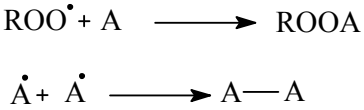




The autooxidation of organic compouns is usually inhibited by the addition of antioxidants. These compounds, which are usually phenols or secondary amines, destroy the chain carrying radicals.

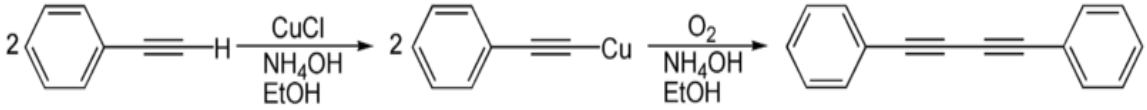


The radical A. is resonance stabilisd and relatively unreactive thus, it is not capable of initiating a fresh chain. It is destroyed either by combination with a peroxy radical or with a similar radical species.



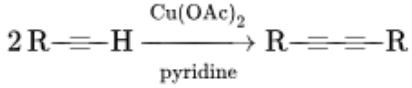
8.7 COUPLING OF ALKYNES

The Glaser coupling is a type of coupling reaction. It is by far the oldest acetylenic coupling and is based on cuprous salts like copper (I) chloride or copper (I) bromide and an additional oxidant like oxygen. The base in its original scope is ammonia. The solvent is water or an alcohol. The reaction was first reported by Carl Andreas Glaser in 1869.

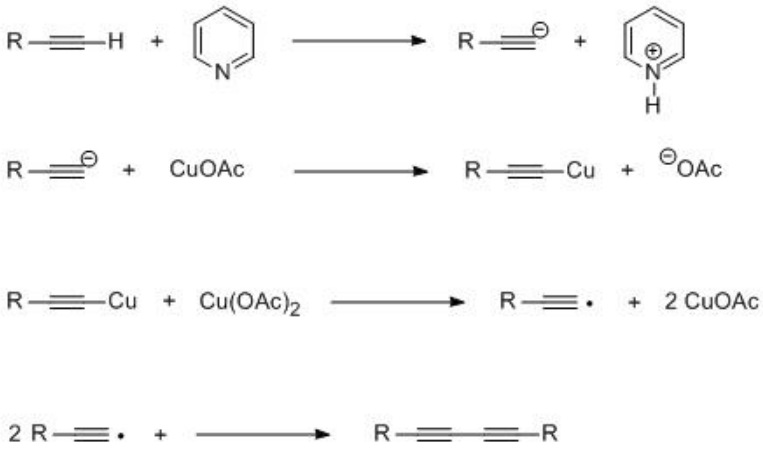


8.7.1 Modifications: Eglinton reaction

In the related Eglinton reaction two terminal alkynes are coupled directly by a copper (II) salt such as cupric acetate.



The Eglinton Reaction has been used to synthesize a number of fungal antibiotics and is important for carbon-carbon bond formation via the oxidative coupling of alkynes.



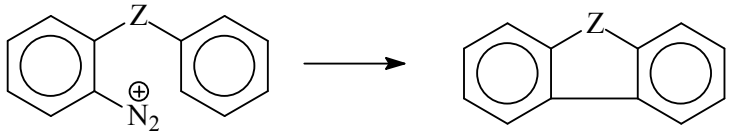
This procedure was used in the synthesis of cyclooctadecanonaene. Another example is the synthesis of diphenyldiacetylene from phenylacetylene.

8.8 ARYLATION OF AROMATIC COMPOUNDS BY DIAZONIUM SALTS

8.8.1 Gomberg or Gomberg-Bachmann reaction

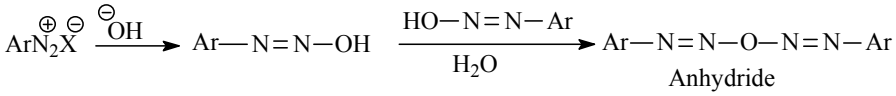
$$Ar'H + ArN_2X \xrightarrow{\ominus OH} Ar—Ar'$$

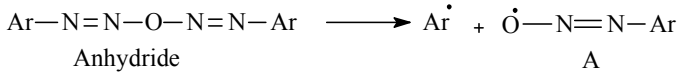
When diazonium salt solution is made alkaline, the aryl portion of the diazonium salts can couple with aromatic ring. This reaction is known as the **Gomberg or Gomberg-Bachmann reaction** and has been permormed on several types of aromatic rings and on quinines. When the Gomberg-Bachmann reaction is performed intramolecularly, either by alkaline solution by the alkaline solution or by the copper ion procedure, it is called Pschorr ring closer.

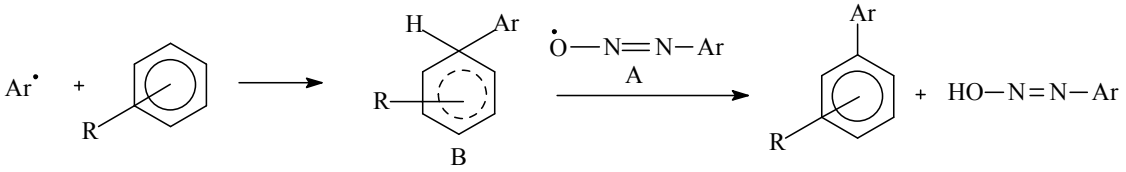


[Z= CH=CH, CH_2CH_2, NH, C=O, CH_2]

Mechanism

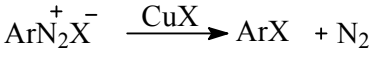






The aryl radical thus formed attacks the substrate to give the intermediate B, from which the radical A abstracts hydrogen to give the product. It has been shown that whatever is the nature of substituents (R) in substrate, ortho or para substitution always predominents but small amount of meta product is also formed.

8.8.2 Sandmeyer reaction:

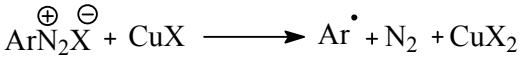


[X=Cl or Br]

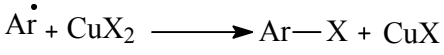
Treatment of diazonium salts with cuprous chloride or bromide gives aryl or bromide gives aryl chlorides or bromides respectively. This reaction is called the Sandmeyer reaction. The reaction can also be carried out with copper and HBr or HCl, in this case it called the Gattermann reaction. The Sandmayer reaction is not useful for the preparation of fluorides and iodides but it is probably the best way of introducing brominr or chlorine in to an aromatic ring.

Mechanism:

Step 1: The reduction of diazonium ion by cuprous ion to give an aryl radical:



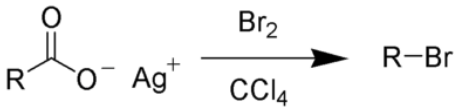
Step 2: The aryl radical abstract halogen from cupric chloride, reducing it. CuX is regenerated and is thus a true catalyst.



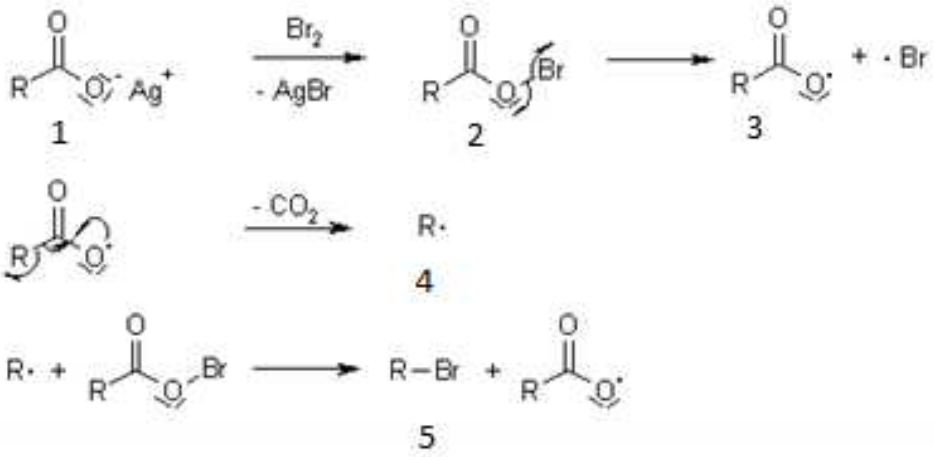
Mention must be made about Radical Redox Reacions of all Sandmeyer type reactions

8.9 HUNSDIECKER REACTION

The Hunsdiecker reaction (also called the Borodin reaction or the Hunsdiecker–Borodin reaction) is a name reaction in organic chemistry whereby silver salts of carboxylic acids react with a halogen to produce an organic halide. It is an example of both a decarboxylation and a halogenation reaction as the product has one fewer carbon atoms than the starting material (lost as carbon dioxide) and a halogen atom is introduced its place. The reaction was first demonstrated by Alexander Borodin in his 1861 reports of the preparation of methyl bromide from silver acetate. Shortly after, the approach was applied to the degradation of fatty acids in the laboratory of Adolf Lieben. However, it is named for Cläre Hunsdiecker and her husband Heinz Hunsdiecker, whose work in the 1930s developed it into a general method.

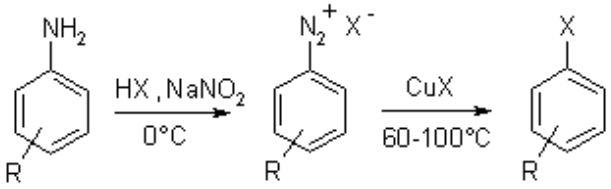


The reaction mechanism of the Hunsdiecker reaction is believed to involve organic radical intermediates. The silver salt of the carboxylic acid **1** will quickly react with bromine to form acyl hypohalite intermediate **2**. Formation of the diradical pair **3** allows for radical decarboxylation to form the diradical pair **4**, which will quickly recombine to form the desired organic halide **5**. The trend in the yield of the resulting halide is primary > secondary > tertiary.



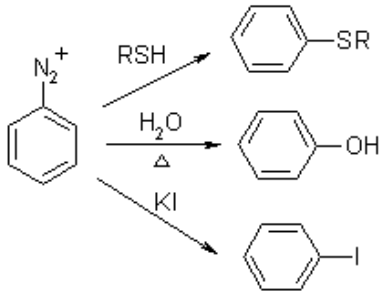
8.10 SANDMEYER REACTION

The Sandmeyer reaction is a chemical reaction used to synthesize aryl halides from aryl diazonium salts. It is an example of a radical-nucleophilic aromatic substitution. The Sandmeyer reaction provides a method through which one can perform unique transformations on benzene, such as halogenation, cyanation, trifluoromethylation, and hydroxylation. The reaction was discovered in 1884 by Swiss chemist Traugott Sandmeyer, when he synthesized phenylacetylene from benzenediazonium chloride and cuprous acetylide. The reaction is a method for substitution of an aromatic amino group via preparation of its diazonium salt followed by its displacement with a nucleophile, often catalyzed by copper(I) salts. The nucleophile can include halide anions, cyanide, thiols, water, and others. The reaction does not proceed well with the fluoride anion, but fluorination can be carried out using tetrafluoroborate anions (Balz–Schiemann reaction).



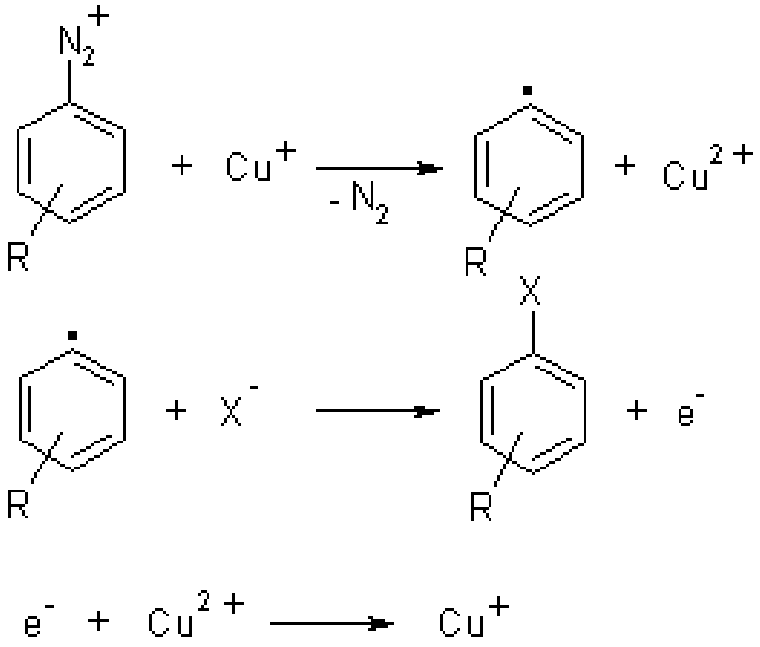
X= CN, Br, Cl, SO_3H

The substitution of an aromatic amino group is possible via preparation of its diazonium salt and subsequent displacement with a nucleophile (Cl^-, I^-, CN^-, RS^-, HO^-). Many Sandmeyer Reactions proceed under copper (I) catalysis, while the Sandmeyer-type reactions with thiols, water and potassium iodide don't require catalysis.



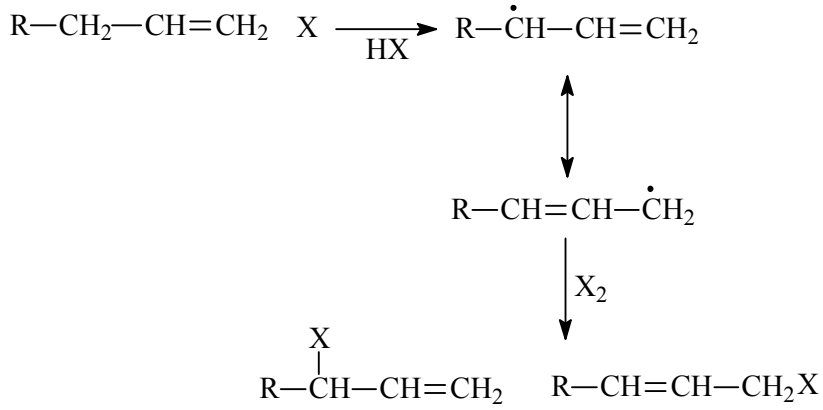
Reaction mechanism

The nitrous acid is typically prepared *in situ* from sodium nitrite and acid. Following two protonation steps, one equivalent of water is lost to form the nitrosonium ion. The nitrosonium ion then acts as an electrophile in a reaction with an aromatic (or heterocyclic) amine, such as aniline, to form a diazonium salt, proceeding through a nitrosamine intermediate. The substitution of the aromatic diazo group with a halogen or pseudohalogen is initiated by a one-electron transfer mechanism catalyzed by copper (I) to form an aryl radical with loss of nitrogen gas. The substituted arene is formed through a radical mechanism with regeneration of the copper (I) catalyst. This reaction is known as the Sandmeyer reaction and is an example of a radical-nucleophilic aromatic substitution. The radical mechanism of the Sandmeyer reaction was resolved through the detection of biaryl byproducts. It proceeds through the following mechanism.

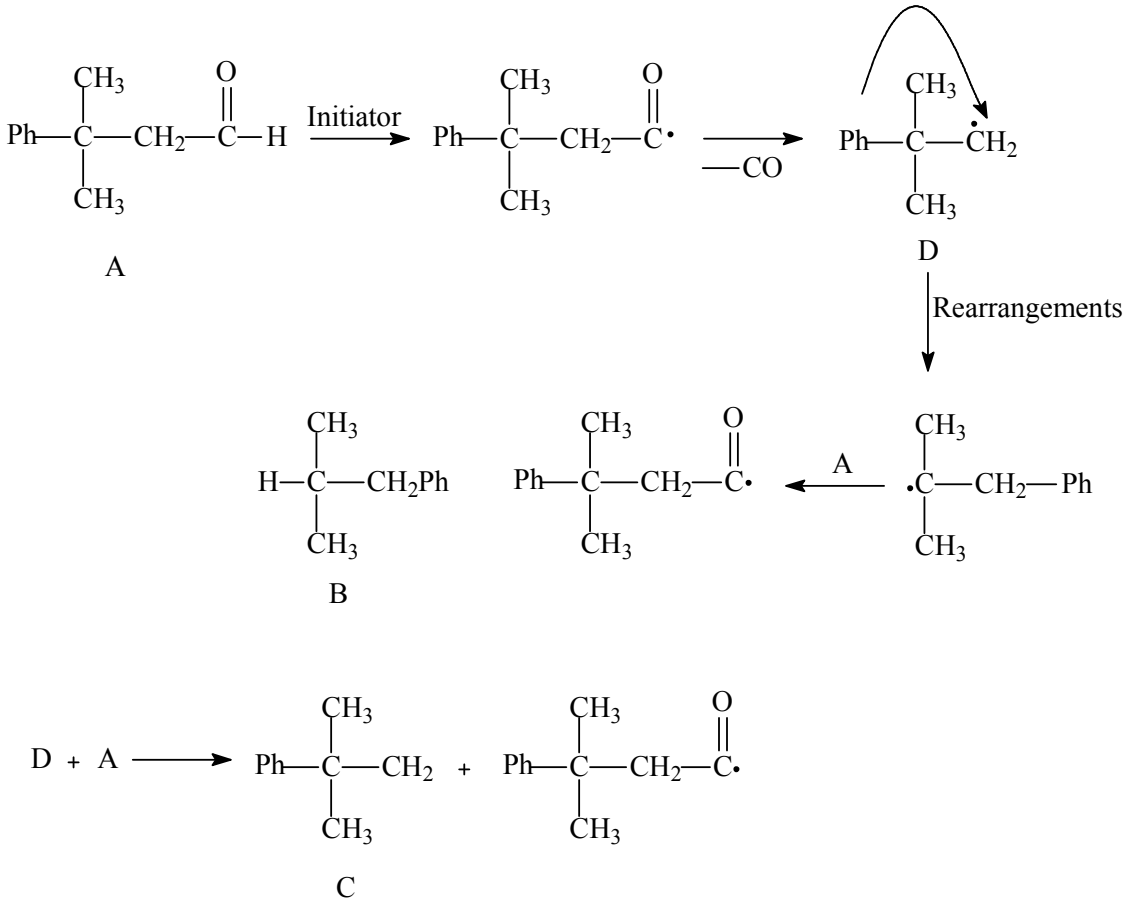


8.11 FREE RADICAL REARRANGEMENT

Allylic rearrangements are very common in free radical reactions on allylic substrates, for examples:



A primary radical may sometimes produce a tertiary radical by migration by migration of a substituents from the neighbouring carbon atom. However, such radical rearrangements are less common than carbocation rearrangements because the stability differencesbetween a primary and a tertiary radical is not as much as that between a primary and a tertiary radical is not as much as that between a primary and tertiary carbocation. Most of the published rearrangement involves the shift of an aryl group from one atom to the adjacent atom. For example the rearrangement of beta-phenylisovaleraldehyde A accompanying decarbonylation. The reaction is initiated by t-butyl peroxide and yields a mixture of almost equal amounts of isobutyl benzene B and t-butylbenzene C.



The yield of the rearranged product B increases with dilution of the reaction mixture. This supports the above mechanism because a decrease in concentration of a hydrogen donor A would increase rearrangement at the expense of the hydrogen abstraction by the radical D. Additional; the rate of the rearrangement is inhibited by addition of an effective hydrogen donor such as thiophenol. The above rearrangement proceeds through the intermediate bridged radical.

8.12 SYMMARY

In this chapter provided us concise knowledge about about free radical reactions, mechanism of free radical substitution, reactions on aromatic substrates and neighboring group assistance. We also studied about reactivity for aliphatic and aromatic substrates at a bridgehead carbon, reactivity of the attacking radicals, the effect of solvents on reactivity and allelic halogenations (NBS). We learned about oxidation of aldehydes to carboxylic acids, auto-oxidation, coupling of alkynes and arylation of aromatic compounds by diazonium salts. Besides many important name reactions of synthetic utility alongwith Sandmeyer reaction, free radical rearrangement and Hunsdiecker reaction.

8.13 TERMINAL QUESTIONS

1. Which one of the following alkenes will undergo free radical bromination most readily?

A. CH_3COOH

B. CH_3COCl

C. CH_3CH_2COOH

D. $HOOCCH_2CH_2COOH$

2. Free radical monobromination of n-butane gives:

A. (+)-2-bromobutane

B. (-)-2-bromobutane

C. (±)-2-bromobutane

D. achiral 2-bromobutane

3. Using the given codes, arrange the following compounds in decreasing order of reactivity with $NBS/CCl_4/hv$:

1. $PhCH_3$
2. $PhCH_2CH_2CH_3$
3. $PhCH_2CH{=}CH_2$
4. $Ph{-}\underset{\displaystyle CH_3}{\underset{|}{CH}}{-}CH{=}CH_2$

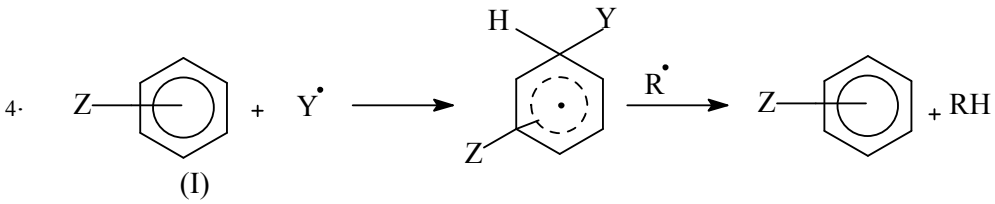
Codes:

A. 4, 3, 1, 2

B. 4, 3, 2, 1

C. 1, 2, 3, 4

D. 1, 3, 2, 4

4. 

(I)

In the above reaction I will be least reactive if Z is:

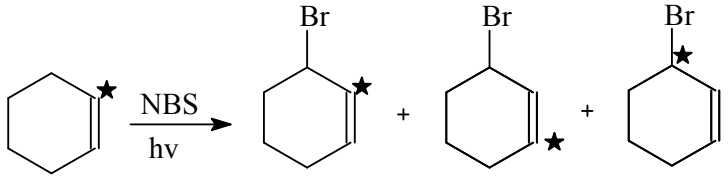
A. H

B. NO2

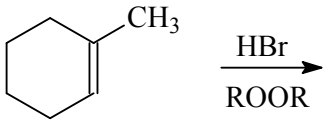
C. Cl

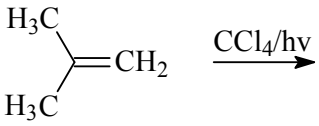
D. OH

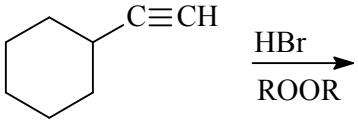
5. How will you account for the formation of the following products on treatment of labeled (* = ^{14}C) cyclohexene with NBS?



6. Give major products expected for each of the following reactions. Pay attention to regiochemistry and stereochemistry where appropriate.

1. 

2. 

3. 

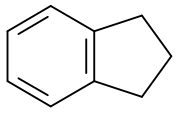
7.Give the structures of all the free radical monochlorination products of 1,2-dichloropropane and indicate them as chiral or achiral.

8. Give the mechanism of photobromination of 1-bromo-2-methylbutane and indicate the stereochemistry of the reaction, if any.

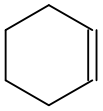
9. Complete the following reaction and indicate the configuration(s) (*R* or *S*) of the product(s) formed.

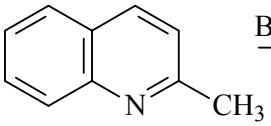
$$CH_3—CH_2—C\equiv CH \xrightarrow[h\nu]{NBS/CCl_4}$$

10. Predict the product (s) in the following reactions:

1.  NBS/hv →

2. $PhCH_2CH_2CH_3$ NBS/hv →

3.  $Ph^{\bullet}$, O_2 →

4.  Br_2/hv →

8.14 ANSWERS TO TERMINAL QUESTIONS

1. C

2. C

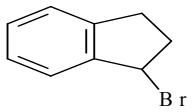
3. B

4. A

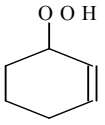
5. Hint: write all the resonating structures of the radicals generated at both the allylic positions. The addition bromine to the radical carbon gives the observed products.

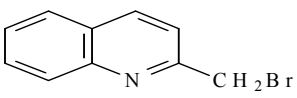
7. $ClCH_2CHClCH_2Cl$ (Achiral),
   $CH_3C^*HClCHCl_2$ (Chiral),
   $CH_3CCl_2CH_2Cl$ (Achiral)

10.

1. 

2. $PhCHBrCH_2CH_3$

3. 

4. 

8.15 REFERENCES

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UNIT 9- EILECTROCYCLIC REACTIONS

CONTENTS:

9. Objectives

9.1 Introduction

9.2 Molecular orbital symmetry

9.3 Frontier orbitals of ethylene, 1,3-butadiene, 1,3,5-hexatriene and allyl system.

9.4 Classification of pericyclic reactions.

9.5 Woodward-Hoffmann correlation diagrams

9.5.1 Correlation diagram Electrocyclic reaction

9.5.2 Frontier Molecular Orbital (FMO) aproach for electrocyclic reactions

9.5.3 Perturbation Molecular orbital (PMO) Aproach for electrocyclic reactions(H-M) Huckel-Mobius system

9.6 Summary

9.7 Terminal questions

9.8 Answers (MCQ) terminal questions

9.9 References

9.0 OBJECTIVES

Objectives of this unit are to make aware students about concerted reactions, Concept of molecular orbital symmetry conservation Principle given by Woodward-Hoffmann, correlation diagrams, different methods for the explanation of electrocyclic reactions, conrotatory and disrotatory mode of ring opening and ring closer reactions and Feasibility of thermally or photochemically induced reaction, reactions of 4nπ and 4n +2π systems interconversion through thermal or photochemical induction.

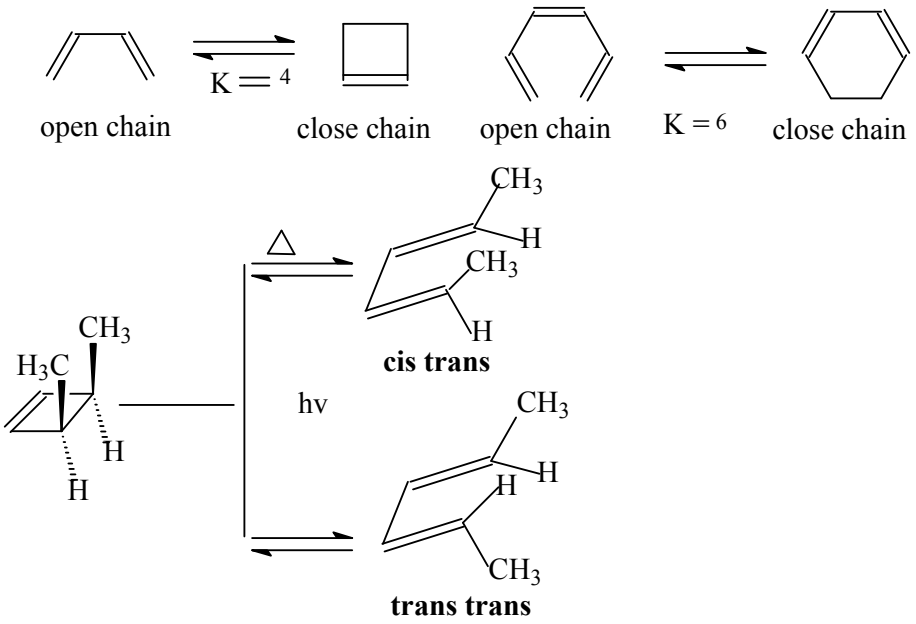
9.1 INTRODUCTION

Electrocyclic reaction is a type of pericyclic reaction.Pericyclic reactions are also known as concered reactions in which bond breakin in reactant and bond formation in product takes place simultaneously in a single step. These reactions are:

1. Characteristic reactions of olefinic cimpounds
2. Cyclic Transition State
3. Stereospecific in nature
4. Initiated by heat or electromagnetic radiation
5. No reaction intermediates are formed

Pericyclic reactions have been classified in different category (electrocyclic reactions, cycloaddition reaction, sigmatropic reaction and group transfer reactions) electrocyclic reactions is one of them. In these reactions a concerted shift of electron takes place which ivolve conversion of two pie bonds to a pie bond and sigma bond if a reactant is open chain. A pie bond and a sigma bond are converted to two pie pie bond if the reactant is close chain in nature. In brief

If open chain partner contain Kπ electrons, its cyclic partner will contain K-2 π e- + a σ bond



9.2 MOLECULAR ORBITAL SYMMETRY

According to Woordword and Hoffmann 1965 the symmetry of molecular orbitals are conversed during interconvertion of open to cyclic parterner and vice-versa.K. Fukuii proposed another explanation based upon the frontier molecular orbitals.The theory proposed is known as FMO method. The Woodward- Hoffmann rule and Huckel-Mobius(H-M) method or perturbation of molecular orbitals (PMO) are also used for the explanation of pericyclic reactions.These foure theories predict the same explanation of pericyclic reactions.

To understand the theories of pericyclic reactions, we must first understand the molecular orbitals and their symmetry of compounds containing π-bonds.

The two molecular orbitals are important in understanding pericyclic reactions. One is the occupied molecular orbital of highest energy known as highest occupied molecular orbital (HOMO). The other is unoccupied molecular orbital of lowest energy known as lowest unoccupied molecular orbital (LUMO). Both HOMO and LUMO orbitals are referred to as frontier molecular orbitals (Fig 1)

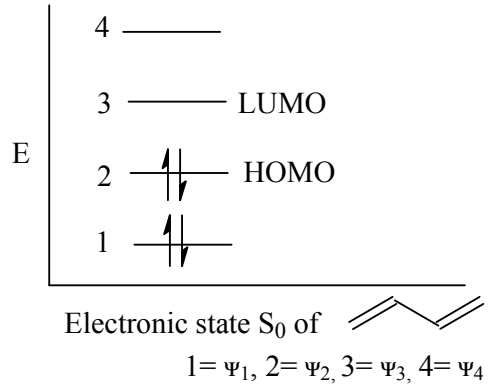


Fig 1. HOMO, LUMO orbitals of 1,3-butadiene

The molecular orbitals π and σ have two types of symmetry.

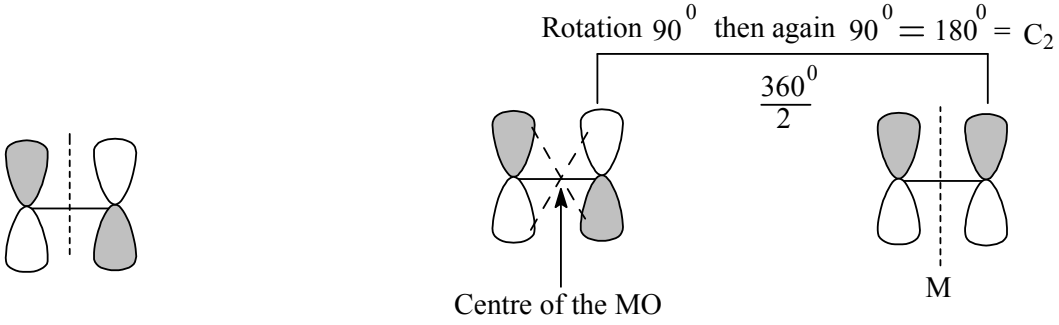
1. ***Mirror plane of symmetry***: in this symmetry the molecular orbitals have two halves having mirror image of each other **fig 2**

2. ***C_2 or two fold axis of symmetry***: in this type of symmetry the molecular orbitals posses center of symmetry or mirror image of each other if rotated by 180^0 or $360^0/2$

Miror plane of symmetry a pi molecular orbital Mirror plane of symmetry a sigma bonding MO

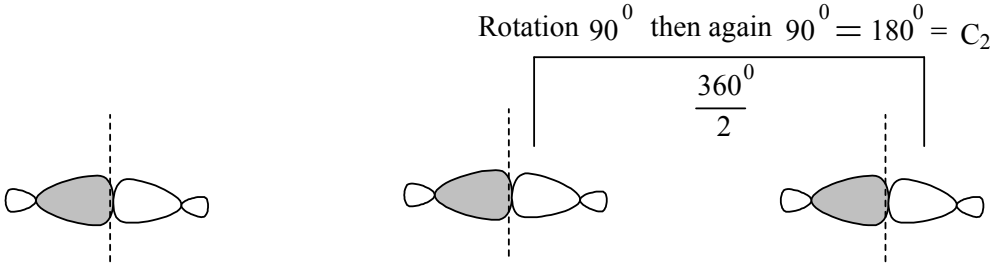
Fig.2 Mirror plane of symmetry in π and σ bonding molecular orbitals

In C_2 symmetry keeping one orbital in position rotate second by two fold first by 90^0 then again by 90^0 which makes two rotations (or simply 180^0 or $360^0/2$ in total). After doing this if the molecular orbital posses mirror plane bisecting the orbitals in to mirror image, then it is called C_2 symmetry of two fold axis of symmetry Fig 3. On the other hand if the molecular orbitals (MO) have centre of symmetry, then it is simply called C_2 symmetry.



Both the orbitals are not mirror image hence there is no M symmetry

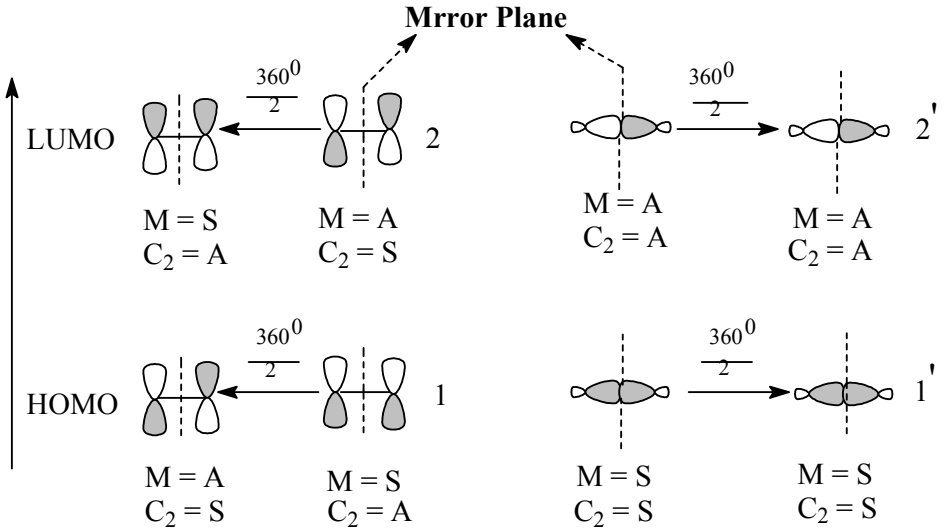
There is a centre of symmetry (i.e. C_2 symmetry)



Nomirror plane of symmetry

No centre of symmetry i.e. no C_2 symmetry

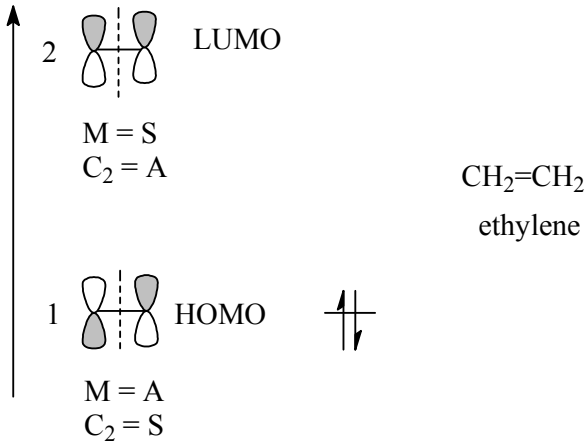
Fig.3 Two fold axis or C_2 of symmetry in π and σ bonding molecular orbitals



1=π_1 2=π_2, 1'=σ and 2'=σ^*

Fig.4 Molecular orbital symmetry in π and σ molecular orbitals of ethylene molecule

9.3 FRONTIER ORBITALS OF ETHYLENE, 1,3-BUTADIENE, 1,3,5-HEXATRIENE AND ALLYL SYSTEM



Molecular orbital symmetry of ethylene with HOLO, LUMO orbitals

1=π_1 / Ψ_1 2=π_2/ Ψ_2

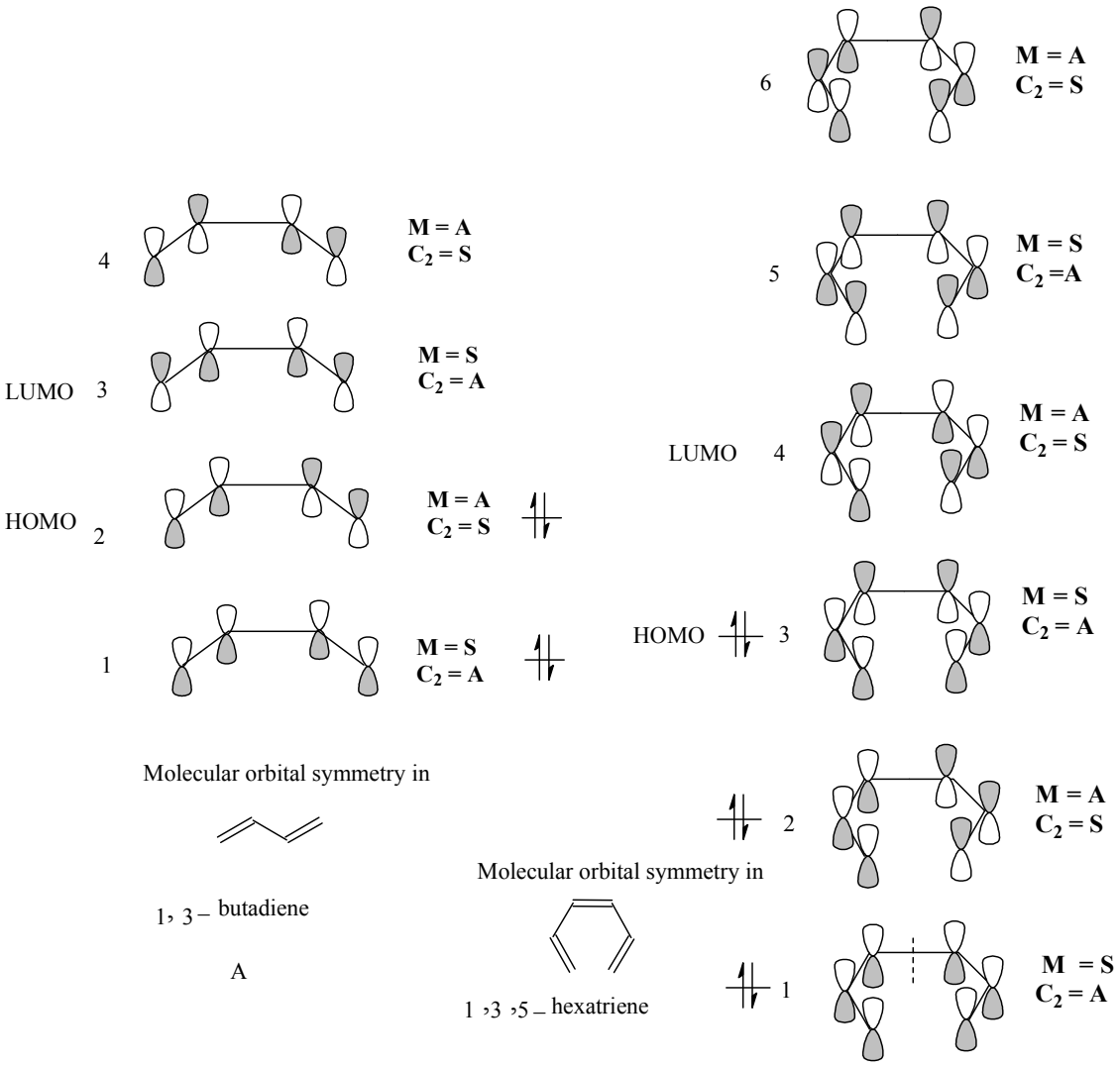
Fig 5. Moleculer orbitals symmetry in ethylene

When no of nodes (n-1) is zero or even, Ψ_n will be symmetric with M and symmetric with C_2 while if (n-1) is an odd, Ψ_n will have the symmetric exactly opposite

Nodes	**M**	**C_2**
0 or even	S	A
$\Psi_1, \Psi_3, \Psi_5, \Psi_7$,------- Odd	A	S

Table: 1 Moleculer orbital symmetry properties and Frontier orbitals of ethylene

(n-1)	**Orbital**	**Symmetry**		**Frontier MO**
		With respect to mirror Plane (M)	C_2	
1	Ψ_1/π_1	S	A	HOMO
2	Ψ_2/π_2	A	S	LUMO



A = 1= ψ_1/π_1, 2= ψ_2/π_2, 3= ψ_3/π_3, 4 = ψ_4/π_4

B= ψ_1/π_1, 2= ψ_2/π_2, 3= ψ_3/π_3, 4 = ψ_4/π_4, 5= = ψ_5/π_5, 6 = = ψ_6/π_6

Fig 6. Molecular orbitals of A 1,3-butadiene and B 1,3 5- hexatriene

Table 2 Moleculer orbital symmetry properties and Frontier orbitals of 1,3-butadiene

(n-1)	**Orbital**	**Symmetry property**		**Frontier MO**
		With respect to mirror Plane (M)	C_2	
1	ψ_1/π_1	S	A	HOMO

2	Ψ_2/π_2	A	S	LUMO
3	Ψ_3/π_3	S	A	
4	Ψ_4/π_4	A	S	

Table 3 Moleculer orbital symmetry properties and Frontier orbitals of 1,3 5- hexatriene

(n-1)	Orbital	Symmetry property		Frontier MO
		With respect to mirror Plane (M)	C_2	
1	Ψ_1/π_1	S	A	
2	Ψ_2/π_2	A	S	
3	Ψ_3/π_3	S	A	HOMO
4	Ψ_4/π_4	A	S	LUMO
5	Ψ_5/π_5	S	A	
6	Ψ_6/π_6	A	S	

Ther are two p-orbitals in the molecule of ethylene (ignoring σ-skeleton). Their combinations give us two π-MO designated as 1= Ψ_1/π_1 and 2= Ψ_2/π_2, thermodynamically with different energy. The energy of 1 = Ψ_1/π_1 is lowest and it acoomodate both the electrons. This MO is also designated as bonding MO. Since both the electrons are acccomdated in it hence also known as HOMO in ground state (highest occupied molecular orbitals i.e. the orbital which occupy the last electron/s). 2= Ψ_2/π_2 is vacant and higher in energy is known as LUMO (lowest unoccupied molecukar irbital i.e. the orbital which lowest in energy and vacat) in ground state (**fig.5**). So far the symmetry properties of these MOs are concerned the Ψ_1/π_1 orbital is symmetric (zero node) with respect to mirror plane and asymmetric with respect to C_2 similary Ψ_2/π_2 is asymmetric (one node, odd no) with respect to mirror plane ans symmetric with respect to C_2 plane(**fig.5, table 1**).

There are four p- orbitals in the molecule of 1,2-butadiene (ignore σ-skeleton in this treatment) and their possible combinations provide us an approximation set of four molecular π- orbitals designated as Ψ_1/π_1, Ψ_2/π_2, Ψ_3/π_3 and Ψ_4/π_4 have different energies.The energy of 1= Ψ_1/π_1 is considerably lower than any of the other approximations and it is

therefore reasonable that two out of four electrons in the ground state are accomomodated by this orbital. The enery of next higher orbital 2= Ψ_2/π_2 is also lower than other two molecular orbitalshence remaining two electrons out of four are accommodated in it. These two MO are designated as bonding MO while remainin two (3= Ψ_3/π_3, 4 = Ψ_4/π_4) vacant MO are higher in energy and are anti bonding in nature (**fig 6A**). Six p- electrons of 1,3,5-hexatriene are similarly accommodated in the first three MOs viz; 1 = Ψ_1/π_1, 2= Ψ_2/π_2 ,3 = Ψ_3/π_3 (bonding MOs), while remaining three MOs viz; 4= Ψ_4/π_4, 5= Ψ_5/π_5, 6 = Ψ_6/π_6 (anti-bonding MOs) are unoccupied in ground (S_0) state(**fig.6B**). As per the description 2= Ψ_2/π_2 is HOMO and 3 = Ψ_3/π_3 is LUMO in 1, 3-butadiene in S_0 (**fig. 6A table 2**). Similarly 3 = Ψ_3/π_3 is HOMO and 4 = Ψ_4/π_4 is LUMO in ground state of 1, 3, 5-hexatriene respectively.(**fig. 6B table 3)**

Conjugated unbranched ions (cations and anions) and radicals have an odd number of carbons. First member of these classes are **allyl carbocations, allyl carbanions and allyl free radoicals.**

$CH_2=CH-\overset{\oplus}{C}H_2$ allyl carbocation

sp^2 sp^2 sp^2

This system has three isolated p- orbitals and has only one π- bond (two π electrons)

$CH_2=CH-\overset{\ominus}{C}H_2$ allyl carbanion

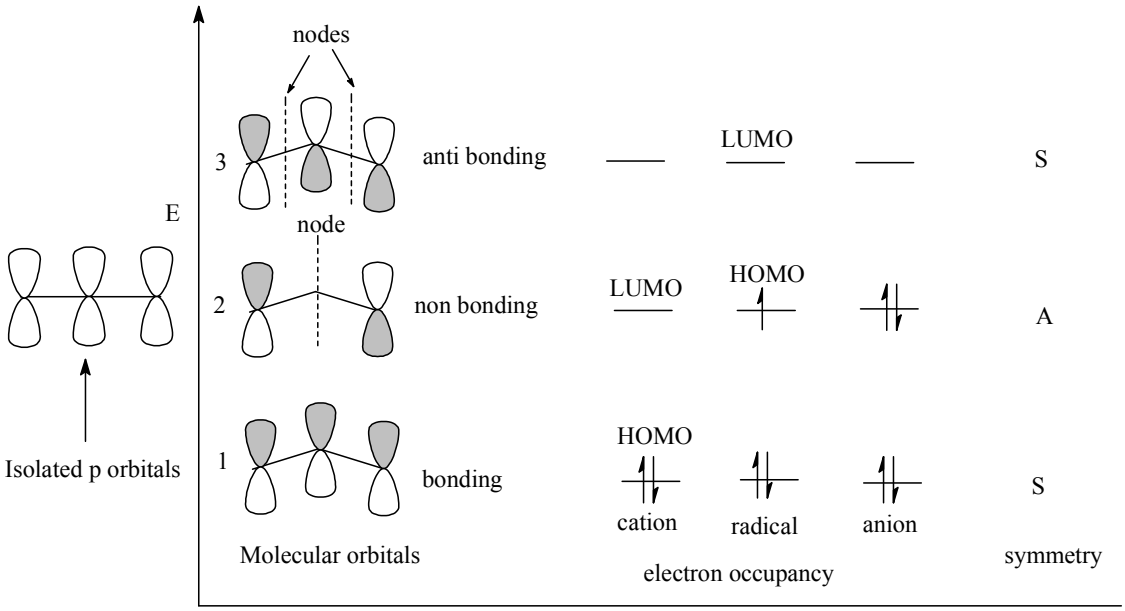
This system has three isolated p- orbitals and has only one π- bond and one lone pair of electrons.

Similarly in following system there are three p-orbitals and has one π-bond and one electron in unhybrid p-orbital. The electron occupiency in these systems can be represented as follow

$CH_2=CH-\dot{C}H_2$ allyl free radical

The MOs of allyl shows two important differences between these MOs and those of conjugated polyenes.

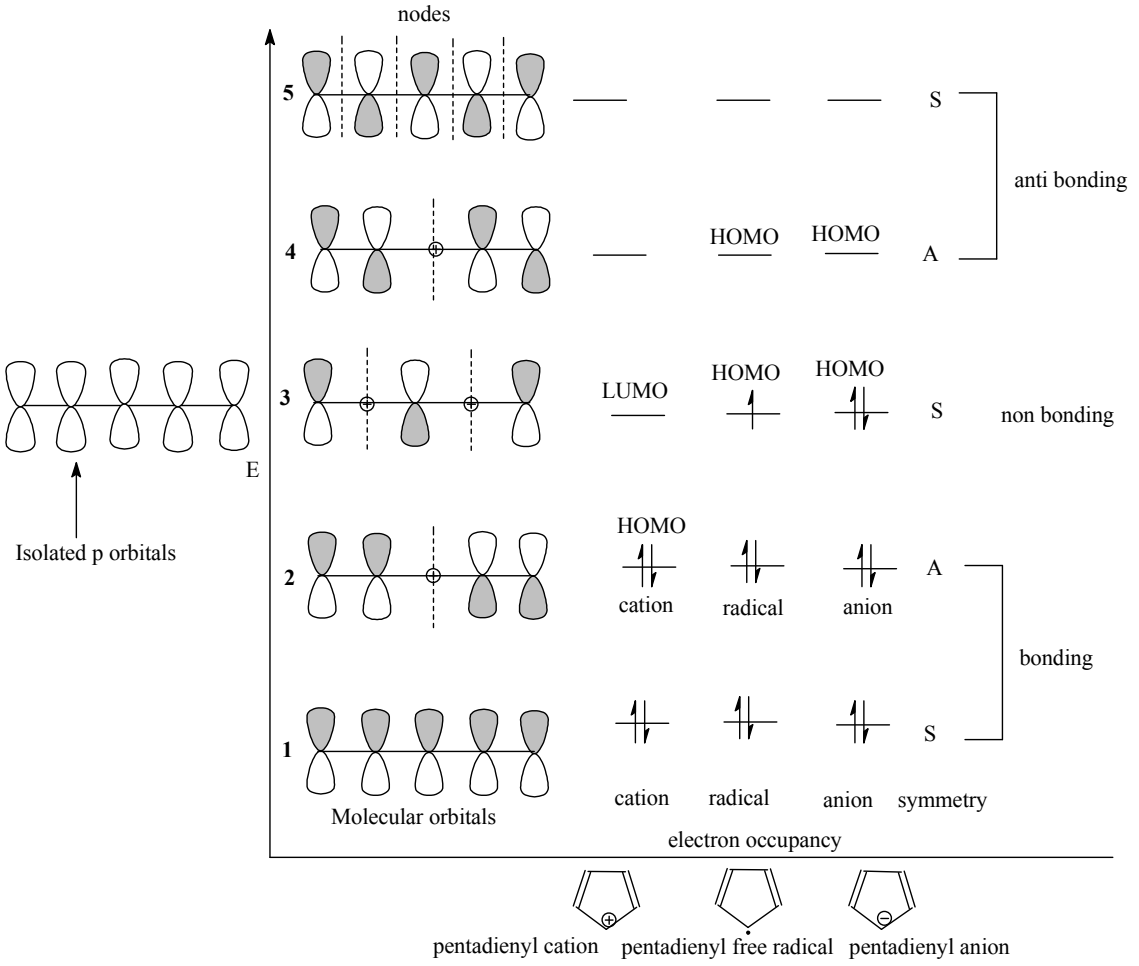
A. One MO in allylic system is neither bonding MO nor anti-bonding MO but has the similar energy as the isolated p-orbitals This MO is called nonbonding MO.The nonbonding MO in allylic system is 2= Ψ_2. The remaining MOs are bonding and anti-bonding (half are bonding and half are anti-bonding)(**fig7**



$1 = \psi_1,\ 2 = \psi_2,\ 3 = \psi_3$

Fig. 7 π- molecular orbitals with HOLMO- LUMO designation and symmetry properties of allyl system

B. In some of the MO's nodes pass through carbon atom viz; in allyl free radical there is node on the central carbon atom of $2 = \Psi_2$. The cation anion and free radicals involving the same π- system have the same MOs because all three species contain similar number of p-orbitals (**fig 7**). Similarly the the π- MOs of 2,4- pentadienyl system are shown in **fig 8.**

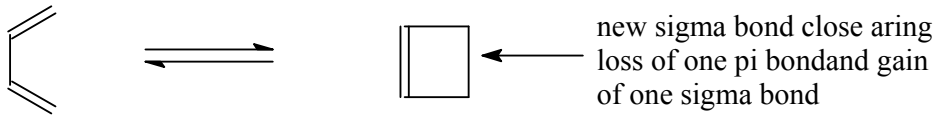


$1 = \Psi_1,\ 2 = \Psi_2,\ 3 = \Psi_3,\ 4 = \Psi_4,\ 5 = \Psi_5$

Fig. 8 π- molecular orbitals with HOLMO- LUMO designation and symmetry properties of 2,4-pentadienyl system

9.4 CLASSIFICATION OF PERICYCLIC REACTIONS

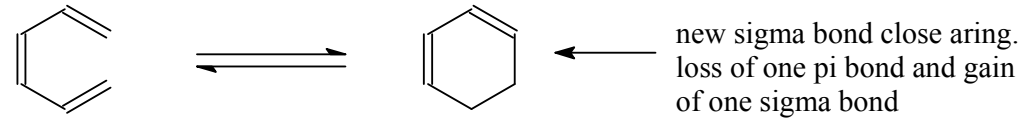
As also mentioned earlier pericyclic reactions are of four types. The first type is the electrocyclic reaction: A reaction in which a ring is closed (or opened) through a cyclic shift of electrons at the expense of conjugated double bond or a pi bond. If open chain partner contain Kπ electrons, its cyclic partner will contain K-2 π e- + a σ bond.



1,3 – butadiene cyclobutene

open chain closed chain

K = 4 (4 – 2) = 2 pi electron + a sigma bond

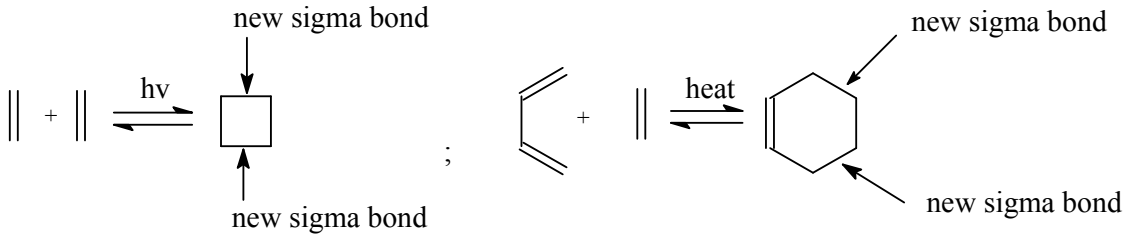


1, 3, 5 – hexatriene cyclohexadiene

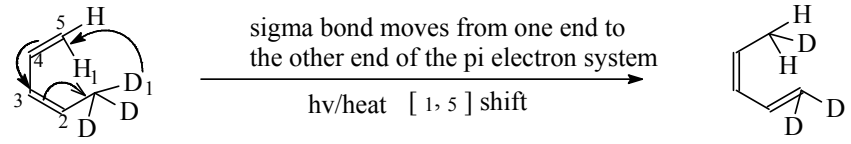
K = 6 (6 – 2) = 4 pi electron + a sigma bond

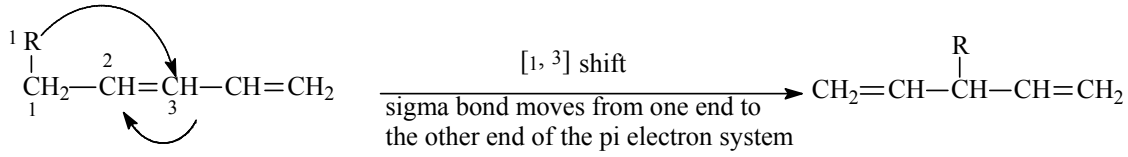
open chain closed chain

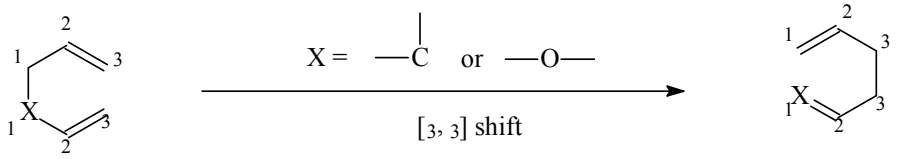
The second type of pericyclic reaction is cycloaddition reaction: a reaction in which two or more π-electron system reacts to form aring at the expense of one π-bond in each of the reacting parterns



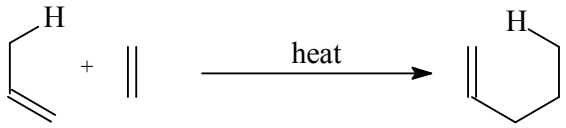
The third type of reaction is the sigmatropic rearrangement (or reaction): a reaction in which a σ-bond formally migrates from one end to the other end of π-electron system and net number of π- bonds remains the same. The reactions are often classified with two numbers,*i* and *j* set in brackets [*i, j*] and the system is numbered by starting at the atoms forming the migrating σ-bond. These (i and j) indicates the new positios of the σ-bond whose termini are i-1 and j- 1 atoms removed from the original loci.







The fourth type of reaction is group transfer: a reaction in which one or more groups or atoms transfer from one molecule to another molecule. In this reaction both the molecules are joined by a sigma bond.



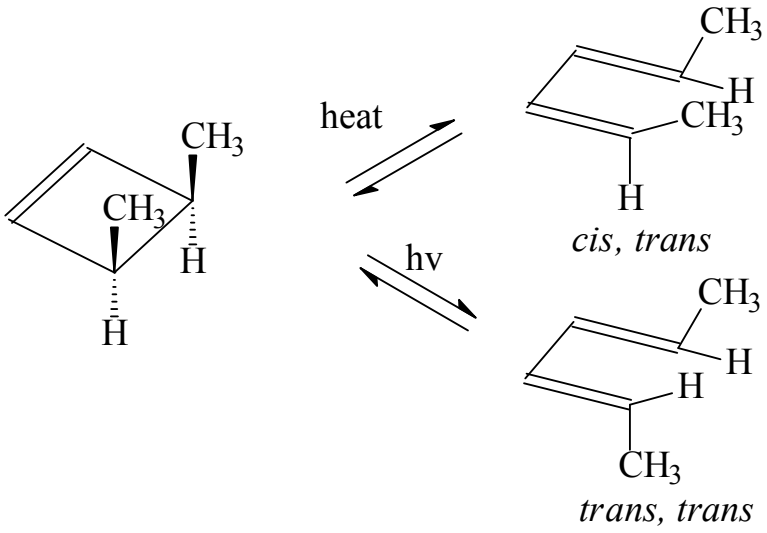
9.5 WOODWARD-HOFFMANN CORRELATION DIAGRAMS

According to Woodward –Hoffmann rule the pericyclic reactions can be interpreted by correclation diagram methods. In correclation diagram method if the MOs of reactant (open chain/ close chain) correlate with the MOs of product (open/close chain) molecule in ground state, the reaction is considered to be feasible in through thermal induction and if theexcited state molecular symmetry of reactant species correlate with excited stae molecular symmetry of the product, the the reaction is possible by phytochemical induction.

9.5.1 Correlation diagram of electrocyclic reaction:

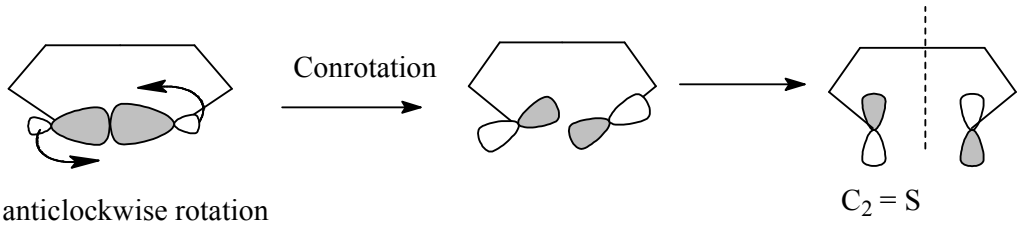
As also mentioned earlier an electrocyclic reaction is interconversion of cyclic to close chain molecules containing double bonds. The reaction is initiated by heat of EMR. The reactions are stereospecific in nature.

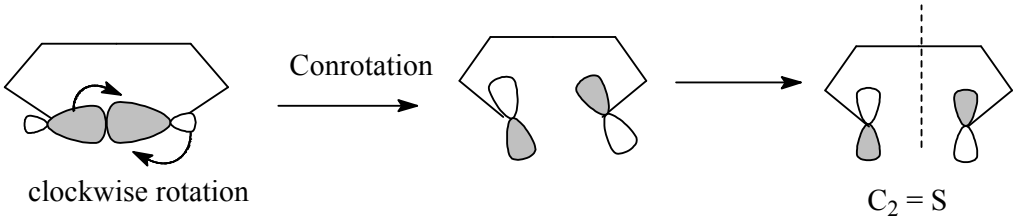
Let us consider the simplest example in which a cyclobutene system opens to a 1, 3-butadiene. This reaction can be performed thermally or photochemically and under either condition the reaction is completely stereospecific.



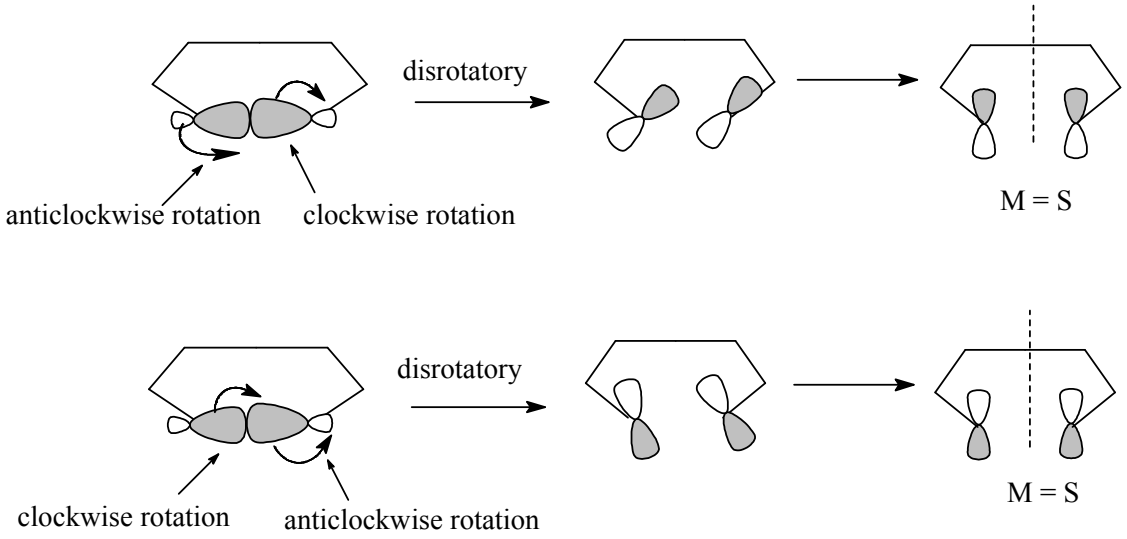
For above conversion of close chain of cyclobutene to open chain 1,3 –butadiene a σ-bond of cyclobutene must break break to yield open chain butadiene. In reverse reaction ring closer also involve σ- bond. The ring opening and ring closer takes place by two different methods as discussed follow.

A. conrotatory motions: In conrotatory motion the orbitals rotate in same directions either clockwise or anticlockwise direction. During corotation C_2 symmetry is maintained.





B. disrotatory motions: In disrotatory motion the orbitals rotate in opposite directions, one clockwise and the other anticlockwise mirror plane (M) symmetry is maintained in disrotation



The stereochemical significance of these two modes of ring – opening /closing becomes apparent when we consider substituted reactants.

An electrocyclic reaction is a concerted reaction. The transition state of electrocyclic reaction should be intermediate between electronic ground stats of starting material and product. The most stable transition state will be the one which conserve the symmetry of reactant MOs in passing to MOs of products. In other words the the symmetry(S) MOs in the reactant must transform into symmetry (S) MOs in the product and asymmetric (A) MOs of reactant must transform into asymmetry (A) MOs of the product. In case the symmetry properties of MOs are not sustained during the reaction, the reaction will not take place in a concerted manner.

Let us analyse the cyclobutene-1, 3-butadiene interconversion. The ring opening/closing in such transformation may take place by disrotation or conrotation. To analyse this transformation construct symmetry properties of MOs of cyclobutene and 1,3 – butadiene as follow (**fig.9,10**)

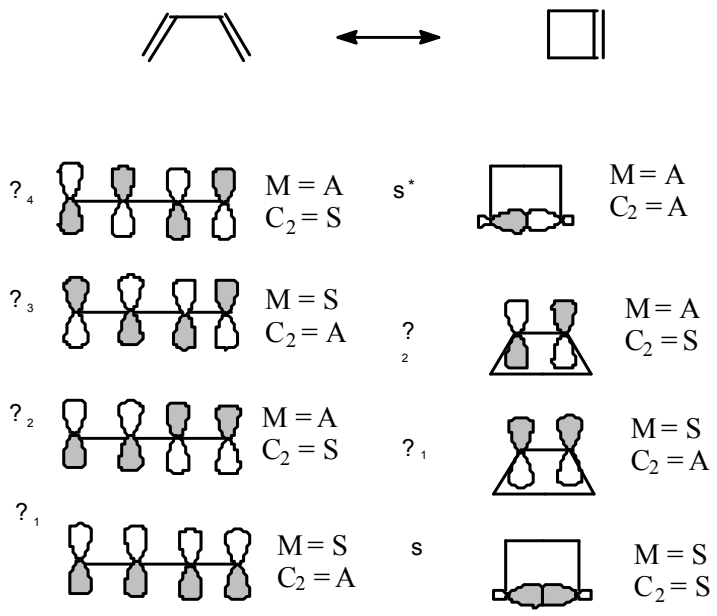


Fig. 9 Symmetry properties of molecular orbitals (MOs) of cyclobuten and 1,3- butadiene

Analysis through coorelation diagram can be done either presuming the disrotation or conrotation. In disrotation M symmetry in suctained while in corotation C_2 symmetry is maintained.

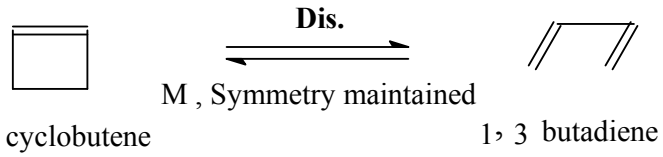
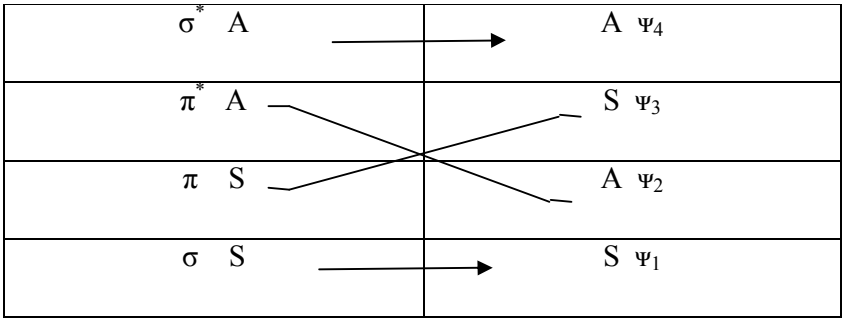
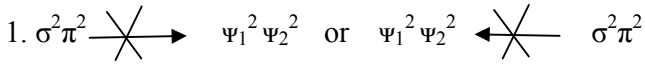


Fig 10. Correlation for disrotatory interconversion of cyclobutene- butadiene system M symmetry mainitained



Disrotation mode for ring closing/opening



$$2.\ \sigma^2\pi^2 \longrightarrow \sigma^2\,\pi\,\pi^* \longleftrightarrow \Psi_1^2\,\Psi_2\,\Psi_3 \longleftarrow \Psi_1^2\,\Psi_2^2$$

S_0 S_1 S_1 S_0

Ground state first excited state first excited state ground state

Two conclusions can be drawn from above correlation diagram

1. We expect a thermal transformation to take place only if the S_0 i.e ground state orebital symmetry of reactant correlates with the S_0 state of the products. While considering condition 1 as above although the cyclobutene ground state orbital symmetry of σ-orbital correlate with S_0 state of 1,3- butadiene Ψ_1, the π-orbital symmetry of former does not correlate with Ψ_2 of the latter. It correlate with Ψ_3 which is an excited state and antibonding orbital.Thermal transformation of cyclobuten to 1,3-butadiene by dirotatory process through concerted manner is thus symmetry-forbidden and or not allowed.

2. Irrediation of cyclobutene produce the first excited state (S_1) as point 2 above in which an electron is promoted from π^* orbital and in this case σ, π and π^* orbitals of cyclobutene correlate with Ψ_1, Ψ_2, and Ψ_3 orbitals of 1, 3- butadiene. In other words the first excited state ($S_1 = \sigma^2\,\pi\,\pi^*$) of cyclobuten correlate with first excited state ($S_1 = \Psi_1^2\,\Psi_2\,\Psi_3$) of 1, 3-butadiene hence disrotatory ring opening (and ring cosing) is allowed process by concerted manner (**fig.11**)

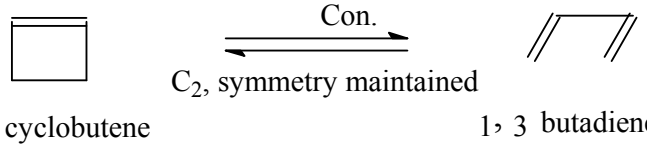
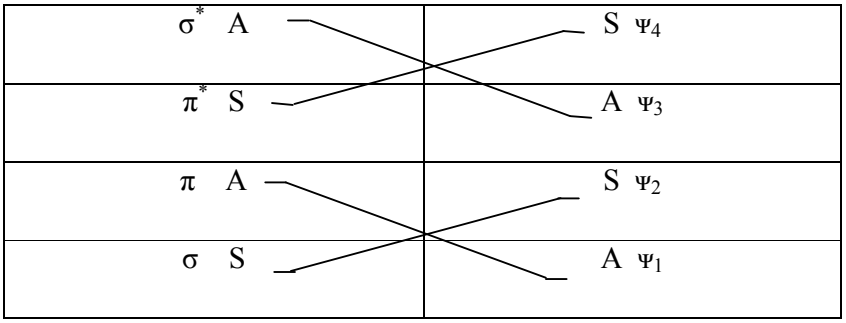
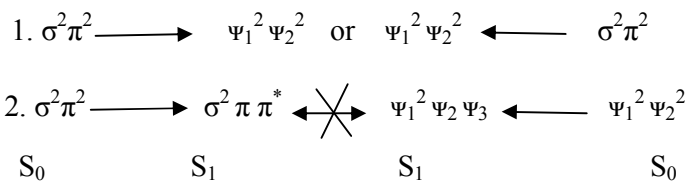


Fig.11 Correlation diagram for conrotatory interconversion of cyclobutadiene- butadiene system C_2 symmetry mainitained



Conrotation mode for ring closing/opening

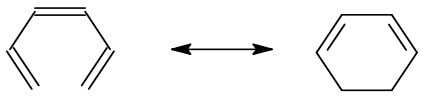


Two conclusions can again be drawn from above correlation diagram.

1. Since there is correlation between the ground state (S_0) orbital symmetry of cyclobutene ($\sigma^2\pi^2$) and 1, 3 –butadiene ($\Psi_1^2\Psi_2^2$). Hence the cyclobetene – butadiene interconversion by conrotation mode is symmetry allowed by thermal induction and will take place by concerted manner.

2. The first excited state ($S_1 = \sigma^2\pi\pi^*$) correlate with the upper excited state ($S_1 = \Psi_1^2\Psi_2\Psi_3$) of 1, 3- butadiene thus making it a high energy symmetry forbidden process. Similarly, the first excited state of butadiene ($S_1 = \Psi_1^2\Psi_2\Psi_3$) correlate with a high energy upper excited state ($S_1 = \sigma^2\pi\pi^*$) of cyclobutene.In other words, a photochemical conrotatory process in either direction is symmetry- forbidden and will not proceed by concerted manner.

From above statements it becomes clear that thermal opening of cyclobutene proceeds in a conrotatory process while photochemical involvs adisrotatory mode. These generalizations are true for all the systems containing 4nπ electrons where n= 0, 1, 2 etc.However, for system containing (4n + 2)π electrons theoretical prediction is entirely differentand is in conformity with actual observations. A typical system of this type is interconversion of cycloheadiene and 1, 3, 5-hexatriene as follow.



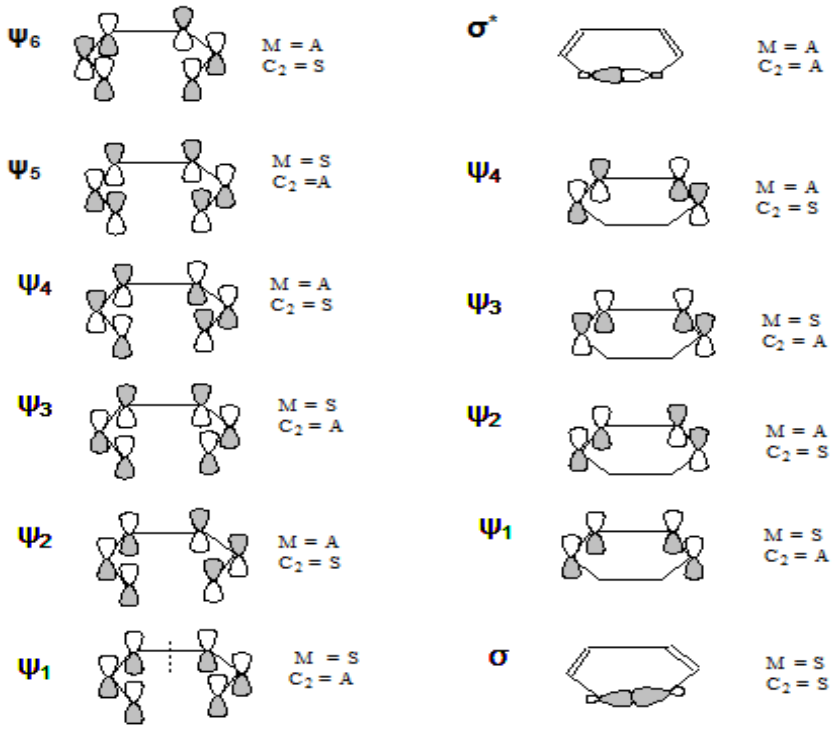
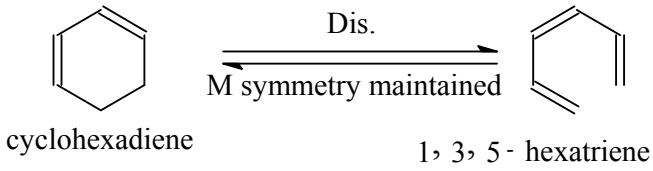


Fig. 12 Symmetry properties of molecular orbitals (MOs) cyclohexadiene to 1,3,5-hexatriene

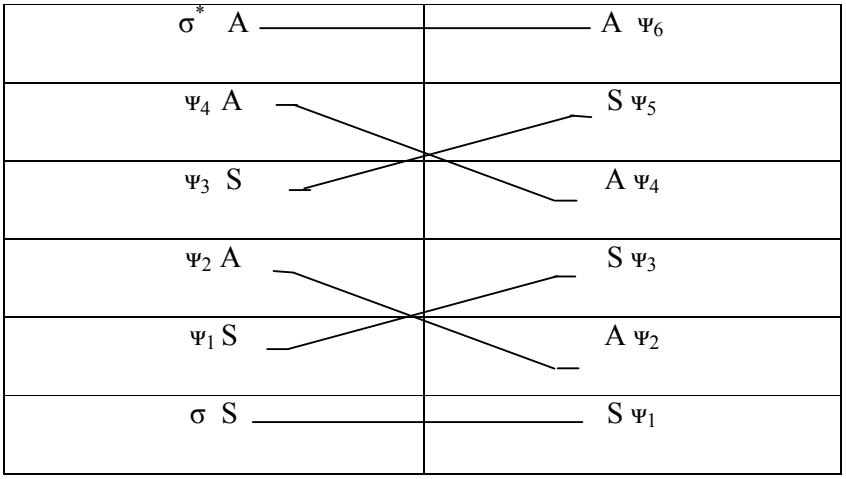
In above transformation of cycloheadiene and 1, 3, 5-hexatriene MOs (Ψ_1 to Ψ_6) of hexatriene and six MOs (four $\pi = \Psi_1, \Psi_2, \Psi_3$ and Ψ_4 and two σ and σ^*) of cyclohexadiene system are actually involved and need to be considered for explation. Symmetry properties of six MOs of hexatriene and cyclohexadiene have been constructed (**fig 12, 13**).

Analysis through coorelation diagram can be done either presuming the disrotation or conrotation.



Conrotation mode for ring closing/opening

Fig 13 Correlation diagram for disrotatory interconversion of cyclohexadiene- hexatriene system M symmetry mainitained



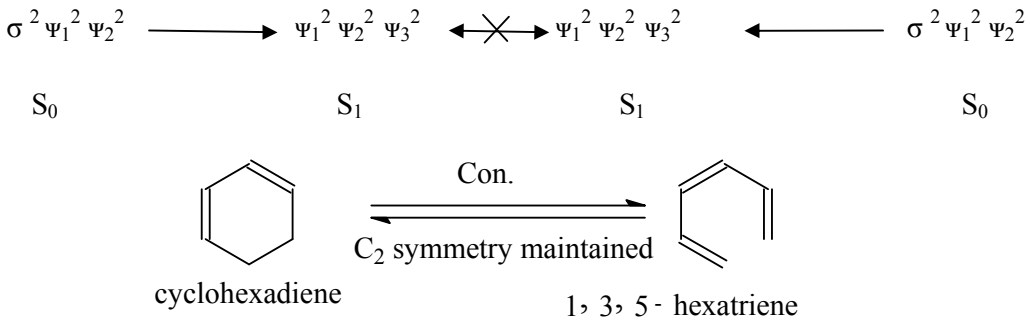
The correlation diagram as above (fig 13) for disrotatory pathways is constructed in the similar way as in the case of cyclobutene-butadiene system.

The following inferences may be drawn from the above correclation diagrams

1. In the disrottory mode (M symmetry) S_0 bonding MOs of cyclohexadiene correlate with the S_0 bonding MOs of hexatriene and and is thus the interconersion of cyclohexadiene to hextriene and vice-versa is a thermally allowed process.

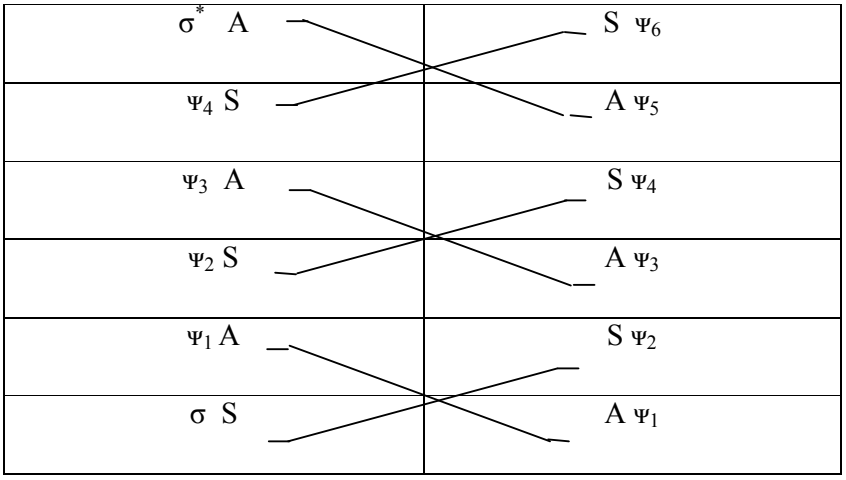
$\sigma^2 \Psi_1^2 \Psi_2^2 \longrightarrow \Psi_1^2 \Psi_2^2 \Psi_3^2$ Or $\sigma^2 \Psi_1^2 \Psi_2^2 \longleftarrow \Psi_1^2 \Psi_2^2 \Psi_3^2$

2. In conrotatory mode (C_2- symmetry), ground state(S_0) bonding MOs of cyclohexatriene do not correlate with S_0 bonding MOs of hexatriene Since the presence of two electrons in Ψ_4 is a very high energy process, a conrotatory mode for the interconersion of cyclohexadiene to hextriene and vice-versa is prohibited under thermal condition(fig13).



Conrotation mode for ring closing/opening

Fig 14 Correlation diagram for conrotatory interconversion of cyclohexadiene- hexatriene system C_2 symmetry mainitained



3. If we promote an electron from Ψ_2 to Ψ_3 in cyclodiene or Ψ_3 to Ψ_4 in hexatriene by irradiation then the MOs of cyclohexadiene correlate with the MOs of hexatriene with first excited (S_1) states of each other. Ψ_3 is S_1 state of cyclohexadiene while Ψ_4 is S_1 for hexatriene (fig.12 & 14).

$$\sigma^2 \Psi_1^2 \Psi_2^2 \longrightarrow \sigma^2 \Psi_1^2 \Psi_2 \Psi_3 \longleftrightarrow \Psi_1^2 \Psi_2^2 \Psi_3 \Psi_3 \longleftarrow \Psi_1^2 \Psi_2^2 \Psi_3^2$$

S_0 S_1 S_1 S_0

In is inferred therefore, that photochemical interconversion is symmetry allowed in conrotatory pathways.These generalizations are true for all the systems containing $(4n + 2)\pi$ electrons, where n= 0,1, 2,---etc. The Woodward- Hoffmann rules for electrocyclic reactions may be summed upin the form of **table 4.**

Table 4. Selection rules for electrocyclic reactions.

Number of π electrons	Thermal mode (Δ)	Photochemical mode(hv)
5 nπ electrons	Con.	Dis.
(4n +2)π electrons	Dis.	Con.

Woodward- Hoffmann have explained that under severe thermal conditions, symmetry-forbidden reactions may also take place but they follow a non-concerted pathway and their energy of activation is 10-15 kcl/mole higher than those of symmetry allowed processes.

9.5.2 Frontier Molecular Orbital (FMO) aproach for electrocyclic reactions

FMO approach is quick method for the interpretation of electrocyclic reactions. In this approach our guide for explanation is HOMO orbitals of open chain parterner.In this approach if the MO of open chain has C_2 symmetry then the reaction follow conrotatory mode of cyclization and if it has M symmetry, it will follow disrotatory mode. It has already been mentioned above in section 9.3 that the the MOs with zero or even number of nodes (n-1) posses M symmetry while with odd numer of nodes (n-1) exhibit symmetry with respect to C_2. So far the 1,3- butadiene - cyclobutene is concerned. In ground state (S_0) of butadiene Ψ_2 is HOMO and since it has one node and display C_2 symmetry. Hence according to FMO approach the ring closere/ ring opening in the intercoversion will follow conrotatory mode. Irradiation of butadiene by EMR promote electrone from Ψ_2 (HOMO in S_0) to Ψ_3 (LUMO in S_0) which becomes now HOMO (because possing last electron in it). Since this orbital has two nodes and it display M symmetry, hence as per FMO approach the ring closere/ ring opening in the intercoversion will follow disrotatory mode. The explanation based on the fact that overlapping of wave function of same sign is essential for bond formation (**fig.15**)

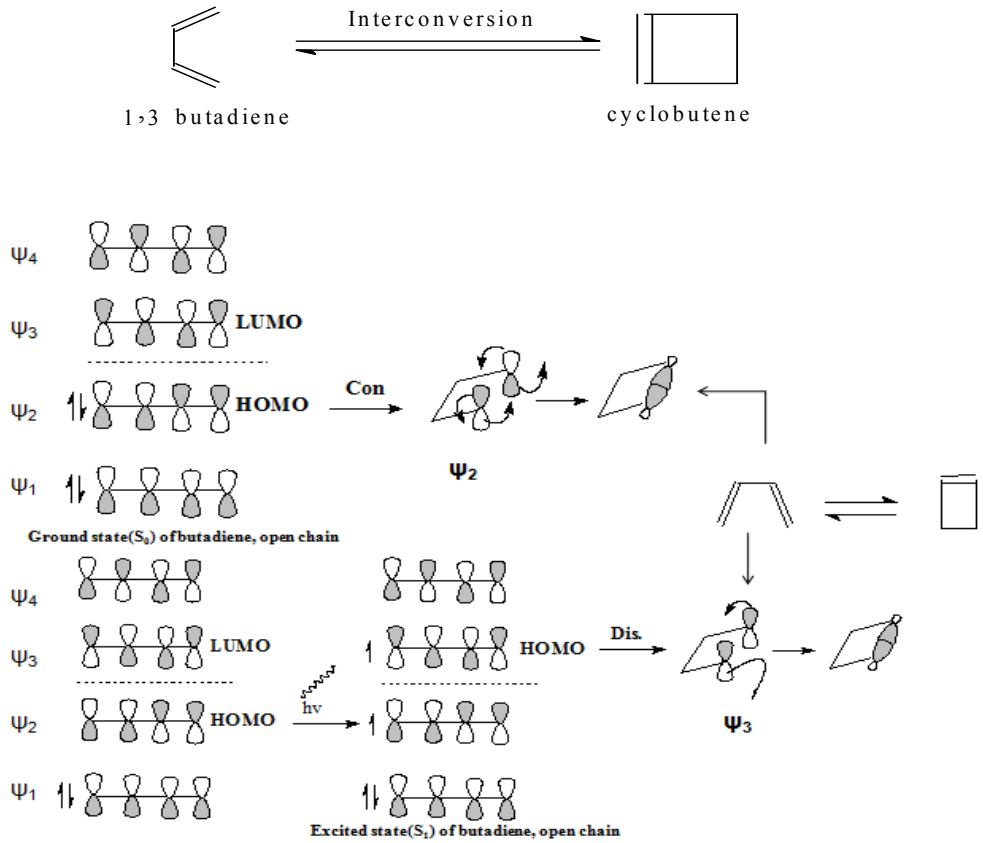


Fig 14. FMO approach for electrocyclic interconversion of butadiene- cyclobutene system.

Similarly, in hexatriene – cyclohexadiene interconversion Ψ_3 is HOMO in ground state. It displays M symmetry which is maintained in disrotation hene the hexatriene-cyclohexadiene interconversion will follow disrotatory path in concerted reaction as shown in **fig 16**.

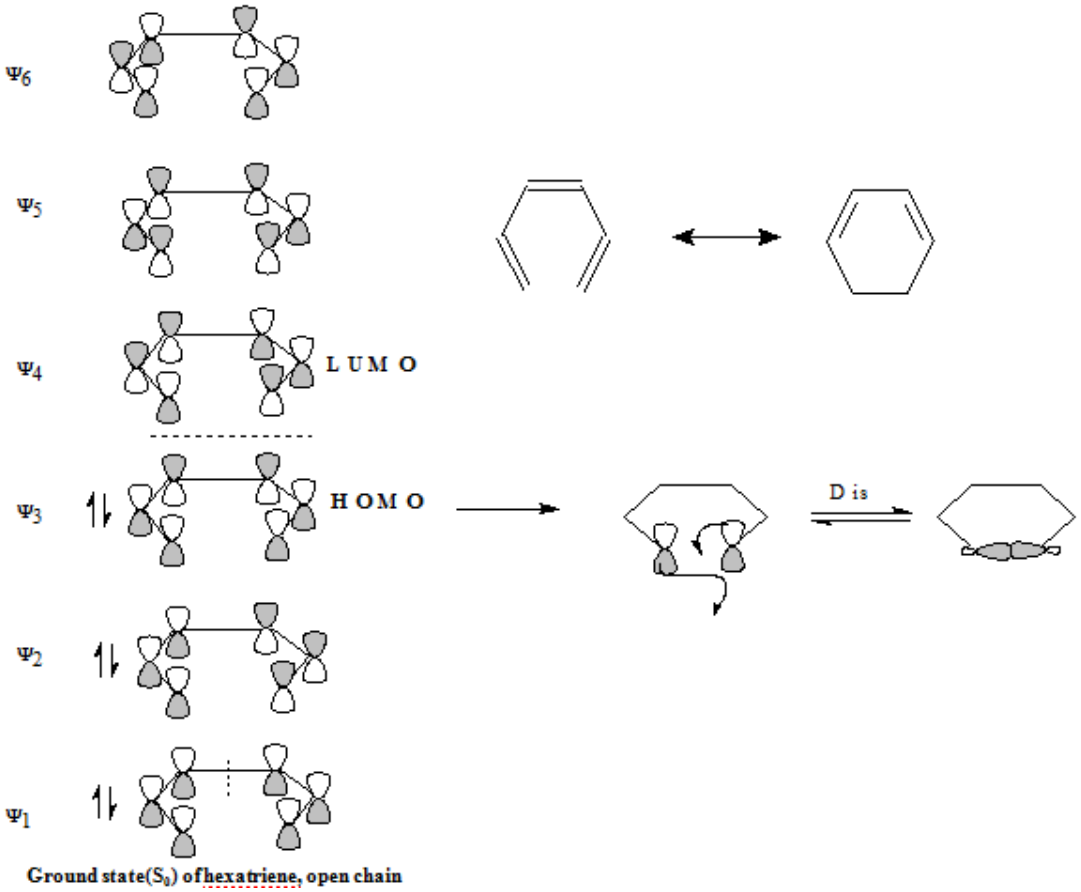


Fig 15. FMO approach for electrocyclic interconversion of hexatriene –cyclohexadiene system. Disrotatory process

Similarly when hexatriene, the open chain parterner in the above conversion is irradiated, electron is promoted to Ψ_4 orbital which now is a photochemically HOMO orbital and posses three nodes. Based on number of nodes, this orbital display C_2 symmetry which in maintained in conrotatory mode of ring cycling or closing. Hence based on FMO approach the ring closing of hexatriene to cyclohexadien will follow photochemical mode of activation through conrotatory mode fig.16. It is clear from above approach that conrotatory or disrotatory mode of ring opening (or the reverse process) takes plae in two directions each. The preferred direction will depend on its stereochemical factor involving the end groups in transtition state **fig 16.**

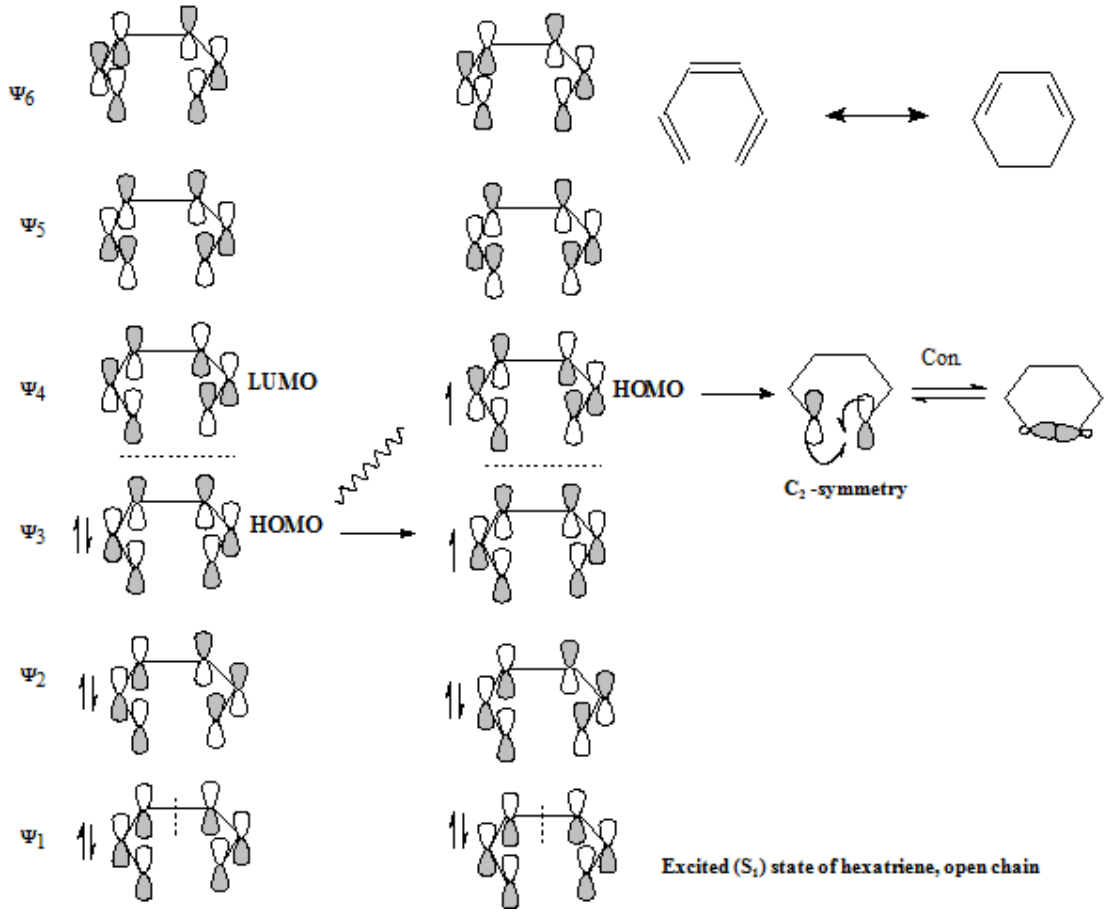


Fig 16. FMO approach for electrocyclic interconversion of hexatriene –cyclohexadiene system.

conrotatory process

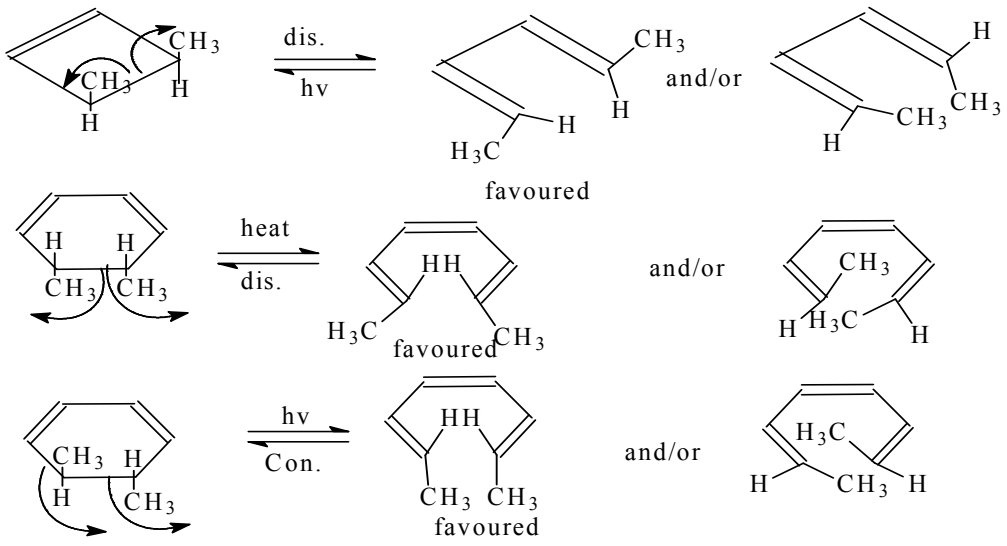


Fig 17 prefrred directions of ring opening

9.4.3. Perturbation Molecular Orbital (PMO) aproach for electrocyclic reactions (H-M) Huckel-Mobius System:

Another method for quickly assessing whether a given pericyclic process is allowed is to examine the cyclic array of orbitals at the transition state of the preicyclic reaction. This method was popularized by H. Zimmerman and M.J.S. Dewar.

According to Huckel- Mobius system (developed by Zimmerman & Dewar), monocyclic, conjugated, planar system with $4n + 2\pi e$ are aromatic and stable in S_0 and the monocyclic, conjugated, planar system with $(4n)2\pi e$ are antiaromatic and unstable in S_0

Calculation shows that these rules are reversed by the presence of a NODE in the array of atomic orbital thus:

If system has no NODE

- $4n + 2\pi e$ = Aromatic and stable in S_0
- $(4n)2\pi e$ = Antiaromatic and unstable in S_0

If system has NODE

- $4n + 2\pi e$ = Antiromatic and unstable in S0
- $(4n)2\pi e$ = Aromatic and stable in S0
- ✓ If system has no node, it is called Huckel system & array is called Huckel array.
- ✓ If system has node, it is called Mobius system & array is called Mobius array

Application of these rules to pericyclic reactions led to the generalization that thermal reactions take place via aromatic transition state [i.e.$(4n + 2)\pi$ electrons having no node or $4n\pi$ electrons having one node]where as photochemical reaction proceed via antiaromatic transition state [i.e. $(4n\pi)$ electrons having no node or $(4n + 2)\pi$ electrons having one node].

A cyclic transition state is said to be aromatic with corresponding aromatic system if the number of the conjugated atoms and that of the π-electrons involved are the same as in the corresponding aromatic system. Similarly, a cyclic transition atate is said to be antiaromatic with the corresponding antiaromatic syatem if the number of conjugated atoms and that of the π-electrons involved are the same as in the corresponding antiaromatic system. We have only to consider a cyclic array of atomic orbitals representing those orbitals which undergo change in the transition state and assign signs to the wave function in the best mannar for overlap. Then the number of nodes in the array and number of electrons involved are

counted (**fig.18 &19**). For convenience the selection rule by PMO or Huckel- Mobius approach to electrocyclic reactions are given in **table 5.**

Table 5: Selection rule for electrocyclic reactions by H-M Method/PMO approach

Array of πelectrons involved	No. of nodes	Aromaticity	Δ allowed	hv allowed
4nπ	zero	antiaromatic	-	disrotatory
4nπ	one	aromatic	conrotatory	-
(4n + 2) π	zero	aromatic	conrotatory	-
(4n + 2) π	one	antiaromatic	-	disrotatory

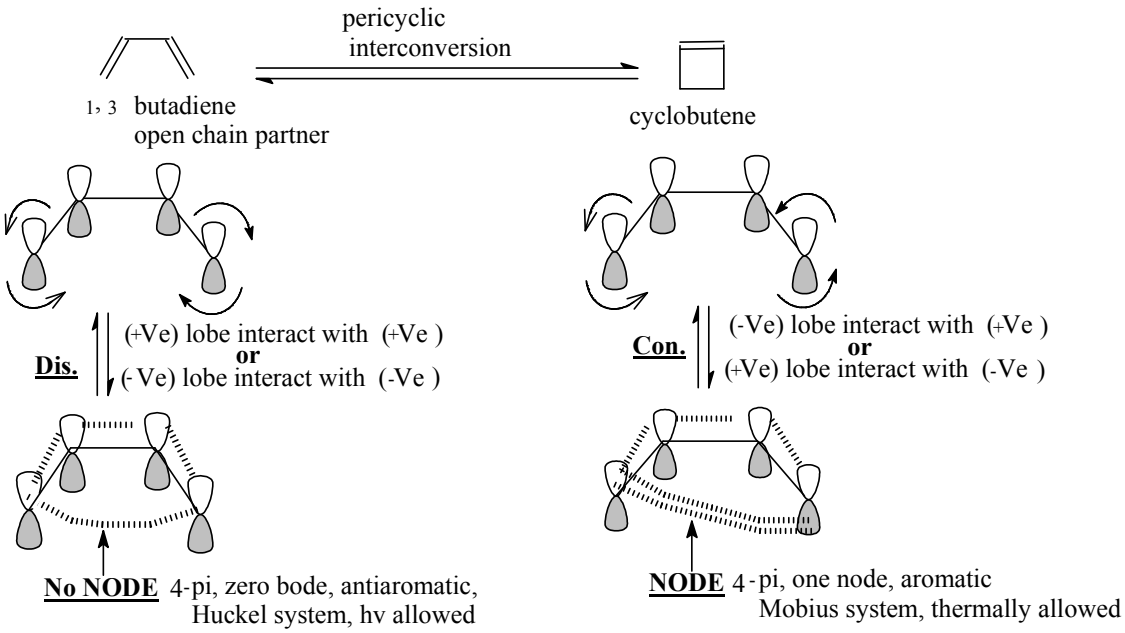


Fig 18. Array diagram for 4nπ system

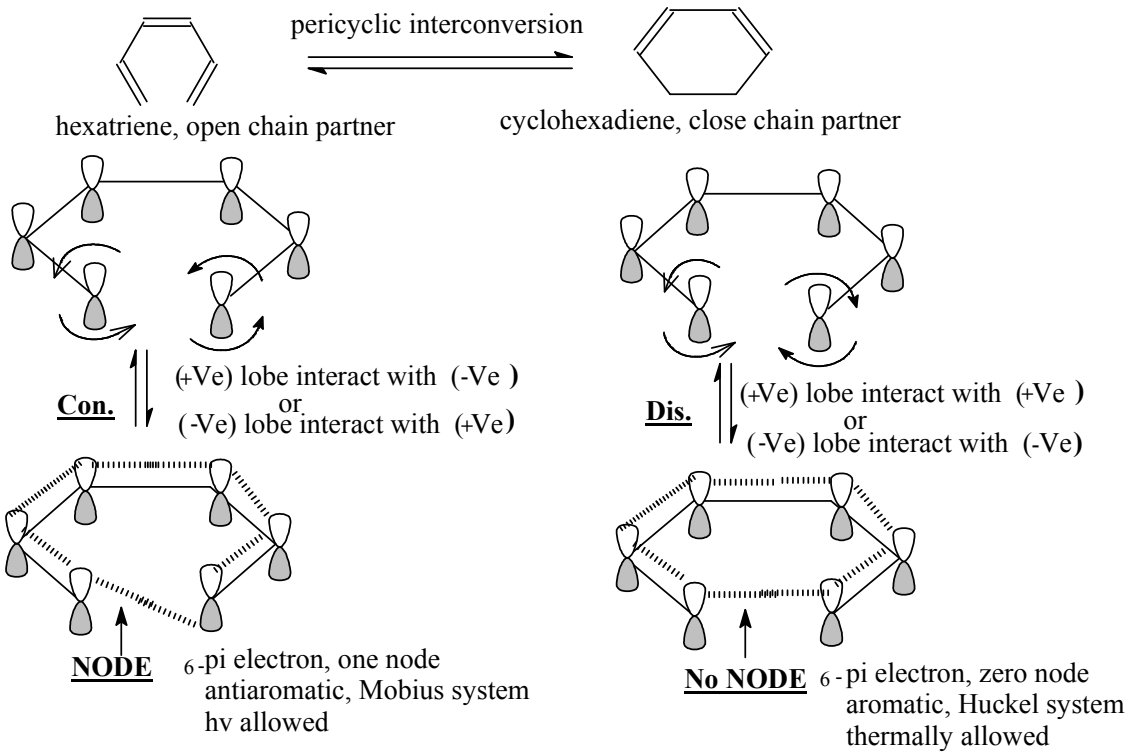


Fig 19. Array diagram for (4n +2) π system

9.6. SUMMARY

In present unit we discussed about pericyclic reactions, how these reactions are different from other reactions. We discussed the types of pericyclic reactions. Electrocyclic reactions which one of the type of pericyclic reactions has been discussed in details The correlation diagram of different olefinic system viz; ethylene, 1,3-butadiene, 1,3,5-hexatriene alongwith the description of their HOMO , LUMO orbital has been described. The allylic system with cationic form, free radical form and anionic form has been interpreted with their MOs alongwith description of HOMO, LUMO orbitals. The bond braking/making during ring closere/opening through conrotatory and disrotatory mode has been described. The interconversion of 4nπ and (4π + 2) π system by correlation diagram, FMO approach and PMO (Huckel-Mobius system) have been well described alongwith selectin rules. Finally it can be inferred that this unit educates us how concerted reactions in olefinic system takes place by electrocyclic (cyclic array of electrons) mode.

9.6 TERMINAL QUESTIONS

Q1. Tick the correct answer (MCQ)

i The HOMO orbital in 1,3,5-hexatriene is:

A. Ψ_1

B. Ψ_2

C. Ψ_3

D. Ψ_4

ii Pericyclic reaction are:

A. Concerted and stereospecific

B. Concerted and non stereospecific

C. Reactions of olefinic compounds

D. Both A and C

iii Pericyclic reaction are activated by

A. Heat and EMR

B. Polar solvent

C. Catalyst

D. None of them

iii M- symmetry is maintained in

A. Conrotatory mode

B. Disrotatory mode

C. Both A and B

D. None of them

iv Interconversion of butadiene-cyclobutene in S_0 is feasible by:

A. Thermally by disrotation

B. Thermally by conrotation

C. Photochemically by disrotation

D. Photochemically by conrotation

v. Which is the quickest mode for the explanation of electrocyclic reactions?

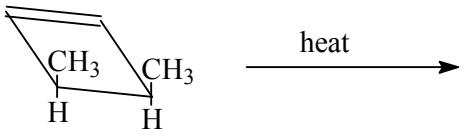
A. Correlation diagram

B. PMO and FMO mode

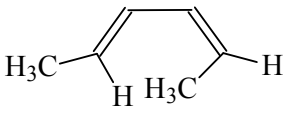
C. Only PMO

D .All of them

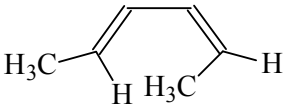
vi What will be the mode of ring opening and structure of the product in following reaction?



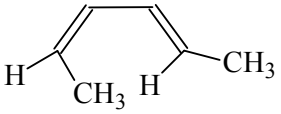
A. Conrotatory,



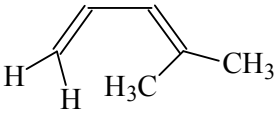
B. Disrotatory,



C. Disrotatory,



D. Conrotatory,



vii LUMO orbital in 1,3,5 hexatriene under photochemical condition is:

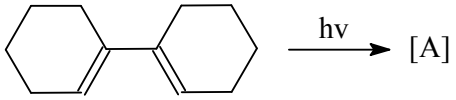
A. Ψ_1

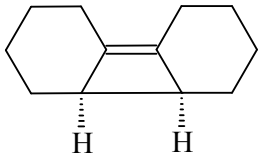
B. Ψ_2

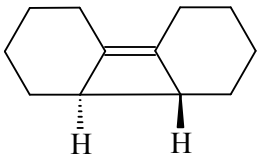
C. Ψ_3

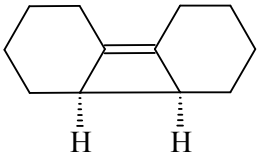
D. Ψ_4

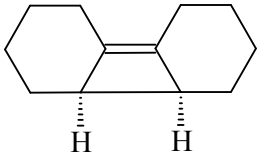
viii. Predict the product of the following reaction.



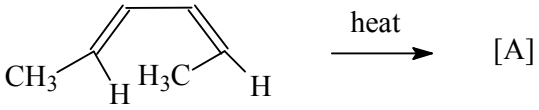
A. Conrotatory, 

B. Disrotatory, 

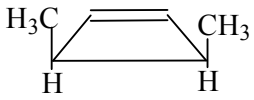
C. Disrotatory, 

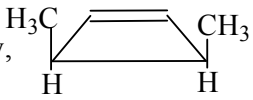
D. Conrotatory, 

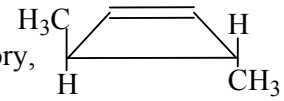
ix Give product with its stereochemistry in the following reaction.

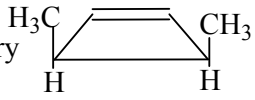


2 E,3Z

A. Conrotatory, 

B. Disrotatory, 

C. Disrotatory, 

D. Conrotatory 

x. Who popularized correlation diagram and molecular orbital symmetries for pericyclic reactions?

A. Woodwar- Hoffmann

B. Huckel Mobius

C. Dewar

D. Zeimermann

9.7 ANSWERS (MCQ) TERMINAL QUESTIONS

i C

ii D

iii A

iv B

v B

vi A

vii D

viii C

ix A

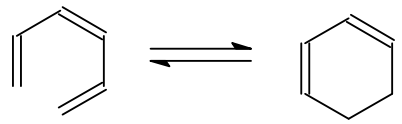
x. A

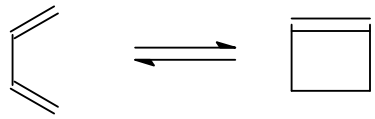
Q.2. What are pericyclic reactions? Discuss classification of pericyclic reactions

Q.3. Draw and discuss the symmetry properties of molecular orbitals of 1,3 –butadiene and 1,3,5-hexatriene

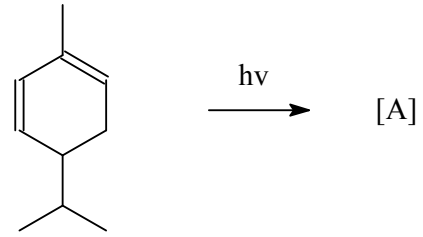
Q.4 What do you understandand by conrotation and disrotation? Discuss with example

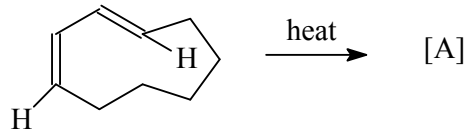
Q.5. Find out the selection rules for following interconversion using FMO and PMO meyhod

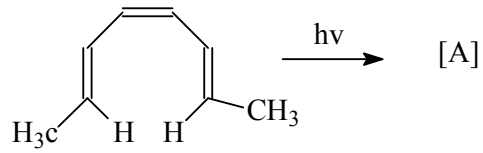
A. 

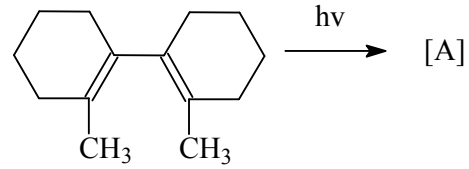
B. 

Q.6. Predict the product in the following reactions.

1· 

2· 

3· 

4· 

Q.7. What is meant by "conservation of molecular orbital symmetry"? What are the symmetry elements which control the course of a reaction?

9.8 REFERENCES

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2. Singh, J and Yadav, L.D.S, Advanced organic chemistry 2004, Pragati Prakashan, Meerut. 336-379.

3. Mukherji, S.M., Singh, S.P. and Kapoor, R.P. 1998, 978-1006, New Age International (P) Limited, Publisher, New Delhi, India

UNIT-10 CYCLOADDITIONS AND SIGMATROPIC REACTIONS

CONTENTS:

10. Objectives

10.1 Introduction

10.2 Antarafacial and suprafacial additions

10.3 Cycloaddition in 4n π and [4n +2] π system

10.4 2+2 Cycloaddition Reaction

10.5 cheleotropic reactions

10.5.1 [2 + 2] Chelotropic cycloaddition

10.6: [1, 3]-dipolar cycloadditions

10.7. Sigmatropic reactions/rearrangement

10.7.1 Explanation of [1, 3] and [1, 5] sigmatropic shift

10.8 Sigmatropic shifts of alkyl group

10.9 Huckel- Mobius approach in sigmatropic rearrangemant

10.10 [3,3] sigmatropic rearrangements Cope rearrangements

10.11 Claisen rearrangement

10.12 [5, 5] rearrangement reactions.

10.13 Aza-Cope rearrangements:

10.14. Fluxional tautomerism

10.15 Ene reaction

10.16 Summary

10.17 Terminal questions

10.18 Answers (MCQ) terminal questions

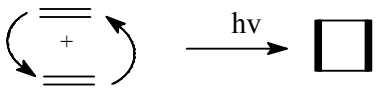
10.19 References

10. OBJECTIVES

Objective of this unit are to make aware students about cyclodiition and sigmatropic concerted reactions. Introduction, antarafacial and suprafacial additions, 4n and 4n+2 systems, 2+2 addition of ketenes, 1,3-dipolar cycloadditions and cheleotropic reactions. Sigmatropic rearrangements- suprafacial and antarafacial shifts of H, Sigmatropic shifts involving carbon moieties, 3,3- and 5,5 sigmatropic rearrangements. Claisen, Cope and Aza-Cope rearrangements. Fluxional tautomerism, Ene reaction.

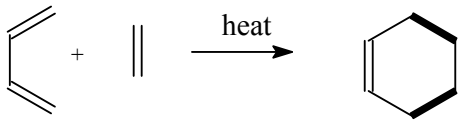
10.1 INTRODUCTION

As also discussed in unit 9 electrocyclic reactions, that cycloaddition, sigmatropic and chaelotropic reactions are also type of pericyclic reactions, i.e. these reactions are concerted and given by olefinic compounds. Incyloaddition reactions two or more unsaturated molecules undergo an addition reaction to yield a cyclic product. Formation of cyclic product takes place at the expense of one π- bond in each of the reacting partener and gain of two σ-bonds at the end of the both components having π-bonds. Thus there is aloss of two π-bonds of the reactants and gain of two σ-bonds in the product.



[2 +2] cycloaddition

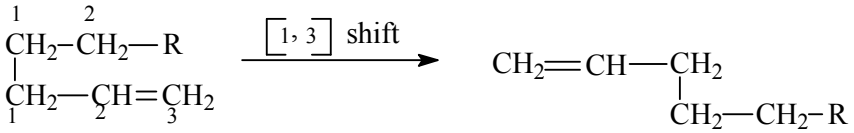
loss of two pi bond and gain of two sigma bonds



[4 + 2] cycloaddition

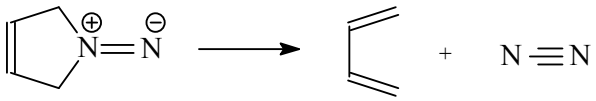
loss of two pi bond and gain of two sigma bonds

Similarly sigmatropic reactions are another class of concerted reactionsgoverned by orbital symmetry. This rearrangement involves aconcerted reorganization of electrons during which a group attached by σ-bond migrates to the terminus of an adjacent π- electron system. The reactions are called sigmatropic because a σ-bind move from one place to another during reactionThere is simultaneous shift of π-bond, The number of π and σ-bonds remains separately unchanged.

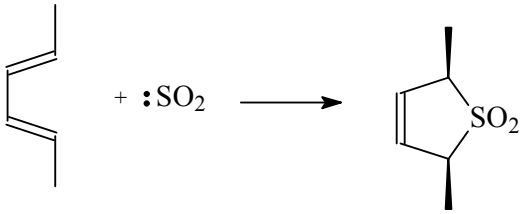


migration of sigma bond from one position to other position
net number of sigma and pi bonds remains the same

In chelotropic reactions two σ-bonds are formed or broken on the same atom



two sigma bonds are broken on nitrogen



two sigma bonds are formen on sulphur

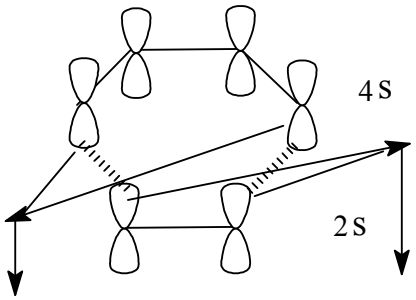
In this unit we will discuss various types of cycloaddition and sigmatropic reactions, their explanations by different methods alonwith their selection rules. The chelotropic and dipolar reactions will be discussed in this unit.

10.2 ANTARAFACIAL AND SUPRAFACIAL ADDITIONS

The cycloaddition reactions are caterogised with respect to three facts of the reactions:

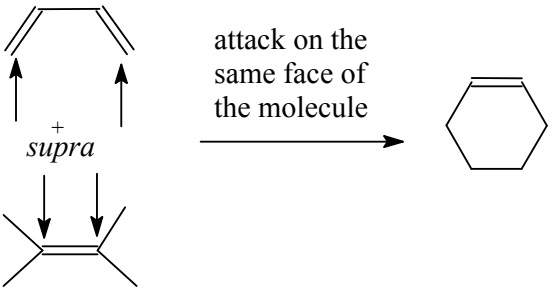
1. The number of electrons of each unit participating in cycloaddition
2. The nature of orbitals undergoing change (π or σ) and
3. The sytereochemical mode of addition [***supra (s)/syn or antara(a), anti***]

The stereochemical mode is generally given by subscript **s** or **a**, **which** reavels whether the addition occurs in *supra* or *antara* mode on each unit. A cycloaddition may occur either across the similar face or across the opposite faces of the planes in each reacting component.If the reaction takes place across the same face of a π-system, the reaction is said to be **suprafacial** with respect to that π- system. It is nothing than a ***syn*** addition.



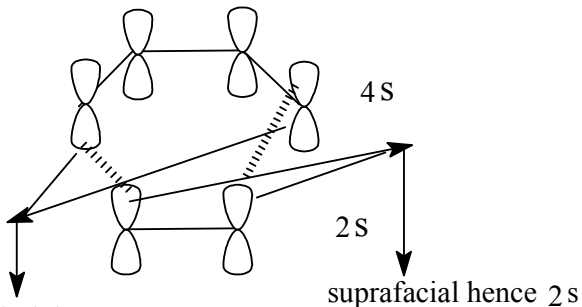
both the lobes are above the plane of the molecule or both the lobs are in same plane, hence suprafacial (a) $[4s + 2s]$ cycloaddition reaction

This reactioncan also be represented as follow



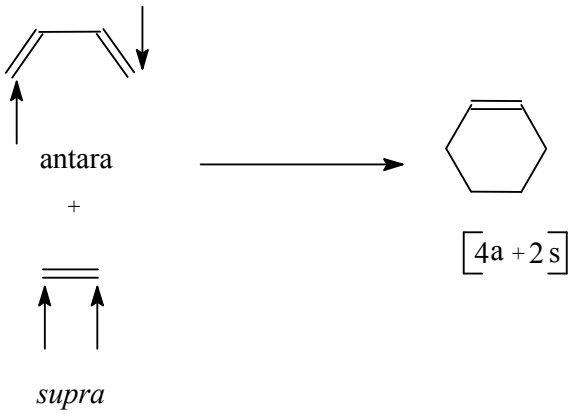
If the reaction takes place across the opposite face of a π- system, it is said to be **antarafacial**

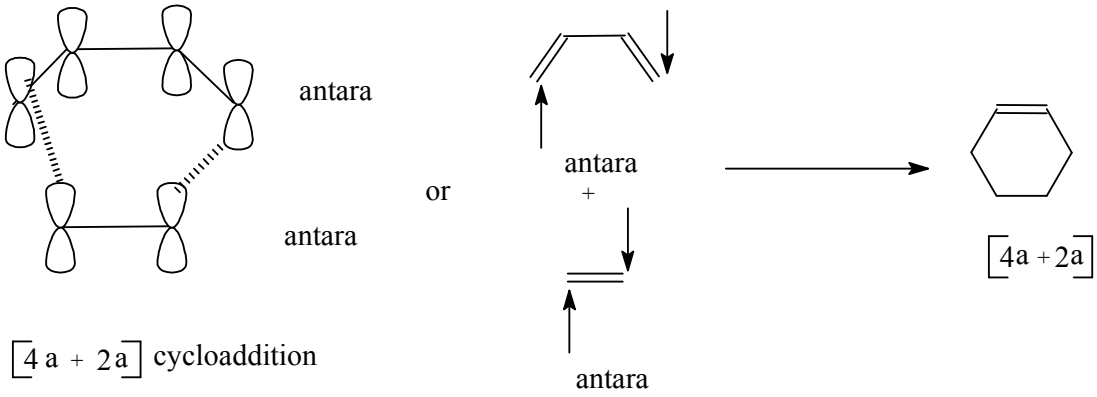
(a)



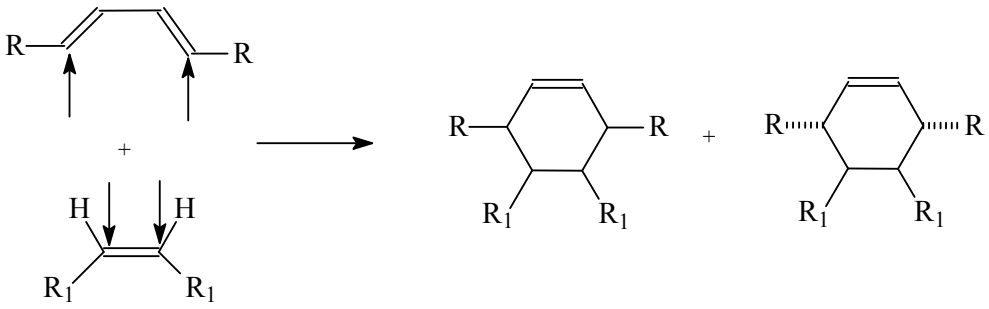
$[4a + 2s]$ cycloaddition reaction

This reaction can also be represented as:





In antarafacial, attack takes place with one bond forming to one surface but other bond forming to other surface. It is rare, it dose not occur in any reaction. Almost all cycloaddition reactions are suprafacial on both components.



10.3 CYCLOADDITION IN 4n AND [4n + 2]π SYSTEM

In 4π electron system there are [2 + 2] cycloaddition of two ethylene molecules.Like electrocyclic reactions the cycloaddition reactions viz; [2 + 2] and [4 + 2] cycloaddition reactions can be interpreted by different merhods like correlation diagram, FMO and PMO methods.

1. Orbital symmetry in cycloaddition reaction: correlation diagram: To illustrate the contrl of orbital symmetry on cycloaddition reactions, we choose the example [2 + 2] cycloaddition in which two ethylene molecules approach each other vertically to form a molecule of cyclobutane. Such a system has vertical and horizontal plane of symmetry which is referred to as 1 and 2 respectively.

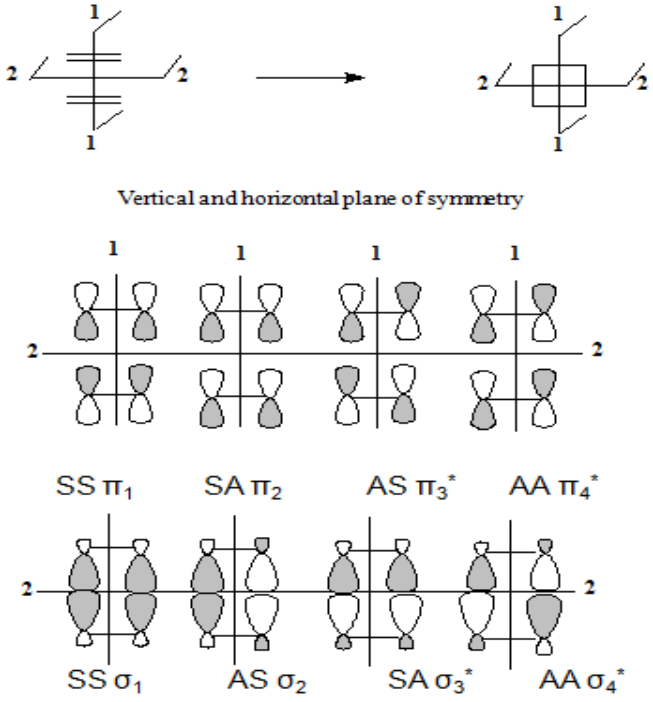


Fig. 1 Symmetry properties of interacting ethylene π-orbitals and cyclobutane σ-orbitals.

In above transformation we are concerned with the four π orbitals of two ethylene molecules and four orbitals of cyclobutane. Since the symmetry properties of the remaining orbitals remain unchanged during the reaction hence are not to be considered. The symmetry classification mentioned are with respect to plane of symmetry 1 and then 2. Based on the above information as in fig.1 a correlation diagram for ethylene [2 + 2] cycloaddition can be constructed,

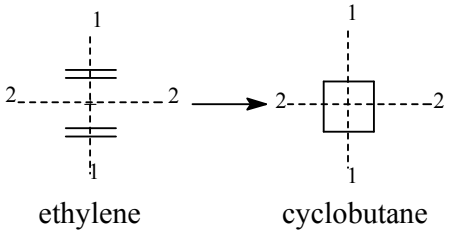
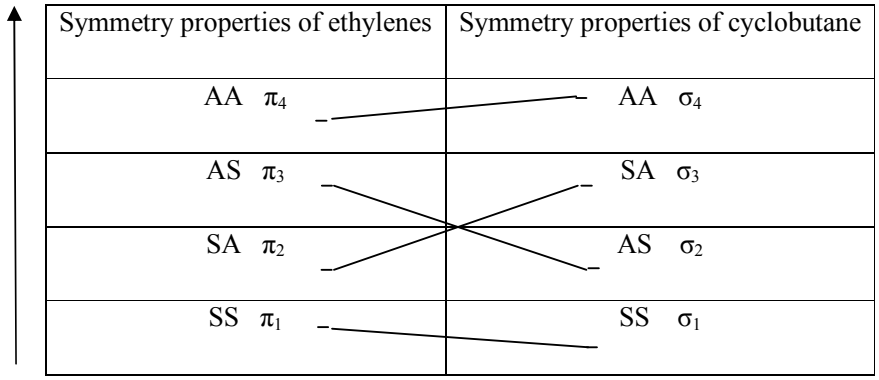


Table 1. Correlation diagram for cycloaddition and of ethylene-cyclobutane system



The examination of the diagram leads the following conclusions:

A. The S_0 prbitals of ethylene correlate with an excited state (S_1) of cyclobutane, $\pi_1^2\ \pi_1^2 \rightarrow \sigma_1^2\sigma_3^*$ i.e. the combination of two ground state ethylene molecules cannot result in the formation of ground state cyclobutane while conserving the orbital symmetry.Hence thermal process is symmetry forbidden.

B. There is correlation between the first excited state of the ethylene system and cyclobutane, $\pi_1^2\ \pi_1\ \pi_1^* \rightarrow \sigma_1^2\sigma_2\sigma_3^*$ the photochemical process is symmetry allowed in aconcerted manner.

Similarly correlation diagram may be constructed for [4 + 2] π cycloaddition (**fig.2**) viz; for Diels – Alder reaction which is 4s + 2s cycloaddition.In this case there is only asingle vertical plane of symmetry

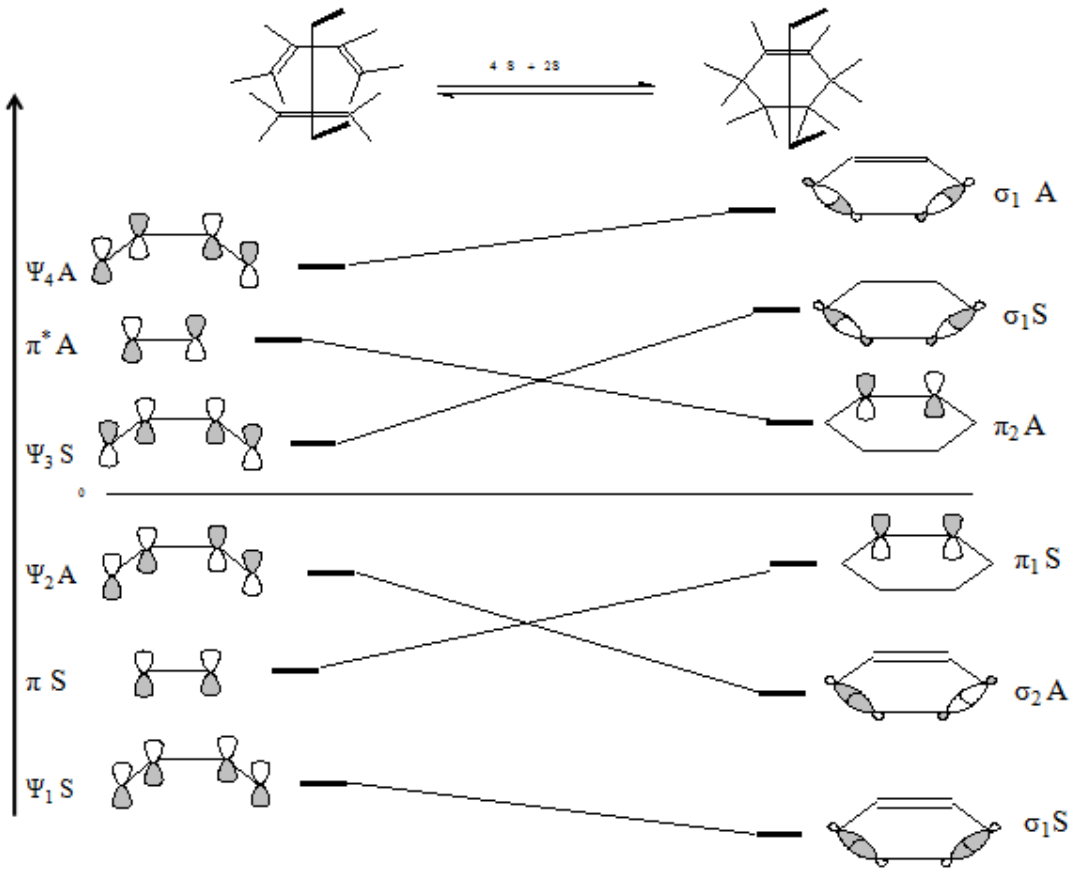


Fig. 2 *correlation diagram for 4s + 2s cycloaddition (Diels-Alder reaction) and the reverse process*

It is clear from above correlation diagram (fig. 2) that there is smooth transformation of the reactant orbitals into the product orbitals. Again following conclusions can be drawn.

A. $\psi_1^2\pi_1^2\psi_2^2 = \sigma_1^2\sigma_2^2\pi_2^2$ i.e. the molecular orbital symmetries of ground states (S_0) of reactants (ethylene and 1,3-butadiene) correlate to the ground states(S_0) of products (cyclobutene). Hence the transformation of ethylene and butadiene 4s + 2s, (Deils-Alder reaction) is thermally allowed process and takes place in a concerted manner.

B. $\psi_1^2\pi_1^2\psi_2\psi_3 \neq \sigma_1^2\sigma_2^2\pi_1\pi_2$ i.e. the MOs symmetries of excited state (S_1) of reactant do not correlate with S_1 of product and there is symmetry imposed barrier to photochemical reaction, Hence the 4s + 2s transformation is photochemically not allowed. The reaction under irradiation will not take place by concerted manner.

2. Frontier molecular orbital (FMO) method: The cycloaddition reactions can also be explained by using FMO approach like in electrocyclic reaction. In this approach symmetry properties of HOMO orbital of one reactant and LUMO of other reactant are to be considered. A favourable interaction is possible only if the sign of the coefficient of HOMO and LUMO are similar. In [2 +2] cycloaddition of CH_2=CH_2 to form cyclobutane, lobes of HOMO in one molecule and LUMO of other molecules are not same, hence the conversion of ethylene to cyclobutane under thermal activation is symmetry forbidden. However when ethylene is irradiated, electron promotes to the antibonding π^* orbital, which now becomes HOMO orbital This orbital now interact with LUMO of the second unexcited ethylene molecule. Since now the sign of coefficient of HOMO and LUMO orbital are similar. Hence the interconversion of ethylene to cyclobutane system proceeds smoothly i.e. the reaction is photochemically allowed (fig 2).

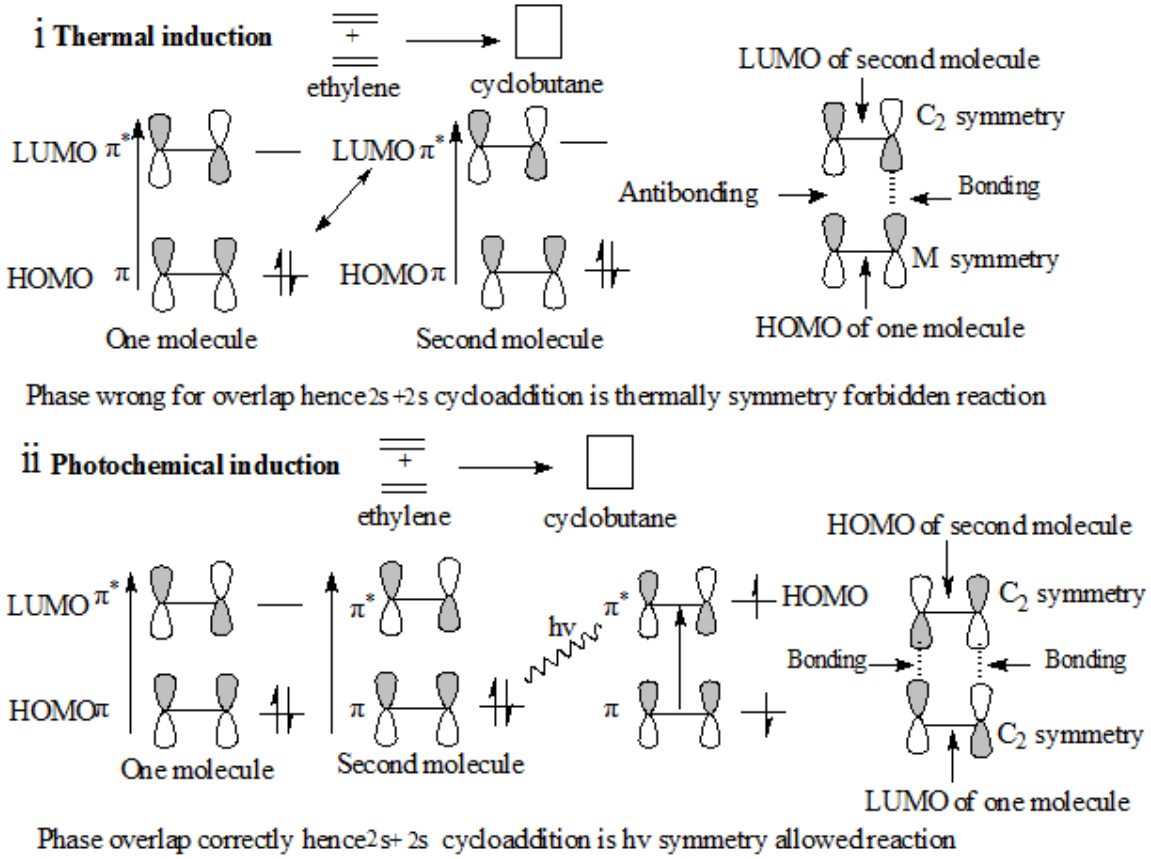


Fig.3 [2 + 2] cycloaddition of CH_2=CH_2 under thermal and hv condition by FMO method.

Similarly the Diels-Alder reaction may also be analysed of the molecular orbitals of ethylene and butadiene [4n + 2] system.

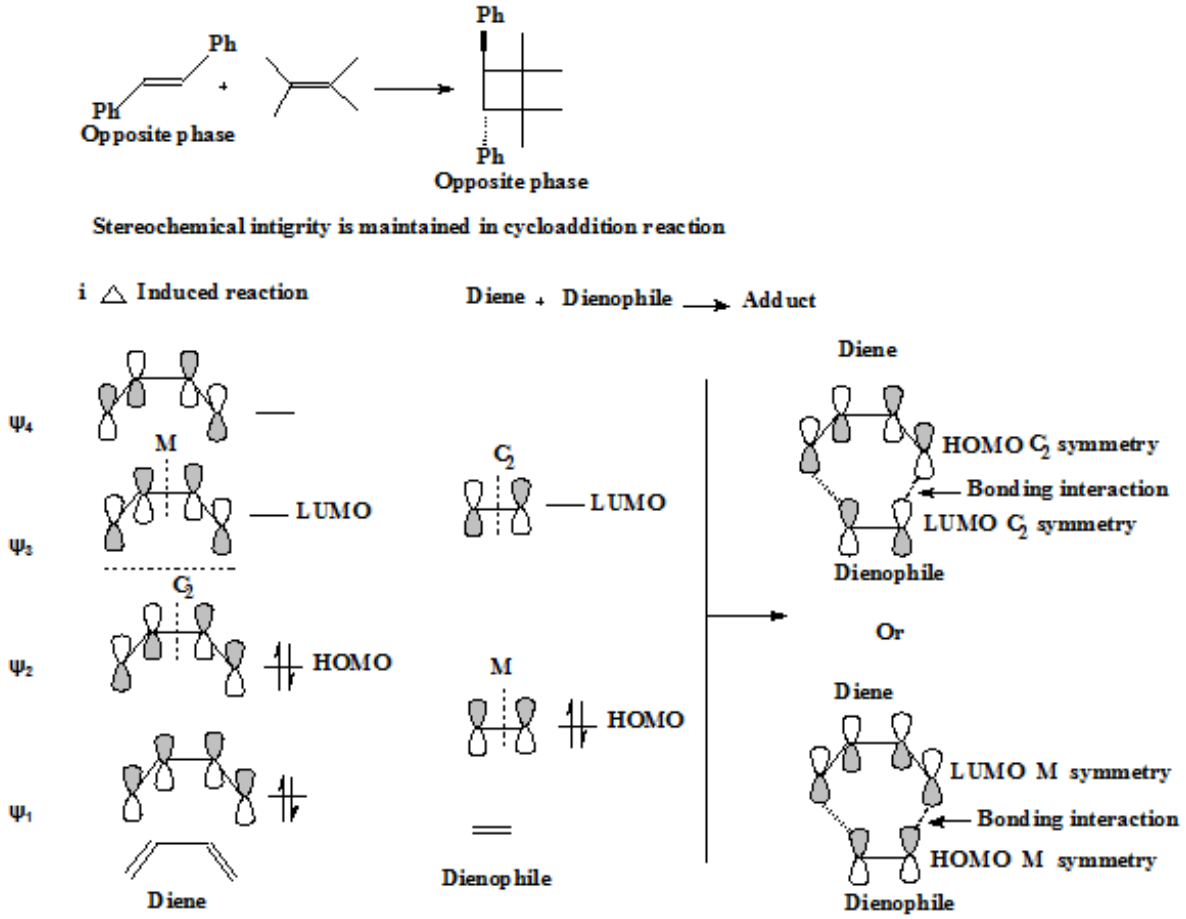
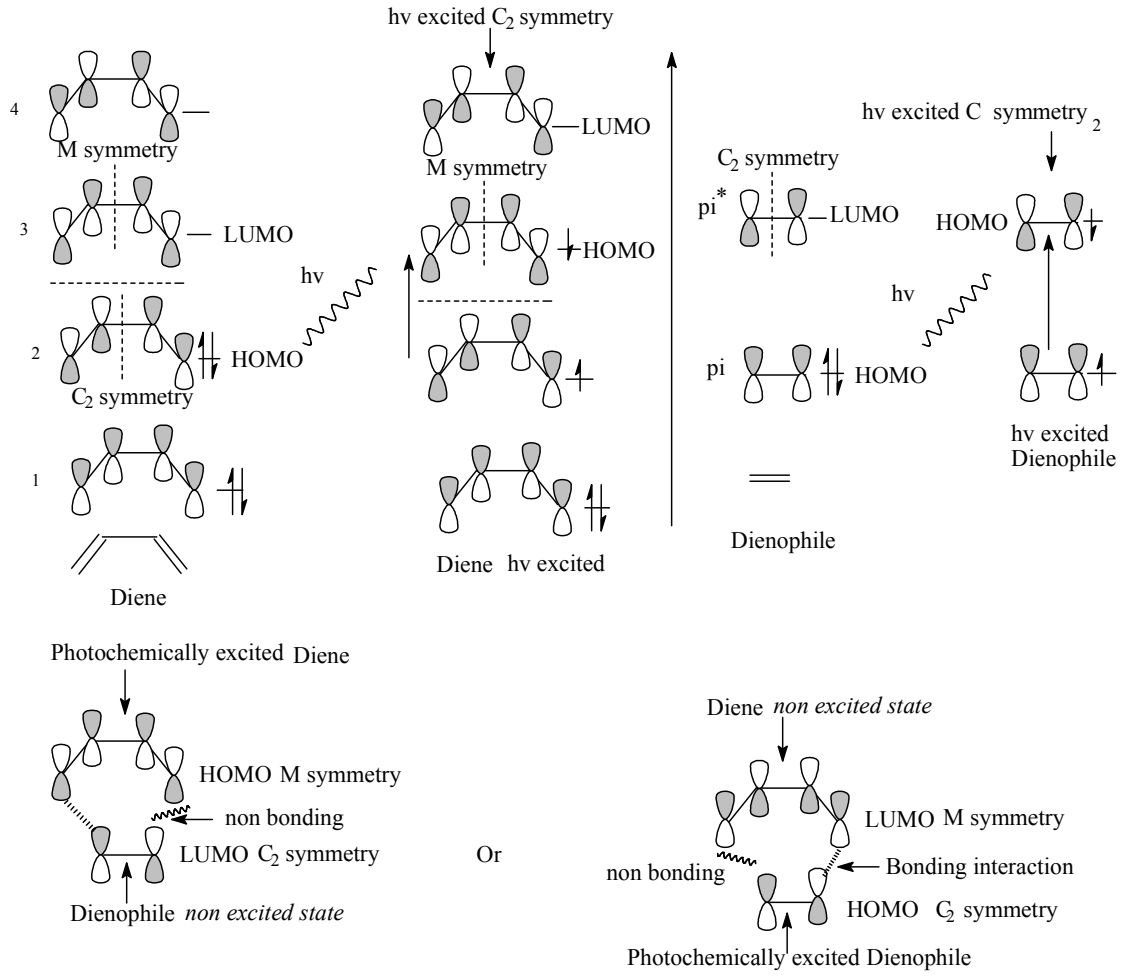


Fig. 4 [4 + 2] cycloaddition of CH_2=CH_2 and butadiene by thermal induction (FMO method).

In above transformation the HOMO of one reactant butadiene when intreact with the LUMO of other reactant ethylene or vise-versa, the sign of coefficient of HOMO-LUMO are same. Hence this transformation is symmetry allowed in ground state and is thermally allowed (fig.4).

However when butadiene is irradiated then Ψ_3 orbitals becomes HOMO because of the promotion of electron from Ψ_2 orbital or if ethylene is irradiated, π^*/ Ψ_2 becomes HOMO. Now according to FMO approach HOMO of one (butadiene/ethylene) intract with LUMO of other (ethylene/butadiene), the sign of coefficient of HOMO-LUMO do not intract through bonding intraction. The process is thus photochemically symmetry forbidden and can not take place by concerted manner (fig5).

ii Photochemical(hv) induction



Phase wrong for overlap Diels Alder reaction hence the reaction is photochemically forbidden

1= Ψ_1, 2= Ψ_2, 3= Ψ_3, 4= Ψ_4 and pi* = π^*/ Ψ_1, pi = π/ Ψ

Fig. 5[4 + 2] cycloaddition of CH_2=CH_2 and butadiene by hv(photochemical) induction (FMO method).

An intresting example of the role of FMO is determining the product is the Diels-Alder reaction of cyclopentdiene forming dicyclopentadiene. In this reaction endo product is formed rather than exo because of the favourable secondary forces which lowers the energy of the transition state. In exo product the secondary interactions are absent. Thus the endo transition state for the reaction is stabilized vis-à-vis the exo and therefore the endo attack should be favoured. However in some cases the steric factors may be of greater magnitude than this effect (fig.6).

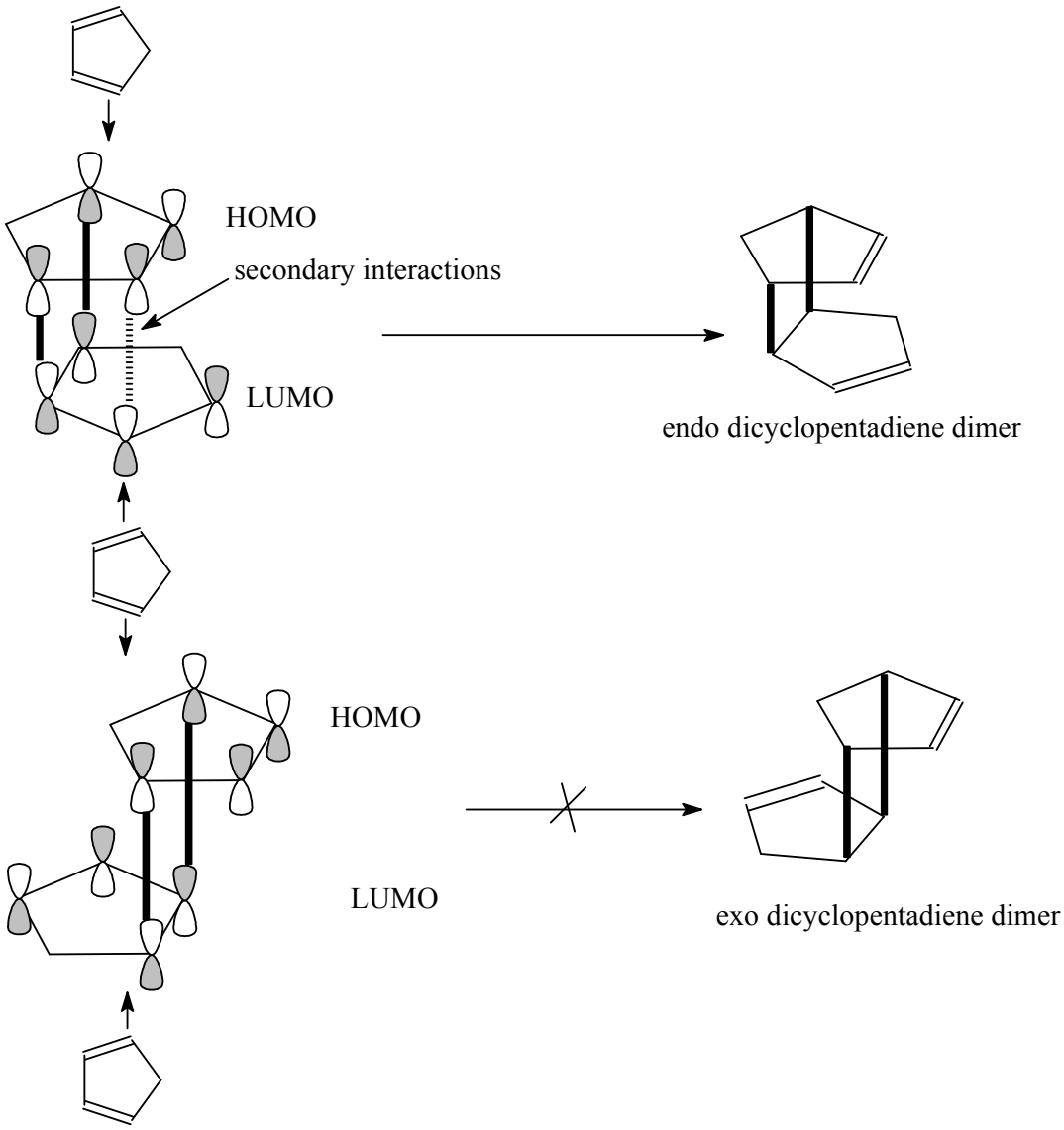


Fig.6. Orbital interaction in Diels-Alder reaction of cyclopentadiene by FMO approach.

The cycloaddition reactions can be summarized in tabular for their selection rules table 2

Table 2: Selection rules for cycloaddition reactions

m + n electrons	Mode ofactivation	Allowed stereochemistry
4n	Photochemical	supra-supra
4n	Thermal	supra- antara
4n + 2	Thermal	supra- supra
4n + 2	Photochemical	supra- antara

3. Perturbation of molecular orbital (PMO) approach: The alternative mode for the explanation of cycloaddition reaction is PMO method which is based on the concept of aromaticity as discussed in electrocyclic reaction in unit 9. This system is also known as Huckel- Mobius (H-M) system. According to this system if system has no node then it is called Huckel system and array is called Huckel array. Similarly if system has node it is called Mobius system and array is called Mobius array. Use of above concepts to cycloaddition reactions led to the generalization that thermal reactions take place via aromatic transition state whereas photochemical reactions proceed via antiaromatic transition state (fig. 7)

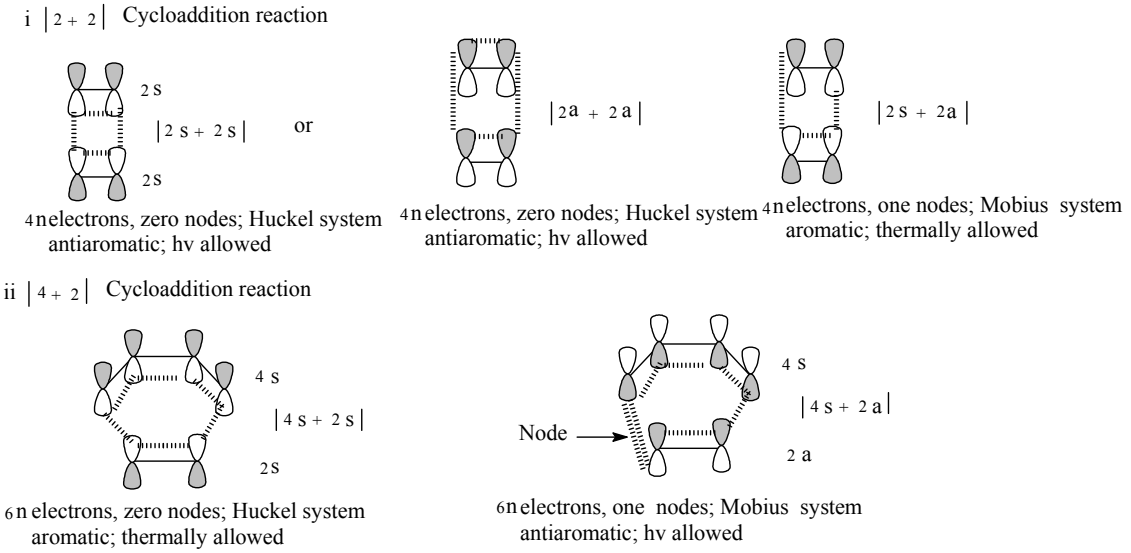


Fig 7 PMO approach for cycloaddition reactions

The PMO approach can also be summed up in table for cycloaddition reactions Table 3)

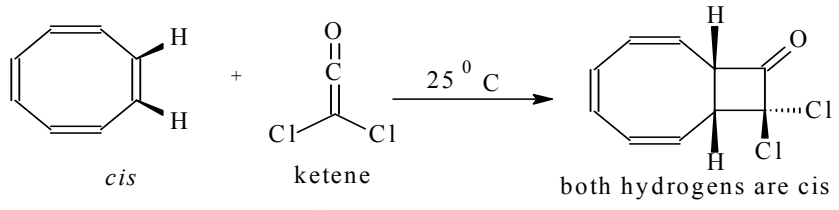
Table.3: Selection rules for cycloaddition by PMO approach

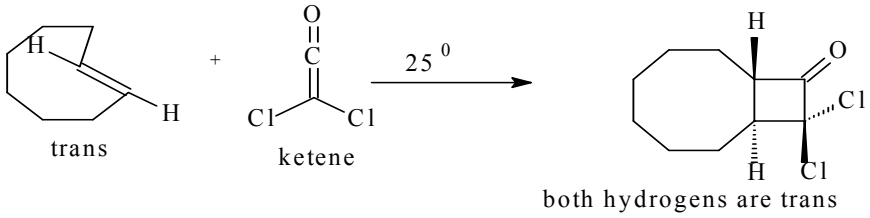
m + n electrons	Number of nodes	Aromaticity	Thermally allowed	Photochemically allowed
4n	Zero	Antiaromatic	-	supra-supra antara-antara
4n	One	Aromatic	supra-antara antara-supra	-
4n + 2	Zero	Aromatic	supra-supra antara-antara	-

4n + 2	One	Antiaromatic	-	supra-antara antara-supra

10.4 2+2 CYCLOADDITION OF KETENES

The reaction of ketene with olefinic compound (alkene) shows some characteristics of pericyclic cycloaddition. The reaction is syn addition and geometry of reactant is maintained in the product.





In above reactions stereochemistry of the reactant is sustained in the product.These two reactions are pericyclic [2 +2] cycloaddition and thermally allowed reactions. It is known to us that [2+ 2] cycloaddition is photochemical reaction and suprafacial- suprafacial. If reaction is thermally allowed then reaction should be suprafacial-antarafacial reaction i. e. [π 2s + π 2a]cycloaddition (table 3)

Two molecules approach each other at right angle for overlapping in an antarafacial sense of the ketene. Making the reaction the allowed [π 2s + 2πa] cycloaddition that we have dismissed as being unreasonable. This is the simplest explanation. The [2 + 2] cycloadditions of ketenes being concerted is more likely to be a consequence of the fact that ketenes have two sets of π orbitals at right angle to each other and overlap can developed to orthogonal orbitals (dashed lines) and in addition there is transmission of information from one orbital to its orthogonal neighbor (heavy line) (fig.8)

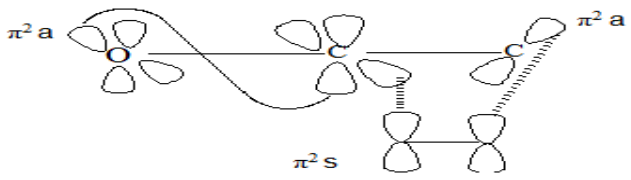


Fig. 8 overlapping orbitals of ketene and alkene

The vision identifies the reaction as an allowed [π 2s +π 2a +π 2S] cycloaddition reaction. The FMO approach exhibit that the bond formation between C-1 and C-1' develops mainly from the interaction of the LUMO of ketene (π^* of C=O) and HOMO of alkene and that the bond between C-2 and C-2' develops mainly from the interaction of HOMO ketene [Ψ_2] the three atom linear set of orbitals analogous to the allyl anion] and LUMO of the alkene (fig.9).

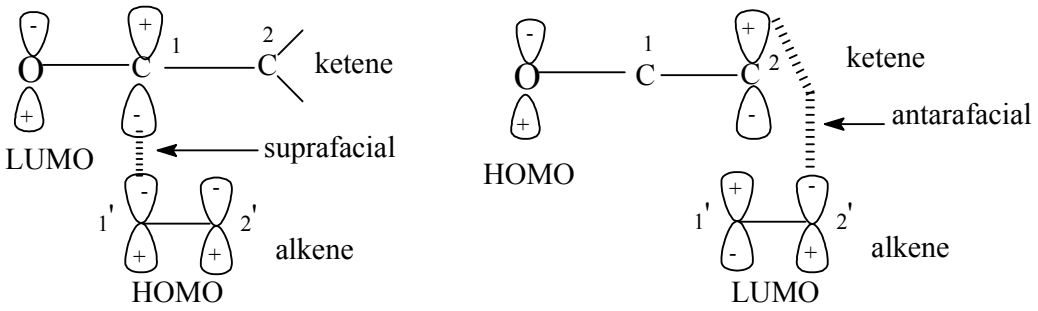
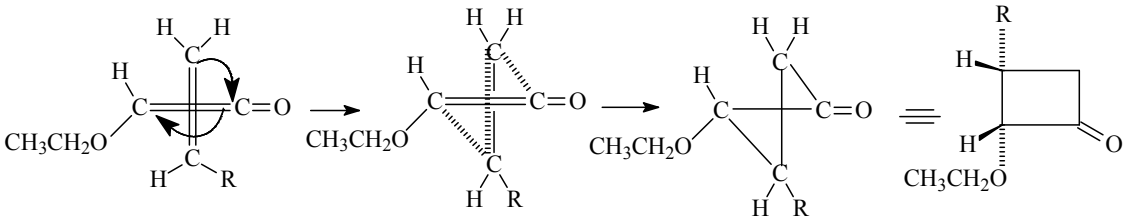


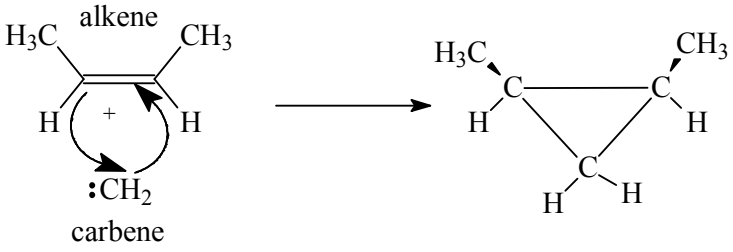
Fig .9 Bond formation between C-1 of keten and C-1' of alkene and between C-2 of ketene and C-2' of alkene

The reaction can br represented as follow:



10.5 CHELOTROPIC REACTIONS:

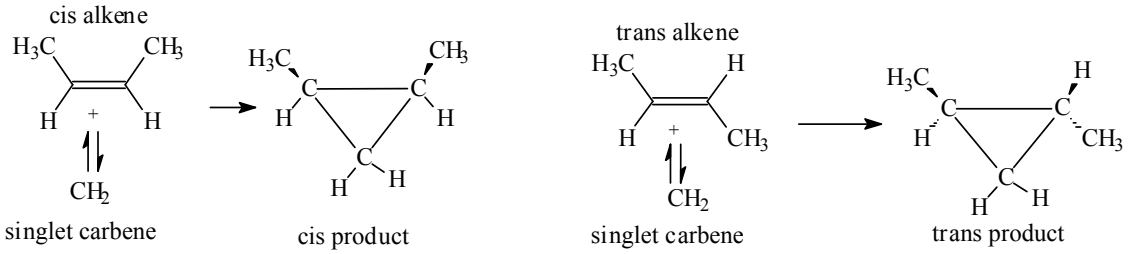
As also discussed in section 10.1 introduction part of this unit the,chelotropic reactions are those reactions in which either two σ-bonds are formed or broken on same atom, viz trapping reactions of carbenes with alkenes.



two sigma bonds are formed on the carbon of carbene in product

10.5.1 [2 + 2] Chelotropic cycloaddition:

Chelotropic reaction of alkenes with singlet carbine can be considered here for [2 + 2] chelotropic cycloaddition reaction. In this reaction alkene reacts with carbine to form cyclopropane or substituted cyclopropane. The reaction is highly stereospecific in nature while reacting with singlet carbenes. The reaction is thermally allowed.



The above reaction is pericyclic type and is concerted in nature. Examination of MOs properties of carbine shows that a bonding interaction between HOMO of a carbine and LUMO of an alkene or vise-versa is possible.

Carbon in signlet carbine is sp^2 hybridised and having three sp^2 hybrid orbitals and one empty p-orbital which is perpendicular to the plane defined by the carbon atom and the two substituents on it. Among three sp^2 hybrid orbitals two are bonding and one is non- bonding having two electrons in it (**fig.10**).

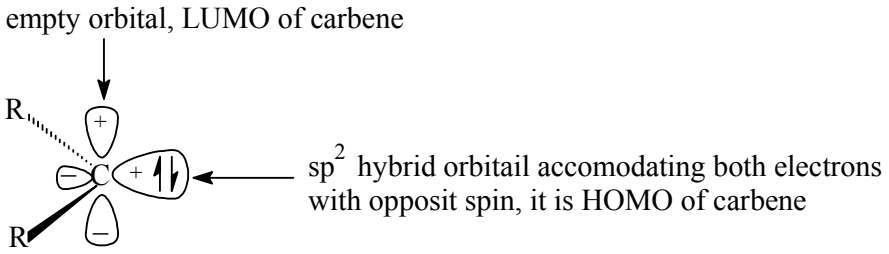
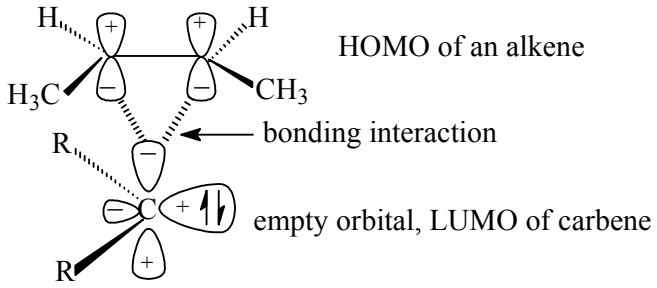


Fig. 10. Molecular orbital diagram of singlet carbene

The cycloaddition of carbine carbine and alkene is [2 + 2] cycloaddition reaction. This reaction is possible only if the carbine approaches the alkene sideways so that the plane defined by the carbon atom and its two substituents parallels the plane of the alkene. In this orientation, the empty p- orbital of the carbine pointing towards the electrons of the π-bond of alkene (**fig 11**).



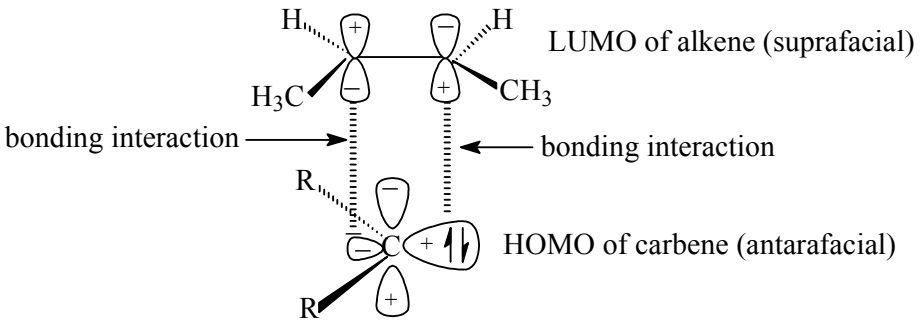
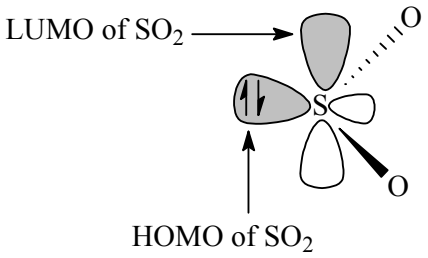


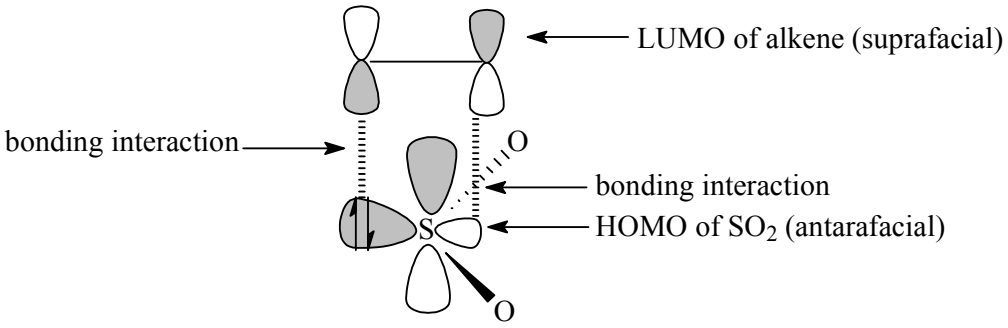
Fig 11 interaction beween HOMO of alkene and LUMO carbine and vise-versa

Chelotropic reaction of carbine with alkene (trapping reaction) is [2 + 2] cycloaddition. As per the explanation in fig 11 above chelotropic reaction of carbine with alkene is symmetry forbidden if both the reactant interact suprafacially Antarafacial reaction of alkene is very unlike thus the reaction is likely to involved the CH_2 antarafacial.

Chelotropic reaction of alkene with SO_2 can also be explained in similar fashion as above for carben and alkene.



Molecular orbital diagram of SO_2

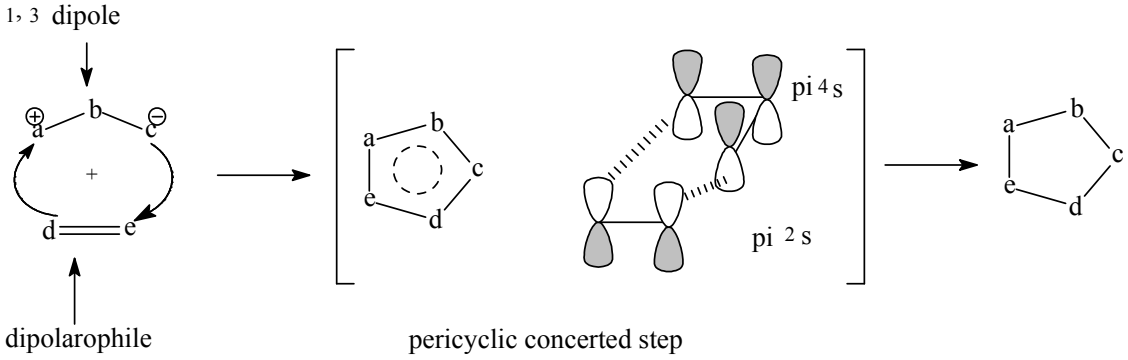


Interaction of MOs of alkene and SO_2 (HOMO LUMO interaction)

10.6 1,3-DIPOLAR CYCLOADDITIONS

The 1,3 –dipolar cycloaddition reactions are analogous to Diels-Alder reaction in which a 1,3-dipole react with a dipolarophile to form a five membered ring. The 1,3-dipolar cycloadditions were described in the late 19th century to the early 20th century, following the discovery of 1,3-dipoles. Mechanism and synthetic application of these reactions were , primarily established by Rolf Huisgen in 1960 . Thus, the reaction is also designated as **Huisgen cycloaddition.**

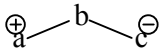
There were two proposals that describe the mechanism of the 1,3-dipolar cycloaddition: first, the concerted pericyclic cycloaddition as developed by Rolf Huisgen in 1963 and the second, was stepwise mechanism which involved diradical intermediate. This mechanism was, proposed by Firestone in 1968. The former proposal is generally accepted. The 1,3-dipole reacts with the dipolarophile in a concerted and symmetry-allowed $_{\pi}4_s + _{\pi}2_s$ fashion through a thermal six-electron Huckel aromatic transition state. Although, there are few examples of stepwise mechanism of the catalyst free 1,3-dipolar cycloaddition reactions for thiocarbonyl ylides and nitrile oxides.



pericyclic concerted step

six electron Huckel aromatic transition state
symmetry allowed under thermal condition

The 1,3–dipolar molecule are isoelectronic and with the allylcarbanion and have four electrons in a π system. All 1,3- dipoles contain 4π(pi) electrons in three parallel p-orbitals of a, b and c. Stereochemically the reaction are syn addition analogous to Diels-Alder cycloaddition reaction.



1, 3 dipole

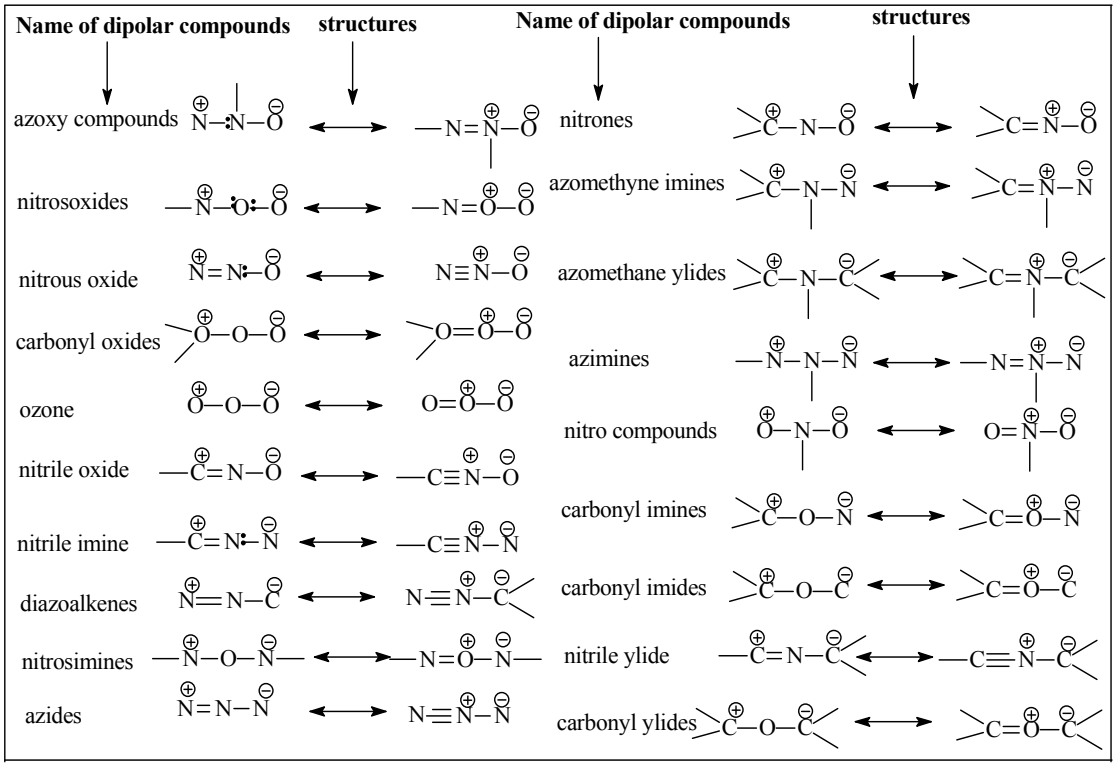
a. **a** has six electrons in its orbit. **b** has its complete octet having at least one lone pair of electron. **c** has its complete octect having negative charge.

b. **a** may be C, O or N **b** may be N or O and **c** may be C, O or N

c. If **b** is N then it has single or double bond. If **b** is o then it has single bond only.

Few 1, 3 –dipolar species are given here in table 4.

Table 4 Name and structures of some 1, 3 –dipoles



The dipolarophile are alkenes, alkynes, imines, nitriles and carbonyl compounds. The steric and electronic factors play a role in determining the regioselectivity of the addition. The justified explanation is based on FMO concept. The HOMO- LUMO interaction of 1, 3-dipole and dipolarophile take place. In most of the dipolar addition LUMO of the dipolarophile intracts with the HOMO of the 1, 3 –dipole. However in certain cases the condition is reversed. 1, 3- dipolar species has three p- orbitals with four electrons hence HOMO will be π_2 or Ψ_2 which has C_2-symmetry. For example say the dipole is diazomethane. Its HOMO will be π_2 or Ψ_2 and suppose the dipolarophile is ethylene, its LUMO will be π^* or Ψ_2 . The cycloaddition between these two species by concerted manner well be as follow (**fig. 12**).

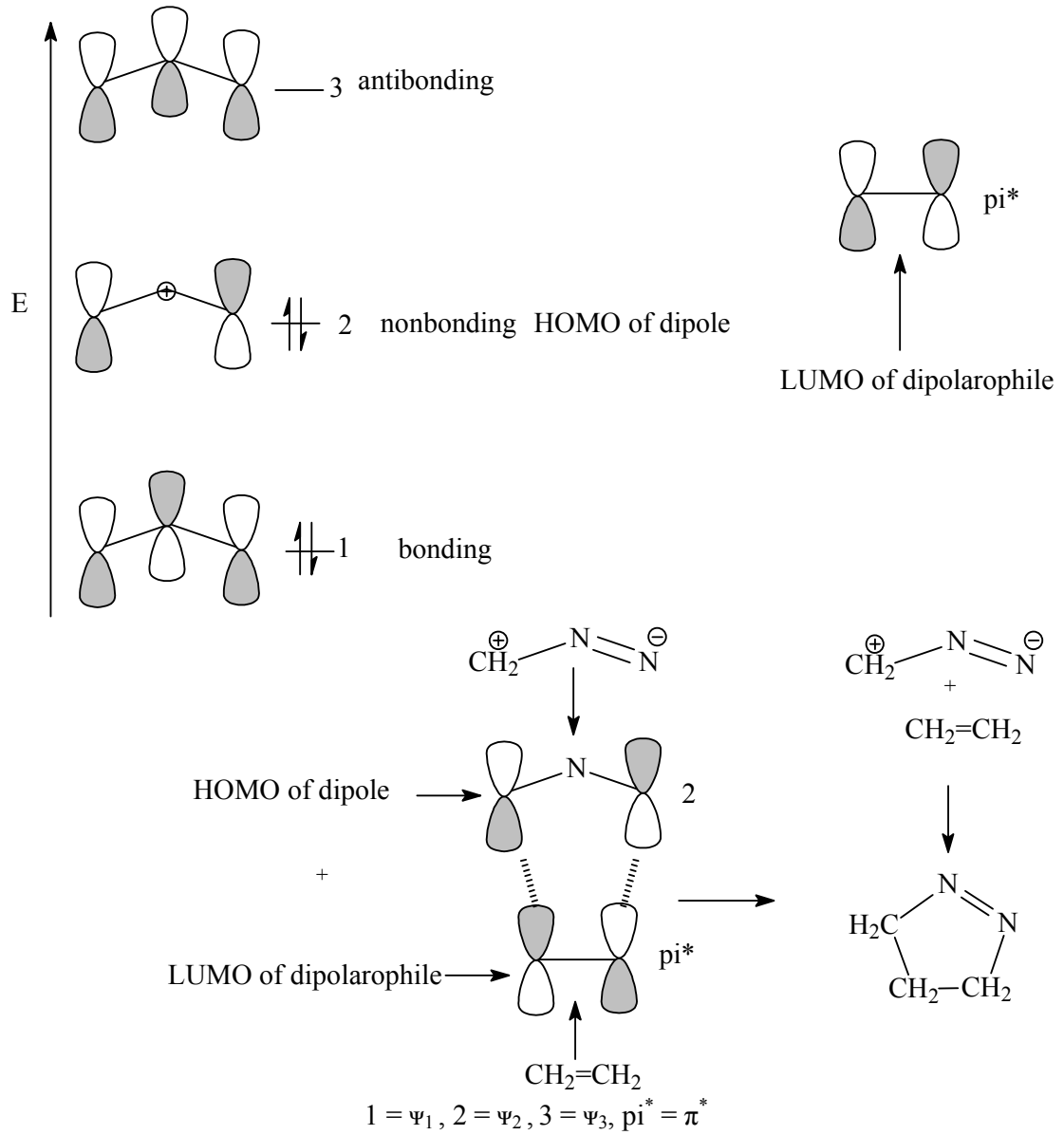
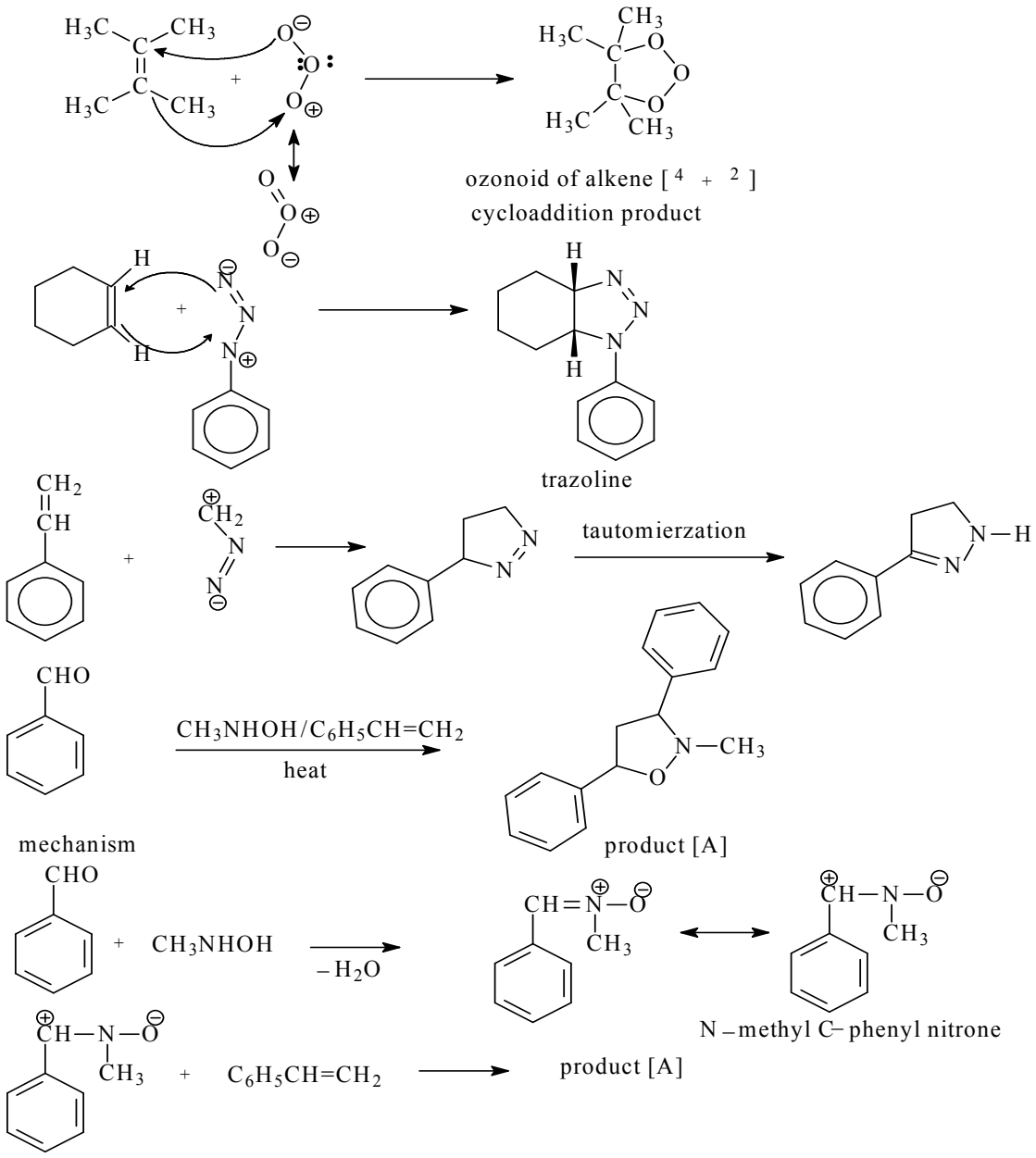
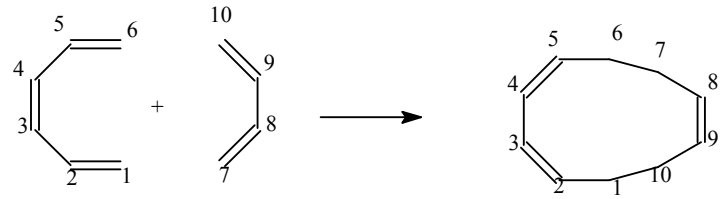


Fig. 12. Concerted cycloaddition reactions of 1,3-dipoar and dipolarophile.

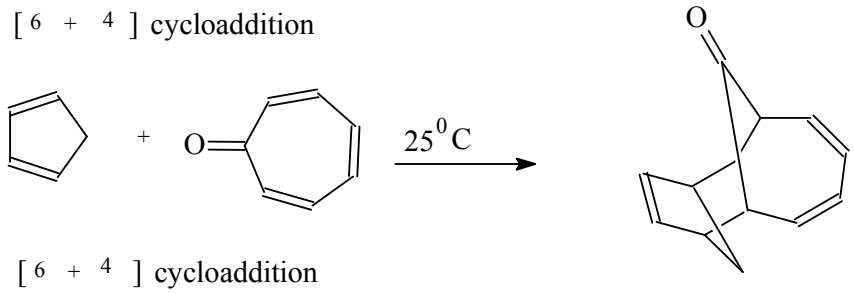
Some of the dipoles are stablecompounds like O_3, diazomethane and suitably substituted azides, nitrones and nitrile oxides. Others like ylides, imines and carbonyl oxides are reactive intermediates. In most reactions the 1, 3 –dipole is not isolated but generated in situ in the presence of the dipolarophile.viz;:



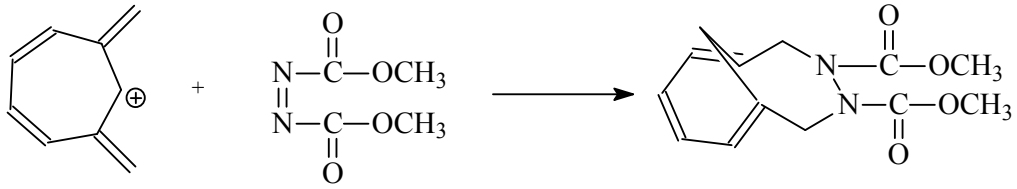
All the reactions explained above have six electrons in the T.S. In some reactions more than six electrons take part in cyclic T.S. during concerted reaction of cycloaddition The common example are [8+ 2] and [6 + 4] cycloadditions.



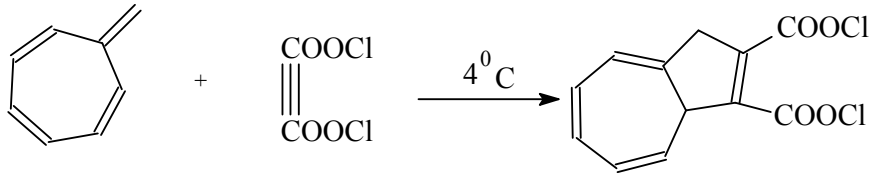
[6 + 4] cycloaddition



[6 + 4] cycloaddition



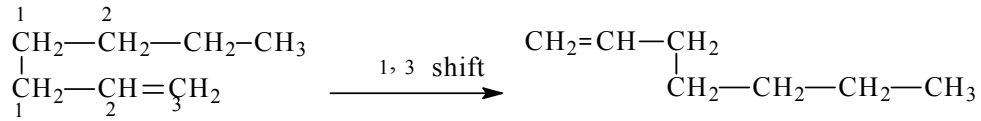
[8 + 2] cycloaddition



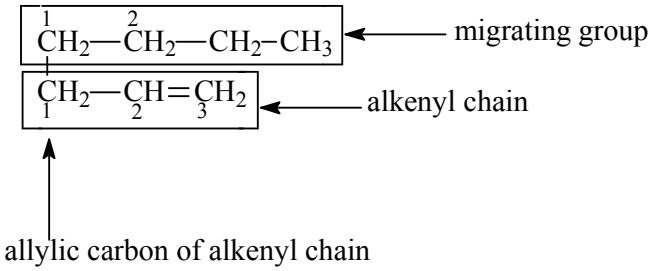
[8 + 2] cycloaddition

10.7 SIGMATROPIC REACTIONS/REARRANGEMENT

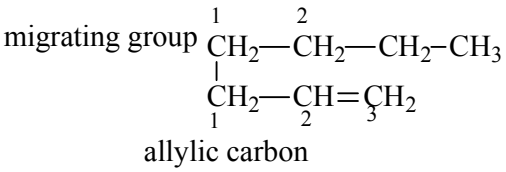
As discussed in 10.1 many thermal or photochemical reactions of olefinic compounds involve shift of a σ- bond from one position to the other position of π-electron system. Such reactions take place by concerted manner and known as sigmatropic reactions. The sigmatropic reactions are caterogised bya double numbering system termed as i, j or m, n which refers to the relative positions of theatom or group involved in the migration or shift. This classification is different from cycloaddition where it is bases on the number of π-electrons involved in the T.S. This classification in sigmatropic reactions can be well understood by following example.

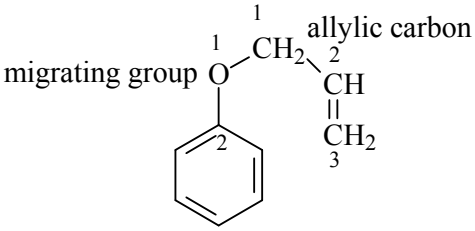


For easy understanding in sigmatropic rearrangement reaction the substrate can be divided in two parts. The alkenyl or polyalkenyl chain and, the migrating atom/group. The alkenyl chain should have at least one allylic group for concerted sigmatropic rearrangement as follow.



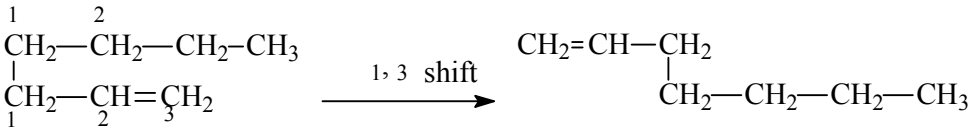
The numbering in both migrating group and alkenyl chain is done separately. In alkenyl chain numbering is started from the allylic carbon which is numbered as 1. In migrating group the atom (H, C or hetero atom) directly bonded with allylic carbon by σ-bond is always numbered as 1 viz;

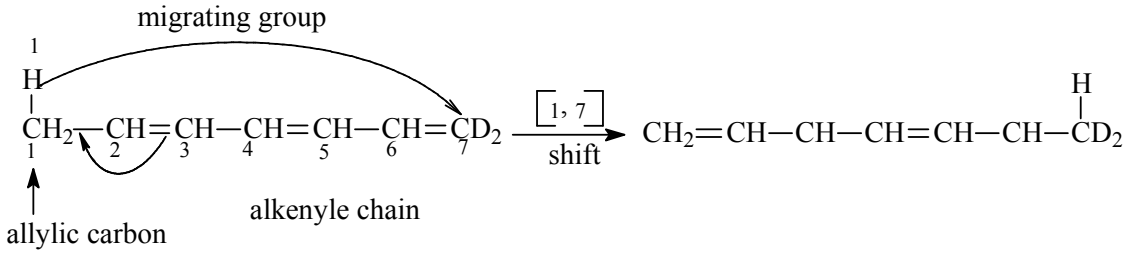




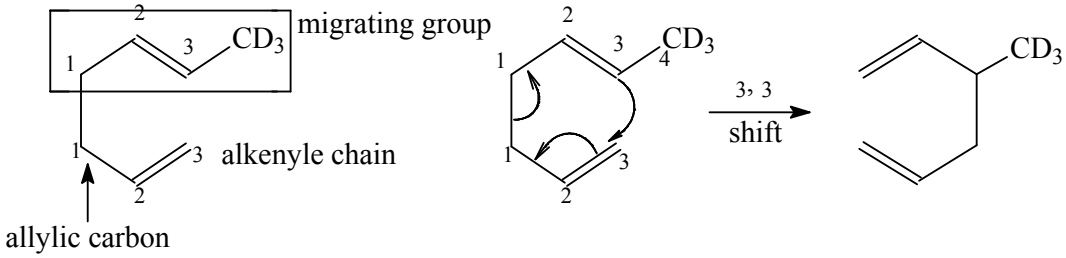
As discussed above the sigmatropic reactions are named as i, j or m, n as in case of the following example atom -1 of the migrating group shift on the atom-3 of the alkenyle chain. Hence theclassification is mentioned as [1, 3] sigmatropic rearrangement.

Where 1, 3 (i. e. i, j) i or m = 1 and j or n = 3 similarly in second example i or m= 1 and j or n = 7





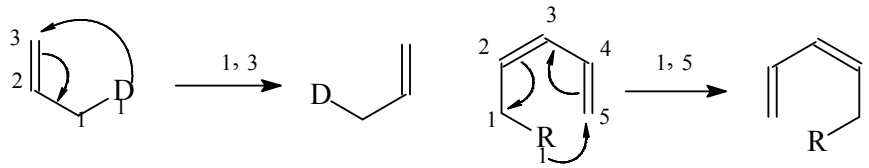
It is not always the first atom of the migrating group shift to the alkenyl chain in the rearrangement viz;



In this rearrangement atom m=3 of the migrating group shift to atom n= 3 of the alkenyl chain hence this rearrangement is an example of [3, 3] sigmatropic shift. Based on this fact. The sigmatropic rearrangement can be categorized in two different classes.

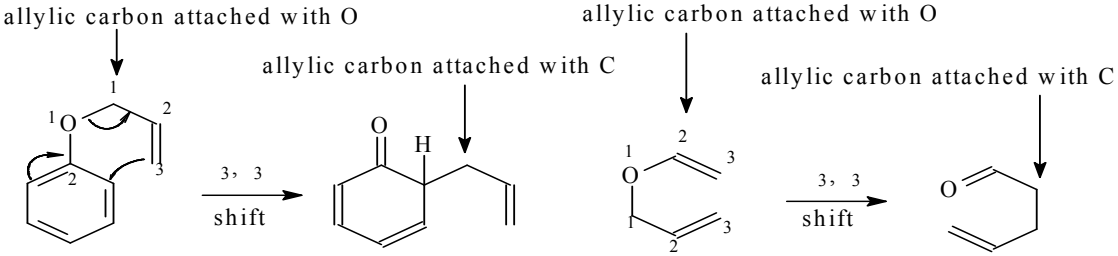
1. The rearrangements in which the migrating atom or group is attached via the same atom in both reactant and product

2. Those reactions in which the migrating atom or group is bonded through different atoms in reactant and in product



D is bonded to carbon both in reactant and product

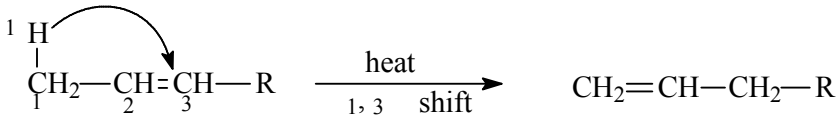
R is bonded to carbon both in reactant and product



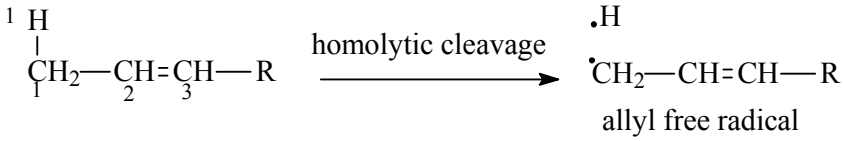
carbon of allylic group is bonded to oxygen in the reactant and carbon in the product

10.7.1 Explanation of [1, 3] and [1, 5] sigmatropic shift:

It is generally argued that the [1, 3] sigmatropic shift requires short path than the [1,5] shift. It is also assumed that [1, 3] shift are induced photochemically while [1, 5] are by thermally. FMO approach can be used to explain and analyse these reactions.Let us start with the following thermally induced [1, 3] sigmatropic rearrangement.



In order to analyse the orbitals, it is presumed that the σ-bond connecting the migrating group undergo hemolytic fission to produce free radicals.



The product of the hypothetical fission is hydrogen atom and an allyl free radical, which contain three p-orbitals. The symmetry oroporties of these orbitals are following (**fig.13)**

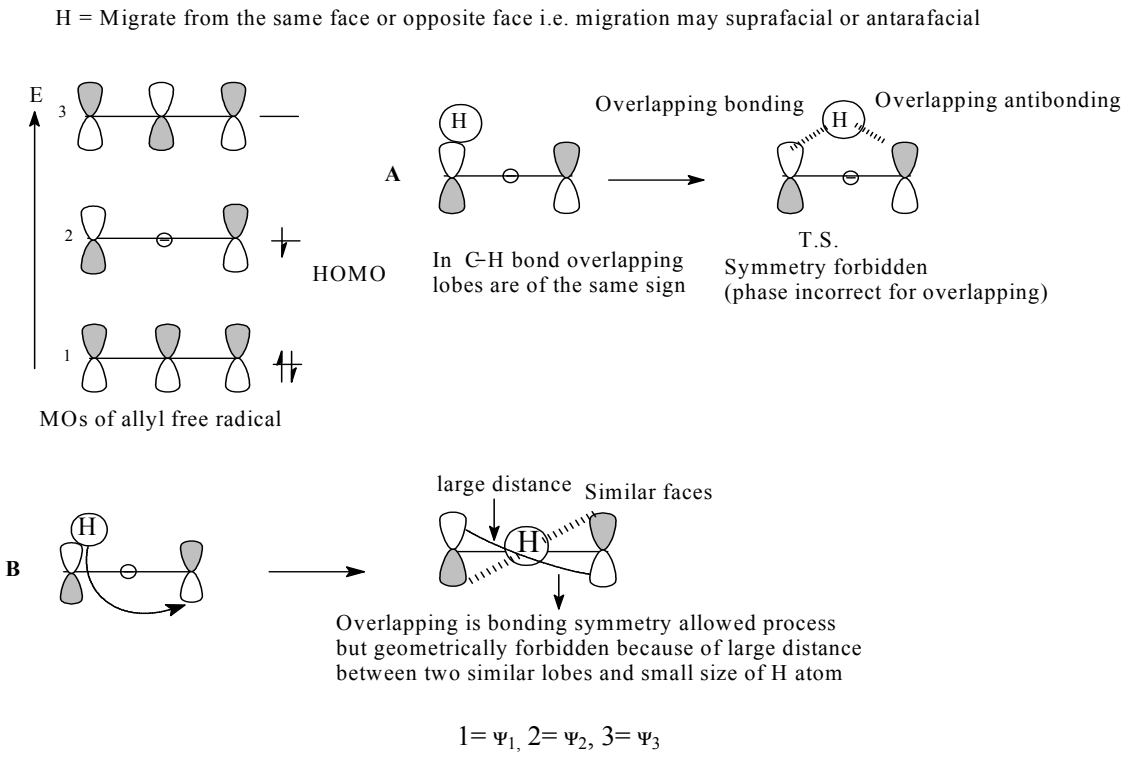
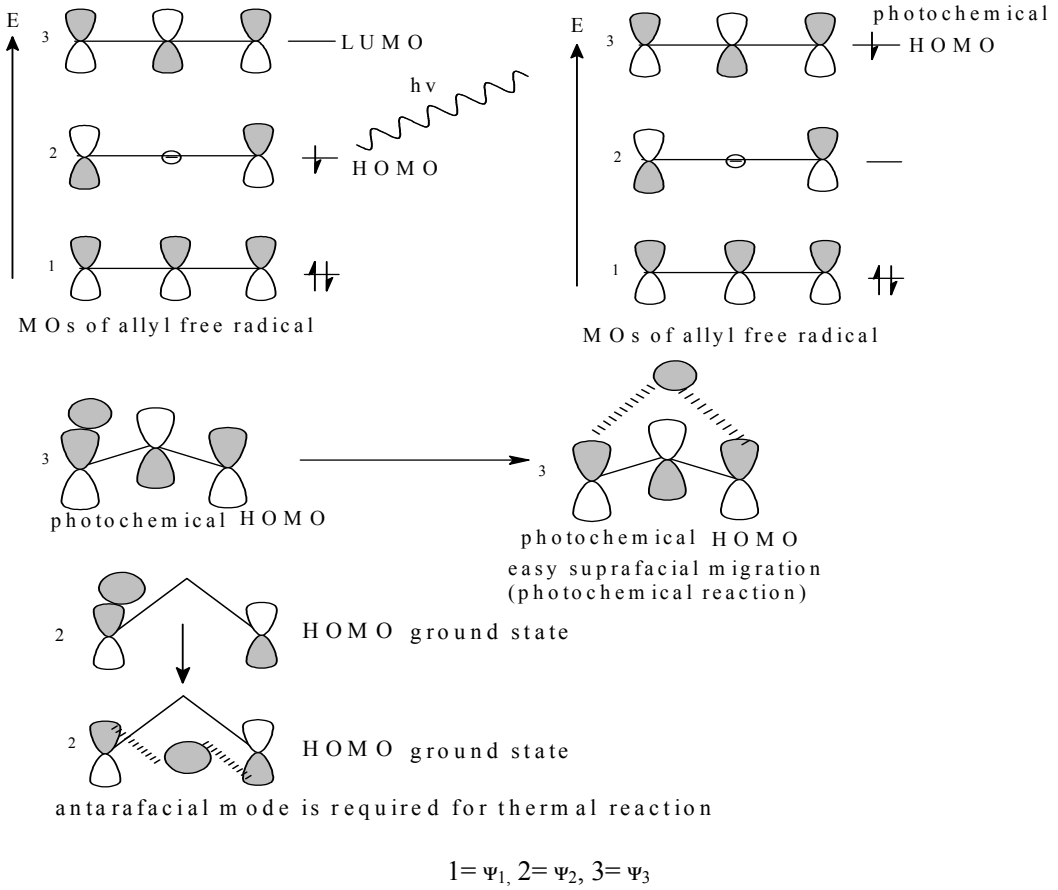


Fig 13. Aanlysis of [1,3] sigmatropic rearrangement A suprafacial B antarafacial migration

In case A the migrating group remains on the same side of the π-orbital system. It is called suprafacial migration. In thermal [1,3] sigmatropic shift a suprafacial migration is geometrically feasible but symmetry forbidden. In case B (fig.12) a symmetry allowed [1,3] sigmatropic shift to occur. The migrating group must shift by antarafacial process.However the symmetry allowed [1,3] antarafacial sigmatropic rearrangement of hydrogen is not geometrically favourable because the 1s orbital is smallest and cannot effectively span the distance required for antarafacial shift. Alternatively the size of 1s orbital of H is smallest and distance between two lobes of interacting p-orbitals of carbon is maximum hence 1s-orbital cannot intrect effectively with p-orbitals at same time in the formation of T.S.

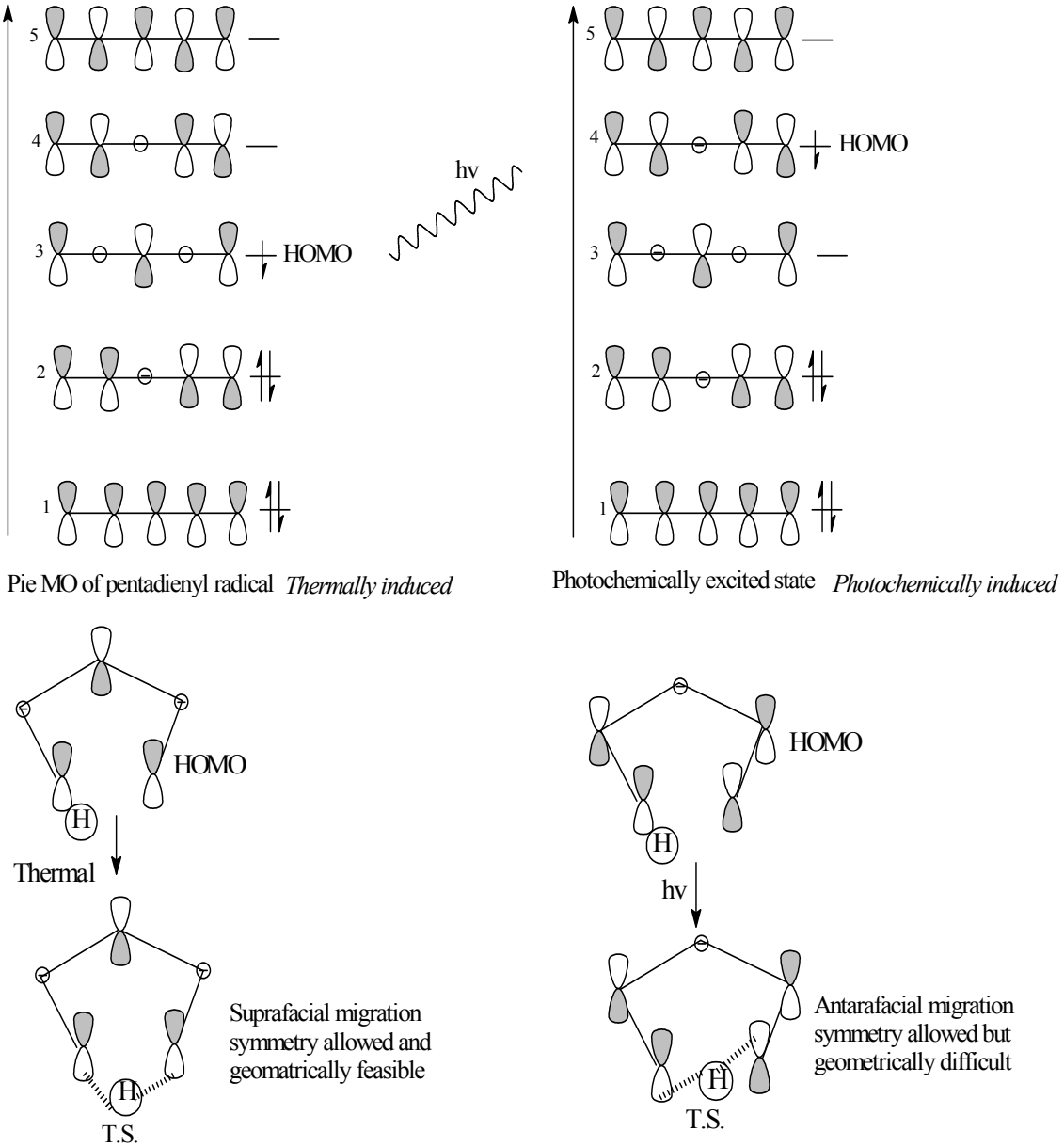
[1, 3]-sigmatropic shift take place in presence of UV-light but examples are rare. Let us obserb again wht happen when a molecule absorb photon. The electron from Ψ_2 promot to Ψ_3 which now becomes HOMO of excited state known as photochemical HOMO. In this reaction the suprafacial migration in Ψ_3, the HOMO and reaction is feasible **(fig.14)**



$1 = \Psi_1, 2 = \Psi_2, 3 = \Psi_3$

Fig. 14.[1,3] suprafacial migration is possible in 3= Ψ_3 and antrafacial in 2= Ψ_2 under photochemical and thermal inductions

In similar fashion [1,5] sigmatropic rearrangement can be explained. This reactionis feasible thermally and forbidden photochemically through concerted manner (**fig. 15**).



$1 = \Psi_1, 2 = \Psi_2, 3 = \Psi_3, 4 = \Psi_4, 5 = \Psi_5,$

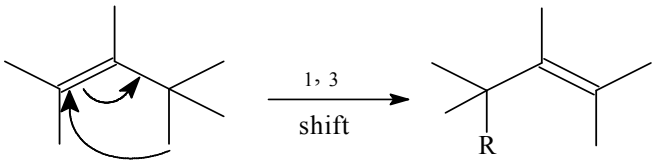
Fig. 15. MO symmetries of pentadienyl radical with thermal and photochemical [1, 5] migration.

10.8 SIGMATROPIC SHIFTS OF ALKYL GROUP

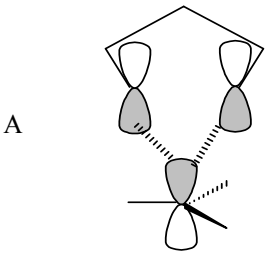
The shift of alkyl group during sigmatropic migration can also occur. If an alkyl group shifts there is additional stereochemical feature to be taken into account. The shift can occur with

retention(r) or inversion (i) at the migrating centre. The allowed process includes the suprafacial 1,3- shift with inversion and the suprafacial 1,5-shift with retention.

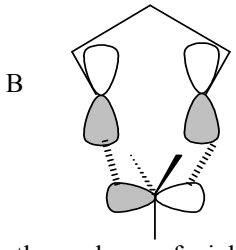
In comparasion to hydrogen atom which has its electron in 1s orbital has only one lobe while carbon free radical has its odd electron in ap-orbutal having two lobes of opposite saign. The imaginary T.S. show that if in place of H one has C then during athermal suprafacial [1,5] process, symmetry can be conserved only provided the shift carbon in amanner that the lobe which was origionally attached to the π-system remains attached to it(fig 15 A). The only way for this happen is the retention of configuration within the migrating group. However, a related [1, 3] thermal suprafacial would involve opposite lobes. Thus if the migrating carbon was origionally bonded via its positive lobe, it must now use its negative lobe to form the new C-C bond. The stereochemical outcome of such a process is the inversion of configuration in the migrating group (fig 15 B)



1, 3 alkyl shift

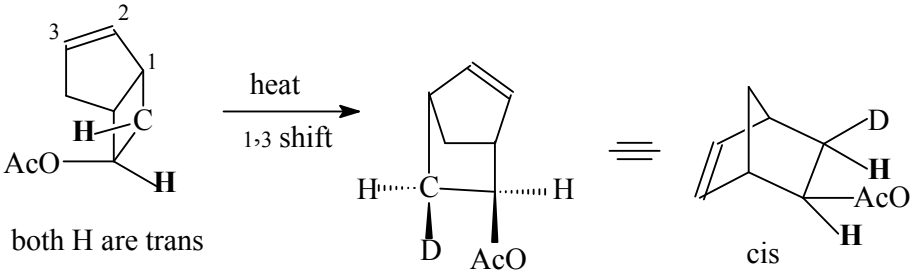


a thermal suprafacial [1, 5] migration. configuration is retained within the migrating group



a thermal suprafacial [1, 3] migration. configuration in the migrating group will be inverted

Fig 16. A [1, 5] and B [1, 3] thermal suprafacial migration of carbon (alkyl shift)



both H are trans

cis

In above reaction there is a [1,3] shift with inversion of configuration at the migratin centre.This can be explained by orbital symmetry. The hemolytic cleavage takes place in this reaction to as also discussed earlier. The bond between the alkyl system and the migrating carbon stretches during T. S., the phase relationship between two bonded lobes is mentioned as follow.The explanationcan be understand from following MOs representation through FMO approach (fig 16)

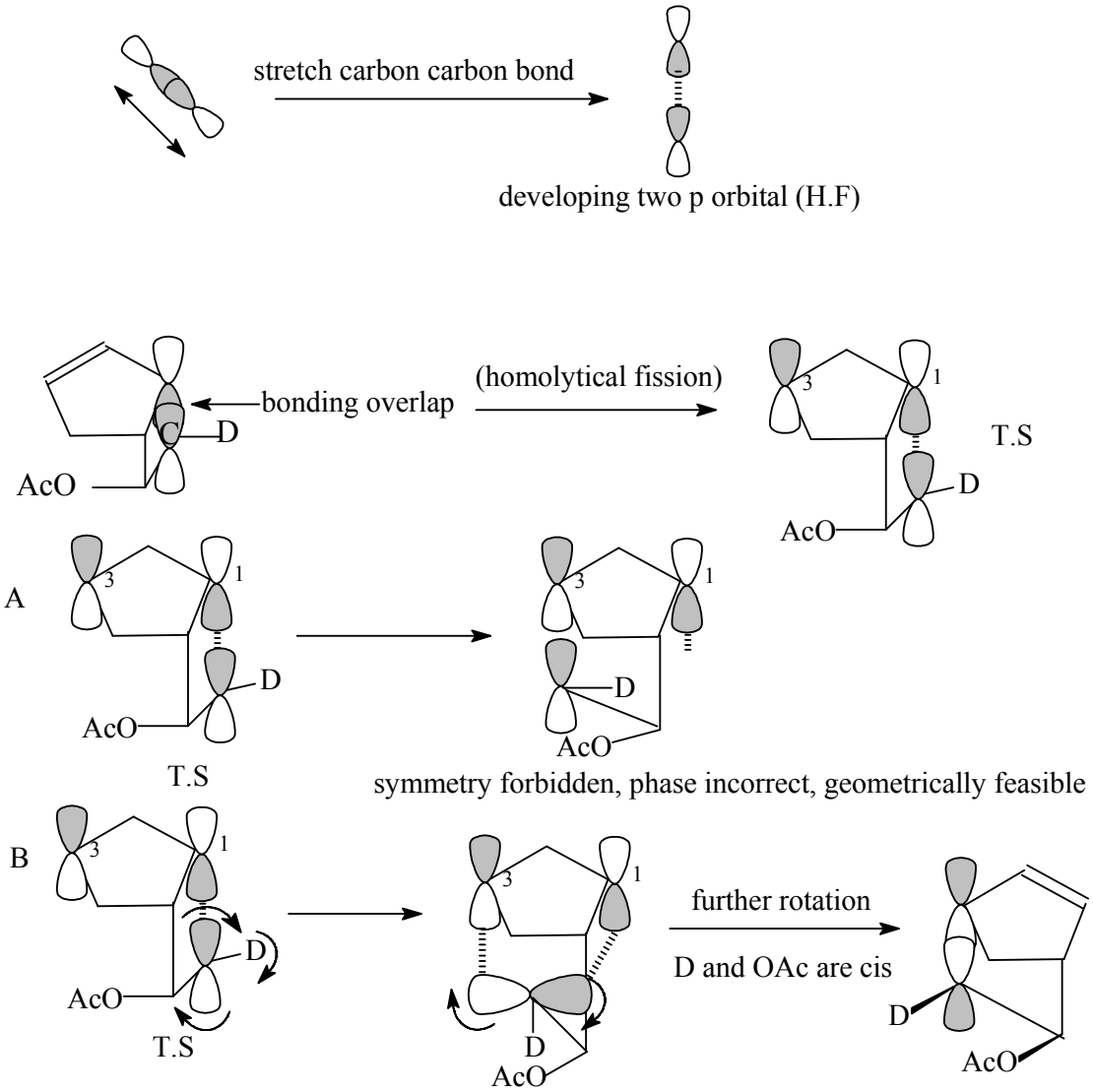


Fig 16 B.Explanation for [1, 3] allylic shift with stereochemistry of the reaction.

The suprafacial/antarafacial shift in sigmatropic rearrangement can be summed in selection rule for thermal and photochemical mode of activation (table 5).

Table:5 Selection rule for [1 +n] in which migrating group is hydrogen

m + n	Thermally allowed Photochemically forbidden	Photochemically allowed Thermally forbidden
4n	antara	supra
4n +2	supra	antara

Table:5 Selection rule for [1 +n] in which migrating group is carbon

m + n	*Thermally allowed*	*Photochemically allowed*
4n	*ar*	*sr*
4n	*sr*	*ai*
4n +2	*sr*	*ar*
4n +2	*ai*	*si*

s= supra, a = antara, r= retention, i = inversion

10.9 HUCKEL-MOBIUS APPROACH IN SIGMATROPIC REARRANGEMANT

PMO method or H-M methods as also discussed for electrocyclic and cycloaddition reaction can be applied for sigmatropic rearrangements. According to this system, which is based on the concept of aromaticity and antiaromaticity point no 3 section 10.3, the thermal sigmatropic rearrangement take place through aromatic transition state whereas photochemical sigmatropic rearrangement take place through antiaromatic transition state. The moleculat orbital symmetries alongwith thermal and photochemical feasibility through suprafacial and antarafacial under aromatic and antiraomatic system has been depicted in fig.17 as under.

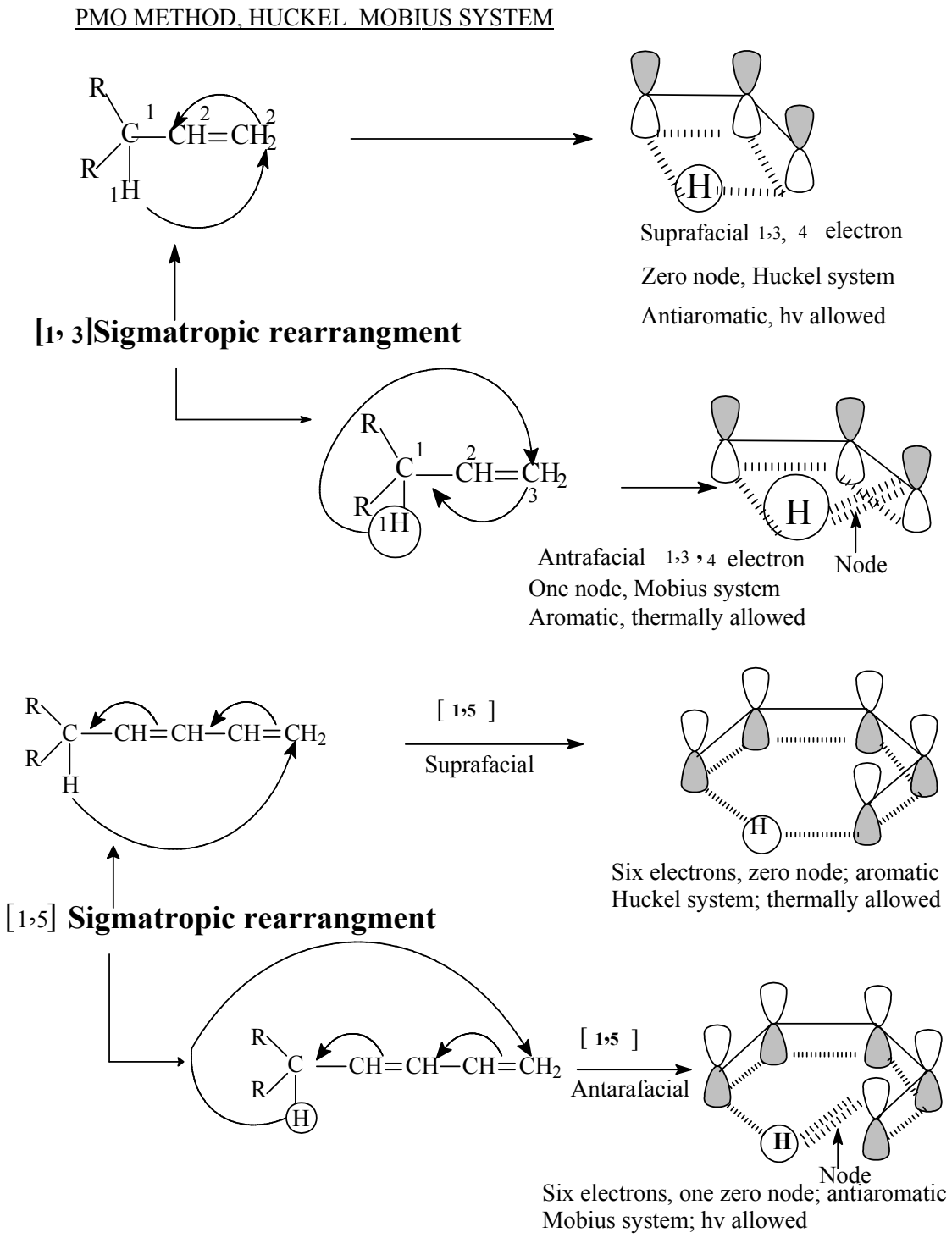


Fig.17. The Huckel-Mobius (PMO) approach for sigmatropic rearrangements

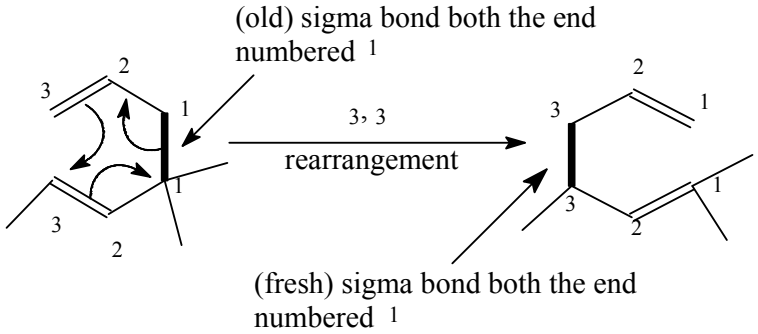
Finally based on above explanation the selection rules for sigmatropic rearrangement are summerised in table 6.

Table: 6 Selection ruls for sigmatropic rearrangement by H-M (PMO) method

No. of electrons involved	No. of nodes	Aromaticity	Shift mode	Mode of activation
4n	zero	aniaromatic	supra	photochemical
4n	one	aromatic	antara	thermal
4n + 2	zero	aromatic	supra	thernal
4n + 2	one	antiaromatic	antara	photochemical

10.10 [3, 3] SIGMATROPIC REARRANGEMENTS (COPE REARRANGEMENT

The [3, 3] sigmatropic rearrangements are very important rearrangements, which involve carbon-carbon bond. The thermal rearrangement of 1, 5 –diene by [3, 3] sigmatropic shift is known as **Cope rearrangement**. The reaction takes place in thermodynamically favoured direction as:-



In above rearrangement the new sigma bond formed has 3, 3 relationship hence thisrearrangement is called [3, 3] sigmatropic rearrangement or [3, 3] sigmatropic shift or Cope rearrangement. Donor substituents at C-2, C-3, C-4 or C-5 accelerate the rearrangement. Donor group at C-2 and C-3 have accelerating effect, which can be rationalized in term of stabilization of T>S. by depecting their different effect on two niteractiong system (fig. 18).

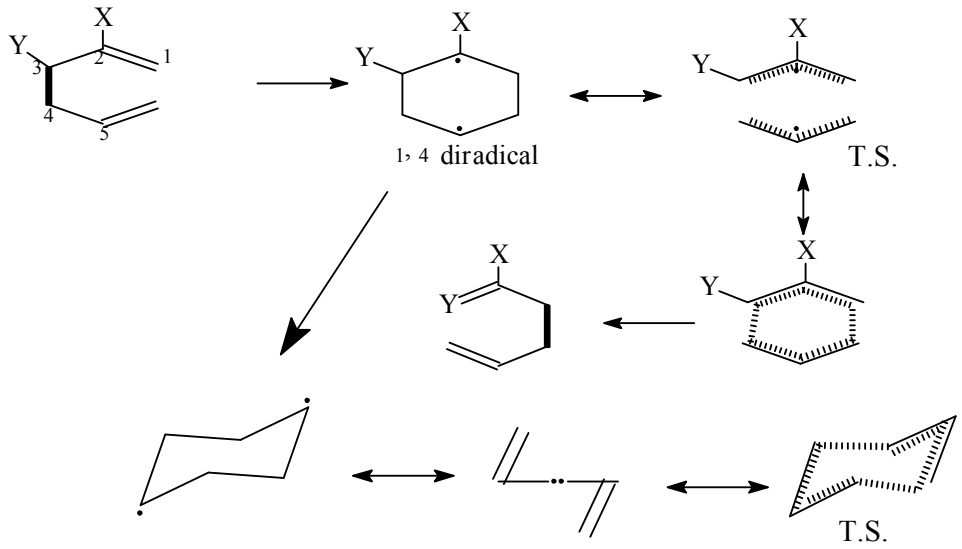


Fig.18. Rationalisation of [3,3] shift in 1,5- pentadiene system via concerted mechanism

The T.S. as above involve six electrons being converted from one 1,5-diene system to another. The T.S. range from 1, 4-diradical to two nearly independent allyl radical depending upon whether the bond making or bond breaking is more advanced. The general framework for understanding the effect of substituents is that the the reaction are concerted with relatively late T.S. with well developed C-1-C-6 bond (**fig 18**).

In case of Cope rearrangement the migrating group is allylic radical. An alalysis of symmetry of MOs involved shows why this reaction is facile thermally but not observed commonly by photochemical induction. As we break the C-(1) - C-(1) bond the phase of the overlapping lobes must be the same. The HOMO of the allyl radical Ψ_2 and that information allows us to fill the symmetries of the two allyl radicals making up of T.S. (**fig 19**).

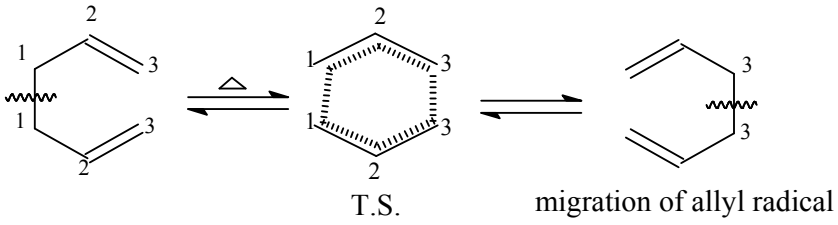
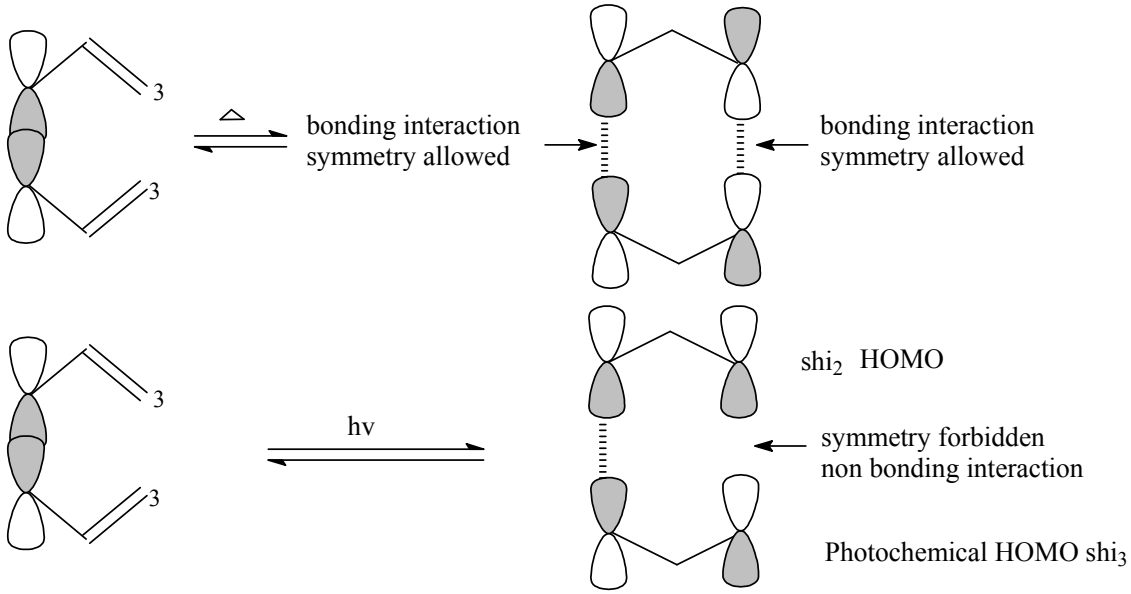


Fig 19. Bond breaking at C-(1)-C(1) and making at C-(3)-C(3) in allylic transformation during T.S.

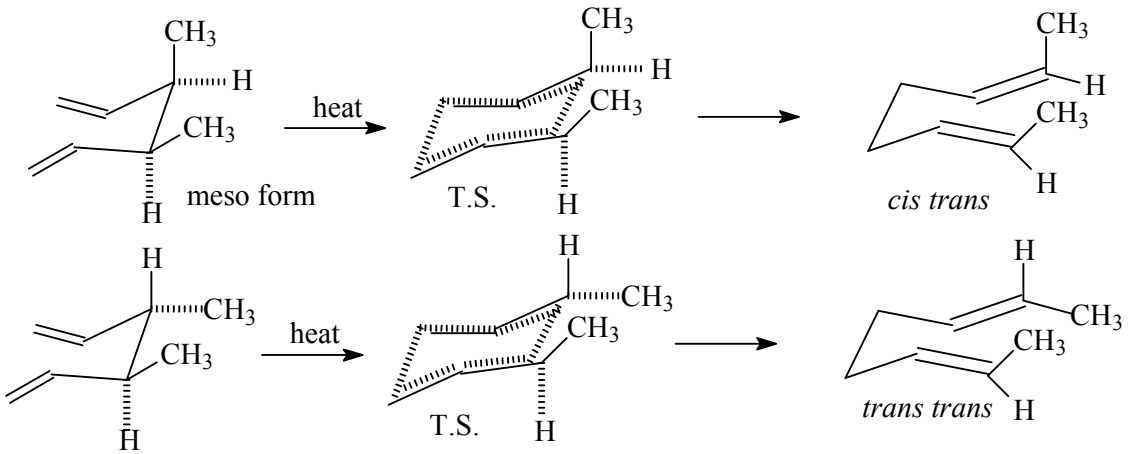
Reattachment the two C (3) position is allowed because the interation of the two lobes on C(3) in bonding. If interaction is carried out in the presence of UV-light than one electron is excited from HOMO to the LUMO which now become photochemically HOMO (**fig. 20**)



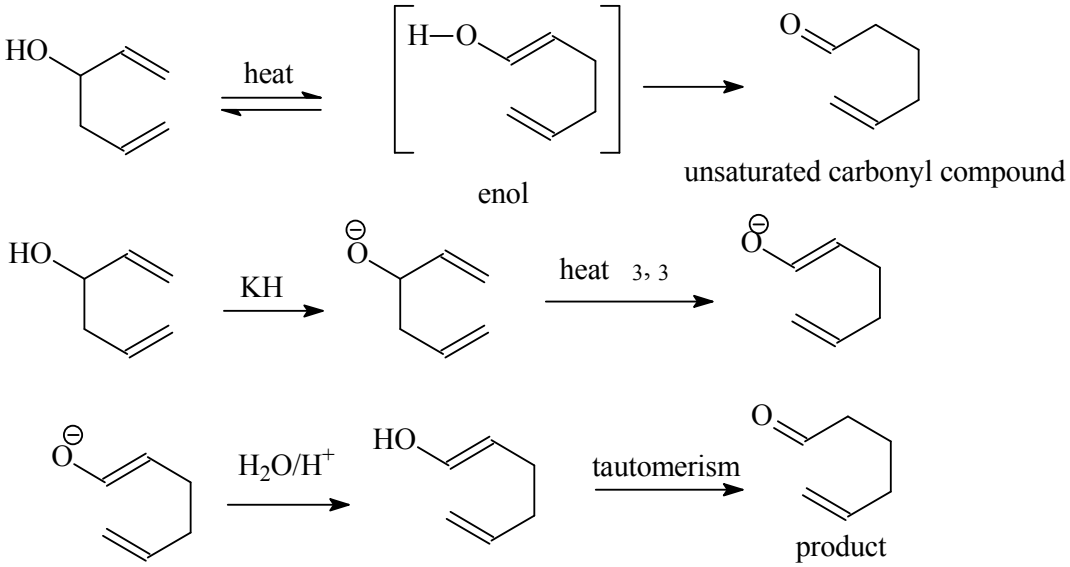
$shi_2 = \Psi_2$, $shi_3 = \Psi_3$

Fig. 20 [3, 3] Cope rearrangement of allyl radical under thermal ahnd photochemical conditions

Stereochemically the Cope rearrangement procceds via the chair like T.S. gives the following stereospecific product.This reaction has made [3, 3] shift valuable in enantiospecific synthesis.



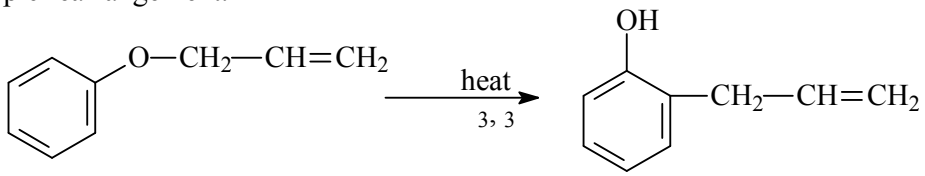
Unsaturated carbonyl compounds can be synthesized with the lelp of Cope rearrangement viz; heating of 1,5-pentadiene-3-ol under go Cope rearrangement with the formation of unsaturated carbonyl compounds.. The reaction is asselerated in presence of strong bas as follow.



10.11 CLAISEN RERRANGEMENT

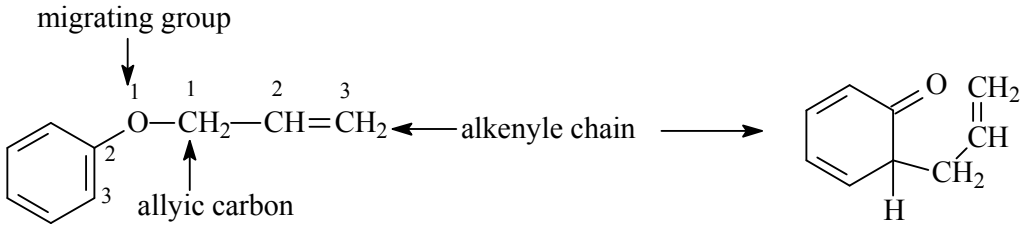
The Claisen rearrangement was the first sigmatropic rearrangement which was discovered by Rainer Ludwig Claisen in 1912. This reaction should not be confused with the Claisen condensation. The Claisen rearrangement is a powerful carbon–carbon bond-forming chemical reaction. The heating of an allyl vinyl ether without solvent rearrange to a product

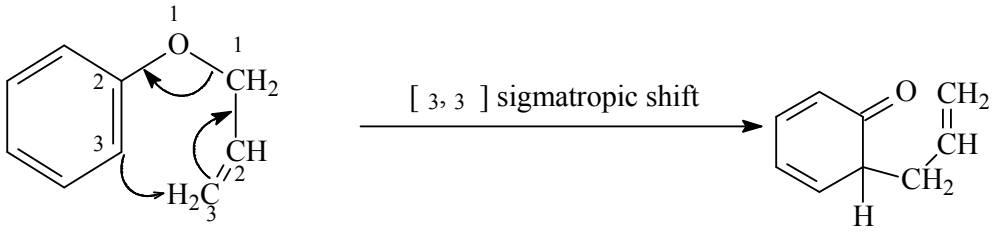
called O-allylphenol. The formation of product is atwo step reaction. The first step is [3, 3] sigmatropic rearrangement.



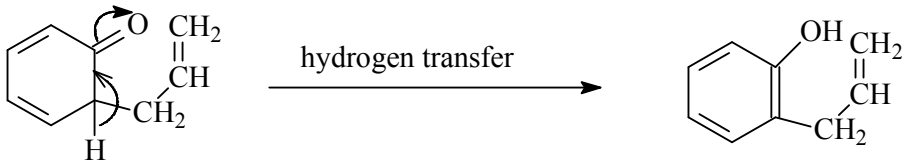
Mechanism: In order to conveniently understand the mechanism, the Claisen Rearrangement can be explained in two steps.

The I-step is [3, 3] sigmatropic rearrangement as follow:

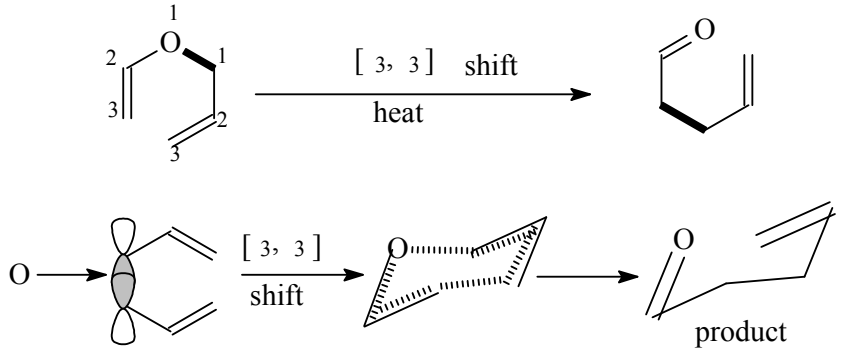




In step II, the product simply undergo ionic proton transfer to regenerate aromaticity of the phenyl ring.

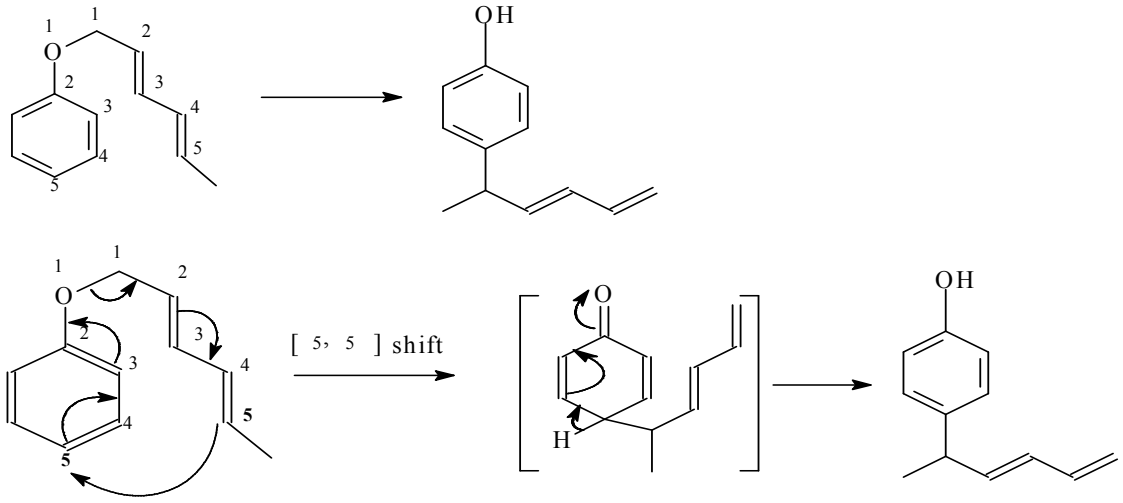


Claisen rearrangement is also given by allyl vinyl ether but in this reaction the rearrangement is called aliphatic Claisen rearrangement or ClaiseniCope rearrangement. These [3, 3] sigmatropic rearrangements take place by chair-like six membered T.S. as in thecase of Cope rearrangement (section 10.10). The chair like T.S. to predict the stereochemistry if any of the new double bond in the product.

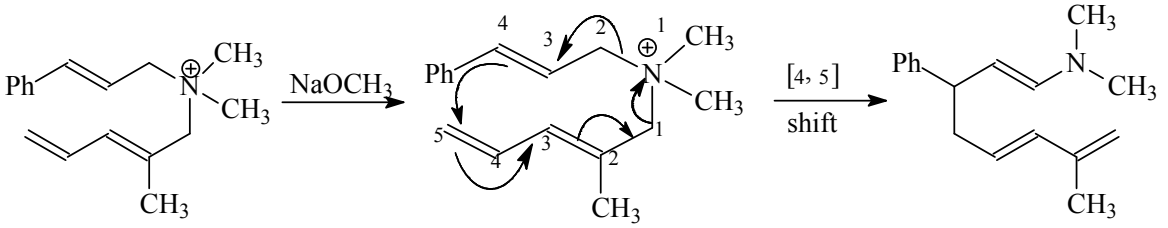


10.12 [5 5] RARRANGEMENTS REACTION

Like [3,3] sigmatropicrearrangements, the Woodward-Hoffman rules predicted that [5,5] sigmatropic shifts would proceed suprafacially, Huckel topology transition state. These reactions are rarer than [3, 3] sigmatropic shifts, but this is mainly a function of the fact that molecules that can undergo [5, 5] shifts are rarer than molecules that can undergo [3,3] shifts.

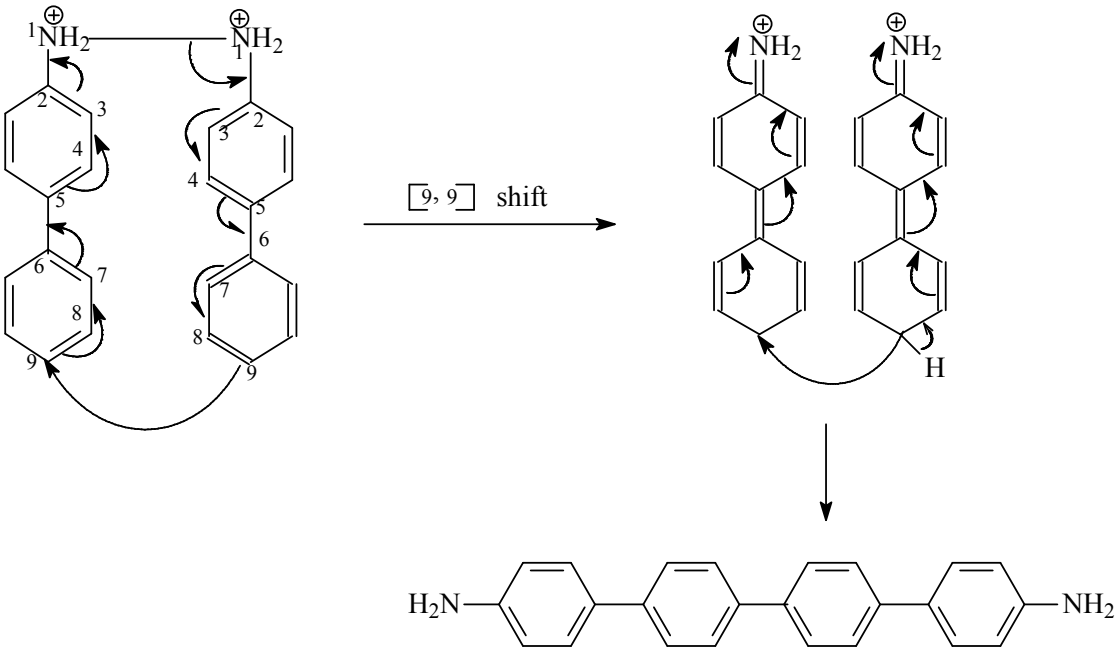


Similarly examples of [4.5] sigmatropic shift anf [9, 9] sigmatropic shift are available as follow.



quaternary ammonium ion

sigmatropic rearrangement product



product

Benzidine rearrangement is an example of [9, 9] sigmatropic rearrangement

10.13 AZA-COPE REARRANGEMENTS:

Like Cope rearrangement the aza-Cope rearrangement reactions are an examples of [3, 3] rearrangement reactions. The only difference between Cope and aza Cope reaction is that the aza cope reaction is a heteroatom version of the Cope rearrangement. In this reaction [3, 3]-sigmatropic rearrangement shifts single and double bonds between two allylic components. According to Woordward and Hoffmann the aza cope reactions takes place in concerted manner via suprafacial mode. The first example of an aza-Cope rearrangement was the cationic 2-aza-Cope Rearrangement, which takes place at temperatures 100-200 °C lower than the Cope rearrangement due to the facile nature of the rearrangement. The facile nature of this rearrangement is attributed both to the fact that the cationic 2-aza-Cope is inherently thermoneutral, meaning there's no bias for the starting material or product, as well as to the presence of the charged heteroatom in the molecule, which lowers the activation barrier(**fig 21**).

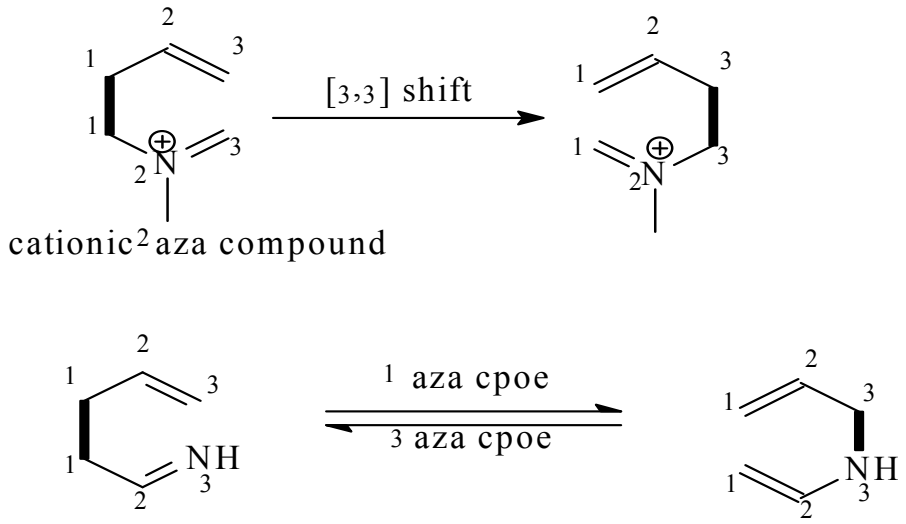
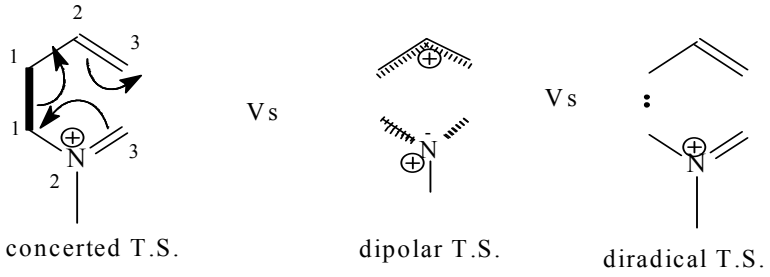


Fig. 21 [3, 3] aza-cope sigmatropic rearrangement

The aza-Cope rearrangements wer predicted by the Woodward-Hoffman rules to proceed suprafacially. However, while never explicitly studied, Overman and coworkers have hypothesized that, as with the base-catalyzed oxy-Cope rearrangement, the charged atom distorts the sigmatropic rearrangement from a purely concerted reaction mechanism (as expected in the Cope rearrangement), to one with partial diradical/dipolar character, due to delocalization of the positive charge onto the allylic fragment, which weakens the allylic bond. This results in a lowered activation barrier for bond breaking. Thus the cationic-aza-Cope rearrangement proceeds more quickly than more concerted processes such as the Cope rearrangement.



10.14 FLUXIONAL TAUTOMERISM

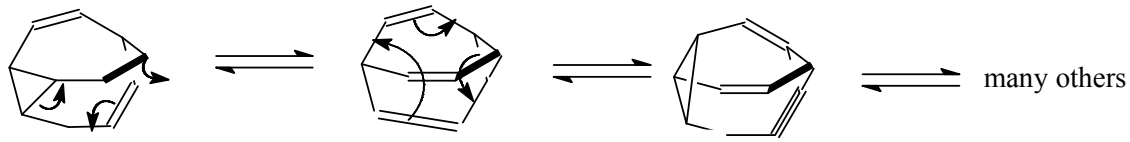
Molecules that undergo rapid bond shift are called fluxional molecules. In fluxional molecules their atoms are in a continual state of motion associated with rapid changes in bonding. The rearrangement may involve either bond reorganization or atm/group migration, In general fluxional molecules are a unique class of molecules with no permanent structure

Almost all molecules are fluxional in certain respects, for example:bond rotations in many of the organic compounds. A molecule is considered to be fluxional if it shows line broadening in spectroscopic signature due to chemical exchange (which is beyond Heisenberg's uncertainity principle).

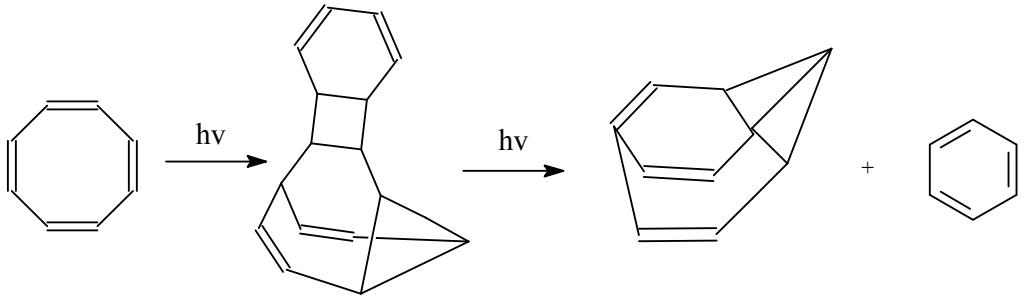
A few common features of fluxional molecules are;

- Fluxional molecules behave differently at different temperatures
- While interchanging between different conformations many intermediates and meta-stable forms are reached
- Fluxionality provides diversity in structure of a molecule.

The [3, 3] sigmatropic rearrangement in bullvalene interconvert identical forms of the molecule is an example of fluxional molecule. Bullvalene may undergo 1209600 Cope rearrangements and still maintain the same structure due to its fluxional nature.



bullvalene: tricyclo [3, 3, 2, 0] deca 2,7 tricyclo



$C_{16}H_{16}$ $C_{10}H_{10}$

The cyclooctttetraene molecule undego dimerization to give a product which is afluxional molecule (**fig 22**). The fluxional molecules behaves differently at different temperature,

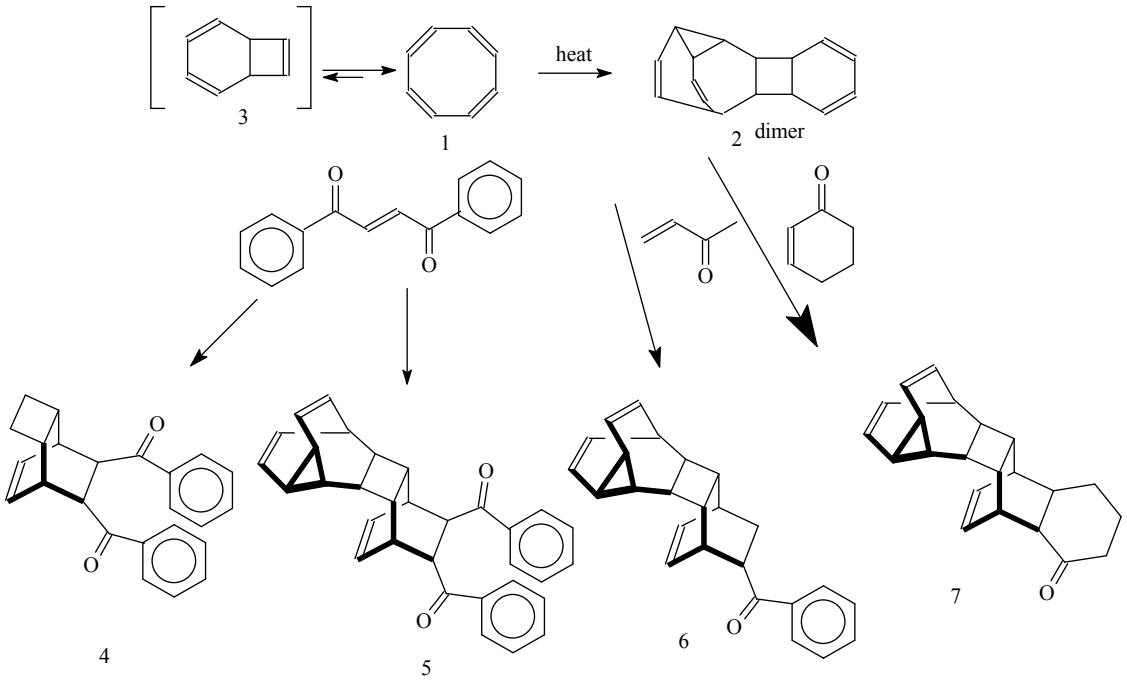


Fig.22. Dimerization of cyclooctatetraene and further Diels Alder reaction with unsaturated ketones

Ladderane are an interesting class of compounds containing two or more fused cyclobutane Rings. The name arises from the resemblance of a series of fused cyclobutane rings to a ladder.A useful mechanism for synthesis for ladderanes involves[2 + 2] photocycloadditions,which is a useful reaction for creating strained 4 membered rings.The molecule 1 shown below belongs to ladderane polymer class. In a study it was shown that shiftamer 2 is fluxional at room temperature and undergoes degenerate Cope rearrangement to give rise to 2', which is equivalent to 2. Continued indefinitely, the Cope rearrangement process leads to a pair of double bonds running down the polymer chain running back and forth along the polycyclo butane framework (**Fig 23**).

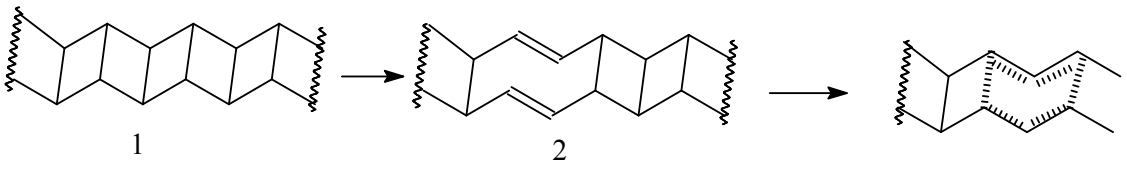
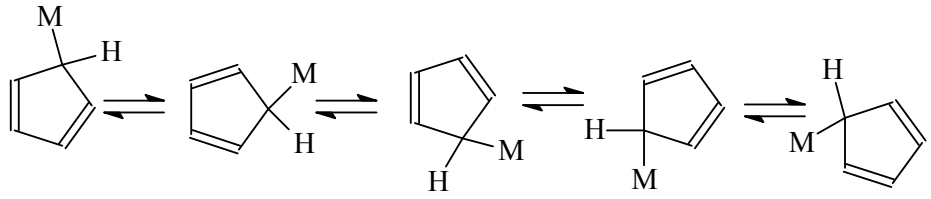


Fig. 23 Fluxional tautomerism in ladderaness

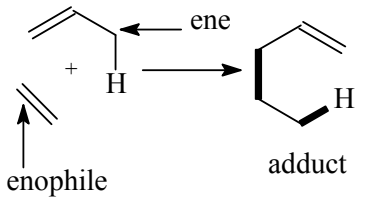
The phenomena of fluxionality appear to be rather more common in organic cations and organometallic compounds. The fluxionality of the σ-bonded metal cyclopentadienide involves migration.



Fluxionality is most readly ascertained by means of NMR. Conversion of one structure into other in fluxional molecule is known as valence tautomerism and isomers are known as valence tautomers.

10.15 ENE REACTION

In pericyclic reaction groups or atoms transfer from one molecule to another. Such reactions are called group transfer reactions. Ene reaction is one of the common group transfer reaction. The ene reaction also known as the Alder-ene reaction), is a chemical reaction which takes place between ene and enophile. An alkene with an allylic hydrogen is generally called ene while a molecule with multiple bond is known as enophile.In ene reaction there is a formation of new σ-bond with migration of the ene double bond and 1,5 hydrogen shift.



ene: alkene, alkyne, arene , allene, C–heteroatom bond

enophile: C=C, C=O, C=S,C=N,C≡C, O=O,N=N,C≡N etc

Ene component: Enes are π-bonded molecules containin at least one active hydrogen atom at the allylic, α-position. Possible ene components include olefinic, acetylenic, allenic, aromatic, cyclopropyl, and carbon-hetero bonds. Usually, the allylic hydrogen of allenic components participates in ene reactions, but in the case of allenyl silanes, the allenic hydrogen atom α to the silicon substituent is the one transferred, affording a silylalkyne. Phenol can act as an ene component, for example in the reaction with dihydropyran, but high temperatures are required (150–170 °C). Nonetheless, strained enes and fused small ring systems undergo ene reactions at much lower temperatures. In addition, ene components containing C=O, C=N and C=S bonds have been reported, but such cases are rare.

Enophile components: Enophiles are π-bonded molecules which have electron-withdrawing substituents that lower significantly the LUMO of the π-bond. Possible enophiles contain carbon-carbon multiple bonds (olefins, acetylenes, benzynes), carbon-hetero multiple bonds

(C=O in the case of carbonyl-ene reactions, C=N, C=S, C≡P), hetero-hetero multiple bonds (N=N, O=O, Si=Si, N=O, S=O), cumulene systems (N=S=O, N=S=N, C=C=O, C=C=S, SO_2) and charged π systems ($C=N^+$, $C=S^+$, $C\equiv O^+$, $C\equiv N^+$).

Mechanism: According toFMO approach the interaction takes place between HOMO of ene and LUMO of enophile (**fig 24).**

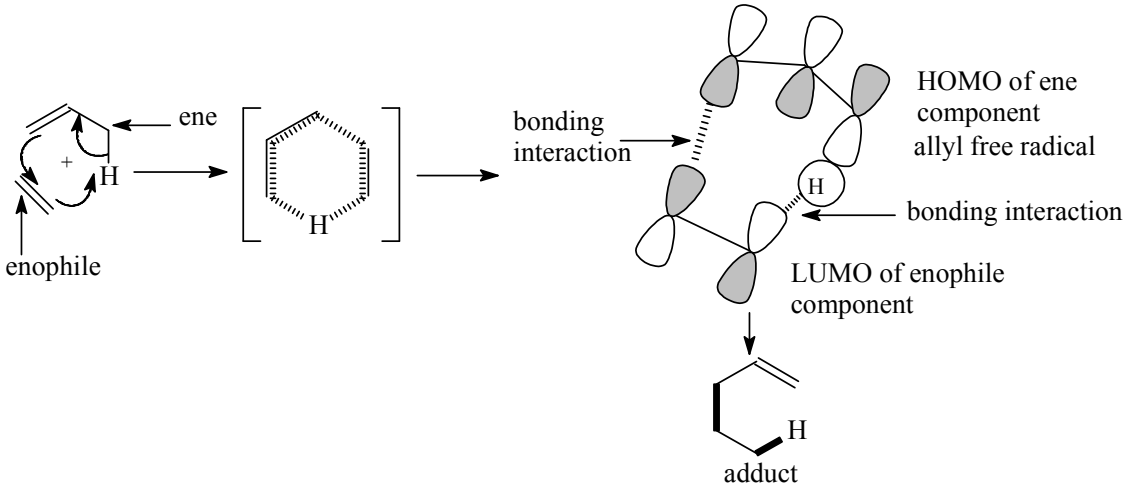
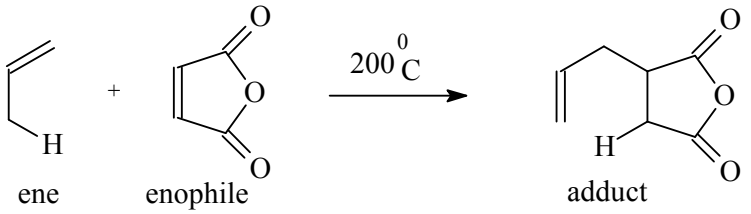
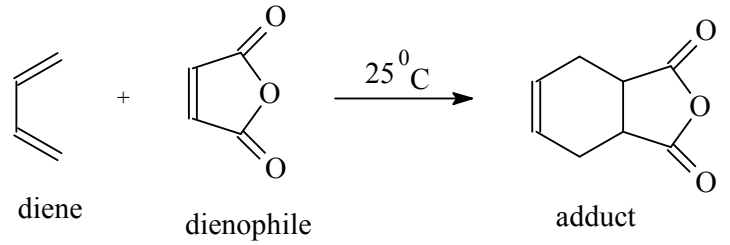


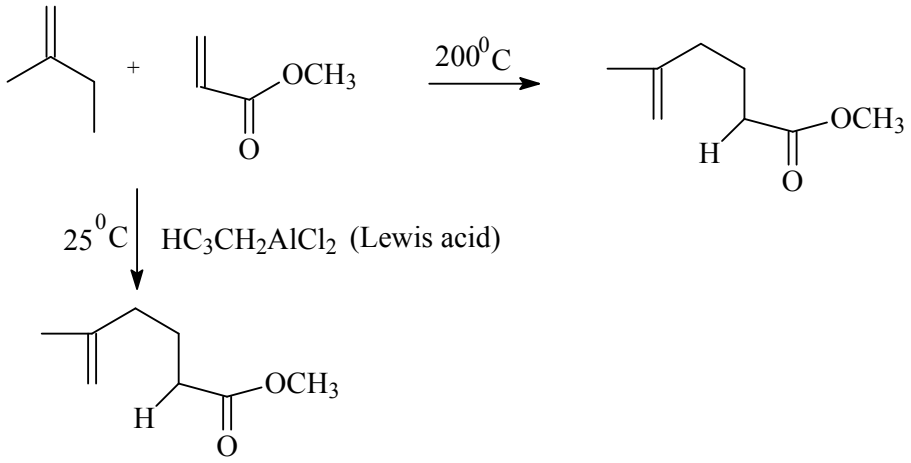
Fig.24 Concerted mechanism for the ene reaction

The energy of activation for ene reaction is greater than that of Diels-Alder reaction due to this reason the ene reactions take place at higher temperature than Diels-Alser reaction

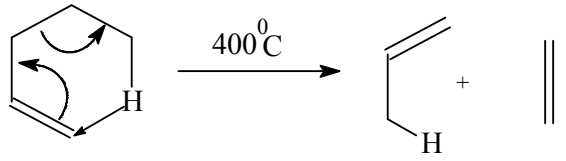




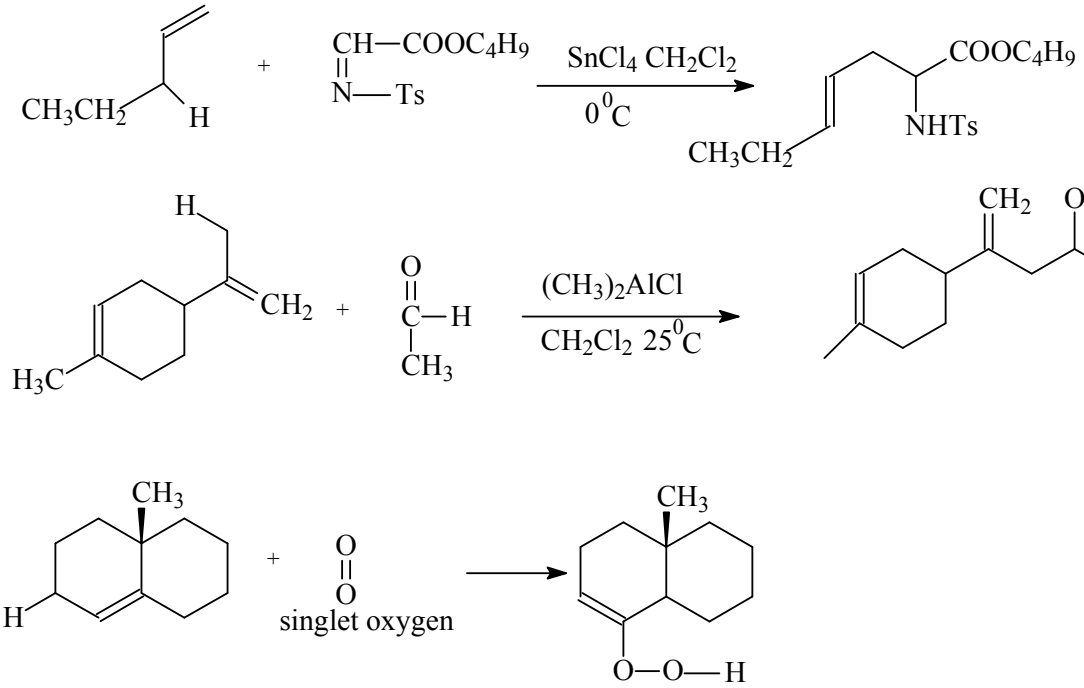
Many ene reactions can be catalysed by Lewis acids like $AlCl_3$ under mild conditions



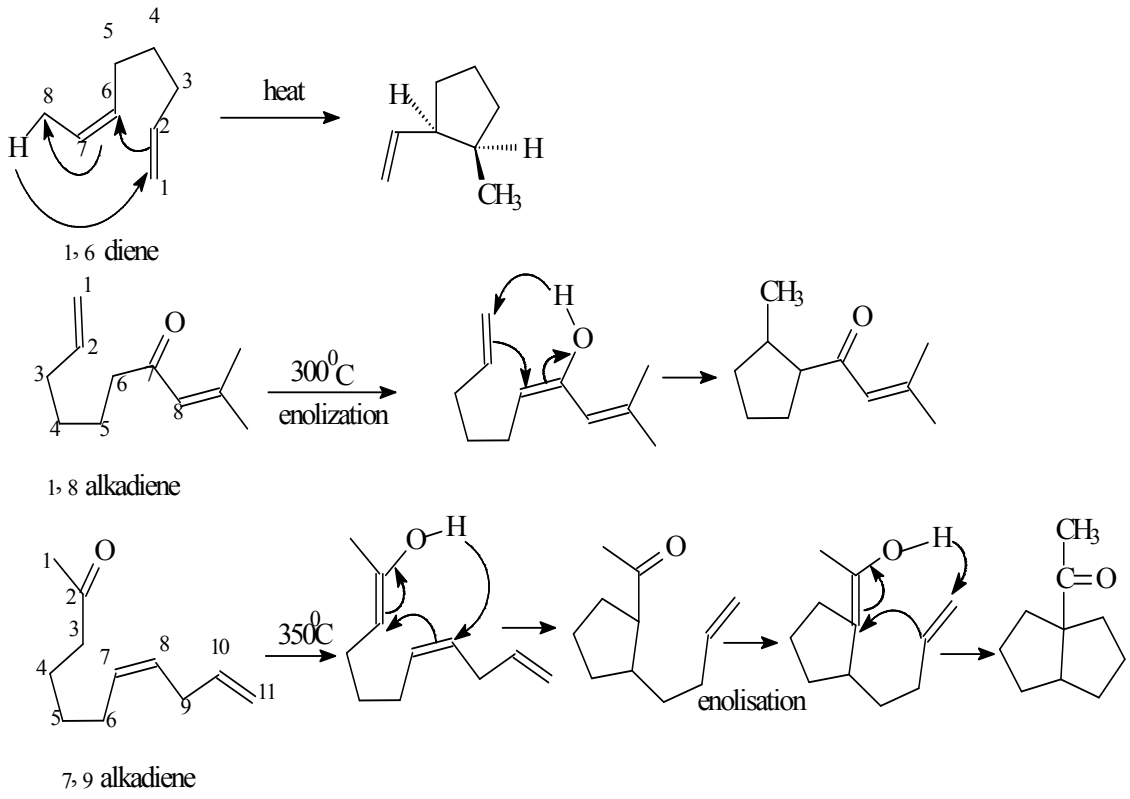
The ene reaction is reversible like Diels-Alder reaction



The enophile as also mentioned above can alo be heteroenophiles



Intramolecular ene reactions has great importance for the synthesis ofcyclic compounds particularly five membered ring compounds from 1, 6- diene and 1,8 and 7,10- dienes etc.



10.16 SUMMARY

In continuation to electrocyclic reaction in unit 9 this unit describes cycloaddition in 4n and 4n +2 systems, their explanation by using correlation diagram, FMO and PMO approach. Sigmatropic rearrangements in various systems like [1, 3], [1, 5], [1, 7], [3, 3], [5, 5] system have been described with their mechanism. Chelotropic reaction in which two σ-bonds are either formed or broken at the same atom has been narrated with mechanism. This unit also explains sigmatropic shift of alkyl group, mechanism of Cope rearrangement, Claisen rearrangement, Aza-Cope rearrangement, fluxional tautomerism with example, mechanism and applications. Ene reactions, the important class of reactions for synthesis point of view has been explained in detail.

10.17 TERMINAL QUESTIONS

Q.1 Tick the correct opetion (MCQ):-

i Which one an example of chelotropic reaction?

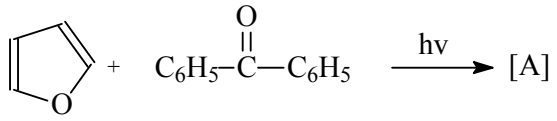
A. Alkene + carbine

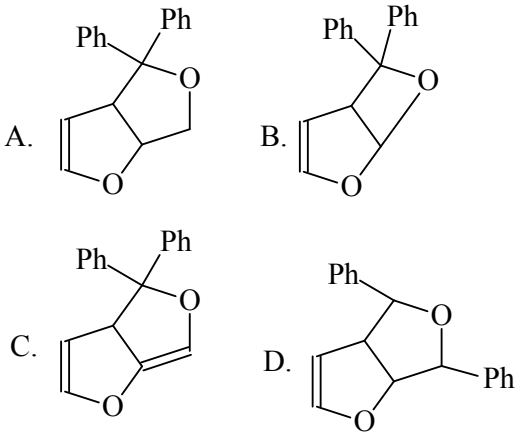
B. Alkene + phenol

C. Alkene + ketone

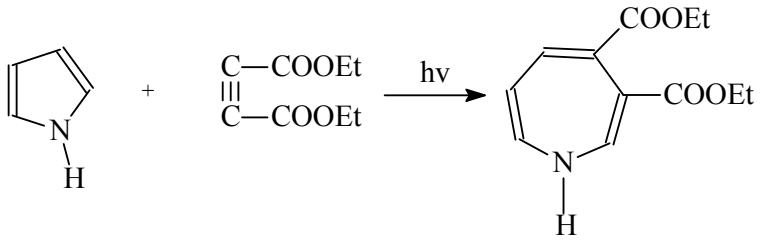
D. Ene + diene

ii What [A] in the following reaction?





iii. The process followed by following reaction is:



A. [2 + 2] cycloaddition followed by sigmatropic rearrangement

B. [2 + 2] cycloaddition followed by another [2 + 2] cycloaddition

C. [2 +2] cycloaddition followed by electrocyclic reaction

D. [2 +2] cycloaddition reaction only

iv Aza-Cope rearrangement follow

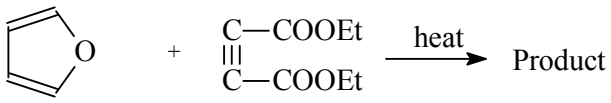
A. sigmatropic rearrangement followed by elimination

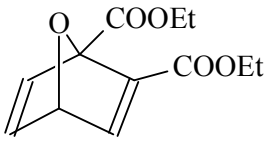
B. [5, 5] group transfer reaction

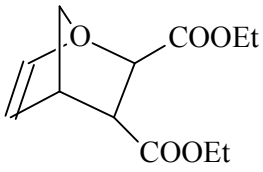
C. [1,7] sigmatropic shift

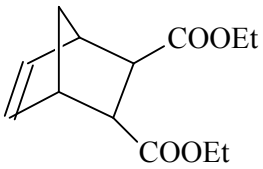
D. [3, 3] sigmatropic rearrangement

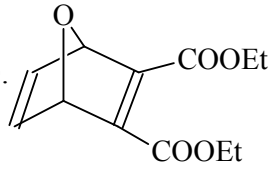
v . The chief product in the following thermal product will be ?



A. 

B. 

C. 

D. 

vi. Which condition favour the sigmatropic shift of 4n +2 system via suprafacial shift under thermal condition?

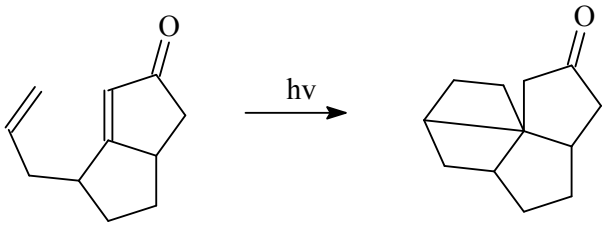
A. 4n + 2, number of electrons, with zero node and antiaromatic character

B. 4n +2, number of electrons with one node and aromatic character

C. 4n +2, number of electrons with zero node and aromatic character

D. None of them

vii The following reaction is an example of:



A. [[3, 3] shift

B. [2 + 2] cycloaddition

C. [3, 4] sigmatropic shift

D. Electrocyclic ring closing

viii. Trapping reaction of alkene with carbine gives.

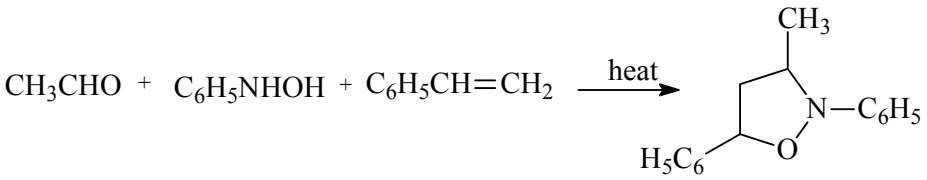
A. Chelotropic reaction

B. Sigmatropic reaction

C. 1,3-dipolar reaction

D. It is simply fluxional change

ix. The following reaction takes place through:



A. Elimination of CO_2 followed by addition of C_6H_5=CH_2 with the generated 1,3-dipole

B. Elimination of H_2O followed by addition of C_6H_5=CH_2 with the generated 1,3-dipole

C. Elimination of H_2O followed cycloaddition reaction.

D. Elimination of CO_2 chelotropic addition

x. In sigmatropic reartrangement

A. A sigma bond migrate from one place to the other place of compound containing pi-bond

B. Transfer of pi-bond

C. Formation of pi-bond and sigma bond durin cyclization

D. Addition of functional group to pi-system

Q.2. What do you understand by cycloaddition reaction ? Discuss various approaches to exaplain cycloaddition reactions

Q.3. What are chelotropic reaction? Discuss maechanism of chelotropic reaction following FMO approach

Q.4. What are dipolar reactions? Discuss their importance in organic chemistry

Q.5. Write short notes on:

1. Fluxional tautomerism

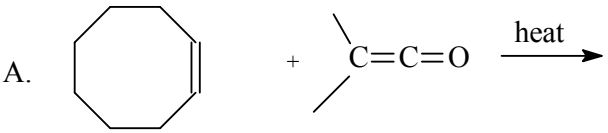
2. Ene reaction

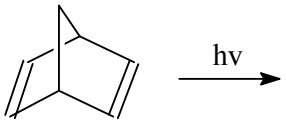
3. Aza-Cope reaction

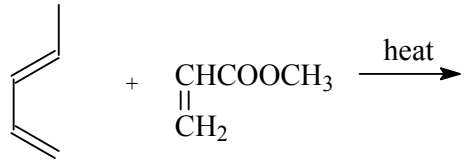
4. Claisen rearrangement

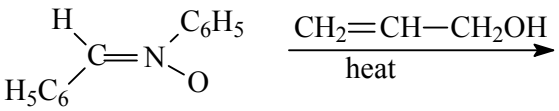
5. Cope rearrangement

Q.6. Complete the following reaction and discuss the type of reaction and mechanism.

A. 

B 

C. 

D. 

10.18. ANSWERS (MCQ) TERMINAL QUESTIONS

i A

ii B

iii C

iv D

v D

vi C

vii B

viii A

ix B

x. A

10.19. REFERENCES

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