

Organic Reaction Mechanisms

Fourth Edition

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Chemical Kinetics and Reaction Pathways

1.1 Introduction

Organic compounds can be transformed into product and the process i.e. organic reaction is represented by a stoichiometric equation. Most organic reactions belong to one of the five main classes:

- Substitution
- Addition
- Elimination
- Rearrangement
- Oxidation-reduction reactions (Redox reactions)

However a given reaction may fall in more than one category, for example, substitution with rearrangement. A detailed study of the sequence of steps which are involved in the conversion of reactants into product(s) is known as **reaction mechanism**. The reaction mechanism is a detailed knowledge of what takes place as the reactant molecule is transformed into the product(s). Organic reactions proceed by the rupture of covalent bonds and formation of new bonds. The bonds are broken in one of the two ways: by homolytic or heterolytic bond fission.

1.1.1 Homolytic bond fission

In homolytic bond fission, the covalent bond is broken symmetrically so that one electron of the bonding pair remains with each of the originally bonded atoms. Consider a molecule X-Y where two electrons are shared between atoms X and Y.



If the chemical bond between X-Y is broken symmetrically each atom gets one electron. Homolytic bond fission results in neutral, highly reactive free radicals and is exemplified by the fission of Br-Br bond when bromine gas is subjected to sunlight.



The shift of a single electron is represented by a fish hook arrow.

2 Organic Reaction Mechanisms

1.1.2 Heterolytic bond fission

In heterolytic bond fission, the covalent bond is broken in such a way that the shared electron pair remains attached with only one of the two originally bonded atoms. Heterolytic bond fission results in ions (negative and positive) and when X-Y are two different atoms, the cleavage of bond may occur in either of two ways as shown below.



For example, hydrolysis of t-butyl chloride to tertiary butyl alcohol involves heterolytic cleavage of C-Cl covalent bond. In this case the electron pair remains with departing Cl, which is called leaving group and tertiary butyl group carries positive charge.

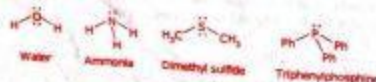


A full arrowhead denotes the shift of an electron pair. It must be stated that most of the organic reactions with which we will be concerned are heterolytic reactions. Free radical reactions are less numerous but still play an important role particularly in the gas phase and in non-polar solvents. Thus, when bonds are broken, either ions or free radicals are produced. Therefore, we can classify all reaction mechanisms into two classes, viz., ionic reactions and free radical reactions.

The new bond is formed by reversal of the homolysis and heterolysis processes e.g., radical combination, combination of a carbocation with a nucleophile and combination of a carbanion with an electrophile.

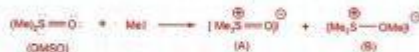
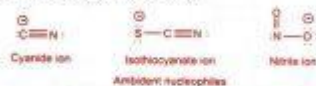
1.1.3 Nucleophiles and electrophiles

Nucleophiles (nucleus-loving) are electron donor species. They may be neutral having nonbonding lone pair(s) of electrons such as water, ammonia, alcohols, dimethylsulfoxide and triphenylphosphine or negatively charged species (anions) such as hydroxide, halide, alkoxide ions etc. Nucleophilic reagents tend to attack the electron deficient species (electrophiles).





The nucleophiles which have more than one (generally two) suitable atoms through which they can attack the substrate are known as **ambident nucleophiles**. Cyanide, isothiocyanate and nitrite ions are some examples of ambident nucleophiles, since they have more than one reactive site. DMSO is also an ambident nucleophile owing to the presence of O and S with unshared pairs of electrons. For example methylation of DMSO with MeI gives two isomers, (A) and (B), from S-methylation and from O-methylation, respectively. Since S is a better nucleophilic site (because O is much more electronegative than S), (A) is the major isomer.



For a given atom its nucleophilicity increases with increase in electron density, therefore a nucleophile with a negative charge is stronger than its conjugate acid. For instance alkoxide and hydroxide ions are more nucleophilic than their corresponding conjugate acids i.e., alcohol and water. Within a period of the periodic table, nucleophilicity (parallels basicity) decreases with increasing atomic number of the atom having negative charge.



The nucleophilicity is also related to basic strength when the nucleophilic atom is the same.

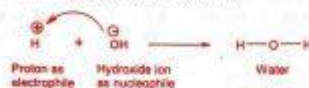


Within a group, in contrast, nucleophilicity increases with increasing atomic number (but basicity decreases as atomic number increases). The solvation of anions helps to stabilize them and results in lowering of their nucleophilicity. Polarizability of a nucleophile is related to the ease with which its valence electrons interact with a nearby electrophile. In general, large atoms or ions are more polarizable than small ones. Thus, nucleophiles having large attacking atom, weakly solvated and having high polarizability are better nucleophiles. For example, iodide ion being large, highly polarizable and weakly solvated, is a very strong nucleophile as compared to the small, less polarizable, and strongly solvated fluoride ion. The nucleophilicity varies in the order:



In general, nucleophilicity of a reagent might perhaps be related to basicity, but this is not always true. It has been shown that methyl mercaptide (MeS^-) is more nucleophilic than methoxide (MeO^-), although the former is a weaker base than the latter.

Electrophiles (electron-loving) are electron-deficient species and tend to attack the substrate at a site of high electron density. Electrophilic reagents are characterized by an atom with an incomplete outer electron shell and therefore, are very reactive. They may be neutral species as exemplified by Lewis acids (such as BF_3 , $AlCl_3$, $ZnCl_2$) and carbenes ($Cl_2C:$) or positively charged species as exemplified by proton (H^+), cations (such as Cl^+ , NR_4^+) and carbocations. They have six valence electrons (except H^+) and can accept an electron pair from a nucleophile to acquire the stable octet. For example, hydroxide ion combines with a proton to give water.



1.1.4 Leaving group

The leaving group is the functional group that is eliminated with electrons of the σ bond in a reaction. The nature of the leaving group is important to both the S_N1 and S_N2 reactions. Better the leaving group, faster is the reaction. The relative leaving ability of leaving group, Y, in R-Y is influenced by: (i) the strength of the R-Y bond; (ii) the polarizability of R-Y bond; (iii) the stability of Y^- and (iv) the degree of stabilization, through solvation of Y^- .

In general good leaving groups are large, of low electronegativity and of low nucleophilicity. A good leaving group should have a very weak and highly polarized R-Y bond. The substitution of halogens by different functional groups occurs easily because the halides are good leaving groups. Among halides iodide is a better leaving group than bromide and bromide is a better leaving group than chloride. Thus, the order of leaving group ability for halides is:

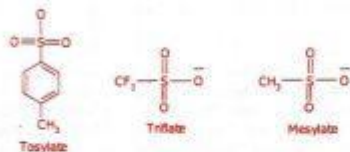


The iodide ion (I^-) is larger in size, thus has high polarizability, and is better solvated by the solvent, therefore, it is better leaving group than fluoride ion. The stability of halide ions can be measured by using the pKa values of the corresponding acids (HX). The strength of C-X bonds can also be related to pKa values (Table 1.1).

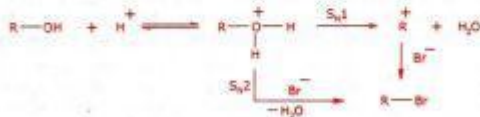
Table 1.1		
Halogen (X)	Strength of C-X bond (kJ mol ⁻¹)	pKa of HX
Fluorine	118	+3
Chlorine	81	-7
Bromine	67	-9
Iodine	54	-1

It is clear from table 1.1 that C-I bond is easiest to break and C-F bond is the most difficult to break. It is also clear from pKa values that the I^- is more stable than F^- . Therefore, iodide is an excellent leaving group and fluoride a very bad one with other halides in between.

The conjugate bases of strong oxygen acids such as tosylate (*p*-toluenesulfonate, $MeC_6H_4SO_3^-$), triflate (trifluoromethanesulfonate, $CF_3SO_3^-$), and mesylate (methanesulfonate, MsO^-) anions are good leaving groups because of the relative weakness of the C-O (sulfonate) bond, and the resonance stabilization of the departed ion.



The HO^- , RO^- and NH_2^- are strong bases and therefore are bad leaving groups. However, through protonation the strong bases can be converted into very weak bases which are much better leaving groups. For example, $-OH$ group cannot be directly displaced by $-Br$ group but this displacement can be accomplished if it is protonated first. Protonation of alcohols with strong acids converts the poor leaving group, hydroxyl group, into much better leaving group. Water is a weak conjugate base of strong acid, hydronium ion, therefore, it is easily displaced by a good nucleophile.



Another way to convert the hydroxyl group into a good leaving group is by reaction of alcohols with *p*-toluenesulfonyl chloride (tosyl chloride, abbreviated as $TsCl$) in pyridine. In this reaction, the hydroxyl group (poor leaving group) is converted into a good leaving group, the tosylate. The good leaving group is then displaced through an S_N2 reaction with a nucleophile. For example, pentanenitrile can be prepared from 1-butanol via formation of the tosylate.



Organic Reaction Mechanisms

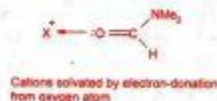


With strong bases, such as *t*-BuOK, DBU (1,8-diazabicyclo[5.4.0]undec-7-ene) or NaOEt, tosylate esters undergo elimination reactions.

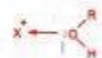


1.1.5 Solvent

The role of solvent is to separate and solvate the ions involved in the reaction. The solvent molecules tend to orient themselves in such a way so as to decrease the electrostatic forces between the ions. The ability of a solvent to separate ions is determined by its dielectric constant. The second solvent effect is solvation, in which both cations and anions are stabilized by surrounding weakly bonded solvent molecules. Water is probably the most commonly used solvent. Polar molecules which can dissolve in water are termed hydrophilic (water-loving) while nonpolar molecules are termed hydrophobic (water-hating). The solvents may be divided into two classes: (a) aprotic solvents and (b) protic solvents. The aprotic solvents, such as DMSO (dimethyl sulfoxide), DMF (dimethyl formamide), CS_2 , CCl_4 etc., do not possess an acidic proton whereas the protic solvents, such as water, carboxylic acids and alcohols, possess an acidic proton. The protic polar solvents (hydroxylic solvents) solvate both cations and anions and are able to form hydrogen bonds. Aprotic polar solvents (such as DMSO and DMF) are the solvents with a high dipole moment, but lack the ability to form hydrogen bonds. These solvents are still able to solvate cations by donating electrons from oxygen atom.



Solvation of cations by polar aprotic solvents



Cations solvated by electron-donation from oxygen atom

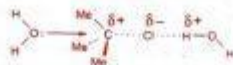


Anions solvated through hydrogen bonding

Solvation of cations and anions by hydroxylic solvent

The rate of reaction is dependent on the nature of the solvent. Let us consider the solvolysis reaction of *t*-butyl chloride to *t*-butyl alcohol. The rate-determining step in this reaction is the formation of *t*-butyl cation. At the transition state, the C-Cl bond is partially broken and the shared pair of electrons has been considerably displaced towards Cl.

So that there is a separation of unlike charges in passage from reactant to transition state. This process will be facilitated by a polar solvent because transition state is more polar than the reactant and so is stabilized by the polar solvent. Hence, rate of reaction increases with increase in the dielectric constant of the protic polar solvent used.



1.2 Chemical kinetics, equilibria and energetics of reactions

1.2.1 Rates of reactions (Chemical kinetics)

Most chemical reactions proceed by a series of steps, rather than one single step. In reactions that proceed by a mechanism of more than one step, the slowest step is the rate-determining step. Once it is completed the subsequent steps occur at a faster rate than the slowest step. Thus, the slow step in any reaction sequence determines the overall rate of the reaction.

The rate of most organic reactions either depend only on the concentration of a single reactant (for example, S_N1 or $E1$), called first order reaction or upon the concentrations of two species (S_N2 or $E2$), called second order reactions. The hydrolysis of *t*-butyl chloride follows first order kinetics and the rate of reaction, at temperature T , is expressed by equation given below:

$$\text{Rate of reaction} = k[\text{tert-BuCl}] \quad \text{where } k \text{ is rate constant}$$

The reaction of ethyl bromide with sodium hydroxide follows second order kinetics and the rate of reaction is expressed as follows:

$$\text{Rate of reaction} = k[\text{EtBr}][\text{NaOH}]$$

There are some reactions called pseudo first-order reactions. For example, the S_N2 solvolysis reaction of CH_3I with ammonia. Here solvent is present in excess, therefore the concentration of the nucleophile does not change during the reaction.

The rate of reaction not only depends upon the concentration of the reactants but also on the temperature. It is common for the rates of organic reactions to double with every 10 to 15°C rise in temperature. In addition, many reactions are influenced by the presence of catalyst.

1.2.2 Transition state and activation energy

Before the reaction can occur, the molecules must come in contact with each other, that is to say, they must collide. However, reaction occurs only if the collision of reactant molecules is accompanied by a minimum amount of energy, called the **activation energy**. Moreover, such a collision must occur with the proper orientation of reactant molecules with respect to each other. The particular arrangement of reactant molecules at the peak of the energy mountain is called the **transition state**. Nearly all reactions must pass through an unstable high-energy transition state in proceeding from reactants to products. Consider the reaction of HCl and a water molecule in an inert solvent.

Somewhere between the reactants and products there must come a point where the H-Cl bond is not yet completely broken and H-O bond is not yet completely formed. This is the least stable structure in the whole reaction sequence and is known as transition state. A transition state cannot be isolated and represents an energy maximum on passing from reactants to products. In an energy profile diagram, the highest point on the profile is labeled transition state. The activation energy is the energy necessary to get reactants to the transition state. Thus, the activation energy is the height of the transition state, above the reactants in an energy profile diagram. Activation energy ($\Delta G^\ddagger$) is shown for the above reaction in diagram that plots energy versus reaction progress (Fig. 1.1).

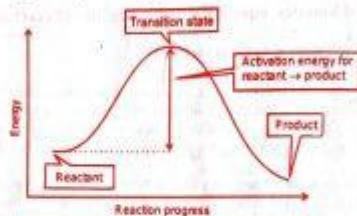


Fig. 1.1 : A typical Energy versus reaction progress diagram

The rate of reaction is a function of the activation energy which represents the energy necessary to get reactants to the transition state. Let us consider the displacement reaction (S_N2) of methyl iodide with CN^- . The activation energy is $\Delta G^\ddagger$, which must be supplied to start the reaction (Fig. 1.2).

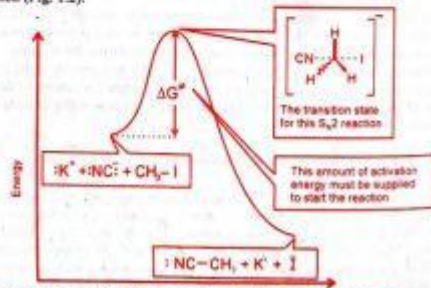


Fig. 1.2 : An energy diagram for the S_N2 displacement of iodide by cyanide (and its reverse reaction). The much less favorable displacement of the strong nucleophile (cyanide) by iodide. The activation energy for the displacement of iodide by cyanide is shown.

Consider the backward reaction, in which methyl iodide is formed from methyl cyanide and iodide ion. The transition state is exactly the same as that for the forward reaction. However activation energy is much higher than that for the forward reaction (Fig. 1.3).

$$\Delta G^\ddagger (\text{forward}) < \Delta G^\ddagger (\text{backward})$$

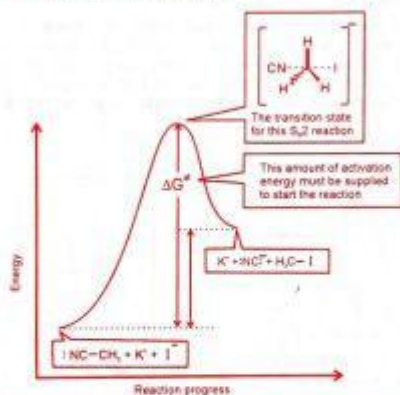


Fig. 1.3 : This energy diagram for the same reaction emphasizes the reversal. Here the activation energy for displacement of cyanide by iodide is shown.

Therefore, the backward reaction will not be very successful. Thus, the change in free energy $\Delta G^\ddagger$ required to form transition states from reactant molecules is a direct measure of the ease of the reaction.

1.2.3 Equilibrium constant and free energy difference between reactants and products

The equilibrium constant K is related to the free energy difference between reactants and products.

$$\Delta G^\circ = -RT \ln K$$

Where, ΔG° is called Gibbs free energy of the reaction

T is the absolute temperature

R is the gas constant

This equation indicates the equilibrium composition. For instance, if the difference in energy between reactants and products is so great that at equilibrium all we have are the products, the reaction therefore is irreversible. Thus ΔG° tells us about the position of equilibrium. If ΔG° for a reaction is negative, the products will be favored at equilibrium.

1.2.4 Exothermic and endothermic reactions

In exothermic reaction the products are more stable than reactants, and in endothermic reaction, the products are less stable than the reactants. For the exothermic reaction the difference in enthalpy (ΔH°) between products and reactants is negative, and the equilibrium constant (K) is generally greater than 1 (Fig.1.4). Whereas, for an endothermic reaction the enthalpy difference (ΔH°) is positive and K is less than 1 (Fig.1.5).

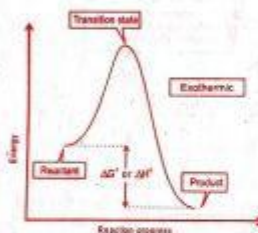


Fig. 1.4 : An exothermic reaction in which products are more stable than starting materials. In such a case, ΔH° is negative and the equilibrium constant K is greater than 1.

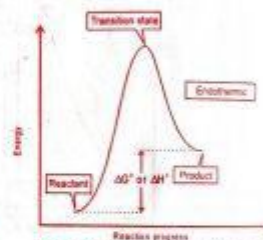


Fig. 1.5 : An endothermic reaction. The products are less stable than the starting materials. In this case, ΔH° is positive and K is less than 1.

1.2.5 Temperature and equilibrium constants

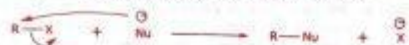
The equilibrium constant varies with the temperature. How the equilibrium constant varies with temperature depends on whether the reaction is exothermic or endothermic. If the reaction is exothermic then at higher temperatures the equilibrium constant will be smaller. For an endothermic reaction, the equilibrium constant increases with the increase in temperature, which in turn means that more products must be formed at higher temperatures.

Plot of $\ln K$ against $1/T$ would give a straight line with slope $-\Delta H^\circ/RT$. Since, T is always positive (in Kelvin), thus whether the slope is positive or negative depends on the sign of ΔH° .

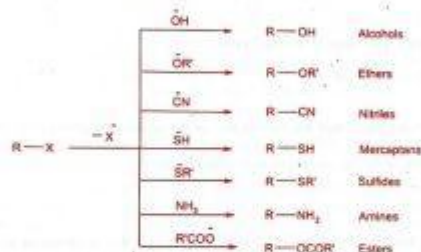
1.3 Nucleophilic substitution at saturated carbon atom

The replacement of one group by another is called substitution reaction. There are three main types of these reactions: radical, electrophilic and nucleophilic substitution. In this section we will deal with nucleophilic substitution at saturated carbon atom.

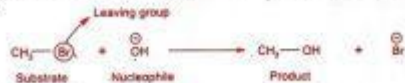
Attack of a nucleophile at a saturated carbon atom bearing a substituent, known as leaving group, results in substitution reaction. The group that is displaced (leaving group) carries its bonding electrons. The new bond is formed between nucleophile and the carbon using the electrons supplied by the nucleophilic reagent.



This is exemplified by the displacement of halogen atom with a hydroxide ion in the conversion of alkyl halide into an alcohol. Alkyl halides undergo substitution reactions with a variety of different nucleophilic reagents and are extremely important synthetically, as can be seen by the wide variety of compounds which can be prepared by its applications. The halogen is lost as a halide ion.



The compound on which substitution takes place is called the **substrate** and the group that becomes displaced from carbon, taking the electron pair with it, is called **leaving group**. The leaving group often leaves as an anion but may also be a neutral molecule. The substrate consists of two parts, alkyl group and leaving group. For example, reaction of methyl bromide with sodium hydroxide affords methanol and sodium bromide. In this reaction methyl bromide is substrate, bromide is leaving group and hydroxide ion is the nucleophile.



Nucleophilic substitution reactions have been studied extensively from a mechanistic viewpoint. Many factors influence the course of nucleophilic substitution reactions, including the nature of the nucleophile, its strength and concentration, the solvent, the nature of substrate, and the nature of leaving group. Substitution reactions at saturated carbon can be mechanistically categorized as unimolecular (S_N1) or bimolecular (S_N2).

12 Organic Reaction Mechanisms

1.3.1 S_N1 (Substitution Nucleophilic Unimolecular)

An S_N1 reaction proceeds in two steps. The first step (slow step) is the rate determining step and involves the ionization of the reactant to form a carbocation intermediate. The breaking of C-X bond in RX takes place in a heterolytic fashion, in which both the bonding electrons go to the leaving group. In the second step (fast step), the intermediate carbocation is attacked by the nucleophile to give the final product.

Step 1. Formation of carbocation



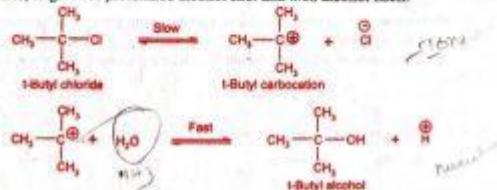
Step 2. Capture of the carbocation by the nucleophile



The S_N1 reaction shows first-order kinetics as rate of the reaction depends only on the concentration of the substrate (RX) and does not depend on the concentration of the nucleophile reacting with it. The rate expression is therefore:

$$\text{Rate} = k[RX]$$

In several reactions, nucleophile is a solvent molecule such as water, ammonia or alcohol such substitution reactions are called **solvolysis**. For example, hydrolysis of tert-butyl chloride to tert-butyl alcohol follows S_N1 process. In the first step, tert-butyl chloride ionizes to a tert-butyl carbocation, which is captured in a second step by the nucleophilic solvent, water, to give the protonated alcohol first and then alcohol itself.



An energy diagram (Fig. 1.6) for S_N1 reaction involves two transition states. The transition state for the slow step (the ionization step) is higher in energy than the transition state for the fast step (second step, the capture of the ion by a nucleophile).

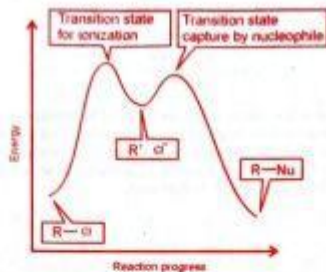
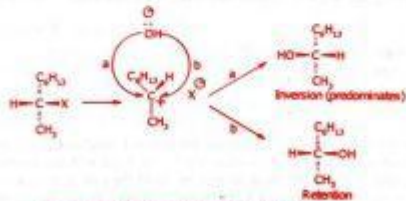


Fig. 1.6 : An energy diagram for the S_N1 reaction. Notice that the transition state for the slow step in the reaction, the ionization, is higher in energy than the transition state for the capture of the ion by a nucleophile.

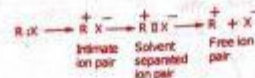
Stereochemistry of the S_N1 reaction

Ionization of optically pure alkyl halide molecule leads to the planar, achiral (symmetrical) carbocation with an empty p-orbital perpendicular to the plane. Addition of nucleophile can take place at both sides of the carbocation with equal ease owing to the symmetry of carbocation, resulting in a racemic mixture (equal amounts of R and S products). But in actual practice, depending on the nature of substrate, solvent and leaving group, there may be a preferred side for its attack by nucleophile, in which case the product will contain unequal amounts of the two enantiomers, yielding partially optically active product.

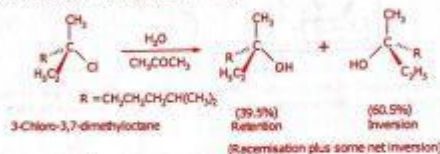


S_N1 reaction leads to racemization plus inversion

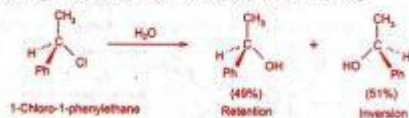
It is believed that carbocation and leaving group exist for a while as an intimate ion pair and the attack of nucleophile during this time takes place only on the back side of carbocation, but not on the front side, giving rise to inversion. Then these ions diffuse apart as solvent intervenes, and become free ions. Now attack of nucleophile on free symmetrical carbocation occurs from the back side or from the front side with equal probability.



If the carbocation is less stable, it is more likely to be attacked by nucleophile before leaving group separates from it, giving rise to inversion. Thus in this case the reaction proceeds with racemization plus some net inversion. For example, when 3-chloro-3,7-dimethyloctane is hydrolyzed in presence of acetone, there is a 21% excess of the product resulting from inversion of configuration.



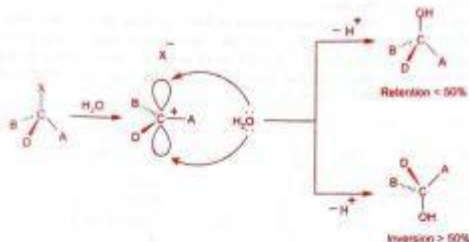
However, if the carbocation is stable enough to survive the attack of nucleophile during the ion pair stage, the observed product becomes completely racemized. For example, hydrolysis of 1-chloro-1-phenylethane occurs with extensive racemization (98%) and only 2% inversion. 1-chloro-1-phenylethane ionizes to give benzylic carbocation which is stabilized because of resonance and the ions can diffuse apart before nucleophile attacks the carbocation. Now reaction of free carbocation with nucleophile can take place from both sides of the cation to give the 51% inverted alcohol and 49% alcohol with retention of configuration (98% racemization and 2% net inversion).



Thus, we can interpret these facts to mean that the S_N1 mechanism proceeds via an intermediate carbocation that is not completely free to react with nucleophile on both sides. The leaving group is still close enough to shield the side of the carbon atom of carbocation for some time to which it was attached from nucleophilic attack. The result is usually an excess of inversion in most S_N1 reactions.

Effect of solvent

The solvent plays an important role in S_N1 reactions as the energy required to effect the initial ionization is largely recovered from the energy evolved through solvation of the resulting ion pair. The S_N1 process requires the ionization of a covalent bond which is



encouraged by solvents with high dielectric constants. There is a greater charge on the intermediate ions than that on starting substrate as majority of the substrates are neutral. Polar protic solvent (such as water or alcohol) will thus solvate and stabilize the intermediate ions more than it does the reactant. Since ions are usually formed in the rate determining step (slow step) of the reaction, therefore the S_N1 reaction will usually be favored by a polar protic solvent. Good solvents for S_N1 displacements almost always contain hydroxyl groups (as in water, alcohols, or carboxylic acids) because the electronegative oxygen atom interacts with the incipient positive charge, and the electropositive hydrogen atom (through hydrogen bonding) interacts with the incipient negative charge. Thus, in addition to dielectric constant, the ability to form hydrogen bond with X^- makes a protic solvent the better solvent than aprotic solvent which cannot form hydrogen bond. The S_N1 process occurs mainly when water is present as a solvent or as a co-solvent.

Effect of nucleophile on rate

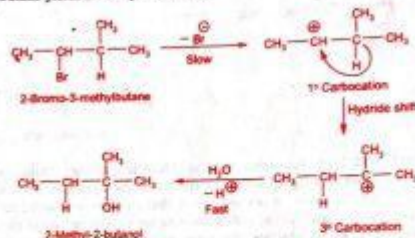
The rate of S_N1 reaction is independent of the nucleophile. A better nucleophile will not accelerate the S_N1 reaction, and yet it may determine which product is formed. For example, *t*-butyl bromide in water containing small amount of cyanide ions gives *t*-butyl cyanide. This is because the cyanide is many times more reactive towards carbocations than the water. Weak nucleophiles with low concentrations favor the S_N1 mechanism.

Effect of leaving group on rate

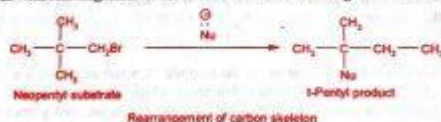
The rate of S_N1 reaction is largely influenced by the nature of the leaving group. The rate of ionization is affected by the stability of the leaving group, X^- . The more stable the leaving group, the more easily it will be lost. S_N1 reactions therefore are favored by the presence of good leaving group such as sulfonates (tosylate or mesylate). The weaker the Bronsted basicity of X^- , the better leaving group is X . In case of halides the order of basicity is: $I^- < Br^- < Cl^- < F^-$, therefore, iodide is a better leaving group than bromide and bromide is a better leaving group than chloride. Presence of acid catalysts or metal ions sometimes favor the departure of the leaving group, e.g., silver ions aid the departure of halide ion from alkyl halides.

Rearrangement in S_N1 reactions

The evidence for the formation of carbocations is that they undergo reactions other than simple addition to nucleophiles. For example, carbocations may rearrange before combining with nucleophiles. Since S_N1 mechanism involves carbocation intermediate, therefore, unexpected products are also formed. For example, hydrolysis of 2-bromo-3-methylbutane yields 2-methyl-2-butanol.



We see that in S_N1 reactions, a carbocation is formed by loss of the leaving group from the substrate. If a 1,2-shift of hydrogen can form a more stable carbocation, then such a rearrangement takes place. The rearranged carbocation can react with nucleophile to afford the substitution product or it may lose proton to yield alkene. If the intermediate carbocation can rearrange to more stable carbocation via 1,2-alkyl shift, the reaction often proceeds with rearrangement of the carbon skeleton of the organic substrate.



Effect of the nature of substrate on the rate

The rate determining step is the formation of planar carbocation in S_N1 process. Therefore, the order of reactivity among organic substrates will depend upon the stability of carbocation formed after ionization of substrate. Hence tertiary alkyl halides, which give rise to tertiary carbocations, react faster than secondary ones, which react faster than primary halides.

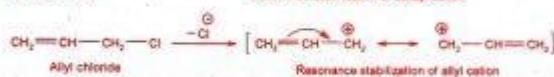
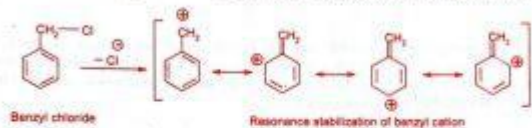
The introduction of a methyl group in place of a hydrogen atom attached to the positive carbon of a carbocation appears to stabilize the ion by 15 to 30 kcal/mol (through inductive and hyperconjugation effects). In most of the cases, the substituents which have +I and/or +M effects, stabilize the carbocations. Allylic, benzylic, and tertiary carbocations are relatively stable carbocations, therefore, allylic, benzylic and tertiary halides can react by an S_N1 mechanism.

Stability of carbocations

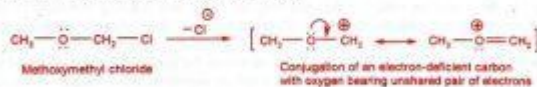


Both benzyl and allyl carbocations disperse the charge by resonance and are more stable than primary alkyl or secondary alkyl carbocations. The primary alkyl and methyl halides, which would form extremely unstable carbocations, do not generally react by the S_N1 process. The order of reactivity among organic halides is as follows:

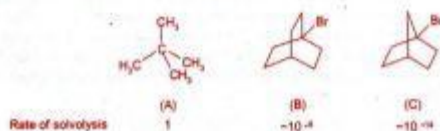
t -alkyl halides $>$ allyl halides $\sim$ benzyl halides $>$ s -alkyl halides $>$ 1° -alkyl halides.



Methoxymethyl chloride undergoes hydrolysis more than 10^4 times faster than methyl chloride. This is because, the carbocation formed after ionization of methoxymethyl chloride is resonance stabilized. The $\text{CH}_3\text{O}-$ group has unshared pairs of electrons that it tends to share, thus acquiring a positive charge.



S_N1 displacement in bridged bicyclic compounds at bridgeheads is very slow or does not take place. This is expected as a flat (planar) intermediate carbocation can not be formed at the bridgehead carbon because of the rigid framework of bicyclic systems. Greater is the rigidity about the bridgehead carbon, lower will be its reactivity. For instance, rate of solvolysis of compounds A, B and C in 80% aqueous ethanol at 25°C decreases as the rigidity about the bridgehead carbon increases ($A < B < C$).



18 Organic Reaction Mechanisms

1.3.2 S_N2 (Substitution Nucleophilic Bimolecular)

S_N2 process proceeds in one step via a transition state. The nucleophile attacks the substrate carbon simultaneously pushing out the leaving group in a concerted fashion.



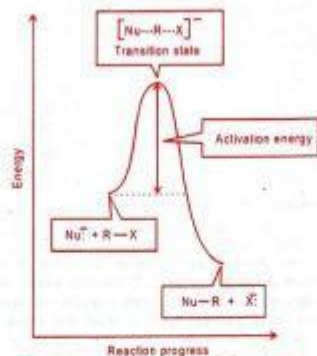
The reaction between methyl iodide and hydroxide ion is an example of the S_N2 mechanism. Kinetic evidence shows that the rate of this reaction is proportional to both the concentrations of substrate and nucleophile. Thus, S_N2 reactions follow second-order kinetics and is described by the rate expression:

$$\text{rate} = k[\text{RX}][\text{Nu}]$$

where k is rate constant and quantities in square brackets represent concentrations.

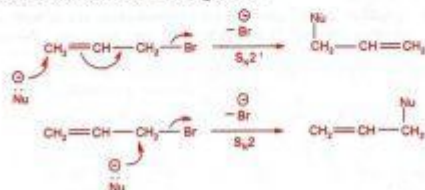
In S_N2 process there is synchronous attack by the nucleophile from the opposite side of the carbon atom of substrate bearing the leaving group, such that C-X bond of the substrate breaks only as the new C-Nu bond of the product is forming. Therefore, in transition state, the nucleophile-carbon bond is partially formed and the C-X bond is partially broken. The approach of the nucleophile from the side of the molecule bearing the leaving group is unfavorable due to electrostatic repulsion and also due to steric factors. In the transition state for this reaction, the three non reacting substituents on carbon lie in a plane with the carbon undergoing reaction. This plane is between the incoming and outgoing groups.

An energy diagram (Fig. 1.7) for S_N2 process shows the reactants being converted to products by way of one transition state, with no energy minimum representing a reactive intermediate. The reactants and products are separated by the high energy point of the reaction, the transition state. The energy difference between the reactants and transition state is called the **activation energy** and is related to the rate of reaction. Higher the activation energy, slower the reaction. The reactants and products are not at the same energy level therefore, the forward reaction is exothermic reaction, as read from left to right and backward reaction is endothermic, as read from right to left.

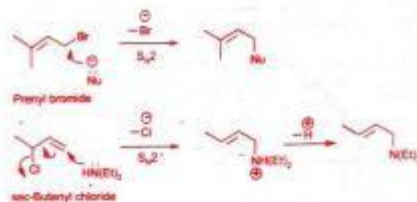
Fig. 1.7 : An energy diagram for the S_N2 reaction.

Rearrangement

Since no free carbocation is generated, therefore, S_N2 displacements afford unrearranged products. However, some times S_N2 reaction, leads to allylic rearrangement. The attack of nucleophile takes place at the end of the π -system i.e. on C-3 of the allylic system, with simultaneous expulsion of a leaving group. Such reactions are referred to as S_N2' , to distinguish them from the normal S_N2 process.



S_N2' mechanism leads to the same product as S_N2 , however, if the allylic halide is unsymmetrically substituted, we can tell which mechanism operates and the product formed will be from the nucleophilic attack at the less hindered end of the allylic system. Prenyl bromide, for example, reacts entirely via S_N2' process. If we react the secondary butenyl chloride with an amine we get the product from S_N2' mechanism. Simple alkyl copper reagent complexed with BF_3 generally favours the S_N2' reaction.



Stereochemistry of reaction

Most of the S_N2 reactions proceed with complete inversion of configuration of the substrate. The observation of inversion in S_N2 reaction means that the nucleophile (incoming group) must be approaching the substrate from the side opposite (back-side) to the group being displaced (leaving group). Such an attack will flip the other three groups from one side of the carbon atom to the other. This process is known as **Walden inversion** and produces a product of the opposite configuration.



For example, when optically active substrate, (-)-2-bromooctane reacts with sodium hydroxide under conditions where S_N2 mechanism are followed, inversion of configuration is observed.



Effect of the nature of substrate on rate

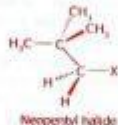
The steric hindrance around the carbon site makes a huge difference in the rate of the S_N2 reaction. The central carbon atom in reactant and product is tetrahedral, whereas carbon in the transition state is bonded to five atoms or groups therefore, there will be an increase in crowding on going from the starting substrate to the transition state. A transition state with five groups crowded around the central carbon atom is a high-energy

transition state. The more crowded the transition state relative to substrate, the higher its energy will be, and the slower it will be formed. As hydrogen atoms are replaced by the larger methyl groups, there is increased crowding about the carbon. Therefore, the methyl compounds react faster than primary substrates and primary substrates react faster than the secondary substrates. Tertiary substrates have three bulky alkyl groups attached to reaction center which hinder the approach of the entering nucleophile. Thus, tertiary alkyl halides such as *t*-butyl bromide normally do not undergo substitution via this mechanism. The reactivity of substrates in S_N2 reactions is:



This order is the reverse of that in S_N1 reactions.

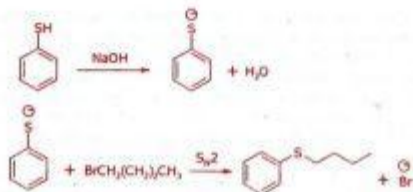
Even though the site of reaction in neopentyl derivatives is primary, the *t*-butyl group is large enough to slow down the bimolecular (S_N2) displacement.



In allyl and benzyl halides, the π -bond assists in expelling the leaving group, and both halides react faster than the alkyl halides.

Effect of the nucleophile

The rate of S_N2 reaction is strongly dependent on the nature of nucleophilic reagent used, it increases with the nucleophilic strength of the incoming nucleophile. Thus, with the change of nucleophile a shift in mechanistic type may occur, for example, the mechanism which is S_N1 with water may become S_N2 with hydroxide ion. Sulfur nucleophiles are better than oxygen nucleophiles in S_N2 reactions. For example, thiolate anions (excellent nucleophiles in S_N2 reactions) react with alkyl halides to give good yield of the sulfide as illustrated by the following reaction.



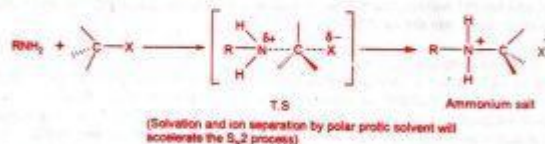
Effect of the leaving group

Weak base of strong acid is best leaving group, thus, the rate of S_N2 reaction (same as for S_N1) is higher if the leaving group is a stable ion and a weak base. In case of alkyl halides the order of reactivity is:



Effect of solvent

Normally, S_N2 process involving reaction of anionic nucleophiles with the alkyl halides is suppressed in the presence of polar protic solvent (such as water), since a polar protic solvent will interact (through hydrogen bonding) more favorably with anionic nucleophiles than with the transition state. Therefore, polar protic solvents slow down the reaction, and polar aprotic solvents are preferred for S_N2 reactions. Polar protic solvents can solvate ionic reagents (both the cations and anions), as a result, the anion is "caged" by the solvent molecules. This stabilizes the anion, and makes it less reactive. Thus, S_N2 mechanism becomes less important. However, polar aprotic solvents are not able to form hydrogen bonding with anionic nucleophiles, as a result, nucleophiles are "naked" and more reactive. However, if both substrate and nucleophile are neutral but the product is charged, as in the substitution by amines or phosphines on an alkyl halide, the polar protic solvent will solvate and separate the developing charge in the transition state, ultimately accelerating the S_N2 process.



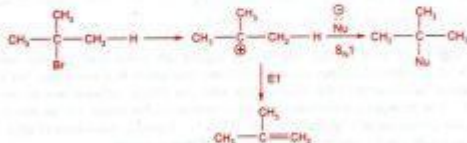
1.3.3 Competition between S_N1 and S_N2

The structure of substrate, the nature of the nucleophilic reagent, polarity of solvent, and other experimental conditions determine whether nucleophilic substitution will take place by S_N1 or by S_N2 mechanism. In general, primary halides undergo substitution by S_N2 mechanism and tertiary halides undergo substitution by S_N1 mechanism. Secondary halides may undergo substitution by both S_N1 and S_N2 mechanisms, however, one mechanism may be maximized by the selection of appropriate conditions. High concentration of the nucleophile and/or presence of strong nucleophile favors S_N2 , while the factors promoting the S_N1 are, lower concentration of nucleophile or the absence of strong nucleophile, solvents of great ionizing power (such as water) and substrate leading to stable carbocations. The reaction rates of both the S_N1 and S_N2 reactions are increased if the leaving group is a stable ion and a weak base.

1.3.4 Competition between substitution reaction and elimination reaction

Besides undergoing substitution reaction, another common reaction of substrate is an elimination reaction where nucleophile acts as a base to remove HX instead of adding to the substrate. Elimination can therefore, compete with substitution. Many factors influence the extent of this competition, including the nature of nucleophile, its strength, the solvent and the substrate. The strong bulky Brønsted bases favor E2 and strong nucleophiles favor S_N2 process. For instance, bulky *tert*-butoxide anion (Me₃CO⁻) can abstract a proton from the periphery of the molecule but is hindered as a nucleophile. However, some anions such as thiol anion (RS⁻) are less basic and more strongly nucleophilic. The E2 : S_N2 ratio increases with increased substitution by alkyl groups. Primary alkyl halides will usually undergo S_N2 substitution reaction in preference to E2 elimination reaction. As base strength increases, the rate of competitive elimination will increase, but substitution reactions compete when the base is also a good nucleophile. Polar aprotic solvents are used to maximize the yield of S_N2 products and suppress side reactions such as elimination.

The E1 and S_N1 involve the formation of the same intermediate, carbocation, by the same rate-controlling ionization step. However, the course of the reaction can often be controlled by specific reaction conditions. A high concentration of nonbasic nucleophiles in aqueous media favors the unimolecular substitution (S_N1), whereas unimolecular elimination (E1) processes are favored with bases of weak to moderate strength that are also poor nucleophiles (see sec. 1.5.2). In general, unimolecular substitution is faster than unimolecular elimination, since the cationic carbon is more strongly attracted to the electron-rich center.

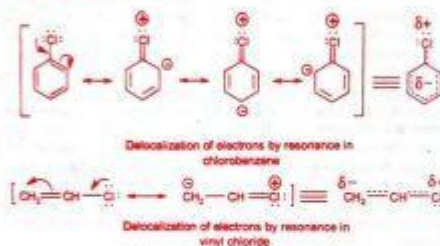


1.3.5 Low reactivity of vinyl and aryl halides

Halogen attached to a doubly bonded carbon or on aromatic nucleus is usually quite unreactive. The aryl halides show extremely low reactivity towards nucleophilic substitution reactions. They usually do not undergo nucleophilic substitution reactions unless electron-withdrawing groups are located *ortho* or *para* to the halogen on the aromatic ring. Similarly, vinyl halides are very much unreactive toward nucleophilic substitution reactions than their saturated counterparts.

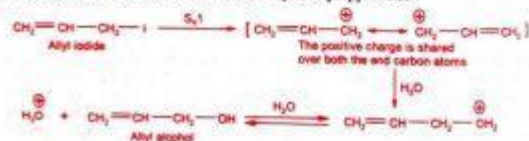
The low reactivity of alkyl and vinyl halides is because of the fact that they contain shorter and stronger carbon-halogen bond. For example, in chlorobenzene and vinyl chloride the C-Cl bond length is 1.69 Å, as compared with a bond length of 1.77-1.80 Å in a large number of alkyl chlorides. This is attributed to the sp² hybridization of the carbon atom holding halogen. Since, carbon atom having sp² hybridization is more

electronegative than sp³ hybridized carbon atom, therefore, the carbocation intermediates formed by the ionization of aryl and vinyl halides are thermodynamically less stable than alkyl carbocations. This prevents the S_N1 mechanism from operating in aryl and vinyl halides. The other reason for this unreactivity is that the π-orbital of the double bond overlaps with the p-orbitals of the halogen atom to form delocalized cloud of the π-electrons with the result that C-X bond attains a partial double bond character. The partial double bond character of the C-X bond results in strengthening of the bond and hence it is difficult to break as compared to single bond. Both of these effects inhibit nucleophilic substitution reactions of either the S_N1 or S_N2 type, thus net reactivity of the molecule is considerably less than that of saturated alkyl halides.



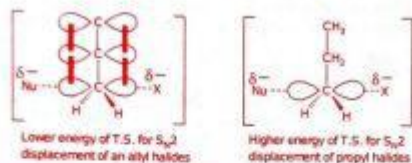
1.3.6 High reactivity of allyl and benzyl halides

On the other hand, allyl halides and benzyl halides are more reactive than saturated halides. Allyl and benzyl halides are especially reactive under S_N1 conditions because of the resonance stabilization of the intermediate allyl and benzyl carbocations, respectively (sec. 1.3.1). The resonance stabilization of intermediate carbocations has an acceleration effect on the ionization of allyl and benzyl halides. For example, solvolysis of allyl iodide in water proceeds much faster than the solvolysis of propyl iodide.



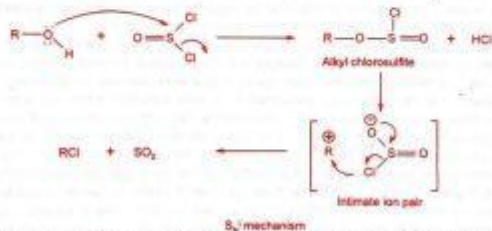
Allyl and benzyl halides not only react faster than simple halides in S_N1 reaction, but they react much faster than simple halides in S_N2 reaction as well. Allyl bromide, for example, is about 100 times more reactive towards simple S_N2 reactions than is propyl bromide. The double bond stabilizes the S_N2 transition state by conjugation with p orbital

at the carbon atom under attack. Any stabilization of the transition state will, of course, accelerate the reaction by lowering the energy barrier.

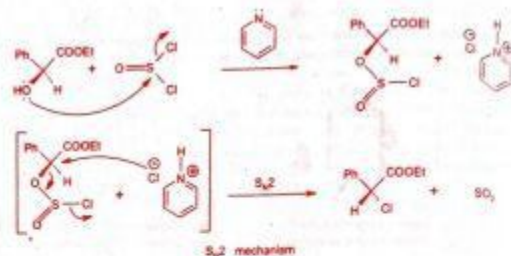


1.3.7 S_N1 (Substitution Nucleophilic internal)

In this process part of leaving group which attacks the substrate detaches itself from the rest of the leaving group. This is exemplified by the conversion of (R)-2-butanol to (R)-2-chlorobutane with SOCl_2 in nonpolar solvent and absence of base. The product formed is with complete retention of configuration, i.e., in which the starting material and product have the same configuration. The mechanism appears to involve the formation of intermediate chlorosulfite ester, ROSOCl (R = sec-butyl group), which dissociates into an intimate ion pair, $\text{R}^+ \text{ } ^-\text{OSOCl}$ as in S_N1 mechanism. The Cl^- with pair of electrons, of the anion attacks the R^+ from the same side of the carbocation from which $^-\text{OSOCl}$ departed and the product (RCl) is formed with complete retention of configuration.



It is interesting to note that if a tertiary amine such as pyridine is added to the reaction mixture, the product RCl is found now to have undergone inversion of configuration. The pyridine co-ordinates with the HCl produced during the formation of intermediate chlorosulfite from ROH and SOCl_2 , to form pyridine hydrochloride and the Cl^- is an effective nucleophile. The displacement of the chlorosulfite ester by Cl^- via S_N2 mechanism gives product with complete inversion of configuration. The reaction of alcohols with thionyl chloride in presence of pyridine is known as **Darzen's procedure**.



1.3.8 Neighbouring group participation in displacement reactions

If a second functional group is present in the substrate molecule, in many cases, there is substantial evidence for internal participation of this group in the displacement processes, known as **neighbouring group participation**. Substitution reactions that involve the neighbouring group participation are thousand times faster than the comparable intermolecular reactions because of the proximity of the reactive centers. For example, hydrolysis of $\text{PhSCH}_2\text{CH}_2\text{Cl}$ occurs 600 times faster than $\text{CH}_3\text{CH}_2\text{CH}_2\text{Cl}$ and reaction of $\text{PhSCH}_2\text{CH}_2\text{OTs}$ with CF_3COOH occurs 3000 times faster than $\text{CH}_3\text{CH}_2\text{OTs}$. Nearby groups can evidently increase the rate of substitution reaction significantly. The resulting increase in rate over what would otherwise be expected is termed **anchimeric assistance** (Greek *anchi* means neighbouring, *mer* means part).

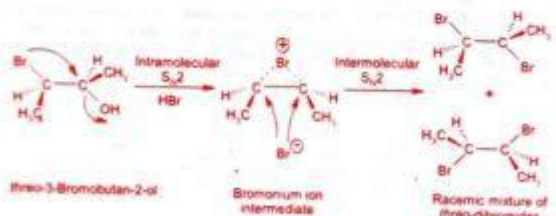
Almost any nucleophilic group with a pair of electrons and which is suitably located in a substrate molecule can provide assistance in displacement reaction. Ethers, sulfides, carboxylates, amines, esters etc. can assist substitution through neighbouring group participation. For steric reasons, participation is only effective when the interaction involves three or five-membered cyclic intermediate, less often six-membered ones. For the neighbouring group participation to be operative the neighbouring group must be suitably placed stereochemically also with respect to the leaving group; this is the *trans* configuration (*anti* stereochemistry). For example, it has been observed that acetolysis of *trans*-2-halogeno-cyclohexylbromosulfates proceeds faster than the *cis*-isomer. Neighbouring group participation requires the participant group and leaving group to be *anti*-coplanar. This geometry prevails only in *trans*-stereoisomers. Therefore, the *trans*-form permits ready attack at the rear of the bromosulfate group by halogen, but this is not so for the *cis*-form, which can react only by the slower S_N2 pathway. Thus *trans*-isomer reacts faster than the *cis*-isomer.

Heteroatoms such as O, N, S or X with pair of electrons or a double bond can attack the carbon undergoing substitution from back side, pushing out the departing group to give a cyclic intermediate. This in turn undergoes a nucleophilic attack by the external nucleophile to give the product with **retention of configuration**. Retention of configuration results because both the formation and opening of the cyclic intermediate

involves an S_N2 attack on carbon with inversion of configuration. Since two such attacks are involved, the net result is overall retention. Thus, the neighbouring group assisted displacement processes consist essentially of two S_N2 substitutions. In the first step the neighbouring group acting as an internal nucleophile pushes out the leaving group and forms a cyclic intermediate. In the subsequent step the external nucleophile displaces the neighbouring group by a backside attack. The neighbouring group goes back to its original position.

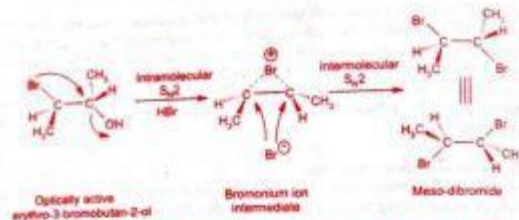
A. Halogens as neighbouring groups

Conversion of the diastereoisomeric 3-bromo-2-butanol to isomeric 2,3-dibromobutane is an example of neighbouring bromine participation in substitution reaction. The optically active *threo*-diastereomer when treated with hydrogen bromide gives an equimolar mixture of *R,R* and *S,S* enantiomers (racemic mixture). After the hydroxyl group is protonated, it is displaced by the bromine atom in an intramolecular S_N2 process and not by the external bromide ion. The displacement of OH_2^+ by bromine atom takes place from the rear to give three membered cyclic intermediate, bromonium ion. Opening of intermediate three-membered ring by external bromide ion occurs at two sites from front side leading to the mixture of racemic products.



Bromine atom is acting as neighbouring group and the result is bromonium ion.
Opening of bromonium ion by bromide ion gives a pair of enantiomers.

The *erythro* diastereomer (optically active), also reacts with retention of configuration, giving an optically inactive *meso*-product.



Bromine atom is acting as neighbouring group and the result is bromonium ion.
Opening of bromonium ion by bromide ion gives *meso*-dibromide.

These results can be explained by the formation of cyclic bromonium-ion intermediate. If the reaction were normal S_N2 , complete inversion would have occurred at the carbon undergoing substitution. If the reaction were S_N1 , racemization would have occurred at the carbon undergoing substitution.

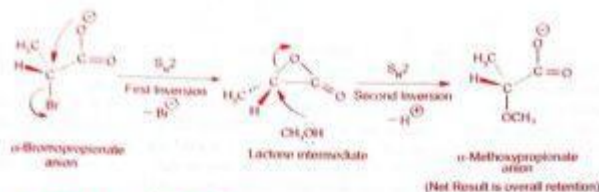
B. Oxygen as neighbouring group

Hydroxyl group itself or via the alkoxide ion may participate as a neighbouring group. The methoxy group, for example, can assist substitution reactions through neighbouring group participation. Thus, 4-methoxy alkyl sulfonate reacts with alcohols 4000 times faster than *n*-butyl sulfonate.



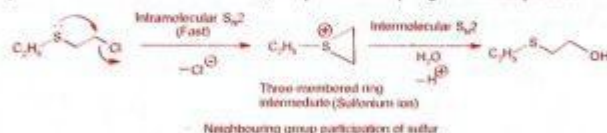
In contrast to the weak anchimeric assistance by alkoxy groups in displacement reactions, the corresponding carboxylates (acetate and benzoate) often show substantial participation. For example, treatment of optically active α -bromopropionate anion with methanol gives the optically active α -methoxypropionate anion with retention of configuration. A normal S_N2 displacement of bromide by methyl alcohol would give the product with inversion of configuration.

However, the product is formed with the stereochemistry exactly the reverse of what we might expect. In this reaction, the carboxylate group acts as an internal nucleophile and displaces bromide in an intramolecular fashion to give as intermediate a lactone. As with all S_N2 reactions, there will be inversion of configuration. Now a second S_N2 displacement (this time by the intermolecular attack of methyl alcohol) occurs with the opening of lactone ring to give α -methoxypropionate. Once again there will be inversion of configuration. The net result of this double inversion mechanism is retention.



C. Sulfur as neighbouring group

Like alkoxy group, the sulfur analogue can also enter into neighbouring group participation. The sulfur atom is more powerful nucleophile than oxygen and the participation of sulfur as a neighbouring group is stronger. Thus, sulfides can assist substitution, through neighbouring group participation, better than ethers. This is illustrated by the hydrolysis of 2-chloroethyl ethylsulfide to corresponding alcohol. In this case the rate of reaction is about 10^7 times faster than that of the hydrolysis of 1-chlorohexane to 1-hexanol. The hydrolysis of 1-chlorohexane proceeds by simple S_N2 process, in which chloride is displaced by water acting as nucleophile. However, unlike the 1-chlorohexane, the chloroalkyl alkyl sulfide reacts in two steps. Sulfur atom of the sulfide acts as neighbouring group participant and displaces the leaving chloride in an intramolecular S_N2 displacement reaction. The resulting cyclic sulfonium ion is opened by water in a second intermolecular S_N2 displacement step to give the final product.

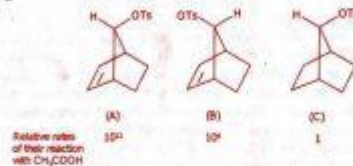


In contrast to negligible anchimeric assistance by oxygen in solvolysis reactions of β -haloethers, the corresponding sulfides show strong anchimeric assistance, as evident by the results of hydrolysis rates of oxygen- and sulfur-substituted alkyl chlorides.

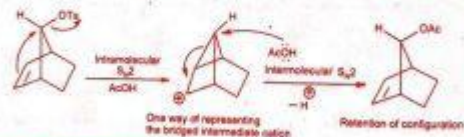


D. Carbon-carbon double bond as neighbouring group

Neighbouring carbon-carbon double bond in bicyclic tosylates can enhance the rate of acetolysis reaction and control the stereochemistry of a reaction. For example, the rate of acetolysis reaction of tosylate of *anti*-7-hydroxybicyclo [2.2.1] hept-2-ene (A) in acetic acid proceeds about 10^7 times as fast as that of *syn*-isomer (B) and 10^{11} times as fast as that of the saturated compound (C). The product formed is exclusively the *anti*-acetate i.e. with retention of configuration. The acceleration in rate is due to assistance by the neighbouring double bond in the departure of the tosylate group (OTs).

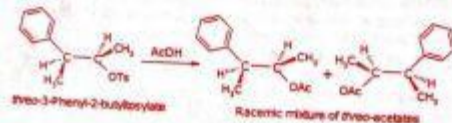


When carbon-carbon double bond is *anti* with respect to tosylate, it can assist the displacement of the leaving group in an intramolecular S_N2 reaction. The opening of the resulting non classical carbocation must give the *anti*-acetate as the opening is also an S_N2 reaction. The *anti*-tosylate has the leaving group in an especially favorable position for backside attack on the carbon bearing the departing group.

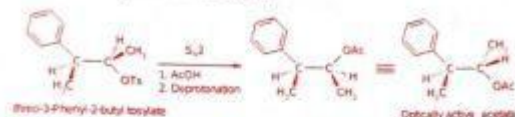


E. Aromatic groups as neighbouring group

The π -system of aromatic rings in the β -position may enter into neighbouring group participation. This is illustrated by the reaction of optically active *threo*-3-phenyl-2-butyl tosylate with acetic acid to give racemic mixture of the corresponding 3-phenyl-2-butyl acetates.

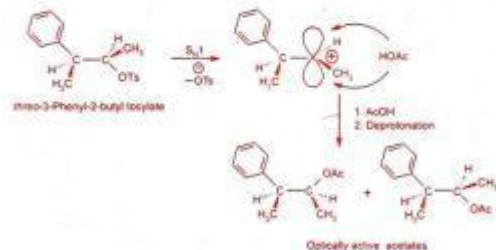


The simple acetolysis of 3-phenyl-2-butyl tosylate via S_N2 mechanism would lead to inversion in the substitution, and so must form the optically active acetate. Since the inversion occurs only at the C-OTs carbon atom, *threo*-tosylate would give the *erythro*-acetate and *erythro*-tosylate the *threo*-acetate.



Simple S_N2 reaction must give optically active acetate (inversion of configuration).
But this product is not formed by the reaction of *threo*-3-phenyl-2-butyl tosylate with acetic acid.

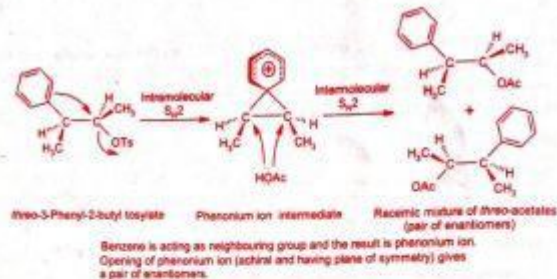
Similarly, reaction via S_N1 mechanism should result in two different optically active products i.e. mixture of *threo*- and *erythro*-acetates.



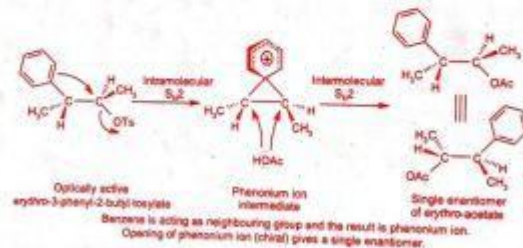
Simple S_N1 reaction should result into the mixture of two optically active acetates.
But these products are not formed by the reaction of *threo*-3-phenyl-2-butyl tosylate with acetic acid.

However, Cram observed that the optically active *threo*-tosylate gave the racemic mixture of *threo*-acetates. Thus, these results can be explained on the basis of the formation of bridged carbocation intermediate i.e. phenonium ion. The π -system of the aromatic ring acts as internal nucleophile and displaces the tosylate in an intermolecular S_N2 mechanism. The resulting phenonium ion (similar to the one produced in electrophilic aromatic substitution) is opened in a second intermolecular S_N2 reaction. Since there are two possible sites for attack of acetic acid (nucleophile), thus a pair of enantiomers (a racemic mixture) is obtained.

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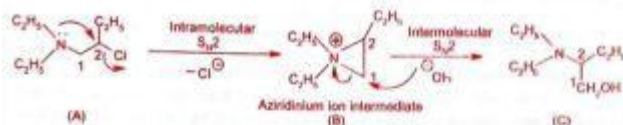


Similar reaction of optically active *erythro*-diastereomer gives optically active *erythro*-acetate (single enantiomer). The phenonium ion is chiral but has an axis of symmetry (and not the plane of symmetry), therefore can be attacked by acetic acid molecule at carbons 1 and 2 with equal probability to give the same optically active product.



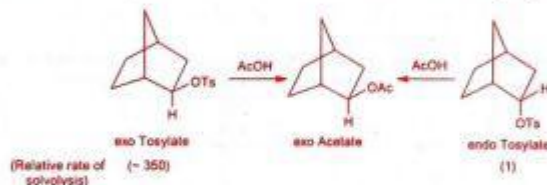
F. Nitrogen as neighbouring group

There are examples in which the nitrogen with nonbonding electrons assists the substitution of hydroxyl group for halogen. But, substitution goes with complete rearrangement. For example, alkaline hydrolysis of (A) produces the cyclic intermediate, aziridinium ion (B), and the hydroxide ion attacks only at the less hindered carbon atom, to give the product (C) in which amine group has migrated from carbon 1 to carbon 2.



G. Single bonds as neighbouring group (non classical carbocation)

There are evidences that even C-C sigma bond electrons can assist in the ionization of a nearby leaving group. This is exemplified by the solvolysis reaction of diastereomeric *exo*- and *endo*-2-norbornyl tosylate in acetic acid, both give *exo*-2-norbornyl acetate. The *exo*-2-norbornyl tosylate reacts 350 times faster than the *endo*-2-norbornyl tosylate.



In *exo*-isomer, carbon-carbon bond gives anchimeric assistance to the expulsion of a leaving group and an intermediate bridged ion is formed. Opening of this ion by acetic acid, followed by deprotonation gives the *exo*-2-norbornyl acetate.

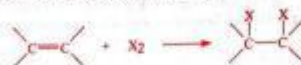


Bridged ions of this kind are known as non-classical carbocations (see chap. 2, sec. 2.2.5).

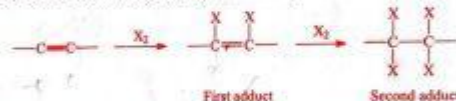
The back side attack by sigma electrons on carbon having tosylate group helps to push out tosylate and yields the bridged ion in a single step. The geometry of the *endo*-tosylate does not permit back-side attack. Since *exo*-tosylate reacts with anchimeric assistance, therefore, it reacts at the faster rate.

1.4 Addition reactions

These reactions are characteristic of compounds containing multiple bonds (e.g. alkenes and alkynes). The alkenes (containing a carbon-carbon double bond) and alkynes (containing carbon-carbon triple bond) react by addition to the multiple bond. We know that a carbon-carbon double bond is made up of a strong σ bond and a weak π bond and that a carbon-carbon triple bond is made up of a σ bond and two π bonds. It needs less energy to break a π bond than a σ bond. It is found that an ethylenic π bond is about 15 kcal/mol weaker than a σ bond. It is therefore expected that in addition reaction to a carbon-carbon double bond (alkenes) the weaker π bond breaks open leaving a σ bond intact. The addition of halogen to alkene is represented as:



On the other hand, since a carbon-carbon triple bond contains two π bonds and one σ bond, the addition of a reagent is expected to take place in two steps.



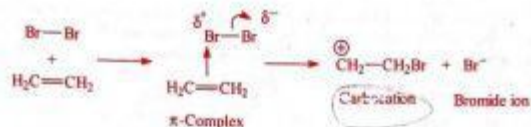
Besides $C=C$ and $C\equiv C$, the addition reactions also occur with other multiple bonds, such as carbonyl, cyano groups etc. Normally the reagents which add on to multiple bonds are halogen, hydrogen, halogen acids, sulfuric acid etc. The addition reactions can be divided into four types i.e., electrophilic additions, nucleophilic additions, free radical additions and concerted additions.

1.4.1 Electrophilic additions

It is known that compounds containing multiple bonds (e.g., alkenes and alkynes) decolourise a solution of bromine in a suitable solvent like carbon tetrachloride. This decolourisation is due to the formation of an addition product and the reaction is called addition reaction.



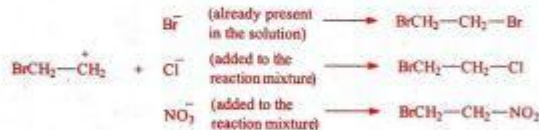
In the above addition reaction it is believed that when an alkene comes in proximity of a bromine molecule, it gets polarized due to π electrons of the alkene. This results in the creation of a dipole in bromine molecule. The positive end of the polarized bromine molecule gets loosely attached to the π -electron cloud of the alkene leading to the formation of a π complex.



The π -complex formed above breaks down to form a carbocation and bromide ion. The carbocation thus produced reacts with the nucleophilic bromide ion leading to the formation of the addition product.



The above proposed mechanism is supported by the observation that mixed products are obtained when an alkene is treated with bromine water in presence of other nucleophiles such as chloride or nitrate ions. In these cases the stepwise addition takes place and not the direct addition of a halogen molecule to an alkene.

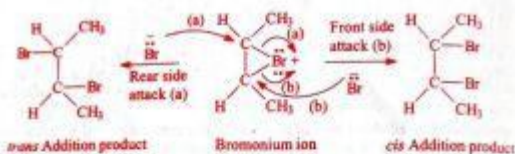


The above reaction is initiated by the positive end of the bromine dipole (electrophile) and is called electrophilic addition reaction.

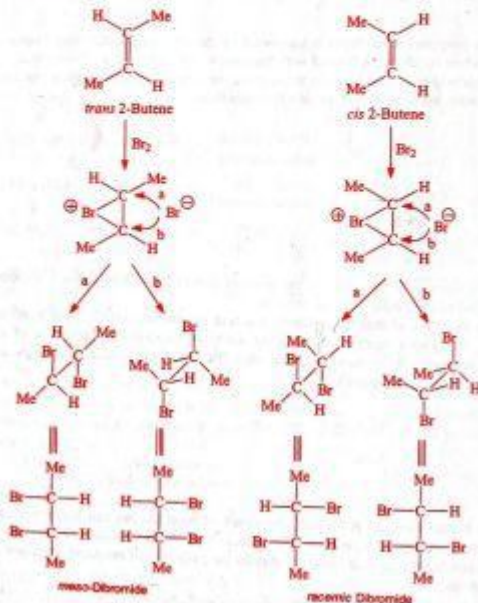
It has been found that the addition reaction of alkenes usually give *trans*-addition products. The above reaction mechanism does not explain the formation of a *trans*-addition products. It is now believed that the reaction proceeds through a cyclic intermediate (bromonium ion).



Once the bromonium ion is formed, the attack of bromide ion can occur from the back side giving *trans*-addition product. The attack from the front side will give *cis*-addition product. The latter attack is hindered due to the presence of bromine atom and so does not take place.



It is interesting to note that bromination of *trans*-2-butene gives *meso*-dibromide and that bromination of *cis*-2-butene gives racemic modification (pair of enantiomers). This can also be explained by the addition of bromine on the cyclic intermediate bromonium ion. Thus, the reaction is stereoselective.

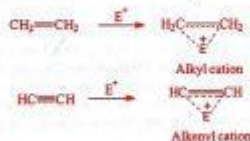


In addition to alkenes, as we know, the π bond is broken and its pair of electrons are used in the formation of two new σ bonds. In fact the sp^2 hybridized carbon atoms are rehybridized to sp^3 in the process. Compounds containing π bonds are, in general of higher energy, than those having σ bonds. So the addition reaction is usually an exothermic process.

Reactivity of alkenes versus alkynes

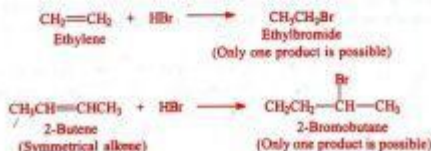
We know that alkynes undergo the same type of addition reactions as alkenes. Since the electron density around carbon-carbon triple bond is higher than around carbon-carbon double bond, it is expected that alkynes would be more reactive towards electrophilic reagents than alkenes. However, the reverse is true, i.e. alkenes are more reactive than alkynes. This could be explained in the following way. The carbon atoms in alkenes are sp^2 hybridized and in alkynes these are sp hybridized. As an sp hybridized carbon is more electronegative than the sp^2 hybridised carbon atom, the π electrons are more tightly held by the carbon nuclei in alkynes and so are less easily available for combination with an electrophile. In view of this the electrophilic addition in case of alkyne is less facile than in case of alkene.

The cyclic alkenyl cation from an alkyne is strained and unstable compared to strain-free alkyl cation formed from an alkene. This explains the above results.

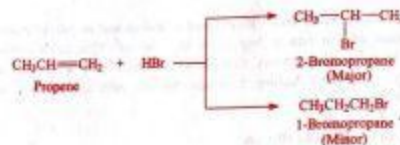


Addition to unsymmetrical alkenes

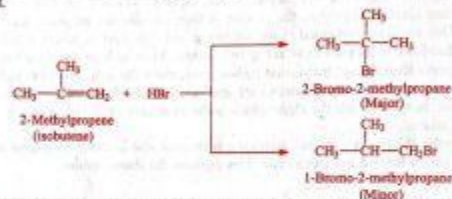
The addition of symmetrical reagents (like Br_2) to symmetrical alkenes (like ethylene) gives only one product. If the reagent is unsymmetrical (like halogen acid, e.g. HBr) but the alkene is symmetrical (like 2-butene), in this case also, only one product is possible.



However, if both the reagent and the alkene are unsymmetrical, the situation becomes different. For example, when HBr adds to an unsymmetrical alkene like propene, one would in principle expect two products, viz. 1-bromopropane and 2-bromopropane.



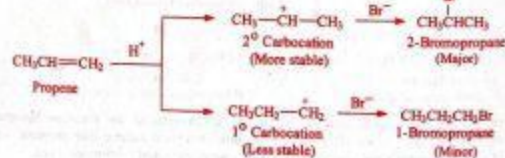
However, the product, 2-bromopropane is formed in major amount. In a similar way, the reaction of HBr with 2-methylpropene gives 2-bromo-2-methylpropane as a major product.



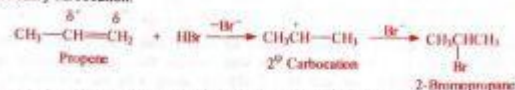
A Russian chemist V. Markownikoff on the basis of extensive studies on the addition of unsymmetrical reagents (like, HCl , HBr , HI , H_2O , H_2SO_4 , HOCl etc.) to unsymmetrical alkenes, formulated an empirical rule known as **Markownikoff's rule**. According to this rule the negative end of the reagent goes to the carbon atom containing lesser number of hydrogen atoms. However, when both the carbon atoms forming the double bond have the same number of hydrogen atoms in an unsymmetrical alkene (e.g., 2-pentene), a mixture of two products are obtained.



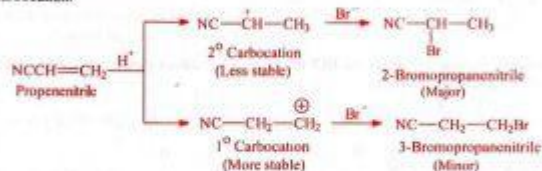
Markownikoff's rule can be explained on the basis of relative stabilities of the intermediate carbocations. The addition of H^+ to propene may give rise to the formation of either primary or secondary carbocation. As the secondary carbocation is more stable, it will be exclusively formed, resulting in the formation of 2-bromopropane.



Markownikoff's rule can also be understood by a consideration of the electronic effect of the substituents on the double bond. In case of propene, due to +I effect of the methyl group, the π electrons are displaced towards the terminal carbon atom which in turn acquires a partial negative charge. So the proton (H^+) adds on to the carbon atom which is farthest from the methyl group, followed by addition of halide ion to the formed secondary carbocation.



The Markownikoff's rule as stated above is not applicable in case of those alkenes which contain electron-withdrawing groups. Propenenitrile, for example, on reaction with HBr gives 3-bromopropenenitrile as the major product which is obtained from primary carbocation.

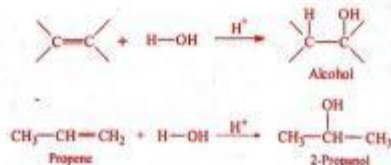


In the above case of propenenitrile, due to strong electron-withdrawing effect of CN-group, the secondary carbocation is less stable than the primary carbocation. In primary carbocation the carbon carrying positive charge is separated from the CN-group by two carbon atoms and the destabilisation by the inductive effect is less.

In view of the above observations, the Markownikoff's rule can be modified as "The addition of hydrogen halide to alkene leads to the formation of a more stable carbocation, which then adds the negative ion to form the product."

Addition of water

Water adds on to the more reactive alkene in presence of acid catalysts (H_2SO_4) to form alcohol. The addition of water to unsymmetrical alkenes follows the Markownikoff's rule.



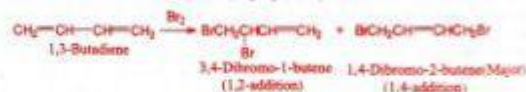
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Addition to conjugated dienes

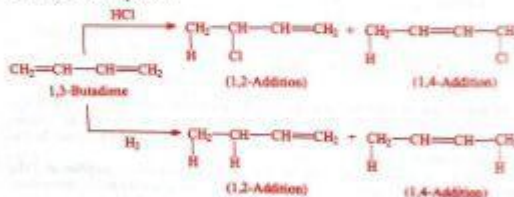
as isolated dienes (e.g., 1,4-pentadiene) both the double bonds react independently as if they are in different molecules.



On the other hand, conjugated dienes behave differently from isolated dienes. When a conjugated diene, e.g., 1,3-butadiene reacts with bromine the product obtained is the expected 3,4-dibromo-1-butene due to 1,2-addition along with the unexpected 1,4-dibromo-2-butene due to 1,4-addition (major product).



Similarly, the reaction of H_2 and HCl with conjugated dienes give corresponding 1,2- as well as 1,4-addition products.

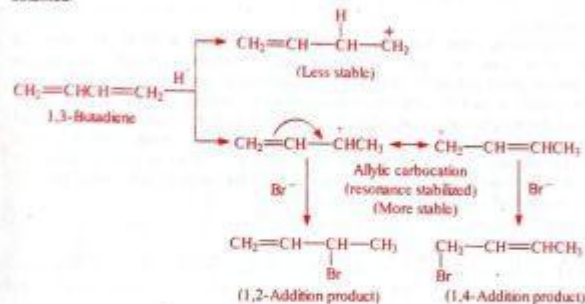


The formation of 1,2- and 1,4- addition products in case of the addition of bromine to 1,3-butadiene can be explained as follows. In case of conjugated dienes there is preferential formation of a resonance stabilized allylic carbocation (as the first step) in which the positive charge resides on both C-2 and C-4. Either of these allylic carbocations can be attacked by the nucleophile in the second step to give 1,2- and 1,4-addition products.



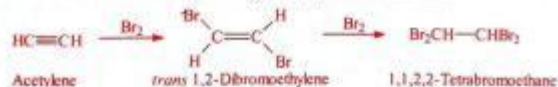
In the above addition the 1,2-addition product predominates at lower temperature and 1,4-addition product predominates at higher temperature. This is attributed to stabilisation of 1,4-addition product by hyperconjugation.

Let us consider the addition of HBr to 1,3-butadiene. The first step involves the formation of carbocation. The hydrogen may attach itself either to C-1 or C-2. Addition of hydrogen to C-2 will give unstable primary carbocation. However, addition of hydrogen at C-1 will give rise to the formation of resonance stabilized allylic carbocation. As in the addition of Br_2 in this case also 1,2-addition product is obtained in 80% yield at low temperature at -70°C and 1,4-addition product is obtained in 80% yield at $40-45^\circ\text{C}$. It is interesting to note that if 1,2-addition product is warmed at $40-45^\circ\text{C}$, 1,4-product is obtained.

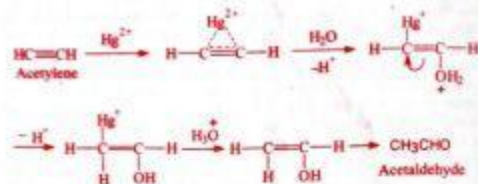


Addition to alkynes

Electrophilic addition to alkynes are similar to those of alkenes. Thus, one molecule of bromine first adds to acetylene to give *trans*-1,2-dibromo-ethylene, which then reacts with a second molecule of bromine to give 1,1,2,2-tetrabromoethane.

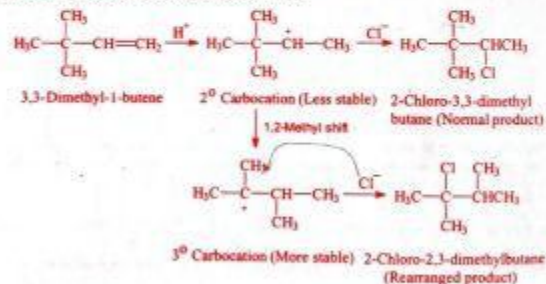


It has already been stated that alkynes are less reactive than alkenes as the π electrons are more tightly held by the carbons in alkynes. Alkenes add on H_2O molecule in presence of acid to form alcohols as per Markownikoff's rule, the alkynes such as acetylene, on reaction with sulfuric acid in presence of a mercuric salt as catalyst gives a vinyl alcohol, which tautomerises to an aldehyde or ketone.



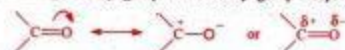
Rearrangements

It has already been stated that during the addition of halogen acids to unsymmetrical alkenes carbocations are formed as intermediates. These carbocations may undergo rearrangement (alkyl or hydride shift) to give a more stable carbocation, which may react with nucleophile to give the addition product. As an illustration, addition of HCl to 3,3-dimethyl-1-butene gives as a first step a secondary carbocation (which is less stable) and undergoes rearrangement (by methyl shift) to give a tertiary carbocation (which is more stable). The secondary carbocation reacts with nucleophile (Cl^-) to give 2-chloro-3,3-dimethylbutane (normal product). On the other hand the tertiary carbocation gives 2-chloro-2,3-dimethylbutane (rearranged product).

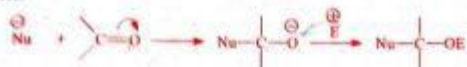


1.4.2 Nucleophilic additions

Such reactions are usually encountered in compounds containing polar functional groups, e.g., carbonyl, $\text{C}\equiv\text{N}$, $\text{C}=\text{S}$ etc. The most important examples are encountered in compounds containing carbonyl group. The carbonyl group is represented as:

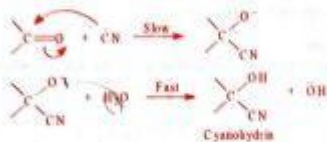


The heteroatom i.e., oxygen in the case of aldehyde or ketone, reduces the π -electron density on the carbonyl carbon. Thus, attack of nucleophile takes place at carbonyl carbon.

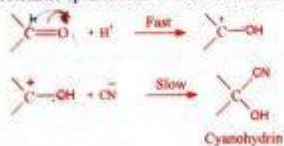


Addition of HCN to carbonyl group

The addition is catalysed by base or acid. The base catalysed nucleophilic additions are common. The base increases the concentration of CN^- ion.

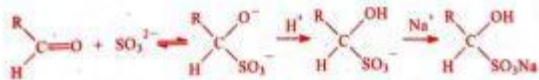


In case of acid catalysed addition of HCN, the acid protonates the negatively charged oxygen. The protonated species react with CN^- as shown below:



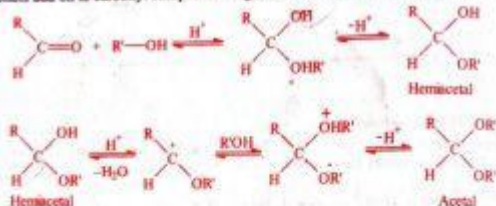
Bisulphite addition

The effective nucleophile in this case is SO_3^{2-} , which is a strong nucleophile and so no catalyst is required. The product obtained is bisulphite crystalline adduct and the reaction takes place in aqueous solution.



Addition of alcohols

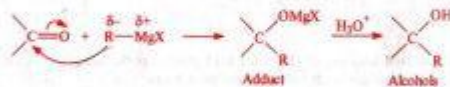
Alcohols add on to carbonyl compounds to give first hemiacetal and then acetal.



The formation of hemiacetal is catalysed by both acid and base. However, the formation of acetal from hemiacetal is catalysed by acids only.

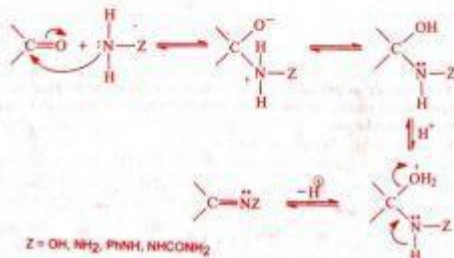
Addition of Grignard reagents

Addition of Grignard reagent to carbonyl compound gives the adduct, which can be hydrolyzed to alcohols.



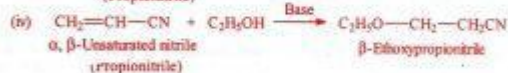
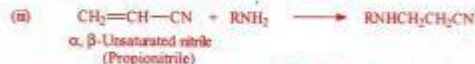
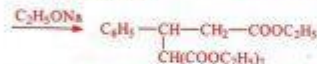
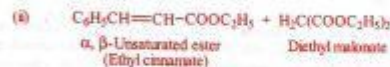
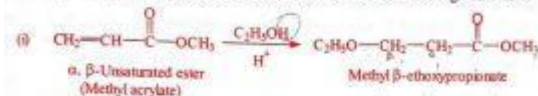
Addition of derivatives of ammonia

Aldehydes and ketones react with compounds related to ammonia like hydroxylamine, hydrazine, phenylhydrazine and semicarbazide to form oximes, hydrazones, phenylhydrazones and semicarbazones, respectively.

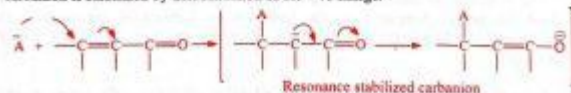


Nucleophilic addition to activated carbon-carbon double bond

We have seen that simple double bonds undergo electrophilic additions (1.4.1). However, compounds containing carbon-carbon double bonds conjugated with electron-withdrawing substituents (such double bonds are called activated carbon-carbon double bonds) undergo nucleophilic addition. The nucleophilic additions are observed in α,β -unsaturated aldehydes, ketones, esters, nitriles etc. Such addition reactions are catalysed by base, which converts the nucleophile (HA) to a strong nucleophile (A^-). Some nucleophilic additions to activated carbon-carbon double bonds are given below:



The nucleophilic addition to activated carbon-carbon double bond takes place as follows. The electron-withdrawing substituents reduce the π -electron density in carbon-carbon double bonds and this results in promotion of nucleophilic attack. The intermediate carbanion is stabilized by delocalization of the $-ve$ charge.



The most important nucleophilic addition reaction to activated carbon-carbon double bond is **Michael addition reaction** (sec. 5.63).

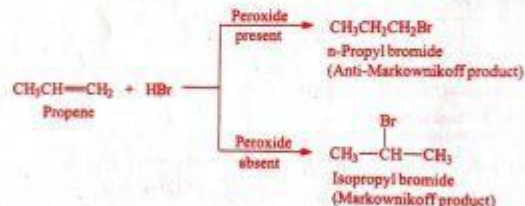
C=C vs C=O

It is clear that carbon-carbon double bond undergoes electrophilic addition reactions and that C=O undergoes nucleophilic addition reactions. However, when C=C and C=O groups are conjugated, the substrate undergoes nucleophilic addition reactions. As C=O is a stronger bond than C=C, the preferential addition is to C=C.

In these additions steric hindrance may play an important factor. Thus, $\text{C}_6\text{H}_5\text{MgBr}$ adds to C=O in $\text{C}_6\text{H}_5\text{CH}=\text{CH}-\text{CHO}$. However, the addition takes place to C=C in $\text{C}_6\text{H}_5\text{CH}=\text{CH}-\text{COC}(\text{CH}_3)_3$. In the latter case steric effect of the bulky alkyl group is an important factor.

1.4.3 Free radical additions

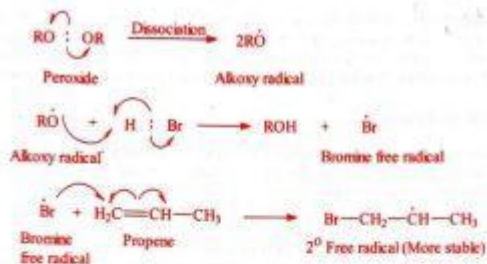
We have seen (1.4.1) that the addition of halogen acids to unsymmetrical alkenes give Markownikoff's addition products. However, this is not always the case. **Kharasch** and **Mayo** found that the addition of HBr to unsymmetrical alkenes in presence of a peroxide



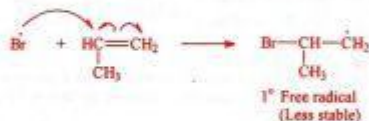
gives a product which is different from the Markownikoff's product. In presence of a peroxide the orientation is reversed. This is also known as **Peroxide effect**. Thus, the addition of HBr to propene in presence of peroxides gives 1-bromopropane rather than 2-bromopropane.

The formation of anti-Markownikoff's addition product is explained by the free radical mechanism compared to the formation of carbocation intermediate for Markownikoff's addition product. Following steps are involved in the free radical mechanism.

(i) Peroxide dissociates into two free radicals called alkoxy radicals. These in turn attack HBr to form bromine free radical.

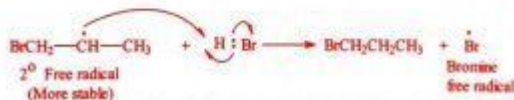


(ii) The bromine free radical attacks the alkene molecule to give two possible alkyl free radicals.



Since secondary free radical is more stable than the primary free radical, so product is formed from 2° free radical.

(iii) The secondary free radical being more stable reacts with HBr forming anti-Markownikoff addition product and another bromine free radical is formed, which in turn propagates the chain.



Only HBr gives the anti-Markownikoff product in presence of peroxide. HCl and HI do not give anti-Markownikoff products in presence of peroxide. This is because HCl and HI do not undergo free radical addition reactions. In case of HCl the cleavage of H-Cl bond to give chlorine free radical in step (i) is unfavourable as H-Cl bond is stronger than H-Br bond. However, in case of HI, iodine free radical is easily obtained as the H-I bond is weak. However, the iodine radicals immediately combine together to give I₂ and so iodine radical is not available for the reaction.

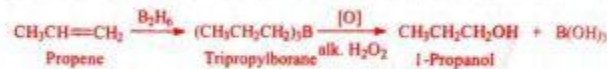
The polymerization of ethylene, propylene etc. to give the polymers i.e., polyethylene and polypropylene in presence of a free radical initiator (e.g., benzoyl peroxide or azobisisobutyronitrile) proceed to free radical polymerization. Also a number of reactions e.g., Sandmeyer reaction, Gomberg reaction etc. proceed by free radical mechanism.

1.4.4 Concerted additions

In concerted addition reactions, the reagents react with double bond from the same face and do not involve charged species like carbocation. Some examples of concerted addition reactions are given below.

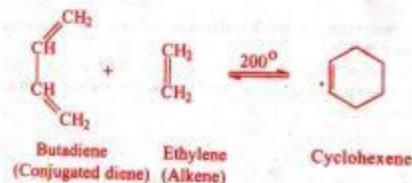
Hydroboration

Basically it involves the addition of BH₃ to carbon-carbon double or triple bond. The alkyl or alkenylboranes thus formed may undergo oxidation with alkaline hydrogen peroxide to give alcohols. For further details see chap. 8, sec. 8.9.



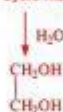
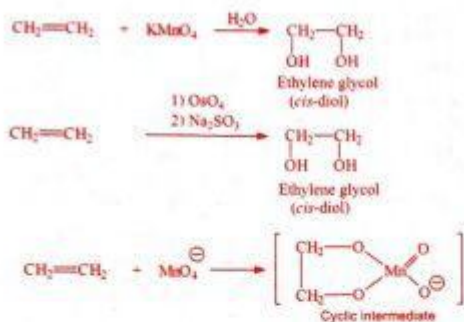
Diels-Alder reaction

Diels-Alder reaction involves the 1,4-addition of an alkene to a conjugated diene to form an adduct (six-membered ring). This reaction is initiated by heat or by Lewis acid. For further details see chap. 5, sec. 5.29.



Hydroxylation

Alkenes can be easily hydroxylated (hydroxyl groups are added to both the carbon atoms forming the double bond) to give dihydroxy compounds known as glycols (or 1,2-diols). The reagents used for this purpose is potassium permanganate or osmium tetroxide. Both these reagents are used for *cis*-hydroxylation of alkenes.



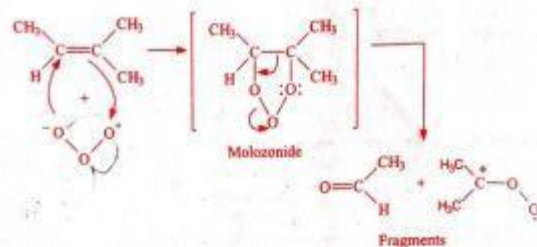
Alkenes can be hydroxylated with peroxy acids to epoxides, which on ring opening give *trans* diols (see chap. 3, sec. 3.4.1).

Addition of ozone to alkenes (Ozonolysis)

Ozone can be represented as resonance hybrid of the following contributing structures.



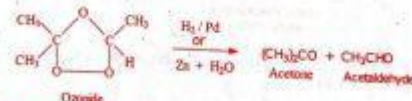
Ozone adds on to carbon-carbon double bond to give an adduct called ozonide. The formation of ozonide is given below.



The first step is the 1,3-dipolar addition of ozone to the double bond forming a molozonide, which being unstable decomposes into fragments. These fragments recombine in a different way to yield the ozonide.



The ozonide on treatment with a reducing agent like zinc and water or hydrogen in presence of palladium gives aldehydes and / or ketones depending upon the structure of alkene. The process of preparing an ozonide and then decomposing it to get carbonyl compounds is called **ozonolysis**. This process is used to locate the position of the double bond in an alkene (also see sec. 3.5.3).

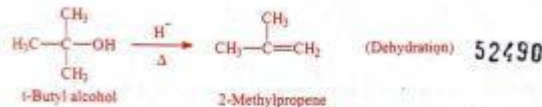
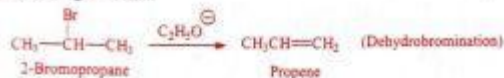


1.5 Elimination reactions

The elimination reactions are reverse of addition reactions. In these reactions two atoms or groups attached to the adjacent carbon atoms of the substrate molecule are eliminated to form a multiple bond. In these reactions a atom or group from α -carbon atom and a proton from the β -carbon are eliminated.



This method is commonly used for the preparation of alkenes or alkynes. Some typical eliminations are given below.



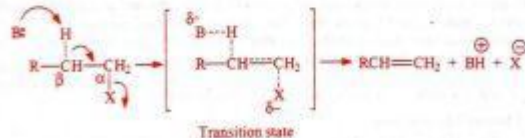
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In all these elimination reactions, the presence of one hydrogen on the β -carbon atom is necessary. In general, the elimination reactions are divided into two types, i.e., bimolecular elimination reactions (E2) and unimolecular elimination reactions (E1).

1.5.1 Bimolecular elimination reactions (E2)

In these elimination reactions, the rate of elimination depends on the concentration of the substrate and the nucleophile and the reaction is of second order. It is represented as E2. Like $\text{S}_{\text{N}}2$ reaction, the E2 reaction is also one step process. In these reactions abstraction of proton from the β -carbon atom and the expulsion of an atom or group from the α -carbon atom occur simultaneously. The mechanism of this reaction is represented as follows:

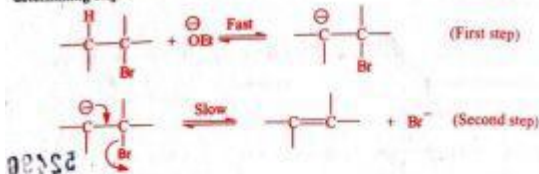


The above reaction is a one step process and passes through a transition state. This reaction is also known as 1,2-elimination or simply β -elimination. In these reactions, the two groups to be eliminated (i.e., H and X) are *trans* to each other and hence E2 reactions are generally *trans* elimination.

The second-order elimination reaction may also proceed in two steps (as in E1 elimination which will be discussed subsequently). In this mechanism, the base removes the hydrogen in the first step to form an intermediate carbanion. In the second step, the

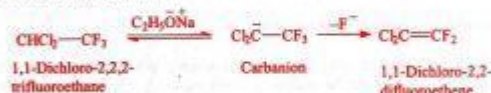
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intermediate carbanion loses the leaving group. The second step is slow and is the rate determining step.



The rate of this reaction is dependent on the concentration of the carbanion (conjugate base of the substrate). So this mechanism is called E1cB mechanism (Elimination, Unimolecular from conjugate base).

E1cB mechanism is not common for the E2 reactions. The carbanion mechanism occurs only where the carbanion from the substrate is stabilized and where the leaving group is a poor leaving group. A typical example, which follows E1cB mechanism is the formation of 1,1-dichloro-2,2-difluoroethene from 1,1-dichloro-2,2,2-trifluoroethane in presence of sodium ethoxide.

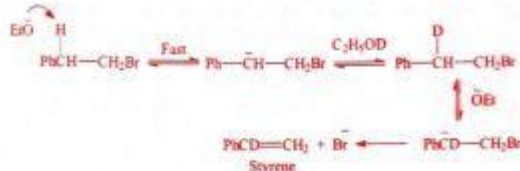


In the above case the carbanion is strongly stabilized due to $-I$ effect of halogens. Also F^- is a poor leaving group.

A distinction between the E2 and E1cB mechanism can be made by tracer experiments. Thus, the reaction of 1-bromo-2-phenylethane (this substrate was selected as Ph group is expected to increase the acidity of β -hydrogen and also to stabilize the carbanion) with $\text{C}_2\text{H}_5\text{OD}$ gives back the starting 1-bromo-2-phenylethane. If the carbanion mechanism had operated, the deuterium would have been found in the recovered 1-bromo-2-phenylethane, which is not the case.



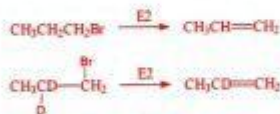
In case the above reaction is allowed to go to completion, the product obtained will be styrene.



The styrene obtained does not contain any deuterium (contrary to what has been shown in the above E1cB mechanism). So in the above reaction E2 mechanism operates.

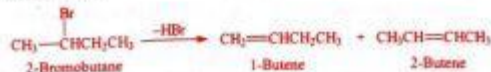
The E2 mechanism is supported by the following evidences.

- (i) During elimination, there is no rearranged product obtained. This is due to the fact that E2 is a single step process and does not involve the formation of intermediate carbocation (the carbocations are known to undergo rearrangement).
- (ii) The E2 mechanism finds support from isotope labeling experiments. Dehydrohalogenation of unlabelled 1-bromopropane is seven times faster than the dehydrohalogenation of $\text{CH}_3\text{CD}_2\text{CH}_2\text{Br}$.



In E2 mechanism a hydrogen (from $\text{CH}_3\text{CH}_2\text{CH}_2\text{Br}$) or a deuterium (from $\text{CH}_3\text{CD}_2\text{CH}_2\text{Br}$) has to be abstracted. It is known that the C-D bond is stronger than the C-H bond and requires more energy to be broken. Therefore, rate of elimination in $\text{CH}_3\text{CD}_2\text{CH}_2\text{Br}$ should be slower. In fact, it has been found that in the unlabelled alkyl halides the elimination rate is seven times more than in labelled alkyl halides.

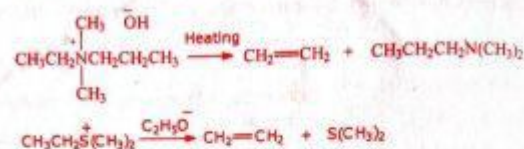
Unsymmetrical substrate which has hydrogen attached to two different β -carbons can afford two alkenes. For example, 2-bromobutane on dehydrohalogenation may give 1-butene or 2-butene.



In a similar way, decomposition of sec-butyl-trimethylammonium hydroxide may give a mixture of two alkenes. The question arises as to which alkene will be obtained in major amount in the above dehydrohalogenation. The orientation of the reaction is determined by **Hofmann Rule** and **Saytzeff Rule**.

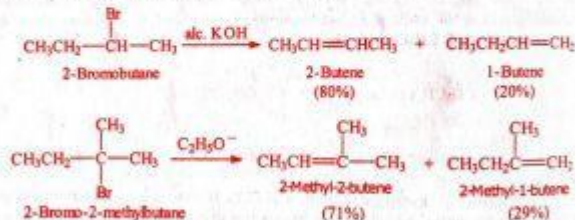
Hofmann Rule

This rule is applicable for those substrates in which α -carbon atom is attached to a positively charged atom. According to this rule, in the elimination reaction of positively charged species, the major product will be the alkene which is least substituted.



Saytzeff Rule

In case of unsymmetrical alkyl halides, for example in 2-bromobutane, the course of elimination is determined by Saytzeff Rule. According to this rule, hydrogen is eliminated preferentially from the carbon atom which has less number of hydrogen atoms and so the highly substituted alkene is the major product.



The formation of highly substituted alkene can be explained as follows.

The transition states of less substituted and more substituted alkenes from an alkyl halide are represented as shown below:



Both the transition states have partial double bond character. However, the transition state leading to more stable alkene is more stabilized and is of lower energy (Fig. 1.8). Thus, the more stable alkene is formed as the major product.

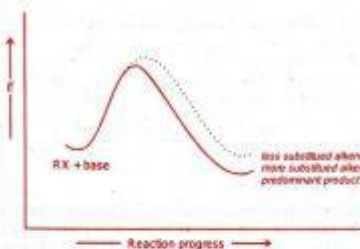
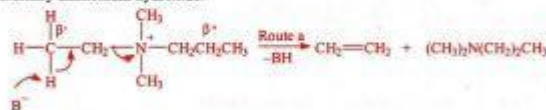
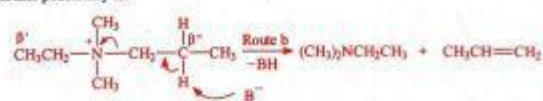


Fig. 1.8 : Energy diagram for a typical E2 reaction, showing why the more substituted alkene predominates

Hofmann rule can be understood by considering the mechanism of elimination reaction of quaternary ammonium hydroxide.



Another possibility is:

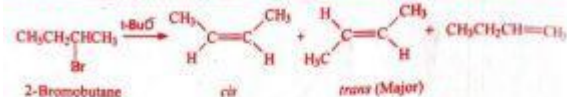


In the above reaction the strong electron-withdrawing group makes the hydrogens of the β -carbons more acidic for facile abstraction by the base. In this compound, with alternate β -hydrogens (marked β' and β''), the β'' hydrogen are less acidic due to +I effect of the adjacent methyl group. Hence β' -hydrogen is relatively more acidic and is removed to give the alkene (ethene) by route a.

In elimination reactions steric effect also plays an important role. Thus, dehydrohalogenation of alkyl halide using the bulky base leads to the formation of terminal alkene as the major product.

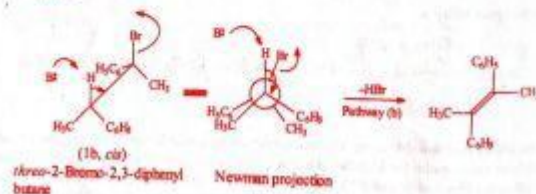
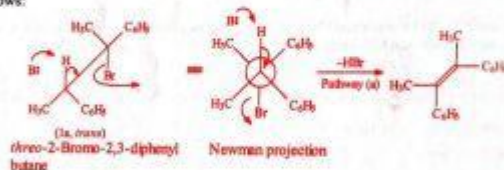


Also in elimination reactions, the more stable *trans*-alkene is formed as a major product.



Stereochemistry of E2 reactions

We know that E2 elimination is an *anti*-elimination. The reaction is facile when both the leaving groups and the carbon bearing them are in the same plane (*trans* coplanar). For example in *trans*-2-bromo-2,3-diphenylbutane, when the two leaving groups are planar there are two conformations, (i) the two groups are in *trans* position (1a) (*anti*-periplanar) and (ii) the two are in *cis*-position (1b) (*syn*-periplanar). The elimination may proceed as follows:

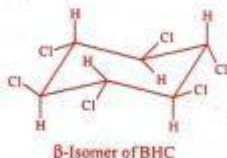


On examination of the **Newman projections** of the *trans* (staggered) and *cis* (eclipsed) conformations, we found the elimination is more facile from the *trans* conformation (1a) than from the *cis* conformation (1b). This is because in *trans* conformation (1a) the base approaches from the farthest side of the leaving group while in *cis* conformation (1b) the

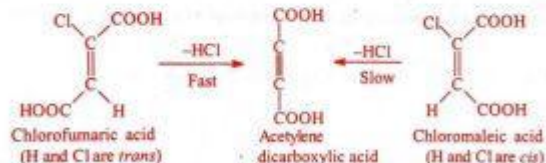
attack is from the same side of the leaving group, which causes repulsion. Also the elimination occurs from the lower energy staggered conformation (1a) than from the higher energy eclipsed conformation (1b). In view of the above fact the elimination occurs through pathway (a).

That the E2 reaction is *anti*-elimination is supported by the following illustrations.

(i) Benzene hexachloride, $C_6H_6Cl_6$ can exist in eight isomeric forms. One of these isomeric forms (β -isomer) loses HCl , 10,000 time more slowly than the others. This is because of the fact that this isomer has no adjacent chlorine and hydrogen atoms *trans* to each other. All the six chlorines are in equatorial positions so that they are *trans* to each other and no hydrogen is available in the *trans* position.

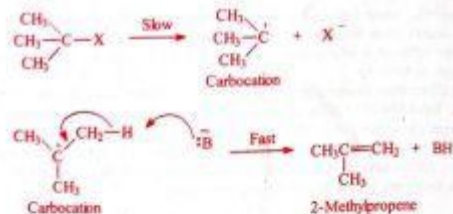


(ii) The isomeric chloromaleic acid (H and Cl are *cis*) and chlorofumaric acid (H and Cl are *trans*) both give acetylene dicarboxylic acid on treatment with base. However, *trans* isomer (chlorofumaric acid) reacts about 50 times faster.

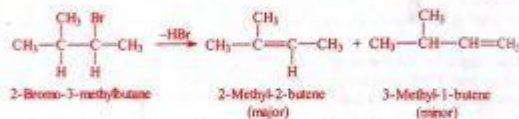


1.5.2 Unimolecular elimination reactions (E1)

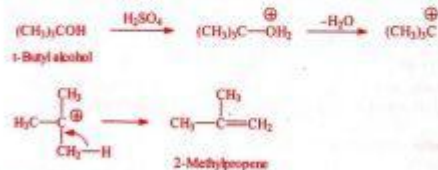
In these reactions the rate of elimination is dependent only on the concentration of the substrate and is independent of the concentration of the nucleophile and the reaction is of first order, (E1). Like S_N1 reaction the E1 reaction is also a two step process. The first step is the slow ionization of alkyl halide to give the carbocation. The second step involves the fast abstraction of a proton from the adjacent β -carbon atom giving rise to the formation of an alkene.



In case the substrate is such that more than one alkenes can be formed, that alkene will predominate which has larger number of alkyl groups on the double bonded carbon (this is as per Saytzeff's rule; see also sec.1.5.1). This can be visualised since the substituted alkyl groups will stabilise the alkene by hyperconjugation.



The acid catalysed dehydration of alcohols also follows E1 mechanism.



In the E1 mechanism the rate of reaction is determined by the rate of formation of carbocation, which in turn depends on the stability of carbocation. Due to the formation of carbocation, these may undergo rearrangements. This has been experimentally confirmed.



Orientation in E1 reaction

We have seen that orientation in E2 reaction is determined by Saytzeff rule (for alkyl halide, the product is highly substituted alkene) and by Hofmann rule (for quaternary ammonium salts, the product is less substituted alkene). However, in case of E1 reaction whether the substrate is an alkyl halide or a quaternary ammonium salt, the same orientation is expected since the same carbocation would arise from the ionization of alkyl halide or a quaternary ammonium salt. This has been experimentally verified by showing that E1 reaction of both halides and quaternary ammonium salts give the same product, i.e. the Saytzeff product (more substituted alkene).

1.6 Electrophilic substitution in aromatic systems

Normally reactions are irreversible and the products formed are kinetically controlled. Sulfonation is the exception which is reversible and at high temperature thermodynamically stable product predominates.

Mechanism

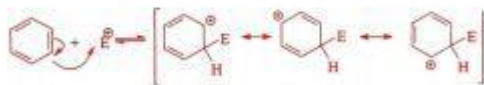
The mechanism of electrophilic substitution reactions of benzene is described below:

(i) Generation of electrophile

The substituting reagent is ionized in such a way as to generate an electrophile or polarized to create an electron-deficient species.

(ii) Attack of electrophile on π -electron system

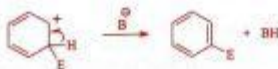
The electrophile attacks a benzene ring to give an intermediate, often called benzenonium ion intermediate, which is resonance stabilized. The carbocation intermediate (benzenonium ion) is too unstable to be isolated as salts except in special circumstances.



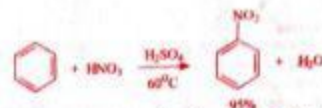
This step is rate-determining step in most electrophilic substitution reactions.

(iii) Removal of proton by base

In the last step proton is removed from the intermediate benzenonium ion by a base to restore the aromatic ring. Thus the aromatic system remains intact. This is the fast step.

**Nitration**

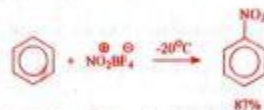
Nitration is carried out in most of the cases with a mixture of concentrated nitric acid and sulfuric acid (called nitrating acid or mixed acid). For example, a mixture of concentrated nitric acid and sulfuric acid converts benzene into nitrobenzene.

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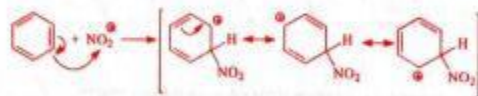
In the mixture of concentrated nitric acid and sulfuric acid (1:2 ratio) used for the nitration reaction, it has been shown that a positive nitronium ion (NO_2^+) is present. In strong acid, such as sulfuric acid, HNO_3 is protonated to form $\text{H}_2\text{O}^+\text{NO}_2$, which loses water to give the nitronium ion.



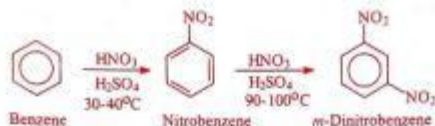
The salts of nitronium ion such as $\text{NO}_2^+ \text{ClO}_4^-$ (nitronium perchlorate) and $\text{NO}_2^+ \text{BF}_4^-$ (nitronium fluoroborate) are also effective nitrating agents. Nitration of benzene can be accomplished by treating it with $\text{NO}_2^+ \text{BF}_4^-$.



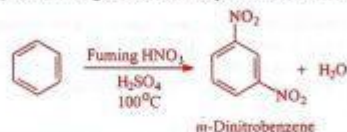
Nitronium ion is the electrophile and attacks one of the carbon atom of aromatic ring. The resulting carbocation intermediate is resonance-stabilized. In the last-step a proton is removed from the carbocation by a base and aromatic ring is restored on which a substituent has replaced a hydrogen atom. This is the fast step.



Nitro group is a ring deactivating group. Therefore, it makes it harder to introduce a second nitro group onto an aromatic ring. For example, benzene gives nitrobenzene at 30–40°C. However only when temperature is raised to 90–100°C, *m*-dinitrobenzene is formed as a main product. Since, nitro group is *m*-directing, the new nitro group takes a position *meta* to the first one.



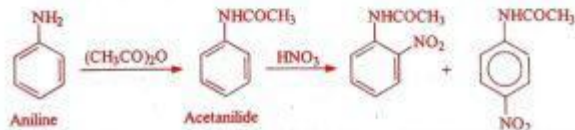
Benzene can also be converted into *m*-dinitrobenzene when treated with fuming nitric acid, which is more powerful reagent than ordinary concentrated nitric acid, at 100°C .



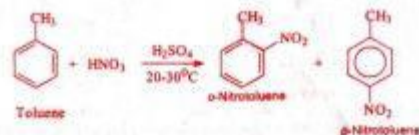
On the other hand, hydroxy group in phenols is ring-activating and *ortho* / *para* directing. Phenol when treated with dilute nitric acid at room temperature gives the mixture of *o*-nitrophenol and *p*-nitrophenol.



Aniline is readily oxidised with nitrating mixture. So the amino group of aniline is first protected by acetylation. The resulting acetanilide is nitrated to *o*- and *p*-derivatives, which can be deacetylated to yield the corresponding nitro anilines.

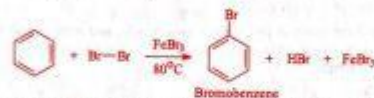


Alkylbenzenes are more readily nitrated than unsubstituted benzene, due to the presence of ring-activating alkyl group on aromatic ring. The alkyl group is *o*- and *p*-directing as shown by the nitration of toluene.

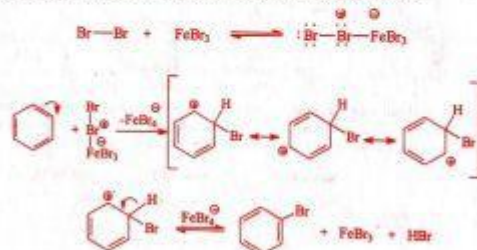


Halogenation

Benzene can be halogenated with chlorine and bromine in the presence of a Lewis acid catalyst, such as FeBr_3 , FeCl_3 , AlCl_3 etc. Lewis acid assists polarization of the attacking halogen molecule, thereby making it more reactive. For example, the bromine reacts with benzene in presence of FeBr_3 at 80°C to form bromobenzene.



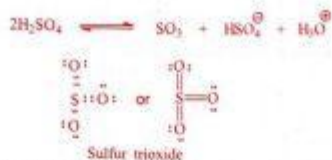
It is necessary to catalyse the halogenation reactions with Lewis acid.



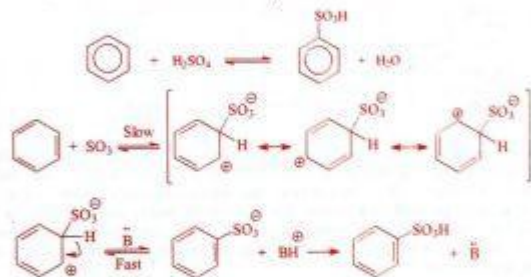
Fluorine reacts vigorously with aromatic hydrocarbons even in the absence of catalyst, however, iodine is very unreactive even in the presence of catalyst.

Sulfonation

Aromatic hydrocarbons react with concentrated sulfuric acid to give arenesulfonic acids. The active electrophile in sulfonation reaction is sulfur trioxide, which is present in concentrated sulfuric acid as a result of the equilibrium. Sulfonation can also take place in presence of a solution of sulfur trioxide in sulfuric acid, i.e., oleum. Although SO_3 has no positive charge, it is a strong electrophile. This is because the octet of electrons around the sulfur atom of SO_3 is incomplete. Benzenesulfonic acid, for example, is prepared by heating the benzene with concentrated sulfuric acid.



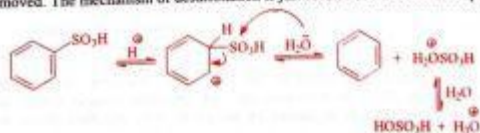
During electrophilic substitution the aromatic ring forms a bond with sulfur of SO_3 and one of the π bonds between sulfur and oxygen is broken. The mechanism of sulfonation is essentially the same as that of other electrophilic substitution reactions.



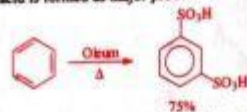
Sulfonation is a reversible process, especially at high temperatures. However, high yields of sulfonic acids are obtained when a solution of sulfur trioxide in sulfuric acid is used.



When benzenesulfonic acid is heated with aqueous sulfuric acid, the sulfonic acid group is removed. The mechanism of desulfonation is just reverse of the sulfonation process.



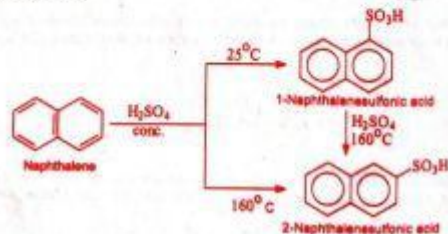
Since sulfonic acid group is ring-deactivating, the disulfonation is very slow and requires forcing conditions. For example, when benzene is heated at 200°C with excess of *oleum*, benzene-*m*-disulfonic acid is formed as major product.



Aniline reacts with sulfuric acid to give a salt, which on strong heating rearranges to sulfanilic acid.

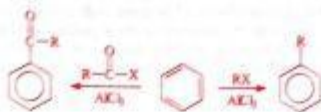


When naphthalene is sulfonated at low temperature (40°C) with concentrated sulfuric acid the kinetically controlled product, 1-naphthalenesulfonic acid is formed as a major product. Whereas at high temperature the thermodynamically more stable 2-naphthalenesulfonic acid predominates. The α -isomer is readily converted into the β -isomer when heated with concentrated sulfuric acid. The α -isomer is sterically hindered by the hydrogen in the 8-position and at high temperature it is converted into the unhindered β -isomer.



Friedel-Crafts alkylation

Friedel-Crafts alkylation and acylation are two other examples of electrophilic substitution reactions. These reactions are particularly important because they allow the construction of larger organic molecules by adding alkyl or acyl side chains to an aromatic ring.

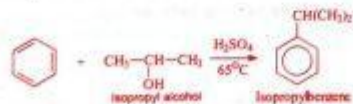
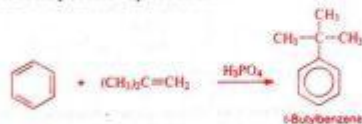


Alkylation of aromatic hydrocarbons is achieved by using a mixture of alkyl halide and aluminium trihalide (Lewis acid). The function of Lewis acid is to generate strong electrophile related to carbocation for attack on the aromatic ring.



The reaction is closely related to halogenation of aromatic ring. A complex is first formed between alkyl halide and Lewis acid. This complex is attacked by π -electrons of aromatic ring to give a resonance stabilized arenium cation. The base abstracts a proton to yield the substitution product alkylbenzene.

Variety of alkyl halides can be used in Friedel-Crafts alkylation such as primary, secondary and tertiary alkyl chlorides and bromides. Since, carbocation can be generated from alkenes or alcohols, therefore, alcohols or olefins also react with aromatic compounds in the presence of protic acids.



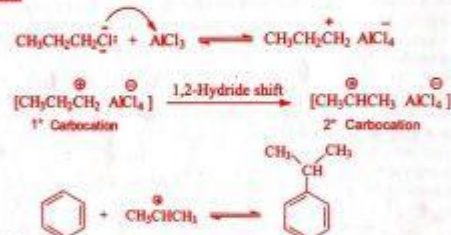
Strong electron-attracting groups on the aromatic ring slow down or prevent the reaction. For example, nitrobenzene may be used as solvent for the alkylation reaction. Substituents that have an unshared pair of electrons such as OH and NH₂ coordinate with Lewis acid, thus, the yield of reaction is very low.

There are limitations of the Friedel-Crafts alkylation. The Friedel-Crafts alkylation suffers from two practical limitations or disadvantages i.e., isomerisation and polyalkylation. Since, carbocations are generated initially in Friedel-Crafts alkylation of aromatic hydrocarbons, molecular rearrangements are sometimes observed and isomeric

products are obtained. The alkylation of benzene with *n*-propylchloride, for example, affords isomeric product, isopropylbenzene as major product and only small amount of expected *n*-propylbenzene is obtained. The initially formed intermediate, primary *n*-propyl carbocation, rearranges to stable secondary isopropyl carbocation prior to its attack on the benzene ring.



Mechanism



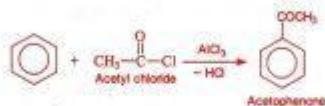
Similarly, the reaction of 1-chlorobutane with benzene gives two products with only 34% of the desired product. This is due to the fact that the primary carbocation which is generated rearranges to a more stable secondary carbocation.



Since the alkyl group is ring activating, the mono alkylbenzene product is more readily alkylated than benzene itself. When benzene is treated with 3 equivalents of methyl chloride in the presence of a large excess of AlCl₃ catalyst, the product is mesitylene.

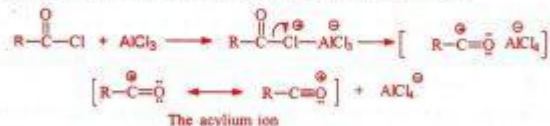
**Friedel-Crafts acylation**

Acid chlorides react with aromatic compounds in presence of Lewis acid such as AlCl_3 to give the ketone. Since, an acyl group has been substituted on the aromatic ring, so the stoichiometric amount of AlCl_3 is required in this reaction. Acetyl chloride, for example, reacts with benzene in the presence of AlCl_3 to give acetophenone.

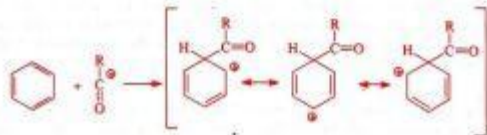


The mechanism of the Friedel-Crafts acylation, is similar as in the case of Friedel-Crafts alkylation, involving an acylium ion instead of a carbocation.

Step 1: Acid chloride forms complex with AlCl_3 which can dissociate to give the acylium ion. But unlike a carbocation the acylium ion does not rearrange.



Step 2: Addition of acylium ion to the aromatic ring generates an intermediate arenium cation, which is resonance stabilized.



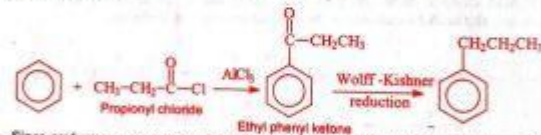
Step 3: Removal of proton from arenium cation by base completes the reaction and aromatic ketone is formed.



Acid anhydrides can also be used in Friedel-Crafts acylation reactions, for example, acetic anhydride reacts with benzene in the presence of aluminium chloride to give acetophenone.



Friedel-Crafts acylation, followed by reduction of the carbonyl group to CH_2 (methylene) provides the most important method for introduction of an alkyl side chain into the benzene nucleus.



Since acylium ion does not undergo rearrangement, therefore, the acid chlorides having long-straight chain R group can be used to introduce acyl group. Reduction of carbonyl group to methylene group converts the ketone to alkyl group. Thus, Friedel-Crafts acylation followed by reduction of the carbonyl group to CH_2 provides the most important method to introduce unbranched alkyl group on to an aromatic ring.

Another difference between Friedel-Crafts acylation and alkylation is that the acylation reaction does not give polysubstitution products as observed in Friedel-Crafts alkylation. This is because the carbonyl group deactivates the ring towards further substitution reaction.

Activation and deactivation

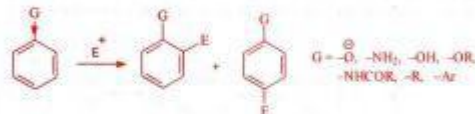
The substituent already present on an aromatic ring effects the reactivity of the ring towards further electrophilic substitution. The electron-donating groups (either through resonance or by their combined inductive and hyperconjugation effects) activate the ring towards electrophilic substitution. These groups are known as ring-activating groups. The electron-withdrawing groups make the ring less reactive than benzene towards electrophilic substitution. These groups are called ring-deactivating groups. The

hydroxyl group in phenol is ring-activating group, while nitro group in nitrobenzene is ring-deactivating group.

Directive abilities of substituents

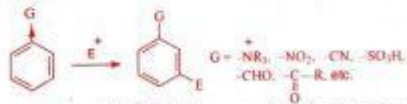
The substituent already present on an aromatic ring can direct the incoming group either to the *meta* position or to the *ortho* and *para* positions. Substituents may be divided into three main classes. These classes show characteristic orientation patterns as well as rate effects.

(a) The groups, which enhance further electrophilic substitution i.e. activating groups and direct the incoming group primarily to *ortho* and *para* positions are called ring-activating and *ortho* and *para* directors. For example, alkyl group activates aromatic ring towards electrophilic substitution because it has an inductive effect (+I). The nucleophilicity of the ring increases and also the positively charged intermediate is stabilized.

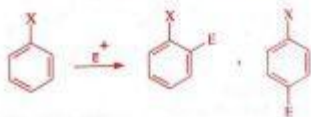


The groups having lone pairs of electrons such as, -OH, -OR, -NH₂ etc. activate the ring by resonance and also direct substituents to the *ortho* and *para* positions.

(b) The groups which deactivate the aromatic ring, make the aromatic ring less nucleophilic and less reactive towards electrophilic substitution. They direct the incoming groups to *meta* position.



(c) Halogens are ring deactivating but direct the new group to *ortho* and *para* positions.



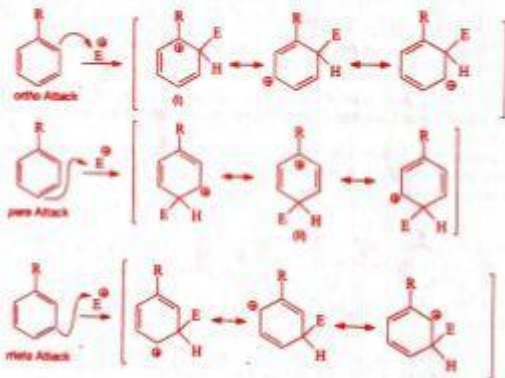
Thus, a substituent can either activate or deactivate the ring towards electrophilic substitution and determine the orientation of substitution i.e., direct substitution either to the *meta* position or to the *ortho* and *para* positions.

Alkyl groups

Alkyl group pushes electron density into the ring, thus increasing the nucleophilicity of the ring and also stabilizes the carbocation intermediate. Alkyl group directs the attacking reagent to the *ortho* and *para* positions of the ring. Therefore, alkyl groups are activating and are *ortho* and *para* directing. In order to explain the directive effect of alkyl group, let us see the mechanism involved in generating the *ortho*, *meta* and *para* isomers.

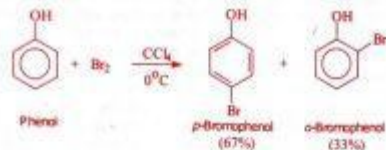
When the attack occurs at the *ortho* position, out of three canonical structures, the structure (I) is especially stable, because in this structure positive charge is placed on the carbon atom immediately next to the alkyl group. Alkyl group stabilizes a neighbouring positive charge most strongly by an inductive effect (+I). Similarly, one of the canonical forms i.e., (II), in case of *para* attack has positive charge on the carbon atom adjacent to the alkyl group.

There is no such equivalent structure formed by attack at the *meta* position, therefore, the carbocation resulting from attack at the *ortho* and *para* positions are more stable than the carbocation formed from attack at *meta* position. Thus, the preferred reaction pathway will be the one which goes through the most stable intermediate.

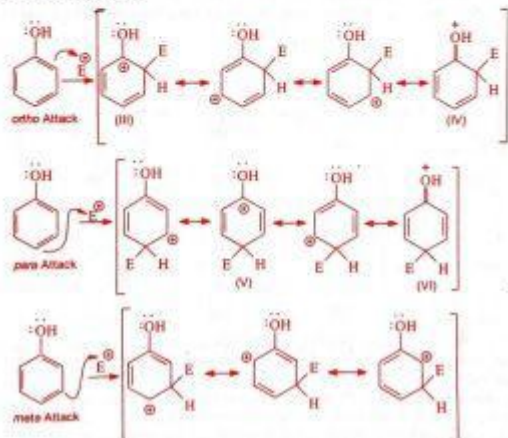


-OH, -OR, -NHCOR, -NR₂, etc. groups

Substituent (such as, -OH, -OR, -NHCOR or -NR₂) in phenols, ethers, amides or amines activates the aromatic ring through +M(mesomeric) effect. These groups direct substitution to the *ortho* and *para*-positions. For example, bromination of phenol proceeds about 10¹¹ times faster than that of benzene and forms 67% *p*-bromophenol and 33% *o*-bromophenol.



This can be explained by comparing the intermediate canonical structures arising from *ortho*, *meta* and *para* attacks. The structures (III) and (V) arising from *ortho* and *para* attack have the positive charge on the carbon atom adjacent to the substituent. Oxygen and nitrogen are nucleophilic and can share lone pairs of electrons to form a new π bond to the neighbouring electrophilic center. This results in a fourth resonance structure (IV) and (VI), where the positive charge is on the hetero atom. In this case the resonance effect is more important than the inductive effect of electronegative hetero atom. Thus, further delocalization of the positive charge stabilizes the intermediate carbocation. Since none of the canonical structures arising from *meta* attack places the positive charge on the carbon atom next to the substituent, the extra fourth structure is not possible. Therefore, *meta* attack is not favoured.



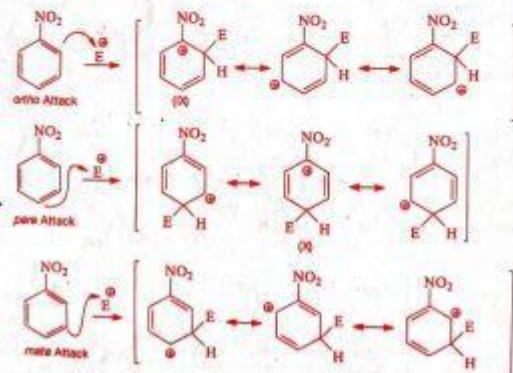
Similarly, *ortho* and *para* orientation of -NH₂ group is accounted for by contribution of structures like (VII) and (VIII). The amino substituent activates the aromatic ring and directs substitution to *ortho* and *para* positions. Aniline, for example, is halogenated directly by aqueous bromine or chlorine so that the trihalo product, 2,4,6-trihaloaniline, is formed. However, bromination of aniline can be controlled by converting aniline to its acetyl derivative.



Electron-withdrawing groups

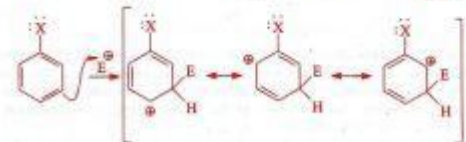
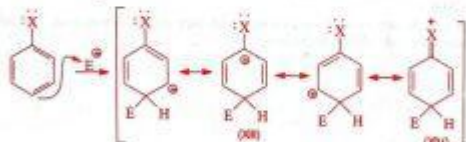
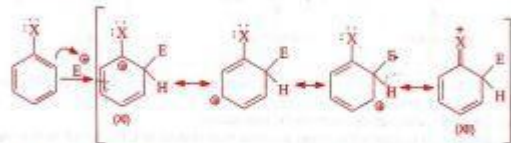
The electron-withdrawing group present on aromatic ring tends to intensify the positive charge and destabilizes the intermediate carbocation. This destabilization is more pronounced in the intermediate arising from *ortho* and *para* attacks. Thus, *meta* attack is favoured.

In the resonance structures (IX) and (X), the positive charge is placed on the carbon atom next to the electron-withdrawing group. These canonical structures are greatly destabilized. There is no such equivalent structure arising from *meta* attack and so *meta* attack is favoured.



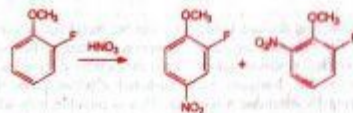
Halogens

Halogens deactivate the ring through inductive effect but direct substitution to the *ortho* and *para* positions. The halogens are more electronegative than carbon and as a result, withdraw (-I effect) the electrons away from the aromatic ring, leaving it less nucleophilic. However, the halogens have unshared electron pairs which can be delocalized to the ring by extended π -bonding. This is possible only when the attack occurs at *ortho* or *para* position. The resonance structures (XI) and (XIII), formed from *ortho* and *para* attacks have the halogen bonded directly to the carbon on which positive charge is placed. The halogen atom is able to effect a further delocalization of positive charge by sharing one of its non-bonding electron pairs to give fourth resonance structure (XII) for *ortho* attack and (XIV) for *para* attack. The halogen can not exert its stabilizing influence on the intermediate when *meta* position is attacked. As a result halogens deactivate the ring by one effect and direct substitution to *ortho* and *para* positions by another effect.

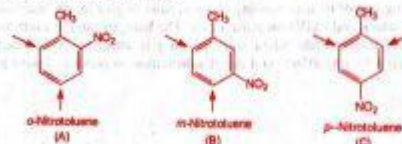


Combined directive effect of two or more than two substituents

Electrophilic substitution reactions are applicable to a variety of other aromatic derivatives such as naphthalene, biphenyl, di- or tri-substituted benzene. When there are two groups on an aromatic ring, and one is *ortho* and *para* directing and other is *meta* directing, the one that is strongly activating and *ortho* and *para* directing will determine the orientation of the incoming electrophile. For example, 2-fluoromethoxybenzene is nitrated at *ortho* or *para* position to the methoxyl group.



Preferred positions most likely to undergo electrophilic substitution in three isomers of nitrotoluene are indicated by an arrow.

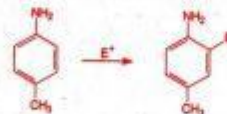


(A) CH_3 direct electrophile (E^+) to *ortho* and *para* positions with respect to itself, both the positions are also *meta* with respect to NO_2 .

(B) The *o* and *p*-directing group controls the orientation.

(C) Electrophile (E^+) is directed to *ortho* position with respect to CH_3 , which is also *meta* with respect to NO_2 .

When both groups are *o*- and *p*-directing and they are in opposition, the more strongly activating one controls the orientation.

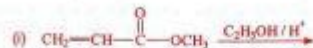


The polycyclic aromatic hydrocarbons such as naphthalene, anthracene and phenanthrene are generally more reactive than benzene toward electrophilic substitutions. The reason for this is that the activation energy for the formation of the intermediate ion is lower in these cases than for benzene, because more of the initial resonance stabilization is retained in intermediates that have a fused benzene ring.

For anthracene, the preferred site for electrophilic attack is on the center ring. This is because of the fact that the intermediate carbocation which results from attack on the center ring has two benzene rings intact.



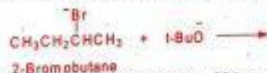
17. Explain the addition of HBr to butadiene. What products are obtained? Give mechanism.
18. What happens when 3,3-dimethyl-1-butene is treated with HCl? Explain.
19. What products are obtained in the following?



20. Explain the addition of HBr to $\text{CH}_3\text{CH}=\text{CH}_2$ by free radical mechanism.
21. What are concerted addition reactions? Explain by giving two examples.
22. Explain the mechanism involved in the following reactions, give the products obtained.



23. How will you differentiate between E2 and E1cB mechanism? Explain with examples.
24. Explain Saytzeff rule and Hofmann rule.
25. Why the reaction of 2-methyl-2-bromobutane with sodium ethoxide gives 2-methyl-2-butene as the major product? Explain.
26. Explain why ethylpropyldimethylammonium hydroxide on heating give ethylene as major product and not propene.
27. What products are obtained in major and minor amounts in the following reaction?



28. What product is obtained by the reaction of 2-bromo-2,3-diphenylbutane with a base? Give mechanism.
29. Explain why a Friedel-Crafts reaction cannot be carried out with (a) nitrobenzene, (b) aniline, and (c) phenol.
30. Arrange the following compounds in order of increasing tendency to undergo electrophilic aromatic substitution:
(a) Nitrobenzene, (b) benzene, (c) phenol, and (d) toluene
31. Which is the rate-determining step in electrophilic aromatic substitution?
32. Write the electrophile formed in the reaction of ethyl chloride with AlCl_3 .
33. Give the product of acylation of naphthalene with CH_3COCl and AlCl_3 in the solvent (a) CS_2 , and (b) nitrobenzene.

2 Reaction Intermediates, Ylides and Enamines

The most common reaction intermediates which we usually come across are carbocations, carbanions, free radicals, carbenes, nitrenes and benzyne. The ylides and enamines are stable intermediates, which can be isolated and characterised. For the sake of convenience these are also discussed in this chapter. This chapter is divided into two parts, part A deals with reaction intermediates and part B deals with ylides and enamines.

2[A] Reaction intermediates

2.1 Introduction

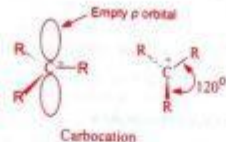
Majority of organic reactions take place via the formation of intermediates. These intermediates are of transitory existence and take part in the reaction as soon as they are formed. Being very reactive, these cannot be isolated under normal reaction conditions. However, their structures are established by indirect means either chemically or spectroscopically, or sometimes by isolating them at very low temperature. For a clear understanding of the reaction mechanism, a thorough knowledge and understanding of the reaction intermediates is essential.

2.2 Carbocations

It is a common knowledge that in the heterolytic fission of a C-X bond in an organic molecule, if X is more electronegative than carbon atom, the former takes away the bonding electron pair and becomes negatively charged (X^-). In this case an ion bearing a positive charge is also produced.

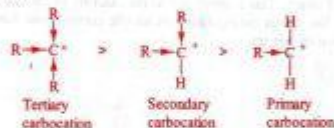


This positively charged species is called a carbocation. For many years these species were called 'carbonium ion'. However, now they are referred to as carbocations. A carbocation is also defined as a carbon atom which is trivalent, contains an even number of electrons and carries a positive charge. The carbon atom in a carbocation is sp^2 hybridized and it uses all its three hybridized orbitals for forming bonds with other atoms. The remaining p_z orbital is empty and is perpendicular to the plane of the other three bonds. A carbocation may be described as planar (trigonal coplanar) with bond angle of 120° . Because carbocation assumes a planar structure, its formation is inhibited in compounds which do not permit attainment of a planar geometry as in bridge head compounds.



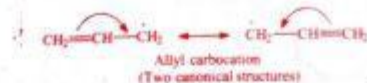
2.2.1 Stability of carbocations

If an electron-releasing group such as alkyl group is present adjacent to the carbon atom bearing positive charge, then the stability of the carbocation increases. This explains why a tertiary carbocation is more stable than a secondary carbocation which in turn is more stable than a primary carbocation. Thus, ethyl carbocation (CH_3CH_2^+) is more stable than methyl carbocation (CH_3^+).



Two factors are deemed to play a role in this case: (i) electron-donating inductive effect of alkyl group, the more alkyl groups attached to the C, the greater is the stabilizing effect and (ii) by hyperconjugation some charge delocalization occurs between the p orbital of positively charged carbon and σ bond of the β C-H. However, the presence of electron attracting groups (like nitro, carbonyl etc.) adjacent to the carbon atom bearing positive charge makes the carbocation less stable. Thus, $\text{O}_2\text{NCH}_2\text{CH}_2^+$ is less stable than $\text{CH}_3\text{CH}_2\text{CH}_2^+$.

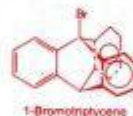
The stability of a carbocation can also be explained by resonance. By resonance the positive charge on the central carbon atom gets dispersed over other carbon atoms and this renders stability to the carbocation. The more the canonical structures for a carbocation, the more stable it will be. This explains why benzyl carbocation ($\text{C}_6\text{H}_5\text{CH}_2^+$) and allyl carbocations are more stable than propyl carbocation ($\text{CH}_3\text{CH}_2\text{CH}_2^+$).



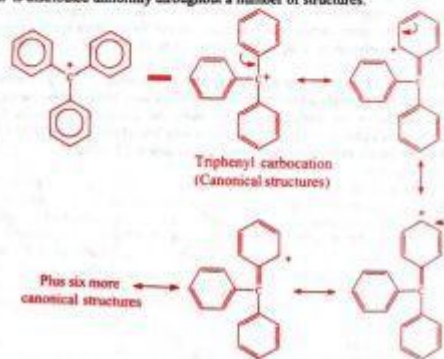
So the order of reactivity of the three carbocations is:



The basic requirement for a carbocation to be stable is that it should be planar, as it is only in this configuration that effective delocalization can occur. Also on the basis of quantum mechanical calculations for simple alkyl carbocations it has been found that the planar (sp^2) configuration is more stable than the pyramidal (sp^3) configuration by about 84 KJ (20 kcal) mol^{-1} . The difficulty in the formation of carbocations increases as the attainment of planarity is inhibited. As an illustration, 1-bromotriptycene is very resistant to $\text{S}_{\text{N}}1$ attack. This is attributed to the inability to assume planar configuration of carbocation. The planar configuration of simple carbocations has been confirmed by NMR analysis and IR spectra.

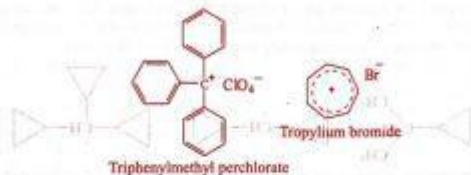


Some carbocations are very stable and so can be isolated and studied. The stability of such carbocations is explained in terms of resonance, i.e., the positive charge on the carbon is distributed uniformly throughout a number of structures.

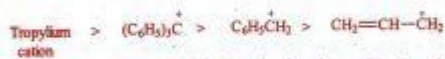


In other words a number of canonical structures are possible. The most common example is of triarylmethyl carbocation (e.g., triphenylmethyl carbocation).

In certain cases, the carbocations are so stable that their solid salts have been isolated. For example, triphenylmethyl perchlorate exists as a red crystalline solid and tropylium bromide has been isolated as a yellow solid. The tropylium bromide is stabilized by aromatization. The tropylium cation is planar and has 6 π electrons like benzene.



The order of stability of some carbocations is given below:



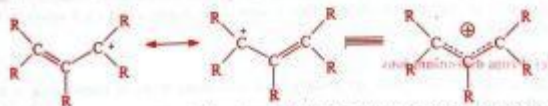
Triphenylmethyl carbocation Benzyl carbocation Allyl carbocation



Tertiary butyl carbocation Isopropyl carbocation Ethyl carbocation Methyl carbocation

The stability of carbocations is increased due to one or more of the following reasons:

(i) When the positive carbon is in conjugation with a double bond the stability of carbocation is greater due to increased delocalization of positive charge, which spreads over two atoms instead of being concentrated on one. Conjugated dienes in concentrated sulfuric acid give stable allylic type carbocations.

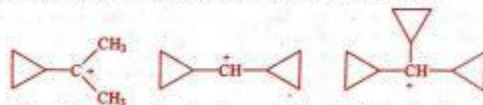


(ii) The carbocation stability is also increased due to the presence of heteroatom having an unshared pair of electrons, e.g., oxygen, nitrogen or halogen, adjacent to the cationic centre. Such carbocations are stabilized by resonance.



The methoxymethyl cation is obtained as a stable solid, $\text{MeOCH}_2^+\text{SbF}_6^-$.

(iii) Treatment of alcohols like cyclopropyl carbinol give the cyclopropylmethyl carbocations. Similarly, dimethylcyclopropyl, dicyclopropyl and tricyclopropyl cations can also be obtained from corresponding alcohols in $\text{FSO}_3\text{H}-\text{SO}_2-\text{SbF}_6$.



The stability of the cyclopropyl cation increases with each additional cyclopropyl group.

2.2.2 Generation of carbocations

Carbocations have been postulated as intermediates in a number of reactions. Following are some of the methods which are generally used to generate carbocations.

(a) From alkenes

In presence of acidic media, alkenes are protonated and give carbocations.



(b) From alkyl halides

The alkyl halides on ionization give carbocations.



The process is accelerated by the presence of powerful ion-solvating medium or metal ions such as Ag^+ ions. In place of alkyl halides, alkyl tosylates and alkyl mesylates can also be used.

(c) From diazonium ions

The alkyl diazonium ions are unstable and decompose at room temperature to give carbocations.

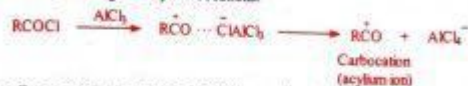


(d) From alcohols

Alcohols on treatment with concentrated acids get protonated and the protonated alcohols lose a molecule of water to form carbocations.

**(e) From acyl halides**

The acyl halides on treatment with anhydrous aluminium chloride gives a complex, which decomposes to give alkyl carbocations.



For details, see mechanism of Friedel-Crafts reaction (see sec. 1.6).

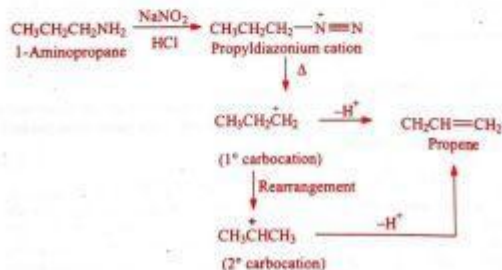
2.2.3 Reactions of carbocations

The carbocations being very reactive and unstable, undergo reactions (as soon as they are formed) to give stable products. In general carbocations undergo the following types of reactions.

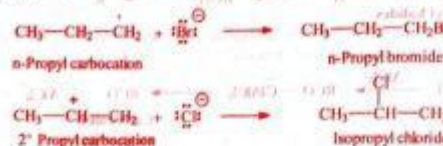
- Elimination of a proton
- Reaction with nucleophiles
- Addition to unsaturated compounds
- Molecular rearrangements

(a) Elimination of a proton

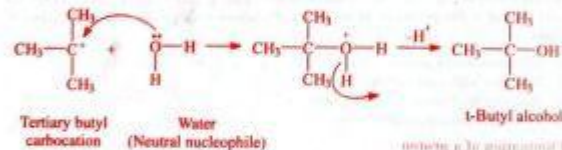
A carbocation may lose a proton to form an alkene. Thus, 1-propyl carbocation (which can be generated from 1-aminopropane by diazotization, followed by decomposition of the formed diazonium salt) may eliminate a hydrogen ion to form an alkene (propene). Alternatively, 1-propyl carbocation may rearrange to more stable secondary carbocation, which may lose a proton to give propene.

**(b) Reaction with nucleophiles**

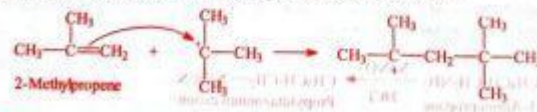
A carbocation may combine with a nucleophile to form a new bond. For example, propyl carbocation on reaction with Br⁻ (bromide ion) forms n-propyl bromide. Similarly, 2^o propyl carbocation reacts with chloride ion to form isopropyl chloride.



The reaction of a carbocation with a neutral nucleophile such as water gives a protonated alcohol. Tertiary butyl carbocation, for example, reacts with water (neutral nucleophile) to give protonated tertiary-butyl alcohol, which eliminates a proton to give tertiary-butyl alcohol.

**(c) Addition to unsaturated compounds**

A carbocation may react with an alkene to produce another carbocation.

**(d) Molecular rearrangements**

A carbocation undergoes molecular rearrangement to produce a more stable carbocation.

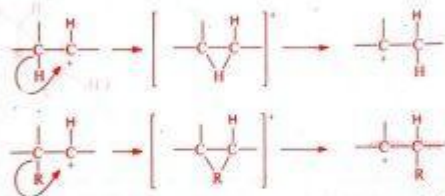
(i) A primary carbocation on rearrangement gives a more stable carbocation (secondary carbocation or tertiary carbocation).



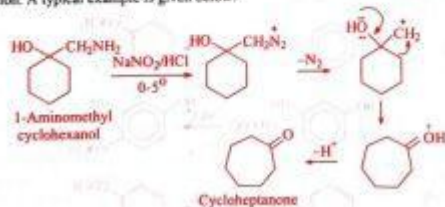
(ii) A secondary carbocation on rearrangement gives a tertiary carbocation.



The above rearrangements take place either by migration of a hydrogen with its pair of bonding electrons or by migration of an alkyl group with its pair of bonding electrons. The former is called **hydride shift** and later is called **alkyl shift**. The rearrangements in which the migrating group migrates from one atom to the very next atom is called **1,2-shift**. Mechanisms of both the rearrangements are depicted below:



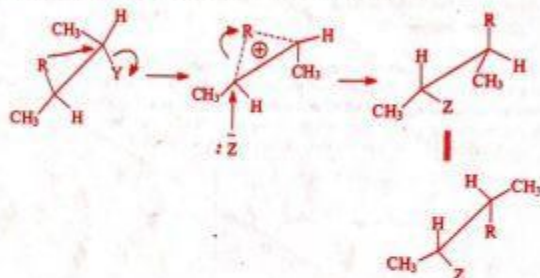
In some cases molecular rearrangements involving carbocations may lead to ring expansion. A typical example is given below.



Stereochemistry of rearrangements

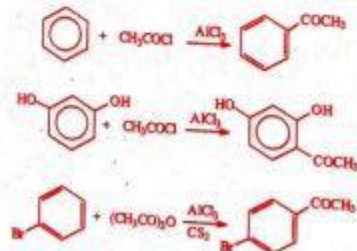
In rearrangements involving carbocations, there are three centers of stereochemical interest, the configuration of the carbon atom from which migration takes place (migration origin), the configuration of the carbon atom to which migration takes place (migration terminus) and the configuration of the migrating group (if it is chiral).

It was observed that in intramolecular rearrangement, the migration of group proceeds through the formation of a bridged intermediate. Thus, the migrating group gets associated with the migration terminus before it has completely broken its connection with the migration origin. Due to this there is no chance for change in its configuration i.e., there is retention of configuration in a chiral migrating group (R). Further evidences show that the configuration at both the chiral centers (migration terminus and migration origin) is inverted which is a typical of a molecular rearrangements.



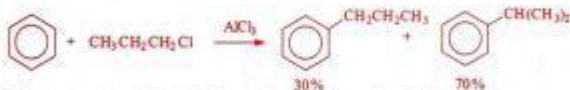
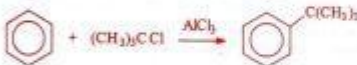
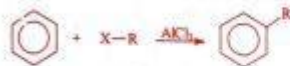
2.2.4 Applications

Generation of carbocations in a large number of synthetic sequences is very well established. Thus, Friedel-Crafts reaction is useful for introducing $-\text{COCH}_3$ group in an aromatic moiety (acylation) and also for introducing alkyl group (alkylation). Some common examples of acylation are:





The yield of the acyl products is good (70-80%). Some examples of alkylation are given below:



For the mechanism of Friedel-Crafts reaction see chapter 1, sec. 1.6.

There are some other useful reactions involving carbocations, for example, Baeyer-Villiger oxidation, Beckmann rearrangement, pinacol-pinacolone rearrangement and Wagner-Meerwein rearrangement (for detail see chap 5 and 6).

2.2.5 Non-classical carbocations

Carbocations which are more than tri-coordinate are called non-classical carbocations. These carbocations are cyclic, bridged ions and possess a three center bond in which three atoms share two electrons (three-center, two-electron bonding) e.g., the norbornyl carbocation.

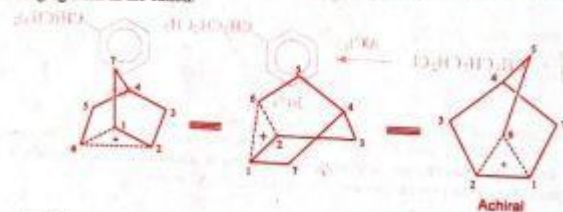
It is well known that acetolysis of both *exo*-2-norbornyl brosylate and *endo*-2-norbornyl brosylate produce exclusively *exo*-2-norbornyl acetate. The *exo*-brosylate is more reactive than the *endo* isomer. Further, optically active *exo*-brosylate gives completely racemic *exo*-acetate.



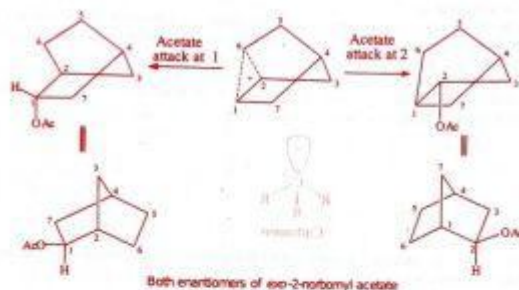
Both acetolyses proceed via formation of a carbocation. The rate of ionization of the *endo*-brosylate was considered normal, since its reactivity is comparable to that of cyclohexyl brosylate. Ionization of the *exo*-brosylate is assisted by the C-1—C-6 bonding electrons (neighbouring single bond participation, for details, see sec. 1.3.8) and led to the formation of non-classical carbocation as an intermediate.



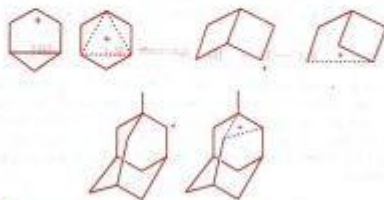
This intermediate is achiral and has a plane of symmetry passing through C-4, C-5, C-6 and the mid point of C-1-C-2 bond. Carbon-6 is penta co-ordinate and serves as a bridging atom in the cation.



Attack by acetate at C-1 or C-2 would be equally likely and would result in equal amounts of enantiomeric acetates. The acetate ester would be *exo* since reaction must occur from the direction opposite that of the bridging interaction. The non-classical carbocation can be formed only from the *exo*-brosylate, because it has the proper orbital relationship between C-1-C-6 bond and the leaving group. The bridged ion can be formed from the *endo*-brosylate only after an unassisted ionization (See also Chapter 1, 1.3.8).

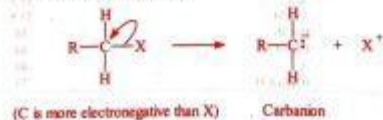


The non-classical ion is stabilized relative to a secondary ion by C-C σ bond delocalization. Some other examples of non-classical carbocations are given below.



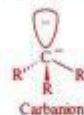
2.3 Carbanions

Carbanions are considered to be derived by the heterolytic fission of the C-X bond in an organic molecule, in which carbon is more electronegative than the atom X. In this fission the carbon takes away the bonding electron pair and acquires a negative charge and X acquires a positive charge (X^+).



The species with a negative charge on the central carbon atom having a pair of electrons is called a carbanion.

A carbanion can be considered as a species containing a trivalent carbon with a lone pair of electrons and the carbon is negatively charged. It is understandable that there are 8 electrons around the carbon atom and so it is not electron deficient. The geometry of simple carbanions determined on the basis of a number of experiments is found to be pyramidal, similar to that of amines. The central carbon atom is sp^3 hybridized with the unshared pair occupying one apex of the tetrahedron.



However, when the carbanion is stabilized by delocalization, it assumes sp^2 hybridization for effective resonance.

2.3.1 Stability of carbanions

In practice any organic compound having a C-H bond (all such compounds can be considered to be an acid in the classical sense) can donate a proton to a suitable base, the species obtained as a result is the carbanion.



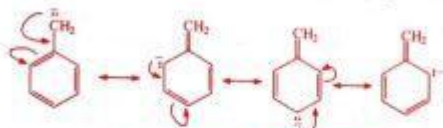
A carbanion possesses an unshared pair of electrons and is therefore a base. Thus, the carbanion may accept a proton to give its conjugate acid. In fact, the stability of a carbanion depends on the strength of the conjugate acid. The weaker is the acid, the greater is the base strength and therefore lower will be the stability of the carbanion. Following table (table 2.1) gives the base obtained from the corresponding acid along with pK_a values.

Table 2.1 : Relative stability of the carbanions

Acid	Base	Approx. pK_a
RCH_2CN	RCH_2CN^-	25
$HC\equiv CH$	$HC\equiv C^-$	25
Ar_3CH	Ar_3C^-	31.5
Ar_2CH_2	$Ar_2CH_2^-$	33.5
$PhCH_3$	$PhCH_2^-$	38
$CH_3-C\equiv CH$	$CH_2-C\equiv C^-$	44
Cyclopropane, (Δ)	Δ^-	46
$(CH_3)_3CH$	$(CH_3)_3C^-$	51

The carbanions being electron rich are very reactive intermediates and are readily attacked by electrophiles (electrons-deficient reagents). The stability of carbanion is increased if an electron-attracting group (like $-C\equiv N$ or carbonyl) is present in the molecule. However, the stability is decreased if an electron-releasing group is present in the molecule.

Like carbocations, the carbanions are also stabilized by resonance. Thus, benzyl carbanion ($C_6H_5CH_2^-$) is more stable than ethyl carbanion ($C_2H_5^-$). The stabilization by resonance is due to the delocalization of the negative charge, which is distributed over other carbon atoms. The canonical forms of benzyl carbanion are given below.



(Canonical forms of benzyl carbanion)

The stability of the carbanions is found to be in the order:

benzyl > vinyl > phenyl > cyclopropyl > ethyl > n-propyl > iso-butyl > neopentyl > cyclobutyl > cyclopentyl

The stability of the carbanion when a functional group (X) is present in the α -position, is of the order:

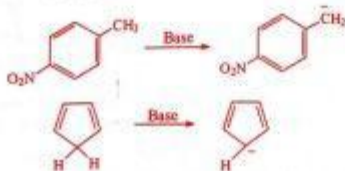


2.3.2 Generation of carbanions

Carbanions have been generated as intermediates in a large number of organic reactions. Following methods are generally used for their generation.

(a) Abstraction of H by a base

An appropriate organic substrate having a C-H bond on treatment with a suitable base results in abstraction of hydrogen to generate a carbanion.



In general an acidic hydrogen can be abstracted using an appropriate base, such as $NaOH$ / ether, aqueous $NaOH$, $t-BuO^-$ / $t-BuOH$, RLi / DMF, HMPA or N-methylpyrrolidine (NMP) in ether.

(b) From unsaturated compounds

Addition of a nucleophile to an unsaturated C-C bond generates a carbanion.



(c) From alkyl halides

Reaction of alkyl halide with Mg turning in presence of anhydrous ether as solvent generates Grignard reagent. The Grignard reagent behaves like a carbanion.

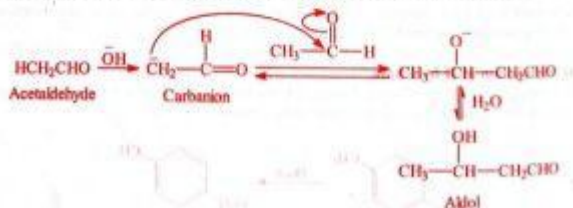


2.3.3 Reactions of carbanions

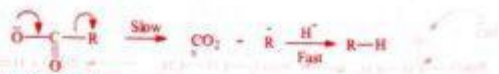
Being very reactive in nature, the carbanions undergo reactions as soon as they are formed. Carbanions take part in the usual types of reactions, viz., addition, elimination, displacement, rearrangement etc. Let us discuss each type of these reactions.

(a) Addition reactions

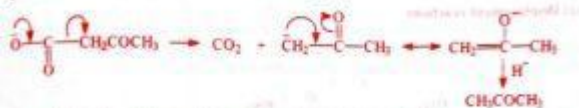
The carbanions being electron rich behave like nucleophiles. These add to the carbonyl group of aldehydes (for example in **aldol condensation**, see sec. 5.2) or ketones.



In decarboxylation, the loss of CO_2 from carboxylate anion is believed to involve carbanion intermediate, which acquires a proton from solvent or other sources.

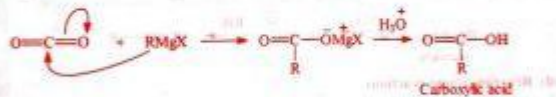
**Carboxylate anion**

The anion of β -keto acids can undergo facile decarboxylation. This is attributed to the presence of $\text{C}=\text{O}$ group, which can act like NO_2 group.



Other reactions which involve the addition of carbanions are reactions like **Perkin reaction**, **Claisen condensation**, **Dieckmann condensation**, **benzilic acid rearrangement** and **Michael addition** (for detail see chapter 5).

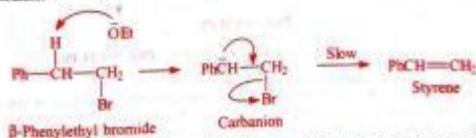
Another interesting example of addition reaction of carbanions is carbonation. In this reaction organometallic compounds (e.g., Grignard reagent RMgX) acts as a source of negative carbon and reacts with a very weak nucleophile, CO_2 , to form the corresponding carboxylic acid.



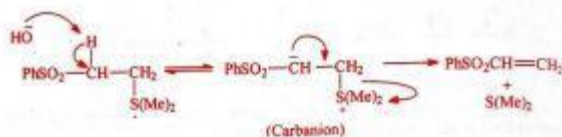
For further details see Grignard reaction, sec. 7.2.

(b) Elimination reactions

Carbanions are involved as intermediates in elimination reactions. For example, β -phenylethyl bromide on treatment with a suitable base (like NaOEt) results in the formation of styrene. The reaction proceeds via the formation of a carbanion intermediate.



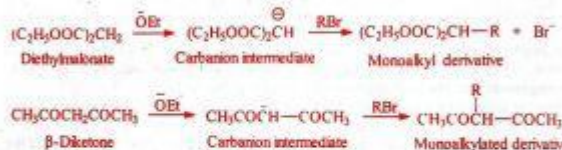
It is found that the presence of a positively charged substituent on the α -carbon atom promotes the acidity of the β -H atom. The following reaction illustrates the above contention.



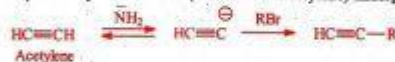
(Carbanion)

(c) Displacement reactions

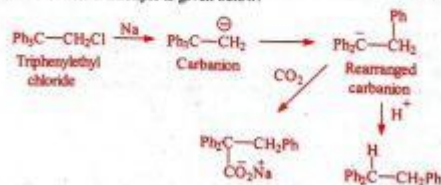
The carbanions are involved in a number of displacement reactions. The synthetic applications of β -ketoesters (like diethylmalonate) and 1,3-diketones (like acetylacetone) are due to the formation of the reactive intermediates, carbanions.



In a similar way the acetylide carbanion (obtained from acetylene) undergoes alkylation.

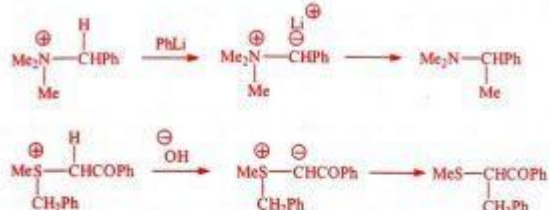
**(d) Rearrangement reactions**

Rearrangements involving carbanions are much less common than those involving carbocations. One such example is given below.



As seen, in the above case the carbanion formed undergoes rearrangement; in this case the migrating group moves to the carbanion carbon without an electron pair, compared to rearrangements involving carbocations in which the migrating group migrates with an electron pair. The rearranged carbanion may react with an alcohol or carbon dioxide to give the final products.

Simple 1,2-shifts of alkyl from carbon to carbon are not many. However, examples are recorded in literature in which the alkyl is involved in the 1,2-shift from N or S to a carbanion carbon (see **Stevens rearrangement**, sec. 6.4.2).

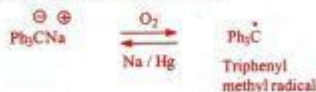


As seen in the above examples (first example) very strong base like PhLi is used to remove proton from a positively charged species. However, the presence of electron-withdrawing substituents, like carbonyl, facilitates the removal of the proton. From the second example given above, it is clear that PhCH₂ migrates in preference to Me.

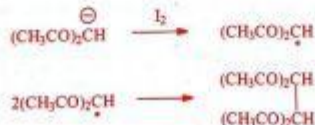
Some base induced carbanion rearrangements which involve a 1,3-elimination are also known (see **Favorskii rearrangement**, sec. 6.4.1).

(e) Oxidation of carbanions

Under suitable conditions the carbanions can be oxidised. Thus, triphenylmethyl carbanion is oxidised slowly by air. The triphenylmethyl radical so obtained can be reduced back to the carbanion with sodium amalgam.



In certain cases, the carbanions can be oxidised with one-electron oxidizing agents (e.g., iodine).



This is a useful reaction for forming a C-C bond via dimerization of the formed radical.

2.4 Free radicals

When a covalent bond undergoes homolytic fission, the two departing atoms take one electron of the bonding pair of electrons. The two fragments produced carry an odd electron each and are called free radicals.



The term free radical is used for any species which possess an unpaired electron (single nonbonding electron). The free radicals are the most important neutral reaction intermediates and are transitory. These radicals react with other radicals or molecules by gaining one more electron to restore the stable bonding pair. In fact, the high reactivity of free radicals is due to the tendency of the odd electrons to 'pair up' with another available electron.

A radical is paramagnetic and so can be observed by electron spin resonance (e.s.r.) spectroscopy. For simple free radicals two possible structures have been postulated. The first is a planar sp² hybridized radical (A), similar to carbocation. The second is a pyramidal sp³ hybridized radical (B), similar to a carbanion.

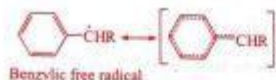


There is no chemical evidence which supports either a planar structure (A) or pyramidal structure (B) for simple free radicals. However, using physical methods like e.s.r., UV and IR, it is believed that simple free radicals have the planar structure (A).

2.4.1 Stability of free radicals

As in the case of carbocations, the order of stability of free radicals is: tertiary > secondary > primary. This can be explained on the basis of hyperconjugation as in the case of carbocations. The stability of the free radicals also increases by resonance possibilities. Thus, allylic and benzylic free radicals are more stable and less reactive than the simple alkyl radicals. This is due to the delocalization of the unpaired electron over the π orbital system in each case.

The stability of a radical increases as the extent of potential delocalization increases. Therefore, Ph₃CH• is more stable than PhCH₂• and Ph₃C• is a reasonably stable radical. The stability of Ph₃C• is explained by the delocalization of the unpaired electron. The e.s.r. spectrum of Ph₃C• supports its delocalization. The extent of delocalization is maximum in Ph₃C• than in Ph₂CH• or even in PhCH₂•.



Certain free radicals have rigid molecular structures with fixed bond angles and dihedral angles. These are known as bridgehead free radicals and have pyramidal structure. This has been supported on the basis of physical and chemical evidences. Following are some bridgehead radicals. These bridgehead radicals can be conveniently formed.

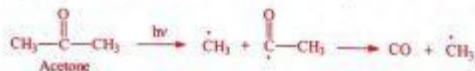


2.4.2 Generation of free radicals

The homolytic cleavage of a covalent bond generates a pair of free radicals. Following are some of the methods used for the generation of free radicals.

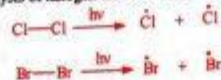
(a) Photolysis

In this method a suitable organic molecule is subjected to UV radiation. The organic molecule should be able to absorb radiation in the ultra-violet or visible range. The cleavage of a molecule into two parts by using UV light is known as photolysis. As an illustration, acetone in vapour phase is decomposed by light having a wave length of about 320 nm (3200 Å). In this reaction two molecules of methyl free radicals are generated.



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The photolytic homolysis of halogen molecules is very well known.



These free radicals in turn can initiate the halogenation of alkanes or addition to alkenes. Certain other species that undergo easy photolysis are alkyl nitrites and alkyl hypochlorites. Both these molecules generate alkoxy radicals.



Alkyl nitrites



Alkyl hypochlorites

The photolysis method has two basic advantages over the thermolysis (see below) for the generation of free radicals.

(i) Photolysis can cleave strong bonds that are difficult to cleave by thermolysis.



Azoalkanes

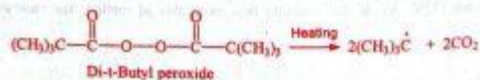
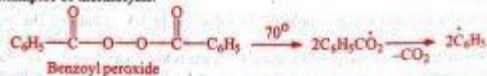
(ii) In photolysis energy of only one particular wavelength is transferred to a molecule and in this way photolysis is a specific method for homolytic cleavage than pyrolysis. Thus, acyl peroxide on photolysis generates the free radicals.

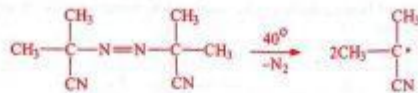


However, in thermolysis besides the above a number of other byproducts are obtained.

(b) Thermolysis

In this method, the organic substrate is heated at suitable temperature. Following are some examples of thermolysis.



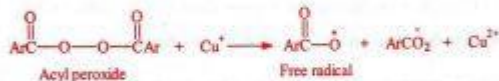


Azobisisobutyronitrile
(AIBN)

It is appropriate to mention that benzoyl peroxide and azobisisobutyronitrile (AIBN) are used as a free radical initiator for the manufacture of polymers. The free radicals generated by the so called radical initiations are responsible for propagation of the polymer chain.

(c) Redox reactions

In redox reactions there is one-electron transfer in generating the free radicals. The source of one-electron transfer is the metal ion (e.g. Cu^+ , Fe^{2+} etc.). Thus Cu^+ ions are used for the decomposition of acyl peroxides.



This is a convenient method for the generation of $\text{ArCOO}^\cdot$ radicals especially because in thermolysis the $\text{ArCOO}^\cdot$ radicals further decomposes to $\text{Ar}^\cdot + \text{CO}_2$.

Cu^+ also finds application in **Sandmeyer reaction**, involving decomposition of diazonium salts. In this reaction the free radical, $\text{Ar}^\cdot$, is formed as an intermediate.

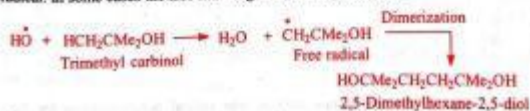


Both the above reactions can be described as cases of reductions.

Fe^{2+} is known to catalyse the oxidation reactions of aqueous solution of H_2O_2 . The mixture of H_2O_2 and Fe^{2+} is known as **Fenton's reagent**. The effective oxidising agent is the hydroxyl radical, $\text{HO}^\cdot$, and the reaction is known as **Fenton's reaction**.



The $\text{HO}^\cdot$ radical can abstract H from a suitable substrate and generates another free radical. In some cases the free radical generated may dimerize.



The autoxidation of benzaldehyde is also catalysed by metal ions which are capable of one electron transfer.



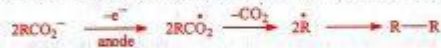
Stable phenoxy radical can also be generated by one electron oxidation by $\text{K}_3\text{Fe}(\text{CN})_6$.



The dimerization of carbanions with iodine also take place via a free radical.



In **Kolbe electrolytic reaction**, the free radicals are the intermediate (see sec. 5.56).



Free radicals are also formed as intermediates in pinacol reductions with sodium or magnesium and in acyl ion condensation.

2.4.3 Reactions of free radicals

We know that free radicals are very reactive reaction intermediates and that their half-life period is very short. Since the free radicals have a odd electron, these have the natural tendency to pair its odd electrons with another electron from any available source. A free radical may couple with any free radical or attack an electrically neutral molecule and generate a new free radical. Some of the reactions of free radicals are given below.

(a) Recombination

The free alkyl radicals may recombine to form hydrocarbons.



The reaction is used in the termination step in free radical polymerization for the production of polymers.

b) Disproportionation

At higher temperature the alkyl radical may undergo disproportionation. The ethyl radical disproportionates (i.e. one radical $\text{CH}_3\text{CH}_2^\bullet$ takes up hydrogen from another free radical) to give ethylene and ethane.



It is found that coupling takes place with unbranched free radicals while disproportionation predominates with branched radicals.

(c) Reaction with olefins

The alkyl radicals react with olefins to form a new free radicals.



The newly formed free radical further adds on to another molecule of olefin.

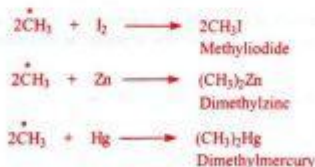


The reaction continues till the formed free radical couples with another free radical and termination of the reaction takes place.

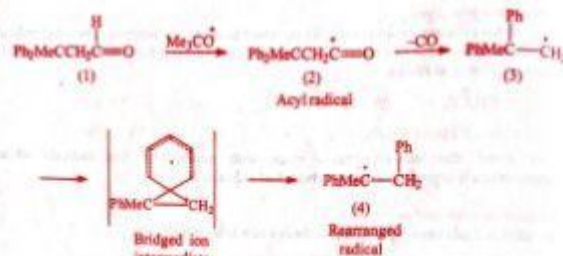
The above reaction is used as the propagation step in the polymerization of ethylene.

(d) Reactions with iodine and metals

The alkyl radicals may combine with iodine or other elements to form alkyl derivatives.

**(e) Rearrangements**

Like carbanions, the free radicals undergo rearrangements involving 1,2-shifts of aryl group via bridgehead intermediate. Thus, the aldehyde (1) undergoes H-abstraction from the CHO group by $\text{Me}_3\text{CO}^\bullet$ to yield the acyl radical (2), which loses CO to form the radical (3). The radical (3) undergoes rearrangement to give radical (4). The rearrangement involves the migration of Ph (instead of Me) via the bridged ion intermediate.

**2.4.4 Mechanism of free radical reactions**

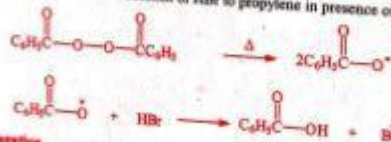
The free radical reactions take place in three steps, i.e., initiation, propagation and termination.

(a) Initiation

In this step the free radicals required for a reaction to be carried out are generated *in situ* by irradiation or heating (the former method is clean and is mostly used). Thus, a molecule of bromine on irradiation generates two free radicals ($\text{Br}^\bullet$).



Alternatively, the free radical ($\text{Br}^\bullet$) can be generated by using an initiator like benzoyl peroxide (as in the case of the addition of HBr to propylene in presence of peroxide).

**(b) Propagation**

The free radical ($\text{Br}^\bullet$) formed in first step can abstract a hydrogen atom from the substrate and generates a new free radical.



The generated free radical ($\text{C}_6\text{H}_5\dot{\text{C}}\text{H}_2$) may react with another molecule (Br_2) to form the substitution product and generating another free radical ($\text{Br}^\bullet$).



Alternatively, the free radical formed in the initiation step can react with an olefinic compound (ethylene) to form a new free radical.



This new free radical may abstract a proton from the reagent (HBr) to form the addition compound.



(c) Termination

The reaction is terminated by coupling of two free radicals (same or different radicals) or by disproportionation.



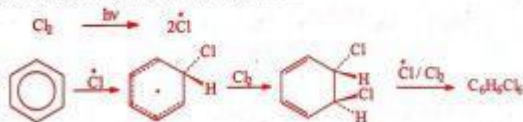
A chain reaction can also be terminated by addition of free-radical inhibitors like benzoquinone, phenols, amines, thiols, oxygen etc. Thus, in presence of O_2 the methyl free radical forms a new free radical, $\text{CH}_3-\text{O}-\text{O}^\bullet$, which is much less reactive than $\text{CH}_3^\bullet$ and so the reaction slows down and finally terminated.

14.5 Applications of free radicals

Free radicals play an important role in a large number of reactions. Following are some of the important applications of free radicals.

(a) Conversion of benzene into benzene hexachloride

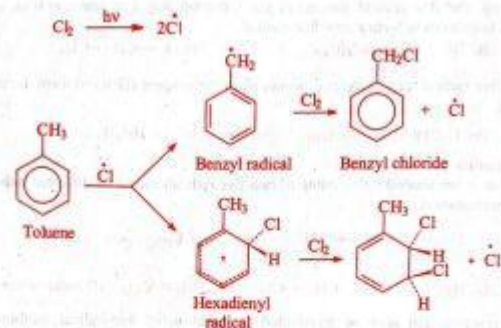
The addition of Cl_2 to benzene proceeds via a free radical pathway. The reaction is catalysed by light or by the addition of peroxides.



The reaction product is a mixture of eight non-interconvertible stereoisomers of hexachloro benzene. The gamma isomer, known as **Lindane (gammexane)** is a useful insecticide.

(b) Conversion of toluene into benzyl chloride

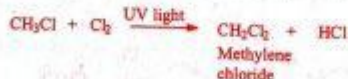
The reaction of toluene with chlorine in presence of sun-light gives benzyl chloride. The $\text{Cl}^\bullet$ abstracts a hydrogen from CH_3 group to give delocalized benzyl radical, $\text{C}_6\text{H}_5\dot{\text{C}}\text{H}_2$ (which is resonance stabilized) rather than hexadienyl radical, in which the aromatic stabilization of the starting substrate is missing.



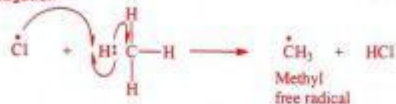
Due to the above consideration toluene gives benzyl chloride as a major product.

(c) Conversion of methane into carbon tetrachloride

The reaction of methane with chlorine in presence of UV light gives a mixture of methyl chloride, methylene chloride, chloroform and carbon tetrachloride. When excess of chlorine is used and by prolonging the time of the reaction, the final product is predominantly carbon tetrachloride.



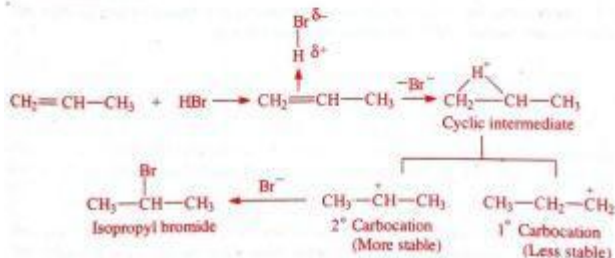
The above chlorination proceeds via the free radical pathway. Various steps are given below:

Initiation**Propagation**

The reaction continues and finally CCl_4 is obtained as the final product.

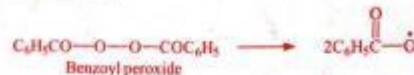
Termination**(d) Conversion of propylene into n-propyl bromide**

It is well known that HBr adds on to propylene to give isopropyl bromide. In this case the reaction proceeds via a carbocation ion intermediate (the secondary carbocation being more stable than the primary carbocation). The reaction takes place in accordance with Markownikoff's rule.

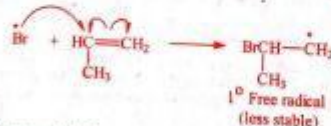
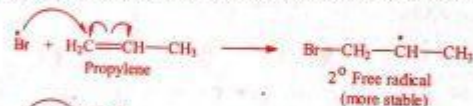


However, in the presence of peroxide the product obtained is n-propyl bromide. This is known as peroxide effect and the addition of HBr takes place in anti Markownikoff fashion. This addition proceeds by free radical mechanism.

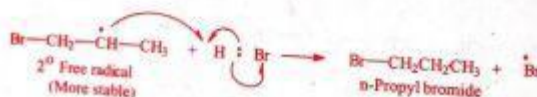
(i) The peroxide on dissociation gives two alkoxy radicals, which attack HBr to form bromine free radical ($\text{Br}^\cdot$).



(ii) The bromine free radical then attacks the alkene molecule giving two bromo alkyl free radicals (the 2° free radical and 1° free radical, the former is more stable than latter).



(iii) The more stable free radical reacts with HBr forming anti Markownikoff product and another bromine radical, which propagates the chain reaction.

**(e) Conversion of ethylene into polyethylene**

Ethylene on polymerization in presence of a free radical initiator such as benzoyl peroxide gives polyethylene. The polymerization takes place via free radical mechanism and involves 3 steps.

- (i) Benzoyl peroxide on heating gives benzoyloxy free radical, which in turn gives phenyl free radical.



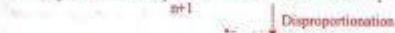
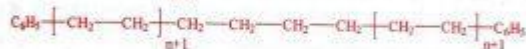
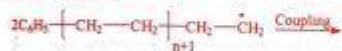
The formed phenyl free radical adds onto a molecule of ethylene producing another free radical.



- (ii) The free radical ($\text{C}_6\text{H}_5\text{CH}_2\dot{\text{C}}\text{H}_2$) formed above adds on to another molecule of ethylene. The successive addition of free radicals on to alkene results in the propagation of the chain reaction.



- (iii) The long chain free radical can be terminated by radical coupling or disproportionation.



Similarly, vinyl polymerization takes place by the free radical mechanism.

Besides the above applications, free radicals are obtained as intermediates in a large number of reactions like Sandmeyer reaction, Gomberg reaction, Wurtz-Fittig reaction, Hunsdiecker reaction, Kolbe's electrolytic method etc. (For details see chapter 5).

2.5 Carbenes

The carbenes are highly reactive species having a life time less than one second. The parent species, $:\text{CH}_2$ is known as methylene. The derivatives of carbene are named by the so called carbene nomenclature. As an example, $:\text{CCl}_2$ is known as dichlorocarbene. However, it can also be called dichloromethylene.

The two nonbonding electrons of carbene are derived by the homolytic fission of two bonds. The carbon atom in carbene has six electrons and so is electron deficient species analogous to carbocation. Thus, carbene normally reacts as a strong electrophile.



A carbene is known to exist as a singlet or triplet. If both the electrons go into one orbital (antiparallel spin), the carbene is in singlet state. There is no magnetic moment in this state. On the other hand, if the two electrons go into different orbitals, they will have parallel (unpaired) spins, such a carbene would have a magnetic moment and is called the triplet state.



Singlet state of carbene

Triplet state of carbene

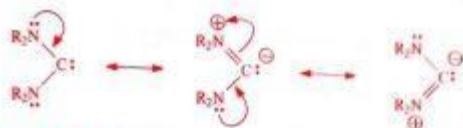
In singlet state of carbene (or methylene) the carbon atom is sp^2 hybridized. Two of the sp^2 hybrid orbitals are bonded to two hydrogen atoms and the third contains a lone pair of electrons. The unhybrid p orbital is unoccupied. The bond angle is 103° and a C—H bond length is 1.12 Å (see representation of singlet carbene).

On the other hand, in triplet carbene, the carbon atom is sp hybridized. The two sp hybridized orbitals are bonded to two hydrogen atoms and the two unhybridized p-orbitals contain one electron each. The triplet state of carbene is also a bent molecule with an angle of about 136° and C—H bond length is 1.03 Å. A singlet carbene is diamagnetic, while the triplet carbene is paramagnetic.

Since the triplet carbene is a diradical, it has been investigated by e.s.r. measurements. The results show that the triplet carbene is a bent molecule with an angle of about 136° . However, e.s.r. measurements cannot be made with singlet carbene. On the basis of electronic spectra of $:\text{CH}_2$ formed in the flash photolysis of diazomethane, it was found that the singlet carbene is also a bent molecule with an angle of about 103° . Singlet $:\text{CCl}_2$ and $:\text{CBr}_2$ have also been found to be bent molecules with angles of 100° and 104° respectively.

2.5.1 Stability of carbenes

Carbenes in which the carbene carbon is attached to two atoms, each bearing a lone pair of electrons, are more stable due to resonance.

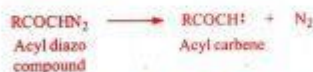
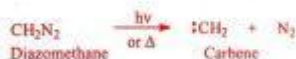
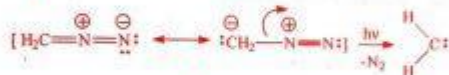


2.5.2 Generation of carbenes

Following methods are used for the generation of carbenes.

(a) From aliphatic diazo compounds

Aliphatic diazo compounds can be decomposed either photolytically or thermally to generate carbenes.



(b) From ketenes

Ketenes can be decomposed thermally or photolytically to generate carbenes.



The starting ketene can be obtained by pyrolysis of acetone or from diazoketones.



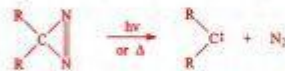
(c) From epoxides

Photolytic decomposition of epoxides generate carbenes.



(d) From diazirines

Decomposition of diazirines generate carbenes.



Diazirines

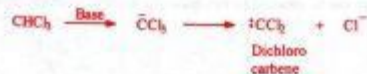
(e) From tetrazoles

Thermal decomposition of tetrazoles generate carbenes.



(f) From alkyl halides

This method is commonly used for generation of chlorocarbenes. Thus, loss of a proton from chloroform by a base followed by expulsion of chloride ion generates dichloro carbene.



(g) From ylides

Thermal or photolytic decomposition of ylides generate carbenes.

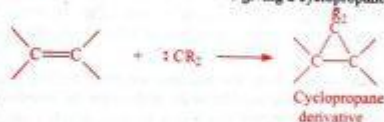


2.5.3 Reactions of carbenes

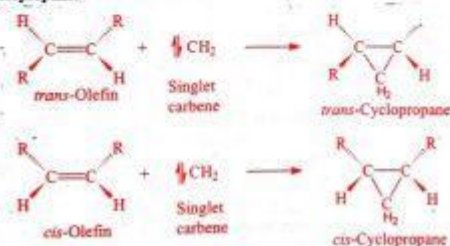
Carbenes are unstable but very reactive intermediates. Therefore, carbenes are prepared *in situ* in presence of a substrate with which it has to be reacted. Following are some important reactions of carbenes.

(a) Cycloadditions

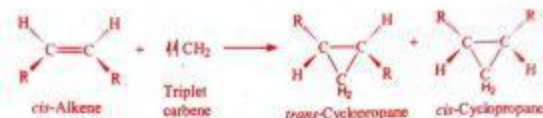
Carbenes add on to an olefinic double bond giving a cyclopropane derivative.



When the reaction is performed in liquid medium singlet carbene is formed, which adds on in stereospecific way. Thus, *cis*-alkene gives *cis*-cyclopropane and *trans*-alkene gives *trans*-cyclopropane.



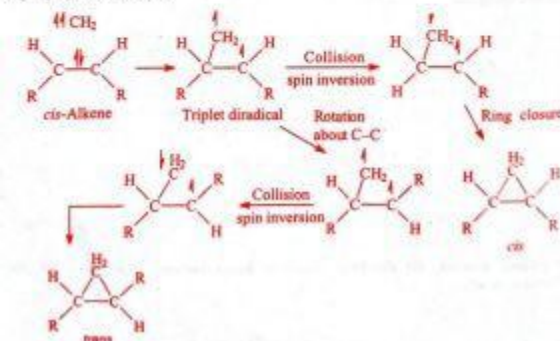
In gaseous medium, the attacking species is triplet carbene, which does not add stereospecifically.



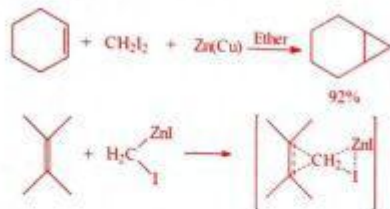
The stereochemistry of these cycloadditions is so specific that Skell used it as a diagnostic test for distinguishing between singlet and triplet carbenes. According to Skell, the addition of singlet carbene to an olefin occurs in a concerted manner and therefore is stereospecific.



However, in case of triplet carbene, both the unpaired electrons cannot form a new covalent bond because of their parallel spins. Therefore, in this case the reaction will take place in two steps. In the first step a triplet diradical is formed, which undergoes spin inversion and then ring closure. For this the radical has to wait for appropriate type of collision. During this time, there is free rotation, and a mixture of *cis* and *trans*-cyclopropane is obtained.



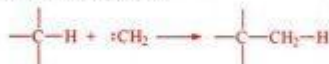
In the above cycloaddition reactions, carbene is generated *in situ*. A more convenient way is to use **Simmons-Smith reagent** which transfers methylene from methylene iodide and zinc-copper couple to a carbon-carbon double bond. In the above reaction free carbene is not generated. The intermediate is believed to be ICH_2ZnI , which behaves as an electrophile (see sec. 7.6).



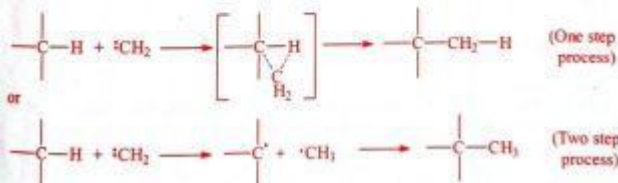
Instead of expensive methylene iodide, comparatively cheaper dibromomethane with zinc dust and cuprous chloride can be used to give better yield of the adduct.

(b) Insertion reactions

Carbenes can insert into a C-H single bond.

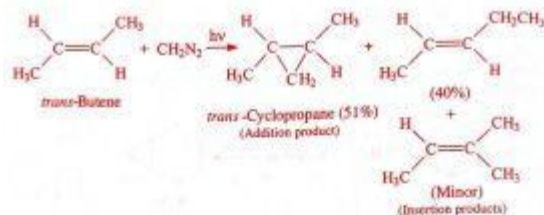


The reaction occurs in the following way.



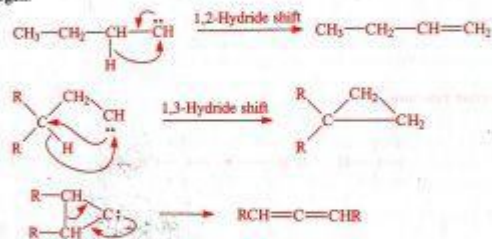
This insertion reaction shows that carbenes are very reactive.

In the above mentioned cycloaddition reactions, along with cyclopropane, products in which methylene is inserted into C-H single bonds are also obtained.



(c) Rearrangements

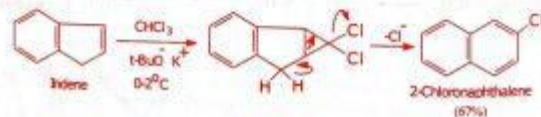
Alkyl carbenes can undergo rearrangement involving migration of an alkyl group or hydrogen.



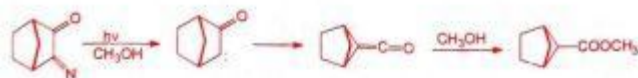
These reactions can be regarded as intramolecular insertion reactions.

(d) Ring expansion

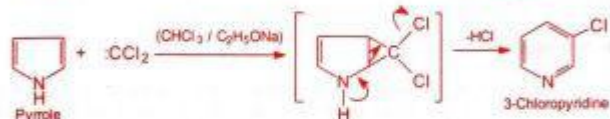
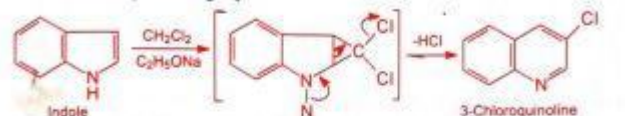
In certain substrates, addition of carbene involves ring expansion. Thus, the reaction of indene with dichlorocarbene (:CCl_2) gives 2-chloronaphthalene.



When a cyclic diazoketone is decomposed the rearrangement results in ring contraction. The reaction takes place via the intermediate carbene.



Some other examples of ring expansion are:



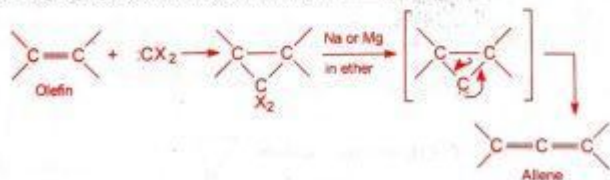
(e) Dimerization

Carbene can couple with one another forming alkenes.



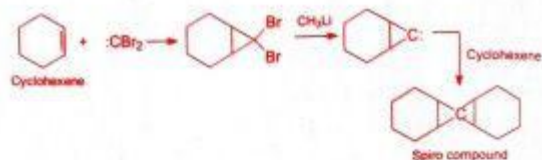
(f) Synthesis of allenes

Dihalocyclopropanes on heating with metal yield allenes.



(g) Synthesis of spiro compounds

Dihalocyclopropanes, obtained from cycloalkenes and carbene, on treatment with LiMe gives spiro compound.



Besides the above, carbene is also obtained as intermediates in a number of reactions. Some examples are: **carbylamine reaction**, **Wolff rearrangement**, **Reimer-Tiemann reaction** etc. (for detail see chapter 5).

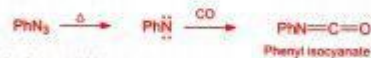
2.6 Nitrenes

Nitrenes are the nitrogen analogues of carbenes. These are electron-deficient monovalent nitrogen species. The nitrogen atom in nitrenes has a sextet of electrons. As in the case of carbenes, the nitrenes exist in singlet and triplet states.

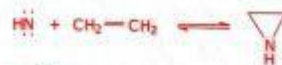


2.6.1 Stability of nitrenes

Nitrenes are very reactive species and cannot be isolated. However, a nitrene has been trapped by its reaction with carbon monoxide to yield an isocyanate.



Nitrenes can also be trapped in presence of ethylene.



2.6.2 Generation of nitrenes

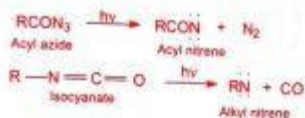
(a) From azides

Thermal or photolytic decomposition of azides give nitrenes.



This is the most common method for the generation of nitrenes.

Acyl and alkyl nitrenes can also be obtained by the photolysis of acyl azides and isocyanates, respectively.



(b) From sulfinylamines

Pyrolysis of sulfinylamines generate nitrenes



(c) From N-benzenesulfonyl carbamates

The reaction of N-benzenesulfonyl carbamate with a base results in the formation of carboalkoxynitrene with the elimination of benzenesulfonate anion.



2.6.3 Reactions of nitrenes

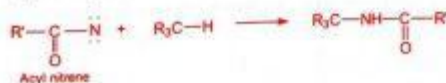
(a) Addition to C=C bonds

Like carbenes, the addition of nitrenes to a C=C bond is stereospecific with singlet and non-stereospecific with triplet nitrenes (see sec. 2.5.3).

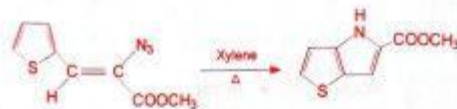


(b) Insertion

Nitrenes, particularly acyl nitrenes and sulfonyl nitrenes can insert into C-H bonds.



Nitrenes can also undergo insertion into C-H single bonds leading to ring closure. Thus, vinyl azidothiophenes have been found to be useful precursors for annulation of pyrroles and thiophenes.



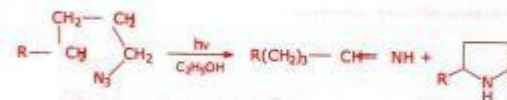
(c) Dimerization

The dimerization of aryl nitrenes give azobenzene.



(d) Hydrogen abstraction

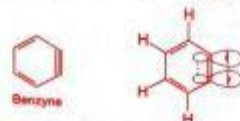
Hydrogen abstraction from the carbon α to the nitrogen leads to the formation of imines. This process is of considerable synthetic importance. When hydrogen abstraction takes place from 4- and 5-position which is followed by ring closure, the product formed are pyrrolidines and piperidines, respectively.



Nitrenes are also obtained as reaction intermediates in **Hofmann**, **Curtius**, **Schmidt** and **Lossen** rearrangements (for details see chapter 6, sec. 6.2).

2.7 Benzyne

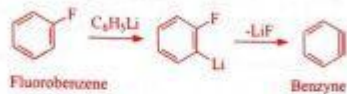
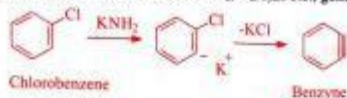
Benzyne are neutral, highly reactive reaction intermediates, in which the aromatic character is not markedly disturbed. Benzyne (or arynes) contain a carbon-carbon triple bond and may be regarded as aromatic counterpart of acetylene. As is clear, benzyne is benzene minus two σ -hydrogens and so it is also called dehydrobenzene. The benzyne bond is not like the triple bond of acetylene where the two carbons form a σ -bond using sp orbitals and the remaining p orbitals are used to form π -bonds. Such a structure is not feasible in case of benzyne due to hexagonal geometry associated with the benzene ring. It is believed that the new bond of benzyne is formed by the overlap of sp^2 orbitals belonging to two neighbouring carbon atoms. As the sideways overlapping is not very effective, the new bond is weak and so the benzyne is highly reactive species.



2.7.1 Generation of benzyne

(a) From aryl halides

Aryl halides on treatment with strong base like KNH_2 , $\text{C}_6\text{H}_5\text{Li}$ etc., generate benzyne.



(b) From o-aminobenzoic acid

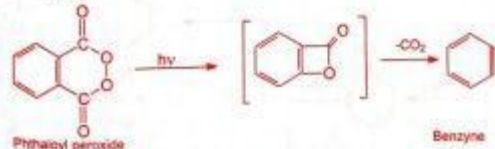
The o-aminobenzoic acid on diazotization followed by decomposition of the formed diazo compound generates benzyne.



This is a convenient method for the generation of benzyne.

(c) From phthaloyl peroxide

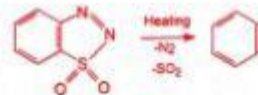
Phthaloyl peroxide on photolytic decomposition generates benzyne via lactone intermediate.



(d) From benzothiadiazate-1,1-dioxide

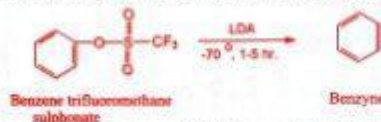
Thermal decomposition of benzothiadiazate-1,1-dioxide generates benzyne.

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(e) From benzenetrifluoromethane sulphonate

Benzenetrifluoromethane sulphonate on treatment with a strong base generates benzyne.



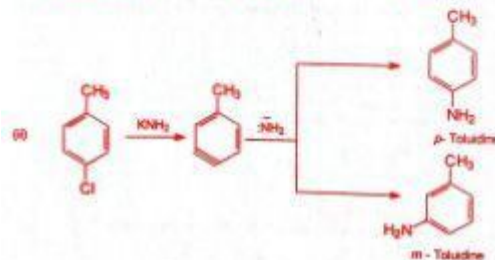
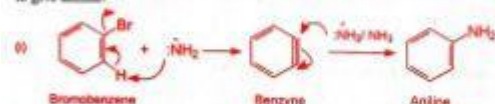
This is the most recent and convenient method for the generation of benzyne.

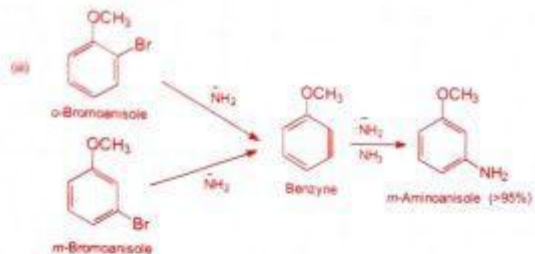
2.7.2 Reactions of benzyne

Benzyne is an extremely reactive species and is generated *in situ* for obtaining various products. In fact benzyne generated is trapped by various substrates.

(a) Reaction with nucleophiles

As already stated aryl halides on treatment with KNH_2 (strong base) generates benzyne. When KNH_2 is used, the available nucleophile (NH_2^-) reacts with the generated benzyne to give aniline.

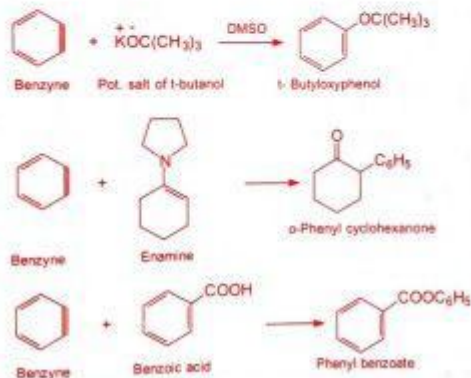




All the above reactions show that benzyne is obtained as a reaction intermediate.

(b) Synthesis of simple molecules

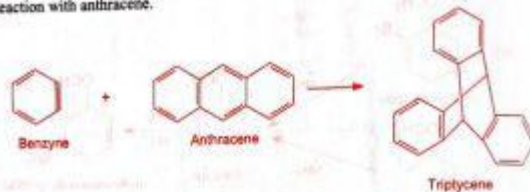
A number of products can be synthesised by the reaction of a benzyne with simple reagents.



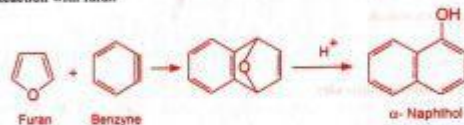
(c) Synthesis of unusual type of products

Several types of compounds which are difficult to obtain or cannot be obtained by other methods can be conveniently obtained via benzyne intermediate. Thus the generated benzyne can be trapped with anthracene, furan and their derivatives.

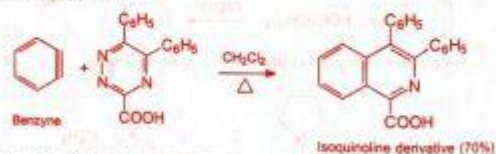
(i) Reaction with anthracene.



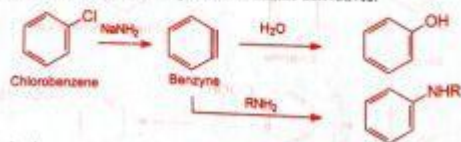
(ii) Reaction with furan



(iii) Reaction with triazines



(iv) Conversion of chlorobenzene to phenol and aniline derivatives.



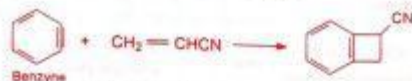
(v) Dimerization

In the absence of any nucleophiles benzyne undergoes dimerization.

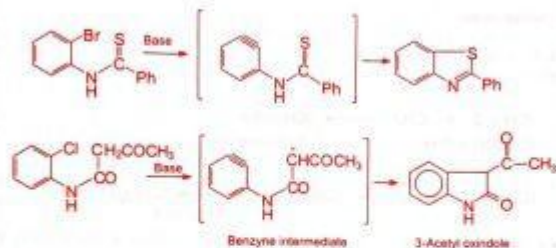


(vi) Reaction with olefins

Benzynes reacts with olefins to give four-membered rings.



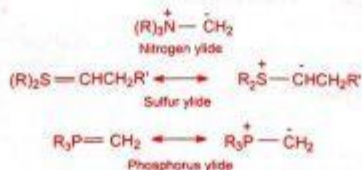
(vii) Synthesis of heterocyclic compounds



2 [B] Ylides and enamines

2.8 Ylides

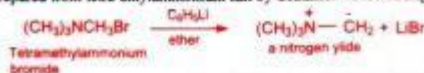
Ylides are defined as compounds in which a positively charged hetero atom (e.g., N, P or S) is connected to a carbon carrying a negative charge. They are also referred as vicinal ionic (i.e., with positive and negative charges on adjacent atoms) intermediates. There are three main type of ylides: phosphorus, nitrogen and sulfur, although arsenic, selenium etc., ylides are also known. Phosphorus and sulfur ylides can be represented in two canonical forms but nitrogen ylides have only one structure. Phosphorus ylides are much more stable than nitrogen ylides. Sulfur ylides have a low stability. The three ylides are represented as shown below:



2.8.1 Generation of ylides

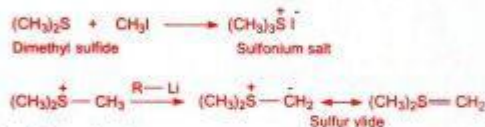
(a) Nitrogen ylides

These are prepared from tetra-alkylammonium salt by treatment with a strong base.

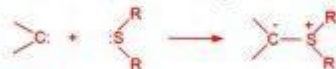


(b) Sulfur ylides

The sulfonium salts on treatment with a base (like alkyl-lithium) eliminate an α -hydrogen to form dialkylsulfonium methyide (a sulfur ylide). This is the most commonly used method for the preparation of sulfur ylides.

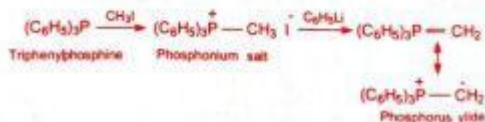


Sulfur ylides can also be prepared by the reaction of a carbene with a sulfide. The required carbene is generated by any of the methods given earlier.



(c) Phosphorus ylides

Phosphorus ylides are prepared from phosphonium salts by deprotonating them with a strong base. The method consists in the alkylation of triphenylphosphine with methyl iodide. The resulting phosphonium salt is treated with a strong base to give a phosphorus ylide.

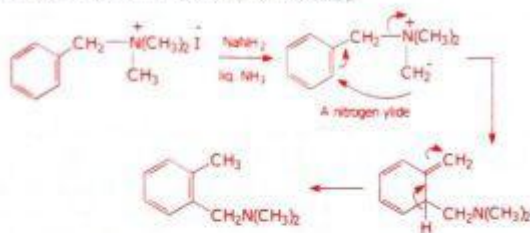


2.8.2 Reactions of ylides

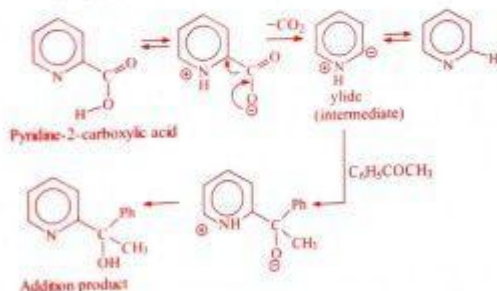
A number of ylides have been isolated in crystalline state. However, some of the ylides are transient intermediates in some of the reactions. Most of the ylides are strong nucleophiles or bases and are very important in organic synthesis.

(a) Nitrogen ylides

The nitrogen ylides are formed as intermediate in the **Sommelet rearrangement**. The method is used for the conversion of the tetra-alkylammonium halides (having hydrogen in a α -position to N) into a tertiary amines (see sec. 6.4.3).



It is found that pyridine 2-carboxylic acid undergoes decarboxylation readily compared to its 3- or 4-isomer. This is due to stabilization of carbanion by N^- which is adjacent to the carbon carrying negative charge in the intermediate ylide.



The formation of ylide intermediate has been confirmed by its trapping with carbonyl compounds, e.g., acetophenone to yield the addition product.

(b) Sulfur ylides

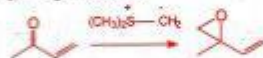
Sulfur ylides have numerous applications in organic synthesis. These ylides are considered as zwitterions in which a carbanion is stabilized by interaction with an adjacent sulfonium centre.



Two of the most widely used types of sulfur ylides are unstabilized sulfonium ylides, such as dimethylsulfonium methylide $[(CH_3)_2S^+-CH_2^-]$, and stabilized sulfonium ylides, such as dimethylthioxosulfonium methylide.



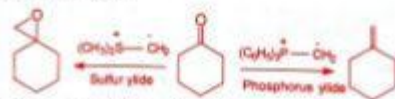
These ylides show different reactions with α,β -unsaturated carbonyl compounds; the former give epoxides and the latter give cyclopropanes. In the absence of the double bond, both give an epoxide. The epoxide formation (i.e., 1,2-addition) is kinetically favourable while cyclopropane formation (i.e., 1,4-addition, **Michael addition**) is energetically favourable. The former reaction (epoxide formation, which is irreversible) is faster with the unstabilized ylides. But, the stabilized ylides is sufficiently stable, and adds to the α,β -unsaturated ketone in a 1,4-fashion to give cyclopropane, which is the thermodynamic product (1,4-addition, although slower, is energetically more favourable because the new C-C bond is formed at the expenses of a, relatively, weak C-O bond rather than, relatively, strong C=O bond).



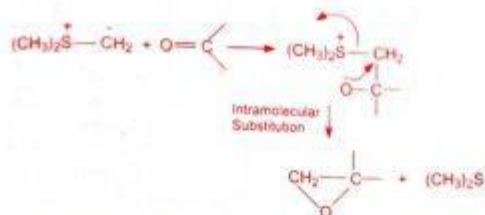
The sulphur ylide is a very important class of stabilized sulfur ylide and reacts with α,β -unsaturated carbonyl compounds to give cyclopropane derivatives. However with unsaturated compounds, sulfonium ylides react in the same way as the stabilized ylides.



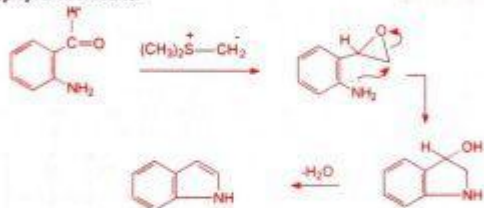
The sulphur ylides on reaction with ketones (unsaturated ketones) give epoxides while phosphorus ylides give alkenes.



The first step is same in both reactions. However, the intermediate decomposes by intramolecular nucleophilic substitution of $(CH_3)_2S$ by the oxyanion to give the epoxide. Instead, in Wittig reaction the intermediate cyclizes to give a four-membered ring, which decomposes to give alkene.



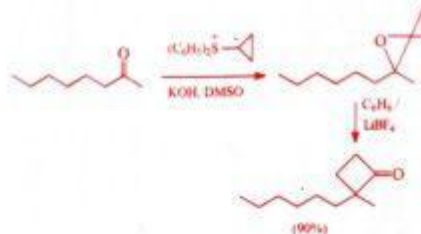
The above reaction is useful for the preparation of epoxides and heterocyclic compounds from appropriate substrates.



Sulfur ylides undergo a number of rearrangements, one such rearrangement is given below:

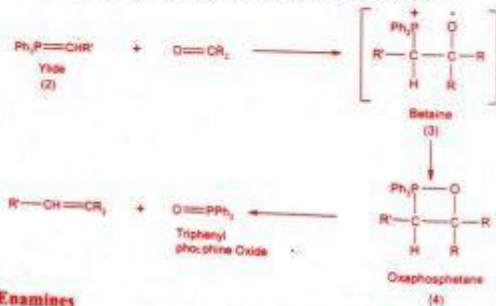


A useful sulfonium ylide is diphenylsulfonium cyclopropylide. It is usually generated *in situ* by the action of potassium hydroxide on cyclopropyldiphenylsulfonium fluoroborate. The attack of ylide at the C-C double bond of an α, β -unsaturated ketone, followed by rearrangement with acid or lithium fluoroborate in refluxing benzene gives cyclobutanone. The cyclobutanones are also valuable intermediates.



(c) Phosphorus ylides

The phosphorus ylides (or the phosphoranes) have tremendous synthetic potentialities. The most well known reaction of phosphorus ylides is their reaction with carbonyl compounds to give olefins (**Wittig reaction**). The phosphorus ylide reacts with aldehyde or ketone to form an intermediate betain, which eliminates triphenylphosphine oxide to give an alkene. Wittig reaction is very useful for the introduction of exocyclic double bond. For example, cyclohexanone is converted into methylenecyclohexane in 99% yield. For other applications and properties of phosphorus ylides see sec. 8.14.

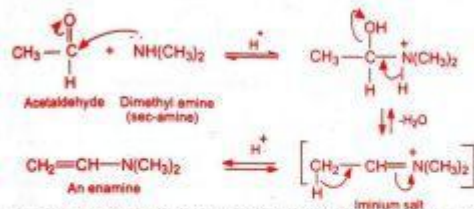


2.9 Enamines

Enamines are α, β -unsaturated amines.



Enamines are obtained by the reaction of an carbonyl compound (aldehyde or a ketone) with a secondary amine in presence of a suitable dehydrating agent such as potassium carbonate, or better by refluxing in benzene solution in presence of catalytic amount of *p*-toluenesulfonic acid with azeotropic removal of the formed water. The secondary amines which are commonly used are pyrrolidine, morpholine and piperidine in descending order of reactivity. The reaction proceeds through the intermediacy of iminium ion which loses a proton from a carbon atom β to the nitrogen resulting in the formation of a double bond between α and β -carbon atoms.

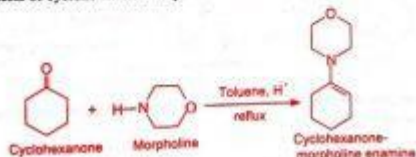


Enamines can be considered as nitrogen analogues of enolates. Their reactivity as nucleophiles is due to the dipolar character of one of the resonating structures which show that the carbon β to the nitrogen has a partial negative charge.



2.9.1 Generation of enamines

Enamines are generated from a carbonyl compound and a secondary amine (see sec. 5.32). Synthesis of cyclohexanone-morpholine enamine is described below.

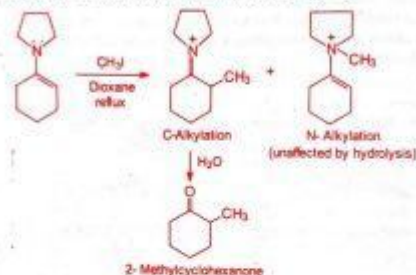


2.9.2 Reactions of enamines

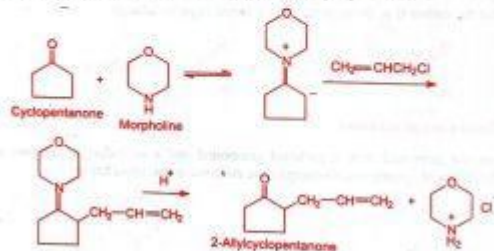
The enamine reaction was introduced by Stork and his coworkers (1963) and provides a valuable alternative method for the selective alkylation and acylation of aldehydes and ketones.

(a) Alkylation of ketones

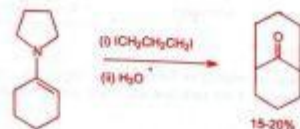
It is found that the reaction of enamines with alkyl halides initially forms the C-alkylated iminium salt, which gives the α -alkylated ketone. The N-alkylated product is also formed, but it is water soluble and is unaffected by hydrolysis.



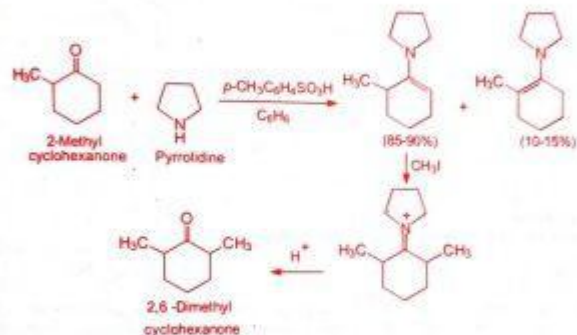
The above principle is used for the synthesis of 2-allylcyclopentanone.



The alkylation procedure has also been used for the synthesis of bicyclic compounds. The following example is illustrative.



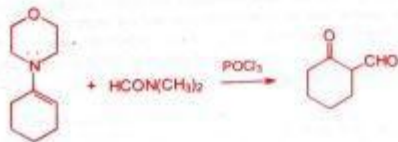
A valuable feature of the enamine reaction is that it is regioselective. Thus, in the alkylation of an unsymmetrical ketone (e.g., 2-methylcyclohexanone), the substitution takes place at the less substituted α -carbon atom. However, direct base catalysed alkylation of unsymmetrical ketones gives usually a mixture of products. Also in the enamine reactions, since no alkali is used, there is no possibility of side products, which are normally obtained from carbonyl compounds. For example, the reaction of enamine of 2-methylcyclohexanone with methyl iodide gives almost exclusively 2,6-



Thus, in the case of unsymmetrical ketone, the selectivity of the reaction is due to the fact that the enamine consists mainly of the more reactive isomer in which the double bond is directed towards the less hindered carbon.

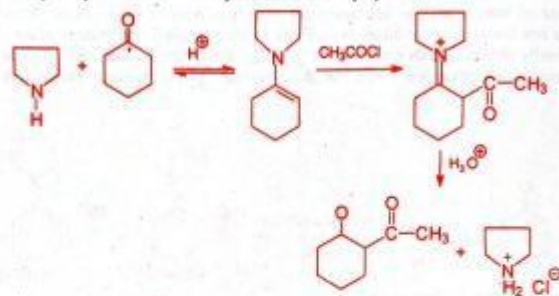
(b) Formylation

Formylation can be achieved with dimethylformamide.



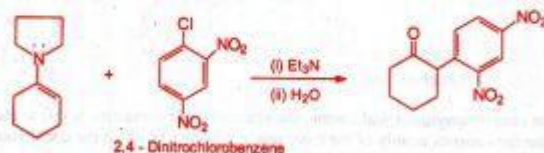
(c) Acylation of ketones

The above principle is used for the synthesis of 2-acetylcyclohexanone.



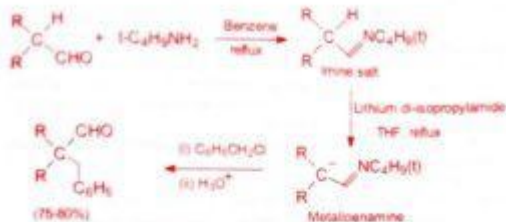
(d) Arylation

Arylation can be achieved by activated aryl halides.

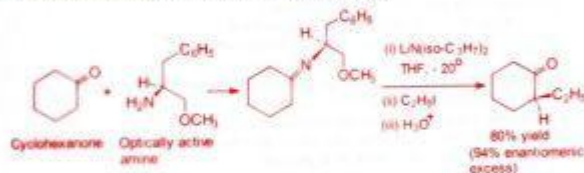


2.9.3 Metalloenamines

It is found that many imines, formed from enolizable aldehydes and ketones on reaction with aliphatic primary amines, can be easily deprotonated on treatment with lithium diisopropylamide or Grignard reagents. The metal salts so formed are called metalloenamines. The metal salts on reaction with primary or secondary alkyl halides give monoalkylated carbonyl compounds.



The metaloenamine reaction is used for enantioselective alkylation of ketones, using optically active amine. A typical example is given below.



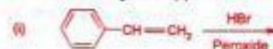
It is found that the methoxy group in metaloenamine plays an important role in asymmetric induction, in its absence optical yields are much lower.

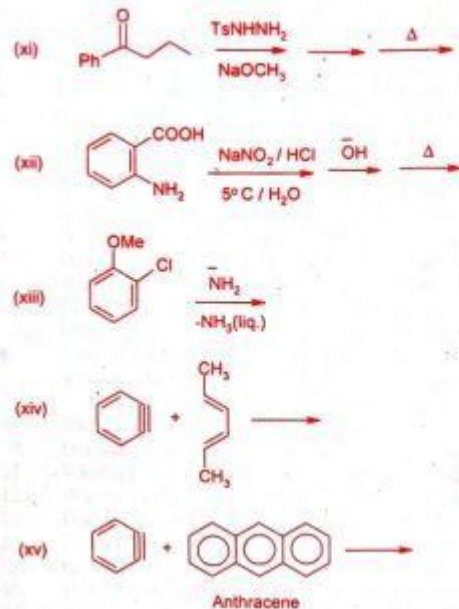
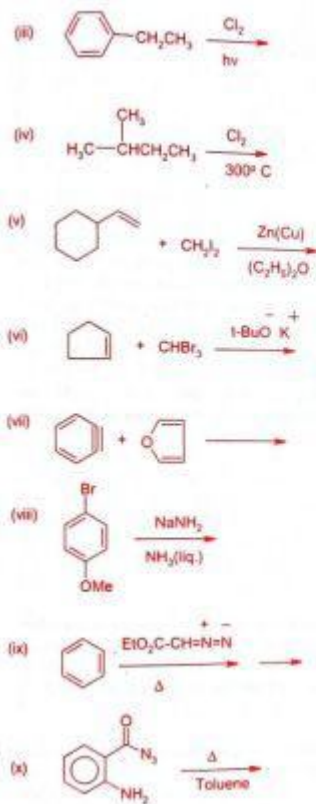
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Problems

1. What are carbocations? How they are formed? Give their structure.
2. (i) Give the order of stability of 1°, 2° and 3° carbocations.
(ii) Explain why allyl carbocation is more stable than propyl carbocation.
(iii) Give the order of stability of following carbocations:
Benzyl, allyl, propyl and methyl.
(iv) What factors are responsible for increasing the stability of carbocations.
3. Give some important reactions of carbocations.
4. What are nonclassical carbocations?
5. Discuss the stereochemistry of rearrangements involving carbocations.
6. What are carbanions? How they are generated? Discuss their structure.
7. Give the order of stability of the following carbanions.
Benzyl, phenyl, cyclopropyl, n-propyl, neopentyl, cyclobutyl, and cyclopentyl.
8. If the following functional groups are present in the α-position of the carbanion, what will be the relative order of their stability?
NO₂, RCO, COOR, CN, halogen and alkyl
9. Give the mechanism of two reactions involving carbanions.
10. Discuss the rearrangement reactions of carbanions.
11. What are free radicals? How they are generated? Discuss their structure.
12. What are bridgehead radicals? Give two examples.
13. Discuss the mechanism of free radical reactions.
14. Discuss the mechanism of the addition of HBr to propylene. How the course of the reaction is changed if peroxide is present?
15. Give the mechanism of the conversion of propene into polypropylene.
16. What are carbenes? How they are generated? Give their structure.
17. Discuss cycloaddition reactions of carbenes.
18. Discuss rearrangements involving carbenes.
19. What are nitrenes? How they are generated? Discuss their structure and stability.
20. Give some reactions of nitrenes.
21. What are benzyne? Discuss their structure. How they are formed?
22. How is triptycene obtained from anthracene and benzyne?
23. What are ylides? Discuss their structure. How are they generated?
24. What are enamines? How they are formed? Discuss some of their reactions.
25. What are metaloenamines?
26. Give the product(s) obtained in the following reactions.



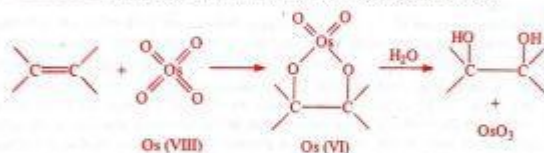


3 Oxidation

3.1 Introduction

A large number of reactions described in literature involve oxidation. However, a precise and comprehensive definition of oxidation is difficult. A convenient definition of oxidation for an organic compound is the addition or gain of oxygen or removal of hydrogen. Thus, oxidation of an aldehyde to a carboxylic acid or conversion of ethylene into ethylene oxide involves addition of oxygen. On the other hand, oxidation of ethanol to acetaldehyde involves removal of hydrogen.

One of the important criteria to decide whether a particular organic reaction is an oxidation reaction is that the reagent used in the reaction is reduced. For example in the conversion of an olefin to glycol, osmium (VIII) is converted to osmium (VI).



In the above example the reagent is reduced and so the organic compound is oxidised. In a similar way in oxidation with potassium permanganate Mn(VII) is converted to Mn(II) or Mn(IV).

Oxidation in inorganic chemistry refers to loss of one or more electrons.



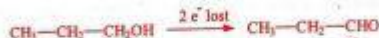
A most important definition of oxidation is that an oxidation reaction involves loss of electrons or increase in the oxidation state. In organic reactions it is not easy to determine whether a carbon atom loses or gains electrons. But it is easy to calculate the change in oxidation state of the carbon atoms and so classify a particular reaction as oxidation or reduction. Thus, the conversion of a functional group in a molecule, from a lower oxidation state to a higher one will be termed as oxidation, while the opposite of it would be reduction. It is therefore, necessary to understand what the oxidation state is.

Oxidation state

A comparison of the oxidation states of atoms in reactant and product enable us to keep a track of the transfer of electrons in a chemical reaction. Oxidation state is equal to the charge an atom would have if all the electrons in a covalent bond were assigned to the

more electronegative atom. A number of rules were formulated¹. A simplified procedure for determining the oxidation number was subsequently given.^{2,3} These rules were applied to only those atoms, which are commonly encountered in simple organic molecules, viz., H, O, C, N and halogens. The following convention for assigning oxidation number is used. Oxidation numbers for hydrogen is -1; oxidation number for carbon (bonded to same atom) is 0; oxidation number for carbon bonded to a hetero-atom (oxygen or halogen) is +1.

The oxidation number of only those atoms that are changed in the reaction have to be examined. If the sum of the oxidation numbers of various atoms in the substrate and in the product is compared, the change in oxidation number can be calculated and then we can find out whether the reaction is an oxidation or reduction. Let us consider the conversion of n-propanol to propanal.



In n-propanol, the carbon bearing the hydroxyl group has an oxidation number of -1 (C is 0, H is -1, O is +1). The oxidation number of this carbon in propanal is +1 (C is 0, H is -1, O is +1 and O from the second bond to the carbonyl is +1). We find that the change in oxidation number is $-1 \rightarrow +1$, for a net loss of 2 electrons. So this is an oxidation reaction.

The oxidising power of the oxidising reagent depends on their oxidation potential. The oxidation potential represents the ability of a metal atom to be ionized to an ion ($M \rightarrow M^+$) with loss of an electron. The oxidation of organic substrate is carried out by transition metal compounds containing chromium, manganese, ruthenium, selenium, silver or cerium. The pH of the medium in which the reaction is carried out also plays an important role in the oxidising power of a reagent. In the following discussion, the terms acidic, neutral or basic media are used. The product obtained in an oxidation reaction depends on the nature of the substrate, the reagent and the conditions (temperature, pressure, solvent etc.).

The following is given a brief account of various types of oxidizing agents and their applications. The mechanism of important oxidation reactions all also discussed.

3.2 Manganese(VII) oxidants

3.2.1 Potassium permanganate

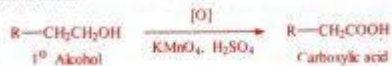
Potassium permanganate, a derivative of heptavalent manganese is a very powerful oxidising agent. Its reactivity depends on whether it is used in acid, neutral or basic conditions. In acid solution, Mn(VII) is reduced to divalent manganese (II) with a net transfer of five electrons ($\text{Mn(VII)} \rightarrow \text{Mn(II)}$). However, in neutral or basic medium, manganese dioxide is usually formed, corresponding to a three-electron change ($\text{Mn(VII)} \rightarrow \text{Mn(IV)}$). Potassium permanganate is normally used in aqueous solution. Since all compounds are not soluble in water, the use of potassium permanganate is limited. However, solvents which are not effected by potassium permanganate, such as, acetic acid, acetone, pyridine or t-butanol can also be employed.

It is now well known that the yields in potassium permanganate oxidations are considerably improved by the use of a phase transfer catalysts (PTC) (e.g., certain tetraalkylammonium or phosphonium salts) and crown ethers (e.g., dicyclohexano-18-crown-6). Even the time required for oxidation is considerably shortened.

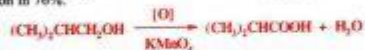
Following are given some of the applications of potassium permanganate oxidations.

3.2.1.1 Oxidation of alcohols

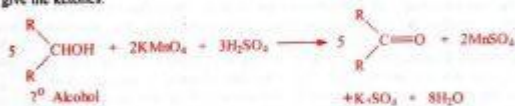
The oxidation of primary alcohols to aldehydes is not normally carried out by potassium permanganate, as the reaction proceeds to the carboxylic acid. Primary and secondary alcohols are oxidized to carboxylic acids and ketones, respectively, containing the same number of carbon atoms.



For example, 2-methylpropan-1-ol is oxidized to 2-methylpropanoic acid with $\text{KMnO}_4/\text{Na}_2\text{CO}_3$ solution in 76%.



Secondary alcohols, however, can be oxidised by KMnO_4 in acidic or alkaline conditions to give the ketones.



The utility of this method lies in the fact that the product of oxidation (i.e. ketone) should be removed as the reaction proceeds by distillation.

Use of a mild oxidising agent like barium permanganate (which is quite stable and readily available) also oxidises primary and secondary alcohols into carbonyl compounds. N-Bromosuccinimide is also used for the oxidation of secondary alcohols to ketones (sec. 8.2.7).

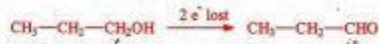
3.2.1.2 Oxidation of alkenes

Alkenes on treatment with dilute KMnO_4 solution in presence of alkali give 1,2-diols. In this reaction, the purple KMnO_4 is reduced to MnO_2 , a brown solid. This change in color is the basis of a test for the presence of double and triple bonds known as the **Baeyer test** for unsaturation.

The hydroxylation of alkenes with KMnO_4 is carried out by stirring alkene and the aqueous KMnO_4 solution, either neutral or slightly alkaline at room temperature. For example, oleic acid on oxidation in basic medium gives a glycol.

more electronegative atom. A number of rules were formulated¹. A simplified procedure for determining the oxidation number was subsequently given.^{2,3} These rules were applied to only those atoms, which are commonly encountered in simple organic molecules, viz., H, O, C, N and halogens. The following convention for assigning oxidation number is used. Oxidation numbers for hydrogen is -1; oxidation number for carbon (bonded to same atom) is 0; oxidation number for carbon bonded to a hetero-atom (oxygen or halogen) is +1.

The oxidation number of only those atoms that are changed in the reaction have to be examined. If the sum of the oxidation numbers of various atoms in the substrate and in the product is compared, the change in oxidation number can be calculated and then we can find out whether the reaction is an oxidation or reduction. Let us consider the conversion of n-propanol to propanal.



In n-propanol, the carbon bearing the hydroxyl group has an oxidation number of -1 (C is 0, H is -1, and O is +1). The oxidation number of this carbon in propanal is +1 (C is 0, H is -1, O is +1 and O from the second bond to the carbonyl is +1). We find that the change in oxidation number is -1 $\rightarrow$ +1, for a net loss of 2 electrons. So this is an oxidation reaction.

The oxidising power of the oxidising reagent depends on their oxidation potential. The oxidation potential represents the ability of a metal atom to be ionized to an ion ($\text{M} \rightarrow \text{M}^+$) with loss of an electron. The oxidation of organic substrate is carried out by transition metal compounds containing chromium, manganese, ruthenium, selenium, silver or cerium. The pH of the medium in which the reaction is carried out also plays an important role in the oxidising power of a reagent. In the following discussion, the terms acidic, neutral or basic media are used. The product obtained in an oxidation reaction depends on the nature of the substrate, the reagent and the conditions (temperature, pressure, solvent etc.).

The following is given a brief account of various types of oxidizing agents and their applications. The mechanism of important oxidation reactions all also discussed.

3.2 Manganese(VII) oxidants

3.2.1 Potassium permanganate

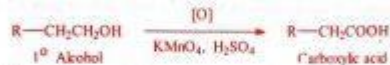
Potassium permanganate, a derivative of heptavalent manganese is a very powerful oxidising agent. Its reactivity depends on whether it is used in acid, neutral or basic conditions. In acid solution, Mn(VII) is reduced to divalent manganese (II) with a net transfer of five electrons ($\text{Mn(VII)} \rightarrow \text{Mn(II)}$). However, in neutral or basic medium, manganese dioxide is usually formed, corresponding to a three-electron change ($\text{Mn(VII)} \rightarrow \text{Mn(IV)}$). Potassium permanganate is normally used in aqueous solution. Since all compounds are not soluble in water, the use of potassium permanganate is limited. However, solvents which are not effected by potassium permanganate, such as acetic acid, acetone, pyridine or t-butanol can also be employed.

It is now well known that the yields in potassium permanganate oxidations are considerably improved by the use of a phase transfer catalysts (PTC) (e.g., certain tetraalkylammonium or phosphonium salts) and crown ethers (e.g., dicyclohexano-18-crown-6). Even the time required for oxidation is considerably shortened.

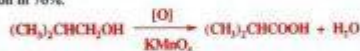
Following are given some of the applications of potassium permanganate oxidations.

3.2.1.1 Oxidation of alcohols

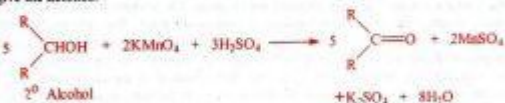
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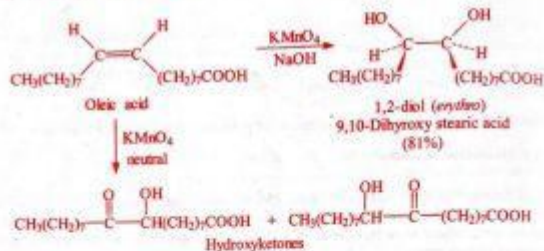
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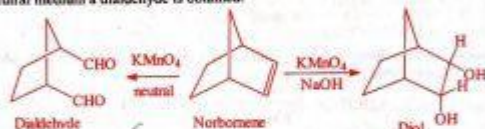
3.2.1.2 Oxidation of alkenes

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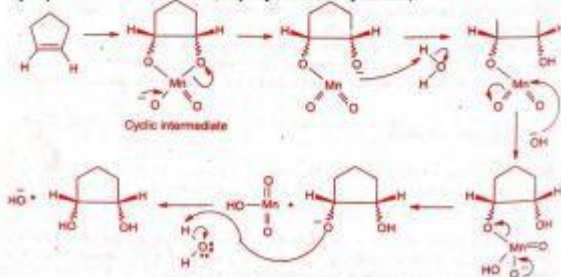


Similarly, oxidation of norbornene with KMnO_4 in basic medium gives 1,2-glycol, while in neutral medium a dialdehyde is obtained.

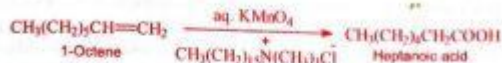


Mechanism

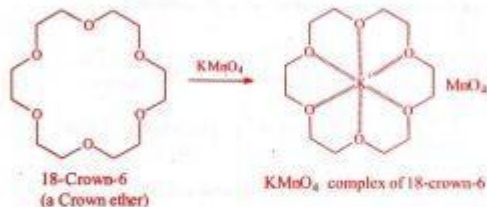
In the above reactions, the diols obtained are *cis* diols. The hydroxylation of alkenes with KMnO_4 involves the cyclic intermediate, a manganate ester. The intermediate breaks down in water to give *cis*-1,2-diol. The manganate ion is converted to MnO_2 , which precipitates. Evidence by the work of Wiberg *et al* supports the mechanism proposed, who used KMnO_4 labelled with ^{18}O . The diol obtained is enriched with ^{18}O . This indicates that both oxygen atoms of the diol come from permanganate ion. For example, cyclopentene is oxidized to *cis*-1,2-cyclopentanediol by KMnO_4 .



The oxidation of alkenes with aqueous solution of KMnO_4 can also be effected in presence of PTC^d and crown ethers. The catalytic action of the quaternary salt (PTC) is due to the ability of their organic soluble cations to transfer anions (e.g. MnO_4^-) from the aqueous into the organic phase. For example, 1-octene gives the heptanoic acid by using a PTC and aq. KMnO_4 .

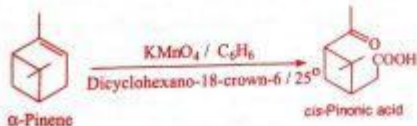


In place of PTC, crown ethers (a group of cyclic polyethers) can also be used. The crown-ethers form permanganate complex with KMnO_4 as shown below.



The formation of the complex depends on the cavity in 18-crown-6-molecule (the cavity in the 18-crown-6 has a diameter of $2.7\text{\AA}$, which is just sufficient for K^+ ion having diameter of $2.66\text{\AA}$) to fit. As an illustration toluene can be oxidised with KMnO_4 in presence of crown ether.

For example, using a crown ether as catalyst, α -pinene gives pinonic acid in 90% yield.



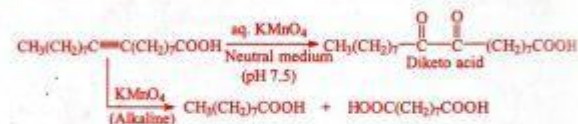
In place of phase transfer catalysts or crown ether, it is also possible to carry out oxidations by using permanganate salts, which are soluble in organic solvent. One such salt is tetra-*n*-butylammonium permanganate^e.

3.2.1.3 Oxidation of alkynes

Alkynes can be oxidised with KMnO_4 to give a mixture of carboxylic acids.

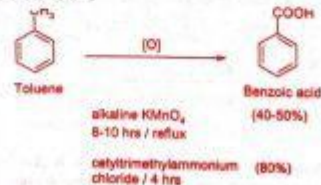


The later degradation (oxidation) is used for structure elucidation of alkynes (compare with the oxidation of alkenes, which give diol under mild conditions but carboxylic acid using strong conditions). In case of alkynes, it is sometimes possible to stop the oxidation at an intermediate stage. For example, the acetylene analogue of oleic acid on oxidation with KMnO_4 in neutral condition give the corresponding diketone acid. If the oxidation is carried out in alkaline medium, a mixture of two acids is obtained.

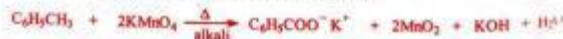


3.2.1.4 Oxidation of aromatic side chains and aromatic ring systems

Benzene is an exceptionally stable compound and is not effected by usual oxidising agents. It is for this reason that benzene is used as a solvent in most of the organic reactions. If an alkyl group is present in benzene nucleus (e.g., toluene) the side chain is oxidised to the corresponding carboxylic acid. Thus, toluene on oxidation with alkaline KMnO_4 gives benzoic acid in 40-50% yield. However, the oxidation of toluene with KMnO_4 in presence of PTC catalyst, viz., cetyltrimethylammonium chloride gives about 80% yield in a much shorter time.

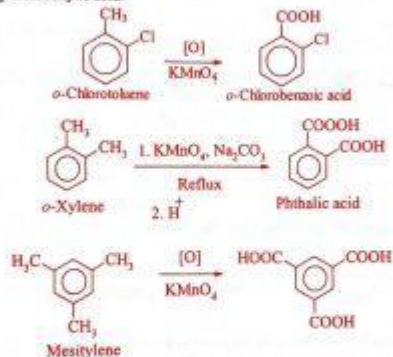


The oxidation of toluene with KMnO_4 is represented below.

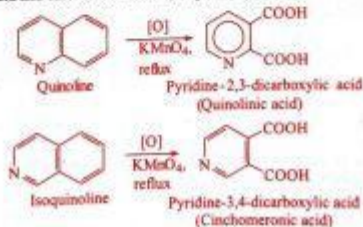


In a similar way isopropyl benzene on oxidation also gives benzoic acid. However, tertiarybutylbenzene is resistant to oxidation by KMnO_4 . This is attributed to the absence of H atom in the α -position (benzylic position), which is susceptible to attack by oxidising agent. There must be at least one hydrogen in the benzylic position for the reaction to succeed.

Oxidation with KMnO_4 is a standard method for identifying the positional isomers of monosubstituted alkylbenzenes. For examples, *o*-chlorotoluene on oxidation gives an *o*-chlorobenzoic acid and *o*-Xylene gives phthalic acid. Similarly, mesitylene is oxidised to corresponding tricarboxylic acid.

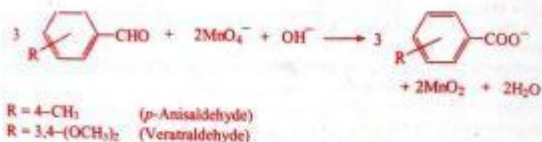


It has already stated that benzene ring is resistant to the action of KMnO_4 . However, the benzene ring can be cleaved if it is fused to a heterocyclic ring system. Thus, quinoline and isoquinoline on oxidation with alkaline KMnO_4 give the corresponding dicarboxylic acids, quinolinic acid and cinchoneric acid, respectively.

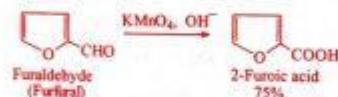


3.2.1.5 Oxidation of aldehydes and ketones

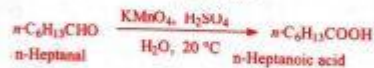
Potassium permanganate oxidises aldehydes and ketones to corresponding carboxylic acids in alkaline medium.



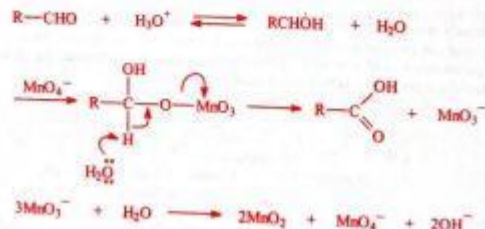
In a similar way furfural (2-furaldehyde) is oxidised to 2-furoic acid in 75% yield.



The aldehydes can also be oxidised in acidic medium.



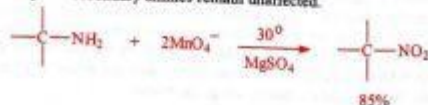
The mechanism for oxidation in acidic medium is given below.



As in the case of aldehydes, the ketones can also be oxidised with alkaline KMnO_4 to the corresponding carboxylic acids.

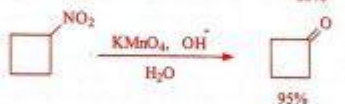
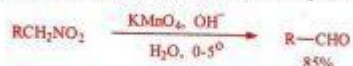
3.2.1.6 Oxidation of amines into nitro compounds

Alkaline KMnO_4 oxidises tertiary amines into nitro compounds.⁷ Only tertiary amines are oxidised. Primary and secondary amines remain unaffected.

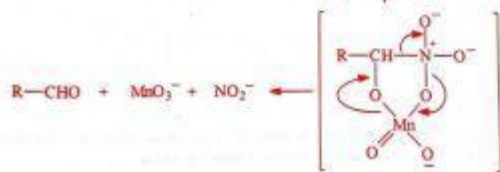


3.2.1.7 Oxidation of nitro compounds into carbonyl compounds

Alkaline KMnO_4 oxidises primary and secondary nitro compounds into the corresponding carbonyl compounds (aldehydes and ketones, respectively).

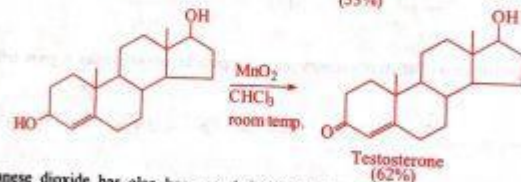
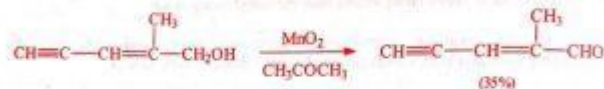


The mechanism of oxidation of primary nitro compounds into aldehydes is given below.

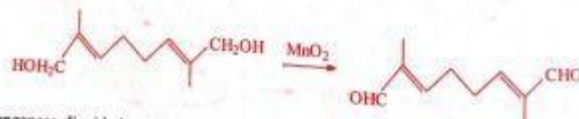


3.2.2 Manganese dioxide

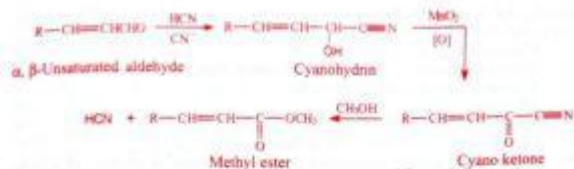
Manganese dioxide is a mild reagent and is useful⁸ for the oxidation of primary and secondary alcohols to carbonyl compounds. This reagent is specific for the oxidation of allylic and benzylic alcohols. The reaction takes place under mild conditions (room temperature) and in neutral solvent (benzene, petroleum ether, chloroform, water). For oxidation, manganese dioxide must be freshly prepared⁹ by the reaction of a manganese (II) sulfate with KMnO_4 in alkaline solution. MnO_2 does not effect C-C double bonds and triple bonds. Some typical oxidations are given below.



Manganese dioxide has also been used for oxidation of polyunsaturated alcohols in vitamin A series.



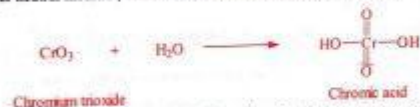
Manganese dioxide has also been used to convert¹⁰ conjugated aldehyde to a conjugated ester in presence of CN^- . The reaction takes the following course.



The mechanism of oxidation and some other applications of MnO_2 have been discussed in sec. 8.8.

3.3 Chromium (VI) oxidants

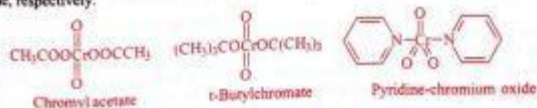
One of the most versatile oxidising agents is chromic acid, a derivative of hexavalent chromium. It reacts with almost all types of oxidisable groups. During oxidation the hexavalent chromium(VI) is reduced to chromium(III), the most stable oxidation state of chromium, with a net transfer of 3 electrons ($\text{Cr(VI)} \rightarrow \text{Cr(III)}$). Chromium(VI) oxide (chromium trioxide) and potassium and sodium dichromate are the most common reagents employed. Chromium trioxide dissolves in water to form chromic acid, which, in fact a powerful oxidising agent. Unlike KMnO_4 , which can oxidise both in acid and alkaline or neutral medium, chromic acid is used only in acidic solution.



Instead of chromium trioxide (which gives chromic acid on treatment with water) a solution of sodium or potassium dichromate in aqueous sulfuric acid can also be used; the latter contains an equilibrium mixture of the acid chromate (VI) ion and dichromate(VI) ion.



Chromium trioxide is also used in acetic anhydride, t-butanol or pyridine. In these solutions the reactive species are chromyl acetate, t-butylchromate or pyridine-chromium oxide, respectively.



Following are some of the chromium(VI) reagents which have been used for different types of oxidations.

- (i) Chromium trioxide in water
- (ii) Sodium dichromate or potassium dichromate in dilute sulfuric acid.
- (iii) Chromium trioxide in acetic anhydride
- (iv) Chromium trioxide in t-butanol
- (v) Chromium trioxide in pyridine (Collins reagent).
- (vi) Chromyl chloride (CrO_2Cl_2) in CCl_4 (Etard reagent).
- (vii) Chromium trioxide in combination with sodium borate in presence of a phase transfer catalysts.
- (viii) Jones reagent – An 8N chromic acid solution in aqueous sulfuric acid.
- (ix) Pyridine-chlorochromate (PCC) – A solution of chromium trioxide in pyridine in presence of hydrochloric acid.
- (x) Chromium pillard clay catalyst (Cr-PILC) in combination with butyl hydroperoxide (heterogeneous catalyst).

Following are some of the applications of chromium (VI) oxidants.

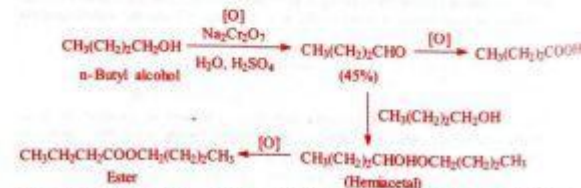
3.3.1 Oxidation of alcohols / phenols

3.3.1.1 Chromic acid and sodium or potassium dichromate

Primary alcohols on oxidation with sodium or potassium dichromate in dilute sulfuric acid give the corresponding aldehydes, which are oxidised further by the same reagent to carboxylic acids.



Also the aldehyde formed may react with the unchanged alcohols under acidic conditions to form hemiacetal, which is easily oxidised to an ester (the main by-product).



The formation of carboxylic acid and the above side products can be avoided and satisfactory yield of the aldehyde can be obtained by continuously distilling the aldehyde formed during the oxidation. Alternatively, oxidation of primary alcohols with pyridine-chromium(VI) oxide complex gives better yields of the corresponding aldehydes (sec. 3.3.1.3).

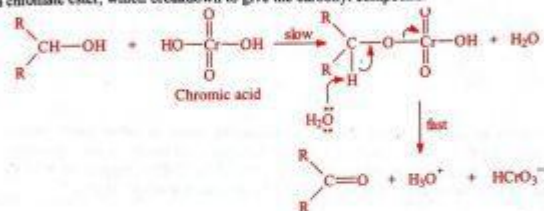
Secondary alcohols on oxidation with sodium dichromate (or potassium dichromate) in dilute sulfuric acid gives ketones in high yields. Ketones usually do not undergo further oxidation.



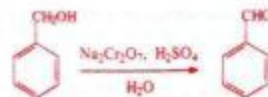
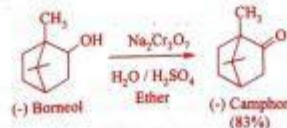
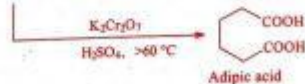
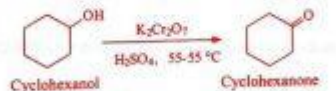
In the above oxidation three moles of secondary alcohols react with two moles of Cr(VI) to yield three moles of ketones and two moles of Cr(III).

Mechanism

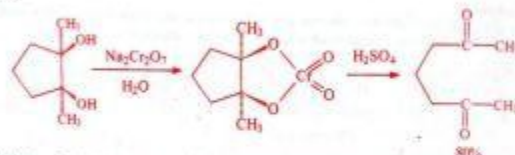
The oxidation of alcohols by chromic acid is believed to take place by initial formation of a chromate ester, which breakdown to give the carbonyl compound.



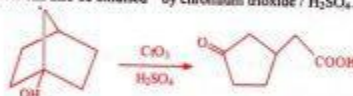
Some examples of oxidation with Cr(VI) reagents are given below.



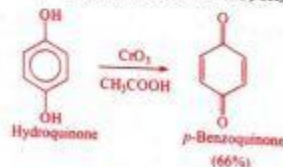
Tertiary alcohols do not contain a α -hydrogen and so cannot be oxidised by chromic acid. However, 1,2-diols are easily cleaved with chromic acid, provided they can form cyclic chromate esters. In this case the *cis*-1,2-diols are oxidised much faster than the *trans*-diols.



Oxidation of alcohols which contain acid-sensitive group or other easily oxidisable groups (like C-C double bonds or allylic or benzylic C-H bonds) is not convenient. In such cases oxidation can be conveniently effected by Collins reagent or with PCC. Bridged head alcohols can also be oxidised¹¹ by chromium trioxide / H_2SO_4 .

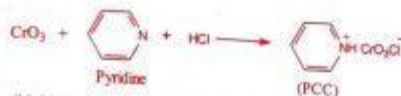


Hydroquinone is oxidised to *p*-benzoquinone in 66% with CrO_3/CH_3COOH .



3.3.1.2 Jones reagent

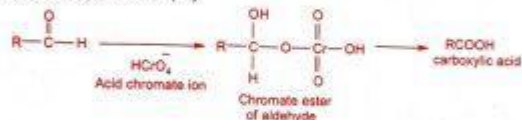
The oxidation of alcohols with chromium trioxide-acetic acid reagent (Jones reagent¹²) is known as Jones oxidation. This reagent is very selective as it is useful for oxidation of alcohols which contain C-C double or triple bonds, allylic or benzylic C-H bonds and other sensitive groups. The reaction is carried out at 0-20° C.



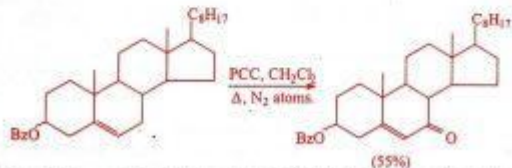
PCC is a mild, highly selective reagent and is used in organic solvents such as CH_2Cl_2 . PCC can oxidise primary¹⁶⁻¹⁷ and secondary alcohols to the corresponding carbonyl compounds.



The oxidation of primary alcohols with PCC stops at aldehyde stage because acid chromate is not present in reaction mixture. The acid chromate is required to form chromate ester of aldehyde which is necessary intermediate for further oxidation to the carboxylic acid by chromium (VI).



PCC is also useful for oxidising an allylic carbon to keto group. However, in such cases the alcoholic group if present must be protected before oxidation.



PCC can also be used for selective oxidation of alcohols containing other acid sensitive groups such as double bonds.

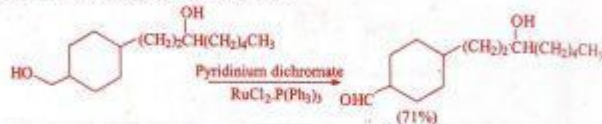
3.3.1.5 Pyridinium dichromate

Pyridinium dichromate $(\text{C}_5\text{H}_5\text{NH}^+)_2\text{Cr}_2\text{O}_7$ is a good oxidising agent and is obtained by the reaction of chromium trioxide with pyridine in presence of water. It oxidises¹⁸

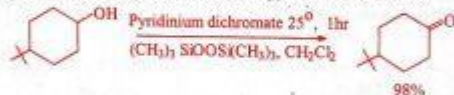
primary alcohols in dichloromethane solution to aldehydes in excellent yield. Pyridinium dichromate also oxidises allylic alcohols to α, β -unsaturated carbonyl compounds.



In presence of rutheniumdichlorotriphenylphosphine, pyridinium dichromate selectively oxidises¹⁹ a primary alcohol to an aldehyde.

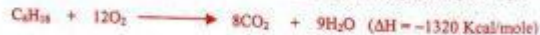


Excellent yields are obtained by the oxidation of secondary alcohols by using trimethylsilyl peroxide $[(\text{CH}_3)_3\text{SiOOSi}(\text{CH}_3)_3]$ and pyridinium dichromate.



3.3.2 Oxidation of alkanes

Chromic acid (and also KMnO_4) oxidises alkanes under vigorous conditions to give a mixture of products. Complete combustion of alkanes occur to give CO_2 and H_2O .

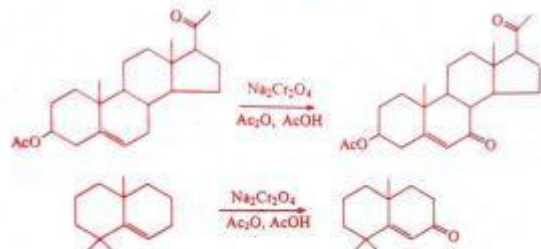
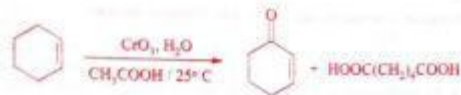


This reaction has a little synthetic value.

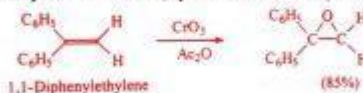
3.3.3 Oxidation of alkenes

Oxidation of alkenes may take place at the double bond and at the adjacent allylic positions with chromic acid and a mixture of products is obtained and therefore it is virtually of no synthetic importance. However, oxidation of alkenes can be effected with KMnO_4 , peroxy acids (sec. 3.4.1), ozone (sec. 3.5.3), selenium dioxide (sec. 3.5.8; 8.12) and other reagents.

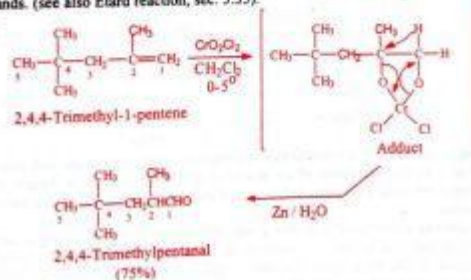
Chromium trioxide or sodium dichromate in acetic anhydride has been used²⁰ to oxidise polycyclic olefins (mostly in steroids and terpenoids) to α, β -unsaturated carbonyl compound.



Chromium trioxide in aqueous sulfuric acid is known to cleave C–C double bond into a carboxylic acid and a ketone. However, in certain cases (by the action of chromium trioxide in acetic anhydride or acetic acid) epoxide formation takes place.²¹

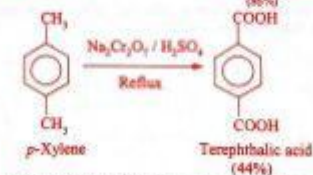
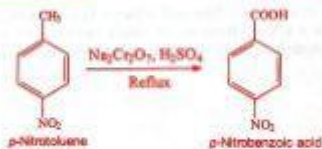
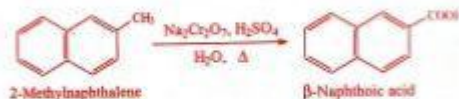
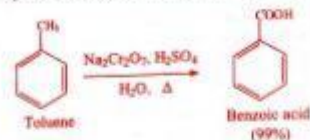


Alkenes can also be oxidised by chromyl chloride²² at low temperature to give carbonyl compounds. (see also Etard reaction, sec. 5.35).



3.3.4 Oxidation of aromatic side chains and aromatic nucleus

Benzene being exceptionally stable compound is not effected by most of the oxidising agent. However, if an alkyl group is present in benzene nucleus the side chain can be oxidised to the corresponding carboxylic acid. Some examples are given below.

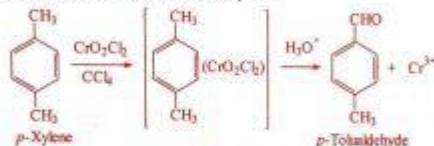


This method is used for the preparation of benzene carboxylic acids and also for the determination of the orientation of the unknown polyalkylbenzenes. If hydroxyl groups are present these should be protected by acetylation or methylation before carrying out the oxidation.

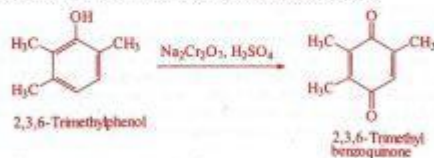
The selective oxidation of a methyl group attached to an aromatic ring is carried out with CrO_3 in acetic anhydride and acetic acid. Thus, p-nitrotoluene is converted into p-nitrobenzaldehyde diacetate (gem-diacetate), which on further hydrolysis under acid conditions gives p-nitrobenzaldehyde.



Another useful chromium reagent is chromyl chloride (CrO_2Cl_2). It oxidises a methyl group to a formyl group. This reaction is known as **Etard reaction** (see also sec. 5.35). Unlike other oxidising agent (like KMnO_4 or Cr_2O_3 etc.), chromyl chloride does not oxidise aldehyde to carboxylic acid. Thus chromyl chloride oxidise *o*-, *m*- or *p*-xylenes to the corresponding tolaldehydes in 70-80% yield.



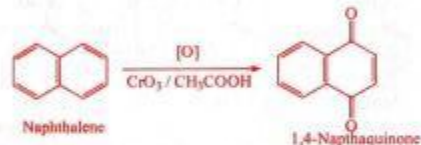
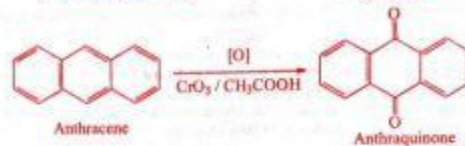
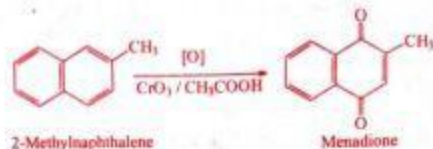
In case, a hydroxyl group is present (as in the case of 2,3,6-trimethyl phenol), a quinone results by oxidation with sodium dichromate and dilute sulfuric acid.



Similarly, oxidation of hydroquinone with CrO_3 in acetic acid yields *p*-benzoquinone.



Chromium trioxide has also been used for partial oxidation of cyclic hydrocarbons to the quinones, some examples are given below.

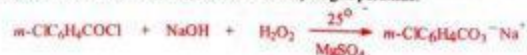


3.4 Oxidation with peracids

A number of peracids having the general formula, RCO_3H have been used to effect oxidation. Some common peracids are: performic acid (HCO_3H), peracetic acid ($\text{CH}_3\text{CO}_3\text{H}$), perbenzoic acid ($\text{C}_6\text{H}_5\text{CO}_3\text{H}$), trifluoroperacetic acid ($\text{CF}_3\text{CO}_3\text{H}$), *m*-chloroperbenzoic acid (*m*- $\text{ClC}_6\text{H}_4\text{CO}_3\text{H}$) and monoperphthalic acid (*o*- $\text{HOOCCH}_2\text{CH}_2\text{CO}_3\text{H}$). Performic and peracetic acids are generally prepared *in situ* by the action of hydrogen peroxide on the corresponding carboxylic acids.



Trifluoroperacetic acid is obtained from trifluoroacetic acid and H_2O_2 as a 90% solution. *m*-Chloroperbenzoic acid is available commercially as a crystalline solid. It can also be prepared from *m*-chlorobenzoyl chloride and hydrogen peroxide.



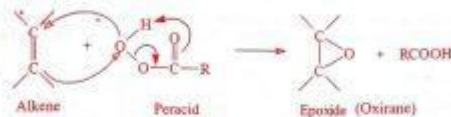
Following are given some of the applications of peracids.

3.4.1 Oxidation of alkenes

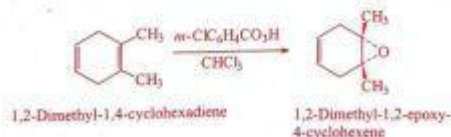
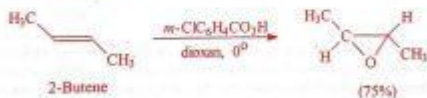
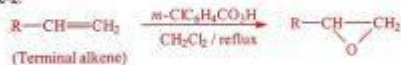
Percids react with alkenes to give stable three-membered rings containing one oxygen atom, epoxides or oxiranes.

Mechanism

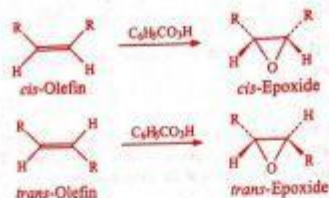
The reaction is believed to take place by transfer of oxygen atom from peracid to the alkene. The reaction involves a one-step process without intermediates. The epoxidation is stereospecific leading to the *syn* addition of the oxygen atom.

**EXPOXIDATION**

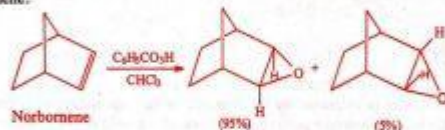
The rate of epoxidation is increased by the presence of electron withdrawing groups in the peroxy acid; thus, trifluoroperoxy acid is more effective than peracetic acid. The rate of epoxidation is also increased if the alkene has electron-donating substituents. Thus, terminal alkenes react slowly with peracids compared to alkyl substituted alkenes like butene-2.



The epoxidations with peroxy acids are stereoselective and take place by *syn*-addition to the double bond, which is established by X-ray analysis of the products obtained. As the *cis* alkene gives only *cis* epoxide and *trans* alkene gives *trans* epoxide, the reaction must be concerted i.e. the one-step mechanism retains the stereochemistry of the starting alkenes.



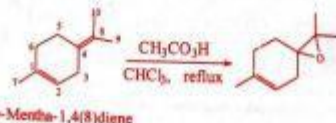
In case of cyclic alkenes, which are conformationally rigid, the reagent approaches from the less hindered side of the double bond. This is illustrated in the epoxidation of norbornene.



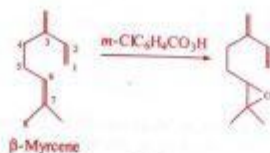
However, unhindered olefinic bond yields a mixture of epoxides. This is because the two potential modes are not markedly different.



It has already been mentioned that alkylsubstituted alkenes react faster than the terminal alkenes. This has been made use of in the preferential epoxidation of the substrate having two double bonds (dienes). This is illustrated by the epoxidation^{23,24} of *p*-mentha-1,4(8)-diene.

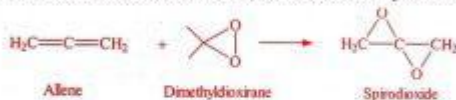


The isolated alkenes (unconjugated) are epoxidised before the conjugated alkenes. This is believed to be due to diminution of reactivity of conjugated alkenes in epoxidation. This is illustrated by the epoxidation of β -myrcene.

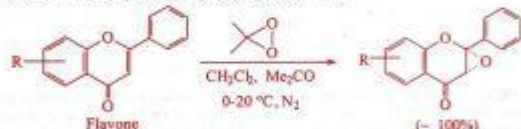


In cumulated dienes (allenes) of the type $\text{RHC}=\text{C}=\text{CHR}$, the two double bonds are in different planes at right angle to each other. The epoxidation of allenes takes place from the less hindered face of the molecule²⁵.

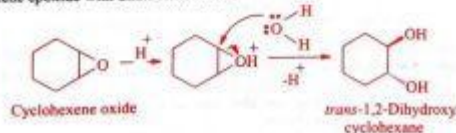
Another reagent, which is used for epoxidation, is dimethyldioxirane²⁶. This reagent can be used in case of allenes and alkenes, which may be electron rich or electron deficient. Thus, simple allene reacts with dimethyldioxirane to form spirodioxides²⁷.



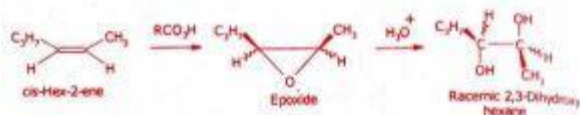
Flavones can also be epoxidised by dimethyldioxirane.²⁸



It has been found that besides the peroxy acids a versatile epoxidation reagent is *t*-butylhydroperoxide. The epoxides are useful in synthesis as they react with a variety of nucleophiles resulting in opening²⁹ of the epoxide ring. The epoxides are essential intermediates for the synthesis of *trans*-1,2-dihydroxycyclohexane by the ring opening of cyclohexene epoxide with dilute mineral acid.

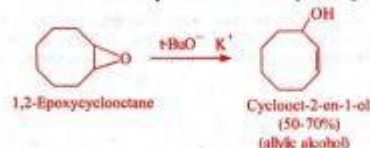


The procedure of epoxidation followed by hydrolysis of the epoxide is commonly used for the preparation of *trans*-1,2-diols from alkenes. For example, *cis*-2-hexene on epoxidation with peracid, followed by ring opening gives racemic 2,3-dihydroxyhexane.



The *anti*-hydroxylation of alkenes, by above method, is in contrast to KMnO_4 and $(\text{OsO}_4)_2$ hydroxylation, which give diaxial (*cis*)diols. *Anti*-hydroxylation of alkenes, however, can also be achieved by iodine-silverbenzoate.³⁰

The epoxides are also used in the synthesis of allyl alcohols by treatment with potassium *t*-butoxide or lithium alkylamides. Some examples are given below.

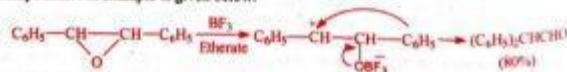


The ring opening of the epoxide ring can also be accomplished by reaction with Grignard reagent. This leads to the formation of a new carbon-carbon bond. Thus, cyclohexene oxide and phenylmagnesium bromide give good yield of *trans*-2-phenylcyclohexanol in presence of catalytic amount of CuI. Without the use of catalysts (CuI) the yield is extremely low³¹ (2-3%).



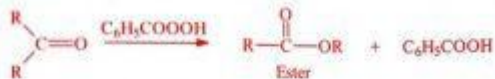
The epoxides can be reduced with lithium aluminium hydride to give alcohols. This reaction takes place at the less substituted carbon atom of the epoxide to give more substituted alcohol.

The opening of epoxide ring can also lead to rearrangements to give carbonyl compounds. An example is given below.

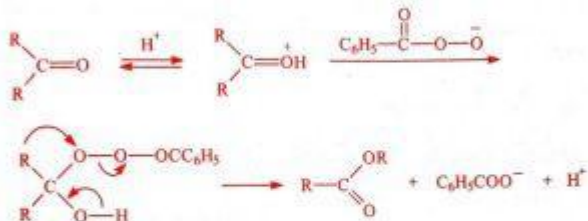


3.4.2 Oxidation of ketones

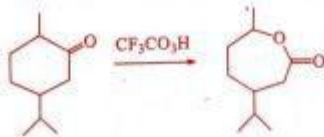
Ketones react with peracids like perbenzoic acid or peracetic acid to give esters by insertion of oxygen.



This reaction is known as Baeyer-Villiger oxidation. Its mechanism and applications are discussed in Chap.6, see sec. 6.3.1.

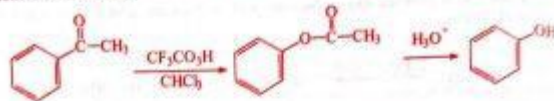


Thus, we have seen that straight chain ketones are converted into esters. However, cyclic ketones give lactones.

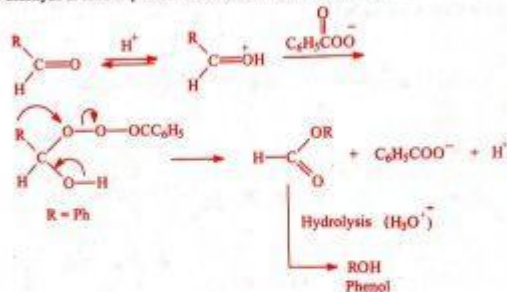


Baeyer-Villiger oxidation of bicyclic ketones is an important reaction and has been used¹² in synthesis. In such cases a methylene or methine migration takes place.⁷¹

The Baeyer-Villiger oxidation serves as a method for the preparation of phenols and alcohols from ketones.



When aldehyde is used in place of ketone, the product is also phenol.

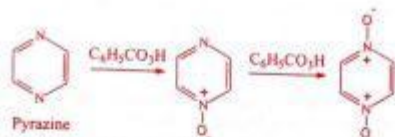


See sec. 5.6; 6.3.1 for Baeyer-Villiger oxidation also see Dakins oxidation (sec. 5.26; 6.3.3).

3.4.3 Oxidation of N-heterocycles

Heterocyclic compounds containing nitrogen(s), e.g., pyridine and diazines on reaction with peracid give rise to the corresponding N-oxides.





These N-oxides are of great synthetic utility. These are also used to catalyse the osmylation reactions of alkenes (see osmium tetroxide, sec. 3.5.9; 8.11.2).

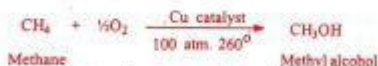
3.5 Miscellaneous oxidants

Besides the oxidising agents mentioned above, a number of other oxidising agents are known, which are used for specific purposes.

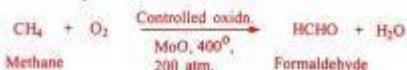
3.5.1 Oxygen

Oxygen by itself is not used as oxidising agent. However, it is used for various oxidations in presence of certain catalysts. This process is commonly known as catalytic oxidation and is used mostly for the industrial preparation of a number of important products. Some of the processes are described below.

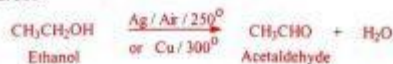
- (i) Methyl alcohol is obtained by the catalytic oxidation of methane. In this process a mixture of methane and oxygen in the ratio of 9:1 is passed over heated copper catalysts under high temperature and pressure.



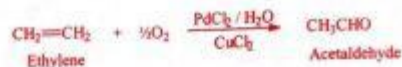
- (ii) Formaldehyde is obtained by the controlled oxidation of methane under pressure in presence of molybdenum oxides.



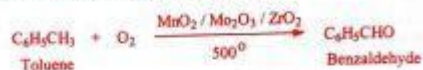
- (iii) Acetaldehyde is obtained by catalytic oxidation of ethyl alcohol with oxygen (air) in presence of silver at 250° or by passing vapor of ethyl alcohol over copper catalyst at 300° .



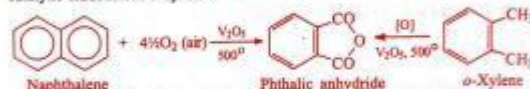
Alternatively, ethylene can be oxidised in presence of palladium chloride and CuCl_2 to give ethanal. This is known as **Wacker Process**



- (iv) Benzaldehyde is obtained by catalytic oxidation of toluene (in vapor phase) in presence of catalysts (MnO_2 , Mo_2O_3 , ZrO_2) at 500° .



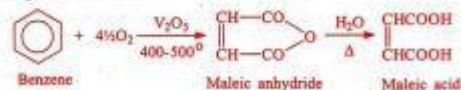
- (v) Phthalic anhydride is obtained by catalytic oxidation of naphthalene or by catalytic oxidation of *o*-xylene.



- (vi) Furoic acid is obtained by the oxidation of furfural with oxygen in presence of silver oxide.



- (vii) Maleic anhydride is prepared by catalytic oxidation of benzene by oxygen (air) at $400\text{--}450^\circ$ in presence of vanadium pentoxide. Maleic anhydride on boiling with water gives maleic acid.



- (viii) Chlorine is obtained by the oxidation hydrogen chloride with oxygen in presence of CuCl_2 catalysts. This process is known as Deacon process.



The above process has been modified. The catalyst used is a didymium promoted catalysts, Dm_2O_3 , and CuCl_2 at a slightly lower temperature at 400° .

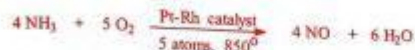
- (ix) In the Birkeland-Eyde process for the manufacture of nitric acid, nitrogen is made to react with oxygen in an electric arc furnace. The formed nitric oxide combines

with more oxygen to give nitrogen dioxide, which on dissolving in water gives nitric acid.



This process is obsolete due to high cost of electricity.

- (x) In the Oswald's process ammonia is oxidised with oxygen in presence of platinum rhodium catalyst at 850° at 5 atmosphere. The formed nitric oxide is converted by oxygen into nitrogen dioxide, which is absorbed in water to give nitric acid.



- (xi) In the contact process for the manufacture of sulfuric acid, sulfur dioxide is oxidised into sulfur trioxide, which is absorbed in water to give sulfuric acid.



- (xii) A large number of applications of the use of oxygen as an oxidising agent have been reported. In most of these methods catalysts based on cobalt(II)-Schiff's base have been used.³⁴

- (xiii) The reaction of oxygen with 1,3-dienes to form endoperoxides is of special interest.^{35,36} In this case the addition of oxygen to dienes takes place under the influence of light, either directly or in the presence of a photosensitiser. The reaction is believed to involve oxidation by singlet oxygen (see below).

3.5.2 Singlet oxygen (Photochemical oxidation)

Singlet oxygen is one of the excited states of molecular oxygen. The ground state of molecular oxygen is a triplet having two unpaired electrons. There are two excited singlet states and are represented as shown below.

Second excited state



First excited state

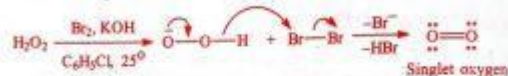


Ground state (triplet state)

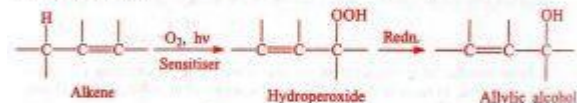


The first excited state is expected to be electrophilic as it has one paired electron. On the other hand, the second excited state would behave like a radical, which has a short life time and is converted into the most stable first excited state. The later (i.e., the first excited state) is known as singlet oxygen and is generally used in oxidation reactions.

The most important method for the generation of singlet oxygen is the photochemical excitation of ground state molecular oxygen in presence of a sensitiser (e.g., rose Bengal). Another method of generation of singlet oxygen is by the oxidation of hydrogen peroxide with other oxidants like sodium hypochlorite, alkaline solution of bromine or alkaline solution of peracids.



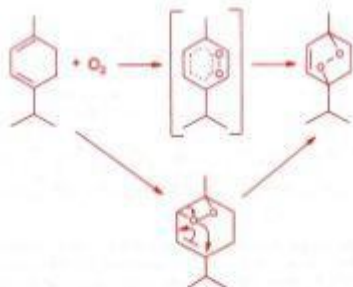
Oxidation by singlet oxygen is generally called photosensitised oxidations or photochemical oxidations. Singlet oxygen reacts with alkenes and conjugated dienes to give hydroperoxides and cyclic peroxides,³⁷ respectively. This reaction is carried out by irradiation of an alkene or diene in presence of oxygen and a sensitiser (such as chlorophyll or dyes).



The reaction of singlet oxygen with alkene is believed to proceed by a concerted cyclic mechanism.^{38,39}



In case of cyclic conjugated dienes the reaction is believed to proceed as follows, as in the case of Diels-Alder reaction.



The reduction of hydroperoxides with mild reducing agent provides a convenient route for converting an alkene into an allylic alcohol with shift in the position of the double bond. Some examples of oxidation by singlet oxygen are given below.



In the case of 2-methyl-2-pentene, a mixture of two methylpentenols corresponding to attack at each end of the double bond is obtained. No reaction takes place if the alkene does not have an allylic hydrogen, or if sensitiser, light or oxygen is excluded. Some of the common sensitisers are organic dyes such as fluorescein derivatives, methylene blue and some porphyrin derivatives.

Some examples⁴⁰ of the reaction of singlet oxygen with 1,3-diene to form cyclic peroxides (Diels-Alder type reaction) are given below.



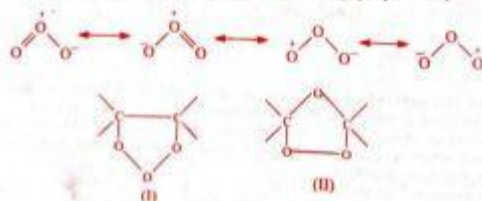
Oxidation by singlet oxygen should be distinguished from radical oxidation of alkenes by triplet oxygen which can also be initiated by sensitisers like benzophenone and which may also give allylic hydroperoxide. It is only in rare cases that the products of these autooxidations are the same as those of photo-oxygenation.

Singlet oxygen has been used for the specific introduction of an oxygen function at the site of the double bond and has been explored in the synthesis⁴¹ of a number of natural products.

3.5.3 Ozone

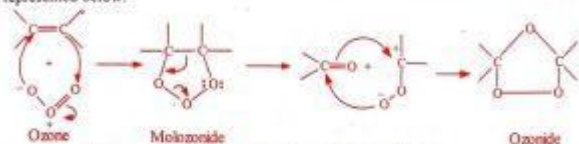
Ozone reacts with alkenes to form an adduct (called ozonide) which on treatment with a suitable mild reducing agent gives two carbonyl compounds. This process is called ozonolysis and is a convenient method for oxidative cleavage of carbon-carbon double bonds. The reaction is generally carried out by bubbling a stream of oxygen containing 2-10% of ozone (this mixture is obtained directly from an ozoniser) into a solution or suspension of the alkene into methyl alcohol or methylene chloride. The reaction is carried out at room temperature or slightly below room temperature. The crude ozonolysis product (i.e. ozonide) is not isolated and is treated with the mild reducing agent like zinc dust and water. The nature of the products formed⁴² depends on the structure of the alkene.

Ozone is an electrophilic reagent. Its structure is considered as a resonance hybrid of the following four canonical forms (each oxygen atom being sp^2 hybridized).



Mechanism

Ozonide was earlier represented as (I). Subsequent work has shown that ozonide in fact has the structure (II). The structure (II) for an ozonide has been assigned on the basis of mechanism proposed by Crilgee.⁴³ According to this mechanism, ozone first reacts with an alkene to form an adduct called molozonide.⁴⁴ The molozonide rearranges to ozonide, which is formed by the recombination of the dipolar ion and aldehyde or ketone as represented below.

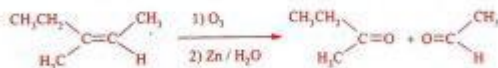


(Mechanism of ozonide formation)

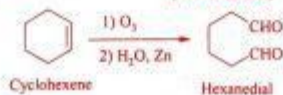
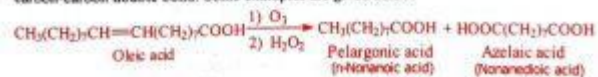
The ozonide obtained by the reaction of O_3 with disubstituted alkene, $RCH=CHR$, can be cleaved by $Zn-H_2O$ (hot) to give two molecules of aldehydes. Alternatively, it can be cleaved by H_2O_2 to give a carboxylic acid and aldehyde. The overall reaction of an alkene with ozone is represented as shown below.



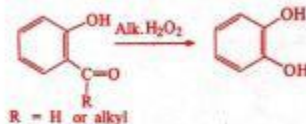
Similarly, 3-methyl-2-pentene on treatment with ozone, followed by reduction of ozonide with zinc and water results in the formation of acetaldehyde and ethyl methyl ketone.



Ozonolysis is used for structure elucidation of unknown organic compounds containing carbon-carbon double bond. Some examples are given below:

**3.5.4 Hydrogen peroxide**

Hydrogen peroxide is used as an oxidising agent in presence of alkali for the oxidation of carbonyl group (aldehydes and ketones) into hydroxyl group. In this case a phenolic group must be present in *ortho* or *para* position to the carbonyl group. This reaction is commonly known as Dakins reaction. For mechanism and other applications see sec. 5.26; 6.3.3.



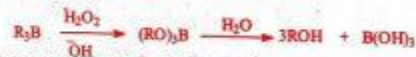
Hydrogen peroxide is also used for the generation of singlet oxygen, which is a versatile reagent for the oxidation of alkenes (sec. 3.5.2).

Following are some other important applications of hydrogen peroxide.

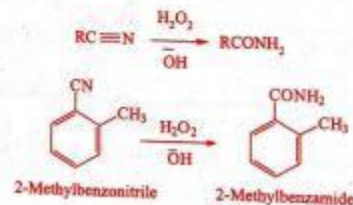
(i) Peracids can be obtained from carboxylic acids



(ii) Hydrogen peroxide oxidises trialkyl boranes in alkaline medium to alkyl borates, which on hydrolysis yield alcohols.



(iii) Hydrogen peroxide oxidises nitriles to amides.



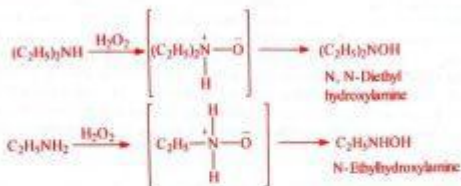
(iv) Tertiary amines are oxidised by H_2O_2 to N-oxides.





Pyridine N-Oxide (78%)

Primary and secondary amines are oxidised to N-alkyl substituted hydroxylamines.



In case of primary amines, the hydroxylamines formed are oxidised to nitro compounds



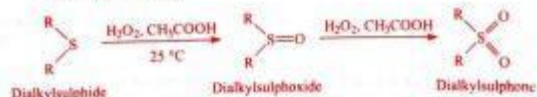
Aromatic amines are oxidised to nitro compounds via the intermediate formation of N-phenylhydroxyl amine.



- (v) Hydrogen peroxide (30% solution) oxidises thiols to sulfonic acid via the intermediate disulfides.



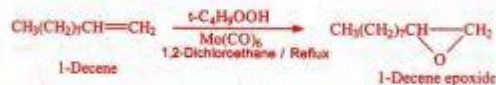
- (vi) Sulfides are oxidised to sulfoxide and sulfones depending on the concentration of H_2O_2 .



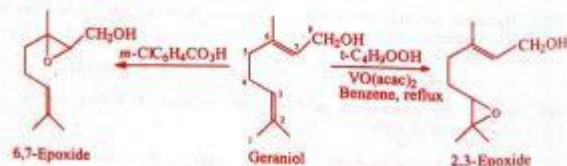
- (vii) Alkyl hydroperoxides can be prepared by reaction of 1-alcohols or alkenes with H_2O_2 in the presence of sulfuric acid.

3.5.5 t-Butyl hydroperoxide

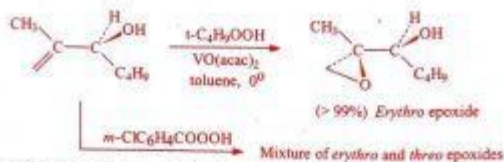
t-Butyl hydroperoxide prepared by reaction of isobutene with oxygen in 75% yield in presence of an initiator. It is commercially available and easier to handle than H_2O_2 . Peroxides are a source of "electrophilic oxygen" and react with alkenes. There are three main categories of peroxides used for epoxidation of alkenes; H_2O_2 , alkyl hydroperoxides, and peroxy acids. The conversion of an alkene into an epoxide has been described earlier (sec.3.4.1). It has been found that a new versatile reagent, t-butyl hydroperoxide in presence of vanadium (V^{5+}) or molybdenum (Mo^{6+}) catalyst (Vanadyl or molybdenyl acetylacetonates have been frequently used) provides an excellent method⁴⁹ for the epoxidation of alkenes. The molybdenum catalysts, such as MoO_3 and $MoO_2(acac)_2$ are most effective for the epoxidation of isolated or exocyclic double bonds and the vanadium catalysts for allylic alcohols. The terminal alkenes, which are most difficult to convert into epoxides with peroxy acids can be readily epoxidised by this reagent. For example epoxidation of 1-decene with t-butyl hydroperoxide in presence of catalytic amount of molybdenum hexacarbonyl in boiling 1,2-dichloroethane gives the 1-decene epoxide.



t-Butyl hydroperoxide can also be used for selective epoxidation which is not easily possible by other reagent. In fact, this reagent^{46,47} shows remarkable reactivity towards the double bond of allyl alcohol. Thus, the reaction of geraniol with t-butyl hydroperoxide in boiling benzene in presence of catalytic amount of vanadium acetylacetonate gives exclusively the 2,3-epoxide. However, with peroxyacids the epoxidation occurs preferentially at the other double bond.



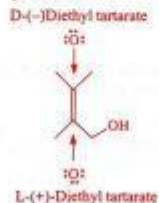
A special advantage of t-butyl hydroperoxide is that the reaction is more stereoselective than with peracids. Thus, the following acyclic allyl alcohol with t-butyl hydroperoxide and vanadium acetylacetonate gives exclusively the *erythro* epoxide. However, with *m*-chloroperoxybenzoic acids, a mixture of *erythro* and *threo* isomers is formed.



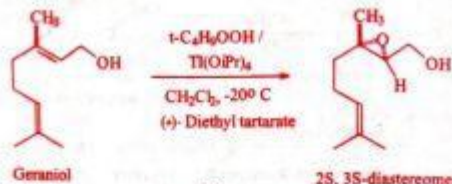
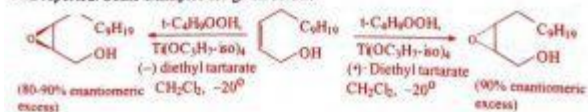
The epoxidation of alkenes with hydroperoxide gives racemic products in most cases. However, by using chiral ligand, chiral epoxide can be obtained. This epoxidation was discovered by Sharpless and so is known as Sharpless asymmetric epoxidation.

A useful new method for the asymmetric epoxidation of allylic alcohols has been developed by Sharpless in 1980. It involves the use of *t*-butyl hydroperoxide using a titanium complex as catalyst, $[\text{Ti}(\text{O}i\text{Pr})_4]$.

The oxidation of allylic alcohols with *t*-butyl hydroperoxide in presence of either (+) or (-) diethyl tartrate and titanium tetraisopropoxide yields the corresponding asymmetric epoxide in high optical yield. This method is more stereoselective than any other method used for this transformation. In this chiral epoxidation there is uniformly high asymmetric induction and the absolute configuration of the epoxide produced can be predicted. It has been established that for a given tartarate, the system delivers the epoxide oxygen from the same face of olefin regardless of the substitution pattern. If allylic alcohol is represented as shown below (so that the CH_2OH group is at the lower right), oxygen is delivered^{44,49} from the top face in presence of D-(-) diethyl tartrate and from the bottom face in the presence of L-(+)-diethyl tartrate.



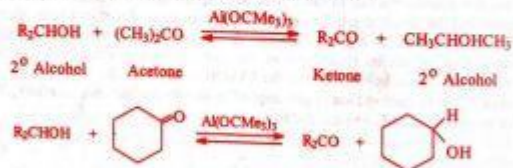
A number of examples of highly enantioselective epoxidations of allylic alcohols have been reported. Some examples are given below:



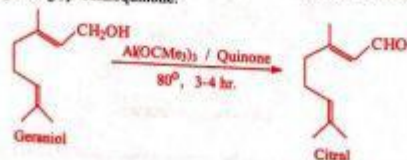
The Sharpless oxidation has been used^{50,51} as a key step in the synthesis of terpenes, carbohydrates, pheromones, macrocyclic natural products and pharmaceuticals.

3.5.6 Aluminium tri-isopropoxide and aluminium tri-*t*-butoxide

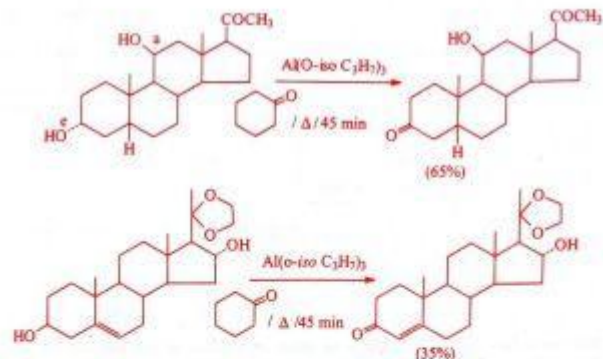
In 1937 Oppenauer used aluminium triisopropoxide $[\text{Al}(\text{OCHMe}_2)_3]$ for the oxidation of unsaturated steroidal alcohols in acetone. The acetone acts as a hydrogen acceptor. The oxidation of alcohols with $[\text{Al}(\text{OCHMe}_2)_3]$ in hydrogen acceptor ketone (such as acetone, cyclohexanone etc.) is known as Oppenauer oxidation.



Primary alcohols can also be oxidised to aldehydes if acetone is replaced by a better hydrogen acceptor e.g., *p*-benzoquinone.



Oppenauer oxidation has mostly been used in steroids. Equatorial hydroxyl groups (e) tend to be oxidised preferentially over axial hydroxyl groups (a). Also the unconjugated carbon-carbon double bonds are isomerised into conjugation with the ketone formed.



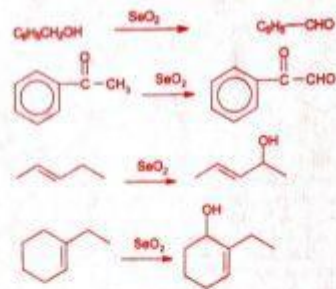
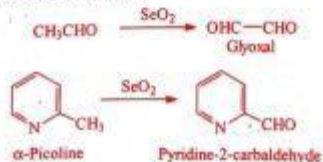
For reaction mechanism and other applications see sec. 5.68; 8.1.3.

3.5.7 Lead tetra-acetate

Lead tetra-acetate has 1.6 V reduction potential in perchloric acid, thus it is one of the more powerful common oxidants. LTA is used in solvents such as acetic acid or benzene. It undergoes oxidative cleavage of 1,2-diols, α -hydroxy ketones, 1,2-diketones, and α -hydroxy acids. Its reaction with diols is analogous to the permanganate reaction and a cyclic intermediate is formed. For mechanism and other applications see sec. 8.6.

3.5.8 Selenium dioxide

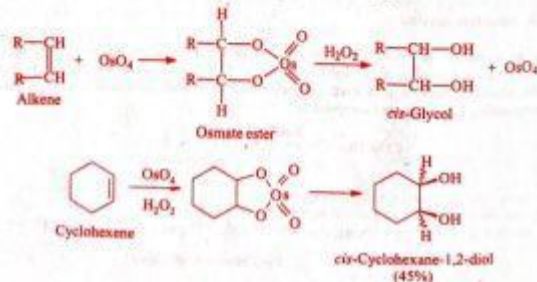
It is an important oxidizing agent used for oxidation of an alkyl fragment. It is used primarily for the oxidation of allylic or benzylic C-H fragments to the corresponding allylic alcohols. SeO_2 is also used for the oxidation of aldehydes and ketones to the corresponding 1,2-dicarbonyl compounds.



The mechanism of oxidation and some other applications of selenium dioxide are discussed in sec. 8.12.

3.5.9 Osmium tetroxide

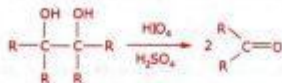
Osmium tetroxide is toxic and volatile and its vapours are extremely dangerous to eyes. It is a reagent, mostly used for *cis*-hydroxylation of carbon-carbon double bonds (like KMnO_4). The hydroxylation of alkene with osmium tetroxide in inert solvent gives cyclic osmate ester, which undergoes hydrolytic cleavage under reducing conditions, such as aqueous sodium sulfite, to give the 1,2-diol. However, *cis*-hydroxylation can be effected by using catalytic amount of OsO_4 together with H_2O_2 .



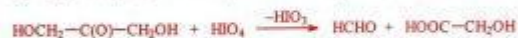
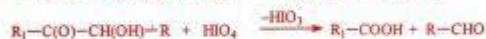
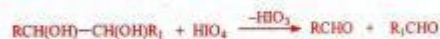
For other application of osmium tetroxide and mechanism see sec. 8.11.

3.5.10 Periodic acid (HIO_4)

Periodic acid is used for the oxidative cleavage of bonds with adjacent oxidisable groups, e.g., 1,2-diols, α -hydroxy carbonyl compounds, 1,2-diketones and α -amino acids. This reaction has been used as a test for 1,2-diols and in the determination of the structures of carbohydrates.

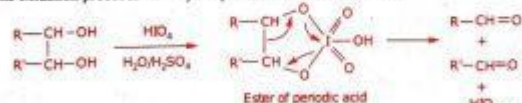


Some representative examples are given below.



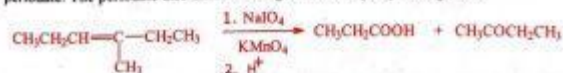
Mechanism

The oxidation proceeds via a cyclic periodate ester intermediate.



The intermediate breaks down to form the two carbonyl compounds.

In conjugation with KMnO_4 or OsO_4 , periodate is used for the cleavage of alkenes. The KMnO_4 hydroxylates the double bond to give 1,2-diol, which is cleaved by periodate. The periodate also oxidises manganate back up to permanganate.



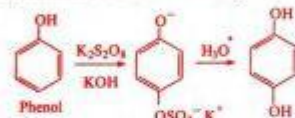
Cyclohexene

Adipic acid

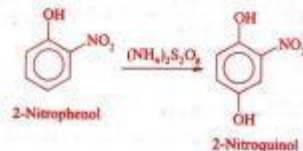
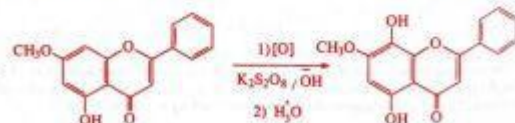
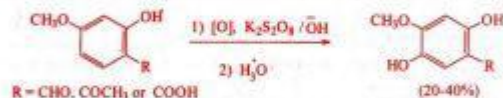
In these reactions sodium iodate is used in place of iodic acid

3.5.11 Potassium persulfate ($\text{K}_2\text{S}_2\text{O}_8$)

Potassium persulfate is used for introduction of hydroxyl group in phenols. The hydroxylation occurs in *para* position to the hydroxyl group present. However, if *para*-position is occupied, hydroxylation takes place in the *ortho* position. The oxidation is carried out in alkaline medium and is known as **Elbs persulfate oxidation**. The yields are low (30-50%). For mechanism of the oxidation and applications see sec. 5.34.

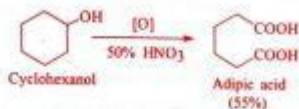


In place of potassium persulfate, sodium persulfate or ammonium persulfate can also be used. Persulfate oxidation is extensively used in the synthesis of a large number of intermediates and natural products. Some examples are given below.



3.5.12 Nitric acid

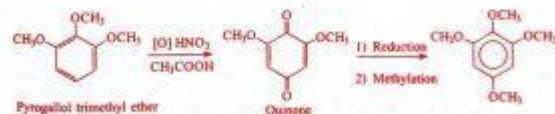
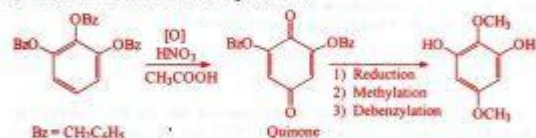
Nitric acid is a vigorous oxidising agent and is seldom used for the selective oxidation of alcohols since better reagents are available for this purpose. However, it is used for commercial preparation of adipic acid (used in the manufacture of nylon) by the oxidation of cyclohexanol.



Nitric acid oxidises a sugar at both ends of the chain to the dicarboxylic acid, known as aldonic acids. For example, glucose is oxidised by nitric acid to glucaric acid.



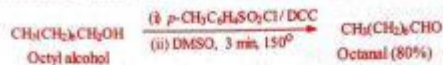
Nitric acid is also used for the synthesis of a large number of intermediate required for organic synthesis. Some of these are given below.



3.5.13 Dimethyl sulfoxide

A number of reagents are available for the oxidation of primary alcohols to aldehydes. However, the aldehydes formed are susceptible to further oxidation to carboxylic acids. On the other hand oxidation of secondary alcohols to ketones can be achieved by some reagents and by controlling the conditions, exclusive formation of ketones can be achieved. A useful and convenient method for the conversion of primary alcohols into aldehydes involves in conversion of primary alcohol into the tosylate followed by

oxidation with dimethyl sulfoxide (DMSO). The formation of tosylate is achieved *in situ* by the reaction of primary alcohol with tosylchloride in presence of dicyclohexyl carbodiimide ($\text{C}_6\text{H}_{11}\text{N}=\text{C}=\text{NC}_6\text{H}_{11}$) (DCC) followed by treatment with DMSO. Thus, octyl alcohol can be oxidised into octanal.

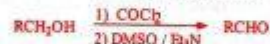


Mechanism

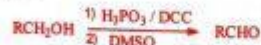
The reaction proceeds according to the following sequence.



Instead of tosylate, the chloroformate of the alcohol (RCH_2OCOCI) can be used. The chloroformate is obtained *in situ* by using carbonyl chloride.



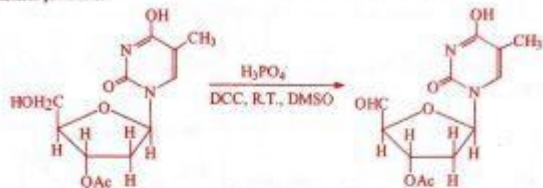
In a similar way, the primary alcohol can be converted into the $\text{R}-\text{CH}_2\text{OPO}_3\text{H}_2$ (by treatment with phosphoric acid in presence of DCC) and subsequent oxidation with DMSO yields aldehyde.



DMSO is also used to convert alkyl halides into aldehydes. Only those alkyl halides which are very reactive towards nucleophilic displacements can be used in this reaction. The halides include all primary alkyl iodides as well as benzylic and allylic chlorides and bromides and those adjacent to carbonyl groups.

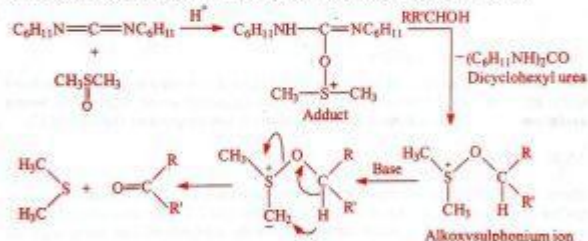


The oxidation with DMSO has been used to synthesize a number of sensitive compounds in natural products.

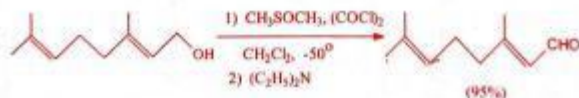


Mechanism

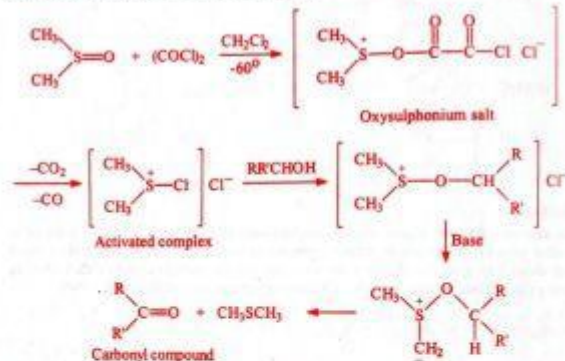
The mechanism of the above reaction as elucidated by tracer experiments is believed to involve initially the formation of a sulphoxide-carbodiimide adduct. This adduct reacts with alcohol to give the alkoxy-sulphonium ion, which undergoes proton abstraction to form a ylide. Ylide collapses to give the carbonyl compound and dimethyl sulfide.



The formed dicyclohexyl urea has to be separated. This problem has been overcome by using reagents like acetic anhydride, trifluoroacetic anhydride, thionyl chloride and oxalylchloride in conjunction with DMSO. Out of these reagents oxalylchloride is found⁵² to be the best. A variety of alcohols (particularly those alcohols which are sensitive to oxidising agents) have been converted into aldehydes by this method



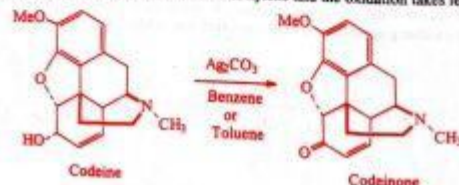
The reaction is believed to proceed via the formation of an activated complex, formed by spontaneous loss of CO_2 and CO from the oxysulphonium salt.



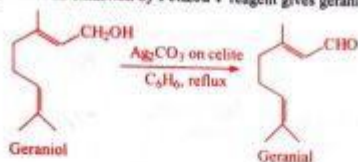
The oxidation of alcohols to aldehydes by oxalyl chloride (or other reagents like trifluoroacetic anhydride) and DMSO in presence of a base (trimethyl amine) is known as **Swern oxidation**. The reaction is done in dichloromethane at low temperature (below -30°C).

3.5.14 Silver carbonate (Ag_2CO_3)

The most common reagents of silver are silver carbonate (Ag_2CO_3 , reduction potential 0.4769V), silver(II) oxide (Ag_2O , reduction potential 0.342 V) and silver(I) oxide (Ag_2O , reduction potential 0.599V). Silver carbonate is not the most powerful oxidising agent but is extremely useful for the oxidation of primary and secondary alcohols to aldehydes and ketones under mild and neutral conditions. Thus, codeine on refluxing with silver carbonate in benzene gives⁵³ 75% yield of codeinone. However, better yield (85%) was obtained if reaction is carried out in toluene or xylene and the oxidation takes less time.⁵⁴

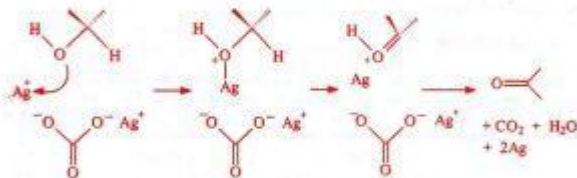


Oxidation of primary alcohols with excess of silver carbonate on celite gives excellent yield of the corresponding aldehydes. This modified reagent is known as **Fetizon's reagent**. Thus, geraniol an oxidation by Fetizon's reagent gives geranial in 97% yield.³⁵

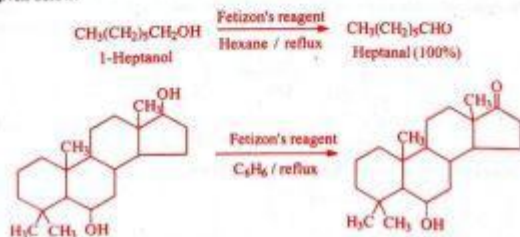


Mechanism

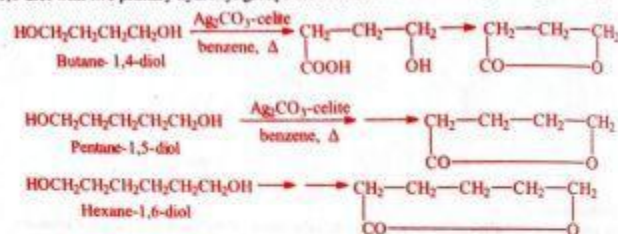
The oxidation is believed to proceed by the adsorption of the alcohol on silver carbonate. Subsequent one-electron transfer via the silver ion results in protonated carbonyl and carbonic acid^{36,37}, later decomposes to CO_2 and H_2O .



In the above oxidation, the use of polar solvents inhibits the rate. The product is obtained in a high state of purity by simply filtering of the spent reagent and evaporating off the solvent. Other functional groups if present are unaffected. Highly hindered hydroxyl groups are not effected, allowing selective oxidation wherever possible. Some examples are given below:



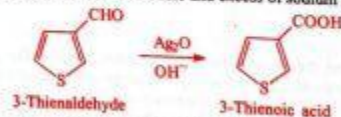
In case of diols, only one of the hydroxyl group is oxidised allowing synthesis of compounds that are not easily available. Butane-1,4-diol, pentane-1,5-diol and hexane-1,6-diol with two primary hydroxyl groups are converted to the corresponding lactones.



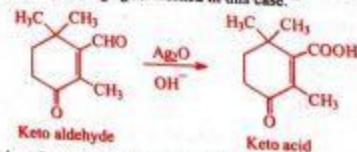
In the above oxidations only one CH_2OH group is oxidised to carboxylic acid, permitting the cyclisation to lactones.

3.5.15 Silver(I) oxide (Ag_2O)

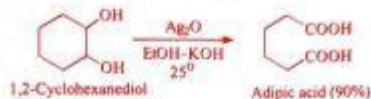
It is reagent of choice for the oxidation of aldehydes (where the substrate bearing the aldehyde group is susceptible to oxidation) to carboxylic acids. Thus, silver(I) oxide oxidises 3-thienaldehyde to 3-thienoic acid in 97% yield.⁵⁸ The reagent, Ag_2O is prepared⁵⁹ by mixing a solution of silver nitrate and excess of sodium hydroxide.



The oxidation of the keto aldehyde to keto acid can be effected by Ag_2O (see below) in excellent yield. No other oxidising agent worked in this case.⁶⁰



Some other examples of the use of Ag_2O are given below.



3.5.16 Silver(II) oxide (AgO)

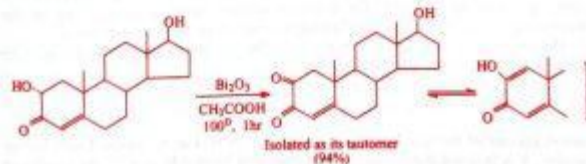
Silver(II) oxide (AgO) is a powerful oxidising agent for the oxidation of aldehydes and ketones. The reagent is prepared^{41,42} by the oxidation of silver nitrate with potassium peroxydisulfate ($\text{K}_2\text{S}_2\text{O}_8$) in alcoholic medium. Thus, in aqueous solution of AgO, benzyl alcohol on oxidation gives benzaldehyde. However, in alkaline or neutral medium, benzoic acid is obtained in 57% yield.

Cyclohexene aldehyde on oxidation with AgO and sodium cyanide gives⁴³ the corresponding acid without isomerisation of the double bond into conjugation.



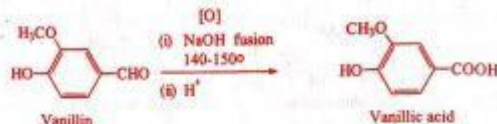
3.5.17 Bismuth oxide

It is a mild oxidising agent and is specific for the oxidation of activated alcohols. For example, it oxidises, α -hydroxy ketones to α -diketones, leaving untouched other functional groups like carbon-carbon double bonds or isolated alcohols.

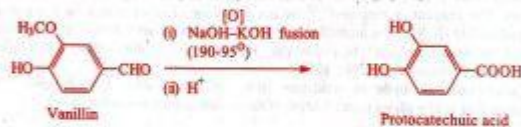


3.5.18 Fusion with alkali

Aromatic aldehydes on fusion with alkali (viz., sodium or potassium hydroxide) give the corresponding carboxylic acid.



If a mixture of sodium hydroxide and potassium hydroxide is used for fusion, the oxidation is also accompanied by demethylation of the methoxyl group.



3.5.19 Halogens-sodium hydroxide

Halogens (mostly iodine) and alkali oxidise methyl ketones and alcohols (which can be oxidised *in situ* to methyl ketones, e.g., isopropanol) to give the corresponding carboxylic acid salt and haloform (iodoform if iodine is used).

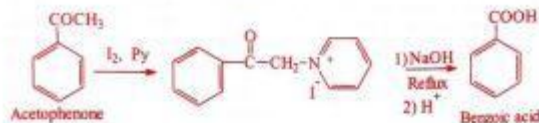


This reaction is known as **haloform reaction**. For mechanism and applications of haloform reaction see sec. 5.36. This is a synthetic method for oxidative cleavage of a methyl group to the carbonyl. The iodoform reaction forms a classical test for the presence of a methyl ketone or methyl carbinol moiety in an unknown compound.

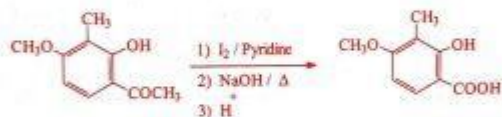
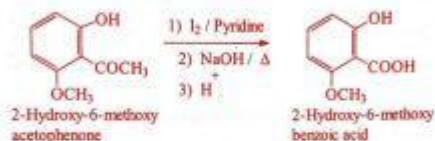
Methyl ketones can also be oxidised to the corresponding carboxylic acid by oxidation with iodine-pyridine (sec. 3.5.20).

3.5.20 Iodine-pyridine

Methyl ketones of the type ArCOCH_3 and $\text{R}_2\text{CHCOCH}_3$ can be oxidised with iodine-pyridine. It is believed that I_2 and pyridine react with ketones to give^{44,45} the pyridinium iodides in 95% yield. The salts are cleaved to the corresponding acids.

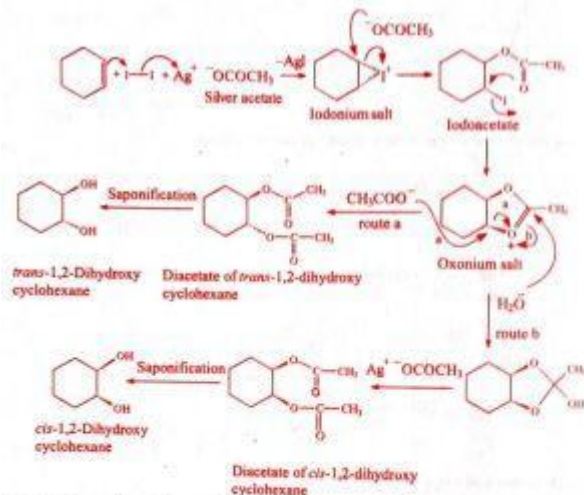


Using this method a large number of ketones can be oxidised.



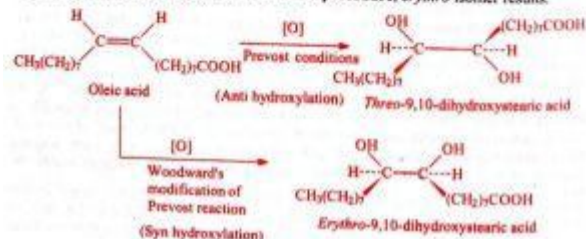
3.5.21 Iodine and silver carboxylates

Under anhydrous conditions a solution of iodine in carbon tetrachloride and equimolar amount of silver acetate or silver benzoate convert the alkenes into the diacetyl derivatives of the *trans* glycol, which on saponification gives *trans* diols. This reaction developed by Prevost is known as **Prevost reaction**.⁶⁶ The reaction proceeds via the formation of an iodonium salt, followed by the reaction with silver acetate to give the *trans* diacetate. The cyclic oxonium salt is opened by silver acetate (route a) to give the *trans* diacetate. Saponification of *trans* diacetate generates *trans* diol. The Prevost reaction generates *trans* diols (in contrast to permanganate and osmium tetroxide hydroxylation, which give *cis* diols). In contrast to the formation of *trans* diacetates under anhydrous conditions, in presence of water, *cis* diacetate is obtained, which on saponification gives *cis* diols. This is called the **Woodward modification**⁶⁷ of the Prevost reaction. Thus, cyclohexene on treatment with iodine and silver acetate in boiling carbon tetrachloride under anhydrous conditions gives the diacetate of *trans*-1,2-dihydroxycyclohexane. However, with iodine and silver acetate in moist acetic acid the diacetate of *cis*-1,2-dihydroxycyclohexane is formed, which on saponification yields *cis*-diol.

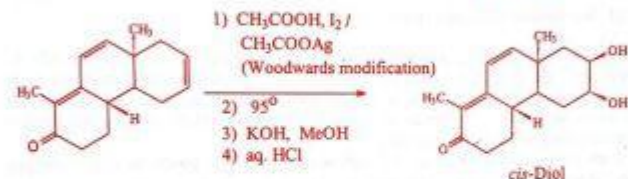
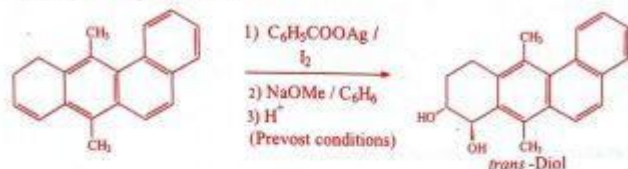


In aqueous medium, the oxonium salt reacts with water (route b), followed by ring opening to give *cis*-1,2-diester. Saponification of *cis*-1,2-diester yields *cis*-1,2-diol in 65% overall yield.

In a similar way, oleic acid on oxidation under Prevost conditions gives *threo*-9,10-dihydroxystearic acid, while by the Woodward procedure, *erythro* isomer results.



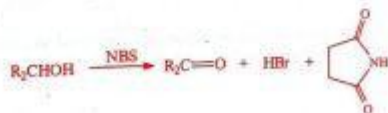
Also the examples given below show hydroxylation under anhydrous conditions (*viz.* Prevost condition) gives *trans* diols while hydroxylation under Woodward's modification of Prevost reaction gives *cis* diols.



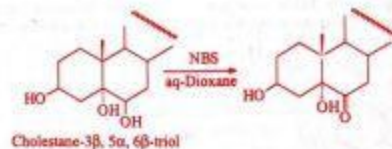
It is appropriate to mention that the route already described for the formation of *trans* diols is by hydrolysis of epoxides (sec. 3.4.1).

3.5.22 N-Bromosuccinimide

N-Bromosuccinimide is mostly used as brominating agent. It is also used as an oxidising agent. It oxidises secondary alcohols to ketones.



In certain cases NBS acts as a highly selective oxidising agent. For example cholestane-3 β , 5 α , 6 β -triol in aqueous dioxane is oxidised by NBS to the corresponding keto compound.

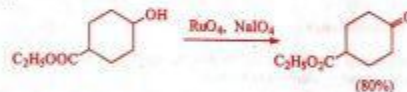


For mechanism and other applications see sec. 8.2.

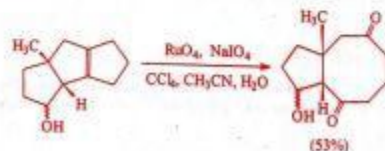
3.5.23 Ruthenium tetroxide (RuO_4)

Ruthenium tetroxide is a powerful oxidising agent (reduction potential of 0.59 v). Oxidations⁸⁸ are generally carried out in carbon tetrachloride-acetonitrile solution. Since ruthenium tetroxide is costly, it is equally convenient to use a catalytic amount of ruthenium tetroxide in presence of sodium periodate, which oxidises the reduced ruthenium back to the active tetroxide.

Ruthenium tetroxide cleaves the carbon-carbon double bonds to give carboxylic acids, aldehydes or ketones. This reagent is a good alternative to ozonolysis. Primary alcohols on oxidation give aldehydes and secondary alcohols give ketones. Ester function, if present is unaffected.



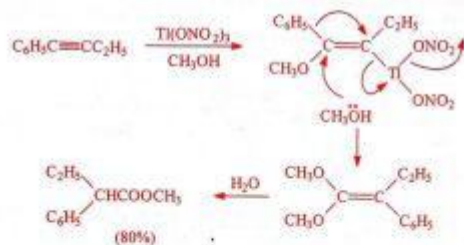
Ketones are stable to further oxidation but aldehydes are converted into carboxylic acids. The alkenes are cleaved⁸⁹ without oxidation of secondary alcohols as seen in the following synthesis.



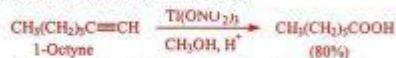
3.5.24 Thallium nitrate [$\text{Tl}(\text{NO}_3)_3$]

Alkenes and alkynes can be oxidised with thallium nitrate due to the following advantages.⁹⁰

(i) The oxidation can be carried out at room temperature.



With monoalkylacetylenes, the reaction takes a different course. The products obtained are carboxylic acids with loss of the terminal carbon.



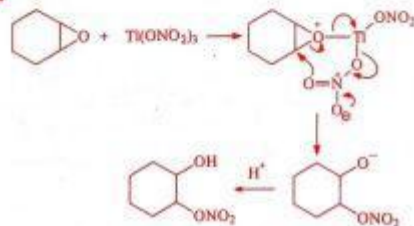
This reaction takes place through the intermediate formation of a α -ketal, which undergoes further reaction to give carboxylic acid.

(iii) Oxidation of cyclohexene oxide

Thallium nitrate oxidises cyclohexene oxide to 2-nitro cyclohexanol.

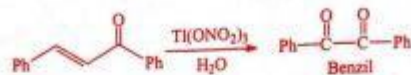


Mechanism

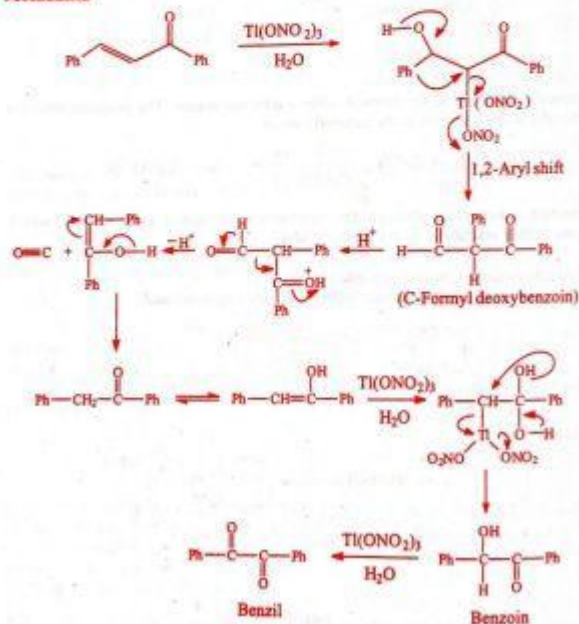


(iv) Oxidation of α, β -unsaturated ketones

Benzalacetophenone on oxidation with thallium nitrate gives benzil via the formation of C-formyldeoxybenzoin. The mechanism is given below.



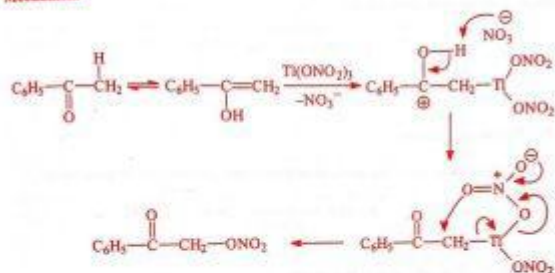
Mechanism



(v) Oxidation of acetophenone gives nitro acetophenone.

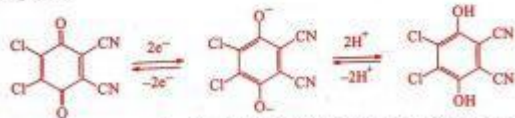


Mechanism



3.5.25 2,3-Dichloro-5,6-dicyano-1,4-benzoquinone (DDQ)

Aromatisation of alicyclic compounds is considered to be an oxidation process. This has been achieved in a number of ways. DDQ is a versatile reagent for achieving this. It functions as an efficient oxidant because of the rapidity with which the quinone-hydroquinone equilibrium is established and the ease with which the dehydrogenation is accomplished.



DDQ is used for aromatisation. For example tetralin is converted into naphthalene and acenaphthene into acenaphthylene. For methods of preparation of DDQ, its applications and mechanism of oxidation see sec 8.4.

3.5.26 Mercuric oxide

It is a mild oxidising agent for some specific use. Thus, oxidation of benzil dihydrazone with mercuric oxide gives diphenylacetylene.



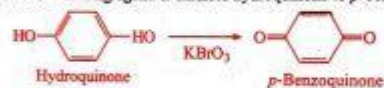
Benzil dihydrazone

Mercuric oxide with boron trifluoride in aqueous THF converts the dithianes to corresponding carbonyl compounds.⁷⁴

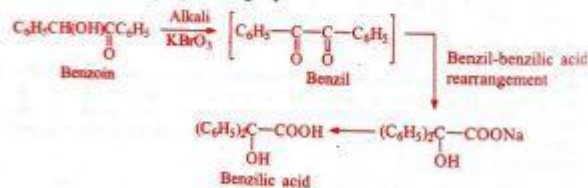


3.5.27 Potassium bromate

It is used as a selective oxidising agent. It oxidises hydroquinone to *p*-benzoquinone.



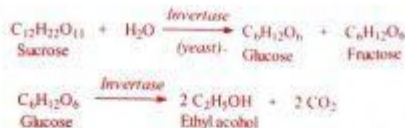
It also oxidises alcoholic group to keto group.



3.6 Enzymatic or microbial oxidations (Bio-oxidations)

Two important enzymatic oxidations have been very well known since early times. These are conversion of alcohol into acetic acid by *Bacterium acetic* in presence of air and the conversion of sucrose into ethyl alcohol by yeast.



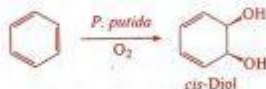


The first process is used to manufacture acetic acid by the well-known **quick-vinegar process** and the second process is used to manufacture ethyl alcohol. In a similar way the formation of lactic acid has been reported from lactose by *Bacillus acidilactis*.



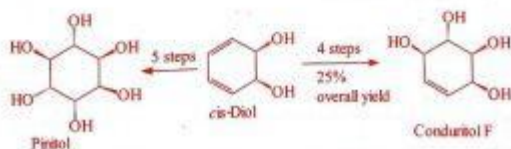
All the above enzymatic oxidations are referred as fermentation.

Considerable amount of work has been reported on enzymatic oxidation in transformation of organic molecules. Thus, benzene is oxidised⁷⁵ in presence of air with *Pseudomonas putida* to *cis*-diol, 3,5-dihydroxy-1,3-cyclohexadiene.

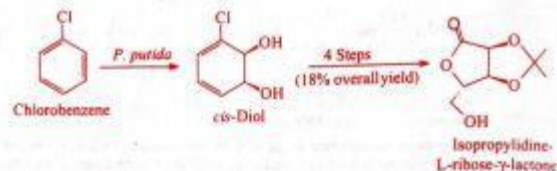


In a similar way toluene, halogen-substituted benzenes and *p*-halogen-substituted toluenes give the corresponding diols by *P. putida*. This reaction involves the conversion of a π -bond in benzene to a *cis*-diol.

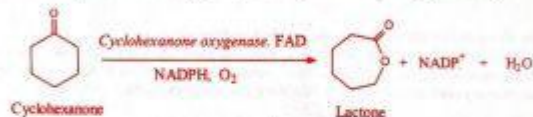
The *cis* diol obtained above can be converted by four steps into 1,2,3,4-tetrahydroxy compound, pinitol, an antidiabetic agent.



In a similar way, the *cis*-diol obtained from chlorobenzene is converted into 2,3-isopropyliden-L-ribose- γ -lactone in four steps.

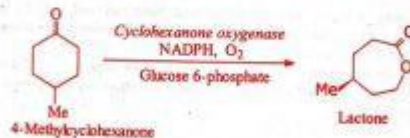


One of the very common microbial oxidation is the enzymatic conversion of ketones to esters. A typical transformation is the enzymatic Bayer-Villiger oxidation, which gives lactone from cyclohexanone using^{36,37} a purified cyclohexanone oxygenase enzyme.



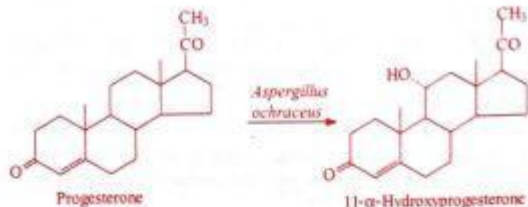
This enzyme also converts phenylacetaldehyde into phenylacetic acid in 65% yield.

Similarly, 4-methylcyclohexanone can be converted into the corresponding lactone in 80% yield³⁸ with > 98% ee with cyclohexanone oxygenase, obtained from *Acinetobacter*.

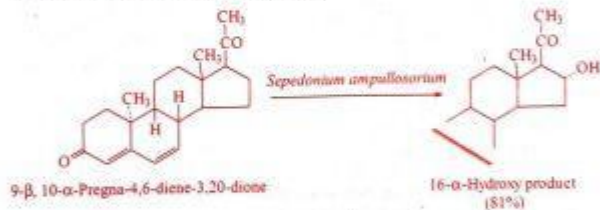


A number of microbial reagents have been used for successful oxidation of steroids, isoprenoids, alkaloids, hydrocarbons and other type of molecules. A number of reviews and monographs are available.⁷⁹⁻⁸⁵ Here we have given few cases which offer synthetic utility because they can afford excellent yields or they give single product that is inaccessible by other methods. Following are some typical microbial oxidations.

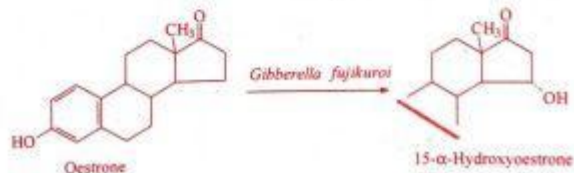
1. Progesterone can be converted by several microorganisms^{84,85} particularly *Rhizopus nigrovarius* and *Aspergillus ochraceus* into 11- α -hydroxyprogesterone. This is a commercial method of manufacturing of 11- α -hydroxyprogesterone as raw material for medicinally important steroids.



2. Hydroxylation of 9 β -10 α -pregna-4,6-diene-3,20-dione to give the corresponding 16- α -hydroxy derivative by *Sepedonium ampullisporium*.⁹⁶ This reaction has been carried out in 81% yield on a kilogram scale.



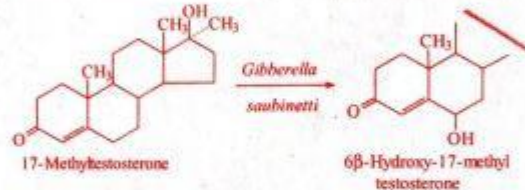
3. Oxidation of oestrone by *Gibberella fujikuroi* gives⁹⁷ 75% yield of 15- α -hydroxyoestrone.



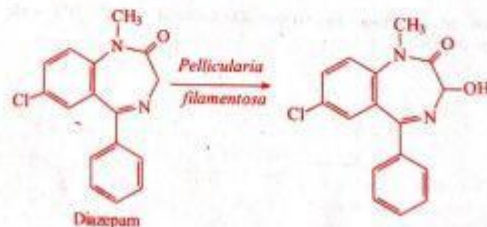
4. Hydroxylation of cholesterol by *Mycobacterium sp.* gives⁴⁸ cholest-4-en-2-one.



5. A large number of attempts for the oxidation in isoprenoids (e.g., terpenes, sesquiterpenes, diterpenes, sesterterpens and triterpenes) and alkaloids have been reported but the yields are very low.^{43,85}
6. Allylic oxidation of 17-methyltestosterone by *Gibberella saubinetii* gives⁹⁹ the corresponding 6 β -hydroxy product.



7. Oxidation of diazepam with *Pellicularia filamentosa* gives¹⁰⁰ the hydroxy derivative (the OH group enters the heterocyclic ring).



8. Oxidation of oleic acid with *Pseudomonas sp.* gives¹⁰⁰ 10-hydroxystearic acid in 14% yield.



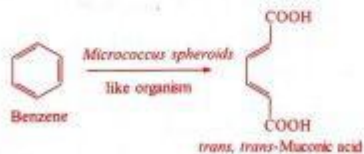
9. Oxidation of 3-(2'-hydroxyphenyl)propanoic acid with an enzyme obtained from *Arthrobacter species* gives¹⁰² the 3-(2',3'-dihydroxyphenyl)propanoic acid in 20% yield.



10. Nicotine is hydroxylated¹⁰³ at position 6 by *Arthrobacter sp.*



11. Benzene is converted¹⁰⁴ into *trans, trans*-muconic acid by *Micrococcus spheroides* like organism.



12. Amino groups can be converted into nitro groups by *Streptomyces thioautotus*.¹⁰⁵



3.7 Correlation tables

These tables are helpful to know oxidizing agents that can be used for oxidations of various types of compounds. The product(s) obtained in each case have also been given.

3.7.1 Oxidation of hydrocarbons

3.7.1.1 Oxidation of alkanes

Alkane	Product	Reagents	Sec.
$\text{C}_n\text{H}_{2n+2}$	$\text{CO}_2 + \text{H}_2\text{O}$	Combustion / chromic acid	3.3.2
CH_4	CH_3OH CH_2O	O_2 / Cu $\text{O}_2, \text{MoO}_3, 400^\circ \text{C}$	3.3.1 3.5.1

3.7.1.2 Oxidation of alkenes

Alkene	Product	Reagent	Sec.
$\text{CH}_3(\text{CH}_2)_7\text{CH}=\text{CH}_2$	$\text{CH}_3(\text{CH}_2)_7\text{COOH}$	Aq. KMnO_4 Cetyltrimethyl ammonium chloride	3.2.12
Cyclooctene	Cyclooctane diol (cis)	$\text{KMnO}_4, \text{H}_2\text{O}, \text{NaOH}$ + $\text{Ba}(\text{NO}_3)_2$	3.2.12
	9,10-Dihydroxystearic acid + $\text{CH}_3(\text{CH}_2)_7\text{COOH} + \text{HOOC}(\text{CH}_2)_7\text{COOH}$	$\text{KMnO}_4 / \text{NaOH}$ Neutral KMnO_4 $\text{O}_3 / \text{H}_2\text{O}_2$	3.2.12 3.3.3
Norbornene	cis diol dialdehyde	$\text{KMnO}_4, \text{NaOH}$ KMnO_4 (neutral)	3.2.12
α -Pinene	Pinonic acid	$\text{KMnO}_4, \text{C}_6\text{H}_6$ dicyclohexano 18-crown-6	3.2.12
		Pyridinium chlorochromate (PCC)	3.3.14

		$\text{Na}_2\text{Cr}_2\text{O}_7 / \text{Ac}_2\text{O} / \text{HOAc}$	3.3.3
		$\text{Na}_2\text{Cr}_2\text{O}_7 / \text{Ac}_2\text{O} / \text{HOAc}$	3.3.3
		$\text{CrO}_3 / \text{Ac}_2\text{O}$	3.3.3
$\text{CH}_3(\text{CH}_2)_7\text{CH}=\text{CH}_2$	$\text{CH}_3(\text{CH}_2)_7\text{CH}(\text{O})\text{CH}_2$	$t\text{-C}_4\text{H}_9\text{OOH}$	3.5.5
$(\text{Me})_2\text{CCH}_2-\text{C}(\text{CH}_3)=\text{CH}_2$	$\text{Me}_2\text{C}-\text{CH}_2-\text{CH}(\text{O})-\text{CH}_3$	CrO_2Cl_2	3.3.3
$\text{H}_3\text{C}-\text{CH}=\text{CH}_2$ trans olefin cis olefin	 trans epoxide cis epoxide	$m\text{-ClC}_6\text{H}_4\text{CO}_2\text{H}$	3.4.1
	 Major Minor	$\text{C}_6\text{H}_5\text{CO}_2\text{H}$	3.4.1
		$\text{CH}_3\text{CO}_2\text{H}$	3.4.1

		$m\text{-ClC}_6\text{H}_4\text{CO}_2\text{H}$	3.4.1
		$t\text{-C}_4\text{H}_9\text{OOH}$ $\text{Ti}(\text{O}-i\text{Pr})_4$	3.5.5
$\text{H}_2\text{C}=\text{C}=\text{CH}_2$			3.4.1
			3.4.1
$\text{CH}_2=\text{CH}_2$	$\text{CH}_3\text{CH}(\text{O})\text{CH}_3$	$\text{O}_2 / \text{PdCl}_2 / \text{CuCl}_2$	3.5.1
		Singlet O_2	3.5.2
		Singlet O_2	3.5.2
		Singlet O_2	3.5.2
		Singlet O_2	3.5.2

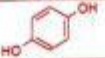
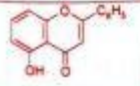
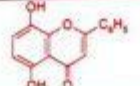
		O_3	3.5.3
		$\text{O}_3 / \text{H}_2\text{O}_2$	3.5.3
		$\text{O}_3 / (\text{CH}_3)_2\text{S}$	3.5.3
		$\text{O}_3 / \text{H}_2\text{O}_2$	3.5.3
	Epinyl epoxide	$\text{t-C}_4\text{H}_9\text{COOH} + \text{VO(acac)}_3$	3.5.5
		$\text{t-C}_4\text{H}_9\text{COOH} + \text{Ti}(\text{OC}_2\text{H}_5)_4$ + (+) - Diethyl tartrate	3.5.5
		$\text{t-C}_4\text{H}_9\text{COOH} + \text{Ti}(\text{OC}_2\text{H}_5)_4$ + (-) Diethyl tartrate	3.5.5
		$\text{t-C}_4\text{H}_9\text{COOH}$ (+) - Diethyl tartrate	3.5.5
		SnO_2	3.5.8
$\text{R}-\text{CH}-\text{OH}$ $\text{R}-\text{CH}-\text{OH}$	$\text{R}-\text{CH}-\text{OH}$ $\text{R}-\text{CH}-\text{OH}$	$\text{OsO}_4 / \text{H}_2\text{O}_2$	3.5.9
Cyclohexene	trans-1,2-dihydroxycyclohexanol	(i) I_2 / silver acetate (ii) Saponification	3.5.21
Oleic acid	Erythro-9,10-dihydroxy stearic acid Threo-9,10-dihydroxy stearic acid	(i) I_2 / silver acetate (ii) Saponification	3.5.21

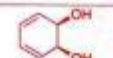
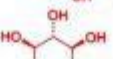
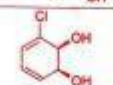
3.7.1.3 Oxidation of alkynes

Alkyne $\text{R}-\text{C}\equiv\text{C}-\text{R}'$	Product $\text{RCOOH} + \text{R'COOH}$	Reagent	Sec.
$\text{CH}_3(\text{CH}_2)_7\text{C}\equiv\text{CCH}_2\text{COOH}$	$\text{CH}_3(\text{CH}_2)_7-\text{C}(=\text{O})-\text{C}(=\text{O})-(\text{CH}_2)_7\text{COOH}$ $\text{CH}_3(\text{CH}_2)_7\text{COOH} + \text{HOOC}(\text{CH}_2)_7\text{COOH}$	Aq. KMnO_4 (pH 7.5) $[\text{KMnO}_4]$ Alkaline	3.2.1.3
$\text{C}_6\text{H}_5-\text{C}\equiv\text{C}-\text{C}_6\text{H}_5$	$\text{C}_6\text{H}_5\text{CO}-\text{CO}-\text{C}_6\text{H}_5$	$\text{Ti}(\text{ONO}_2)_3$	3.5.24
$\text{CH}_3(\text{CH}_2)_7\text{C}\equiv\text{CH}$	$\text{CH}_3(\text{CH}_2)_7\text{COOH}$	$\text{Ti}(\text{ONO}_2)_3$	3.5.24

3.7.1.4 Oxidation of aromatic hydrocarbons

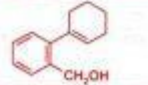
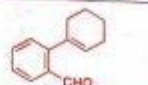
Aromatic hydrocarbon	Product	Reagent	Sec.
Toluene	Benzoic acid	KMnO_4 or $\text{KMnO}_4 / \text{C}_6\text{H}_6 / 18\text{-Crown-6}$ $\text{Na}_2\text{Cr}_2\text{O}_7 / \text{H}_2\text{SO}_4$	3.2.1.4
	Benzaldehyde	$\text{MnO}_2 / \text{MO}_2 / \text{ZrO}_2$	3.2.2
α -Pinene	cit pinonic acid	$\text{KMnO}_4, \text{C}_6\text{H}_6$ dicyclo-18-Crown-6	3.2.1.2
α -chlorotoluene	α -chlorobenzoic acid	KMnO_4	3.2.1.4
2,4,6-Trimethyl benzene	Sym. Benzene tricarboxylic acid	KMnO_4	3.2.1.4
Quinoline	Pyridine 2,3-dicarboxylic acid	KMnO_4	3.2.1.4
Isquinoline	Pyridine-3,4-dicarboxylic acid	KMnO_4	3.2.1.4
2-methylnaphthalene	β -Naphthoic acid	$\text{Na}_2\text{Cr}_2\text{O}_7 / \text{H}_2\text{SO}_4$	3.3.4
p -Nitrotoluene	p -Nitrobenzoic acid	$\text{Na}_2\text{Cr}_2\text{O}_7$, dil. H_2SO_4	3.3.4
		$\text{CrO}_3 / \text{CH}_3\text{COOH}$	3.3.4
		$\text{CrO}_3 / \text{CH}_3\text{COOH}$	3.3.4
		$\text{CrO}_3 / \text{CH}_3\text{COOH}$	3.3.4

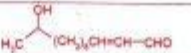
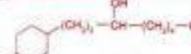
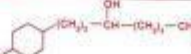
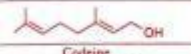
		$\text{CrO}_3 / \text{CH}_3\text{COOH}$	3.3.4
		$\text{Air} / \text{V}_2\text{O}_5 / 500^\circ$	3.5.1
		CrO_2Cl_2	3.3.4
Pyridine	Pyridine N-oxide	$\text{CH}_3\text{CO}_2\text{H}$	3.4.3
		$\text{C}_6\text{H}_5\text{CO}_2\text{H}$	3.4.3
		$\text{C}_6\text{H}_5\text{CO}_2\text{H}$	3.4.3
		$\text{O}_2 / \text{V}_2\text{O}_5$ $400-450^\circ \text{C}$	3.5.1
		$\text{H}_2\text{O}_2 / \text{OH}^-$	3.5.4
		SeO_2	3.5.8
		$\text{K}_2\text{S}_2\text{O}_8 / \text{OH}^-$	3.5.11
		$\text{K}_2\text{S}_2\text{O}_8 / \text{OH}^-$	3.5.11

		Enzymic oxidation	3.6
		Enzymic oxidation	3.6
		Enzymic oxidation	3.6

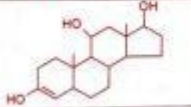
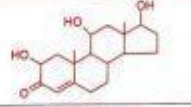
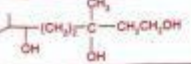
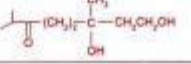
3.7.2 Oxidation of alcohols

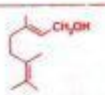
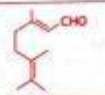
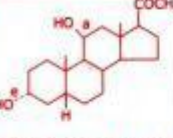
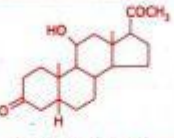
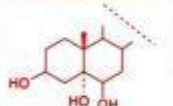
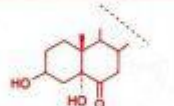
3.7.2.1 Oxidation of 1° alcohols

1° alcohol	Product	Reagent	Sec.
$\text{RCH}_2\text{CH}_2\text{OH}$	RCH_2COOH	$\text{KMnO}_4 / \text{H}_2\text{SO}_4$	3.2.1.1
		$\text{Na}_2\text{Cr}_2\text{O}_7 / \text{H}_2\text{SO}_4$	3.3.1.1
		Collins Reagent	3.3.1.3
$\text{C}_6\text{H}_5\text{CH}_2\text{OH}$	$\text{C}_6\text{H}_5\text{CHO}$	$\text{Na}_2\text{Cr}_2\text{O}_7$	
		Jones Reagent	3.3.1.2
$\text{HC}\equiv\text{C}-\text{CH}=\text{CH}-\text{CH}_2\text{OH}$	$\text{HC}\equiv\text{C}-\text{CH}=\text{CH}-\text{COOH}$	Jones Reagent	3.3.1.2
	$\text{HC}\equiv\text{C}-\text{CH}=\text{CH}-\text{CHO}$	Collins Reagent	3.3.1.3
		Jones Reagent (0°C)	3.3.1.2
$\text{CH}_3(\text{CH}_2)_2\text{CH}=\text{CH}(\text{CH}_2)_2\text{CH}_2\text{OH}$	$\text{CH}_3(\text{CH}_2)_2\text{CH}=\text{CH}(\text{CH}_2)_2\text{CHO}$	Collins Reagent	3.3.3
$\text{HC}\equiv\text{C}-\text{CH}=\text{C}(\text{CH}_3)-\text{CH}_2-\text{OH}$	$\text{HC}\equiv\text{C}-\text{CH}=\text{C}(\text{CH}_3)-\text{CHO}$	MnO_2 / acetone	3.2.2
		MnO_2 / ether	3.2.2
		MnO_2	3.2.2
$\text{C}_6\text{H}_5\text{CH}=\text{CH}-\text{CH}_2\text{OH}$	$\text{C}_6\text{H}_5\text{CH}=\text{CH}-\text{CHO}$	Collins Reagent	3.3.1.3
$\text{C}_6\text{H}_5\text{CH}_2\text{CH}_2\text{OH}$	$\text{C}_6\text{H}_5\text{CHO}$	SeO_2	3.5.8

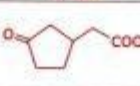
		Pyridinium-dichromate + $\text{RuCl}_2 \cdot \text{P}(\text{Ph})_3$	3.3.1.5
		Pyridinium-dichromate + $\text{RuCl}_2 \cdot \text{P}(\text{Ph})_3$	3.3.15
$\text{CH}_3\text{CH}_2\text{OH}$	CH_3CHO	$\text{Ag} / \text{air} / 250^\circ$	3.5.1
$\text{CH}_3(\text{CH}_2)_3\text{CH}_2\text{OH}$	$\text{CH}_3(\text{CH}_2)_3\text{CHO}$	$\text{PhOAc}_3 / \text{Py}$	3.5.7
$\text{CH}_3(\text{CH}_2)_3\text{CH}_2\text{OH}$	$\text{CH}_3(\text{CH}_2)_3\text{CHO}$	$p\text{-TsCl} / \text{DCC} / \text{DMSO} / (\text{COCl})_2$	3.5.13
		CH_3SOCH_3 , $(\text{COCl})_2 / \text{Et}_3\text{N}$	3.5.13
Codine	Codinone	AgCO_3	3.5.14
Geraniol	Geranial	AgCO_3 or celite	3.5.14
$\text{CH}_3(\text{CH}_2)_3\text{CH}_2\text{OH}$	$\text{CH}_3(\text{CH}_2)_3\text{CHO}$	Felizon's reagent	
$\text{CH}_3\text{CH}_2\text{OH}$	CH_3COOH	Enzymic oxidn.	3.6

3.7.2.2 Oxidation of 2° alcohols

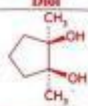
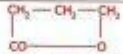
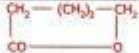
2° Alcohol	Product	Reagent	Sec.
		$\text{KMnO}_4 / \text{H}_2\text{SO}_4$ Pyridinium-chlorochromate (PCC)	3.2.1.1 3.3.1.4
		$\text{MnO}_2 / \text{CHCl}_3$	3.2.2
Cyclohexanol	Cyclohexanone	$\text{K}_2\text{Cr}_2\text{O}_7 / \text{H}_2\text{SO}_4$ (50–55°C)	3.3.1.1
	Adipic acid	$\text{K}_2\text{Cr}_2\text{O}_7 / \text{H}_2\text{SO}_4$ (70°C)	3.3.1.1
		$\text{K}_2\text{Cr}_2\text{O}_7 / \text{H}_2\text{SO}_4$ / DMSO	3.3.1.1
$\text{CH}_3\text{CH}(\text{OH})\text{C}(\text{CH}_3)_2\text{CH}_3$	$\text{CH}_3\text{COC}(\text{CH}_3)_2\text{CH}_3$	Jones Reagent	3.3.1.2
		Collins reagent	3.3.1.3

		$\text{Al}(\text{OCMe}_3)_3$ / quinoline	3.5.6
		$\text{Al}(\text{OCMe}_3)_3$ + 	3.5.6
$\text{CH}_3\text{CHOHCH}_2\text{CHOHCH}_3$	$\text{CH}_3\text{CO-CH}_2\text{-CO-CH}_3$	$\text{Pb}(\text{OAc})_2$ / Pyridine	3.5.7
$\text{RCHO-CH}_2\text{OH}$	$\text{RCHO} + \text{HCHO}$	HIO_4	3.5.10
RCHOHCHOH R'	$\text{RCHO} + \text{RCHO}$	HIO_4	3.5.10
	$\text{HOOC}(\text{CH}_2)_4\text{COOH}$	HNO_3 , V_2O_5	3.5.12
		NBS	3.5.22
$\text{C}_6\text{H}_5\text{OOC-}$ 	$\text{C}_6\text{H}_5\text{OOC-}$ 	RuO_4 , NaIO_4	3.5.23
$\text{C}_6\text{H}_5\text{CH}(\text{OH})\text{COC}_6\text{H}_5$	$\text{C}_6\text{H}_5\text{COCOC}_6\text{H}_5$ + $(\text{C}_6\text{H}_5)_2\text{C}(\text{OH})\text{COOH}$	$\text{KBrO}_3 / \text{OH}$	3.5.27

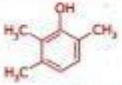
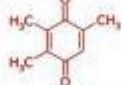
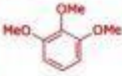
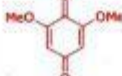
3.7.2.3 Oxidation of 3° alcohols

3° Alcohol	Product	Reagent	Sec.
		$\text{CrO}_3 / \text{H}_2\text{SO}_4$	3.3.1.1

3.7.2.4 Oxidation of diols

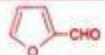
Diol	Product	Reagent	Sec.
		$\text{Na}_2\text{Cr}_2\text{O}_7 / \text{H}_2\text{SO}_4$	3.3.1.1
	$\text{C}=\text{O} + \text{O}=\text{C}$	$\text{Pb}(\text{OAc})_2$	3.5.7
$\text{HOCH}_2\text{CH}_2\text{CH}_2\text{CH}_2\text{OH}$		Ag_2CO_3 -celite	3.5.14
$\text{HOCH}_2(\text{CH}_2)_3\text{CH}_2\text{OH}$		Ag_2CO_3 -celite	3.5.14
	$\text{HOOC}(\text{CH}_2)_4\text{COOH}$	$\text{Ag}_2\text{O} / \text{EtOH-KOH}$	3.5.15

3.7.2.5 Oxidation of phenols

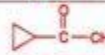
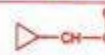
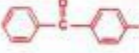
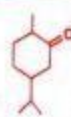
Phenol	Product	Reagent	Sec.
		$\text{K}_2\text{Cr}_2\text{O}_7 / \text{H}_2\text{SO}_4$	3.3.1.1
		$\text{Pb}(\text{OAc})_2$	3.5.7
		$\text{KBrO}_3 / \text{H}_2\text{SO}_4$	3.5.27
		$\text{Na}_2\text{Cr}_2\text{O}_7 / \text{H}_2\text{SO}_4$	3.3.1.1
		$\text{K}_2\text{Cr}_2\text{O}_7 / \text{H}_2\text{SO}_4$	3.3.1.1
		$\text{HNO}_3 / \text{CH}_3\text{COOH}$	3.5.12

3.7.3 Oxidation of carbonyl compounds

3.7.3.1 Oxidation of aldehydes

Aldehyde	Product	Reagent	Sec.
ArCHO	ArCOOH	Alk. KMnO_4	3.2.1.5
n-Hexanal	n-Hexanoic acid	Acidic KMnO_4	3.2.1.5
R-CH=CH-CHO	$\text{R-CH=CH-C(=O)OCH}_3$	$\text{MnO}_2 / \text{CN}^- / \text{CH}_3\text{OH}$	3.2.2
		O_2 / Air	3.5.1
		$\text{Ag}_2\text{O} / \text{OH}^-$	3.5.15
CH_3CHO	CH_3COOH	SeO_2	3.5.8
		$\text{Ag}_2\text{O}, \text{NaCN}$	3.5.16

3.7.3.2 Oxidation of ketones

Ketone	Product	Reagent	Sec.
$\text{R}_2\text{C}=\text{O}$	$\text{R}_2\text{C}=\text{O}$	$\text{C}_6\text{H}_5\text{COOOH}$	3.4.2
		$\text{CF}_3\text{CO}_2\text{H}$	3.4.2
		RCO_2H	3.4.2
		RCO_2H	3.4.2
		$\text{CF}_3\text{CO}_2\text{H}$	3.4.2

		$C_6H_5CO_3H$	3.4.2
		CF_3CO_3H	3.4.2
		CF_3CO_3H / Alkali	3.4.2
CH_3COCH_3	CH_3COCHO	SeO_2	3.5.8
		SeO_2	3.5.8
$RCOOR'$	$RCOOH + R'COOH$	HIO_4	3.5.10
$RCOCH_3$	$RCOOH$	$I_2/Py / \bar{O}H / NaOH$	3.5.20
		$I_2 / Py / \bar{O}H$	3.5.20
$C_6H_5COCH_3$	$C_6H_5COCH_2ONO_2$	$Tl(ONO_2)_3 / CH_3CN$	3.5.24
		Enzymic oxidn.	3.6
		Enzymic oxidn.	3.6

3.7.4 Oxidation of nitro compounds

Nitro compound	Product	Reagent	Sec.
$\begin{array}{c} R \\ \\ R'-CH-NO_2 \end{array}$ 1° or 2° nitro compounds	$\begin{array}{c} R \\ \\ R'-C-CHO \end{array}$	alk. $KMnO_4$	3.2.1.7
		alk. $KMnO_4$	3.2.1.7

3.7.5 Oxidation of amines

Amine	Product	Reagent	Sec.
$\begin{array}{c} \\ -C-NH_2 \end{array}$	$\begin{array}{c} \\ -C-NO_2 \end{array}$	alk. $KMnO_4$	3.2.1.6
$CH_3(CH_2)_nNH_2$	$CH_3(CH_2)_nNO_2$	H_2O_2	3.5.4
$C_6H_5NH_2$	$C_6H_5NO_2$	H_2O_2	3.5.4
		MnO_2 / H^+	3.2.2
$C_6H_5NH_2$	C_6H_5NHOH	H_2O_2	3.5.4
$(C_6H_5)_2NH$	$(C_6H_5)_2NOH$	H_2O_2	3.5.4

3.7.6 Oxidation of cyanides

Cyanide	Product	Reagent	Sec.
$R_2C \equiv N$	$RCONH_2$	H_2O_2 / alk.	3.5.4

3.7.7 Dehydrogenation

Starting compound	Product	Reagent	Sec.
Tetralin	Naphthalene	DDQ	3.5.25
Acenaphthalene	Acenaphthylene	DDQ	3.5.25

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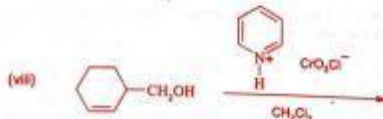
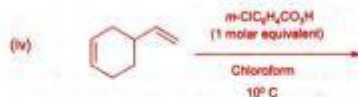
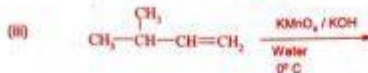
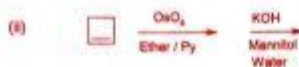
Problems

1. Define oxidation and oxidation number.
2. On the basis of calculation of oxidation number find the change in oxidation number in the following conversions.



3. What products are obtained in the case of following by oxidation with KMnO_4 ?
 - (i) Norbornene in alkaline and neutral media.
 - (ii) α -Pinene in presence of crown ether.
 - (iii) Cyclooctene in presence of PTC.
 - (iv) $\text{CH}_3(\text{CH}_2)_7\text{C}\equiv\text{C}(\text{CH}_2)_7\text{COOH}$ in neutral and acidic medium.
 - (v) Cyclooctene in presence of H_2O , NaOH and $\text{C}_6\text{H}_5\text{CH}_2\text{N}^+(\text{CH}_3)_3\text{Cl}^-$ at 0° .
4. What is the function of using crown ethers in KMnO_4 oxidations?
5. What product or products will be obtained by oxidation of oleic acid with KMnO_4 in neutral and alkaline medium?
6. Give a suitable mechanism for the oxidation of an aldehyde to carboxylic acid with KMnO_4 in acidic medium.
7. In the oxidation of isopropyl alcohol to acetone by chromic acid what is the rate determining step? How will you establish it?
8. What is Jones's Reagent? Give some of its applications.
9. Give the use of *m*-chloroperbenzoic acid in oxidations.
10. In Baeyer-Villiger oxidation of ketones give the relative ease of migration of the following groups: *tert*-alkyl, *sec*-alkyl, benzyl, phenyl, methyl and cyclohexyl.
11. Discuss the use of singlet oxygen in oxidations.
12. Geraniol has two double bonds. How will you obtain the 2,3-epoxidation product and 6,7-epoxidation product?
13. In the oxidation of alkenes with OsO_4 and H_2O_2 , glycol is obtained. The oxygen of glycol is obtained from H_2O or OsO_4 , explain.
14. Discuss the use of periodic acid in oxidations. Give a suitable mechanism.
15. Discuss the mechanism involved in the oxidation of *sec*-alcohol with Dimethylsulphoxide and DCC.
16. Give examples of oxidations involving the use of silver carbonate, silver(I) oxide and silver(II) oxide.
17. Starting with cyclohexene how will you obtain *trans*- and *cis*-1,2-dihydroxycyclohexanes, give mechanisms involved?
18. Starting with oleic acid how will you obtain *threo*- and *erythro*-9,10-dihydroxystearic acid?
19. Discuss the use of thallium nitrate in oxidations.
20. Give applications of DDQ in oxidation.
21. Give use of enzymatic oxidations in industry.

22. Complete the following equations.



4 Reduction

4.1 Introduction

Like oxidation, reduction of organic molecules has played an important role in organic synthesis. Reduction is referred to as addition of hydrogen to an unsaturated group like a carbon-carbon double bond, a carbonyl group or an aromatic nucleus. Typical examples of reduction are conversion of ethylene into ethane, acetaldehyde into ethyl alcohol, acetone into isopropyl alcohol. Addition of hydrogen with fission of a bond between two atoms is also referred to as reduction. For example, conversion of benzoyl phenol into phenol. This example involves fission of a bond between oxygen and carbon.



The concept of oxidation in terms of oxidation number is also useful for reduction (see sec. 3.1). Just like conversion of a functional group in a molecule in case of oxidation changes from a lower oxidation state to a higher one, similarly in reduction the oxidation number changes from higher oxidation states to a lower oxidation state. The oxidation state is calculated as described earlier (see chapter 3, sec. 3.1). Thus, in the reduction of propanal to propanol, the oxidation state of C in CHO changes from +1 to -1 for the C in CHOH.



In the above illustration in propanal, the carbon atom bearing its aldehyde group has an oxidation number +1 (C is 0, H is -1, O is +1 and O from second bond to the carbonyl is -1). The oxidation number of carbon bearing hydroxyl group is -1 (C is 0, H is -1, H is -1 and O is +1). We find that the change in oxidation number is +1 $\rightarrow$ -1, for a net gain of 2 electrons. So this is a reduction reaction.

A number of reagents can be used for the reduction of organic substrates. The reducing power of a reducing agent depends on its reduction potential. For metals to serve as reducing agents, the reverse reaction ($\text{M} \rightarrow \text{M}^+$) must be facile. The high reduction potential of $\text{Li}^+ \rightarrow \text{Li}$ (or $\text{Ca}^+ \rightarrow \text{Ca}$) indicates that the $\text{Li} \rightarrow \text{Li}^+$ (or $\text{Ca} \rightarrow \text{Ca}^+$) reaction is favoured and lithium metal (or calcium metal) is an excellent reducing agent.

The product obtained in a reduction reaction depends on the nature of the substrate, the reagent and the conditions (temperature, pressure, solvents etc.). Following is a brief account of various types of reducing agents and their applications. Both catalytic and chemical methods have been used for reduction. However, the method of choice depends on the selectivity required and on the stereochemistry of the desired product.

When an alkene is mixed with hydrogen in presence of a large number of metallic catalysts, addition of hydrogen converts the alkene into an alkane. The reaction is called hydrogenation. The hydrogenation is of two types, heterogeneous hydrogenation and homogeneous hydrogenation.

4.2[A] Heterogeneous hydrogenation

Catalytic hydrogenation is one of the most convenient method for the reduction of organic compounds. The method consists in stirring the substrate with a catalyst in a suitable solvent in an atmosphere of hydrogen. The apparatus used is such that the uptake of hydrogen can be measured. After the reduction is complete (as seen by its uptake of hydrogen) the catalyst is removed by filtration and the reduced product is obtained in pure state by removal of the solvent from the filtrate. Common unsaturated groups such as C-C double bond, C-C triple bond, carbonyl group, carboxylic group, nitrile group, nitro group and aromatic and heterocyclic nuclei can be reduced catalytically under appropriate conditions.

A number of catalysts have been used for catalytic hydrogenation. They are used mainly as finely divided metals, metallic oxides or sulfides. The most common catalysts are the platinum metals (platinum, palladium, rhodium and ruthenium), nickel and copper chromite. The catalytic reduction takes place between gaseous hydrogen and an organic compound. The reduction takes place at the surface of the catalyst which adsorbs both hydrogen and the organic compound and facilitates their contact. Transfer of hydrogen takes place from the catalyst to the molecule, resulting in reduction. In general it is found that hydrogenation takes place by the addition of hydrogen atoms to the less hindered side of the unsaturated site.

Platinum

Platinum is used in the form of its oxide, PtO_2 (Adam's catalyst). During reductions, the oxide is reduced by hydrogen in the reduction medium. The platinum metal catalysts can be prepared by the reduction of a metallic salt in the presence of a suitable support. Effective platinum catalysts can also be obtained¹ by reduction of metal salts with sodium borohydride or a trialkylsilane.

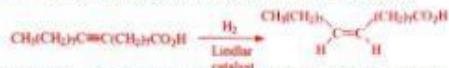
Palladium

Palladium is the most widely used both in industrial and academic laboratories on both a minute and very large scale. Palladium catalyst resembles platinum catalyst in activity and usefulness. It is obtained² by the reduction of palladium chloride with sodium borohydride. Palladium supported catalysts commonly used are palladium on charcoal, CaCO_3 or BaSO_4 . It increases the contact of catalyst with hydrogen. Palladium on BaSO_4 (i.e. for the conversion of acid chlorides into aldehydes, see sec. 5.77). Palladium on CaCO_3 deactivated by lead acetate is known as Lindlar's catalyst, and is used for partial reduction of triple bonds to double bonds.

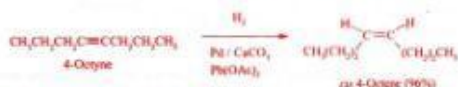
Di-imide (HN=NH) is another reagent which can be used for the selective reduction of alkenes containing other functional groups (see sec. 4.5.2).

4.2.1 Reduction of alkynes

Catalytic hydrogenation of alkynes gives the completely reduced product, viz. alkanes. Alkynes can also be reduced partially to give Z-alkenes by palladium-calcium carbonate catalyst which has been deactivated (partially poisoned) by the addition of lead acetate (Lindlar catalyst) or Pd-BaSO₄ deactivated by quinoline. The lead treatment poisons the palladium catalyst, rendering it less active and the reaction more selective.

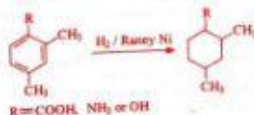
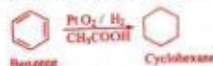


Another example is the reduction of 4-octyne to *cis*-4-octene with Lindlar catalyst.



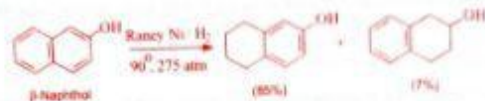
4.2.2 Reduction of aromatic compounds

Aromatic compounds are difficult to reduce by catalytic hydrogenation, also the selective reduction of aromatic compounds is not easy. Common catalysts for reduction of aromatic compounds are platinum, rhodium and Raney nickel. Thus, benzene on reduction with platinum oxide and hydrogen in acetic acid gives cyclohexane. However, substituted benzenes like benzoic acids, phenols and anilines can be reduced more easily.

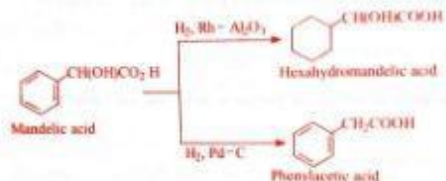


Reduction of β-naphthol with Raney nickel / H₂ produces the tetrahydro-β-naphthol as the major product.

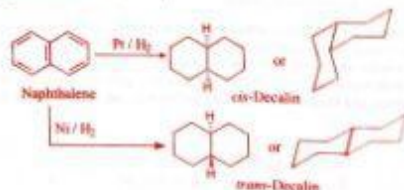
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Mandelic acid gives hexahydromandelic acid on reduction with H₂ and rhodium-alumina in methanolic solution. However, hydrogenolysis to phenyl acetic acid is the main product with palladium-carbon / H₂.



Naphthalene can be reduced partially or completely depending on the reducing agent. Thus, reduction of naphthalene with Pt / H₂ gives *cis*-decalin. However reduction with Ni / H₂ gives *trans*-decalin.



With sodium / ethanol partial reduction of naphthalene occurs and 1,4-dihydronaphthalene (1,4-dialfin) is formed, which isomerises to 1,2-dialfin. On the other hand reduction with sodium and isomyl alcohol at 120-140° gives tetralin as the main product. However, reduction of naphthalene with Raney Ni / H₂ gives tetrahydro- or decahydronaphthalene depending on temperature.

α-Naphthol on reduction with Na-alcohol gives tetrahydro-α-naphthol, whereas reduction with Li-liquid ammonia gives 5, 8-dihydro-α-naphthol.

Table 2.1

Functional group	Product obtained	Catalyst (mol %)	Conditions Temp. in °C (Pressure in atm.)
		CH-1, CH-2, CH-3, CH-4, CH-5 CH-6, CH-7, CH-8	
Alkene	Alkane	CH-1 (5-10 %) CH-2 (0.5-1 %) CH-3 (30-200 %)	25 (1-3) 25 (1-3) 25 (1-3)
Alkyne	Alkyne	CH-4 (8 %) CH-5 (2 % + 2 % quinoline) CH-6 (10 % + 4 % quinoline) CH-7 (3 %) CH-8 (30 %)	25 (1) 20 (1) 25 (1) 25 (1) 25 (1-4)
Carboxylic acid (aromatic)	Hydroaromatic	CH-2 (6-20 % HOAc) CH-7 (40-60 %)	25 (1-3) 25 (1-3)
Heterocyclic (aromatic)	Hydroaromatic	CH-2 (7 % HOAc) CH-8 (20 %, HCl, MeOH) CH-3 (2 %)	75-100 (70-100) 25 (1-4) 65-200 (30)
Carbonyl	Alcohol	CH-2 (2-4 %) CH-1 (3-5 %) CH-3 (30-100 %)	25 (1) 25 (1-4) 25 (1)
Halide	Hydrocarbon	CH-1 (3-15 %, KOH) CH-5 (30-100 %, KOH) CH-3 (10-30 %, KOH) CH-2 (1-5 %)	25 (1) 25 (1) 25 (1) 25 (1)
Nitro, amide	Amine	CH-1 (4-8 %) CH-3 (10-30 %)	25 (1) 25 (1-3)
Oxime, nitrile	Amine	CH-2 (1-10 %, HOAc) CH-1 (5-15 %, HOAc) CH-3 (3-30 %)	25 (1-3) 25 (1-3) 25 (35-70)

CH-1: 5 % Pd-C; CH-2: PtO_2 ; CH-3: Raney Nickel; CH-4: 0.3 % Pd-CaCO₃; CH-5: 3 % Pd-BaSO₄; CH-6: Lindlar's catalyst; CH-7: 5 % Rh-AcO₃; CH-8: 5 % Rh-C.

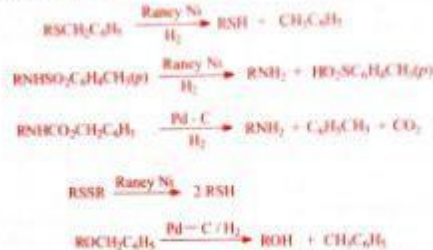
4.2.6 Hydrogenolysis

Some functional groups can be removed under catalytic hydrogenation conditions. This process is known as **hydrogenolysis** or **reductive fission**. These reactions proceed by addition of two electrons from the metal to the bond to be broken. The anions on protonation during working up give the product.



Certain groups like allylic and benzylic hydroxyl groups, amino groups and carbon-sulfur single bonds readily undergo hydrogenolysis resulting in the cleavage of the bond between carbon and the heteroatom. The procedure is used for the reductive removal of protecting groups for amino, imino, hydroxyl and thiol group. Benzyl, *p*-toluenesulfonyl and benzyloxycarbonyl groups are all effectively replaced by hydrogen.

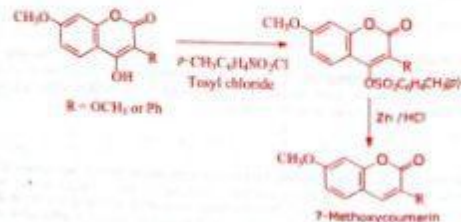
Generally Pd-C or Raney-Ni is used for this purpose. Some examples are given below.



Hydrogenolysis is also used for the removal of hydroxyl group from aromatic compounds. In this method the hydroxyl group is first converted into tosylate ester and then hydrogenolysis carried out with Raney nickel and hydrogen in alcohol.



Acidic hydroxyl groups can be conveniently removed by tosylation followed by treatment with Zn / HCl. Thus, 1,7-dimethoxy-4-hydroxy- and 3-phenyl-7-methoxy-4-hydroxycoumarin on tosylation give the corresponding 4-tosyloxycoumarins, which on reductive desotylation with Zn / HCl result in removal of 4-hydroxyl group to give the corresponding 3-substituted-7-methoxycoumarin¹.



4.2 [B] Homogeneous hydrogenation

The catalytic hydrogenations described earlier are very useful but have some disadvantages. They may show lack of selectivity when more than one unsaturated centers are present and many times hydrogenation may be accompanied by migration of the double bond. Also a number of functional groups suffer hydrogenolysis and the stereochemistry of reductions is difficult to predict. Some of these difficulties have been overcome by the use of a soluble catalyst so that hydrogenation may be possible in homogeneous solutions.⁸ Homogeneous catalysts are those that are soluble in the reaction mixture. The catalysis occurs not at the surface of a metal layer, but throughout the solution. Some soluble transition metal compounds containing organic ligands are used as homogeneous hydrogenation catalysts. They are soluble in the solvent in which the reaction is taking place. The most effective soluble catalysts are the rhodium and ruthenium complexes viz, chlorotris(triphenylphosphine)rhodium (I), $[(C_6H_5)_3P]_3RhCl$, and hydrido-chlorotris(triphenylphosphine)ruthenium, $[(C_6H_5)_3P]_3RuClH$. The rhodium complex is obtained by the reaction of rhodium chloride with excess of triphenylphosphine in boiling ethanol. Thus, this rhodium compound catalyses the hydrogenation of the terminal double bond, leaving the internal double bond untouched.

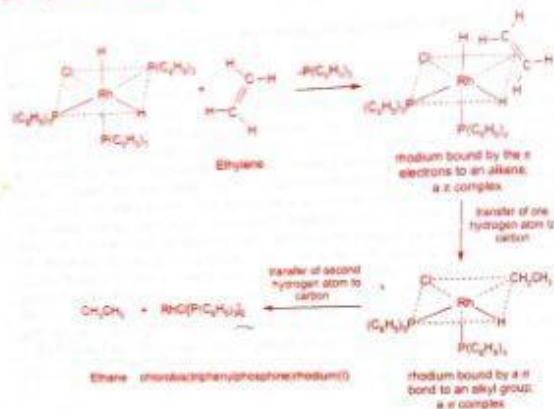


The rhodium complex is an efficient catalyst for the homogeneous hydrogenation of non conjugated alkenes and alkynes in boiling benzene. Functional groups like oxo, cyano, nitro, chloro and azo are not effected by this catalyst under the reaction conditions (ordinary temperature and pressure). Tri- and tetra-substituted alkenes are comparatively difficult to hydrogenate than mono or disubstituted alkenes. This permits partial hydrogenation of compounds containing different kinds of double bonds.⁹ Thus, reduction of linalool gives 90% yield of the corresponding dihydro compound.

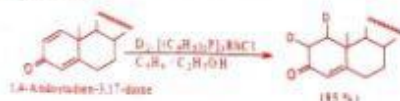
**Mechanism**

Rhodium complex is dissolved in benzene and hydrogen gas is passed in the solution. A new octahedral organometallic compound of rhodium is formed that contains metal-hydrogen bonds. This complex adds on a alkene molecule by displacing one of the triphenylphosphine ligands to give π -complex. Transfer of hydrogens to carbon-carbon double bond gives alkane and chlorobis(triphenylphosphine)rhodium (I). The chlorobis(triphenylphosphine)rhodium (I) reacts with triphenylphosphine to regenerate the chlorotris(triphenylphosphine)rhodium (I) complex, which starts the cycle again.

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**Catalysis of Hydrogenation by a Homogeneous Catalyst**

As in the case of heterogeneous hydrogenation (sec. 4.2[A]), in this case also, hydrogenation takes place by *cis*-additions to the double bond as seen by the reduction of maleic acid in presence of deuterium and rhodium catalyst to give *meso*-dideutero succinic acid (see sec. 7.15). In a similar way 1, 4-androstadien-3,17-dione gives the didero compound by *cis*-addition.



Homogeneous catalysts are useful for selective hydrogenation of the carbon-carbon double bonds without hydrogenolysis of other susceptible groups. For example, benzyl cinnamate is converted into the dihydro compound without hydrogenolysis of the benzyl group.



In a similar way allyl phenyl sulfide on reduction gives 93% phenyl propyl sulfide:



Ruthenium catalysts decarboxylate aldehydes. This is attributed to the strong affinity of $[(C_6H_5)_3P]_2\text{RuCl}_2$ for carbon monoxide. Thus, cinnamaldehyde is converted into styrene in 65% yield. Similarly, benzoyl chloride gives chlorobenzene in 90% yield.



Another still more effective catalyst is the ruthenium complex, $[(C_6H_5)_3P]_2\text{RuCl}_2$, and is specific for the hydrogenation of mono-substituted alkynes, $(RCH \equiv CH_2)$. This catalyst is formed *in situ* from $[(C_6H_5)_3P]_2\text{RuCl}_2$ and molecular hydrogen in benzene in presence of a base like triethyl amine. Disubstituted alkynes are converted into *Z*-alkenes. Thus, stearic acid gives oleic acid and diphenyl acetylene gives *Z*-stilbene.

4.3 Reduction with metal hydrides

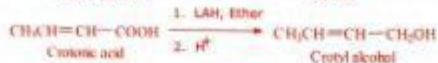
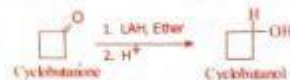
The reduction by metal hydrides proceeds by transfer of hydride ion to the substrate. These selectively reduce a number of functional groups, such as nitro, carbonyl, carboxylic acid, nitrile, ester etc., in presence of carbon carbon double bonds. A number of complex hydrides have been used for reduction. The most common are lithium aluminium hydride (LiAlH_4) and sodium borohydride (NaBH_4). Some reagents derived from NaBH_4 have also been used.

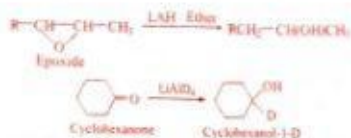
4.3.1 Lithium aluminium hydride

It is prepared by the action of anhydrous aluminium chloride to a paste of lithium hydride in THF (see also sec. 8.7.1).



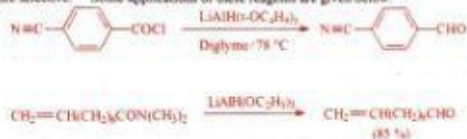
It is one of the most important and useful reagent for the reduction of ketones, carboxylic acids, esters, acid chlorides, anhydrides, epoxides, nitriles and nitro compounds. Some typical examples are given below.





The mechanism of LAH reduction and some other important applications have been discussed in sec. 8.7.

Some other reagents like lithium trimethoxyaluminium hydride $\text{LiAlH}(\text{OMe})_3$, lithium tri-*i*-butoxyaluminium hydride $\text{LiAlH}(\text{OC}_4\text{H}_9)_3$ and lithium diethoxyaluminium hydride $\text{LiAlH}_2(\text{OC}_2\text{H}_5)_2$ have been developed and are less reactive than LiAlH_4 but are more selective.¹⁰ Some applications of these reagents are given below.

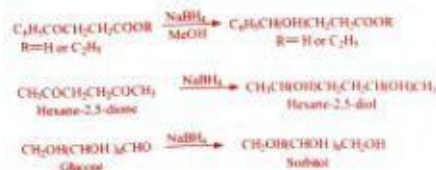


4.3.2 Sodium borohydride

Sodium borohydride is a very selective reducing agent and reduces aldehyde and ketones to alcohols. Groups like halogens, cyano, amide and alkoxycarbonyl are unaffected. It is prepared by the reaction of sodium hydride with trimethylborate.



NaBH_4 is insoluble in ether but soluble in alcohol and water. So it is used in hydroxylic solvents like alcohol, isopropanol etc. Some applications of NaBH_4 are given below.

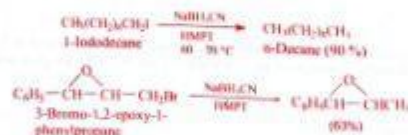


The mechanism of NaBH_4 reduction and some other applications have been discussed in sec. 8.13.

It is possible to phase transfer¹⁸ the borohydride anion from an aqueous basic solution of sodium or potassium borohydride into benzene by a variety of catalytic systems including quaternary ammonium and phosphonium salts, crowns and cryptates. Thus, 2-octanone on reduction with aqueous borohydride in benzene solution with trimethylammonium chloride gives 80% yield of 2-octanol. The crown ethers (e.g., dibenzo-18-crown-6) catalysed sodium borohydride reduction of several ketones in boiling toluene (Shr.) By this method¹⁹ acetophenone, cyclohexanone and 2-heptanone were reduced in 49%, 50% and 41% yields, respectively.

4.3.3 Sodium cyanoborohydride

A number of reagents derived from NaBH_4 by replacement of one or more hydrogen atoms by other groups permit selective reduction. One such useful reagent is sodium cyanoborohydride, NaBH_3CN . It is weaker but more selective¹² than NaBH_4 and is stable in acid (up to pH 3). It can therefore be used for the reductions in the presence of functional groups which are sensitive to more basic conditions of reduction with NaBH_4 . In neutral solutions this reagent is useful for the removal of iodo, bromo and tosyloxy groups. Carbonyl groups are not effected. 1-Iododecane gives decane in 90% yield and 3-bromo-1,2-epoxy-1-phenylpropane is converted into halogen free compound without cleavage of the epoxide ring.



It also reduces oximes to hydroxylamine.



The tosylhydrazones of aldehydes are converted into methyl group by NaBH_4/CN . This provides a convenient method of converting $-\text{CHO}$ into CH_3 .



Sodium cyanoborohydride can be solubilised¹⁸ in dichloromethane by complexation with 18-crown-6. This has been used to reduce O-methylsulfoxonium salts to the corresponding sulfides in good yield.



4.3.4 Diborane

Another weak and selective reducing agent derived from NaBH_4 is diborane.



Diborane is commercially available in THF solution. It reduces carbonyl group to alcohol but is less reactive towards other functional group. A number of other reagents derived from diboranes are called organoboranes and are useful as reducing agents. Diborane reacts with olefins to give monoalkylborane, dialkylborane and trialkylborane, which are used as reducing agent (mechanism and applications are discussed in sec. 8.9.2).

The table 4.2 summarises the products obtained by the reduction of various functional groups with lithium aluminium hydride, sodium borohydride and diborane.

4.4 Reduction by dissolving metals

These reductions take place by the transfer of electrons from the metal and a proton donor which may be water, alcohol or an acid. The group 1 metals, such as Na or Li, give up their outer-shell electron easily and dissolve in solvents such as $\text{NH}_3(\text{liq})$ or alcohol.

4.4.1 Sodium-alcohol

One of the easiest method of reducing ketones to alcohols is with sodium-alcohol. Reduction is carried out by adding sodium to a ketonic compound in boiling alcohol. For example, cycloheptanone on reduction with sodium and alcohol gives cycloheptanol.

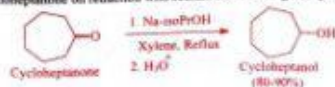
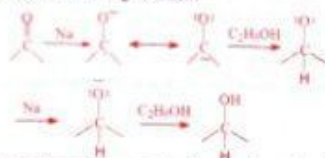


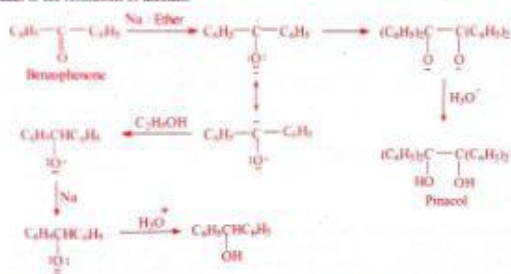
Table 4.2

Substrate	LiAlH_4	NaBH_4	B_2H_6
$-\text{COOH}$	$-\text{CH}_2\text{OH}$	—	$-\text{CH}_2\text{OH}$
$-\text{COOC}_2\text{H}_5$	$-\text{CH}_2\text{OH}$	—	—
$\text{C}=\text{O}$	CH_2OH	CH_2OH	CH_2OH
$-\text{CHO}$	$-\text{CH}_2\text{OH}$	$-\text{CH}_2\text{OH}$	$-\text{CH}_2\text{OH}$
$\text{C}-\text{Cl}$	$-\text{CH}_2\text{OH}$	—	—
$\text{CH}-\text{C}-\text{O}$	$\text{CH}_2-\text{C}-\text{OH}$	$\text{CH}_2-\text{C}-\text{OH}$	$\text{CH}_2-\text{C}-\text{OH}$
$-\text{NO}_2$ Aliphatic	$-\text{NH}_2$	—	—
ArNO_2	Ar CH_2NH_2 or Ar $\text{CH}=\text{N}-\text{Ar}$	—	—
$-\text{CH}_2\text{Br}$	$-\text{CH}_3$	—	—
$\text{CH}-\text{Br}$	CH_3	—	—
$\text{C}-\text{NOH}$	$\text{CH}-\text{NH}_2$	CHNH_2	—
$\text{C}-\text{NHR}$	$-\text{CH}_2\text{NHR}$	$-\text{CH}_2\text{NHR}$	$-\text{CH}_2\text{NHR}$
$\text{C}=\text{N}$	$-\text{CH}_2\text{NH}_2$	$-\text{CH}_2\text{NH}_2$	$-\text{CH}_2\text{NH}_2$
$-\text{CH}=\text{CH}-$	—	—	$-\text{H}_2\text{C}-\text{CH}_2-$ OH

The mechanism of reduction is as given below.



In the reduction of benzophenone with sodium in ether the first product is the resonance-stabilized anion radical, which in the absence of a proton donor, dimerizes to pinacol. However, in the presence of a proton donor source (like alcohol) protonation leads to the formation of alcohol.



Sodium-alcohol also reduces esters to alcohols. This is known as **Bouveault-Blanc reduction**. For details of mechanism and other applications see sec. 5.16.



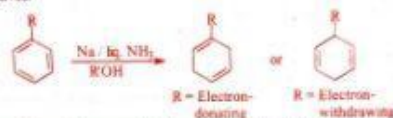
Sodium-alcohol also reduces nitriles, oximes and aldehydes.



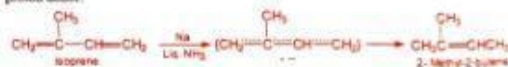
The Bouveault-Blanc reduction is one of the oldest method for reduction of ketones into alcohols. However, this has now been replaced by reduction with LiAlH_4 .

4.4.2 Sodium-liquid ammonia

Sodium and liquid ammonia reduce aromatic rings to give mainly unconjugated dihydro derivatives.

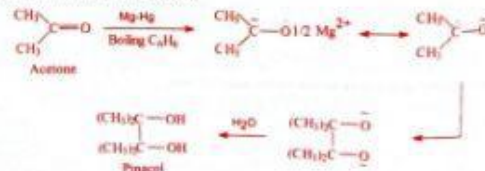


This reduction is known as **Birch reduction**. Instead of sodium, other alkali metals (like potassium or lithium) can also be used. For mechanism and other applications of Birch reduction see sec. 5.15. Isolated carbon carbon double bonds are not reduced by metal ammonia alone, but in presence of an alcohol, terminal double bonds are reduced. Conjugated dienes are readily reduced to 1,4-dihydro derivatives in absence of added proton donor.



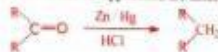
4.4.3 Magnesium

Reduction of ketones with dissolving metals in absence of a proton donor leads to the formation of bimolecular or dimerized products. The reagents for this purpose are magnesium, magnesium-alumagan or aluminium-alumagan. The reduction of acetone by pinacol follows the following course.



4.4.4 Zinc-hydrochloric acid

Aldehydes and ketones on reduction with amalgamated zinc and hydrochloric acid give the corresponding hydrocarbons. This reaction is known as **Clemmensen reduction**. The mechanism of this reduction and its application are described in sec. 5.23.

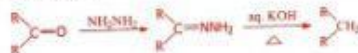


4.5 Reduction by miscellaneous reducing agents

A number of reagents are available for reducing certain functional groups which use non-metallic reagents. These reagents have specific and useful applications. The mechanism of reduction varies with each reagent.

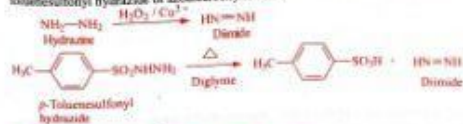
4.5.1 Hydrazine

Aldehydes and ketones can be reduced to the corresponding hydrocarbons by heating their hydrazones with bases like sodium or potassium hydroxide. This reduction is known as **Wittig-Kishner reduction**. The mechanism of this reduction and its applications have been discussed in sec. 5.97.



4.5.2 Di-imide

Di-imide is a highly selective reagent and is useful for the reduction of symmetrical multiple bonds like carbon-carbon triple and double bonds, N=N and O=O. The unsymmetrical, more polar bonds like nitrogen-carbon triple bond, S=O, S=S and C=S are not reduced. This reagent is prepared *in situ* usually by the oxidation of hydrazine with an oxidising agent like hydrogen peroxide or by thermal decomposition of *p*-toluenesulfonyl hydrazide or azodicarbonic acid.

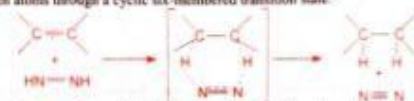


4.5.2 Organic Reaction Mechanisms

The selectivity of the reagent is demonstrated by the reduction of diallyl sulfide to dipropyl sulfide.



The reduction is highly stereoselective and takes place by *cis*-addition of the hydrogen in all cases. The reaction is regarded as taking place by synchronous transfer of a pair of hydrogen atoms through a cyclic six-membered transition state.¹²



This mechanism explains the high stereospecificity of the reduction. The concerted *cis*-transfer of hydrogen is symmetry allowed for the ground-state reaction. Some other applications of di-imide are given below.



In case of a compound containing more than one double bonds, reduction takes place at the least conjugated alkene.¹³



In the above example the conjugated ketone and exocyclic epoxide were not reduced. However, the course of the di-imide reduction could be altered by the addition of cupric salts¹² (e.g. cupric acetate). This reagent is very selective for the reduction of conjugated alkenes with specificity for the less substituted double bond of the diene¹³ as shown below.

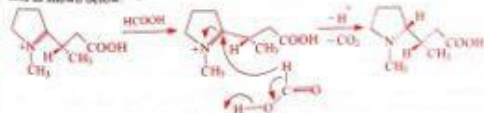


4.5.3 Formic acid

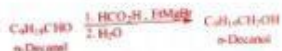
Formic acid has been used for a number of specific reductions. For example, triphenyl carbinol on heating with formic acid yields triphenylmethane.¹⁴



Formic acid is also useful for the stereoselective reduction of enamines.¹⁵ This is illustrated by the reduction of 3-(*-*)-erythro-2-(2*N*-methylpyrrolidinium) butanoic acid as shown below.



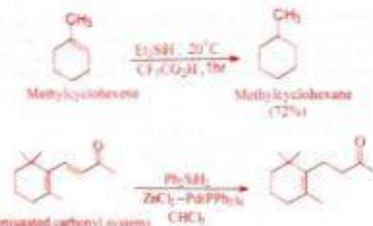
A mixture of formic acid and ethyl magnesium bromide converts decanal to decanol¹⁶ in 70% yield.



The above reduction can also be affected by using sodium formate in *N*-methyl-2-pyrrolidone as a solvent.¹⁷

4.5.4 Silanes

Silicon hydrides reduce carbonyls and alkenes.



Addition of transition metals to silane facilitates the reduction. In acidic medium, silanes reduce aldehydes and ketones. Thus, cyclohexanone gives cyclohexanol in 74% yield with Et₃SiH and CF₃COOH. This reduction is selective for conjugated aldehydes to yield allylic alcohols.



The ketonic moiety is sensitive. Thus, 2-bromoketones give 70% yield of bromohydrins.

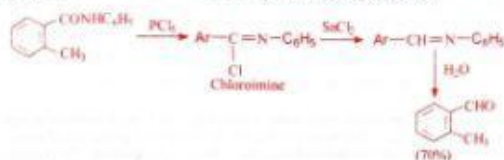


4.5.5 Stannous chloride

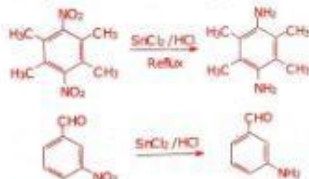
Stannous chloride and hydrochloric acid convert nitriles into aldehydes via the intermediate aldimine salts. The reaction is known as **Stephen reaction**. Its mechanism and applications have been discussed in sec. 5.8b.



Stannous chloride also converts secondary amides into aldehydes via the formation of chlorimine (which is formed from amides by treatment with PCl_5). This reaction is known as **Sonn-Muller reaction** and is closely related to **Stephen reaction**.



The reduction of nitro group to amino group can also be affected by refluxing with stannous chloride and hydrochloric acid. Some examples are given below.



Stannous chloride and hydrochloric acid are also used for the reduction of azo compounds.

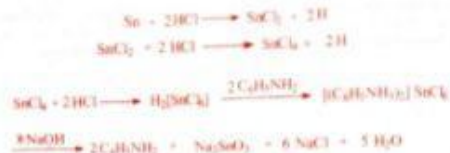


Nitroso compounds can also be reduced to the corresponding amines.

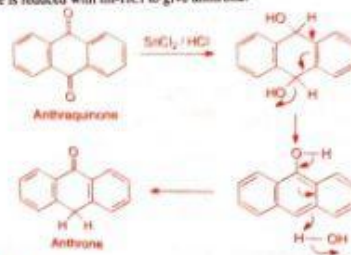


4.5.6 Tin-hydrochloric acid

This reagent is used for the reduction of nitro group to amino group.

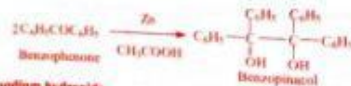


Aniline obtained from nitrobenzene forms a complex, which on decomposition with alkali gives the free base. This method is used for the commercial production of aniline. Tin and hydrochloric acid are also used for partial reduction of *p*-quinones. For example, anthraquinone is reduced with tin-HCl to give anthrone.



4.5.7 Zinc-acetic Acid

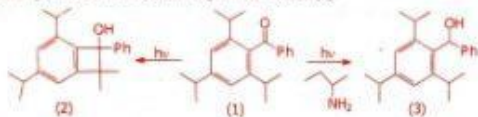
It is used for the reductive coupling of ketones.



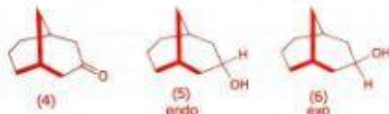
4.5.8 Zinc-sodium hydroxide

It is a mild reducing agent. Thus, reduction of nitrobenzene in alcoholic sodium hydroxide with zinc powder leads to the formation of azo benzene or hydrazobenzene according to the proportion of zinc powder employed.

Photolysis of the ketone (1) gives the benzocyclobutane (2). Similar photochemical reduction in presence of *sec*-butylamine gives the alcohol (3).



Photoreduction is less stereoselective than other reducing techniques. Thus, reduction of the ketone (4) with metal hydride and catalytic hydrogenation give exclusively *endo*-alcohol (5). On the other hand reduction with dissolving metals gives 47% of the *exo* isomer (6). However, photoreduction of (4) gives 54% yield of a 4:1 mixture of (6) and (5).



4.7 Enzymatic or microbial reductions (Bio-reductions)

Enzymatic reductions are highly stereoselective and straight forward. Enzymes are now easily available and are an important tool in organic synthesis. **Prelog** was the first to study the reduction of carbonyl compounds with a number of enzymatic systems. He found that reduction of ketones with *curvularia fulvum* gave stereochemical induction based on the groups (large and small) attached to the carbonyl group. This is known as **Prelog's rule**.²⁶ According to this rule if the steric difference between large (L) and small (S) groups attached to the carbonyl group is large enough the enzyme attacks from the less hindered face (over S) to give the corresponding alcohol, as shown below.



Most common enzyme systems available are yeast alcohol dehydrogenase (YADH) and horse liver alcohol dehydrogenase (LHADH). It is found that the selectivity observed with these enzymes is determined by non-bonded interactions of substrate and enzymes in the hydrogen transfer transition state.²⁷

Baker's yeast (*Saccharomyces cerevisiae*) is known to selectively reduce β -keto-esters and β -diketones. Thus, reduction of ethyl acetoacetate with Baker's yeast gives the (*S*)-alcohol. On the other hand reduction of ethyl β -ketovalerate gives the (*R*)-alcohol.²⁵



The hydroxy-ester (*S*-alcohol) obtained above is an intermediate in the synthesis of (*S*)-(+)-suleston.²⁸ It is also obtained in 96% yield by reduction²⁵ with *Geotrichum candidum*. The cyclic β -keto-ester on reduction with Baker's yeast gives 71% of corresponding alcohol, which is used as an intermediate in the synthesis²⁹ of the sex pheromone of the *Cigarette beetle*.



In a similar way a 1,3-diketone on reduction²⁵ gives (*S*)-5-hydroxy-3-hexanone (a β -ketoalcohol) in quantitative yield (>99% ee, *S*). Reduction of ethyl acetoacetate with *Aspergillus niger* gives 98% of a 75:21 mixture favoring (*R*)-alcohol. This is in contrast to the formation of (*S*)-alcohol with Baker's yeast or *Geotrichum candidum* as shown earlier.

The ketonic moiety in the side chain of the cyclopentanone could be selectively reduced to the (*R*)-alcohol with Baker's yeast. The formed (*R*)-alcohol is used as a intermediate in the synthesis of *isogeratrial*.²⁴



Crotonaldehyde (*trans* isomer) on reduction²⁷ with *Saccharomyces cerevisiae* gives 2-buten-1-ol in 80% yield. On the other hand 2-methyl-2-pentenal gives a mixture of 11% of the conjugated alcohol and 69% of the completely reduced product (2-methyl-1-pentanol).



Thermomonasbrockii has also been used for the reduction²⁷ of smaller ketones like 2-butanone to give (*R*)-alcohol. However, larger ketones are reduced to (*S*)-alcohol. The examples referred to illustrate typical enantioselectivity of the reduction. Also the low cost and high selectivity of such enzymatic reductions indicate their important role in organic synthesis.

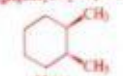
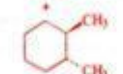
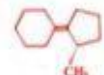
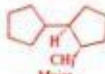


4.8 Correlation tables

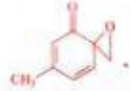
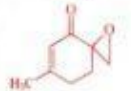
These tables are helpful to know which reducing agents can be used for reduction of the different functional groups. The products obtained in each case are also given. The section number of this book where these reductions have been cited are also included in the tables.

4.8.1 Reduction of alkenes

Alkenes	Products	Reagent	Sec. No.
Alkenes	Alkenes	5% Pd-C; Pt O ₂ ; Raney Ni	4.2.1
Monosubstituted alkenes (RCH=CH ₂)	Alkanes	[(C ₂ H ₅) ₃ P] ₂ RuCl ₂	4.2(b)

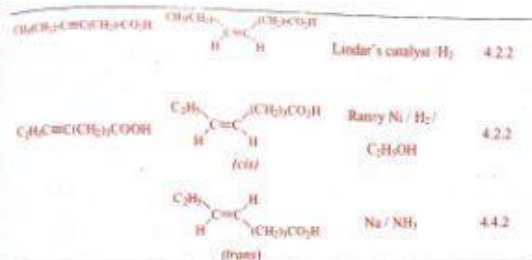
$\text{C}_6\text{H}_5\text{CH}=\text{CHCH}_2\text{OH}$	$\text{C}_6\text{H}_5\text{CH}_2\text{CH}_2\text{CH}_2\text{OH}$	Raney Ni; H ₂	4.2.1
	 Major +  Minor	PtO ₂ /H ₂	4.2.1
	 Major +  Minor	PtO ₂ /H ₂	4.2.1
	 H ₃ C-CH ₂ -CH ₂	PtO ₂ /H ₂	4.2.1
		Pd/H ₂	4.2.1
$\text{O}_2\text{NCH}_2\text{CH}=\text{CHCH}_3$	$\text{O}_2\text{NCH}_2\text{CH}_2\text{CH}_2\text{CH}_3$	Pd/H ₂	4.2.1

		H_2 [(C ₆ H ₅) ₃ PPtCl] (C ₆ H ₅)	4.2[B]
		H_2 [(C ₆ H ₅) ₃ PPtCl] (C ₆ H ₅)	4.2[B]
$\text{C}_6\text{H}_5\text{CH=CHNO}_2$	$\text{C}_6\text{H}_5\text{CH}_2\text{CH}_2\text{NO}_2$	H_2 [(C ₆ H ₅) ₃ PPtCl] (C ₆ H ₅)	4.2[B]
		H_2 [(C ₆ H ₅) ₃ PPtCl] (C ₆ H ₅ -C ₂ H ₅ OH)	4.2[B]
$\text{C}_6\text{H}_5\text{CH=CHCOOC}_6\text{H}_5$	$\text{C}_6\text{H}_5\text{CH}_2\text{CH}_2\text{COOC}_6\text{H}_5$	H_2 [(C ₆ H ₅) ₃ PPtCl] (C ₆ H ₅)	4.2[B]
$\text{CH}_3\text{CH=CHC}_6\text{H}_5$	$\text{CH}_3\text{CH}_2\text{CH}_2\text{C}_6\text{H}_5$	H_2 [(C ₆ H ₅) ₃ PPtCl] (C ₆ H ₅)	4.2[B]
$-\text{CH=CH}-$	$-\text{CH}_2-\text{CH}-$ OH	B_2H_6	4.3.7
$\text{CH}_2=\text{C}(\text{CH}_3)-\text{CH}=\text{CH}_2$	$\text{CH}_3-\text{C}(\text{CH}_3)=\text{CH}-\text{CH}_3$	$\text{NaLi}-\text{NH}_3$	4.4.2
		Dimide	4.5.2
$\text{CH}_3-\text{C}(\text{CH}_3)_2\text{CH}_2\text{COOH}$	$\text{CH}_3\text{CH}_2\text{COOH}$	Dimide	4.5.2

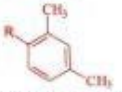
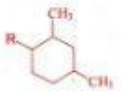
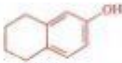
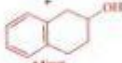
		Dimide	4.5.2
		Dimide	4.5.2
		Dimide	4.5.2
		$\text{Et}_3\text{SiH}-\text{CF}_3\text{COOH}$	4.5.4
		Ph_3SiH_2 $\text{ZnCl}_2-\text{Pd}(\text{PPh}_3)_4$	4.5.4

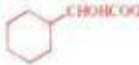
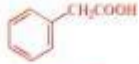
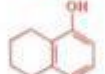
4.8.2 Reduction of alkynes

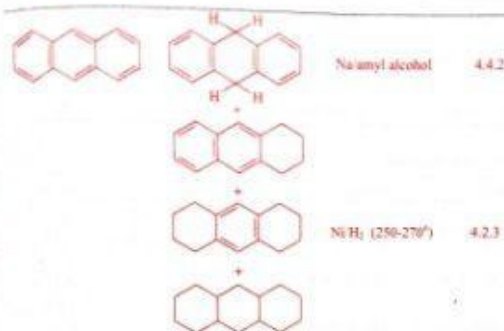
Alkynes	Products	Reagent	Sec. No.
Alkynes	Alkenes	5% Pd-C, or 5% Pd-BaSO ₄	4.2.2
	Alkanes	PtO ₂ or Raney Ni	4.2.2



4.8.3 Reduction of aromatic hydrocarbons

Aromatic hydrocarbons	Products	Reagent	Sec. No.
		$\text{PtO}_2/\text{H}_2/\text{CH}_3\text{COOH}$	4.2.3
		Raney Ni / H_2	4.2.3
R = COOH or NH_2 or OH			
	 Major  Minor	Raney Ni / H_2 / 90°, 275 atm.	4.2.3

		Rh-Al ₂ O ₃ /H ₂	4.2.3
		Pd-C/H ₂	4.2.3
Naphthalene	 cis-Decalin  trans-Decalin	Pt / H ₂ Ni / H ₂	4.2.3
		Na / C ₂ H ₅ OH (75-80°)	4.4.1
		Na-isomyl alcohol (30-40°)	4.4.1
		Na-C ₂ H ₅ OH	4.4.1
		Li/NH ₃	4.4.2
		Na/C ₂ H ₅ OH	4.4.1
Aromatic carboxylic acids	Hydroaromatic carboxylic acid	PtO ₂ or Raney Ni/H ₂ or 5% Rh(Al ₂ O ₃)	4.2.3
	 or 	Na/liq. NH ₃	4.4.2



4.8.4 Reduction of carbonyl compounds

(a) Reduction of aldehydes

Aldehydes	Products	Reagent	Sec. No.
R-CHO	R-CH ₂ OH	Na-C ₂ H ₅ OH	4.4.1
Aliphatic aldehyde	Alcohols	2-4% PtO ₂ / H ₂ 5% Pd/C Raney Ni	4.2.4
CH ₃ (CH ₂) _n CHO	CH ₃ (CH ₂) _n CH ₂ OH	LAH	4.3.1
CH ₃ CH=CHCHO	CH ₃ CH=CHCH ₂ OH	LAH	4.3.1
C ₆ H ₅ CH=CHCHO	C ₆ H ₅ CH ₂ CH ₂ CH ₂ OH	LAH	4.3.1
CH ₃ OHCHOHCH ₂ CHO	CH ₃ OHCHOHCH ₂ CH ₂ OH	NaBH ₄	4.3.2
NCCH ₂ CH ₂ CHO	NCCH ₂ CH ₂ CH ₂ OH	NaBH ₄	4.3.2
CH ₃ CH ₂ CH=NNHNO ₂ ·C ₂ H ₅ NH=CH ₂ Tetrazolones of aldehydes	CH ₃ (CH ₂) _n CH ₂	NaBH ₄ /CN (DMF, 100°)	4.3.3

α -C ₆ H ₁₃ -CHO	α -C ₆ H ₁₃ CH ₂ OH	HCO ₂ H / EtMgBr	4.5.1
		(Et ₃ CN)DMF	4.5.4
CH ₃ CH=CHCHO	CH ₃ CH=CHCH ₂ OH	Enzymic redb	4.7

(b) Reduction of ketones

Ketones	Products	Reagent	Sec. No.
Aliphatic ketone R-CO-R'	Alcohols RCHOHR'	2-4% PtO ₂ /H ₂ 5% Pd/C Raney Ni / H ₂	4.2.4
CH ₃ CH ₂ COCH ₃	CH ₃ CH ₂ CH(OH)CH ₃	LAH	4.3.1
		B ₂ H ₆	4.3.4
CH ₃ COCH ₂ COOCH ₃	CH ₃ CHOHCH ₂ CH ₂ OH	LAH	4.3.1
		NaBH ₄	4.3.2
		LAH	4.3.1
		LAH	4.3.1
CH ₃ COCH ₂ CH ₂ COCH ₃	CH ₃ CHOHCH ₂ CH ₂ CHOHCH ₃	LAH	4.3.1
Cycloheptanone	Cycloheptanol	Na / iso-PrOH	4.4.1
$(C_6H_5)_2CO$	$C_6H_5CH(OH)C_6H_5$ + $(C_6H_5)_2C(OH)_2$	Na / ether	4.4.1
		Mg-Hg	4.4.3
		Photoinduction	4.6
		NH ₂ -NH ₂ , KOH	4.5.1

		(EtO)2SiHMe	4.5.4
$C_6H_5COC_2H_5$		Zn/CH3COOH	4.5.7
$R-C(=O)-R'$	$RCH(OH)R$	Zn/NaOH	4.5.8
		Baker's yeast	4.7
	(S)-Alcohol 	T. brockii	4.7

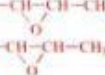
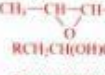
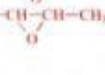
4.5.5 Reduction of nitro and nitroso compounds

Substrate	Products	Reagent	Sec. No.
Nitro compounds	Amine	PO_2/H_2 , 5% $Pd-C/H_2$, Raney Ni	4.2.5
$C_6H_5CH=CHNO_2$	$C_6H_5CH_2CH_2NH_2$	$Pd-C/H_2$ /Alcohol	4.2.5
$RCH_2CH(NO_2)CH_3$	$CH_3CH_2CH(NH_2)CH_3$	LAH	4.3.1
		$SnCl_2/HCl$	4.5.5
$C_6H_5NO_2$	$C_6H_5NH_2$	$Sn + HCl$	4.5.6
$C_6H_5NO_2$	$C_6H_5NHPhCH_2R_2$	$Mg - Alcohol$	4.5.11

		Na/H	4.5.12
Nitroso compounds			
		$SnCl_2/HCl$	4.5.5

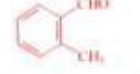
4.5.6 Reduction of nitriles, azides, oximes, halides and epoxides

Substrate	Products	Reagent	Sec. No.
Nitriles	Amines	PO_2/H_2 /Alcohol	4.2.5
	Amines	5% $Pd-C$	4.2.5
	Amines	Raney Ni	4.2.5
$RC\equiv N$	$R-CHO$	LAH	4.3.1
		B_2H_6	4.3.4
$n-C_4H_9CN$	$n-C_4H_9NH_2$	$Na-C_2H_5OH$	4.4.1
C_6H_5CN	C_6H_5CHO	$SnCl_2/HCl$	4.5.5
Azides	Amines	5% $Pd-C$, PO_2 , Raney Ni	4.2.5
	RNH_2	LAH	4.3.1
Oxime	Amine	5% $Pd-C$, PO_2	4.2.5
		$NaBH_4/CN$	4.3.3
$(C_6H_5)_2C=NOH$	$(C_6H_5)_2CHNH_2$	LAH	4.3.3
$n-C_4H_9CH=NOH$	$n-C_4H_9NH_2$	$Na-C_2H_5OH$	4.4.1

Halides	Hydrocarbon	5% Pd-C, Raney Ni or 5% Pd-BaSO ₄	4.2[A]
$R(CH_2)_nCH_2Br$	$R(CH_2)_nCH_3$	LAH	4.3.1
$CH_3(CH_2)_nCH_2I$	$CH_3(CH_2)_nCH_3$	NaBH ₄ CN	4.3.3
Epoxydes			
$CH_2-CH-CH-CH_2Br$ 	$CH_2-CH-CH-CH_3$ 	NaBH ₄ CN	4.3.3
$R-CH-CH-CH_3$ 	$RCH_2CH(OH)CH_3$	LAH	4.3.1
	$RCH_2CH(OH)CH_3$	NaBH ₄	4.3.2
	$RCH_2CH(OH)CH_3$	B ₂ H ₆	4.3.4

4.8.7 Miscellaneous reductions

Substrate	Products	Reagent	Sec. No.
$C_6H_5CH=CHCHO$	$C_6H_5CH=CH_2$	$[C_6H_5)_3P]_2RhCl$ (C_6H_6)	4.2[B]
$RCOCl$	RCH_2OH	LAH	4.3.1
		NaBH ₄	4.3.2
C_6H_5COCl	C_6H_5Cl	$[C_6H_5)_3P]_2RhCl$ (C_6H_6)	4.2[B]
$R(CH_2)_nCOOH$	$R(CH_2)_nCH_2OH$	LAH	4.3.1
$CH_3CH=CH-COOH$	$CH_3CH=CH-CH_2OH$	LAH	4.3.1
CH_3CH_2COOH	$CH_3CH_2CH_2OH$	LAH	4.3.1
$CH_3CH=CH-COOEt$	$CH_3CH=CHCH_2OH$	LAH	4.3.1
		$LiAlH_4 \cdot OC_2H_5$	4.3.1
$CH_2=CH(CH_2)_nCONHCH_3$	$CH_2=CH(CH_2)_nCHO$	$LiAlHOC_2H_5$	4.3.1

$R-\overset{O}{\parallel}C-OR_1$	$RCH_2OH + R_1OH$	$Na + C_2H_5OH$	4.4.1
$(CH_2=CHCH_2)_2S$	$(CH_2CH_2CH_2)_2S$	Dimide	4.5.2
$C_6H_5SO-NC_6H_5$	$C_6H_5NHNC_6H_5$	Dimide	4.5.2
		$PCl_5, SnCl_2$	4.5.5
		$Sn + HCl$	4.5.6
		$Na_2S_2O_4$	4.5.10
$[C_6H_5NaN]Cl$	$C_6H_5NHNH_2$	$NaHSO_3$	4.5.9

4.8.8 Hydrogenolysis

Substrate	Products	Reagent	Sec. No.
		Raney Ni/H ₂ Alcohol	4.2.6
		Zn/HCl	4.2.6

References

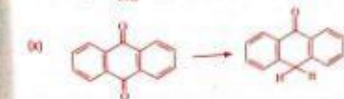
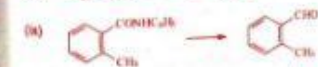
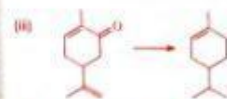
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Problems

1. Define reduction. Discuss the concept of reduction in terms of oxidation number.
2. How acetylene is converted into ethylene?
3. How will you bring about the following conversions?
 - (i) Alkene to alkane
 - (ii) Alkyne to alkene
 - (iii) Aromatic carboxylic acids to hydroaromatic carboxylic acids
 - (iv) Halides to hydrocarbons
 - (v) Oximes to amines
 - (vi) Carbonyl compounds to alcohols
4. What is hydrogenolysis and how it is brought about? Give its uses.
5. How will you remove a phenolic and acidic hydroxyl group?
6. What is homogeneous hydrogenation? What are its special uses compared to heterogeneous hydrogenation?
7. How $[(C_6H_5)_3P]_2RuClH$ is obtained? What are its applications in reduction?
8. Compare the reductions using $LiAlH_4$ and $NaBH_4$.
9. Compare the reductions of sodium cyanoborohydride and sodium borohydride.
10. Discuss the applications of hydroboration.
11. What products are obtained by the reduction with $LiAlH_4$, $NaBH_4$ and B_2H_6 of the following substrates?

(i) $RCOOH$	(ii) $RCOOC_2H_5$
(iii) $RCOCl$	(iv) RCH_2Br
(v) $ArNO_2$	(vi) $RCH=CHR$
12. Give the mechanism of the reduction of cycloheptanone with sodium-isopropyl alcohol.
13. What reducing agents can be used for the conversion of a ketonic group into methylene group?
14. How di-imide is obtained? Discuss its applications in reductions. Give the mechanism of reduction with di-imide.
15. Give use of formic acid as an reducing agent.
16. Give one example each for the use of the following as reducing agent.
 - (i) Sodium sulphide
 - (ii) Sodium dithionite
 - (iii) Magnesium - alcohol
 - (iv) Sodium hydrogen sulfide
 - (v) Sodium cyanoborohydride
 - (vi) Zinc-acetic acid
 - (vii) Diborane
 - (viii) Formic acid
17. How photoreduction is carried out? Give some of its applications.
18. Give some illustrations of enzymatic and microbial reductions.

19. How the following conversions are brought about?



5 Some Reactions, Mechanisms and Applications

Introduction

A organic chemist is primarily concerned with the synthesis of organic molecules. The most important step is to plan a synthesis employing the best procedures available. For this, an understanding of the various organic reactions including molecular rearrangements, oxidation and reduction of various functional groups and understanding of the inter-conversion of various functional groups is important. Following are given some important applications of organic synthesis.

Synthesis of Carboxylic acids and their derivatives

One of the common methods available for the synthesis of aliphatic carboxylic acid is the acetoacetic ester synthesis (5.1). Cannizzaro reaction (5.17) is used for the synthesis of carboxylic acids from aldehydes. Aldehydes on oxidation with suitable oxidising agents also give the corresponding carboxylic acids. Another procedure is to start with compounds containing COCH_3 group and subject it to haloform reaction (5.36). Also the nitriles on hydrolysis give the corresponding carboxylic acids.

α, β -Unsaturated carboxylic acids can be obtained using Knoevenagel condensation (5.52), malonic ester synthesis (5.60), Perkin reaction (5.72), Claisen reaction (5.20) and aldol condensation (5.2).

The phenolic carboxylic acid can be conveniently obtained by Kolbe-Schmidt reaction (5.57) or by oxidation of phenolic aldehyde by Dakin reaction (5.26).

The α -hydroxy acids can be obtained from α -diketones using benzilic acid rearrangement (5.13). The β -ketoesters can be conveniently obtained by Claisen condensation (5.19). The stepwise shortening of carboxylic acids (particularly in the steroids) can be effected by Barbier-Wieland degradation (5.9).

N-Substituted amides can be obtained from ketoximes by Beckmann rearrangement (5.11).

Aldehydes

Aldehydes are most conveniently obtained by oxidation of primary alcohols using suitable oxidising agents or by Sarett oxidation (5.81). Aromatic aldehydes can be obtained by Duff's reaction (5.31), Etard reaction (5.36), Houben-Hoesch reaction (5.47) and Reimer-Tiemann reaction (5.75). The NO_2 group in aliphatic nitro compound can be converted into $-\text{CHO}$ group by Nef reaction (5.65). Also the $-\text{C}\equiv\text{N}$ group can be converted into $-\text{CHO}$ group by Stephen reaction (5.86).

α, β -Unsaturated aldehydes can be obtained by the aldol condensation (5.2) or Claisen-Schmidt condensation (5.22). In fact Sarett oxidation (5.81) is also used for the synthesis of α, β -unsaturated aldehydes.

Synthesis of ketones

Common ketones are obtained by the oxidation of *sec*-alcohols by suitable oxidising agents or by Sarett oxidation (5.81). Ketones can also be obtained by acetoacetic ester synthesis (5.1), benzoin condensation (5.14), enamine reaction (5.32) or pinacol-pinacolone rearrangement (5.73). The ketone group can be most conveniently introduced in the aromatic nucleus by Houben-Hoesch reaction (5.47) or Nencki reaction (5.66). The cyclic ketones can be conveniently obtained by the Dieckmann condensation (5.28).

Synthesis of Phenols

Phenolic group can be introduced into aromatic nucleus by Elbs persulfate reaction (5.34). Dakins reaction (5.26) is used for the conversion of phenolic aldehydes and ketones into phenols.

Synthesis of heterocyclic compounds

The oxygen heterocyclic compounds, for example, coumarins can be synthesised by Pechmann condensation (5.71) and Perkin reaction (5.72). The flavones can be synthesised using Algar-Flynn-Oyamada reaction (5.3), Auwers flavone synthesis (5.5) and Baker-Venkataraman rearrangement (5.7). The chromones are easily obtained by Kostanecki-Robinson acylation (5.58).

The nitrogen heterocyclic compounds, for example, pyrrole can be obtained by Hantzsch pyrrole synthesis (5.38), Knorr pyrrole synthesis (5.54) or Paal-Knorr synthesis (5.69). The pyrazoles are obtained by Knorr pyrazole synthesis (5.53). The indoles are obtained by Madelung indole synthesis (5.59) and oxindoles are obtained by Hinsberg oxindole synthesis (5.41). The pyridines are obtained by Hantzsch pyridine synthesis (5.37) and quinolines are obtained by Doebner-Miller synthesis (5.36) and Skraup synthesis (5.85).

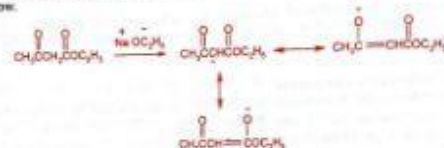
Besides the above, a number of other reactions are used for certain other conversions and transformations.

5.1 Acetoacetic ester synthesis

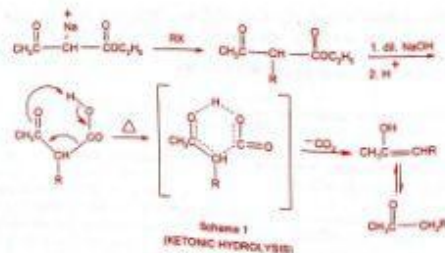
It is the base catalysed reaction of β -keto-esters¹ with alkylating or acylating reagents to give mono or disubstituted β -keto-esters. These on mild hydrolysis with dilute alkali or hydrochloric acid, followed by decarboxylation yield substituted acetones and on treatment with strong alkali give substituted acetic acids.

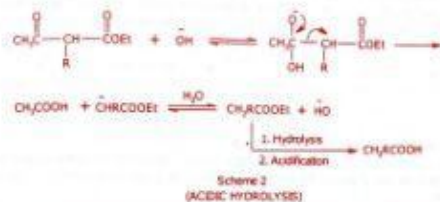
**Mechanism**

The hydrogen attached to a saturated carbon atom that has two strong electron-withdrawing groups is acidic and reacts with base to generate carbanion. Compounds containing these types of acidic $-\text{CH}_2-$ groups are called active methylene compounds, containing these types of acidic $-\text{CH}_2-$ groups are called active methylene compounds, containing these types of acidic $-\text{CH}_2-$ groups are called active methylene compounds. The enolate ion or carbanion (sodioacetoacetic ester) formed from acetoacetic ester (ethyl acetoacetate) on treatment with sodium ethoxide is resonance stabilised as depicted below:

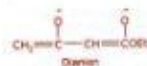


The sodioacetoacetic ester may act as nucleophile and undergo mono- or dialkylation with alkyl halides (or acylation with acyl halides) to give substituted β -dicarbonyl compound. These β -dicarbonyl compounds can undergo two types of hydrolysis with alkali. Hydrolysis of mono or disubstituted derivative of acetoacetic ester with dilute alkali, followed by decarboxylation yields substituted acetone and reaction is called **ketonic hydrolysis** (scheme 1). However, concentrated alkali cleaves substituted β -keto-esters at the position adjacent to the carbonyl group to yield esters and CH_3COO^- . Esters formed are hydrolyzed by the alkali and on acidification with inorganic acid give free acids as the final product and reaction is called **acidic hydrolysis** (scheme 2). Thus two carboxylic acids, one of which is always acetic acid (CH_3COOH), are formed by the hydrolysis of substituted acetoacetic ester with concentrated alkali.





Use of a very strong base, such as LDA or $t\text{-BuLi}$ gives a dianion, which will preferentially alkylate at the methyl group,⁷ the less acidic side of the ketone.

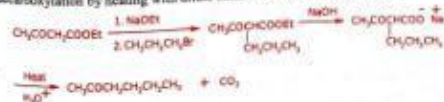


Applications

Sodioacetic ester can be used for the synthesis of variety of compounds such as ketones, carboxylic acids, keto acids or esters etc.

Synthesis of ketones

The reaction of sodium salt of ethyl acetoacetate with an alkyl halide followed by decarboxylation by heating with dilute alkali or dilute acid gives ketone.



Synthesis of monocarboxylic acids

The reaction of sodium salt of ethyl acetoacetate with alkyl halide followed by hydrolysis with strong alkali (acidic hydrolysis) and subsequent acidification gives monocarboxylic acids.



Synthesis of dicarboxylic acids

The reaction of sodium salt of ethyl acetoacetate with ethyl chloroacetate followed by hydrolysis with conc. alkali (acidic hydrolysis) and subsequent acidification gives dicarboxylic acid, succinic acid.



Synthesis of keto-esters³ and keto acids⁴

Ethyl acetoacetate in benzene on heating with acid chloride in presence of magnesium followed by hydrolysis of the resultant product with ammonia-alcohol gives the keto-esters.

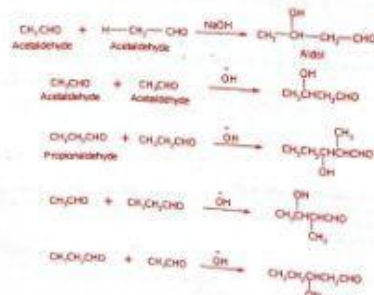


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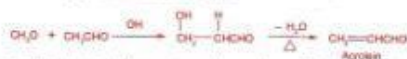
5.2 Aldol condensation

Alddehydes containing a α -hydrogen atom undergo a reversible self-addition in presence of dilute alkali to give condensation products, β -hydroxy aldehydes. The hydroxy aldehyde formed from acetaldehyde is originally called an aldol and the reaction is known as **aldol condensation**.

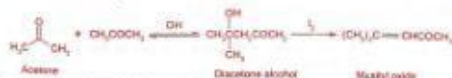


When a mixture of two aldehydes both possessing α -hydrogen atom, is treated with a base, four different aldol products are formed, two by self condensation of the two different aldehydes and two by the cross condensation of two different aldehydes. For example, a mixture of acetaldehyde and propionaldehyde gives four products as shown above.

The aldol condensation between two different aldehydes is not of much value since a mixture of four products are obtained. It is clear that aldol condensation takes place with aldehydes having at least one α -hydrogen atom but not with aldehydes devoid of α -hydrogen. However, cross aldol condensation between an excess of an aldehyde that has no α -hydrogen (such as benzaldehyde or formaldehyde) and a second enolisable aldehyde gives mainly one crossed aldol condensation product. The aldols are sometimes stable and may be isolated. However, in certain cases they lose a molecule of water spontaneously to form α,β -unsaturated aldehydes or ketones. Thus, condensation of formaldehyde with acetaldehyde at a high temperature (to effect dehydration of the intermediate aldol) gives acrolein in 75% yield.

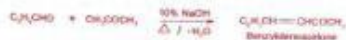


Ketones containing α -hydrogen atom also undergo aldol condensation. However, equilibrium is generally quite unfavourable and the yields are low in case of ketones as compared to aldehydes. Thus, acetone in presence of base, is converted into diacetone alcohol by using special technique of conducting the reaction. The condensation of acetone to diacetone alcohol¹ can be made useful by using barium hydroxide in a Soxhlet extractor and allowing acetone to flow over it.

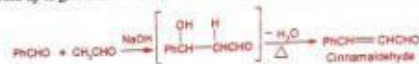


Diacetone alcohol (aldol of acetone) on heating or in presence of iodine as catalyst or dilute mineral acid loses a molecule of water to give mesityl oxide.

Aldol condensation can also take place between an aldehyde and a ketone. This is known as crossed aldol condensation (**Claisen-Schmidt reaction**). The carbonyl group of ketone has less additive power than that of aldehyde, when aldehyde condenses with ketones it serves as a substrate for enolisable ketone. Thus, acetaldehyde and acetone gives 4-hydroxypentan-2-one. Similarly, an aldehyde that has no α -hydrogen (i.e., cannot undergo self-condensation) may undergo condensation with enolisable ketone, for example, condensation of acetone with benzaldehyde in presence of 10% NaOH forms benzylideneacetone.

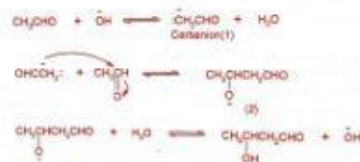


Aldols obtained from the condensation of unreactive aldehydes such as sterically hindered aliphatic or aromatic aldehydes usually undergo dehydration under reaction conditions. Thus, the aldol obtained by the condensation of benzaldehyde and acetaldehyde is unstable and spontaneously loses a molecule of water during aqueous acid work up to give cinnamaldehyde.²

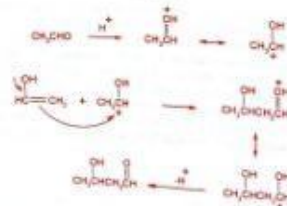


Mechanism

The mechanism of aldol condensation in case of aldehydes (e.g., acetaldehyde) is shown below. The base (hydroxide ion) removes a proton from α -carbon atom to give a carbanion (1). The nucleophilic attack of the carbanion on the carbonyl carbon of other molecule gives the anion (2), which picks up a proton from water to form aldol.



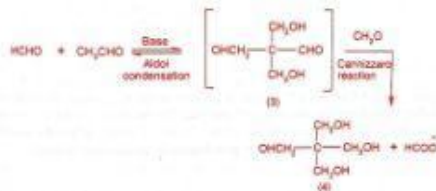
The aldol condensation can be performed in presence of acid as catalyst. The reaction is initiated by protonation of the carbonyl group and followed by the attack on the α -carbon of the enol form of other molecule.



It has been noticed that in aldol condensation, mixtures of *threo* and *erythro* forms are obtained.

**Applications**

Several valuable synthetic procedures are based upon aldol condensation of aldehydes and ketones. When excess of formaldehyde is condensed with acetaldehyde in aqueous solution of calcium hydroxide, trihydroxy aldehyde (3) is formed, which undergoes **crossed Cannizzaro reaction** with formaldehyde to give pentaerythritol (4).² Pentaerythritol is required for the production of explosive, PETN.



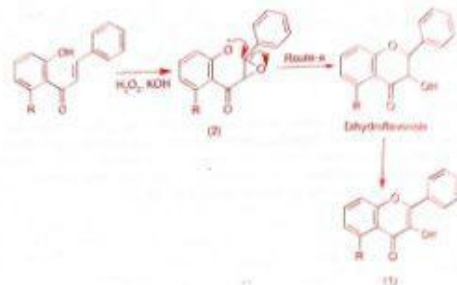
The most important applications of the aldol condensation in organic synthesis are its intramolecular version.

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3. R. B. J. Schuster, OS, 1941, 1, 425.

5.3 Algar-Flynn-Oyamada reaction (AFO)

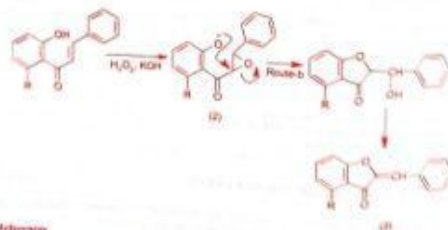
It involves the oxidation¹ of *o*-hydroxyphenyl styryl ketones (2'-hydroxy chalcones) to flavonols (1) with hot alkaline hydrogen peroxide via the formation of intermediate, dihydroflavonols (flavanols).



In this oxidation, if an $-OCH_3$ or $-CH_3$ group is present in the 6'-position of chalcones, aurones (3) rather than flavonols are obtained provided the reaction is effected at room temperature and the 2- or 4- positions do not carry a hydroxyl group. When the reaction is carried out in ethanol, 6'-methoxychalcones give flavonols² as the main product.

Mechanism

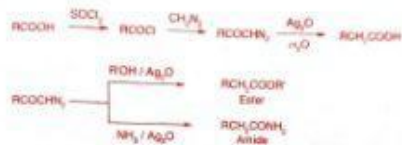
The proposed mechanism³ involves the formation of an intermediate epoxide (2), which undergoes internal nucleophilic attack to afford flavonol (1, ring opening via route a) or aurone (3, ring opening via route b).

**References**

1. J. Algar, J. P. Flynn, Proc. Roy. Irish Acad., 1934, 42B, 1; B. Oyamada, J. Chem. Soc. Japan, 1934, 15, 1234.
2. T. S. Wheeler, Russ. Chem. Rev., 1957, 28, 333; W. P. Cuyler et al., J. Chem. Soc., 1971, 2848.
3. T. R. Cooverly, W. J. Connolly, Tetrahedron, 1973, 29, 309.

5.4 Arndt-Eistert synthesis

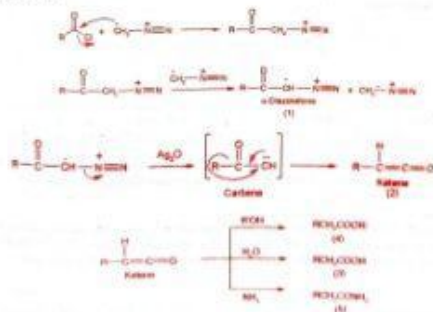
It is a simple general method¹ for converting an acid into its next higher homologue or to a derivative of the homologous acid, such as amide or ester. The various steps involved are as follow:



The last step i.e., conversion of α -diazoketone into carboxylic acid, ester or amide is called **Wolff rearrangement** and can also be carried out under photochemical conditions (see sec. 6.1.3).

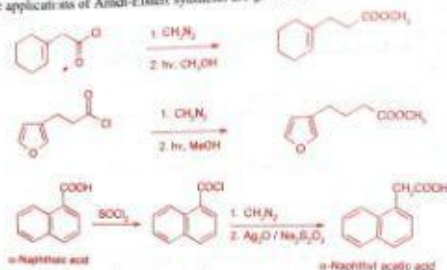
Mechanism

Acid chlorides react with diazomethane to give α -diazoketone (1). α -Diazoketone eliminates nitrogen molecule and rearranges to ketene (2) in the presence of solid silver oxide or by irradiation with light. Ketene is converted to acid (3), ester (4) or amide (5) when treated with water, alcohol and ammonia, respectively. When rearrangement is carried out in the presence of water or an alcohol, the ketene is directly converted into an acid or ester.



Applications^{2,3}

Some applications of Arndt-Eistert synthesis are given below.

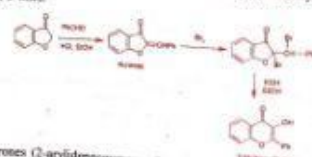


References

1. F. Arndt, B. Eistert, Ber., 1935, 68, 206.
2. A. B. Smith, Chem. Commun., 1974, 685.
3. E. J. Walsh, Jr., and G. B. Stone, Tet. Lett., 1946, 1127.

5.5 Auwers flavone synthesis

It involves the synthesis¹ of benzopyran-4-ones (flavones) from *o*-hydroxychalcones or from benzofuran-3-ones.



The starting aurones (2-acylbenzofuran-3-ones) can be obtained by the oxidation of chalcones with alkaline hydrogen peroxide (See Algar-Flynn-Oyamada reaction, 5.3)

Applications

The reaction of 7-chloroauromaran-3-one with benzaldehyde gives the corresponding 3-benzylidene product, which on bromination gives the dibromo compound. Final treatment with alcoholic potassium hydroxide involves ring expansion to give 8-chloroflavone.

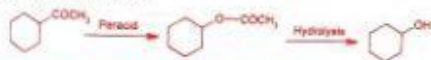


Reference

1. K. Auer, *Chem. Ber.*, 1908, 41, 4233.

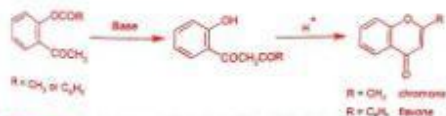
5.6 Baeyer-Villiger oxidation

The oxidation of ketones to esters with peracids or hydrogen peroxide is known as **Baeyer-Villiger oxidation**¹. Further, saponification of esters produces alcohols. Thus, ketones can be transformed to alcohols by this method. For stereochemistry and applications see sec. 6.3.1.



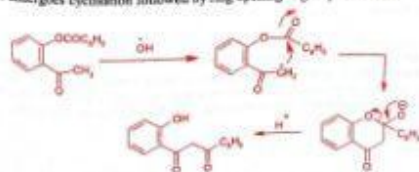
5.7 Baker-Venkataraman rearrangement

The base catalysed rearrangement¹ of *o*-acyloxyketones to β -diketones, important intermediates in the synthesis of chromones and flavones, is known as **Baker-Venkataraman rearrangement**.



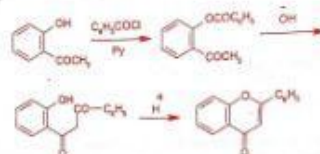
Mechanism

The base abstracts a proton from acetyl group of *o*-acyloxyketone to give a carbanion, which undergoes cyclisation followed by ring opening to give β -diketones.



Applications

o-Hydroxyacetophenone on benzoylation followed by heating with solid potassium hydroxide gives the β -diketone, which on acidification undergoes cyclisation to give flavone.

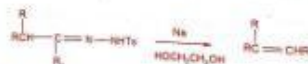


References

1. W. Baker, *J. Chem. Soc.*, 1933, 1381; R. S. Mahal, K. Venkataraman, *J. Chem. Soc.*, 1934, 1762; K. Venkataraman in *Zehmeister, Progress in the Chemistry of Organic Natural Products*, 1959, 17, 2.

5.8 Bamford-Stevens reaction

The formation of alkenes by base catalysed decomposition of *p*-toluenesulfonylhydrazones of aldehydes and ketones is known as **Bamford-Stevens reaction**¹.

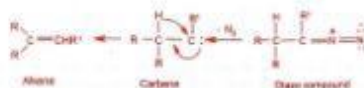
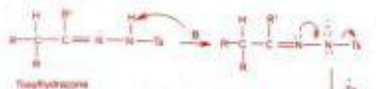


Mechanism

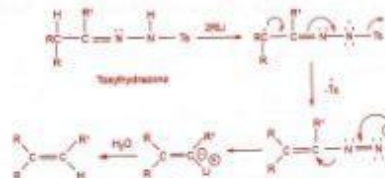
The mechanism depends on the base used. Thus, with sodium-ethylene glycol a carbene mechanism is possible and highly substituted alkene is obtained. However, with other bases, such as organolithium compounds, the anion mechanism may be involved and the alkenes are formed.

Carbene mechanism

Tosylhydrazone of aldehyde or ketone on treatment with base and subsequent loss of *p*-toluenesulfonate (Ts^-) gives the corresponding diazo compound, which generates Carbene. Carbene undergoes 1,2-hydrogen shift to form alkene. The migration of hydrogen may be simultaneous with the elimination of nitrogen.

**Anionic mechanism**

There is much evidence for this mechanism and is as follows:

**Applications¹⁻⁴**

Spin isosylhydrazone (1) on heating with sodium methoxide gave 90% yield of (E)-spin[12,11]tetraene-13-ene (2).

**References**

1. W. R. Bamford and T. S. Stevens, *J. Chem. Soc.*, 1952, 4735; A. G. M. Barrett, *Adv. Chem. Ser.*, 1963, 16, 55.
2. D. G. Farnham, *J. Org. Chem.*, 1973, 38, 870.
3. M. A. Giustano, P. Friedel and V. Flanagan, *Tet. Lett.*, 1965, 1847.
4. G. A. Hugel and P. Bork, *J. Org. Chem.*, 1973, 38, 3637.

5.9 Barbier-Wieland degradation

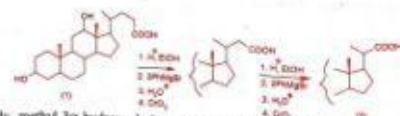
This method involves a stepwise carboxylic acid degradation of aliphatic acid (particularly in steroid side chain) to the next lower homologue. The starting carboxylic acid is converted into its ester, which on reaction with a Grignard reagent gives the corresponding tertiary alcohol. Dehydration of alcohol with acetic anhydride and oxidation of the formed olefin with chromic acid gives the lower homologue of the carboxylic acid. This sequence of reactions is known as the **Barbier-Wieland Degradation**.¹



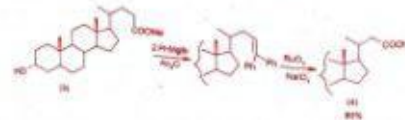
Various oxidising agents can be used in place of chromic oxide in last step, e.g., NaIO_4 in the presence of ruthenium tetroxide (RuO_4 , as catalyst) was used as the oxidising agent in the synthesis of steroid (3- α -acetoxyneocholanic acid).

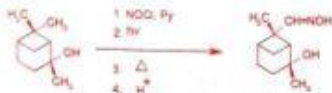
Applications²⁻⁴

Wieland converted desoxycholic acid² (1) to not-desoxycholic acid (2) by using this method.



Similarly, methyl 3 α -hydroxyneocholanoate (3) can be converted into 3 α -acetoxyneocholanic acid (4).



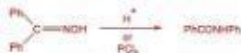


References

1. D. H. R. Barton, J. M. Beaton, L. E. Geller, M. M. Pechet, J. Am. Chem. Soc., 1966, 82, 2640; 1961, 83, 4076; M. Akhtar in *Advances in Photochemistry*, M. A. Noyes et al. Eds. Vol. 2 (Interscience, New York, 1964), 263.
2. D. H. R. Barton et al., J. Chem., Perkin Trans. 1, 1979, 1159.
3. D. H. R. Barton and J. M. Beaton, J. Am. Chem. Soc., 1961, 83, 4083.
4. P. D. Hobbs and P. D. Magnus, J. Am. Chem. Soc., 1976, 98, 4594.

5.11 Beckmann rearrangement

Ketoximes on treatment with an acid catalyst (e.g., PCl_5 , P_2O_5 , SOCl_2 , POCl_3 , H_2SO_4 and H_2SO_4) undergo a rearrangement to form N-substituted amides. This reaction is known as **Beckmann rearrangement**. Thus, benzophenone oxime gives benzanilide in the presence of phosphorus pentachloride in ether solution.

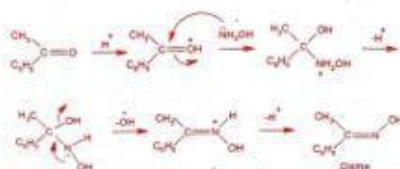


The reaction is highly stereospecific in that the migrating group is *anti* to the oxime hydroxyl group. The migrating group approaches the nitrogen atom from the opposite side to the departing oxygen. This is clearly shown by the transformation of acetophenone oxime to acetanilide in presence of concentrated H_2SO_4 .

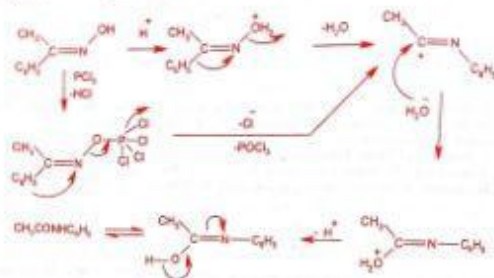


Mechanism

Step (1) Oxime formation



Step (2) Rearrangement

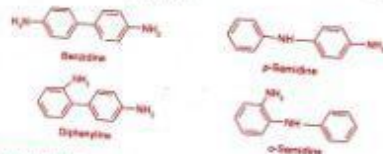


5.12 Benzidine rearrangement

The acid catalysed rearrangement of hydrazobenzene to 4,4'-diaminobiphenyl (*p*-benzidine) is known as **Benzidine rearrangement**.

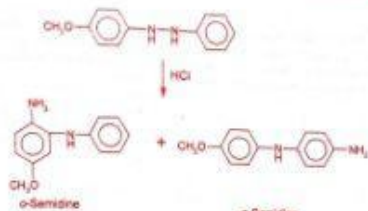


Usually, the major product is benzdine, but other side products called semidines and diphenylene are also formed in low yield.



Effect of substituents

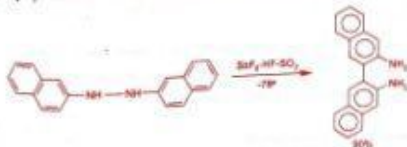
The actual amount of each product formed during benzidine rearrangement is largely determined by the nature of the substituent. If the *p*-position of one nucleus is occupied by a methyl or alkoxy group, the main product formed is an *o*-semidine together with a small amount of the *p*-semidine.



If the para-position is blocked by halogen, both a dipheniline and an o-semidine are formed.



When both para positions are blocked, the major product is 2,2'- isomer. For example, di-*ortho*-phenylhydrazines on treatment with acid rearranges to give 2,2'-isomer.

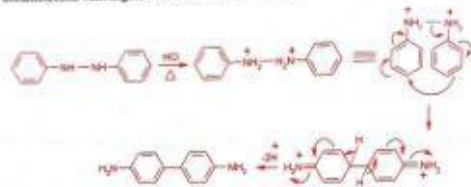


If there is carboxyl or sulfo group attached in phenyl ring in hydrazobenzene, the rearrangement accompanied by the elimination of these groups. For example, hydrazobenzene-4-carboxylic acid gives benzidine.



Mechanism

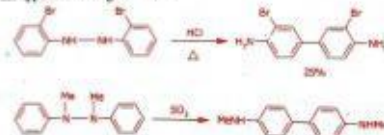
A number of theories have been given to explain the mechanism of benzidine. A number of theories have been given to explain the mechanism of benzidine rearrangement, e.g., caged radical mechanism, π -complex mechanism and polar transition state mechanism. However it is believed that the mechanism involves the intramolecular rearrangement and can be formulated as follows.



Support for this mechanism is afforded by the observation that when two different hydrazobenzenes are rearranged in same solution, only two benzidines are obtained and cross coupling product are not formed.

Applications^{2,4}

Some applications are given below.



References

1. A. W. Hoffmann, *Proc. Roy. Soc. London*, 1867, 12, 576; T. Shirotsuki and S. Aizawa, *Chem. J. Jpn. Chem.*, 1960, 13, 185.
2. G. A. Olah, K. Dumas, D. D. Kelly and Y. K. Mo, *J. Am. Chem. Soc.*, 1972, 94, 7438.
3. H. B. Sessler, C. Weaver and C. D. Marshall, *J. Am. Chem. Soc.*, 1969, 91, 289.
4. M. Nojima, T. Ando and N. Tokura, *J. Chem. Soc., Perkin I*, 1976, 24, 1504.

5.13 Benzilic acid rearrangement

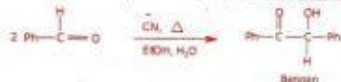
α -Diketones (Benzils) on treatment with a base rearrange to give the salt of α -hydroxy acids (benzilic acid) and the reaction is known as **benzilic acid rearrangement**.¹



For mechanism and applications see sec. 6.1.4.

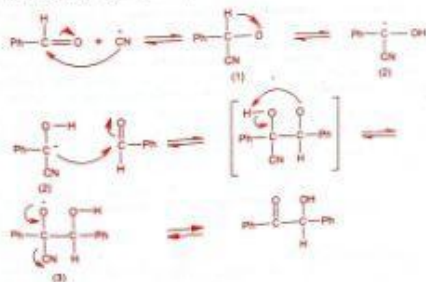
5.14 Benzoin condensation

The self-condensation of aromatic aldehydes (with no α -hydrogen) in presence of cyanide ions as a catalyst to α -hydroxy ketone (benzoin) is called **benzoin condensation**. Benzoin belongs to a class of compounds called acyloins. The reaction is not successful with aliphatic aldehydes under these conditions.



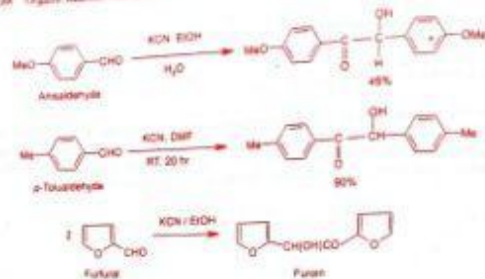
Mechanism

Cyanide ion attacks the carbonyl group to give (1). Cyanide group with its electron withdrawing nature makes aldehydic hydrogen more acidic. The conversion of (1) to (2) is favourable because the ion (2) is stabilised by both the benzene ring and the cyanide group. The anion (2) attacks another aldehyde carbonyl to form the link between the two molecules. The deprotonation-protonation steps give the alkoxide ion (3). Finally, cyanide ion departs from (3) to give benzoin.



Applications^{2,3}

Anisaldehyde and *p*-tolualdehyde give the corresponding α -hydroxy ketones. Similarly furfural gives furoin.

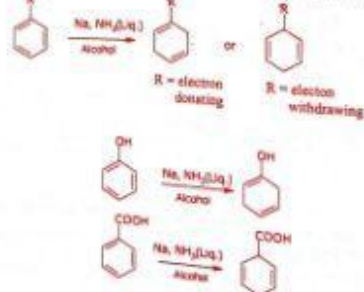


References

1. A. J. Lapworth, *J. Chem. Soc.*, 1903, 47, 955; 1904, 87, 1206; *J. Solvated. For. Lett.*, 1971, 287.
2. G. Szwedli, J. J. Stevens and G. E. Gohren, *J. Org. Chem.*, 1957, 22, 79.
3. G. H. Gholamhossein, R. Halimelahi, C. B. Boyle and R. S. Kaizer, *Mech.*, 1977, 66, 343.

5.15 Birch reduction

Reduction of aromatic rings by means of alkali metals (sodium or lithium) in liquid ammonia or amines with ethanol as proton donor, to give mainly unconjugated dihydroderivatives is known as **Birch reduction**¹. Aromatic rings and conjugated dienes are reduced by this method while isolated double bonds are normally not affected. Sometimes others are used as a co-solvent to dissolve the aromatic compounds. Use of *tert*-butanol fulfils the dual role of proton donor and a co-solvent.

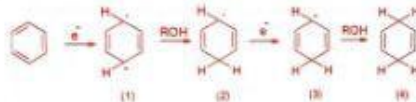


Alkynes are also reduced stereospecifically to *trans* alkenes with sodium or lithium in liquid ammonia and no added proton donor is needed (The best way to reduce them to *cis*-alkenes is via hydrogen and the Lindlar catalyst, see sec. 4.2.2).



Mechanism

The alkali metal donates an electron to the aromatic compound, forming the alkali metal cation and a radical anion (1). Radical anion is very basic and abstracts a proton from protic solvent to give a radical (2), which picks up another electron to give an anion (3). It is quenched again by the proton source (ethanol) to give unconjugated dihydro compound (4). The last double bond is often left unreduced in the ring.



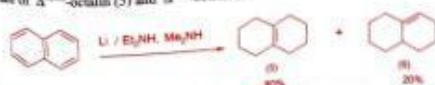
The mechanism of reduction of alkynes follows the same course as the reduction of aromatic rings, but the vinyl anion is basic enough to abstract proton from ammonia, so there is no need to add proton source.

Applications^{1,4}

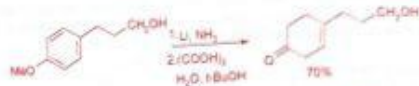
1-Naphthol on reduction with Na/liq. ammonia gives 5,8-dihydro-1-naphthol.



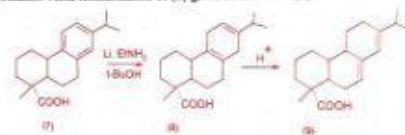
Similarly, naphthalene on reduction with Li and diethylamine and dimethylamine gives a mixture of $\Delta^{8,10}$ -octalin (5) and $\Delta^{10,12}$ -octalin (6).



Some other applications of Birch reductions are given below:



The aromatic ring of dehydroabietic acid (7) is reduced to (8) in presence of more powerful reducing system using lithium and ethylamine together with a protic solvent like *tert*-butanol. Acid isomerization of (8) gives abietic acid (9).



References

1. A. J. Birch, *J. Chem. Soc.*, 1944, 4303; 1945, 809; 1946, 593; 1947, 102; 1947, 1949, 2531; A. J. Birch, *Quart. Rev. (London)*, 1951, 4, 49.
2. A. J. Birch, *J. Chem. Soc.*, 1944, 430.
3. R. A. Benson, *J. Org. Chem.*, 1964, 29, 955; C. J. Moody, *Tet. Lett.*, 1968, 27, 5255.
4. R. Kamm, P. Gerber and S. Swannerton, *Tet. Lett.*, 1964, 1601.
5. E. J. Corey and N. W. Boon, *Tet. Lett.*, 1965, 6015.
6. W. A. Ayer, W. R. Bowman, T. C. Joseph and P. Smith, *J. Am. Chem. Soc.*, 1968, 90, 1648.

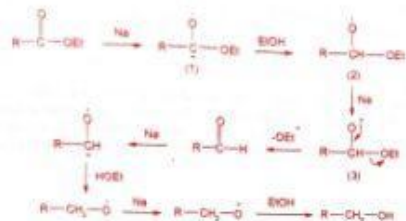
5.16 Bouveault-Blanc reduction

It involves the reduction¹ of esters, aldehydes or ketones with sodium and alcohol to form alcohols. Ketones and aldehydes are also reduced to alcohols by means of excess of sodium and ethanol. However, free acids do not undergo reduction by this method.



Mechanism

Sodium donates an electron to the carbonyl group forming the alkali metal cation and a radical anion (1), which abstracts a proton from alcohol to give a radical (2). The radical (2) reacts with another molecule of Na to give an anion (3), which gives aldehyde. The reduction of aldehyde finally gives the alcohol as shown below.

**Applications^{1,2}**

Some typical applications of Bouveault-Blanc reductions are given below.

**References**

1. G. Bouveault and G. Blanc, *Compt. Rend.*, 1905, 139, 1676; *Bull. Soc. Chim. France*, 1906, 6537, 146; H. O. House, *Modern Synthetic Reactions* (W. A. Benjamin, California, 1972), p. 150.
2. L. A. Paquette, *J. Org. Chem.*, 1962, 27, 2274; K. Ruhmann, *Synthesis*, 1972, 236.
3. G. Hieber, *Ber.*, 1936, 69, 1300.

5.17 Cannizzaro reaction

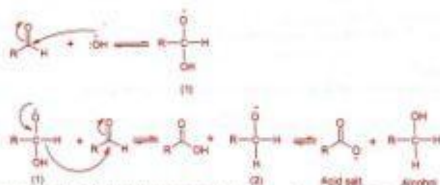
Aromatic aldehydes that do not have α -hydrogen atom(s) on treatment with concentrated aqueous alkali undergo self oxidation and reduction to give alcohol and the salt of the corresponding carboxylic acid.



This disproportionation reaction or self oxidation and reduction reaction of aldehydes devoid of α -hydrogen is known as **Cannizzaro reaction**.¹ *Ortho* and *para* phenolic aldehydes do not undergo this reaction. If an alkoxide is used in the Cannizzaro reaction, the product is an ester.²

**Mechanism**

The mechanism most likely involves the formation of reducing anion (1) by the interaction of the aldehyde with hydroxide ion. This anion may transfer a hydride ion intermolecularly to a carbonyl carbon of another molecule, forming the carboxylic acid and the alkoxide ion (2). The shift of proton from acid to (2) gives the final product.



A mixture of two aldehydes having no α -hydrogen undergo **crossed Cannizzaro reaction** to yield all possible products. However, if one of the aldehydes is formaldehyde, which is more reactive than other aldehydes towards nucleophiles and rapidly gives a high concentration of the donor anion, the products are sodium formate resulting from the oxidation of formaldehyde exclusively and the alcohol corresponding to the other aldehyde. Thus, crossed Cannizzaro reaction between benzaldehyde and formaldehyde yields benzylalcohol and sodium formate.

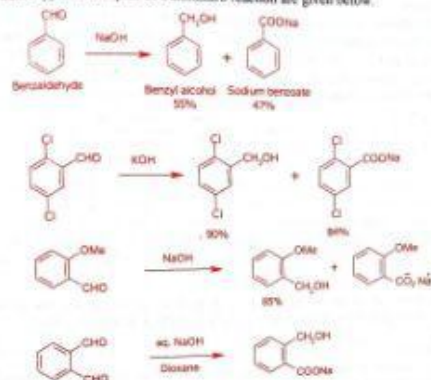


Intramolecular Cannizzaro reaction is also known, for example, glyoxal (3) gives hydroxyacetate anion (4) in presence of concentrated alkali.

**Applications^{1,2}**

Last step in the preparation of tetrahydric alcohol pentaerythritol from formaldehyde and acetaldehyde is crossed Cannizzaro reaction (see aldol condensation, sec. 5.2). Its sodium vasodilator.

Some typical examples of Cannizzaro reaction are given below.

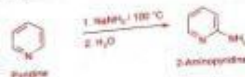


References

1. R. Cannizzaro, Ann., 1853, 68, 129; K. List and H. Limpicht, Ann., 1854, 30, 180.
2. O. Kamm and W. F. Kamm, OS, 1941, 1, 104.
3. C. G. Swain, A. L. Powell, W. A. Sheppard and C. R. Morgan, J. Am. Chem. Soc., 1979, 101, 3576.
4. T. A. Coomans, Org. Reactions, Vol II, 1944, 94.
5. R. S. McDonald and C. E. Sibley, Can. J. Chem., 1981, 59, 3361.

5.18 Chichibabin reaction

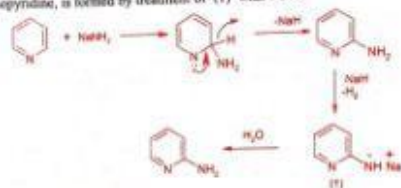
Chichibabin amination reaction¹ is the amination of pyridines, quinolines and other N-heterocycles with alkali-metal amides. Amination of pyridine takes place at the 2-N heterocycles with alkali-metal amides. Amination of pyridine takes place at the 2-position on heating it with sodamide in dry toluene at 100 °C. It is a substitution reaction initiated by the attack of nucleophile. If both the *ortho* positions are blocked then amination takes place at 4-position.



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Mechanism

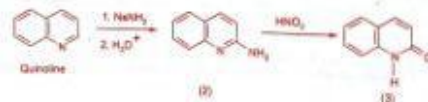
The mechanism involves the nucleophilic aromatic substitution of pyridine or a related heteroaromatic compound. The reaction starts with the attack of nucleophile at 2-position of pyridine, followed by the loss of hydride ion and subsequent elimination of hydrogen results the sodium salt of 2-aminopyridine (1). The final product, 2-aminopyridine, is formed by treatment of (1) with water.



The addition of amide ion at the 2- or 4- position makes it possible for the negative charge to be shared by nitrogen so is preferred to attack at the 3-position.

Applications^{1,2}

Aminopyridines prepared in this way are valuable as reagents for synthesizing more highly substituted pyridines. Carbestyryl (3) may be prepared from quinoline by reaction with sodamide and subsequent treatment of 2-amino quinoline (2) with nitrous acid.



Another application is given below.



Chichibabin pyridine synthesis⁴ deals with synthesis of pyridines from aromatic acetaldehyde and ammonia.

References

1. A. Chichibabin, J. Russ. Phys. Chem. Soc., 1914, 46, 1216; J. F. Bunnett, Chem. Rev., 1951, 49, 275.
2. R. C. Vander Plas, J. Org. Chem., 1981, 46, 2136.
3. E. L. Eliel, J. Am. Chem. Soc., 1955, 77, 4291.
4. A. Chichibabin, J. Russ. Phys. Chem. Soc., 1906, 37, 1229; M. M. Spring, Chem. Rev., 1940, 28, 301.

5.2 Claisen reaction

It is a base catalysed reaction between an aldehyde or a ketone with no α -hydrogen atom (i.e., cannot self-condense) and an ester which has an active hydrogen to give an α,β -unsaturated ester. For example, ethyl acetate and benzaldehyde undergo condensation in the presence of base to afford ethyl cinnamate.

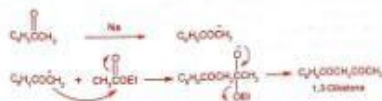


Mechanism

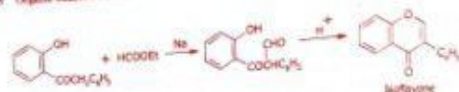
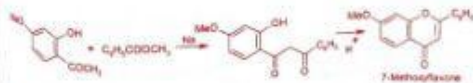
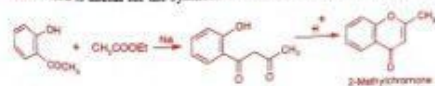
It is an important variation of Claisen condensation.



However, the reaction of aromatic ketones with α -hydrogen and ethyl acetate in presence of pulverised sodium gives β -diketone. In this case a ketone enolate reacts with ester to give a 1,3-diketone and reaction is still referred as the Claisen reaction.

Applications¹⁻³

The method is useful for the synthesis of chromones, flavones and isoflavones.



References

1. W. Wittig, Ber., 1928, 57, 88
2. F. Wheeler, Org. Syn. Coll. Vol IV, 1963, 478
3. J. Verduyn, J. Chem. Soc., 1934, 513

5.2.1 Claisen rearrangement

The allyl phenyl ethers on heating undergo thermal rearrangement to give 2-allylphenols. This is known as **Claisen rearrangement**.



For mechanism and applications see sec 6.5.12.

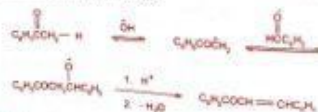
5.2.2 Claisen-Schmidt condensation

The condensation of an aromatic aldehyde (without α -hydrogen) with an aliphatic aldehyde or ketone (having α -hydrogen) in presence of relatively strong base (hydroxide or alkoxide) to form α,β -unsaturated aldehyde or a ketone is known as **Claisen-Schmidt condensation**. For example, benzaldehyde reacts with acetaldehyde to give cinnamaldehyde.



Mechanism

The mechanism is similar to **Alkal condensation**. The enolate is generated from aliphatic aldehyde or ketone and aromatic aldehyde acts as "acceptor". In this case the crossed aldol product spontaneously dehydrates under the reaction conditions to afford α,β -unsaturated aldehyde or ketone.

Applications¹⁻⁴

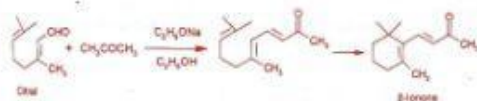
Acetone on condensation with benzaldehyde gives benzalacetone¹ which may react with another molecule of benzaldehyde to yield dibenzylacetone.



Acetophenone and benzaldehyde on treatment with NaOH give benzalacetophenone (chalcone).



β -ionone is the key intermediate in the synthesis of vitamin A, which can be prepared from citral.



References

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2. Kofke, *Chemtech*, *Org. Syn.*, 1922, 2, 1.
3. Cornval, *Deliver. Org. Syn.*, 1939, 12, 22.
4. A. Ruedi, R. L. Krayn, *Org. Syn. Coll. Vol. III*, 1955, 747.

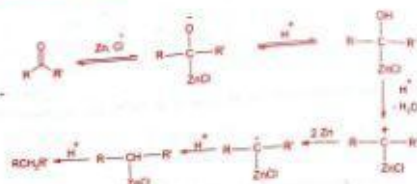
5.23 Clemmensen reduction

Ketones and aldehydes on reduction with zinc amalgam and hydrochloric acid give the corresponding hydrocarbons, i.e., carbonyl group is converted into methylene group. This is known as **Clemmensen reduction**. For example, 4-oxo-4-phenylbutanoic acid is reduced to 4-phenylbutanoic acid.



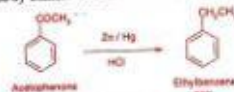
Mechanism

The mechanism of Clemmensen reduction is uncertain. The following reaction pathway involving the transfer of electron from the metal surface to the carbon atom of prominent carbonyl group has been proposed. Transfer of four electrons from zinc metal to one molecule takes place.



Applications

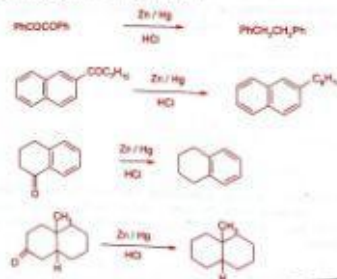
The method is used for the reduction of aromatic aliphatic ketones,^{2,3} thus, acetophenone is reduced by Clemmensen method to ethylbenzene.



Acyclic ketones^{4,5} can also be reduced by this method, for example, cyclohexanone is reduced to cyclohexane.



Some other applications are given below.



References

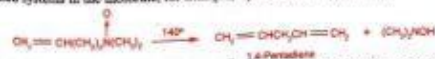
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4. E. L. Martin, J. Am. Chem. Soc., 1936, 58, 141.
5. W. G. Dauben, J. Am. Chem. Soc., 1954, 76, 3864.
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5.24 Cope elimination

The formation of an olefin and a hydroxylamine by thermal decomposition of tertiary amine oxide is known as **Cope elimination**¹. The N-oxide derivatives are prepared by the oxidation of corresponding tertiary aliphatic or aromatic amines with aqueous hydrogen peroxide or *m*-chloroperoxybenzoic acid².



This reaction takes place at much lower temperature (120–150°C) compared to formation of olefin by the decomposition of carboxylic acids or esters and thus the decomposition of the sensitive olefin is often avoided. The added advantage of this reaction is that the olefin obtained is free of other impurities. The pyrolysis of amine oxides is regioselective and takes place normally under mild conditions and this allows formation of a new carbon-carbon double bond without migration into conjugation with other unsaturated systems in the molecule, for example, synthesis of 1,4-pentadiene.

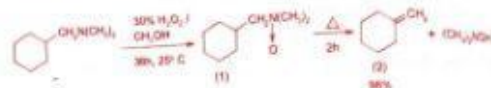


It has been found in general with aliphatic esters, xanthates or amine oxides which could form either a *Z*- or *E*-alkene on pyrolysis that the more stable *E*-isomer is formed in larger amount. Since there is *syn* elimination therefore the *threo* isomer of the amine oxide gives the *E*-alkene. Does the *Z*-alkene while the *erythro* isomer gives the *E*-alkene.



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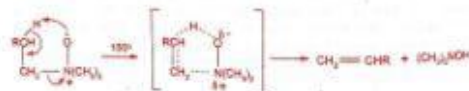
A notable advantage is the case of pyrolysis of acyclic amine oxides, e.g., N-oxide of N,N-dimethylcyclopentanemethylamine (1), which exclusively gives methylenecyclohexane³ (2) compared to mixture of products obtained in the pyrolysis of the acetates and xanthates.



The reason for the above observation is that in the oxide, the coplanar five-membered cyclic transition state only allows abstraction of hydrogen from the methyl substituent, where as with the more flexible six-membered transition state in the ester pyrolysis, hydrogen abstraction is also possible from the ring. In case of larger more flexible ring, where the requisite planar transition state is easily attained, the cycloalkenes is the major product even in the pyrolysis of amine oxides (see applications).

Mechanism

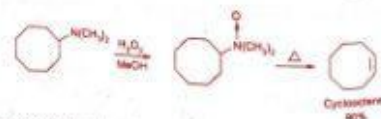
The mechanism is similar to the thermal elimination of acetates. But in Cope eliminates the reaction conditions required are less severe. The mechanism involves a cyclic transition state. The two groups eliminated are *cis* to each other across the central bond which becomes the *n*-bond.



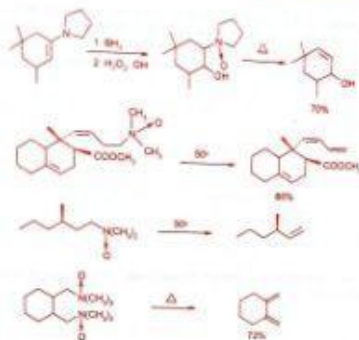
The negative charged nitrogen acts as a strong base and eliminates a proton from within the same molecule.

Applications^{4,5}

Using this method, cyclooctene is synthesised in 90% yield.



Some other applications are given below.



References

1. A. C. Cope, T. T. Foster and P. H. Towns, *J. Am. Chem. Soc.*, 1949, 71, 3929.
2. A. C. Cope and E. Ciganek, *OS*, 1963, IV, 632.
3. A. C. Cope and E. Ciganek, *OS*, 1963, IV, 339.
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5. E. J. Corey and M. C. Dess, *Tet. Lett.*, 1983, 1747.
6. K. Mori, *Tetrahedron*, 1977, 33, 289.
7. L. D. Quir, J. Leinert, E. D. Middleman, R. W. Miller and A. T. Mophill, *J. Org. Chem.*, 1979, 44, 3496.

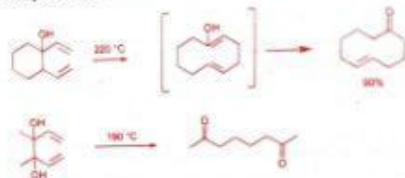
5.25 Cope rearrangement

The thermal isomerisation of 1,5-dienes by a 3,3-sigmatropic shift is known as **Cope rearrangement**.¹ This is illustrated in the equilibration of 3,4-dimethyl-1,5-hexadiene (1) to 2,6-octadiene (2).



A disadvantage of the Cope rearrangement from a preparative standpoint is the high temperature generally required. However, it has now been found² that the reaction can be performed in many cases at room temperature in the presence of catalytic amount of $\text{PdCl}_2(\text{PhCN})_2$. Thus, 2-methyl-3-phenyl-1,5-hexadiene with catalytic amount of $\text{PdCl}_2(\text{PhCN})_2$ in tetrahydrofuran at room temperature for 24 hr gives the dienes in 97% yield in the ratio 97:3 (see applications). In contrast, thermal Cope rearrangement requires high temperature and the reaction is less stereoselective.

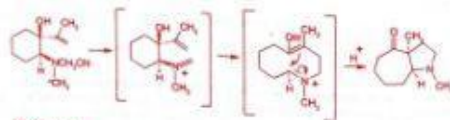
Thermal rearrangement of 1,5-hexadienes with a hydroxyl substituent at C-3 provides a convenient and useful route for the synthesis of unsaturated aldehydes and ketones,¹ if there are hydroxyl substituents at C-3 and C-4 of the dienes, 1,8-dicarbonyl compounds are obtained. Such rearrangements are called **oxy-Cope**



Another type of Cope rearrangement is known as **aza-Cope rearrangement** and occurs under mild conditions.



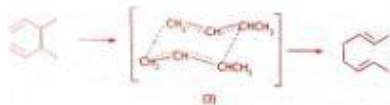
Thus, in the above rearrangement, with a suitably placed hydroxyl or alkyl substituent at C-3 of the butenyl group, the reaction can be made to go in the forward direction by the capture of the rearranged iminium salt in an intramolecular **Massam reaction**. This provides an excellent route for the synthesis of 2-substituted pyrrolidine derivatives² (see applications). However, when the hydroxyl and the amino groups are neighbouring substituents on a ring an interesting conversion takes place to give a bicyclic pyrrolidine derivative³ in which the original ring is expanded by one carbon atom. In this case if the hydroxyl and amino groups are *cis* to each other in the starting material the reaction takes place with high stereoselectivity to give *cis*-fused bicyclic compound.



Mechanism

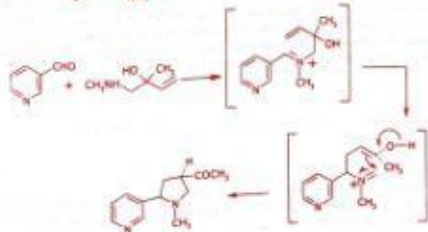
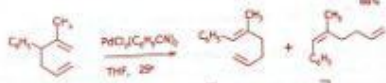
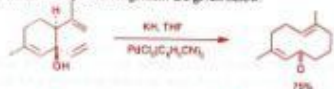
Cope rearrangement proceeds via a chair-like transition state (3), which is energetically preferred over the boat-like transition state by 3.7 kcal/mol. However, if the chair

transition state is inaccessible then the rearrangement proceeds via the boat like transition state.



Applications

Synthetic applications of Cope rearrangement are given below.

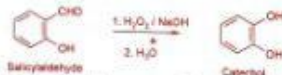


References

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2. L. E. Overman and A. F. Remaldo, Tet. Lett., 1980, 24, 5757.
3. N. Blüher, M. Malacris and J. Goss, Tet. Lett., 1983, 24, 1157.
4. L. E. Overman, M. Kakimoto, M. E. Okazaki, and G. P. Meier, J. Am. Chem. Soc., 1983, 105, 6622.
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6. Woon E. Doering, W. R. Roth, Tetrahedron, 1962, 18, 67.
7. E. Vogel, Liebigs Ann., 1958, 613, 1.
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5.26 Dakin reaction

The replacement of an aldehyde or acetyl group in phenolic aldehydes or ketones by a hydroxyl group by means of hydrogen peroxide in presence of dilute sodium hydroxide is known as **Dakin reaction**. In this case a hydroxyl must be in *ortho* or *para* to the carbonyl substituent. For example, salicylaldehyde is converted into catechol by the action of alkaline hydrogen peroxide.



For mechanism and applications see sec. 6.3.3.

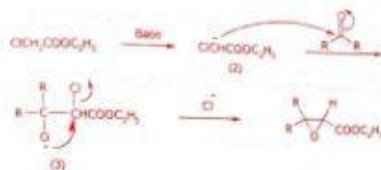
5.27 Darzens glycidic ester condensation (epoxide)

When condensation of aldehydes or ketones with α -haloester takes place in the presence of a base, α,β -epoxy esters called glycidic esters¹ are obtained. These glycidic esters are useful intermediates for the synthesis of aldehydes or ketones. The base used in this reaction is potassium *tert*-butoxide (a hindered base) to avoid the S_N2 displacement of the chloride. For example, ethyl chloroacetate on condensation with acetophenone in the presence of base produces α,β -epoxy ester (1).

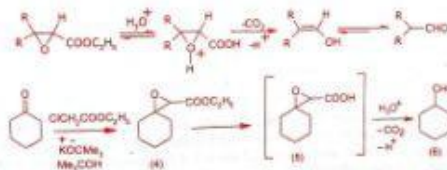


Mechanism

The reaction involves the addition of the carbanion (2) to the carbonyl group of aldehyde or ketone to give an oxyanion (3). The displacement of the halide ion takes place by an S_N2 reaction.

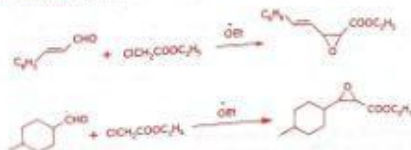


The glycidic ester obtained by above method on alkaline hydrolysis gives glycidic acid, which undergoes decarboxylative rearrangement in presence of acid to give an aldehyde or a ketone. The overall process therefore involves the addition of one more carbon atom, as aldehyde, to a carbonyl group, i.e. an aldehyde (RCHO) is converted to a longer chain aldehyde homologue (RCH_2CHO) and a ketone (R_2CO) is converted to a longer chain ketone (R_2CHCHO). This is known as chain extension reaction. For example, cyclohexanone on reaction with ethyl chloroacetate in presence of tert-butoxide yields glycidic ester (4). Hydrolysis of (4) gives epoxy acid (5), which on decarboxylation produces cyclohexane carboxaldehyde (6).



Applications^{1,2}

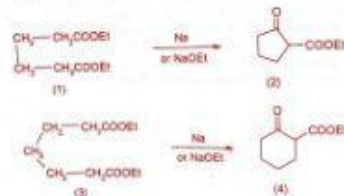
Some important applications are given below.



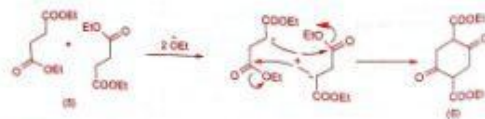
- References
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 2. R. H. Hunt, L. J. Chinn and W. S. Johnson, Org. Synth., 1963, 37, 459.
 3. H. Achenbach and J. Winkler, Tet. Lett., 1979, 1579.
 4. A. Koenig, E. Large and A. Wesselsbohm, C.A., 1939, 28, 2367.

5.28 Dieckmann condensation

It is an intramolecular **Claisen condensation** and is useful for the preparation of cyclic β-keto-esters. Diesters of C_6 and C_7 dibasic acids give good yields of cyclic β-keto-esters. Thus, ethyl esters of adipic and pimelic acids (1 and 3) give 1-carboethoxycyclopentanone (2) and 2-carboethoxycyclohexanone (4), respectively.



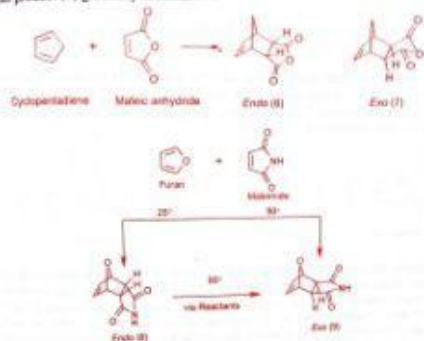
The diesters of short chain dibasic acids due to strain react differently to form cyclohexanediones by intermolecular condensation and cyclisation. For example, ethyl succinate (5) forms cyclohexane-2,5-dione-1,4-dicarboxylic ester (6) in presence of sodium or sodium ethoxide.



Mechanism

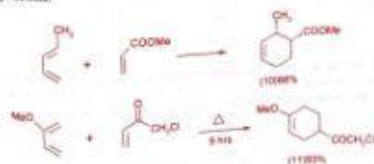
The mechanism involves the intramolecular attack of initially formed enolate anion at the carbonyl group of the other ester group. The expulsion of ethoxide anion (EtO^-) leads to the formation of β-ketoester. Which on hydrolysis, followed by decarboxylation is converted into cyclic ketone.

The reaction of cyclopentadiene with maleic anhydride may form a product with two orientations (i.e., *endo* or *exo*). In this case and most other cases the thermodynamically less stable *endo* product (6) predominates and thermodynamically more stable *exo* product (7) is formed in 1-2% yield. However, reaction of furan with maleimide leads to thermodynamically more stable *exo* product (9). In this case the initially formed kinetically favoured *endo* product (8) dissociates at moderate temperature and more stable *exo* product (9) gradually accumulates.

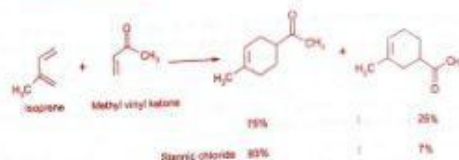


Regiochemistry

1-Substituted dienes usually give a mixture,⁷ in which 1,2-product (10) predominates. Similarly, 2-substituted dienes give a mixture in which 1,4-product (11) predominates. The yield of *para* product can be increased, when the reaction is carried out in the presence of stannic chloride (catalyst) as illustrated by the reaction of isoprene with methyl vinyl ketone.⁸

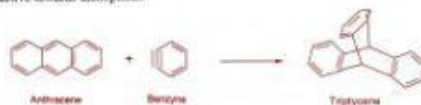


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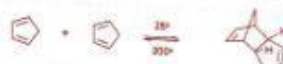
Dienes and dienophiles

A variety of dienes and dienophiles can be used in Diels-Alder Reaction (see Application). Aromatic compounds act as dienes, for example anthracene reacts with benzyne to give triptycene.⁹ But benzene, naphthalene and phenanthrene are very unreactive towards dienophiles.



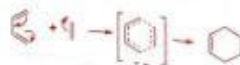
In this reaction, the reactivity increases by the presence of an electron-releasing group (R) in the diene. Thus, isoprene ($\text{CH}_2=\text{C}(\text{CH}_3)\text{CH}=\text{CH}_2$) is more reactive than butadiene. On the other hand, reaction rates are increased when the electron-withdrawing group (X) is conjugated with multiple bond in the dienophiles such as cyano, nitro, or carbonyl. Hence, maleic anhydride is a very potent dienophile because it has two carbonyl groups adjacent to the double bond.

The reaction is reversible and is subject to acid catalysis. A typical example of *retro* Diels-Alder reaction is generation of two equivalents of monomeric cyclopentadiene at heating cyclopentadiene dimer at 200°.



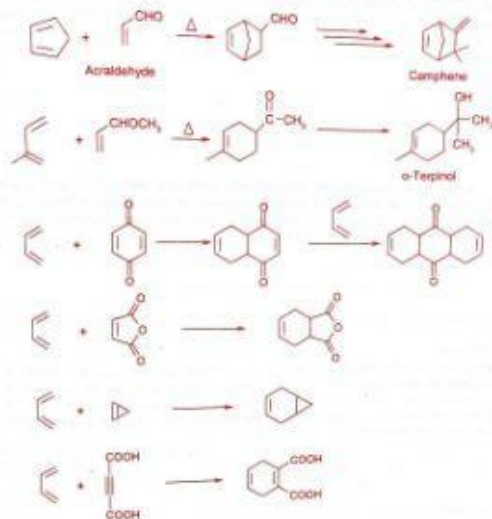
Mechanism

It is believed that the thermal Diels-Alder reaction is a concerted addition. In the cyclic transition state, the bond-formation and bond-breaking takes place simultaneously, but mechanism⁶.



Applications¹⁻⁴

Diels-Alder reaction has been used as an important step in the synthesis of various natural products such as polycyclic hydrocarbons, α -terpineol, camphene, anthranidine etc.

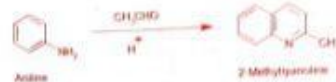


References

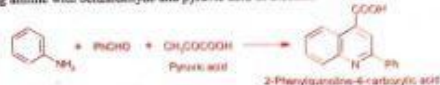
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2. J. S. Mink and J. W. Ragotzke, *J. Am. Chem. Soc.*, 1948, 70, 2502.
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5.30 Doebner-Miller synthesis

This is a modification of **Skraup synthesis** of quinolines (see sec. 5.85) and consists in heating primary aromatic amine and aldehyde with sulfuric acid. In this synthesis glycerol is replaced by two molecules of aldehydes. For example, aniline on heating with acetaldehyde (paraaldehyde) and hydrochloric acid gives 2-methylquinoline (quinoline).

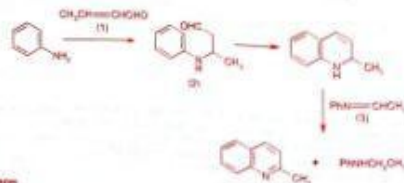


The reaction of aromatic amines with aromatic aldehydes and pyruvic acid to give cinchoninic acids is known as Doebner synthesis of quinoline-4-carboxylic acids (cinchoninic acids). For example, synthesis of 2-phenylquinoline-4-carboxylic acid² by heating aniline with benzaldehyde and pyruvic acid in alcohol.



Mechanism

The α,β -unsaturated aldehyde (1), initially formed from two molecules of aldehydes by acid-catalysed aldol condensation, reacts with aniline to give (2). Its cyclisation in presence of strong acid and dehydration yields quinoline homologue. It is believed that the oxidative step is brought about by the action of Schiff base (3) produced *in situ* (from aniline and aldehyde).

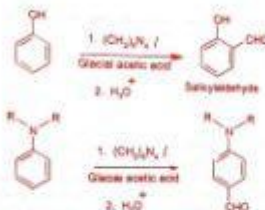


References

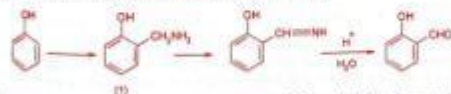
1. A. A. Morton, *The Chemistry of Heterocyclic Compounds*, McGraw-Hill, Inc., New York, N.Y., 1946, 263; Campbell and Schaffner, *J. Am. Chem. Soc.*, 1945, 67, 86.
2. O. Doebner, *Ann.*, 1887, 242, 265; *Ber.*, 1887, 20, 277; 1894, 27, 352, 2620; F. W. Bergmann, *Chem. Revs.*, 1944, 35, 156.

5.31 Duff reaction

Formylation of phenols or amines with hexamine is the **Duff reaction**.¹ The reaction involves *ortho* or *para* formylation of phenols or *para* formylation of aromatic amines with hexamethylenetetramine in presence of an acid catalyst. The phenol is heated with hexamethylenetetramine in presence of glycerol and boric acid or acetic acid at 150–160°. The *o*-hydroxybenzaldehyde is formed by acidification and steam distillation in 15–20% yield.

**Mechanism²**

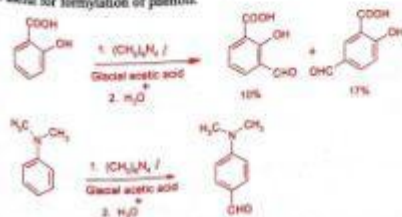
The reaction proceeds via initial aminoalkylation to form (1), which on dehydrogenation, followed by hydrolysis gives final product, salicylaldehyde.



Hexamethylenetetramine is a crystalline oligomer of formaldehyde and ammonia, which is used as a convenient source of formaldehyde.

Application

Due to low yields this reaction is not much used. Instead Reimer-Tiemann reaction is more useful for formylation of phenols.



5.32 Enamine reaction



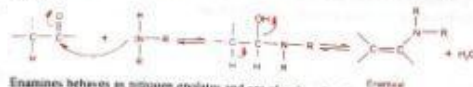
William E. Smith in 1972 found that when CF_3COOH is used as a catalyst, better yield of the product is obtained.

References:

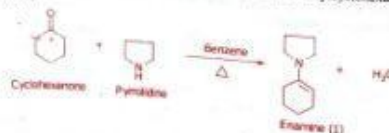
1. J. C. Duff, E. J. Bolls, J. Chem. Soc. 1912, 1917, 1934, 1935, 1941, 1947, 1948, 278; L. N. Engelen, Chem. Rev. 1948, 28, 240.
2. Ogata, Kurokawa and Sugita, Tetrachloride, 1968, 24, 5001.

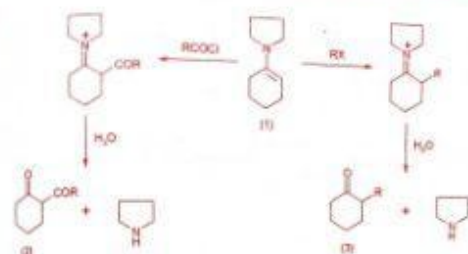
5.32 Enamine reaction

The enamine reaction was introduced by **Stork** and his coworkers¹ and is widely used in organic synthesis. Enamines are α,β -unsaturated amines and are obtained by the reaction² of an aldehyde or ketone having α -hydrogen with a secondary amine in presence of a dehydrating agent (such as, catalytic amount of toluene-*p*-sulfonic acid). The most common amines used are pyrrolidine, morpholine and piperidine. The reaction is reversible but the equilibrium is shifted to the product side by the removal of water.

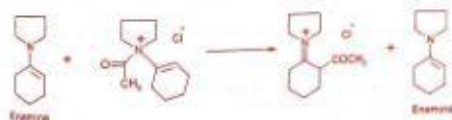


Enamines behave as nitrogen enolates and are closely related to the enolates derived from ketones in their reactions with acyl halides³, alkyl halides and α,β -unsaturated compounds⁴. Thus, enamines act as useful intermediates for the alkylation or acylation of aldehydes or ketones at α -position and the method is known as **Stork enamine synthesis** (see sec. 2.9.2). For example, the enamine (1) obtained from cyclohexanone and pyrrolidine can be acylated and alkylated followed by hydrolysis respectively.

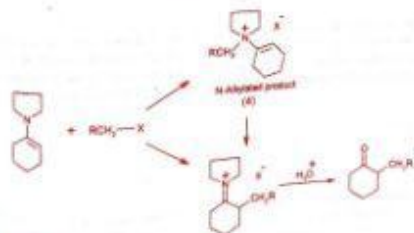




It is believed that in some cases the acylation takes place on the nitrogen. However, the N-acylated product is unstable and instead acts as an acylating agent. Thus, the yield of C-acylated product is high.



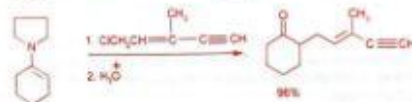
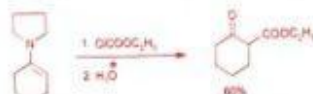
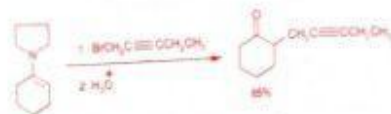
It is believed that in some cases the alkylation also takes place on the nitrogen to give (4) and the C-alkylated product is formed on rearrangement of (4).



Applications

Important synthetic applications of enamine reaction are described below:

5.3.2 Organic Reaction Mechanisms



References

1. G. Stork, R. Terrell and J. Samoshkovich, *J. Am. Chem. Soc.*, 1954, 76, 2029; J. W. Whitesell and M. A. Whitesell, *Synthesis*, 1983, 517; Mickson, *Tet.*, 1982, 58, 1975.
2. G. Stork, A. Brizzolani, H. Landman, J. Samoshkovich and R. Terrell, *J. Am. Chem. Soc.*, 1963, 85, 207.
3. T. Inukai, R. Yoshizawa, *J. Org. Chem.*, 1967, 32, 404.
4. W. R. N. Williamson, *Tetrahedron*, 1958, 1, 314.
5. Elvik, *Bull. Soc. Chem. Fr.*, 1969, 903.

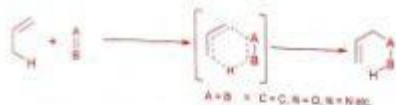
5.3.3 Ene reaction

It involves the addition of an olefin having an allylic hydrogen (ene) to a compound having a double bond (C=C, C=O, N=N, called the enophile) with the formation of a new σ bond to the terminal carbon of the allyl group. This is followed by the 1,5-migration of the allylic hydrogen and subsequent change in the position of allylic double bond.¹



Mechanism

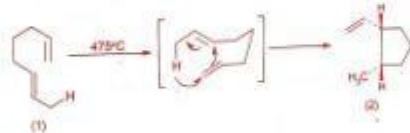
It is a 6 π -electrons electrocyclic reaction. The activation energy is greater and higher temperature is required than in most Diels-Alder reactions. There are evidence which support that the reaction proceeds by a concerted mechanism and involves the cyclic six-membered transition state.



The reaction is reversible, thus, decomposition of 1-pentene at 400°C gives ethylene and propylene. As in case of Diels-Alder reaction, *endo* addition is also favoured in ene reaction.

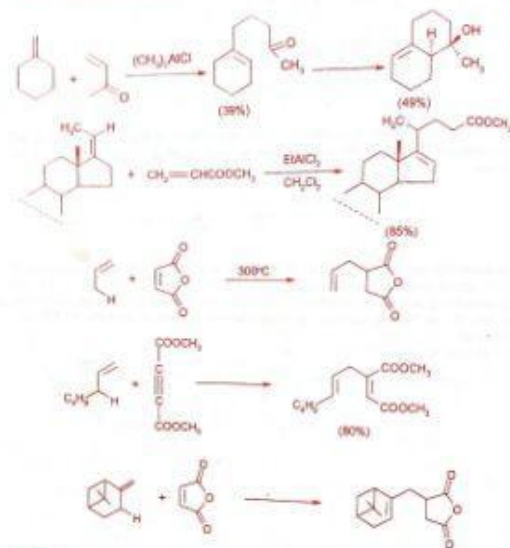


Intramolecular ene reaction⁷ is also possible, for example, 1,6-diene (1) on heating at 475°C forms five-membered ring derivative (2). However, 1,7-diene (3) forms six-membered ring product (4) and reaction requires usually higher temperature. 1,6-Dienes of type (5), on heating undergo intramolecular ene reaction to give spiro(5,4)decane system (6).



Applications^{8,9}

Some important applications are given below:

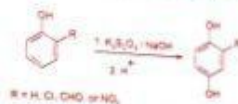


References

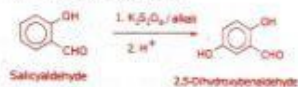
1. K. Alder, P. Pascher, A. Schmitz, Ber., 1947, 76, 27.
2. W. D. Huthman, V. C. Sullivan, D. Ems, J. Am. Chem. Soc., 1958, 80, 5455.
3. B. S. Sander and T. A. Deutsch, J. Org. Chem., 1982, 47, 741.
4. A. D. Basile, D. E. Burger, S. G. Desmar, P. M. Movilich and M. R. Ukolovic, Helv., 1981, 54, 1682.

5.34 Elbs persulfate oxidation

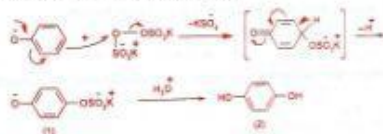
Phenols undergo oxidation with potassium persulfate¹ in alkaline solution and reaction is called **Elbs persulfate oxidation**. In this reaction a monohydric phenol is oxidised to dihydric phenol by alkaline potassium persulfate. Normally -OH group goes to the *para* position and hydroquinone derivative is formed. However, if the *para* position is blocked, the -OH group goes to *ortho* position and a catechol derivative is formed.



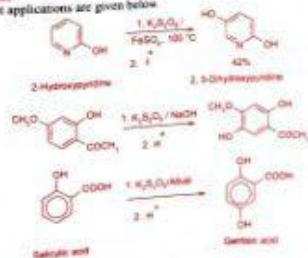
For example, 2,5-dihydroxybenzaldehyde is obtained by the oxidation of *o*-hydroxybenzaldehyde with alkaline potassium persulfate. The reaction is carried out by adding dropwise aqueous potassium persulfate and alkali solution simultaneously through two dropping funnels to a solution of *o*-hydroxybenzaldehyde in alkali solution. The solution is then acidified with HCl.

**Mechanism²**

The mechanism is proposed by Behman *et al* in 1963 and the initially formed persulfate (1) is hydrolyzed to the hydroquinone (2).

**Applications³**

Some important applications are given below.

**References**

1. E. Ebs, *J. Prakt. Chem.*, 1893, 48, 179; S. M. Sohma, *Chem. Rev.*, 1951, 97, 49.
2. W. Baker, C. N. Brown, *J. Chem. Soc.*, 1948, 2303.
3. E. J. Bergman, *J. Am. Chem. Soc.*, 1958, 80, 3717.

5.35 Etard reaction

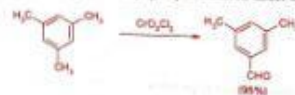
The oxidation of aromatic methyl groups to aldehydes with chromyl chloride (CrO_2Cl_2) is known as Etard reaction.¹



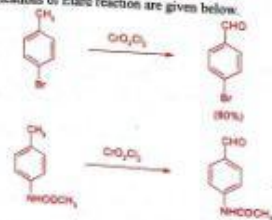
In this reaction chromyl chloride (CrO_2Cl_2) forms a complex with the hydrocarbon, which is decomposed into aldehyde by treatment with water. A solution of chromyl chloride in carbon disulfide or carbon tetrachloride is carefully added to hydrocarbon at room temperature.² The addition product thus formed is decomposed to give the aldehyde, which is removed by distillation to avoid further reaction.



In polymethyl compounds only one methyl group is oxidised under normal conditions.

**Applications**

Some important applications of Etard reaction are given below.





References

1. A. E. Bond. *Comp. Rend.*, 1880, 90, 534; *Ann. Chim. Phys.*, 1881, 22, 218; E. Bisagni, *Bull. Soc. Chim. It.* 1948, 637.
2. Law and Perkins, *J. Am. Chem. Soc.*, 1944, 64, 25.

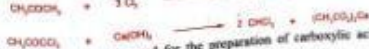
5.36 Haloform reaction

The haloform reaction,¹ also known as Lieben iodoform reaction², consists in the cleavage of methyl ketones (CH_3COR), acetaldehyde, ethanol and secondary methyl carbinols ($\text{CH}_3\text{CH}(\text{OH})\text{R}$) with halogens (mostly iodine) and base to give haloforms (iodoform, if iodine is used) and salt of carboxylic acids. Haloform reaction is specific for methyl ketones and alcohols oxidisable to methyl ketones e.g., ethanol, isopropyl alcohol etc. Thus, haloform reaction constitutes a classical test for methyl ketones and methyl carbinols.



The reaction is carried out by dissolving the compound in dioxane and first adding dilute sodium hydroxide and then a slight excess of iodine in potassium iodide solution. This is then followed by slight warming and finally adding water. If the compound contains the free methyl group, iodoform is precipitated. When a methyl ketone is treated with sodium hypiodite solution (or iodine and sodium hydroxide), iodoform and sodium salt of carboxylic acid is formed. Similarly, a methyl ketone on treatment with sodium hypobromite and sodium hypochlorite yields bromoform and chloroform, respectively, and the general process is called the haloform reaction.

A typical example is the preparation of chloroform by heating ethanol or acetone with bleaching powder, or with chlorine and alkali.

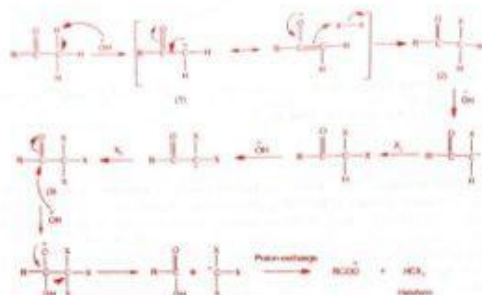


Thus, haloform reaction can be used for the preparation of carboxylic acids by the oxidative cleavage of methyl ketones.

Mechanism

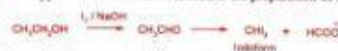
The base abstracts the α -hydrogen from ketone to produce enolate anion (1), which is halogenated to give the α -halomethyl ketone (2). Further halogenation of (2), followed

by cleavage of the resulting trihaloketone (3) yields the haloform and salt of carboxylic acid.

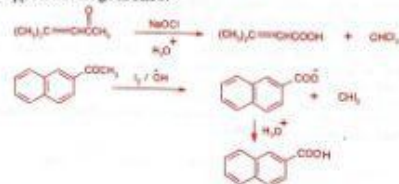


Applications

An important application of haloform reaction is the preparation of iodoform.



Some other applications are given below.



References

1. A. Lieben, *Ann. (suppl.)*, 1870, 7, 218; R. C. Fuson, B. A. Bull. *Chem. Rev.*, 1954, 25, 275.
2. D. A. Evans, J. V. Nelson, E. Vogel, T. R. Taber, *J. Am. Chem. Soc.*, 1981, 103, 3099.

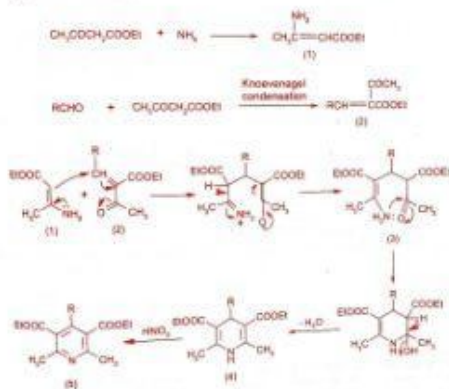
5.37 Hantzsch pyridine synthesis

The Hantzsch synthesis of pyridine¹ involves the condensation of a β -dicarbonyl compound (two molecules) with an aldehyde (one molecule) in presence of ammonia.

(one molecule). The resulting dihydropyridine derivative is dehydrogenated with an oxidizing agent to the corresponding pyridine derivative.

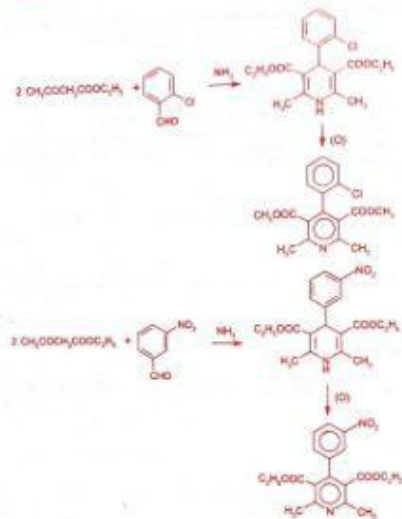
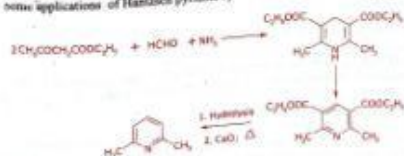
Mechanism

The reaction mechanism depends on the reaction conditions. The reaction is believed to involve **Michael type addition** of β -amino- α,β -unsaturated carbonyl compound (1, formed from β -keto ester and ammonia) to alkylidene-1,3-dicarbonyl compound (2, formed from β -keto ester and aldehyde). The condensation of (1) and (2) gives the intermediate (3), which cyclises to dihydropyridine (4). Oxidation of (4) gives pyridine derivative (5).



Applications

Some applications of Hantzsch pyridine synthesis are given below:



References

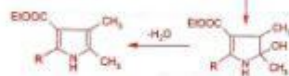
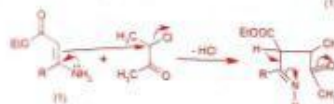
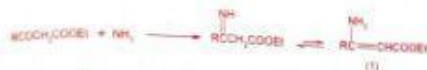
1. A. Hantzsch, Ann, 1882, 217, 1, 72; Ber., 1885, 18, 1744; Ber., 1886, 19, 289.
2. A. Sinner and S. M. McElvain, Org. Synth., Coll. Vol II, 1943, 214.
3. A. P. Phillips, J. Am. Chem. Soc., 1949, 71, 4093.
4. Y. Watanabe, K. Shiota, T. Hirohiko and S. Ozaki, Synthesis, 1983, 761.

5.38 Hantzsch pyrrole synthesis

It deals with the synthesis of pyrrole derivatives¹ by the reaction of β -keto-esters with α -chloroketones in the presence of ammonia or primary amine.

Mechanism

It involves the formation of intermediate β -amino- α,β -unsaturated ester (1) (from β -keto ester and ammonia), which on reaction with α -chloroketone, followed by cyclisation and dehydration gives pyrrole derivative.

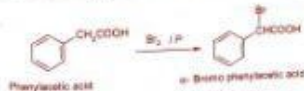


References

1. A. Hantzsch, Ber., 1890, 23, 1474.

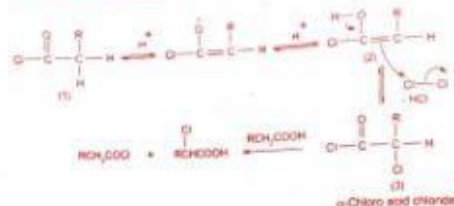
5.39 Hell-Volhard-Zelinsky reaction (HVZ reaction)

α -Chloro or bromocarboxylic acids can be prepared by the action of chlorine or bromine on monocarboxylic acids having α -hydrogen in presence of small amount of red phosphorus. This is known as **Hell-Volhard-Zelinsky reaction**.¹ The reaction is illustrated below for the preparation of α -bromophenylacetic acid² from phenylacetic acid.



Mechanism

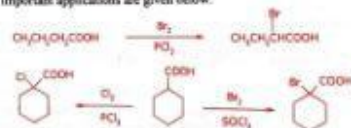
The phosphorus trihalide, which is formed by the action of phosphorus on halogen, acts as a catalyst for the initial conversion of carboxylic acid into acid halide (1). It undergoes as a catalyst for the initial conversion of carboxylic acid into acid halide (1). Halogenation of acid halide halogenation in the α -position via its enol tautomer (2). Halogenation of the enol takes place much more readily due to greater acidity of α -H atom because of the inductive effect of both the carbonyl group and halogen atom. Halogenation of the enol (2) with X_2 gives an isolable α -halo acid and the acid halide. The acid halide continues the reaction.



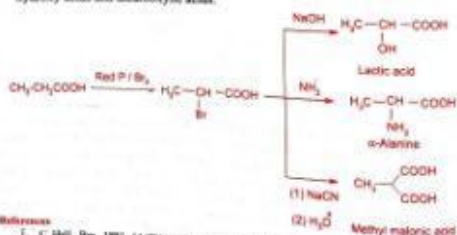
The reaction is not applicable for the preparation of α -iodo or α -fluorocarboxylic acids.

Applications^{3,4}

Some important applications are given below.



The α -haloacids are important intermediates for the synthesis of α -amino acids, α -hydroxy acids and dicarboxylic acids.

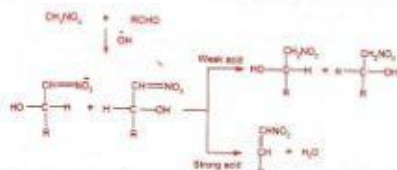


References

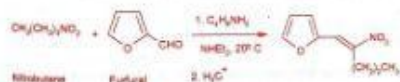
1. C. Hell, Ber., 1891, 14, 891; V. Volhard, Ann., 1881, 262, 341; N. Zelinsky, Ber., 1887, 20, 2028.
2. L. Cuppen and L. McAdams, Org. Syn., Coll. Vol. II, 1955, 35, 31.
3. C. F. Ward, J. Am. Chem. Soc., 1922, 44, 1164.
4. H. Kwart and F. V. Sotiri, J. Am. Chem. Soc., 1964, 86, 5496.
5. J. C. Little, A. R. Sessio, Y.-L. C. Tseng, T. E. Zuretti, J. Am. Chem. Soc., 1969, 91, 7098.

5.40 Henry reaction

Nitroalkanes having α -hydrogen atom undergo aldol type condensation with aldehydes in the presence of base to give β -hydroxy nitro compounds and the reaction is known as **Henry reaction**¹. When aromatic aldehydes are condensed with nitroalkanes in the presence of base, α,β -unsaturated nitro compounds are produced directly. For example, benzaldehyde and nitromethane in the presence of base give α,β -unsaturated compound (nitrostyrene).



Similarly, reaction of nitrobutane with furfural² in the presence of base, followed by hydrolysis gives 82% yield of 2-substituted furan derivative.

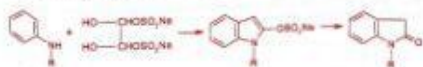


References

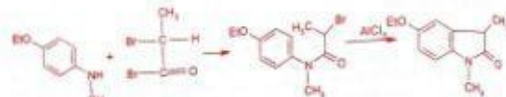
1. H. Henry, *Compt. Rend.*, 1895, 120, 1265; J. Kastle, *U.S. Pat.* 2, 151, 573 (1939); *CA.*, 1939, 33, 5081; H. B. Han and E. F. Riley, *Chem. Rev.*, 1943, 32, 408.
2. H. B. Han, A. G. Suss, R. L. Heider, *J. Org. Chem.*, 1950, 15, 8.

5.41 Hinsberg oxindole synthesis

This is the most important method for the synthesis of oxindoles¹ from secondary arylamines and sodium bisulfite addition compound of glyoxal.

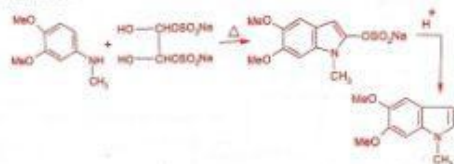


Oxindoles are also obtained from secondary arylamines by reaction with α -haloacyl halides (Stille)².



Application

5,6-Dimethoxy-1-methylindole is obtained by the reaction of 4-methylaminoveratrole in ethanol with sodium bisulfite adduct of glyoxal.



References

1. O. Hinsberg, *Ber.*, 1888, 21, 110, 1892, 25, 2545, 1908, 41, 1367.
2. R. Stille, *Chem. Ber.*, 1913, 46, 3915; W. Senter, *Chem. Rev.*, 1944, 34, 396.

5.42 Hinsberg thiophene synthesis

α -Diketones on heating with diethyl thiodiacetate in presence of base provide a wide variety of thiophene derivatives.¹ This is shown by the interaction of diethyl thiodiacetate with benzil to produce diethyl 3,4-diphenylthiophene-2,5-dicarboxylate.²



Similarly, the reaction of diethyl thiodiacetate with glyoxal gives diethyl 2,5-diphenylthiophene-3,4-dicarboxylate.

References



5.44 Hofmann isonitrile synthesis (Carbonylamine reaction)

The formation of isonitriles by the reaction of primary amines with chloroform in presence of alkali is known as **carbonylamine reaction**¹. As isonitriles have extremely nauseating odour, the reaction is used as a test for primary amines.



Mechanism

The reaction occurs through the formation of dichlorocarbene ($:CCl_2$), which is produced *in situ* in basic solution.



Applications²

Dihaloacetylide is obtained by heating ethylamine with bromoform and a base.

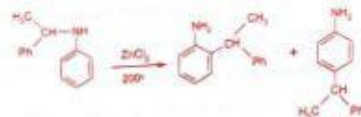
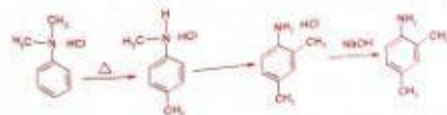


References

1. A. W. Hofmann, Ann. 1868, 146, 107; Ber., 1870, 3, 767.
2. F. A. S. Smith and N. W. Kalende, J. Org. Chem., 1959, 24, 1599.

5.45 Hofmann-Martius rearrangement

It is the thermal conversion of N-alkyl or N,N'-dialkyl aniline hydrochlorides to *ortho* and *para* alkylanilines via the intermolecular migration of alkyl groups. Thus, when *para* alkylanilines via the intermolecular migration of alkyl groups. Thus, when *N,N*-dimethylaniline hydrochloride is strongly heated, one methyl group migrates preferentially to the *para* position of the ring. The *N*-methylaniline hydrochloride so produced then undergoes migration of the remaining methyl group to the *ortho* position, since the *para* position has been blocked. This reaction is known as **Hofmann-Martius rearrangement** and is used for the preparation of homologues of aniline.



For mechanism and applications see sec. 6.5.5.

5.46 Hofmann rearrangement

When an amide is treated with bromine in alkali solution (or sodium hypobromite), it is converted to a primary amine that has one carbon atom less than the starting amide. The reaction is known as **Hofmann degradation** or **Hofmann rearrangement**. This is also referred to as **Hofmann bromamide reaction** and can be used for the preparation of alkyl, aryl or heterocyclic amines.



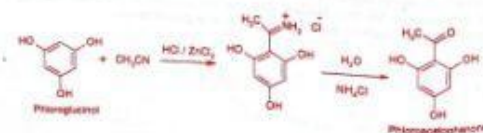
For mechanism, stereochemistry and applications see sec. 6.2.2.

5.47 Houben-Hoesch reaction

Synthesis of *ortho*-hydroxy ketones (acyl phenols) by the condensation of organic nitrile with phenols in presence of hydrogen chloride gas and Lewis acid catalyst (e.g., $ZnCl_2$, $AlCl_3$) is known as **Houben-Hoesch reaction**¹.

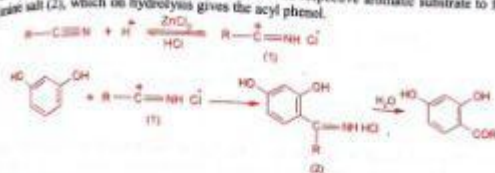


The reaction is an extension of **Gattermann formylation** and is successful only with the highly activated phenols such as di- and polyhydric phenols or their ethers. For example phloroglucinol on reaction with acetonitrile in the presence of hydrogen chloride gas and zinc chloride gives phloracetophenone.

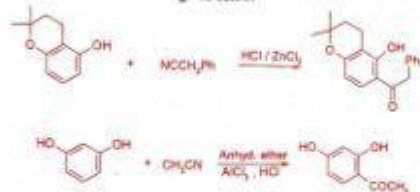


Mechanism

The mechanism of the reaction is uncertain. The accepted view is that it involves the attack of the conjugated acid of a nitrile (1) on the respective aromatic substrate to form acyl salt (2), which on hydrolysis gives the acyl phenol.

**Applications¹**

Some applications of this reaction are given below.

**References**

1. K. Biesch, Ber., 1915, 48, 1122; J. Houben, Ber., 1926, 59, 2878; R. Reger, Chem. Rev., 1961, 41, 206.
2. J. Innes, J. Org. Chem., 1963, 28, 3208.

5.46 Hunsdiecker reaction

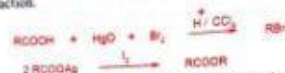
This reaction¹ is very useful for the preparation of organic halides (alkyl or aryl halides) by the thermal decomposition of silver salt of carboxylic acids in presence of halogen. This reaction is described as decarboxylative halogenation.



A typical example² is the conversion of the silver salt of cyclohexane carboxylic acid to bromocyclohexane.



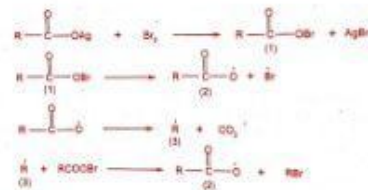
The carboxylic acid can also be converted into organic halides by reaction¹ with bromine in presence of mercuric oxide. This is known as **Cristof-Firth-modification** of Hunsdiecker reaction.



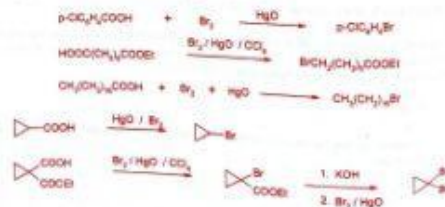
In case iodine is used with two-fold excess of the acid salt, the reaction is known as the **Simons reaction** and the product is an ester.

Mechanism

The reaction is believed to proceed by a free-radical mechanism and involves the formation of an acyl hypobromite (1). Its subsequent decomposition gives acyloxy radical (2), which loses carbon dioxide. The alkyl radical (3) thus formed abstracts bromine from the second acyl hypobromite molecule to give alkyl bromide. The last two steps are known as chain propagation steps.

**Applications^{1,2}**

Some applications of this reaction are given below.

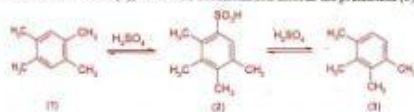


References

1. C. Hunsdiecker, H. Hunsdiecker, E. Vogel, U.S. Pat., 2, 176, 161 (1939); C.A., 1940; *J.C.*, 1940, 1665; H. Hunsdiecker, C. Hunsdiecker, Ber., 1942, 75, 291.
2. E. N. Marvell, H. Sexton, *J. Org. Chem.*, 1964, 29, 2919.
3. S. J. Cristol and W. C. Firth, *N. J. Org. Chem.*, 1981, 56, 280.
4. A. J. Meyers and M. Fleming, *J. Org. Chem.*, 1979, 44, 3405.
5. J. Mark and D. Gupta, *Org. Synth.*, V, 1973, 126.
6. I. P. Barry, G. Rossetto and J. M. Coiro, *Synthesis*, 1983, 915.
7. A. Hammond and C. Brown, *Bull. Soc. Chem. Fr.*, 1978, 299.

5.49 Jacobsen rearrangement

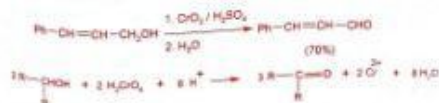
The reaction of polyalkylbenzenes with sulfuric acid to give rearranged polyalkylbenzenesulfonic acids is known as **Jacobsen rearrangement**. Since, sulfonic group can easily be removed, the reaction can be used for the isomerisation of polyalkylbenzenes. For example, durene (1) on sulfonation rearranges to piktatesulfonic acid (2), which on desulfonation affords the piktatene (3).



For mechanism and applications see sec. 6.5.3.

5.50 Jones oxidation

The primary and secondary alcohols are oxidised to aldehydes and ketones by the addition of calculated amount of chromic trioxide in dilute sulfuric acid to a solution of alcohol in acetone. This oxidation is known as **Jones oxidation**. Unsaturated secondary alcohols are oxidised to the corresponding ketones without attack to the carbon-carbon double bond. The method has proved useful for the general oxidation of primary and secondary alcohols, even in the presence of esters, ketones, amides, alkenes and tertiary alcohols. For example, cinnamyl alcohol is oxidised to cinnamaldehyde with chromic trioxide and concentrated H_2SO_4 in acetone.

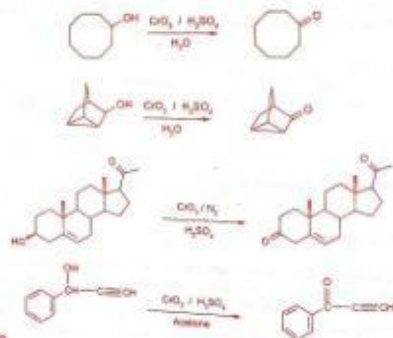


Mechanism

The mechanism proposed by Westheimer¹ is generally accepted, which involves the formation of a chromate ester. Subsequent removal of proton by an external base (water) and loss of HCrO_2^- ion yields the ketone.

Applications^{2,3}

Some important applications of Jones oxidation are given below.



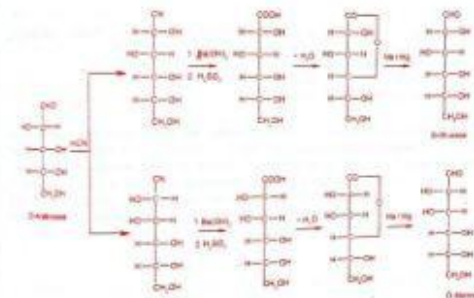
References

1. K. Bowden, I. M. Heilbron, E. R. H. Jones and B. C. L. Weedon, *J. Chem. Soc.*, 1940, 39.
2. N. F. Magn, D. G. I. Kingston, *J. Org. Chem.*, 1986, 51, 797.
3. W. A. Waters, *Quart. Rev.*, 1958, 12, 277; G. T. E. Graham and F. H. Westheimer, *J. Am. Chem. Soc.*, 1958, 80, 3030.

- ⁴ E. I. Lombroso, *Org. Synth.*, 1965, 45, 28.
⁵ Meerwald, J. Crandall and W. E. Hymans, *Org. Synth.*, 1965, 45, 77.
⁶ C. Dumas, R. R. Ugli and A. Browers, *J. Org. Chem.*, 1956, 21, 1547.

4.41 Kiliani-Fischer synthesis

This is also known as **Kiliani-Fischer cyanohydrin synthesis**¹ and is one of the most important methods of extending the carbon chain of a sugar. This method is based on the addition of hydrocyanic acid (HCN) to the carbonyl group of aldoses or ketoses to form cyanohydrins.

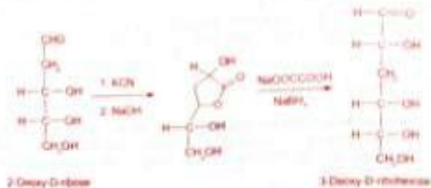


Since an additional asymmetric carbon atom is produced by the addition of hydrocyanic acid, two stereoisomeric cyanohydrins are produced. These cyanohydrins differ only in configuration about the newly introduced asymmetric carbon atom (C-2) and are, therefore, epimers. The cyanohydrins may then be hydrolyzed to carboxylic acids followed by dehydration to form γ -lactones. Reduction of γ -lactones by sodium amalgam yields 2-isomeric sugars containing one carbon atom more than that of the sugar with which the synthesis was started. The application of the Kiliani-Fischer synthesis to the production of two hexoses i.e., D-glucose and D-mannose from a pentose i.e., D-xylose is shown above.

As seen above the Kiliani-Fischer synthesis is the synthesis of C_{n+1} sugars from C_n sugars. In other words it is useful for the lengthening of the carbon chain of aldoses.

Applications: Using Kiliani-Fischer synthesis, 3-deoxy-D-ribose can be obtained from 1-deoxy-D-ribose

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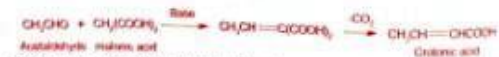


Study purpose

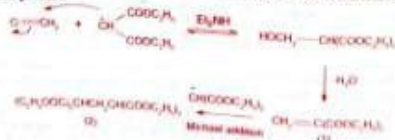
1. H. Kiliani, *Ber.*, 1885, 18, 3566; E. Fischer, *Ber.*, 1889, 22, 2204; C. S. Hudson, *Advances in Carbohydrate Chemistry*, 1945, 1, 2; D. T. Mistry, *Chem. Rev.*, 1948, 42, 234.
2. H. B. Wood, *J. Org. Chem.*, 1961, 26, 1969.

5.52 Knoevenagel condensation

The condensation of α -hydroxy aldehydes or ketones, having no α -hydrogen atom, with active methylene compounds (especially malonic ester) in presence of a very weak base like ammonia or amine (primary or secondary) is known as **Knoevenagel condensation**. However, when condensation takes place with malonic or cyanoacetic acid in presence of pyridine as a base, decarboxylation usually occurs during the condensation. This is known as **Doebner modification**.² For example, when acetaldehyde is reacted with malonic acid in presence of pyridine (base), crotonic acid is formed.



The Knoevenagel reaction is more useful with aromatic aldehydes since with aliphatic aldehydes the product obtained undergoes **Michael condensation**. This is illustrated by the preparation of triethyl propene-1,1,3,3-tetracarboxylate (2) from formaldehyde and diethyl malonate in the presence of diethylamine. The diethyl methylenemalonate (1), which is formed by the Knoevenagel reaction, undergoes Michael addition reaction to



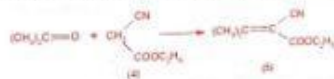
The addition to the C=C of the Knoevenagel condensation product from an aromatic aldehyde is less likely due to loss of conjugation to the aromatic system. For example, benzaldehyde reacts with diethyl malonate in presence of pyridine to give cinnamic acid in 80% yield.



(β -keto esters can be prepared directly by the Knoevenagel reaction. For example, ethyl hydrogen malonate, obtained by partial hydrolysis of diethyl ester of malonic acid, reacts with butanal, followed by decarboxylation to yield ethyl 2-hexenoate (3).

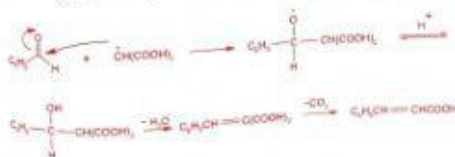


Ketones do not undergo Knoevenagel condensation with malonic ester but can react with more active cyanoacetic acid or its ester. For instance, acetone forms isopropylidene cyanoacetic ester (5) when condensed with ethyl ester of cyanoacetic acid (4).



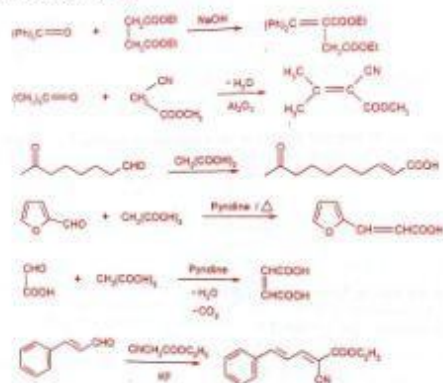
Mechanism

The Knoevenagel reaction is reversible and normally the equilibrium lies towards left and the yield of the product is low. However, Cope introduced an important procedure for shifting the reaction in benzene and removing the water formed as an azeotropic mixture in **Dean Stark apparatus**, thus shifting the equilibrium completely towards right. Such type of Knoevenagel reaction is known as **Cope-Knoevenagel Reaction**.



Applications¹⁻⁴

This reaction is of great synthetic importance because a large number of α, β -unsaturated compounds can be synthesised by using this reaction. Some applications of Knoevenagel condensation are given below.

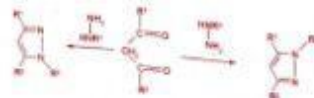


References

1. F. Knoevenagel, Ber., 1898, 31, 2596; J. R. Johnson, Org. Reactions, 1942, 1, 210.
2. O. Doebner, Ber., 1900, 33, 2140.
3. W. S. Johnson, Org. Reactions, 1951, 6, 1.
4. F. Texier-Boullet and A. Foucaud, Tet. Lett., 1962, 4977.
5. C. G. Butler, R. K. Callow and N. C. Johnson, Proc. Royal Soc., 1961, B, 255, 417.
6. Reported in the Review by G. G. Yakubov and N. E. Akhmetova, Synthesis, 1983, 173.

5.53 Knorr pyrazole synthesis

This is the synthesis of pyrazole derivatives¹ by the reaction between β -diketones and hydrazine derivatives.

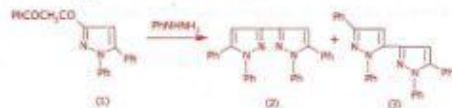


Thus, in above reaction, a mixture of isomeric pyrazoles may be obtained. Contrary to general opinion, the product is only one of the isomers, e.g., benzoylaceto- and phenylhydrazine form only 3-methyl-1,5-diphenylpyrazole. The mechanism of these condensations is uncertain. A possible pathway is as follows:

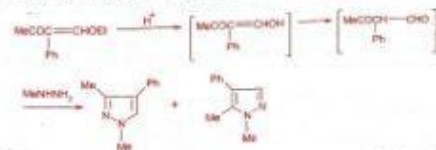


Since the phenyl group can conjugate with an adjacent carbonyl group more than methyl group, nucleophilic attack at the PhCO carbonyl group is decreased.

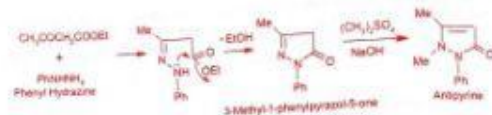
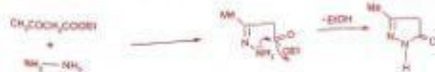
In some cases, two isomers have been isolated. For example 3- α -benzoylacetyl-1,5-diphenylpyrazole (1) reacts with phenylhydrazine to produce a mixture of 1,1',5,5'-tetraphenyl-3,5-bipyrazole (2) and 1,1',3',5'-tetraphenyl-3,5'-bipyrazole (3). In this case conjugation can occur at either end.



Instead of β -diketones, β -ketoaldehydes in the form of their vinyl ethers (enol ethers) can also be used. In this case also, a mixture of isomers may be obtained.



If β -keto-esters are used then pyrazolones are formed. For example, hydrazine and ethylacetoacetate form 3-methylpyrazol-5-one. Similarly, ethylacetoacetate on phenylhydrazine gives 3-methyl-1-phenylpyrazol-5-one. This on methylation, yields 2,1-dimethyl-1-phenylpyrazol-5-one (arizpyrine).

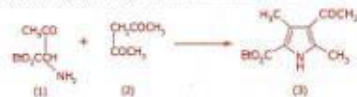


References

1. J. Koser, Ber., 180, 16, 2387; T. J. Jacobs in R. C. Elderfield, Heterocyclic Compound, 1957, 3, 46

5.54 Knorr pyrrole synthesis

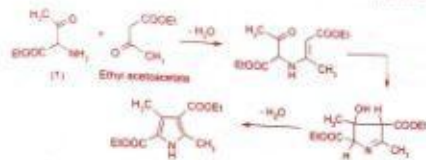
This is the synthesis of pyrrole derivatives¹ by the condensation of α -amino ketones with carbonyl compounds containing active methylene group (such as β -diketones or β -keto-esters). The reaction is illustrated by the synthesis of 3-acetyl-5-carbomethoxy-2,4-dimethylpyrrole² (3) from ethyl α -aminoacetoacetate (1) and acetylacetone (2).



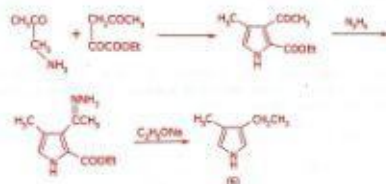
Mechanism

In this reaction, the α -amino ketone (1) is used as such or prepared *in situ*. For example, in the synthesis of 2,4-dimethyl-3,5-dicarboxypyrrole (4) from ethyl acetoacetate. The ethyl acetoacetate is first converted into oximino compound (5) on treatment with nitrous acid, which is further reduced with zinc dust and acetic acid. The resulting amino compound (1) reacts with the remaining ethyl acetoacetate to give the pyrrole derivative (4).



**Applications**

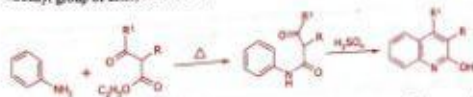
3-Ethyl-4-methyl pyrrole (6) is prepared as follows.

**References**

1. L. Knorr, Ber., 1884, 17, 1635; Ann. 1886, 236, 290; L. Knorr and H. Löss, Ber., 1902, 35, 2998; A. H. Corwin in R. C. Elderfield, Heterocyclic Compounds, 1950, 285.
2. Faber, Org. Syntheses, 1941, 21, 67.

5.55 Knorr quinoline synthesis

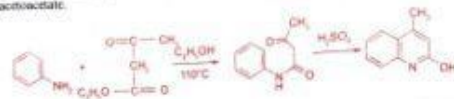
This is carried out by the condensation of β -keto-esters and arylamines at 110° . The resulting anilides on cyclisation with concentrated sulphuric acid give α -hydroxy quinolines.¹ The mechanism involves the nucleophilic attack by aniline at the carbonyl group of ester, followed by the cyclisation of the intermediate anilide.



However, at low temperature, the attack takes place at carbonyl group of ketone and final product, after cyclisation, is 4-quinolone (Conrad-Limpach synthesis).

Applications

2-Hydroxy-4-methylquinoline is obtained by the condensation of aniline and ethyl acetoacetate.

**References**

1. L. Knorr, Ann., 1886, 236, 69; 1888, 245, 357, 378.

5.56 Kolbe electrolysis reaction

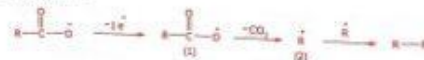
Preparation of hydrocarbons by the electrolysis of sodium or potassium salt of carboxylic acids is known as **Kolbe electrolytic synthesis**.¹ For example, potassium propionate on electrolysis affords n-butane.



Electrolysis of two different carboxylate salts leads to mixture of products.

Mechanism

The free radical mechanism is proposed for this reaction. The anodic oxidation of carboxylate anion gives alkyl radical (2) via an alkoxy radical (1), which dimerizes to yield the alkane.



This reaction is also described as electrochemical decarboxylation-dimerization via free radicals. Thus, acids are electrochemically decarboxylated to give hydrocarbon composed of two acid R groups.

Applications^{1,2}

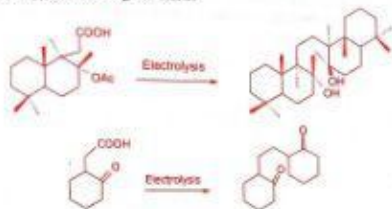
1,1,2,2-Tetraphenylethane is obtained by electrolysis of diphenyl acetic acid.



Salts of half esters of dicarboxylic acids on electrolysis give long chain dibasic esters.



Some other applications are given below.



References

1. H. Kolbe, Ann., 1849, 69, 257; B. C. L. Weedon, Quart. Rev., 1952, 6, 390.
2. M. Finkelshteyn, J. Org. Chem., 1969, 34, 156.
3. D. A. White, Org. Synth., 1963, 60.
4. E. J. Corey and R. R. Sauer, J. Am. Chem. Soc., 1963, 85, 3419.
5. G. Stork, A. Meisels and J. E. Davies, J. Am. Chem. Soc., 1963, 85, 3419.

5.57 Kolbe-Schmitt reaction

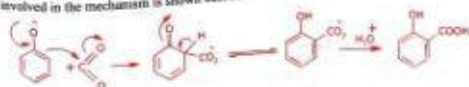
The formation of aromatic hydroxy acids by carboxylation of phenolates, mostly in *ortho* position, by carbon dioxide is known as **Kolbe-Schmitt reaction**.¹ A typical example includes the preparation of salicylic acid by the reaction of sodium phenoxide with carbon dioxide at 120 °C under pressure.



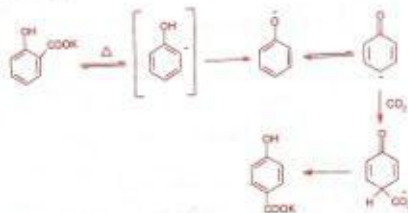
The reaction is particularly facile with dihydroxy or trihydroxy phenols.

Mechanism

The mechanism of this reaction is believed to involve the attack of carbon dioxide (an electrophile) on benzene nucleus of phenoxide ion. The sequence of reactions involved in the mechanism is shown below.

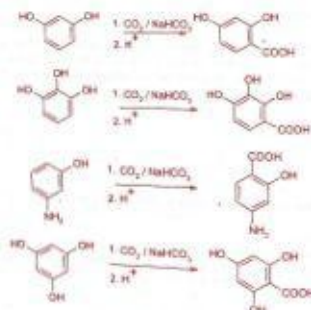


The phenoxide ion is more reactive towards electrophilic attack than phenols. Thus, it will react with weak electrophiles like carbon dioxide. Carboxylation is reversible process and *ortho* product predominates at 120 °C. However, at 230 °C the thermodynamically more stable, *para* product predominates. The carboxyl group migrates to the *para* position when potassium salicylate is heated at 230 °C.



Applications^{2,3}

Kolbe-Schmitt reaction is used industrially to prepare salicylic acid, which is a precursor in making aspirin. Synthesis of some important carboxylic acids are given below.

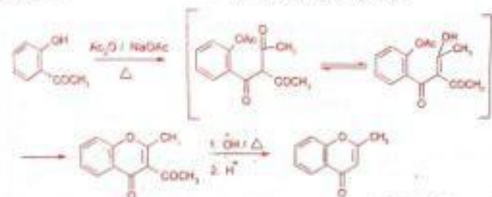


References

1. H. Kolbe, Ann., 1860, 173, 125; R. Schmidt, J. Prakt. Chem., 1865, (2)37, 397; A. S. Lader, H. Inley, Chem. Rev., 1957, 57, 583.
2. Brunner, Ann., 1907, 337, 320; Norrish, Clibborn, Org. Syn., Coll. Vol. II, 1943, 557.
3. L. Dush, J. Org. Chem., 1958, 23, 1422.

5.58 Kostanecki-Robinson acylation

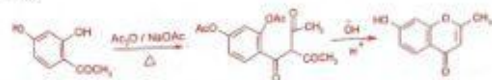
2-Hydroxyacetophenones on heating with sodium acetate and acetic anhydride give the corresponding 2-methyl-3-acetylchromones. These on hydrolysis with aqueous alkali undergo decarboxylation to afford the corresponding 2-methylchromones¹.



The reaction is carried out by heating *o*-hydroxyacetophenone with fused sodium acetate in acetic anhydride under anhydrous conditions. The 3-acetyl-2-methyl chromone thus obtained is refluxed with aqueous sodium carbonate, followed by acidification to give 2-methylchromone.

Applications

2-Methyl-7-hydroxychromone is obtained from 2,4-dihydroxyacetophenone as given below.



References

1. S. Van Kostanecki, A. Rzycki, Ber., 1901, 34, 182; C. R. Hoyer, Org. Reactions, 1954, 8, 91.

5.59 Madelung indole synthesis

Madelung synthesis¹ of indole derivatives consists of intramolecular cyclisation of an *N*-acyl-*o*-toluidines with strong base such as sodamide, sodium or potassium alkoxide at high temperature.

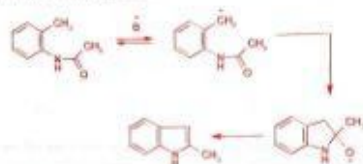


Indole itself can be synthesised by the reaction of *N*-formyl-*o*-toluidine with potassium isocyanide.



Mechanism

The mechanism of this reaction is not clear. The probable mechanism involves an intramolecular **Claisen condensation** with the elimination of water and is as follows.



Applications^{2,3}

Following indole derivatives are conveniently synthesised by the use of this method.



References

1. W. Madelung, Ber., 1912, 45, 1128; R. J. Sundberg, The Chemistry of Indoles Academic Press, 1975.
2. W. J. Boulton, V. A. Furness and V. Ullac, J. Org. Chem., 1961, 26, 4511.
3. C. F. H. Allen and J. Van Allen, Org. Synth., 1955, Coll. Vol. III, 397.

5.60 Malonic ester synthesis

These are based on the strongly activated methylene group of malonic ester, which on reaction with sodium ethoxide forms a resonance stabilised enolate ion (I). Enolate ion reacts with compounds containing reactive halogen atom (alkyl halides, acyl

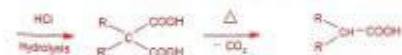
halides and α -halogen ester) to give substituted malonic ester (2). Hydrolysis and acidification of substituted derivative of malonic ester produces substituted malonic acid. This acid, loses carbon dioxide on heating and substituted acetic acid (3) is formed.



Applications¹⁻³

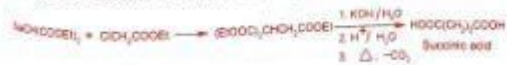
(i) Synthesis of monocarboxylic acids

The mono-sodio derivative of malonic ester undergoes an $\text{S}_{\text{N}}2$ reaction with alkyl halide to yield alkyl-substituted malonic ester. The monosubstituted malonic ester still has an active hydrogen atom. The second alkyl group (same or different) can be introduced in a similar manner. Alkaline hydrolysis of mono or disubstituted derivative of malonic ester, followed by acidification give substituted malonic acid, which on decarboxylation yields the corresponding monocarboxylic acid.



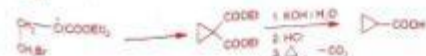
(ii) Synthesis of dicarboxylic acids

Sodium salt of diethylmalonate on reaction with ethyl chloroacetate, followed by hydrolysis, acidification and then decarboxylation gives succinic acid.

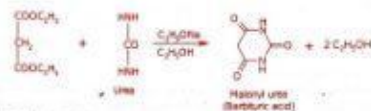


(iii) Synthesis of alicyclic compounds

Three and four-membered alicyclic compounds are synthesised from dibromides.



(iv) Synthesis of heterocyclic compounds



Similarly, barbitol can be prepared by reacting diethyl derivative of diethylmalonate with urea.

(vi) Synthesis of amino acids

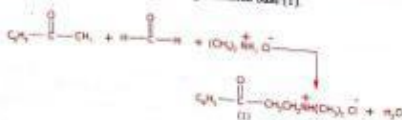


References

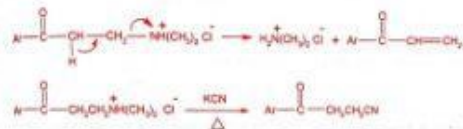
1. H. O. House, *Modern Synthetic Reactions* (W. A. Benjamin), 1972, 510-518, 756-761.
2. R. O. Riley and E. M. Stevenson, *loc. cit.*, 1974, 35, 1171.
3. J. E. McMurry and J. M. Malone, *J. Org. Chem.*, 1975, 40, 2616.

5.61 Mannich reaction

Compound containing at least one active hydrogen atom (ketones, nitroalkanes, β -keto-esters, β -cyano-acids etc.) condenses with formaldehyde and primary or secondary amine or ammonia (in the form of its hydrochloride) to give the product known as Mannich base.¹ Dimethylamine, for example, reacts with formaldehyde and acetophenone to give corresponding Mannich base (1).

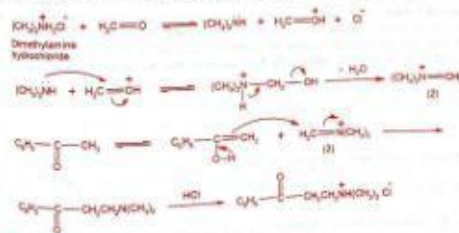


Although, formaldehyde has been most common but other aldehydes have also been used successfully. The Mannich reaction also proceeds with the other activated hydrogen compounds such as indole, furan, pyrrole and phenols. When, primary amine is used, the Mannich base formed is a secondary amine and may undergo further condensation to yield tertiary amine. The Mannich bases produced by the Mannich reaction are of great synthetic importance. Thus, Mannich base eliminates an amine hydrochloride on heating to yield α,β -unsaturated ketones. Another usefulness of Mannich bases is the replacement of dimethylamino group by nitrile group on heating with KCN.



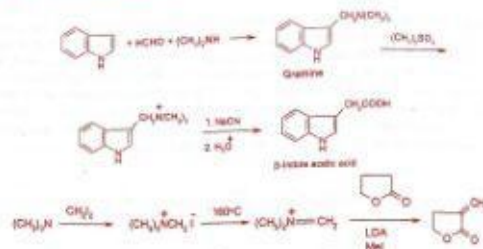
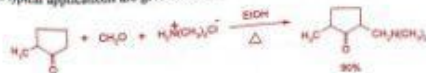
Mechanism

The reaction is believed to involve the formation of the intermediate methyleneammonium salt (2), which condenses either with enol form of the ketone (acid catalyses the conversion of keto form into enol form) or with the carbanion derived from the ketone (small amount of amine acting as base and abstracts the α -hydrogen).



Applications^{1,2}

Some typical applications are given below.



References

1. C. Mannich, W. Knoch, Arch. Pharm., 1912, 230, 647; F. F. Blake, Org. Reactions, 1942, 1, 305.
2. A. Eschenmoser, Angew. Chem. Int. Ed., 1971, 10, 330.

5.62 Meerwein-Ponndorf-Verley reduction

The reduction of aldehydes or ketones to the corresponding alcohols with aluminium alkoxides (e.g., aluminium isopropoxide) in isopropyl alcohol is known as **Meerwein-Ponndorf-Verley reduction**. Aldehydes yield primary alcohols, and ketones yield secondary alcohols. This is the reverse of **Oppenauer oxidation**. In the reduction of aldehydes and ketones, an excess of isopropyl alcohol is employed and acetone is removed from the reaction mixture by distillation so that the equilibrium is displaced to the right.



For mechanism and applications see sec. 8.1.2.

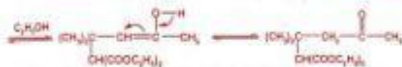
5.63 Michael addition

It is the addition reaction¹ between an α,β -unsaturated carbonyl compound and a compound with an active methylene group (e.g., malonic ester, acetoacetic ester, cyanoacetic esters, nitroparaffins etc.) in presence of a base, e.g., sodium ethoxide or a secondary amine (usually piperidine). The reaction is illustrated as given below.

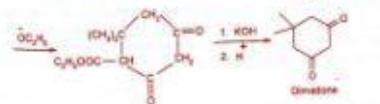
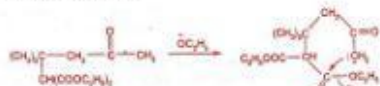


Mechanism

The mechanism of the reaction using malonic ester and mesityl oxide to give dimedone is represented below. The enolate derived from the malonic ester attacks the β -carbon atom of α,β -unsaturated compounds in conjugate addition. The resulting carbanion is stabilised by carbonyl, nitro, or nitrile group and abstracts a proton from ethanol to give the product and generate ethoxide ion. The reaction is reversible.

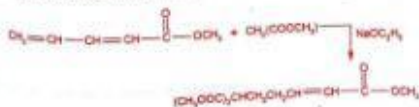


If the Michael addition is followed by an internal **Claisen condensation**, the product obtained is dimedone.



Use of Michael addition followed by aldol condensation is an important route for the synthesis of bicyclic ketones and is known as **Robinson annulation**.

Compounds containing two double bonds conjugated with a carbonyl group react with active methylene compounds to give 1,6-addition products. Thus, methyl vinylacrylate condenses with dimethyl malonate as follows.²

**Applications**

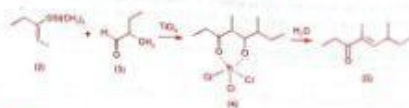
Some typical applications of Michael addition are given below.

**References**

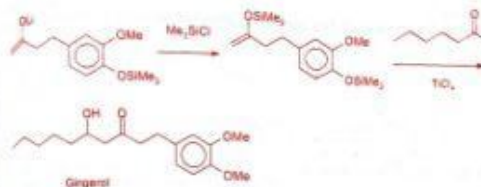
1. S. Michael, *J. Prakt. Chem.*, 1887, (2) 11, 349; E. D. Bergmann, D. Ginsburg, R. Pappo, *Org. Reactions*, 1959, 10, 179-55.
2. Kohler and Butler, *J. Am. Chem. Soc.*, 1926, 48, 1040.

5.64 Mukaiyama reaction

It is a stereoselective aldol condensation¹ in the presence of titanium tetrachloride (TiCl_4). For example, condensation of silyl enol ether (2) of 3-pentanone (1) with aldehyde (3) in the presence of TiCl_4 gives aldolate product (4), which on hydrolysis yields aldol product Manicone (5) an alarm pheromone². Other Lewis acids such as tin tetrachloride (SnCl_4) and boron trifluoride etherate ($\text{BF}_3 \cdot \text{OEt}_2$) can also be used. The required silyl enol ether is prepared by treatment of ketone with LDA, the resulting enolate is trapped with chlorotrimethylsilane to give corresponding silyl enol ether.

**Applications**

Mukaiyama reaction has great significance in the development of the aldol reaction and on other areas of organic synthesis.

**References**

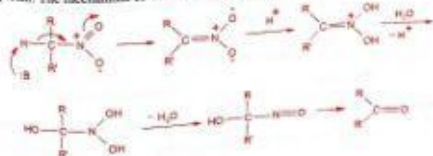
1. T. Mukaiyama, *Chem. Lett.*, 1982, 353; *J. Am. Chem. Soc.*, 1973, 95, 967; *Chem. Lett.*, 1986, 187; *Organic Reactions*, 1982, 24, 187.
2. K. Banno, T. Mukaiyama, *Chem. Lett.*, 1976, 279.

5.65 Nef reaction

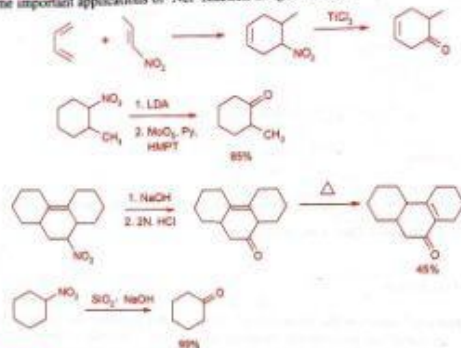
The **Nef reaction**¹ involves the formation of aldehydes and ketones from primary and secondary nitroalkanes, respectively. Nitroalkanes are first converted to their sodium salts and then hydrolyzed with sulfuric acid to give aldehydes or ketones and nitrous oxide. An example is the formation of butanal from nitrobutane. Sodium hydroxide converts nitrobutane into nitronolate, which reacts with concentrated sulfuric acid to produce butanal.

**Mechanism**

The base removes the α -hydrogen from nitroalkanes which is acidic because of strong $-I$ effect of the nitro-group and its ability to accommodate negative charge after the removal of proton. The mechanism of Nef reaction is believed to be as follows.

**Applications²⁻⁶**

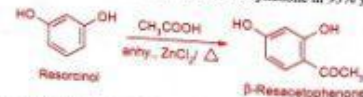
Some important applications of Nef reaction are given below.

**References**

1. J. U. Nef, *Ann.*, 1894, 280, 263; W. E. Noland, *Chem. Rev.*, 1955, 35, 137.
2. B. Weinstein, *J. Org. Chem.*, 1962, 27, 4049.
3. E. Keinan and Y. Manor, *J. Am. Chem. Soc.*, 1977, 99, 3861.
4. M. Gaboarden and H. Plinick, *Tet. Lett.*, 1981, 22, 5235.
5. J. Wakana, T. Sotoda and S. Wakayoshi, *Synthesis*, 1983, 763.
6. J. E. McMurry and J. Mohr, *J. Org. Chem.*, 1973, 38, 4367.

5.66 Nencki reaction

The ring acylation of polyhydric phenols with acylating acids in presence of anhydrous zinc chloride is known as **Nencki reaction**.¹ The monohydroxy phenols give poor yields. Resorcinol condenses with acetic acid to form β -resacetophenone in 93% yield.



β -Resacetophenone can be conveniently obtained by the Houben-Hoesch reaction (sec. 5.47).

Applications

Galaxerophenone is obtained from pyrogallol.

**References**

1. M. Nencki, N. Sieber, *J. Prakt. Chem.*, 1881, 23, 147; M. Nencki and W. Schmidt, *J. Prakt. Chem.*, 1881, 23, 546; M. Nencki, *J. Prakt. Chem.*, 1882, 25, 275.

5.67 Norrish type cleavage

Norrish type I reaction: This reaction¹ occurs by the fragmentation of the carbon-carbon bond adjacent to the carbonyl group. The cleavage (α -cleavage) originates from the carbonyl n, π^* state and proceeds through the homolytic cleavage of one of the carbonyl alkyl groups (i.e., photochemical cleavage at the carbon-carbon bond adjacent to the carbonyl group) as the basic photochemical reaction.



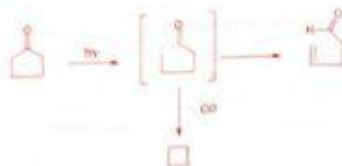
When carried out in the gaseous phase above 100° , the basic reaction is followed by secondary process i.e., decarbonylation leading to the formation of an alkane and carbon monoxide. Acetone, for example, photodissociates to methyl radical and the acyl radical. Fragmentation of acyl radical leads to another equivalent of methyl radical and CO.



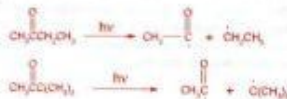
A typical application of Norrish type I cleavage is described below.



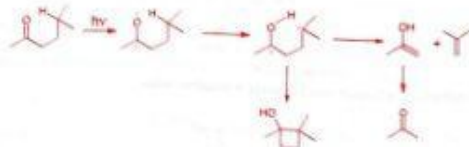
In case of cyclic ketones like cyclopentanone, a diradical is obtained by the photochemical α -cleavage, which then reacts in different ways¹ as shown below.



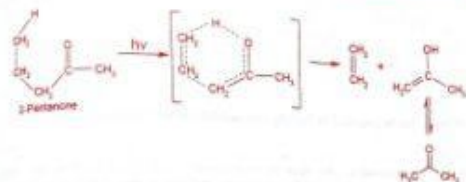
In the case of unsymmetrical ketones, the α -cleavage occurs in such a way so as to give the more stable of the two possible free radicals. The carbonyl group is the chromophore which is photoactivated in an $n \rightarrow \pi^*$ transition and the excitation energy of the lowest triplet state of simple alkyl ketones is quite close to the energy required for homolytic cleavage of the α -carbon-carbon bond.

**Norrish type II cleavage**

This reaction originates from the n, π^* excited state of aldehydes and ketones. It involves intramolecular γ -hydrogen abstraction followed by cleavage of the resulting biradical to an olefin and an enol which tautomerises to the carbonyl compound. The biradical can also cyclise to give cyclobutanol as a side product.

**Mechanism**

The hydrogen abstraction which results in the formation of alkene and aldehyde or ketone (via the enol form) involves a six-center cyclic transition state. For example, 2-pentanone gives ethene and acetone.



References

1. K. G. W. Norrish, C. H. Bamford, *Nature*, 1936, 138, 1016; 1937, 140, 395; J. D. Coyle, R. A. J. Carlos, *Chem. Soc. Rev.*, 1972, 1, 465; P. J. Wagner, *Accts. Chem. Rev.*, 1971, 4, 368
2. R. P. Wayne, *Principles and Applications of Photochemistry*, Oxford Univ. Press, Oxford, 1988, p. 53.

5.68 Oppenauer oxidation

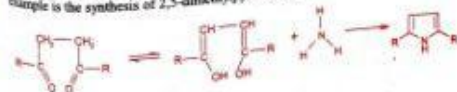
The **Oppenauer oxidation** of secondary alcohols with aluminium alkoxide (aluminium isopropoxide or aluminium *t*-butoxide) to the corresponding ketones is the reverse of **Murwin-Poundorf-Verley reduction**. It has been widely used in the steroid synthesis particularly for the oxidation of allylic secondary hydroxyl groups to α,β -unsaturated ketone.



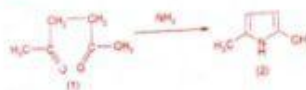
For mechanism and applications of Oppenauer oxidation see sec. 8.1.3.

5.69 Paal-Knorr synthesis

The synthesis of pyrrole derivatives by heating 1,4-dicarbonyl compounds with ammonia, primary amines or hydrazines is known as **Paal-Knorr synthesis** of pyrroles¹. An example is the synthesis of 2,5-dimethylpyrrole (2) from hexane-2,5-dione (1).



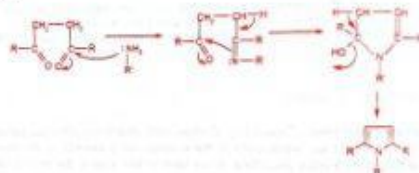
5.62 Organic Reaction Mechanisms



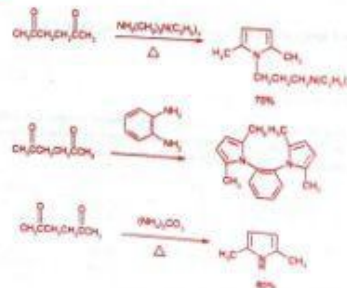
Pyrrole itself can be prepared by heating succinaldehyde with ammonia.

Mechanism

The reaction is believed to take place by the nucleophilic attack of the NH_3 (or NH_2R) at the carbonyl group, followed by cyclization and then aromatization to give pyrrole derivative.



The reaction has limited use because of the availability of the dicarbonyl compounds. A convenient method for the synthesis of pyrrole is that of **Knorr synthesis** (see sec. 5.58).

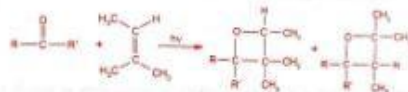
Applications^{2,3}

References

1. C. Paul, Ber., 1881, 18, 167; L. Kaur, Ber., 1885, 18, 209.
2. Ng, Ph. Shu-Ho and Ng, D. Xiang, J. Org. Chem., 1955, 20, 619.
3. D. N. Young and C. F. Allen, Org. Synth., 1956, 16, 25.

5.70 Paterno-Buchi reaction

This is a very convenient method for the synthesis of four-membered ether rings (oxetanes) involving the photochemical cycloaddition of carbonyl compounds (aldehydes or ketones) and olefins.

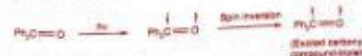


Mechanism

The reaction involves a cycloaddition of an electronically excited carbonyl group (triplet state of the carbonyl group) with the ground state of olefin. This photoaddition occurs more efficiently when the triplet state has the n, π^* configuration rather than π, π^* configuration.

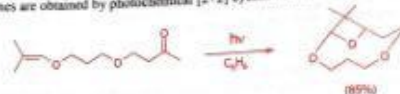


As a first step, the excited carbonyl compound (triplet) adds through its oxygen atom to the olefin to yield the more stable of the two possible biradicals. In the second step, a spin inversion takes place and the second bond is formed. There is sufficient time, before the final spin inversion, for rotation around the single bond leading to loss of stereochemistry. The irradiation of benzophenone with either *cis* or *trans* butene stereoisomers. The reaction is not stereoselective but is regioselective. Both bonds are not formed simultaneously and the oxetane formation is not a concerted reaction.



Applications

Oxetanes are obtained by photochemical [2+2] cycloaddition of carbonyls and olefins.

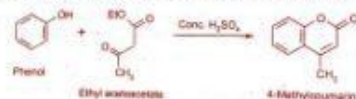


References

1. E. Paterno, G. Chierfi, Gazz. Chem. Ital., 1909, 39, 341; G. Buchi, C. G. Jman, E. S. Lipinsky, J. Am. Chem. Soc., 1954, 76, 4327; G. C. Lunge, Tet. Lett., 1971, 12, 712; H. A. J. Carlen, Tet. Lett., 1987, 28, 5933; Caldwell, Sorenson and Gajewski, J. Am. Chem. Soc., 1973, 95, 2549.

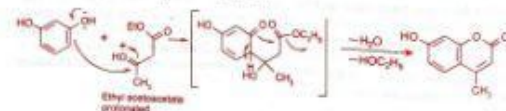
5.71 Pechmann condensation

It is a simple synthesis of coumarins² involving the condensation of phenols with malic acid or β -keto-esters in presence of concentrated sulfuric acid or other condensing agents. The reaction is illustrated by the synthesis 4-methylcoumarin.



Mechanism

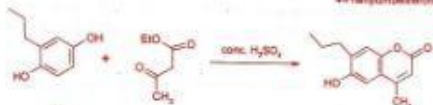
The reaction proceeds by the formation of β -hydroxy ester intermediate, which then cyclises and dehydrates to yield the coumarin.



Several condensing agents, e.g., P_2O_5 , $POCl_3$, $AlCl_3$ have also been used in place of H_2SO_4 . The nature of the product depends on the condensing agent used.

Applications³

Some important coumarins are synthesised by using this method as shown below.

**References**

1. R. V. Peckmann and C. Dauberg, Ber., 1883, 16, 2119; S. Selha, Chem. Rev., 1945, 36, 10, K. D. Kadman, J. Org. Chem., 1967, 32, 504.
2. A. Clayton, J. Chem. Soc. Part I, 1908, 2016.

5.72 Perkin reaction

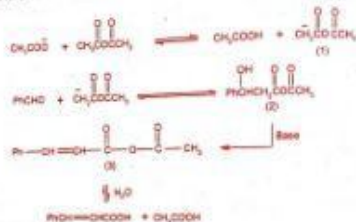
The reaction of an aromatic aldehyde with an aliphatic acid anhydride in presence of sodium or potassium salt of the acid corresponding to anhydride to give an α,β -unsaturated acid is known as **Perkin reaction**. The reaction is carried out by refluxing equimolar quantities of the aldehyde and salt of acid with excess amount of anhydride.



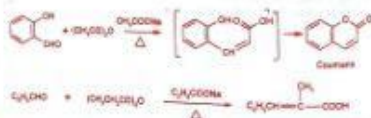
Furfural (furfuraldehyde) condenses with acetic anhydride² to give furfural acrylic acid in good yield.

5.73 Organic Reaction Mechanisms**Mechanism**

The anhydride provides the carbanion (1) under the influence of base, which attacks the carbonyl carbon of aldehyde to yield (2). Abstraction of proton from active methyl group by base from (2), followed by elimination of hydroxyl group gives (3). Hydrolysis of (3) gives α, β -unsaturated acid.

**Applications**

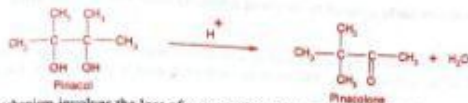
Some important applications of Perkin reaction are given below.

**References**

1. W. H. Perkin, J. Chem. Soc., 1868, 27, 58, 181; 1877, 31, 388; J. R. Johnson, Org. Reaction, 1942, 1, 210.
2. J. R. Johnson, Org. Synthesis, 1940, 20, 55.

5.73 Pinacol-pinacolone rearrangement

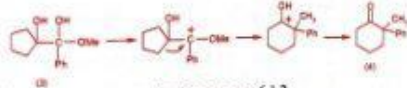
A 1,2-glycol on heating with sulfuric acid or phosphoric acid is transformed and rearranged ketone. It is a dehydration reaction involving molecular rearrangement, known as **pinacol-pinacolone rearrangement**. For example, 2,3-dimethyl-2,3-butanediol (pinacol) on treatment with H_2SO_4 generates 3,3-dimethyl-2-butanone, commonly known as pinacolone.



The mechanism involves the loss of water molecule from protonated diol, followed by 1,2-methyl shift of a group. In case of unsymmetrical glycols the product formation depends mainly by which OH group is lost to leave behind the more stable of the two carbocations, and thereafter by which is the better migrating group. The order of migrating aptitude is $\text{Ar} > \text{H} > \text{R}$. Thus the unsymmetrical pinacol (1) reacts to give (2) as shown below.



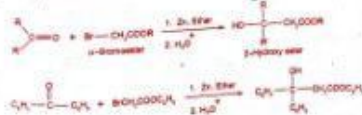
Another example is the rearrangement of the unsymmetrical diol (3) to (4).



For mechanism and some more applications see sec. 6.1.2.

5.74 Reformatsky reaction

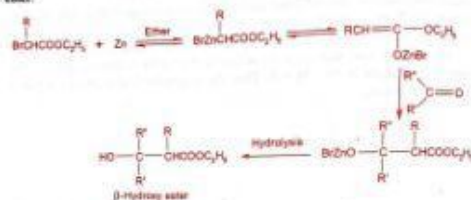
The reaction of α -haloesters (usually α -bromoesters) with carbonyl compounds such as aldehydes and ketones in presence of zinc in an inert solvent (ether-benzene) to produce β -hydroxyesters¹ is known as Reformatsky reaction.



Dehydration can be achieved by distilling β -hydroxy esters with a trace of iodine.

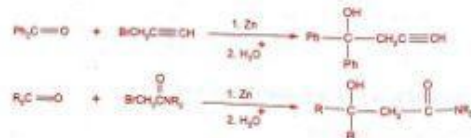
Mechanism

The reaction involves the formation of an intermediate organozinc compound which then adds to the carbonyl group. The resulting complex is readily hydrolyzed to β -hydroxy ester.



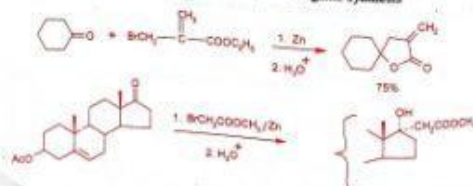
The zinc is preferred to magnesium since the organozinc reagent is generally less reactive than the corresponding organomagnesium reagent and later reacts with ester group.

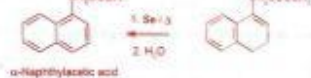
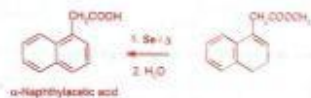
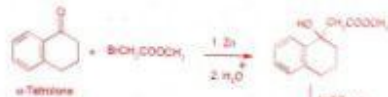
Propargyl bromide² and α -haloamides³ may be substituted for α -halo esters in the Reformatsky reaction.



Applications^{4,5}

Reformatsky reaction has important applications in organic synthesis



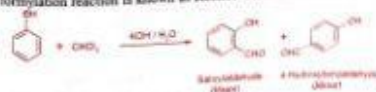


References

1. S. Rofsmansky, Ber., 1887, 20, 1210; J. Russ. Chem. Soc., 1896, 22, 44; R. L. Shriner, Org. Reactions, 142, 1, 1.
2. L. Friedmann, M. Deyers and M. Hamilton, Synth. Commun., 1980, 10, 637.
3. Drake, Eaker and Sherck, J. Am. Chem. Soc., 1948, 70, 677.
4. H. Matz and C. Benner, Tet. Lett., 1985, 5997.
5. J. Wicks and K. Hal, Chem. Commun., 1975, 968.
6. R. Helms and R. Glaser, Bull. Soc. Chim. Fr., 1955, 1586.

5.75 Reimer-Tiemann reaction

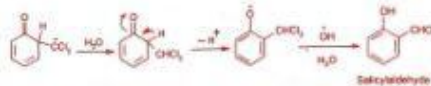
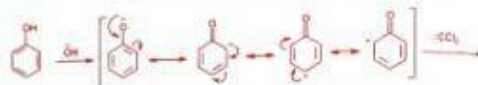
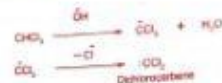
Phenols on reaction with chloroform in the presence of sodium hydroxide (or potassium hydroxide) solution give hydroxy aldehydes. The formyl group is directed to *ortho*-position unless one of the *ortho*-positions or both are occupied, in that case the attack is *para*. This formylation reaction is known as **Reimer-Tiemann reaction**.¹



Mechanism

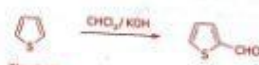
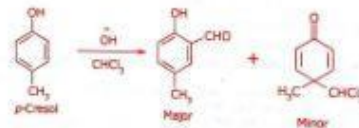
It involves the electrophilic substitution reaction and the electrophile in this reaction is a dichlorocarbene which is produced by the reaction of chloroform with alkali. The attack of phenoxide anion on dichlorocarbene gives benzylidene dichloride, which is hydrolyzed to the corresponding hydroxyaldehyde. The steps involved are shown below.

5.76 Organic Reaction Mechanism



Applications

Some applications of Reimer-Tiemann reaction are given below.

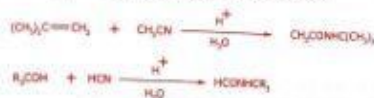


References

1. K. Reimer and F. Tiemann, Ber., 1876, 9, 124, 1248, 1285; H. Wynberg, Chem. Revs., 1960, 40, 169.

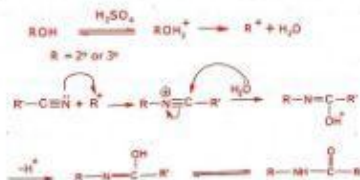
5.76 Ritter reaction

The reaction of olefins or secondary and tertiary alcohols with nitriles in strongly acidic medium gives amides. This is known as **Ritter reaction**.

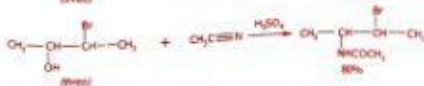
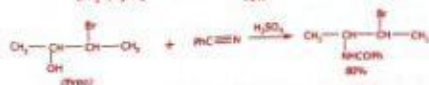


Mechanism

The olefin or alcohol on treatment with H_2SO_4 readily forms carbonium ion which is attacked by the nitrile. The quaternary ion thus formed is decomposed by water to form an amide. Hydrolysis of amide under acidic conditions gives amine. Since the reaction involves the formation of carbonium ion, thus only alcohols that give rise to stable carbonium ion (secondary, tertiary or benzylic alcohols) are used in this reaction.

Applications^{2,3}

Ritter reaction is good method for preparing amides and amines. Some applications are given below.



References

1. J. J. Ritter, P. F. Marini, *J. Am. Chem. Soc.*, 1948, 70, 4045; J. J. Ritter, J. Kalish, *J. Am. Chem. Soc.*, 1948, 70, 4968.
2. T. Ogata, S. Kawanishi, S. Zenshichi and A. Zaiterink, *Synthesis*, 1979, 549.
3. R. A. Wohl, *J. Org. Chem.*, 1973, 38, 5096.

5.77 Rosenmund reduction

Acid chlorides are catalytically reduced with hydrogen in boiling xylene to give aldehydes. This reduction is known as **Rosenmund reduction**.



The reaction is used for the synthesis of aromatic and heterocyclic aldehydes. Palladium on barium sulfate poisoned with quinoline and sulfur is used as a catalyst to bring about the desired reduction. In order to prevent further reduction, the reaction is carried out at a lower temperature. The reaction is applicable to acyl chlorides carrying halogen, nitro, ester groups^{1,2}.

Applications³

2-Naphthaldehyde and 2,4,6-trimethylbenzaldehyde are prepared from 2-naphthyl chloride and 2,4,6-trimethyl benzoyl chloride, respectively.



References

1. Boelter, Schumann, and Hansen, *Arch. Pharm.*, 1932, 271, 490.
2. R. W. Rosenmund and F. Zentrich, *Ber.*, 1921, 54, 425.
3. Skellernath et al., *J. Chem. Soc.*, 1928, 2760.
4. Eliel and Burgin, *J. Am. Chem. Soc.*, 1949, 71, 2251.
5. Hardbery and Cason, *Org. Synthesis*, 1941, 27, 84.

5.78 Rosenmund-Von Braun synthesis

The formation of aromatic nitriles from aryl halides and cuprous cyanide is known as **Rosenmund-Von Braun synthesis**. When sodium or potassium cyanides are used, aryl halides are not converted into aryl nitriles. The reaction is facilitated by the addition of an amine base (pyridine, N-methylpyrrolidine etc.) as a promoter or solvent.



α -Naphthol reacts with CuCN at 202°C to give α -naphthonitrile².



References

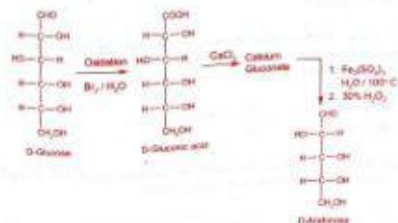
1. E. W. Rosenmund and E. Struck, Ber., 1916, 32, 1749; Von Braun and G. Maza, Ann., 1931, 486, 111; D. T. Moury, Chem. Revs., 1948, 42, 207.
2. Newman, Org. Syntheses, 1941, 27, 89.

5.79 Ruff-Fenton degradation

Compared to **Kiliani-Fischer synthesis**, which is used to lengthen the chain of aldose by one carbon, the **Ruff degradation** is used to shorten the chain¹. This method consists in the oxidation of an aldose to an aldonic acid either electrolytically or by using bromine water. The final step is the oxidative decarboxylation of the formed aldonic acid to the next lower aldose using hydrogen peroxide and ferric sulfate. This procedure is known as **Ruff-Fenton degradation**.



Ruff's method can be illustrated by carrying out the conversion of D-glucose into D-ribose.



The mechanism is not clear, however, it is believed that the metal ions act as efficient electron-transfer agents. Thus, mechanism involves the formation carboxyl radical, decarboxylation, capture of the hydroxyl radical formed, and a final transformation of the hydrate into aldehyde.

The yield has been improved by Bereznovski (1949) who oxidised calcium glucuronate with hydrogen peroxide in presence of ferric sulfate and barium acetate.

Similarly, D-galactose is converted into D-lyxose, in which the ruff degradation shortens the starting sugar by one carbon.

References

1. O. Ruff, Ber., 1896, 31, 1573; 1899, 32, 550; H. J. H. Fenton, Proc. Chem. Soc., 1893, 9, 113; H. E. Inbrell, M. A. Salam, Carbohydr. Res., 1981, 90, 123.

5.80 Sabatier-Senderens reduction

This is the oldest method of hydrogenation¹ and consists in catalytic hydrogenation of organic compounds in the vapour phase by passing over hot finely divided nickel. By this process both alkenes and alkynes can be converted into alkanes.



References

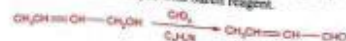
1. P. Sabatier and L. B. Senderens, Compt. Rend., 1899, 128, 1173; H. O. House, Modern Synthetic Reactions (W. A. Benjamin, Calif., 2nd Ed., 1972) chapter 1.

5.81 Sarett oxidation

Oxidation of primary and secondary alcohols to aldehydes or ketones with chromium trioxide and pyridine is known as **Sarett oxidation**.¹ The Method consists in the addition of alcohol to the reagent in pyridine solution at room temperature.

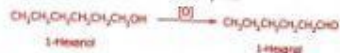


The reagent does not attack olefins, ketals or thioether group. For example, *cinnyl* alcohol is oxidised to cinnamaldehyde with Sarett reagent.



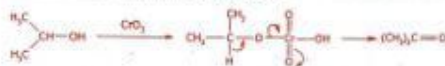
It is useful for the oxidation of secondary, allylic and benzylic alcohols to the corresponding carbonyl compounds. However, primary alcohols give poor yields of aldehydes. The reagent is prepared by adding chromium trioxide to pyridine. Reverse addition may cause the mixture to ignite spontaneously.

An important disadvantage with Sarett oxidation is the difficulty in isolating the products from pyridine in good yield. A modified method is the use of **Collins reagent**, which eliminates this problem. The reagent is prepared by the addition of chromium trioxide to pyridine. The resulting complex ($\text{CrO}_3 \cdot 2\text{C}_5\text{H}_5\text{N}$) is isolated first from the pyridine and subsequently added to dichloromethane. Primary aliphatic alcohols are also oxidised to aldehydes in good yield with this reagent. 1-Hexanol, for example, is converted into hexanal in 80% yield.



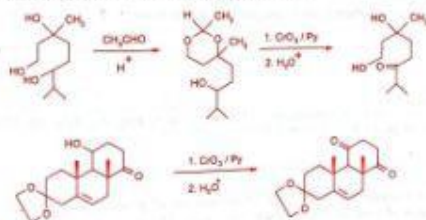
Mechanism

The mechanism of this reaction is shown below.



Applications^{1,3}

Some typical applications of this reaction are given below.

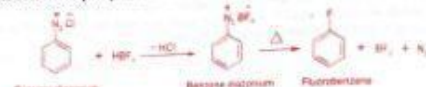


References

1. G. I. Pears, G. E. Ayle, R. E. Bleyer and L. H. Sarett, *J. Am. Chem. Soc.*, 1957, 79, 422; J. R. Wolam, *J. Org. Chem.*, 1967, 32, 4814.
2. R. V. Ratcliffe, *Org. Synthesis*, 1976, 57, 86.
3. L. H. Sarett, *J. Am. Chem. Soc.*, 1953, 75, 422.

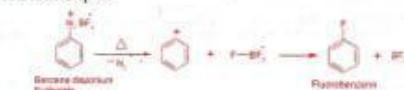
5.82 Schiemann reaction (Balz-Schiemann reaction)

Preparation of arylfluorides by heating arenediazonium fluoroborates is known as **Schiemann reaction**.¹ The diazonium fluoroborates are commonly prepared by adding a cold aqueous solution of HBF_4 to a solution of a diazonium salt. The resulting insoluble precipitates of diazonium fluoroborates are then dried and heated to give the arylfluorides. Fluorophosphoric acid can be used instead of fluoroboric acid.



Mechanism

The mechanism involves $\text{S}_{\text{N}}1$ type of reaction. In this case one of the fluoride ions of BF_4 acts as a nucleophile.



Applications

4,4'-Difluorodiphenyl can be prepared as given below.

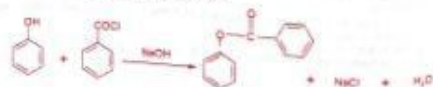


References

1. G. Balz and G. Schiemann, *Ber.*, 1927, 60, 1186; A. Roe, *Org. Reactions*, 1949, 5, 193; B. Suschitzky, *Advances in Fluorine Chemistry*, 1965, 4, 1.

5.83 Schotten-Baumann reaction

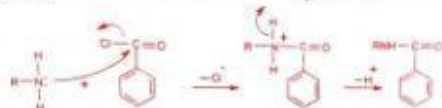
It is a convenient method for benzoylation of phenols with benzoyl chloride in presence of cold aqueous sodium hydroxide. The aqueous alkali acts as a scavenger for the hydrogen halide produced. For example, phenol on reaction with benzoyl chloride in 10% NaOH gives phenyl benzoate.



Aromatic amines (both primary and secondary) can also be benzoylated under the conditions of **Schotten-Baumann reaction**. Aniline forms benzamide on treatment with benzoyl chloride in 10 % NaOH.



Mechanism



Applications

Benzoyl glycine can be prepared by the action of benzoyl chloride on glycine in 10 % sodium hydroxide.



Benzoylation finds its application for the identification and characterization of aromatic amines and phenols.

References

1. Ingrossi, Bahcock, Org. Syn. Coll. Vol. II, 1943, 329.

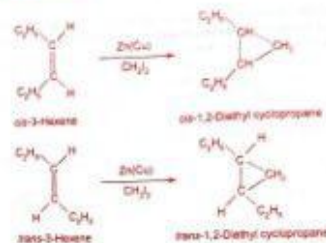
5.84 Simmons-Smith reaction

The reaction involves the treatment of a olefinic compound with diiodomethane (CH_2I_2) and Zn-Cu couple.¹ The attacking species is an organozinc intermediate (ICH_2ZnI), a carbene like species called a **carbenoid**. For example, cyclohexene is converted into bicyclo [4.1.0] heptane. For mechanism see sec. 7.61.



Generally substituted alkenes react somewhat faster than unsubstituted alkenes. Thus, 1-methylcyclohexene reacts faster than cyclohexene. The reaction is **stereospecific** and occurs by the *cis* addition of methylene to the less hindered side of the double bond. For example, *cis*- and *trans*-3-hexene give pure *cis*-1,2-diethylcyclopropane and *trans*-1,2-diethylcyclopropane respectively.

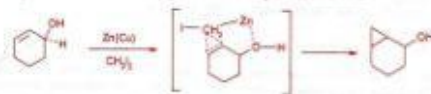
378 Organic Reaction Mechanism



Non terminal acetylenes² also react with the **Simmons-Smith** reagent to give cyclopropanes in low yields.

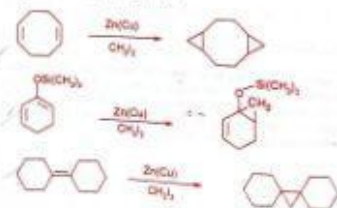


Corry et al³ observed that there is a pronounced effect of neighboring hydroxyl substituents. The oxygen atom of the starting alcohol co-ordinates the zinc, thus increasing the rate and control of the stereochemistry of the addition.



Application^{4,5}

Some important applications are given below.

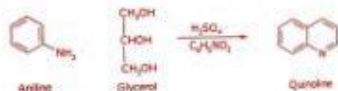


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1. H. E. Simmons and R. D. Smith, *J. Am. Chem. Soc.*, 1958, 80, 5325; H. E. Simmons et al., *Org. Reactions*, 1973, 20, 1.
2. N. T. Castellucci and C. E. Griffin, *J. Am. Chem. Soc.*, 1960, 82, 4107.
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4. S. D. Koch, *J. Org. Chem.*, 1961, 26, 5122.
5. S. D. Koch, R. M. Kliss, D. V. Lepites, R. J. Wineman, *J. Org. Chem.*, 1961, 26, 5122.

5.85 Skraup synthesis

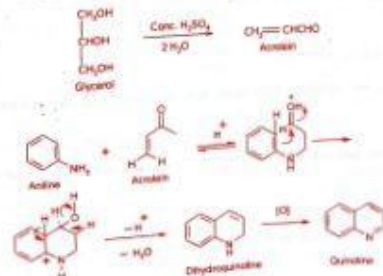
It consists in the synthesis of quinolines¹ from aromatic amines, glycerol, an oxidising agent (nitrobenzene) and sulfuric acid. Ferrous sulfate is employed to make the reaction less violent.



Variation of Skraup synthesis is **Duehner-Müller** quinoline synthesis (see sec. 5.30) of 2-methyl quinoline in which crotonaldehyde formed *in situ*, reacts with aniline.

Mechanism

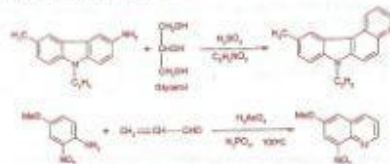
Glycerol is first converted into acrolein by concentrated H_2SO_4 . Michael type 1,4-addition of aniline to acrolein yields β -phenylaminopropionaldehyde, which on cyclisation, dehydration and aromatisation gives the final product i.e., quinoline.

Applications²⁻⁴

3-Aminopyridine reacts with glycerol to produce 1,5-naphthyridine.



Some other applications are given below.

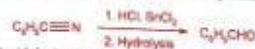


References

1. Z. H. Skraup, *Ber.*, 1880, 13, 2086; R. H. Maske, M. Kufka, *Org. Reactions*, 1953, 7, 80; *Bergman, Chem. Rev.*, 1944, 23, 152.
2. H. Rapoport and A. D. Banville, *J. Org. Chem.*, 1963, 28, 1753.
3. W. P. Utzschelm, *J. Org. Chem.*, 1943, 8, 544.
4. J. C. Perkin, G. S. Kuff and N. P. Ben-Son, *J. Chem. Soc., Perkin I*, 1972, 261.
5. H. L. Yale, *J. Am. Chem. Soc.*, 1948, 70, 254.

5.86 Stephen reaction

It involves the synthesis¹ of aldehydes from nitriles by reduction with stannous chloride



in ether saturated with hydrogen chloride. An example is the reduction of benzonitrile to benzaldehyde.

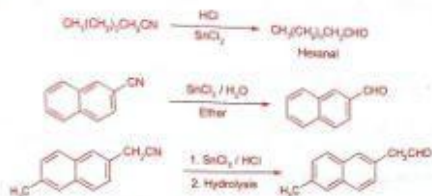
Mechanism

The intermediate aldimine salts on hydrolysis give the aldehydes. The best results are obtained in the aromatic series and the reaction can also be employed in the heterocyclic series.



Applications¹

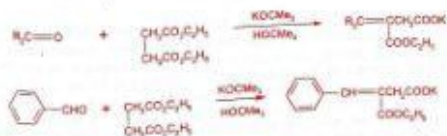
Some important applications are given below.

**References**

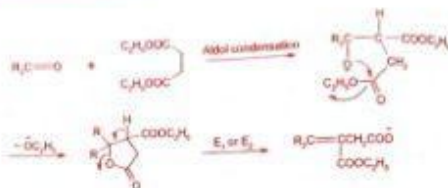
1. H. Stephen, J. Chem. Soc., 1925, 127, 1874; T. Stephen, H. Stephen, J. Chem. Soc., 1956, 4685; L. N. Ferguson, Chem. Revs., 1945, 38, 243.
2. I. Williams, Org. Synth., Coll. Vol., 3, 1955, 626.

5.87 Stobbe condensation

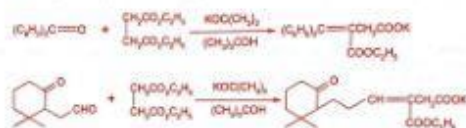
This is a condensation between dialkyl succinates and aldehydes or ketones in presence of base like sodium hydride, potassium *tert*-butoxide or sodium ethoxide to form salts of α,β -unsaturated half esters.¹ Benzaldehyde condenses with diethyl succinate in the presence of base to produce the salt of ethyl α -benzylidene ester of succinic acid.

**Mechanism**

The enolate from diethyl succinate attacks the carbonyl group, followed by cyclization to give lactone intermediate. Lactone then undergoes base catalysed ring opening to give salt of unsaturated half ester. One of the ester groups is hydrolyzed in the course of salt of unsaturated half ester. One of the diesters which do not undergo Dieckmann condensation (see sec. 5.2.81).

5.88 Organic Reaction Mechanism**Applications¹**

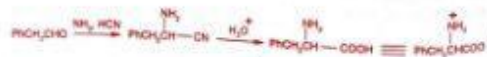
Some important applications are given below.

**References**

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5.88 Strecker amino acid synthesis

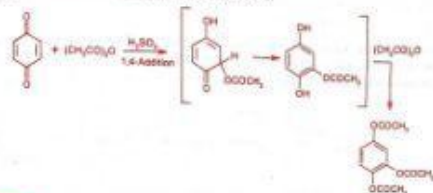
The reaction of an aldehyde with ammonia, followed by reaction with HCN gives α -aminonitrile. α -Aminonitrile intermediate on hydrolysis gives α -amino acid. This reaction is known as Strecker amino acid synthesis.¹ The α -aminonitrile can also be obtained by the treatment of the aldehyde with HCN followed by the reaction of the formed cyanohydrin with ammonia. This method is known as **Erlenmeyer modification**.¹ A more convenient route is to treat the aldehyde in one step with ammonium chloride and sodium cyanide (this mixture is equivalent to ammonium cyanide which in turn dissociates into ammonia and HCN). This procedure is referred to as the **Zelinsky-Stadnikoff modification**.¹ The final step is the hydrolysis of α -amino acid. A simple example is the synthesis of phenylalanine from phenylacetaldehyde.



Red, 2,5- and 2,6-dimethyl-1,4-benzoquinones react with acetic anhydride in the presence of catalyst. However, 2,5- and 2,6-dimethoxy-1,4-benzoquinones do not undergo the Thiele reaction.

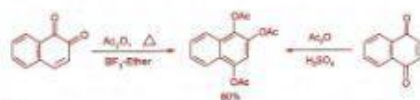
Mechanism

Benzoquinone on reaction with acetic anhydride in H_2SO_4 forms hydroxyquinol acetate. The mechanism of this reaction is as follows.



Applications

1,2,4-Triacetoxynaphthalene can be prepared by Thiele's acylation of *o*-naphthaquinone.

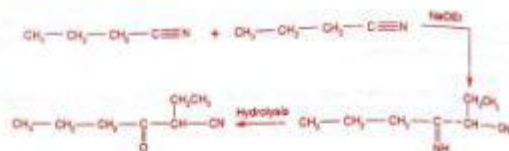
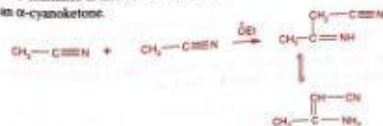


References

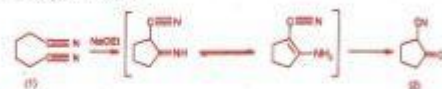
1. J. Thiele, *Ber.*, 1898, **31**, 1247; J. Thiele, E. Wimmer, *Ann.*, 1900, **311**, 341; J. F. W. McOmie and J. N. Bunney, *Org. React.*, 1972, **19**, 200.

5.91 Thorpe (Ziegler) reaction

The base-catalysed condensation of two molecules of nitrile to yield imines which isomerize to enamines is known as **Thorpe reaction**¹. Hydrolysis of intermediate imine generates an α -cyanoketone.

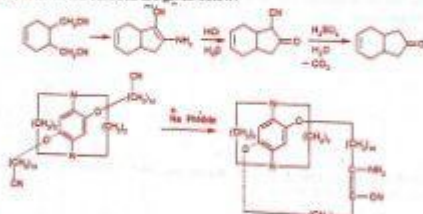


The intramolecular version of this reaction is called **Thorpe-Ziegler method**. The reaction of adiponitrile (1), for example, with sodium ethoxide, followed by hydrolysis gives 2-cyanocyclopentanone (2).²



Applications^{2,3}

Some applications of this reaction are given below.



References

1. H. Harlow, F. G. P. Rendly and Y. F. Thorpe, *J. Chem. Soc.*, 1904, **85**, 1726; K. Ziegler, E. Ebel and M. Olinger, *Ann.*, 1933, **504**, 94; J. P. Schaefer, J. J. Bloomfield, *Org. Reactions*, 1967, **25**, 1.
2. J. J. Bloomfield and P. V. Fennessy, *Tet. Lett.*, 1964, 2273.
3. T. Doornbos and J. Strating, *Synth. Commun.*, 1971, **1**, 192.

5.92 Tischenko reaction

Formation of esters from aldehydes by an oxidation-reduction process in presence of aluminium alkoxide is known as **Tischenko reaction**¹.



All aldehydes i.e., with or without α -hydrogen, undergo this reaction. Like **Cannizzaro reaction**, in this reaction also one molecule of aldehyde is oxidised and another is reduced, but the alcohol and acid are combined to form ester under these conditions. For example acetaldehyde gives ethyl acetate and propionaldehyde gives propyl propionate.

Mechanism

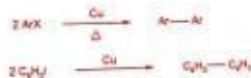
The mechanism of Tischenko reaction is uncertain. However, it is believed that the mechanism involves the hydride-ion shift as in the Meerwein-Ponndorf-Verley reduction (see sec. 5.6.2).

Reference

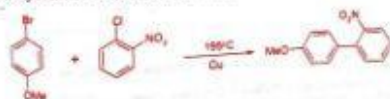
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5.93 Ullmann reaction

The synthesis of biaryls by the copper-induced coupling of aryl halides is called **Ullmann reaction**¹. When iodobenzene is heated with copper powder, biphenyl is formed in 80% yield.



The order of reactivity of aryl halides is, $\text{ArI} > \text{ArBr} > \text{ArCl}$. Aromatic rings having electron-withdrawing groups such as nitro group or carboxy group at *ortho* position, retard the ring towards coupling reaction. Unsymmetrical biaryls can be prepared by using, the ring towards coupling reaction is avoided when one aryl halide is very reactive and the other is relatively unreactive.



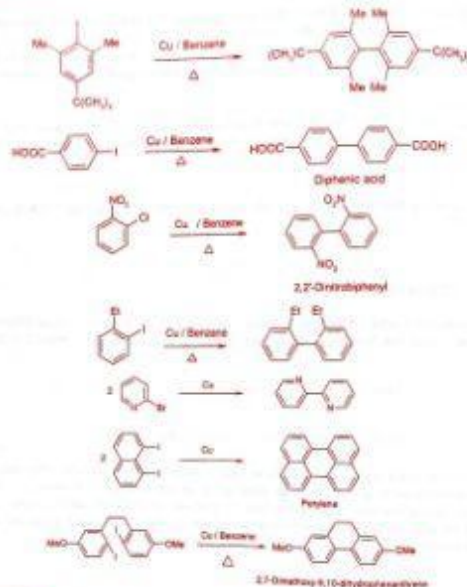
Mechanism

The mechanism of the reaction is uncertain, however, a radical mechanism has been proposed.



Applications²⁻⁴

Following are given synthesis of some biaryls, 2,2'-dipyridyl and other polycyclic aromatic compounds.



References

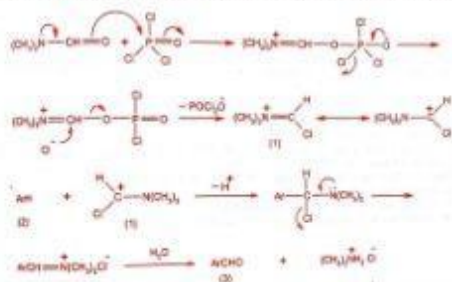
1. F. Ullmann, Ann., 1904, 332, 38; F. Ullmann and P. Sprangell, Ber., 1905, 38, 2211; P. E. Tetl, Chem. Rev., 1946, 36, 139.
2. J. Cornforth, A. Skerzinski and T. Waller, J. C. S. Chem. Commun., 1979, 294.
3. R. C. Fuson and E. A. Cleveland, Org. Synth., 1955, III, 339.
4. Reported in a review, M. Tishchenko, Synthesis, 1979, 933.

5.94 Vilsmeier reaction (Vilsmeier-Haack reaction)

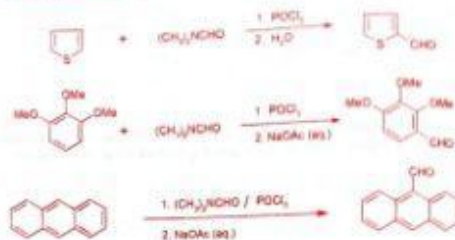
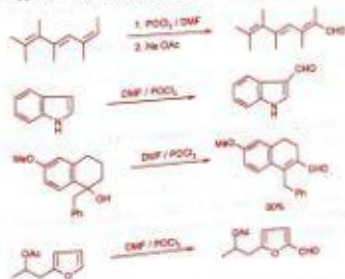
Activated aromatic or heterocyclic compounds react with disubstituted formamides and phosphorus oxychloride to give aldehydes and the reaction is known as **Vilsmeier reaction**¹. For example, formylation of resorcinol dimethyl ether with dimethylformamide in POCl_3 gives 2,4-dimethoxybenzaldehyde.

**Mechanism**

N,N-Dimethyl formamide reacts with POCl_3 to give the reactive species (1), which in turn reacts with the organic substrate (2) to give the aldehyde (3) as shown below.

**Applications²⁻⁷**

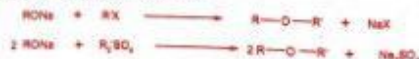
Some important applications are given below.

**References**

1. A. Vilsmeier, A. Haack, Ber., 1927, 60, 119; M. R. DeMaheas, Bull. Soc. Chim. France, 1962, 189.
2. L. N. Ferguson, Chem. Rev., 1946, 36, 236.
3. C. P. Truce, H. J. Takken and H. Bodilena, Tet. Lett., 1977, 2129.
4. G. F. Smith, J. Chem. Soc., 1934, 3842.
5. T. Shono, Y. Matsumura, K. Tsubota and Y. Sugihara, Tet. Lett., 1975, 3391.
6. G. S. Krishna Rao, J. Org. Chem., 1981, 46, 5371.
7. H. G. Viehe, Angew. Chem. Int. Ed., 1971, 10, 575.
8. A. W. Weston and R. J. Michaelis, Jr., OS, 1951, 11, 108.

5.95 Williamson's ether synthesis

The reaction of alkoxides and phenoxides with alkyl halides (or alkyl sulfates), known as **Williamson's synthesis of ethers¹**, is very important and convenient method for the synthesis of simple and mixed ethers.

**Mechanism**

The mechanism involves the nucleophilic displacement ($\text{S}_{\text{N}}2$ type) of a halide ion from an alkyl halide by alkoxide or phenoxide ion.



Since the secondary and tertiary alkyl halides undergo elimination reaction in the presence of a strong base such as alkoxide, thus it is important to use the alkoxide of the secondary or tertiary alcohol.

Applications¹⁻³

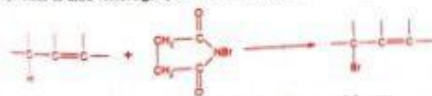
Some important applications are given below.

**References**

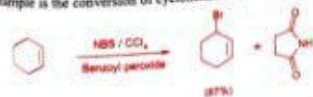
1. A. W. Williamson, *J. Chem. Soc.*, 1852, 4, 229; O. C. Demer, *Chem. Revs.*, 1934, 14, 409.
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3. H. Kozmowski, G. Cross and D. Seibach, *Ber.*, 1981, 114, 477.
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5. J. E. Nye and G. W. Rigby, *J. Am. Chem. Soc.*, 1932, 54, 2088.

5.96 Wohl-Ziegler reaction

The allylic or benzylic bromination with N-bromosuccinimide (NBS) in presence of peroxide or ultra violet light (or both) is known as the **Wohl-Ziegler reaction**.



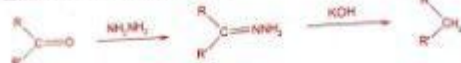
An example is the conversion of cyclohexene to 3-bromocyclohexene.



In general, non polar solvent, carbon tetrachloride is used and after the completion of reaction, the insoluble succinimide is filtered. The final product is obtained after removal of the solvent by distillation or crystallization. The mechanism and applications are discussed in sec. 8.2.2.

5.97 Wolff-Kishner reduction

The aldehydes and ketones can be reduced to the corresponding hydrocarbons by **Wolff-Kishner reduction**²⁴. The reaction is carried out by heating the hydrazones of aldehydes and ketones with base like potassium or sodium hydroxide.

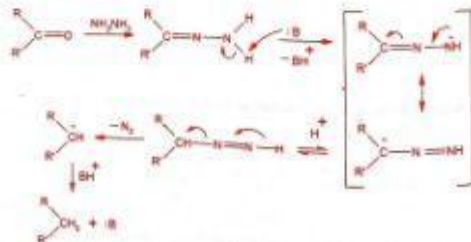


An example of Wolff-Kishner reduction is the synthesis of n-octane from 2-octanone.

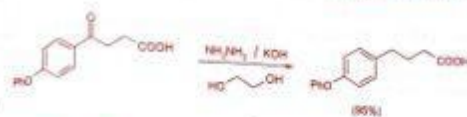


In the **Hunang-Minlon modification** of the above reaction, diethylene glycol is used as solvent. The reaction is carried out in one step and the isolation of the hydrazine is unnecessary. The yields are excellent. More recently, potassium *t*-butoxide as the base and dimethyl sulfoxide as solvent are employed and the reduction occurs at room temperature.

A related reduction of aldehydes and ketones to hydrocarbons is carried out by refluxing the carbonyl compound with amalgamated zinc and HCl (**Clemmensen reduction**). The conditions employed in this method are strongly acidic and may give rise to side reactions.

Mechanism**Applications²⁴**

Some typical applications are given below.

**References**

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2. Harry Minlon, *J. Am. Chem. Soc.*, 1946, 68, 2487; 1949, 71, 3301.
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6. L. J. Durham, D. J. McLeod and J. Cases, *OS*, 1958, 38, 34.

5.98 Wurtz reaction

Coupling of alkyl halides with sodium in dry ether to give hydrocarbons is known as Wurtz reaction¹. Coupling of alkyl halides or sulfonates with Grignard reagents or RLi in presence of Cu (I) salts is also a modified form of Wurtz reaction. An example of Wurtz reaction is the synthesis of hexane from propyl bromide and sodium metal.



The reaction is valuable for the synthesis of alkanes containing even number of carbon atoms (symmetrical). All hydrocarbons prepared by this method contain small amount of alkene as by product. Crossed reaction of alkyl halides gives a mixture of hydrocarbons which may be difficult to separate and the yields are low.



This reaction has limited utility due to many side reactions. The Wurtz-Fittig² variation is the reaction of an aryl and an alkyl halide to form alkylated aromatic ring. For example, 1-phenylbutane (butylbenzene) is prepared by heating a mixture of bromobenzene and butyl bromide with sodium.



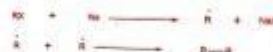
The by-products of the reaction are R-R and Ar-Ar are easily separated, since intramolecular Wurtz reactions have also been shown to give reasonable yields (see applications).

Mechanism

Two mechanisms are proposed for this reaction:

(i) Nucleophilic displacement

It involves the formation of intermediate alkyl sodium, which then reacts with a second molecule of alkyl halide.

**(ii) Radical mechanism****Applications³⁻⁵**

Some important applications of this reaction are given below.

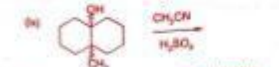
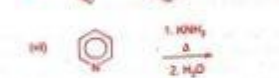
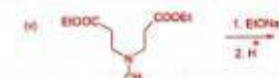
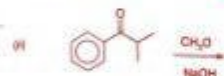


Problems

- How will you obtain diacetone alcohol in yields > 90% starting from acetone? Give the mechanism involved.
- The reaction of benzaldehyde with acetaldehyde in presence of 10% NaOH gives cinnamaldehyde. What is this reaction called? Give its mechanism.
- How α -diketones are obtained? How they are converted into carboxylic acid and amides? Give all mechanistic steps.
- How an α -hydroxyketones can be converted into flavanols? Give the mechanism of the reaction.
- Starting from β -naphthoquinone how will you obtain α -carboxycinnamic acid? Give the mechanism?
- Describe the steps involved in the synthesis of flavone from α -hydroxyacetophenone using Baker-Venkataraman rearrangement.
- How will you establish the structure of cholesterol using Barbier-Wieland degradation?
- Explain Barton reaction. Give important applications of Barton reaction.
- Using Beckmann rearrangement how will you assign the structure of oximes?
- What product is obtained by the reaction of furfural with CN^- ? Give the mechanism involved.
- In Cannizzaro reaction how will you prove that the hydroxide ion is directly transferred from one molecule of the aldehyde to the other?
- Starting with α -hydroxyacetophenone how will you obtain 2-methylchromene? Give the mechanism involved.
- Give the mechanism involved in the Claisen rearrangement of allyl phenyl ether and 2,6-dimethylallyl phenyl ether. What products are obtained?
- What is Cope rearrangement? Discuss by taking a suitable example.
- What product is obtained by the reaction of diethylpinelate with sodium ethoxide? Give the mechanism.
- How can *cis*-Dimethylcyclohexene-4,5-dicarboxylate be obtained by the Diels-Alder reaction of butadiene? Write the structure of the dienophile used in this reaction.
- What product is expected by Ellis persulfate oxidation of coumarin and 5-hydroxyflavone? Give the mechanism of one of the reaction.
- Starting with phenyl acetic acid how will you obtain α -bromophenyl acetic acid?
- Starting with silver salt of cyclohexane carboxylic acid how will you obtain bromocyclohexane?
- Give the mechanism of Knoevenagel reaction.
- Write notes on
 - Mannich reaction
 - Meerwein-Ponndorf-Verley reduction
 - Michael condensation
 - Nef reaction
 - Oppenauer oxidation
- How will you carry out the following transformations?
 - Benzonitrile into benzaldehyde
 - Benzaldehyde into α -aminophenylethanoic acid ($\text{C}_6\text{H}_5\text{CH}(\text{NH}_2)\text{COOH}$)
 - 1-Decanol into decanal

- p*-Benzoquinone into 1,2,4-trimethoxybenzene
- 1,3-Dimethoxybenzene into 2,4-dimethoxybenzaldehyde.
- Cyclohexene into 3-bromocyclohexene.

- What methods can be used for the conversion of keto group into CH_2 ?
- Give the product(s) of the following reactions.



Introduction

Rearrangement is referred to the migration of an atom or a group of atoms from one atom to another within a molecule or from one molecule to another. The migrating group may leave the molecule during migration i.e., the migrating group first gets completely detached from the molecule, subsequently it gets reattached at some other reactive site of the molecule (intermolecular rearrangement). In some cases the migrating group never leaves the molecule during migration (intramolecular rearrangement).

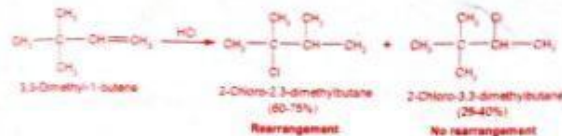
The most important rearrangement reactions involve migration of an atom or group from one atom to an adjacent atom i.e., 1, 2-shift. The most common migrating atoms are carbon or hydrogen, but migration of halogen, oxygen, sulfur and nitrogen is also well known. A group may migrate to an electron-deficient carbon, nitrogen, oxygen or to an electron rich carbon. The most important type of molecular rearrangements involve the 1,2-shift of alkyl or aryl group, with pair of electrons, from one atom to an adjacent electron-deficient atom.

6.1 Rearrangements involving migration to electron-deficient carbon

(A) Migration of carbon

6.1.1 Wagner-Meerwein and related rearrangements

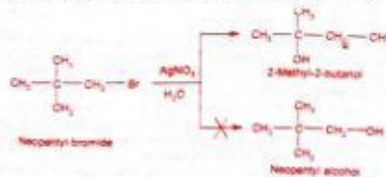
Wagner¹ was the first to recognize that the formation of camphene from bornyl chloride involved rearrangement. Meerwein² also found that molecular rearrangements occurred in the camphene hydrochloride-isobornyl chloride interconversion. He generalized these types of rearrangements indicating that they also occur in compounds other than bicyclic terpenoids and also in various substitution, elimination and addition reactions. Such rearrangements which occur during reaction involving the change in the carbon skeleton through the rearrangement of carbocations as intermediates, are collectively known as **Wagner-Meerwein rearrangements**. For example, 3,3-dimethyl-1-butene adds HCl to give 2-chloro-2,3-dimethylbutane as major product (60-75%), along with the expected 2-chloro-3,3-dimethylbutane, in minor amount (25-40%).



These rearrangements occur via an intermediate carbocation and involve the migration of alkyl group with its pair of electrons to an electron-deficient carbon atom. In terpenoids these rearrangements involve a change in ring structure or migration of methyl group. The rearrangement, which involves the migration of methyl group, is a special case of Wagner-Meerwein rearrangement, and is known as **Nametkin rearrangement**. Nametkin rearrangements often occur in monoterpenes when they are treated with acid. For example, Nametkin rearrangement is observed when 3,3-dimethyl[2.2.1]bicycloheptan-2-ols such as camphenilol or 4-methylcamphenilol are treated with acid.



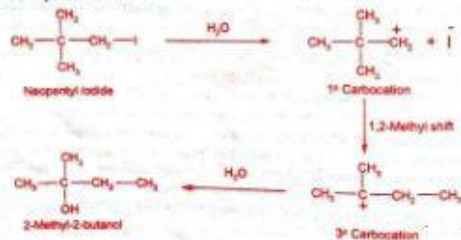
Whitmore³ recognized that when neopentyl alcohol or neopentyl bromide reacts under conditions favoring the $\text{S}_{\text{N}}1$ mode, rearranged products are formed. For example, solvolysis of neopentyl bromide (1-bromo-2,2-dimethylpropane) in water leads to 2-methyl-2-butanol, instead of the expected neopentyl alcohol (2,2-dimethyl-1-propanol). Thus, solvolysis of neopentyl bromide does not take a normal course.



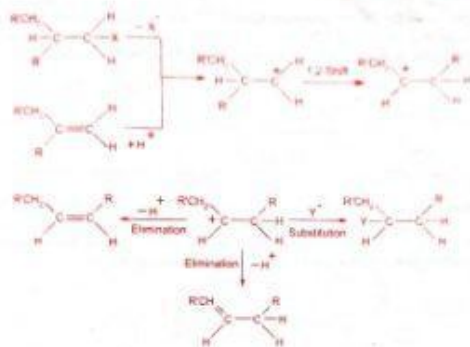
Similarly, action of HBr on neopentyl alcohol gives tert-pentyl bromide (2-bromo-2-methylbutane).

**Mechanism**

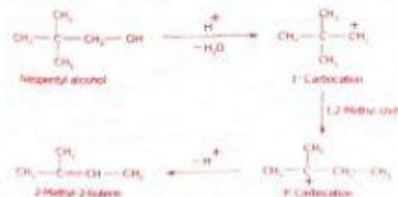
Wagner-Meerwein rearrangements are common in many reactions involving carbocation as intermediate. For example, nucleophilic displacements occur by an $\text{S}_{\text{N}}1$ mechanism and may be accompanied by the 1, 2-methyl shift (rearrangement). In the solvolysis reaction of neopentyl iodide in water, the rearranged alcohol, 2-methyl-2-butanol is formed. The expected neopentyl alcohol is not formed in this reaction. The unstable primary carbocation, formed by the dissociation of C-I bond, rearranges to a much more stable tertiary carbocation.



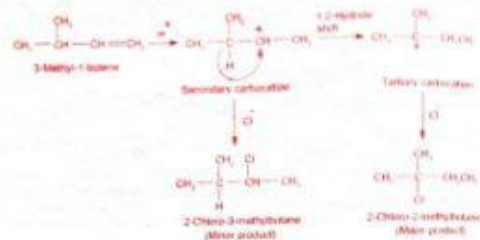
Thus, the first step in these rearrangement reactions is the generation of a carbocation which can take place in a number of ways. Carbocation is formed in the reactions where loss of a leaving group occurs, for instance, loss of a water molecule from protonated alcohols, nitrogen (N_2) from aliphatic diazonium ions or halide ion from alkyl halides. The carbocation can also be formed by the addition of electrophile to a double bond. For example, protonation of alkene produces the carbocation. The addition of proton to step, the shift of a group, along with the pair of electrons, occurs from one carbon atom to the adjacent cationic carbon atom. The resulting rearranged carbocation either combines with a nucleophile or loses proton to give alkene.



Acid-catalysed dehydration of neopentyl alcohol yields 2-methyl-2-butene, obviously a rearrangement has taken place here. When neopentyl alcohol is heated with sulfuric acid, water is eliminated and neopentyl carbocation (primary carbocation) is formed. Neopentyl carbocation undergoes 1,2-methyl shift to give tertiary carbocation. The greater stability of tertiary carbocation as compared to primary carbocation is the driving force for the shift of methyl group. Loss of proton from tertiary carbocation results in 2-methyl-2-butene.



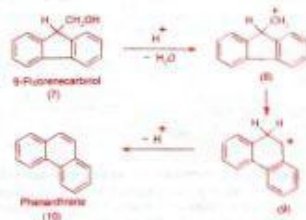
The Wagner-Meerwein type of rearrangements involving carbocation intermediate in cyclic compounds lead to expansion or contraction of cycloalkane ring. For example,



Such shift of hydrogen with its pair of electrons between adjacent carbon atoms is known as **1,2-hydride shift**. The 1,2-hydride shift does not change the carbon skeleton of the molecule.

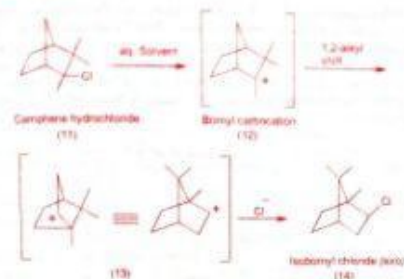
Applications

1. The conversion of 9-fluorencarbinol (7) into phenanthrene (10) involves the Wagner-Meerwein rearrangement. Protonation of the hydroxyl group followed by the loss of water molecule gives the primary carbocation (8). The (8) then rearranges to give much more stable benzyl carbocation (9) which loses a β -hydrogen to give the phenanthrene (10).

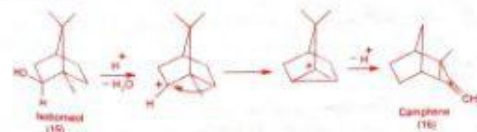


2. Wagner-Meerwein rearrangements are most common in terpenes. In the conversion of camphene hydrochloride (11) to isobornyl chloride (14), the camphene hydrochloride (11) loses chloride ion to form bornyl carbocation (12), which rearranges by a 1,2-alkyl shift to form another carbocation (13). In the final step, the carbocation combines with a chloride ion to yield isobornyl chloride (14). In this case only isobornyl

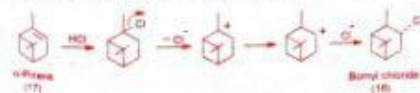
chloride is obtained in which chloride is *exo*. The bornyl chloride, in which chloride is *endo*, is not obtained.



3. Dehydration of isoborneol (15) to camphene (16) is another typical example of this rearrangement.



4. Bornyl chloride (18) can be obtained by the addition of HCl to α -pinene (17).

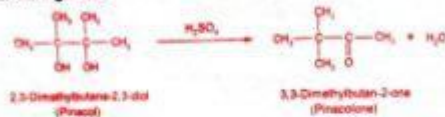


References

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3. F. C. Whitmore, J. Chem. Soc., 1948, 1090; F. C. Whitmore and R. S. Rothrock, J. Am. Chem. Soc., 1953, 75, 1300; 1952, 74, 3431.

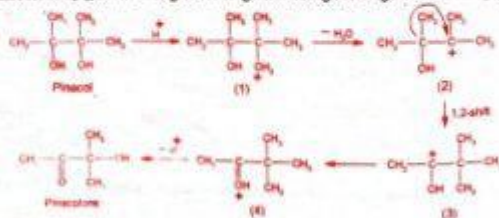
6.1.2 Pinacol-pinacolone rearrangement

Acid-catalysed dehydration of 1,2-diols usually leads to rearrangement with the formation of ketones. In 1860 Fittig¹ observed that when 2,3-dimethylbutane-2,3-diol (pinacol)² is treated with hot 30% sulfuric acid, 3,3-dimethyl-2-butanone (commonly known as pinacolone) is formed. This type of acid-catalysed dehydration reaction involving rearrangement of 1,2-diols (vic-diols) is called **pinacol-pinacolone rearrangement**. The pinacol-pinacolone rearrangement is analogous to a Wagner-Meerwein rearrangement.

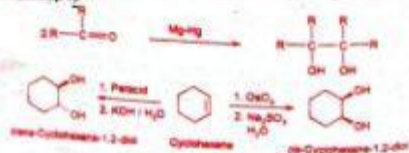


Mechanism

The first step is the addition of a proton to one of the hydroxyl groups in pinacol to give oxonium ion (1), followed by loss of water from the oxonium ion (1). The result is a carbocation (2), which undergoes rearrangement through the migration of a methyl group



Pinacols are readily prepared by reductive dimerisation of ketones with magnesium anion³ or by dehydroxylation of alkenes. Treatment of an alkene with OsO_4 , followed by reduction with Na_2SO_3 , gives vic-diols (see 8.11). Where as, epoxidation of an alkene, followed by cleavage results in overall oxidative dehydroxylation (see chap. 3).



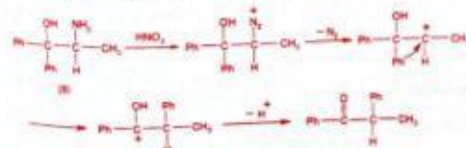
from the carbon adjacent to the carbon that bears the positive charge. The carbocation (3), thus formed is at once stabilized by a shift of the charge from carbon to oxygen. The final step of the reaction is the loss of proton from (4) to give the ketone. The driving force for the 1,2-methyl shift comes from the tendency of initially formed carbocation intermediate (2) to form a stable oxonium ion (4).

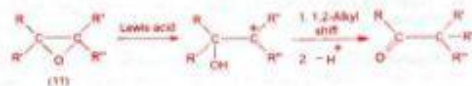
Migratory aptitude

With symmetrical diols, it does not matter which hydroxyl group is protonated and leaves nor which group migrates. When an unsymmetrical diol rearranges, there is choice as to which hydroxyl group will be preferentially removed. The hydroxyl group lost should be the one that leaves behind the more stable carbocation. Carbocation stability, relative migratory aptitude of the substituents and reaction conditions play an important role in deciding which product will be formed. Beckman investigated this rearrangement in unsymmetrical pinacols and found that aryl group migrates preferentially in competition with alkyl groups. The order of migratory aptitude is $\text{Ar} > \text{H} > \text{CH}_3$. For example, in 2-methyl-1,1-diphenylpropane-1,2-diol (5), the OH group removed should be the one on the phenyl side, so that carbocation (6) is formed. Shift of methyl group from adjacent carbon atom in (6), followed by deprotonation of the resulting oxonium ion gives product, 3,3-diphenylpropan-2-one (7). The carbocation (6) is resonance stabilized, thus, will be preferred.



This rearrangement is also observed with other substrates like β -amino alcohols (8), β -hydroxyaldehydes (9), allyl alcohols (10) and epoxides (11). In each case, like in 1,2-diols, the initial intermediate is carbocation. In β -amino alcohols, the carbocation is generated by diazotisation, followed by loss of nitrogen. When acyclic β -amino alcohol is taken as substrate the rearrangement is known as **semipinacol rearrangement**.



R' = CH₃**Applications**

The reaction provides methods for the preparation of many carbonyl compounds which are otherwise difficult to prepare. Benzopinacol (12), for example, rearranges to benzopinacolone (13) when heated in acetic acid in presence of iodine as catalyst.



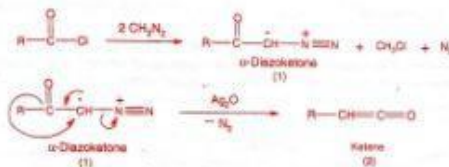
The pinacol-pinacolone rearrangement is a very useful general method for the synthesis of spiro ketones.¹ For instance, both diols, (14) and (15) give the same spiro ketone (16).

**References**

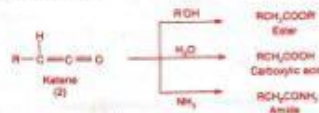
1. R. Fittig, *Ann.*, 1858, 179, 17; 1860, 174, 54.
2. R. Adams and E. W. Adams, *Org. Syn.*, 1941, 1, 459.
3. B. P. Mandy, Y. Kim, R. J. Warrall, *Heterocycles*, 1963, 26, 1723.

6.1.3 Wolff rearrangement

The α -diazoketones (1) undergo rearrangement with elimination of very stable nitrogen molecule in presence of silver oxide to form a ketene (2). The reaction is known as **Wolff rearrangement**.² The α -diazoketones can be prepared by the reaction of acid chlorides with diazo compounds in a normal addition-elimination process. The diazoketones must be treated with great caution as they are liable to explode.



The Wolff rearrangement generates ketene in the absence of any nucleophile, and therefore it can be isolated in this reaction. However, when this rearrangement is carried out in the presence of water, alcohol³ or amine, the ketene is converted into carboxylic acid, ester or amide, respectively. The overall reaction is called **Arndt-Eistert Synthesis** (sec. 5.4). Arndt-Eistert reaction is useful for converting an acid, RCOOH into its next higher homologue, RCH₂COOH.



The Wolff rearrangement can be brought about either thermally or by photolysis. Generally, the thermal reaction is carried out in the presence of silver oxide (colloidal platinum or copper can also be used instead of Ag₂O).

Mechanism

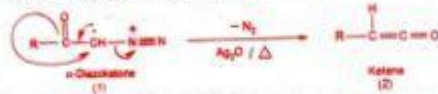
Loss of nitrogen from the α -diazoketone (1) is accompanied by 1,2 shift of the alkyl group with electron pair. The resulting ketene (2) readily combines with the solvent molecule, which may be water to give acid, alcohol to give an ester, or amine to give an amide. When reaction is brought about by photolysis⁴, the Wolff rearrangement is believed to involve formation of a carbene (3). The migration of a group (alkyl or aryl) believed to involve formation of a carbene (3). The migration of a group (alkyl or aryl) with its pair of electrons to electron deficient carbon of carbene (3) gives the ketene (2). The ketene then reacts with solvent to give the final product. The mechanism is analogous to Hofmann and related rearrangements (sec. 6.2.2) where migration of alkyl

group occurs from adjacent carbon to electron deficient nitrogen of nitrene, which is

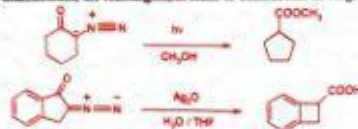


formed as an intermediate.

It is believed that when the rearrangement is carried out thermally in presence of silver oxide, a concerted migration of alkyl group and expulsion of nitrogen is involved and there is no clear evidence that carbene is formed as an intermediate.



With cyclic α -diazo ketones, the rearrangement leads to contraction of rings.



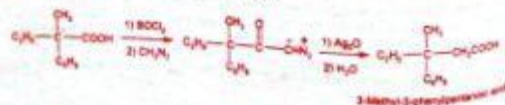
Stereochemistry

It is found that the Wolff rearrangement occurs preferentially from the S-Z conformation² of α -diazo ketone.



Applications

Wolff rearrangement is involved in an important reaction (Arndt-Eistert reaction) for converting an acid into its next higher homologue.

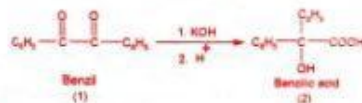


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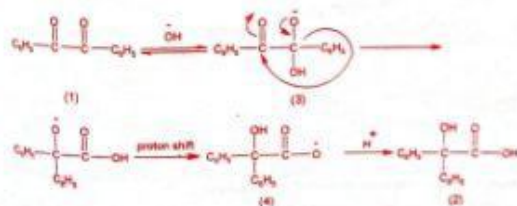
6.1.4 Benzil-benzilic acid rearrangement

α -Diketones (benzils) undergo a base-catalysed reaction called **benzil-benzilic acid rearrangement**¹. The salts of α -hydroxy carboxylic acids initially formed on acidification yield the hydroxy carboxylic acids. For example, benzil (1) on treatment with KOH, followed by acidification yields benzilic acid (2).



Mechanism

The reaction is analogous to intramolecular **Cannizzaro reaction** (sec.5.17) of glyoxal. The mechanism of benzil-benzilic acid rearrangement starts with a reversible nucleophilic addition of hydroxide ion to benzil (1). The resulting hydrate anion (3) undergoes rearrangement by migration of aryl group, followed by shift of proton to give resonance stabilized carboxylate anion (4).



The formation of resonance stabilized carboxylate anion (4) from (3) after 1,2-phenyl shift provides the driving force for the reaction. In the last step, benzoic acid (2) is obtained by acidification of (4).

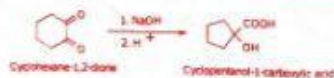
Benzoic acid rearrangement is not limited solely to aromatic α -diketones as aliphatic diketones and α -ketoaldehydes can also undergo the reaction.

Applications

The benzil-benzilic acid rearrangement is particularly useful for the synthesis of citric acid (7) from ketopinic acid (6).



The benzilic acid rearrangements of furil, 9,10-phenanthrenequinone² and cyclohexane-1,2-dione have been described below.



² Alternatively, benzoic acid (2) can be prepared readily from benzoin³ (5), which is more easily available than benzil, by oxidation with sodium bromate and sodium hydroxide.



References

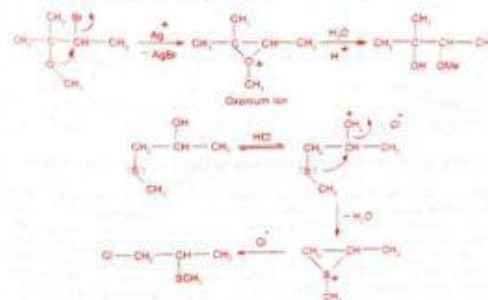
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(B) Migration of heteroatoms

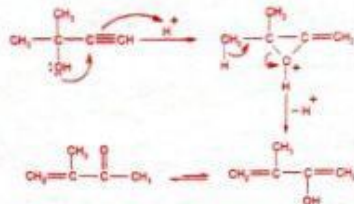
In a system like $X-C-C-Y$, an atom or group, X, migrates with its unshared pair of electrons to the adjacent carbon atom which loses a group, Y, in an internal S_N2 displacement. The migrating group, X, assists the exit of Y. The rearrangement involves the formation of an intermediate bridged cation, which is subsequently cleaved by the attack of nucleophile.



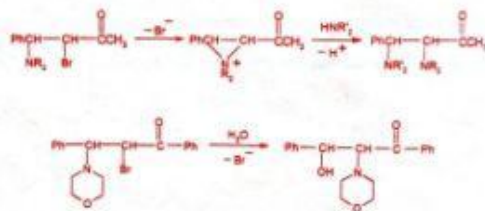
This is illustrated by the following examples.



The bridged ion may be formed by the attack of heteroatom with pair of electrons to the protonated unsaturated bond. For example, initial protonation of the acetylenic bond and attack of heteroatom with its electron pair produces bridged ion in **Rupe rearrangement** of α -acetylenic alcohols. The opening of ring then leads to a rearranged product, α,β -unsaturated ketone.



Similarly, migration of amino group to the adjacent carbon atom via the formation of cyclic intermediate leads to the rearranged products.

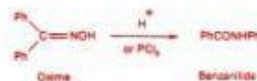


6.2 Rearrangements involving migration to electron-deficient nitrogen

Reactions that generate electron-deficient nitrogen species, such as nitrene often lead to migration of a group from nearby carbon to the nitrogen. Almost invariably the initial migration products involve nucleophilic addition of the hydroxylic solvent in which such reactions are normally carried out. The electron-deficient nitrogen is first generated by loss of a leaving group from the nitrogen atom. The electron-deficient nitrogen actually may not occur as a discrete entity, because, its formation is prevented by concerted migration and cleavage of bond between nitrogen and leaving group. Thus, the rearrangements involving migration to electron-deficient nitrogen are generally considered to follow concerted mechanism with migration occurring at the same time as loss of the leaving group from nitrogen. The migrating group leaves from a carbon atom adjacent to electron-deficient nitrogen (i.e., 1,2-shift). The driving force for these rearrangements is provided by ejecting a stable species, such as nitrogen, water or anions of strong acids.

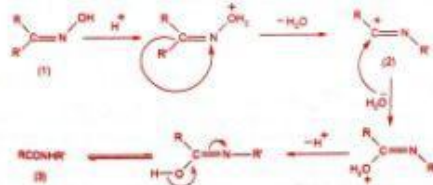
6.2.1 Beckmann rearrangement

The rearrangement of oximes under the influence of a variety of acidic reagents to N-substituted amides is known as **Beckmann rearrangement**¹. Phosphorus pentachloride is commonly used as a catalyst in Beckmann rearrangement, but conc. sulfuric acid, polyphosphoric acid, formic acid, thionyl chloride, silica, etc., have been used successfully. A typical example is rearrangement of benzophenone oxime to benzamide in the presence of phosphorus pentachloride.



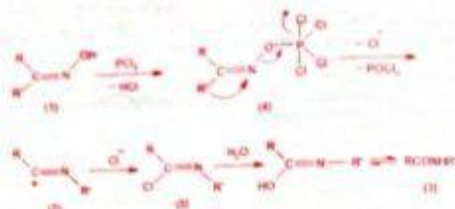
Mechanism

The proposed mechanism is shown below:

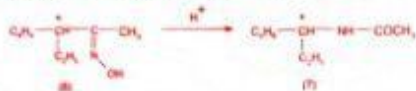


treatment of oxime (1) with acid generates a good leaving group (-OH group is converted to H_2O^+ with H_2SO_4 -OPCL with PCl_5 and -OSOC $_2$ H $_5$ with $C_2H_5SOCl_2$) on the nitrogen atom. Loss of the leaving group generates an electron-deficient species, which is accompanied by migration of a group from adjacent carbon to the electron-deficient nitrogen. The resulting iminocarboxide (2) traps water to give an amide (3) as the final product. The driving force for the 1,2-alkyl shift is the formation of more stable carbocation. It is established that when migrating group is aryl, the electron-withdrawing groups (e.g., *p*-nitro and *p*-chloro) on the migrating group strongly retard rearrangement and electron-donating groups (e.g., *n*-methyl and *p*-methoxy) strongly accelerate it.

The role of most acylating agents in bringing about rearrangement is clearly one of esterification. For most acylating agents the ester esters can be isolated at low temperature but rearrange explosively when brought to room temperature. When phosphorus pentachloride is used to effect rearrangement, a tetrachlorophosphoryl derivative¹ (4) is first produced. This undergoes rearrangement with cleavage of phosphorus chloride and chloride ion. The chloride ion unites with trimethylcarbonium cation (2) to form the imidoyl chloride (5), which reacts with water to yield (3).



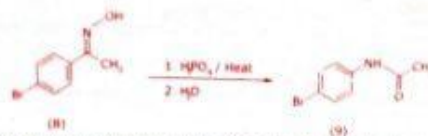
Since chiral groups migrate intramolecularly with retention of configuration, it is most likely that the migrating group is never completely separated from the remainder of the molecule. For example, (+)-methyl-3-heptyl ketoxime (6) is converted by rearrangement to 3-acetamidohexane (7) with retention of configuration¹.



The rearrangement is highly stereospecific, that is, the group *anti*- to the oxime hydroxyl group always migrates regardless of relative migratory aptitude of the two groups. Thus, different geometrical isomers of oximes sometimes give isomeric amides by the Beckmann rearrangement. For example, in acetophenone oxime shown below, it is the phenyl group which migrates and thus the product formed is acetanilide (for its mechanism, see sec. 5.11).



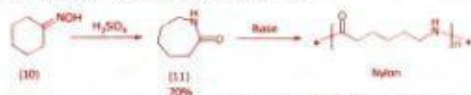
Similarly, *anti*-4-bromophenyl methyl ketoxime (8) when treated with H_3PO_4 gives *p*-bromoacetanilide (9).



Thus, Beckmann rearrangement involves the concerted stereoselective migration of the alkyl group or aryl group *anti* to the OH group in the starting material. However, sometimes *syn-anti* isomerisation under the acidic conditions of rearrangement leads to mixture of isomeric amides. Aldoximes are not usually good substrates for Beckmann rearrangement and the yields of amides obtained from aldoximes are generally poor.

Applications

1. A synthetically useful example of Beckmann rearrangement is the synthesis of caprolactam² from cyclohexanone oxime (10) in presence of concentrated sulfuric acid. Caprolactam (11) upon alkaline polymerization gives nylon.



2. Beckmann rearrangement establishes the stereochemistry of the oxime as it occurs by migration of a group *anti* to the oxime hydroxyl.

3. Some other applications^{3,4} are given below.



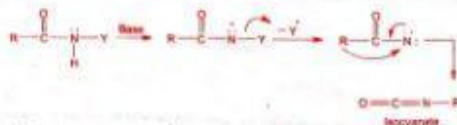
¹ Oximes can exhibit geometrical isomerism. The customary nomenclature for geometrical isomers of oximes is the *cis* and *anti* in place of *ery* and *threo*. The usual convention is to refer the position of the hydroxyl group to the first named portion of the ketone skeleton, or to the hydrogen of aldehydes.

References

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6.2.2 Hofmann rearrangement

There is a group of closely related rearrangements, which convert N-substituted amide to isocyanates. These reactions involve a migration of alkyl or aryl group from adjacent carbon to electron-deficient nitrogen. Although these reactions have a common mechanism and intermediate but their starting materials are different, therefore they are treated individually.

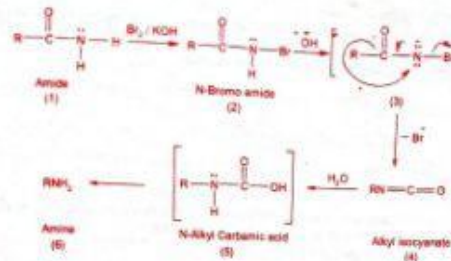


The Hofmann rearrangement¹ refers to the conversion of primary amides into primary amines by the action of sodium hypohalite (usually generated *in situ* from halogen and sodium hydroxide). The most important feature of the rearrangement is that the amine formed has one less carbon atom in the molecule than the original amide. Thus, propanamide gives ethylamine on treatment with sodium hypobromite (or bismine and KOH).

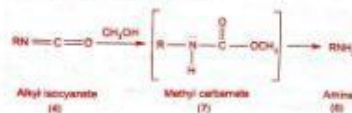


Mechanism

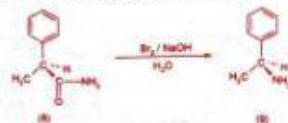
The reaction is believed to proceed by the following sequence of steps. In the first step, N-bromoamide (2) is formed by the action of alkaline hypobromite on the amide (1). The N-hydrogen atom of N-bromoamide (2) becomes acidic because it has electron-withdrawing acyl and electronegative halogen functions. The second step in the reaction involves removal of the acidic hydrogen from the N-haloamide (2) by the hydroxide ion. Removal of this proton by base gives the transit nitrogen anionic species (3), which is unstable and loses bromide ion with the simultaneous migration of aryl or alkyl group from the adjacent carbon atom to the nitrogen. The resulting isocyanate (4) is hydrolyzed under the reaction conditions to N-substituted carbamic acid (5), which is unstable and finally decarboxylates into the primary amine (6).



When the reaction is carried out in methanol, the intermediate isocyanate is converted into methyl carbamate (7), which may be isolated and hydrolyzed subsequently. Hydrolysis of methyl carbamate yields amine.



It is believed that the loss of halogen ion and the shift of alkyl or aryl group occur simultaneously. Migrating group does not break away from the carbon till it has started to bind itself with nitrogen. Hence, the reaction must proceed through a transition state in which the migratory group is partially bonded to both the migrating origin and the migration terminus. Optically active amides undergo rearrangements with complete retention of configuration. Thus, the rearrangement is stereospecific, the stereochemistry of the migrating groups is maintained. For example, (S)-(+)-2-phenylpropanamide (8) gives 96% optically pure, (S)-(-)-α-phenylethylamine (9).

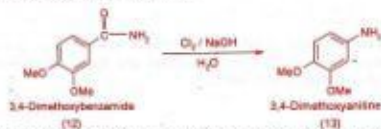


Applications¹⁻⁴

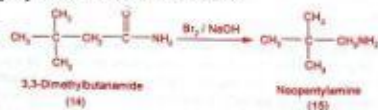
The Hofmann rearrangement has broad scope and is used for the synthesis of aliphatic, aromatic and heterocyclic amines. Preparation of 1-methylcyclohexyl amine (11) from 1-methylcyclohexyl amide (10) illustrates this reaction.



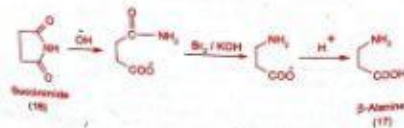
Preparation of 3,4-dimethoxyaniline (13) from 3,4-dimethoxybenzamide (12) is another application of Hofmann rearrangement.



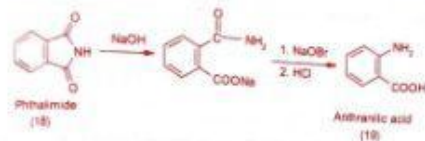
Amines that are difficult to prepare by other methods such as nucleophilic substitution reactions can be prepared by this method. For instance, neopentylamine (15) can be prepared from 3,3-dimethylbutanamide (14) in 94% yield by the Hofmann rearrangement. Direct substitution of neopentyl bromide with ammonia by $\text{S}_{\text{N}}2$ reaction does not give product because of steric hindrance.



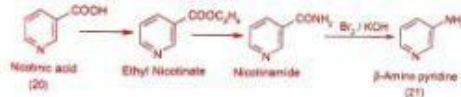
Certain amino acids like anthranilic acid and β -alanine have been prepared from the appropriate imides. For example, succinimide (16) reacts with bromine and aqueous potassium hydroxide to give β -alanine (17) in 45% yield.



Important industrial application of Hofmann rearrangement is the synthesis of anthranilic acid (19) from phthalimide (18).



The reaction is of particular use in cases where it is difficult to introduce amino group on the aromatic ring by direct nitration-reduction sequence. For example, β -aminopyridine (21) is prepared in good yield via Hofmann rearrangement of naturally occurring nicotinic acid (20), since it cannot be prepared in good yield from pyridine via the direct nitration-reduction sequence.



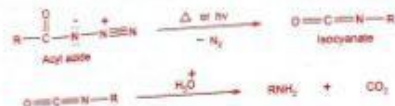
N-Alkyl ureas (22) are converted into corresponding hydrazines (23) via an analogous reaction.

**References**

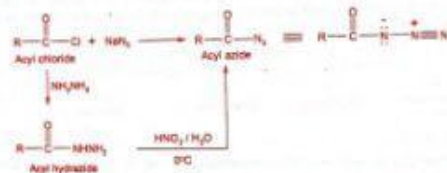
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6.2.3 Curtius rearrangement (reaction)

Thermal rearrangement of acid azides in non aqueous solvents such as chloroform, benzene or ether to an isocyanate, is known as **Curtius rearrangement**. Isocyanate on hydrolysis gives primary amine. The reaction converts acid azide into amine with loss of N_2 .



The acid azides required as starting materials may be prepared either by action of sodium azide on acid chlorides or by action of nitrous acid upon acid hydrazides. The acid hydrazide can be obtained by treatment of an ester or acid chloride with hydrazine.



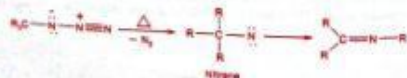
The rearrangement of acid azide to isocyanate is similar to the Hofmann rearrangement. In Curtius rearrangement, however, the intermediate isocyanate may be isolated by performing reaction in an inert aprotic solvent, such as benzene, chloroform etc.

Mechanism

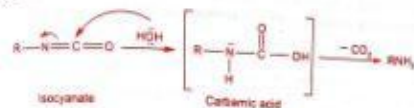
Acid azide loses molecular nitrogen when heated in inert solvent or when irradiated and rearranges to the isocyanate. The reaction probably occurs via a concerted rearrangement without involving intermediate nitrene.



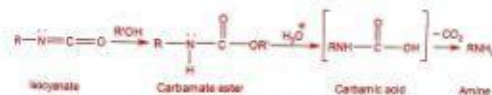
However, there is evidence² to support the existence of nitrene intermediate when tertiary alkyl azides undergo Curtius rearrangement to form imines.



Subsequent hydrolysis of isocyanate gives corresponding primary amine. Isocyanate is unstable and attack by water on the carbonyl group gives a carbamic acid, which decomposes to an amine.

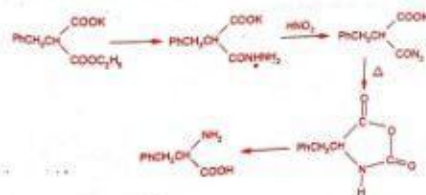


When acid azide is decomposed in the presence of alcohol, the isocyanate formed initially, reacts with alcohol to form a carbamate ester. Hydrolysis of carbamate ester gives the corresponding amine.



Applications

By this method it is possible to prepare aliphatic, alicyclic, aromatic or heterocyclic amines. α -Amino acids¹ may be obtained by applying the Curtius rearrangement. For example, β -phenyl alanine can be prepared from substituted malonic acid ester in good yield.

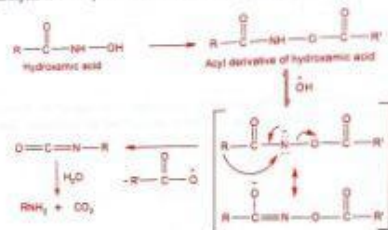


References

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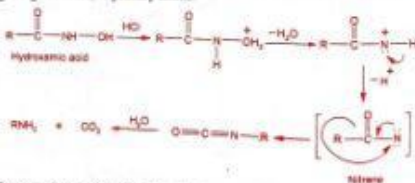
6.2.4 Lossen rearrangement (reaction)

The rearrangement of acyl derivative of hydroxamic acid to isocyanate, followed by hydrolysis to corresponding amine is known as **Lossen reaction**.



This is the another variation of **Hofmann rearrangement** (see sec. 6.2.2). The only difference between Hofmann rearrangement and Lossen rearrangement is that in the latter case the acyl derivative of hydroxamic acid is decomposed in the presence of base and the leaving group is a carboxylate anion rather than bromide ion as in Hofmann rearrangement. Lossen rearrangement has little synthetic importance because hydroxamic acids are not readily available.

Hydroxamic acid itself may undergo the Lossen rearrangement, by the action of strong inorganic acids, to primary amine.



An electron-releasing group on the migrating aryl group accelerates the reaction and electron-withdrawing group retards the reaction, thereby supporting the formation of a phenonium ion.

References

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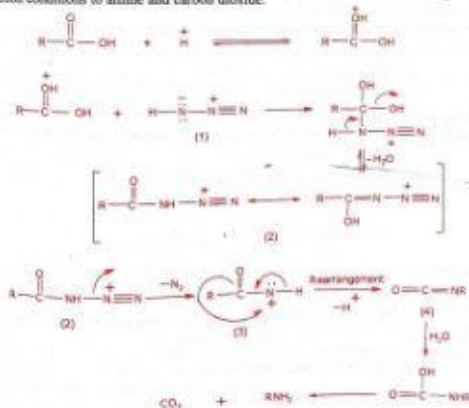
6.2.5 Schmidt rearrangement (reaction)

The conversion of carboxylic acid to primary amine having one carbon less is accomplished by **Schmidt reaction**¹. Schmidt reaction is mechanistically related to **Curtius reaction** (sec. 6.2.3). However, in this case the conversion of carboxylic acid to primary amine occurs in one step by reaction with hydrazoic acid in the presence of concentrated H_2SO_4 . This one-step procedure is convenient and yields are higher than the related Hofmann and Curtius rearrangement procedures and sterically hindered acids react very smoothly. Hydrazoic acid is toxic and explosive and hence it is generated *in situ* by adding sodium azide gradually to the carboxylic acid in the presence of sulfuric acid.



Mechanism

The addition of hydrazoic acid (1) to a protonated carboxylic acid produces protonated acyl azide (2), which loses nitrogen to give the intermediate (3). Subsequent removal of proton and rearrangement in (3) produces isocyanate (4), which is hydrolyzed under the reaction conditions to amine and carbon dioxide.



The ketones² can also react with hydrazoic acid under strong acid conditions to give amides by the Schmidt reaction. For example, benzophenone is converted into benzanilide.



With unsymmetrical ketones, two isomeric amides can be formed. However, with alkyl aryl ketone, it is usually aryl group which migrates. For instance, acetophenone gives acetanilide in 77% yield.



Since the hydrolysis of amides give amines, it is a convenient two step procedure for the conversion of ketones into amines. The product of Schmidt reaction in ketones is amides but aldehydes give mainly mixture of nitriles and N-formyl derivatives.

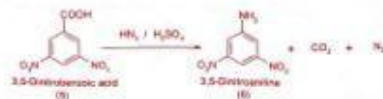


Cyclic ketones undergo a ring enlargement to give lactams, thus, Schmidt reaction provides a synthetic alternative to the Beckmann rearrangement (see sec. 6.2.1).



Applications

A synthetically useful example of this process is the conversion of 3,5-dinitrobenzoic acid (5) to 3,5-dinitroaniline (6) and cyclobutanecarboxylic acid (7) to cyclobutylamine (8).



References

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3. N. W. Werner, *J. Cosanova, Jr.*, *OS*, 1967, 47, 28.

6.3 Rearrangements involving migration to electron-deficient oxygen

This section treats the rearrangements involving migration of an alkyl, aryl, and acyl group, with the pair of electrons, to electron deficient oxygen. The rearrangements in which the migration terminus is an electron-deficient oxygen atom, are parallel to rearrangements in which the migration terminus is an electron-deficient nitrogen. The only difference is that, the leaving group in the former cases is an oxy anion (or the conjugate acid) formed by heterocyclic cleavage of the O-O bond in peroxides.

6.3.1 Baeyer-Villiger oxidation

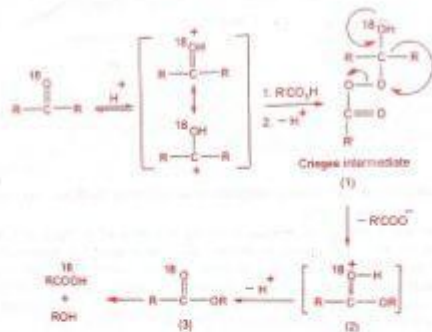
Oxidation of ketones to esters with hydrogen peroxide or with peracids (RCO_3H) is known as **Baeyer-Villiger oxidation**. Baeyer-Villiger used Caro's acid (peroxy sulphuric acid) in their experiments. The reaction can be brought about conveniently by hydrogen peroxide in weakly basic solutions. Typical peracids used are peracetic acid, trifluoroperoacetic acid, perbenzoic acid, performic acid and *m*-chloroperobenzoic acid (*m*-CPBA). A typical example of Baeyer-Villiger oxidation is reaction of acetophenone with performic acid at room temperature to furnish phenyl acetate in 63% yield.



With Caro's acid the rearrangement step is much faster than with performic acid because sulfate is a better leaving group than acetate. Trifluoroperoacetic acid is the most efficient reagent for this rearrangement. For instance, cyclohexanone reacts 200 times faster with trifluoroperoacetic acid than peracetic acid. However, *m*-CPBA is the most common reagent because it is commercially available. An important modification of the Baeyer-Villiger oxidation is **Dakin reaction** (sec. 6.3.3).

Mechanism

The mechanism of Baeyer-Villiger rearrangement is not clear, however it is believed that the reaction proceeds as follows.



The first step involves the protonation of carbonyl oxygen. The addition of peracid to the initially protonated ketone gives a tetrahedral intermediate (1). Elimination of carboxylate anion and migration of R to the electron deficient oxygen atom occur simultaneously. The resulting protonated form of ester (2) loses a proton to yield ester (3). Thus, the reaction involves a migration of alkyl or aryl group from adjacent carbon to electrophilic oxygen. As the leaving group, carboxylate anion departs, partial positive charge develops at the oxygen atom and 1,2-alkyl shift from adjacent carbon to oxygen takes place. It is believed that the loss of carboxylate anion and migration of R are concerted. A mechanistic study using ^{18}O labelled ketone has demonstrated that the carbonyl oxygen of the ketone becomes the carbonyl oxygen of the ester and the ester has the same ^{18}O content as the ketone. These observations support the above mechanism suggested for Baeyer-Villiger oxidation.

Migrating aptitude

The order of preference for migration among alkyl groups is tertiary > secondary > primary > methyl. Aryl group migrates in preference to methyl and primary alkyl groups. In the aryl series, migration is facilitated by electron-releasing *para* substituents. Thus migratory aptitude among aryl groups is $p\text{-CH}_3\text{OC}_6\text{H}_4 > \text{C}_6\text{H}_5 > p\text{-O}_2\text{NC}_6\text{H}_4$. For example, phenyl *p*-nitrophenyl ketone (4) yields only phenyl *p*-nitrobenzoate (5) by migration of phenyl group.



The reaction is faster for peracids substituted by electronegative group and for ketones bearing electropositive substituents. Phenyl groups which are *ortho*-substituted migrate less readily than their *para*-substituted counterparts.

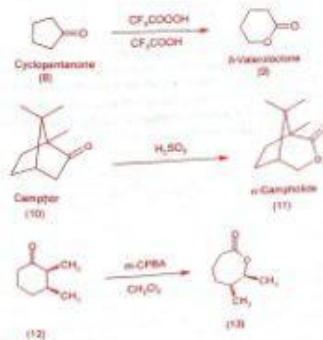
Stereochemistry

The stereochemistry of the Baeyer-Villiger oxidation is same as that of carbon to nitrogen rearrangements. The ketone (6) in which the migrating group has an asymmetric center gives product, (7), with complete retention in configuration.



Applications

Baeyer-Villiger oxidation has great synthetic utility as it permits the transformation of ketones into esters. An oxygen atom is inserted next to the carbonyl group. This reaction is applicable to both acyclic ketones and cyclic ketones. Oxidation of cyclic ketones occurs with ring expansion and form lactones as illustrated in the conversion of cyclopentanone (8) to the δ -valerolactone (9). Similarly, camphor (10) on Baeyer-Villiger oxidation gives α -campholide (11) in 30% yield by use of Caro's acid and 2,3-dimethyl cyclohexanone (12) can be converted into the lactone (13) by this method.



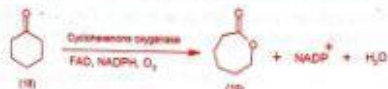
Other carbonyl compounds that undergo oxidation with peracids are 1,2-diketones and α -ketoesters. For example, oxidation of α -diketone (14) gives an anhydride, (15).



Baeyer-Villiger oxidation is a very useful method for the synthesis of large ring lactones, which are otherwise difficult to prepare by intramolecular esterification of long-chain hydroxyacids. For instance, the lactone (17) (from angelica oil) can be prepared by the Baeyer-Villiger oxidation of cyclopentadecanone (16).

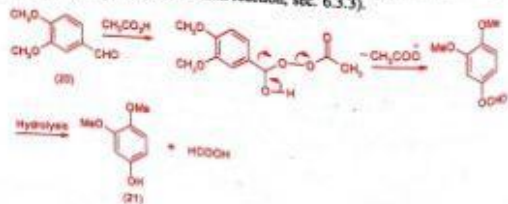


Baeyer-Villiger oxidation is also possible by the action of enzymes.¹ For example, cyclohexanone (18) is converted into (19) by using a purified cyclohexanone oxygenase enzyme.



Aldehydes also undergo the Baeyer-Villiger oxidation to usually give carboxylic acids.¹ The reaction involves either migration of hydrogen or fragmentation of the intermediate.

The ester formed in Baeyer-Villiger oxidation can be hydrolyzed to correspond to phenol, thus it provides a route to transfer aldehydes or ketones to phenol. Veratraldehyde (20), for example, is converted into 3,4-dimethoxyphenol (21) by oxidation with peracid followed by hydrolysis (also see Dakin reaction, sec. 6.3.3).

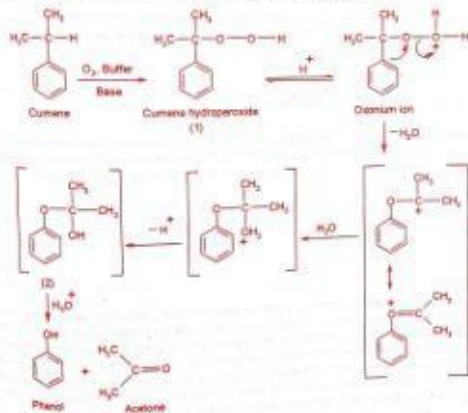


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1. A. V. Bayer and V. Villiger, Ber., 1899, 32, 3625.
2. H. O. House, Modern Synthetic Reactions, 2nd edn., Benjamin, Menlo Park, New York, 1972, pp. 321.
3. W. D. Emmons and G. B. Lucas, J. Am. Chem. Soc., 1953, 75, 3287.
4. C. C. Ryerson, D. P. Ballou, C. Walsh, Biochemistry, 1982, 21, 2644; N. A. Donoghue, D. R. Norris, P. W. Trudgill, Eur. J. Biochem., 1976, 63, 175.
5. R. Kwart and N. J. Wegener, J. Am. Chem. Soc., 1961, 83, 2746.

6.3.2 Hydroperoxide rearrangement

The acid-catalysed rearrangement of hydroperoxides proceeds by a mechanism similar to that of Baeyer-Villiger oxidation (sec. 6.3.1). For example, cumene hydroperoxide (1) when treated with sulfuric acid gives hemiacetal (2). Hydrolysis of unstable hemiacetal gives phenol and acetone. The cumene hydroperoxide can be obtained by autooxidation of cumene. This is the commercial method for the preparation of phenol.



The first step in the mechanism involves the protonation by acid at the oxygen atom of cumene hydroperoxide. This is followed by the cleavage of the peroxide bond and migration of phenyl group to the alkyl or aryl group from adjacent carbon to oxygen. The migration of phenyl group to the resulting electron-deficient oxygen atom is synchronous with the loss of a water. The resulting carbocation intermediate is hydrated to give a hemiacetal.

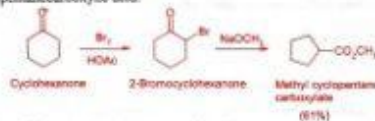
migration of carbon occurs from C, N, S and O to an adjacent atom bearing an unshared electron pair and negative charge. For example, **Wittig rearrangement** involves oxygen to carbon migration. **Stevens rearrangement** involves nitrogen to carbon migration. Carbon to carbon migration is also possible.

6.4.1 Favorskii rearrangement¹⁻³

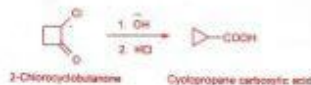
The base-catalysed rearrangement of α -haloketones (chloro and bromo) to carboxylic acid derivatives is called **Favorskii rearrangement** (reaction).



The rearrangement of cyclic ketones involves ring contraction, for example, 2-bromocyclohexanone when treated with sodium methoxide is converted into methyl cyclopentanecarboxylate.

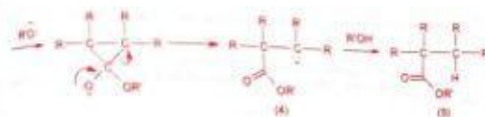
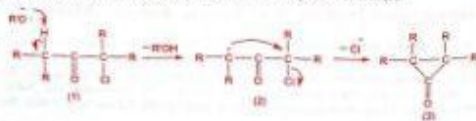


2-Chlorocyclobutanone on treatment with sodium methoxide, followed by hydrolysis is converted into cyclopropanecarboxylic acid.

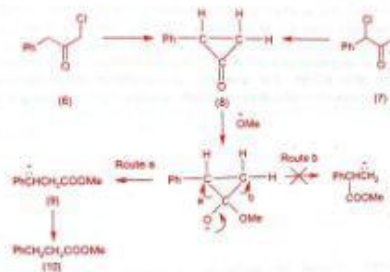


Mechanism

The generally accepted mechanism involves the reactive cyclopropanone intermediate. Base abstracts the α -hydrogen from (1) to give the carbanion (2), which undergoes intramolecular S_N2 displacement of the halide ion. The resulting cyclopropanone intermediate (3) is opened under the reaction conditions to give the more stable carbanion (4), which takes proton from solvent to furnish final product, ester (5).



The above mechanism is supported by the fact that same ester (10) is formed from the *isomeric* haloketones (6) and (7).



Orientation of ring opening of the cyclopropanone intermediate

In the symmetrical cyclopropanone intermediate, the two α -carbons are equivalent, and in the unsymmetrical cyclopropanone intermediate, the two α -carbons are not equivalent. However, unsymmetrical ring opening via route a or route b gives the same carbanion of the two cyclopropanone ring opens in such a way so that the more stable carbanion of the two cyclopropanone ring opens in such a way so that the more stable carbanion is formed. For instance, the cyclopropanone ring (8) opens via route-a to give the more stable of two possible carbanions that can be formed. The carbanion is stabilized by resonance, therefore it is preferred and the product is $\text{PhCH}_2\text{CH}_2\text{COOCH}_3$ (10).

Favorskii rearrangement of α,α and α,α' -dihaloketones leads to the formation of $\beta\beta$ -unsaturated esters. In this case ring opening involves elimination of halide ion.



References

1. A. E. Favorskii, *J. Prakt. Chem.*, 1913, 86(2), 658; *O. Wallach, Ann.*, 1918, 474, 296.
2. H. R. , *J. Org. Chem.*, 1967, 32, 5438.
3. R. B. Wagner, *J. Am. Chem. Soc.*, 1950, 72, 972.
4. N. Schamp, N. Dejonghe, W. Coppens, *Tetrahedron*, 1975, 31, 2081.
5. R. B. Lofield, *J. Am. Chem. Soc.*, 1950, 72, 632; F. G. Bordwell and R. G. Scammon, *J. Am. Chem. Soc.*, 1968, 90, 6791.

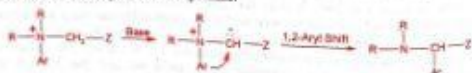
6.4.2 Stevens rearrangement

A quaternary ammonium salt, in which none of the alkyl group is having a β -hydrogen atom but one of the alkyl group has an electron-withdrawing group β - to the nitrogen atom, undergoes base-catalysed rearrangement¹ to yield a tertiary amine. The rearrangement involves migration of a group, without pair of electrons, from nitrogen to carbon having negative charge. For example, phenacylbenzyltrimethylammonium bromide (1) gives α -dimethylamino- β -phenylpropiophenone (2) on treatment with aqueous hydroxide.



Mechanism

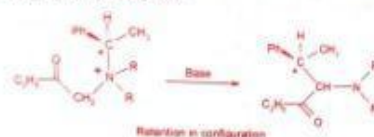
Crossover experiments showed the mechanism of Stevens rearrangement to be intramolecular. It was thought earlier that this rearrangement occurred in a concerted manner. The base abstracts the hydrogen from the ammonium salt to give the ylide which rearranges to give the tertiary amine.



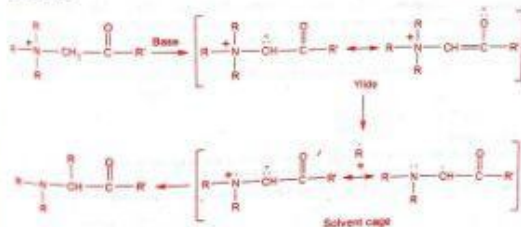
The role of electron-withdrawing group, such as a carbonyl group, is to stabilize the ylide.



However, it was further observed that the rearrangement occurs with retention of absolute stereochemistry at the migrating center.

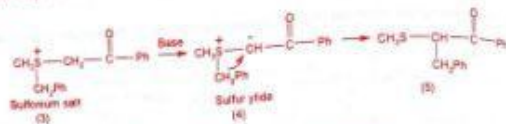


Concerted rearrangement shown above would not be an allowed reaction according to orbital symmetry rules. Such observations, therefore, rule out a concerted mechanism and a radical pair mechanism is proposed. The radical pair mechanism involves deprotonation followed by homolytic fragmentation of ylide to produce a pair of radicals. The rapid recombination of pair of radicals, which remain together in a tight solvent cage, gives the final product. Formation of small amount of coupling product R-R supports this mechanism.



A third mechanism is also proposed, in which ion pairs are formed instead of radical pairs. Benzyl group migrates in preference to alkyl group.

A variant of the Stevens rearrangement is the rearrangement of sulfur ylides². For example, sulfonium salt (3) on deprotonation gives a sulfur ylide (4), which subsequently rearranges to (5). Quaternary salts having β -hydrogen atom undergo elimination with base to give alkene and tertiary amine. The reaction is known as Hofmann elimination (see chapter 1.5; 5.43).

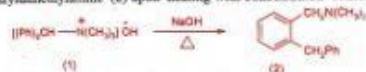


References

1. T. Thomson and T. S. Stevens, *J. Chem. Soc.*, 1932, 55; T. S. Stevens, E. M. Crighton, A. B. Gales, M. MacNicol, *J. Chem. Soc.*, 1928, 3193.
2. R. E. Olsen and J. O. Cosso, *The Chemistry of the Thiol Group* (Ed. S. Patai, Wiley), 1974, 7, 561-566.

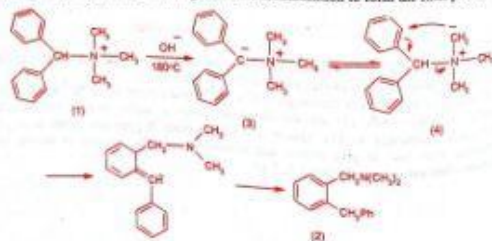
6.4.3 Sommelet-Hauser rearrangement

Sommelet¹ discovered this rearrangement first in 1937. He found *o*-benzhydryltrimethylammonium hydroxide (1) rearranged to *o*-benzylbenzyltrimethylamine (2) upon heating with concentrated sodium hydroxide.

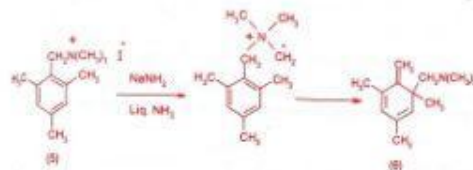


Mechanism

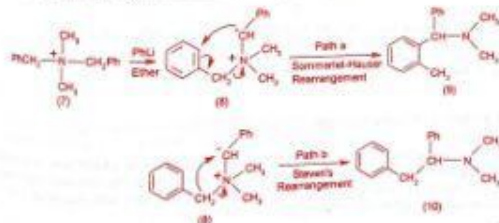
The mechanism involves the initial deprotonation of the benzylic position to produce (3) which is in equilibrium with a second ylide (4). Though ylide (4) is in small amount, it undergoes 2,3-sigmatropic rearrangement and aromatization to form the final product (2).



This mechanism is supported by the fact that when 2,4,6-trimethylbenzyltrimethyl ammonium iodide (5) is treated with sodamide in liq. NH_3 , the product (6) formed is not *o*-methyl.



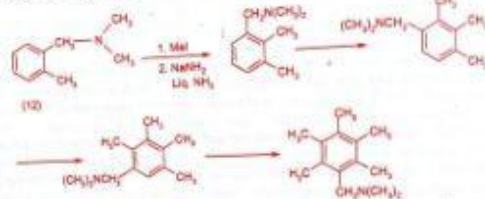
Wing² in 1948 also observed the same product (2) along with Stevens rearrangement product (see sec. 6.4.2) when benzhydryltrimethylammonium bromide was treated with phenyllithium in ether. Thus, the reaction of benzyl quaternary ammonium salts with base often competes with Stevens rearrangement. For example, when dibenzyltrimethylammonium salt³ (7) is treated with phenyllithium in ether (strong base), both the Sommelet-Hauser rearrangement product (9, path a) and Stevens rearrangement product (10, path b) are obtained. Both rearrangements proceed via the same intermediate (8). At high temperature Stevens rearrangement is preferred, while at low temperature, the yield of Sommelet rearrangement product increases.



Hauser⁴ found that Sommelet type rearrangements occur by the use of sodium or potassium amide in liquid ammonia and no Stevens type rearrangement products were observed. Thus, when benzyltrimethylammonium salt (11) is treated with sodamide in liq. NH_3 only Stevens rearrangement product, 2-dimethylaminomethyl toluene (12) is obtained.



The process of methylating around the ring may continue by successively methylating the rearranged product (tertiary amine, 12) and then repeating sodamide treatment.



Method

1. M. Szwarc, *Com. Rend.*, 1937, 205, 56; *Bull. Soc. Chim. France*, 1918, 23, 95.
2. G. Wittig, R. Margold, and G. Feilen, *Chim. Ann.*, 1948, 580, 117.
3. G. Wittig, H. Tishoff, W. Schach, and G. Koenig, *Ann.*, 1951, 572, 1.
4. S. W. Kutter and C. R. Hauser, *J. Am. Chem. Soc.*, 1951, 73, 4122.

6.4.4 Wittig rearrangement

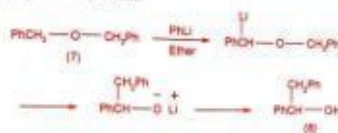
Rearrangement of benzyl and allyl ethers with strong base such as alkyllithium is known as **Wittig rearrangement**. Wittig rearrangement is related to the Stevens rearrangement (see sec. 6.4.2). For example, benzyl phenyl ether (1) on treatment with sodium at 100°C gives benzhydrol (2) in 30% yield.



A powerful base such as phenyllithium or sodamide is required to abstract a proton from ethers. For example, a strong base, phenyl-lithium, abstracts a proton from benzyl methyl ether (3) to afford the conjugate base (4). 1,2-Methyl shift from oxygen, without work up produces the corresponding alcohol (6).

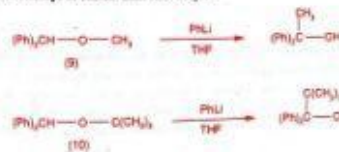


Similarly, dibenzyl ether (7) gives 1,2-diphenylethanol (benzylphenylmethanol) (8) on treatment with phenyl-lithium in ether.

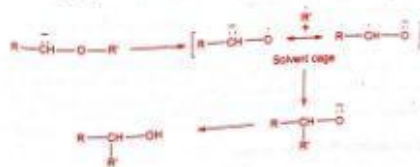


Negotiating aptitude

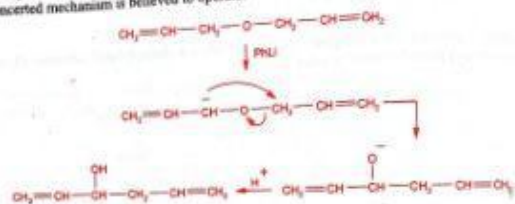
The migratory aptitude of various groups is found¹ to be in the order: Allyl, benzyl > n-ethyl, ethyl, *p*-nitrophenyl > phenyl. Wittig² compared the rates of rearrangement of benzhydryl methyl ether (9) and benzhydryl *tert*-butyl ether (10). It was found that the migration of methyl is faster than *tert*-butyl.



There is enough evidence to support the radical pair mechanism for Wittig rearrangement where migrating group is alkyl or aryl.



Evidence in favor of radical pair mechanism is (a) migratory aptitudes of various groups are in the order of free-radical stabilities, (b) the rearrangement is intramolecular, and (c) the aldehydes are obtained as side products. However, when allyl group migrates, the concerted mechanism is believed to operate.

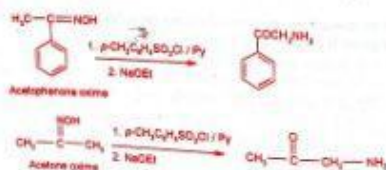


References

1. G. Wittig, *Angew. Chem.*, 1954, 66, 38.
2. G. Wittig and H. Schön, *Chem. Zentr.*, 1959, 1/8, 12183.

6.4.5 Neber rearrangement

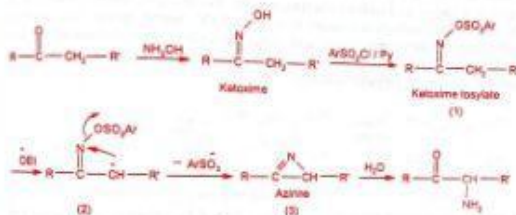
Neber rearrangement¹ (reaction) is closely related to Beckmann rearrangement (see sec. 6.2.1). It is a base-catalysed conversion of oxime tosylate to α -aminoketones via azirines. Tosyl esters of ketoximes having α -hydrogen atoms rearrange to give α -aminoketones under the catalytic influence of base, such as ethoxide ion or pyridine. For example, oximes of acetophenone and acetone are converted into the corresponding α -aminoketones.



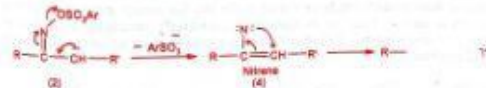
Aldoximes do not undergo this rearrangement.

Mechanism

There is enough evidence for the mechanism which involves the formation of an azirine. Cram and Hatch² have confirmed the structure of isolated azirine. The base removes a proton from (1) to give (2), which undergoes internal displacement to form an intermediate azirine (3). Subsequent attack by water gives the final product, α -amino ketones.



However, it is also suggested that azirine formation might involve the nitrene (4) intermediate.



References

1. C. O'Brien, *Chem. Rev.*, 1964, 64, 81; R. E. Baugarten and F. A. Bower, *J. Am. Chem. Soc.*, 1954, 76, 4561.
2. D. I. Cram and M. J. Hatch, *J. Am. Chem. Soc.*, 1953, 75, 38.

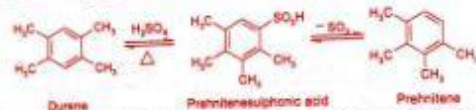
6.5 Aromatic rearrangements

The aromatic rearrangements, we will discuss here, include the rearrangements in which a group migrates from one position to another in an aromatic system or from a side chain to the aromatic nucleus. Such rearrangements are initiated by the generation of an arenium ion. The mechanism of aromatic rearrangements may be considered similar to intramolecular electrophilic aromatic substitution processes.

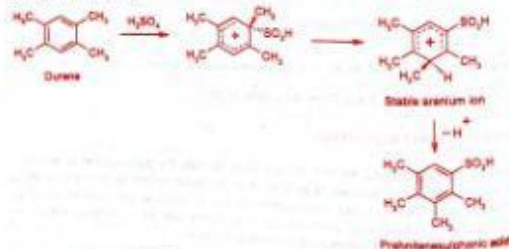
(A) Migration around the aromatic nucleus

6.5.1 Migration of alkyl groups

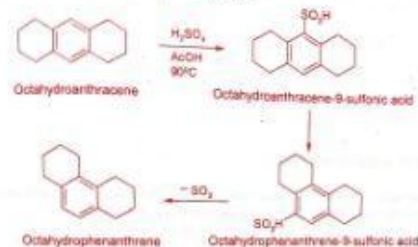
Alkyl groups attached to benzene ring can be migrated from one position to another. Migration of alkyl group from one position to another in polyalkylbenzenes during sulfonation is known as **Jacobsen rearrangement**¹. For example, durene on sulfonation yields a product prehnitenesulfonic acid, in which methyl group has migrated. Desulfonation of prehnitenesulfonic acid yields the hydrocarbon, prehnitene² in 41% yield. Thus, Jacobsen rearrangement, followed by desulfonation sequence can be used as a means of rearranging polyalkylbenzenes.



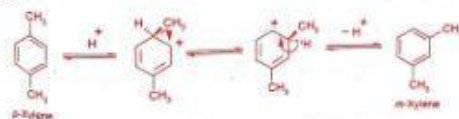
The mechanism involves the *ipso*-sulfonation, followed by intramolecular migration of methyl group without pair of electrons to give most stable arenium ion. In the last step H^+ is lost to regenerate the aromatic ring. The reaction is intramolecular, however, sulfonation of durene gives some trimethyl and pentamethylbenzene sulfonic acids. Formation of these products can be explained by the fact that methyl group migrates from one nucleus to another. Since the mechanism is undoubtedly intramolecular, the cross-migration probably involves a shift of methyl from a benzenonium ion to another nucleus by an S_N2 mechanism:

Applications³

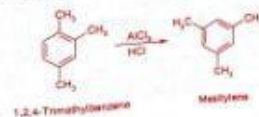
An important application of the Jacobsen rearrangement is the isomerisation of octahydroanthracene to octahydrophenanthrene.



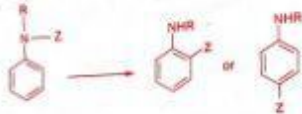
In a number of cases, **Friedel-Crafts alkylation** (see sec. 1.6) leads to a rearranged product, involving change in the relative position of substituents in the benzene ring. Under the influence of Lewis acid, the polyalkylbenzenes undergo isomerisation. Thus, under Friedel-Crafts alkylation conditions *p*-xylene is converted into the more stable *m*-xylene. The mechanism involves the migration of methyl group in the initially protonated species.



Similarly, 1,2,4-trimethylbenzene isomerises to mesitylene in presence of $AlCl_3$ and HCl and 6,7-dimethyltetralin is converted into 5,6-dimethyltetralin.

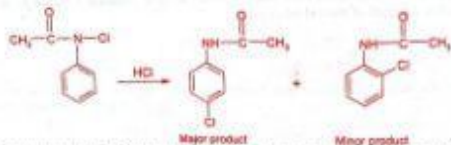


intermolecular or intramolecular mechanism. The aniline derivatives of the type PhN(R)Z , where Z is R, X, NH_2 , NO, or NO_2 etc., undergo this type of rearrangement.

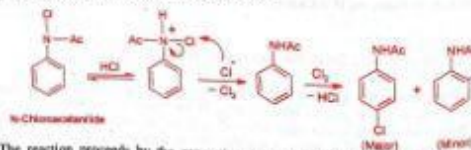


6.5.4 Rearrangement of N-haloacetanilides

Rearrangement of N-haloacetanilides in presence of corresponding aqueous HX to p-haloanilides together with small amount of o-haloanilides is known as **Orton rearrangement**. The rearrangement is also called **chloramine rearrangement** and is most commonly carried out with N-chloro- and N-bromoanilides.



The rearrangement of N-haloacetanilides in aqueous mineral acid takes place by an intermolecular mechanism as shown below.

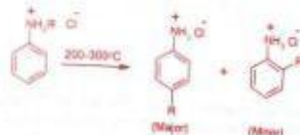


The reaction proceeds by the generation of Cl_2 which becomes attached to p- or o-positions of the aromatic nucleus in an ordinary electrophilic substitution reaction. When reaction is carried out in the presence of HCl having radioactive chlorine, the product contains some radioactive chlorine. Thus, mechanism of this reaction is intermolecular.

6.5.5 Hofmann-Martius rearrangement

The rearrangement¹ of N-alkylaniline hydrochloride salts on strong heating at about 200–300°C is known as **Hofmann-Martius rearrangement**. In this reaction, an alkyl

group migrates from the nitrogen atom to para-position. If para-position is occupied, the ortho isomer is formed.



Mechanism

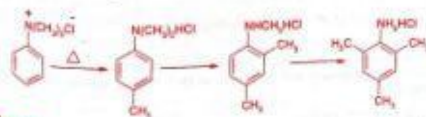
The mechanism of this rearrangement is intermolecular, and involves the formation of alkyl halide by the $\text{S}_{\text{N}}2$ reaction of mono N-alkylanilinium salt with Cl^- . Alkyl halide and aniline then undergo normal Friedel-Crafts alkylation process. However, with secondary or tertiary alkyl group, the reaction proceeds through the carbocations. While alkyl groups which are known to rearrange when set free in the form of carbocations do in fact give rearranged products, for example, n-butylaniline rearranges to tert-butylaniline.



Polyalkylated products may be isolated from the reaction mixture and primary alkyl side chains are isomerised. These observations support the above mechanism.

Applications

Phenyltrimethyl ammonium chloride when heated under pressure is converted to 2,4,6-trimethylaniline as its hydrochloride.

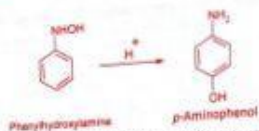


References

¹ A. W. Hofmann and C. A. Martius, Ber., 1871, 4, 742; A. W. Hofmann, Ber., 1872, 5, 720.

6.5.6 Rearrangement of phenylhydroxylamine

p-Phenylhydroxylamine under strong acidic conditions rearranges to p-aminophenol and the reaction is known as **Bamberger rearrangement**¹.



Ingold *et al* carried out this rearrangement in the presence of ^{18}O -labelled water (solvent) and found that the complete exchange of oxygen with the solvent took place. The available evidence shows that the mechanism of the reaction is intermolecular.



References

1. H. J. Shine, *Aromatic rearrangements*, Elsevier, New York, 1967, pp.182-190.
2. H. F. Heller, E. D. Hughes, and C. K. Ingold, *Nature*, 1951, 760, 989.

6.5.7 Rearrangement of diazoamino compounds

Rearrangement of diazoamino compounds to *p*-azo derivatives of primary and secondary aromatic amines occurs by treatment with acid, such as HCl. When *p*-position is blocked the *o*-isomer is obtained.



The mechanism is undoubtedly intermolecular¹ and involves the generation of ArN_2^+ , followed by diazo coupling of diazonium salt and amine.

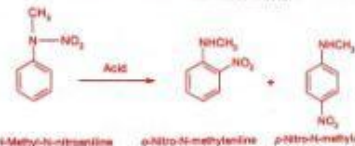


References

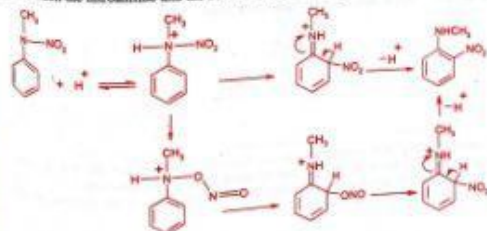
1. R. V. Kidd, *J. Org. Chem.*, 1937, 22, 198.

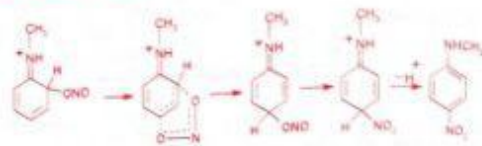
6.5.8 Rearrangement of N-nitroanilines

When treated with acids, N-nitroarylamines rearrange to corresponding *ortho*- and *para*-nitroanilines, but no *meta* isomer is obtained in this reaction.

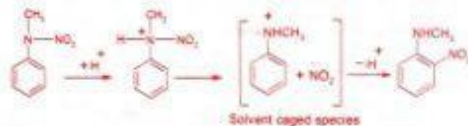


The reaction is intramolecular as indicated by the fact that the products from the rearrangement of N-nitroaniline differed from those obtained by nitration of aniline under the same conditions. For example, rearrangement of N-nitro-N-methylaniline in sulfuric acid gives 93% *ortho* and 7% *para* isomer. However, nitration of aniline yields 6% *ortho*, 34% *meta* and 59% *para* isomer. Hughes and Jones¹ have proposed a mechanism analogous to mechanism of Claisen rearrangement (see sec. 6.5.12). They studied the rearrangement by using ^{15}N as a tracer and found that no exchange of nitro groups took place between the nitroaniline and the added nitric acid during the rearrangement.





Above mechanism has several limitations such as conversion of a nitro compound to its isomeric nitrite and vice versa, which under these conditions have never been observed. The mechanism which is generally accepted is radical pair mechanism.² The homolytic cleavage of the protonated substrate gives the radical cation and a radical, which recombines before diffusing away from each other to give the final product.

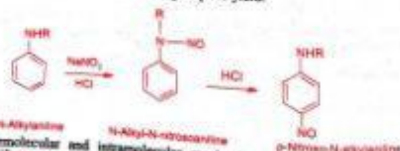


References

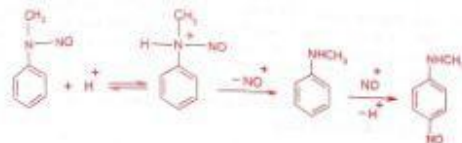
1. E. D. Hughes and G. T. Jones, *J. Chem. Soc. (London)*, 1950, 2678.
2. Ridd and Sandall, *J. Chem. Soc., Chem. Commun.*, 1982, 261.

6.5.9 Rearrangement of N-nitrosoanilines (Fischer-Hepp rearrangement)

N-alkyl-N-nitrosoanilines, obtained by nitrosation of N-alkylarylamines in presence of $\text{NaNO}_2 / \text{HCl}$ at 0°C , undergo rearrangement on treatment with HCl to give mainly the *p*-nitroso product.¹ Acids other than HCl give poor yield.



Both intermolecular and intramolecular mechanisms are proposed for this reaction. However, ^{15}N -labelled studies showed that the mechanism is intermolecular.² The reaction has great synthetic utility as it provides one of the methods for the synthesis of 4-nitroso-N-alkylanilines.



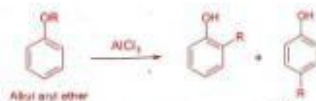
References

1. G. Fischer and E. Hepp, *Chem. Ber.*, 1886, 19, 2991.
2. Williams, *Tetrahedron*, 1975, 31, 1343; *J. Chem. Soc., Perkin Trans II*, 1975, 655; 1982, 801.

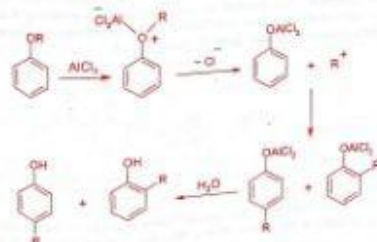
(ii) Rearrangements involving migration from oxygen to ring

6.5.10 Rearrangement of phenolic ethers

When alkyl aryl ethers are treated with Lewis acid, mixture of *o*- and *p*-alkylphenols is formed.



The exact mechanism is not clearly understood, but available evidence suggests that the reaction is intermolecular and involves the dealkylation followed by realkylation, as in *Friedel-Crafts* alkylation (see sec. 1.6).



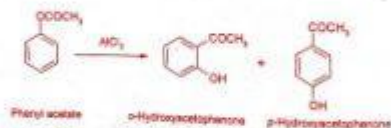
The formation of dialkylphenols as by-product from the reaction and rearrangement of *tert*-butyl aryl ethers to give exclusively *sec*-butylphenols¹ support that the mechanism of reaction is intermolecular. However, there is some evidence for intramolecular mechanism. Sprung and Wallis² have observed that rearrangement of optically active *sec*-butyl tolyl ether to 2-*sec*-butyl-4-methylphenol occurred with some retention of configuration. Thus, the rearrangement of alkyl aryl ethers can take place by both intermolecular and intramolecular routes.

References

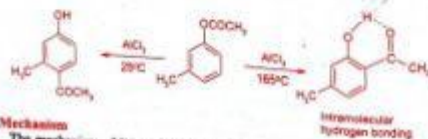
1. M. J. S. Dewar and N. A. Patman, *J. Chem. Soc. (London)* 1959, 4086-4090.
2. Sprung and Wallis, *J. Am. Chem. Soc.*, 1934, 56, 1715.

6.5.11 Fries rearrangement

Esters of phenols on heating with anhydrous aluminium chloride (Lewis acid) undergo rearrangement to give phenolic ketones. This is known as **Fries rearrangement**. A typical example is rearrangement of phenyl acetate to give mixture of *o*- and *p*-hydroxyacetophenone.



The nature of the alkyl residue, the temperature, the solvent and the amount of AlCl_3 used influence the relative amount of each isomer. In general, low temperatures ($< 50^\circ\text{C}$) favour the formation of the *p*-isomer and higher temperatures ($> 160^\circ\text{C}$) favour the formation of the *o*-isomer. The mixture of *o*- and *p*-isomers resulting from the Fries reaction can be separated by steam distillation. The *o*-isomers are intramolecularly hydrogen bonded (chelated) and have greater volatility.



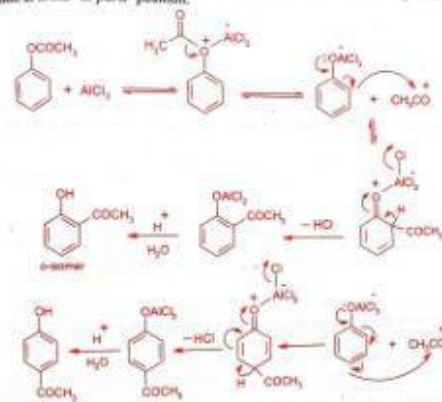
Mechanism

The mechanism of Fries reaction is not certain. There is evidence for an intermolecular mechanism, but recently it has been shown that the rearrangement is at least partly

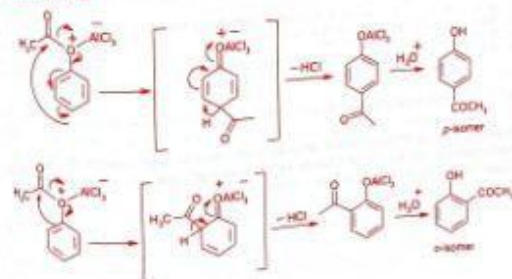
intramolecular. It would appear that the mechanism is best regarded as a combination of the two mechanisms occurring simultaneously.

Intermolecular

The mechanism involves the formation of acylium ion³ followed by Friedel-Crafts acylation at *ortho*- or *para*-position.

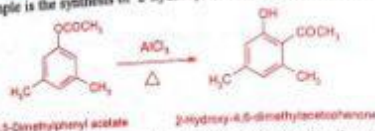


Intramolecular



Applications

An example is the synthesis of 2-hydroxy-4,6-dimethylacetophenone³ in 80% yield.



A synthetically useful example of this process is the preparation of 2,5-dihydroxyacetophenone from hydroquinone diacetate in good yield. 2,5-Dihydroxyacetophenone can not be prepared by Friedel-Crafts acetylation of hydroquinone.

**Photo-Fries rearrangements**

Phenolic esters in solution on photolysis give a mixture of *o*- and *p*-acylphenols. The Fries rearrangement unlike the normal Fries rearrangement does not need a catalyst and predominantly an intramolecular free radical process.

References

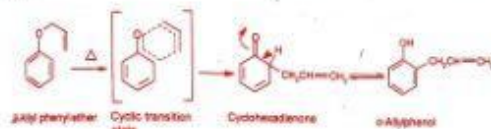
1. K. Fieser and G. Fink, *Ber.*, 1908, 41, 4271; K. Fries and W. Pfaffendorf, *Ber.*, 1910, 43, 212; S. S. Bhat, *Chem. Rev.*, 1940, 27, 429; Eilenberg, *Angew. Chem. Int. Ed.*, 1973, 12, 776; A. B. Ross, *Acc. Chem. Res.*, 1962, 1, 342.
2. N. M. Culver, A. G. Evans and E. T. Lloyd, *J. Chem. Soc.*, 1956, 2222.
3. Smith and Oye, *J. Org. Chem.*, 1941, 6, 427.
4. D. Bellus et al *Chem. Rev.*, 1967, 599.
5. J. C. Anderson and C. B. Reiss, *Proc. Chem. Soc.*, 1960, 217.

6.5.12 Claisen rearrangement

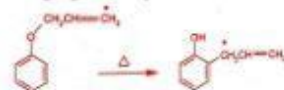
Rearrangement of allyl aryl ethers to *o*- or *p*-allylphenols is an example of sigmatropic rearrangement, and known as **Claisen rearrangement**. The allyl group migrates from oxygen to the ring preferably at *ortho*-position.

**Mechanism**

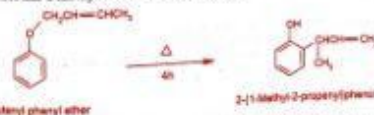
Claisen rearrangement is a [3,3]-sigmatropic rearrangement which leads to an intermediate, cyclohexadienone and proceeds via a cyclic transition state. The cyclohexadienone intermediate regains the aromatic nucleus via tautomerisation to yield rearranged products. Thus, Claisen rearrangement is concerted intramolecular rearrangement. This is illustrated by the rearrangement of allyl phenyl ether to *o*-allylphenol.



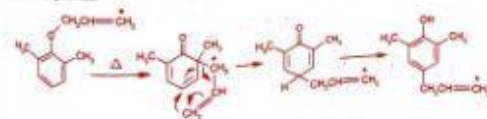
Experiments with ¹⁴C labelling showed that the position of the ¹⁴C atom in the allyl group is inverted during migration to *o*-position.



Further evidence for this mechanism is that if 2-butenyl is present in a phenyl ether, the product phenol has a methyl branch on the side chain.



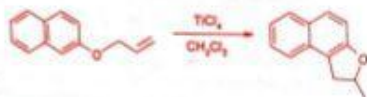
If both the *o*-positions are blocked, *p*-substituted phenol is obtained via two successive shifts of allyl group. Thus, there is double inversion of the position of the ¹⁴C label in the allyl group. For example, 2,6-dimethylallyl phenyl ether rearranges to 4-allyl-2,6-dimethylphenol.



The allyl group is never detached from the oxygen atom unless it is reattached to the aromatic ring.

Application

Claisen rearrangement can be illustrated in the following reactions.²⁻⁴

**References**

1. L. Claisen, *Ber.*, 1912, 45, 3157; L. Claisen, E. Tietze, *Ber.*, 1925, 58, 275; D. S. Tarbell, *Org. Syn.*, 1944, 2, 1.
2. C. F. H. Allen and J. W. Gates, Jr., *OS*, 1955, III, 418.
3. M. R. Sadi, *Heterocycles*, 1982, 19, 1473.
4. E. J. Corey, R. L. Danheiser, S. ChandraSekaran, P. Sures, G. E. Keck and J. L. Gras, *J. Am. Chem. Soc.*, 1978, 100, 8031.

Problems

1. Giving your reasons, predict the structure of the principal product from the pinacol rearrangement of the following glycols:

- (a) 2-Methyl-2,3-pentanediol
- (b) 2-Methyl-3-phenyl-2,3-butanediol
- (c) 3,4-Diphenyl-3,4-hexanediol
- (d) 1,1-Diphenyl-2-methyl-1,2-propanediol

2. How can you establish the structures of *cis* and *anti* aldolimes?

3. Write the mechanism of each of the following rearrangements:

- (a) Beckmann rearrangement
- (b) Fries Rearrangement
- (c) Pinacol rearrangement
- (d) Claisen rearrangement
- (e) Benzilic acid rearrangement
- (f) Favorskii rearrangement
- (g) Wolff rearrangement

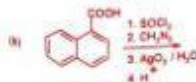
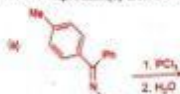
4. What is the stereochemical structure of the oxime of acetophenone which undergoes rearrangement to acetanilide?

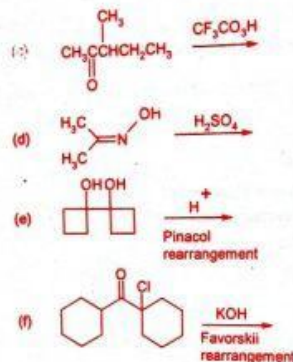
5. Account for the following observations:

- (a) When subjected to the reaction conditions of a Favorskii rearrangement, 1,3-dibromo-3-methyl-2-butanone gave β -methylcrotonic acid.
- (b) Benzamide undergoes Hofmann rearrangement but N-methylbenzamide does not? Offer an explanation.
- (c) Arrange the *p*-nitrophenyl, *p*-cresyl and phenyl acetates in order of increasing ease of Fries rearrangement.
- (d) What are the products formed when following α -diketones undergo the benzilic acid rearrangement?



8. Predict the product(s) from each of the following reactions:





7 Organometallic Compounds

7.1 Introduction

Organometallic compounds are versatile reagents in organic synthesis. An organic compound in which a metal is directly linked to a carbon is known as organometallic compound. These are of two types i.e., 'simple' and 'mixed or complex.' In simple organometallic compounds the metal is linked only to the R group(s), e.g., dimethylzinc ($\text{CH}_3\text{-Zn-CH}_3$). These are covalent in nature. On the other hand, in complex organometallic compounds the metal is attached to R group along with X (halide) group, e.g., CH_3MgBr . These are having carbon metal bond with ionic character. The ionic character of the carbon metal bond depends on the nature of the metal and decreases in the order: $\text{K} > \text{Na} > \text{Li} > \text{Mg} > \text{Al} > \text{Zn} > \text{Cd} > \text{Hg}$. The present discussion is restricted to organometallic compounds containing Mg, Li, Cu, Zn, B, Cd, Hg, Pb, Al, Cr, Fe, Pd, Rh, Ru and Te. The organometallic compounds are of great importance in synthetic chemistry, as they involve the formation of carbon-carbon bonds.

7.2 Grignard reagents

The organomagnesium halides are known as Grignard reagents. These were discovered by Victor Grignard, hence named Grignard reagents. Victor Grignard demonstrated tremendous synthetic potential of Grignard reagents and for this work he was awarded Nobel Prize in 1912. The Grignard reagents are represented as R-Mg-X , where R = alkyl, alkenyl, alkynyl or aryl group and X = Cl, Br or I.

Preparation

Grignard reagents are prepared by the action of magnesium on alkyl halide in anhydrous ether.



For a given halogen the reactivity order of an alkyl group is $\text{CH}_3 > \text{C}_2\text{H}_5 > \text{C}_3\text{H}_7$ or in other words with the increase in carbon atoms the formation of Grignard reagent becomes difficult. Also for an alkyl halide, the ease of formation of Grignard reagent is of the

order: $\text{RI} > \text{RBr} > \text{RCl}$. The reaction is performed under anhydrous conditions. In case the reaction is sluggish, small amount of iodine is added to start the reaction. By this process a solution of Grignard reagent in ether is obtained and is used as such for subsequent reactions.

Aryl halides react with magnesium to form arylmagnesium halides (e.g., phenylmagnesium bromide, $\text{C}_6\text{H}_5\text{MgBr}$). In a similar way vinyl halides ($\text{CH}_2\text{CH}=\text{CHX}$) react with magnesium to form vinyl Grignard reagents (e.g., $\text{CH}_2\text{CH}=\text{CHMgBr}$). In aryl halides and vinyl halides the C-X bond is stronger than the C-Br bond in alkyl halides. Therefore a stronger Lewis base is required for the formation of aryl or vinyl Grignard reagents. The formation of aryl or vinyl Grignard reagent so requires a more basic THF. Though this reaction can work in ether, but the formation of the Grignard reagent is sluggish and the yields are poor.

Mechanism

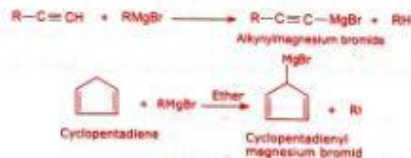
The reaction most likely occurs via free radical mechanism.



This mechanism is supported by the fact that addition of catalytic amount of iodine enhances the formation of Grignard reagent. The iodine reacts with magnesium to give magnesium iodide.



In addition to the method described above, the Grignard reagents are prepared from substrates that have acidic hydrogens, e.g., alkynes, cyclopentadiene etc. by reacting with a preformed Grignard reagent.

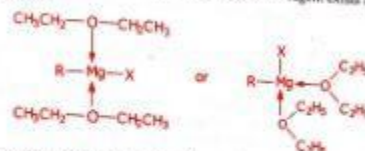


The rate of formation of Grignard reagent can be considerably enhanced by sonication. It is well known that Grignard reagents are very reactive and react with water, alcohols and other groups having active hydrogens. It is therefore important that the substrates for the preparation of Grignard reagents should not have groups like $-\text{COOH}$, $-\text{OH}$, $-\text{NH}_2$, $-\text{C}\equiv\text{CH}$ etc. Therefore, Grignard reagents can not be prepared from compounds that contain acidic hydrogen atoms. Carbonyl, nitro, ester, cyano etc., groups react with

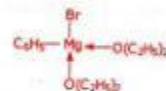
Grignard reagents, therefore, substrate with these groups are also not used for the preparation of Grignard reagents.

Structure

A Grignard reagent is written as RMgX . Its exact structure has been a matter of discussion for a long time. It is believed that a Grignard reagent exists as a co-ordination complex with ether.



The structure of phenylmagnesium bromide, as given below, has been established by X-ray diffraction study.



Reactivity of Grignard reagents

The Grignard reagents may be regarded as polar compounds (since the electronegativities of Mg and C are widely different) and are sources of nucleophilic carbanions.



The Grignard reagents are very reactive and are useful synthetic intermediates. Some of the reactions of Grignard reagents are given below:

1. Reaction with compounds containing active hydrogens

Grignard reagents form hydrocarbons on treating with compounds containing active hydrogen like water, alcohol, amonias and amines.



This method forms the basis for the **Zerewitinoff** determination of active hydrogens. Thus by measuring the amount of methane liberated from a known weight of the compound containing active hydrogens the number of active hydrogens present in a molecule can be obtained.

2. Reaction with carbonyl compounds (Nucleophilic addition reactions)

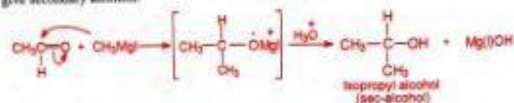
The C-Mg bond in Grignard reagent is polar and generates a nucleophilic carbon (viz., $C^{\delta-}-Mg^{\delta+}-Br$) compared to normal bond polarization of the C-Br bond which generates an electrophilic carbon ($C^{\delta+}-Br^{\delta-}$). This ability to invert the polarity of a carbon atom allows the Grignard reagents to function as a carbon nucleophile. In fact this is an example of reverse polarization (as in the phenomenon of **Umpolung**). The main use of the Grignard reagent is as a carbanion, usually in reactions with carbonyl compounds.



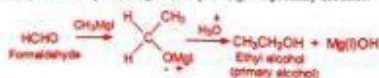
Being nucleophilic in nature, the Grignard reagents attack the carbonyl group of aldehydes, ketones, esters, anhydrides, acid chlorides, and amides. In this reaction the alkyl group having carbanionic character becomes attached to the carbonyl carbon and the magnesium halide to the oxygen of the carbonyl group to give a complex (addition product). These addition products on decomposition with water give the hydroxy compounds (alcohols). The reactions with various carbonyl compounds are given below:

(i) Reaction with aldehydes

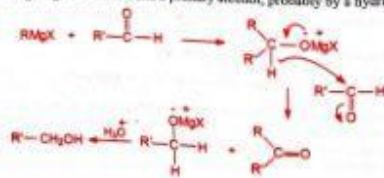
Grignard reagents react with aldehydes to give addition products, which on hydrolysis give secondary alcohols.



However, formaldehyde (being an exception) gives primary alcohol.

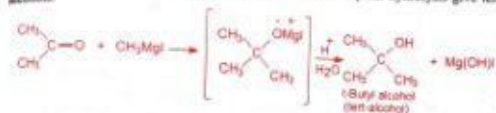


There are however, some instances where the reaction between an aldehyde and a Grignard reagent gives a ketone and a primary alcohol, probably by a hydride transfer.



(ii) Reaction with ketones

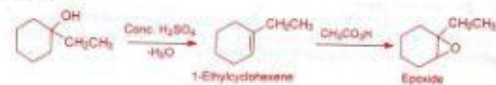
Ketones on reaction with Grignard reagents and subsequent hydrolysis give tertiary alcohols.



In case of cyclic ketones (e.g., cyclohexanone) the reaction takes place as given below:

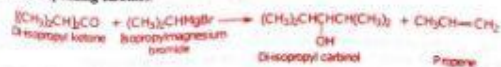


In the above reaction, the formed carbinol on treatment with H_2SO_4 loses a molecule of water to give the corresponding cyclohexene, which on reaction with per acid gives the epoxide.

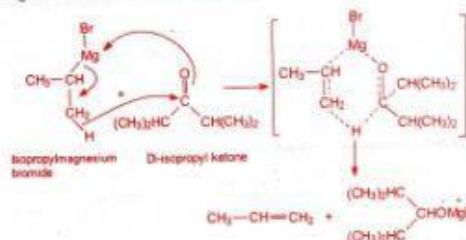


The above sequence of reactions is a convenient route for the synthesis of 1,2-epoxy-1-ethylcyclohexane.

A number of cases are known where a Grignard reagent is made to react with a ketone, which does not give the usual product (i.e., tert-alcohol). Instead, 'abnormal' products are obtained. It is found that branching of the carbon chain near the carbonyl group hinders the nucleophilic addition of the reagent due to steric hindrance. Also in some cases the Grignard reagent has bulky alkyl or aryl group, it does not attack the electrophilic center of the carbonyl compound. Thus, even methylmagnesium bromide does not react with di-tert-butyl ketone. In a similar way, methyl isopropyl ketone reacts with methylmagnesium halides but not with tert-butylmagnesium halides. There are certain reactions in which substituted ketones and reagents react together to form products which are generally not obtained in Grignard normal reactions. One such reaction is the reaction of di-isopropyl ketone with isopropylmagnesium bromide to give the corresponding carbinol.



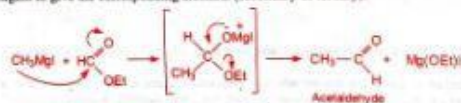
This reaction takes place by a hydride transfer from alkyl group of the Grignard reagent involving a six-membered cyclic transition state.



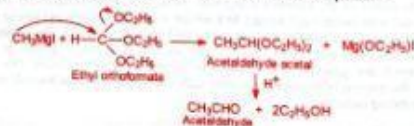
The above reaction is similar to Meerwein-Ponndorf-Verley reduction (see sec. 5.62).

(iii) Reaction with esters

Grignard reagents react with esters, viz., ethyl formate, ethyl orthoformate and ethyl acetate to give the carbonyl compounds, which further react with excess of Grignard reagent to give the corresponding alcohols (secondary or tertiary).

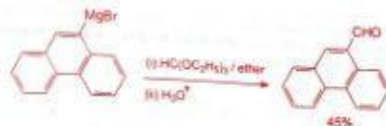


The acetaldehyde obtained by the reaction of CH_3MgI and ethyl formate, reacts with excess of Grignard reagent to give secondary alcohol (see reaction with aldehydes). However, in case of ethyl orthoformate, only aldehyde is the main product.

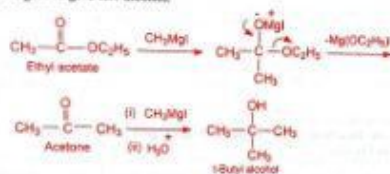


In case of ethyl orthoformate the formation of a secondary alcohol is not possible due to the formation of acetal. So this is a convenient method of making aldehydes.

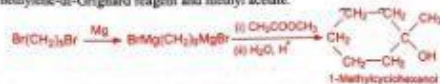
This method is useful for the synthesis of fermyl compounds which are difficult to prepare by usual methods.



Ethyl acetate on reaction with Grignard reagent gives a ketone, which reacts with excess of Grignard reagent to give tert-alcohol.



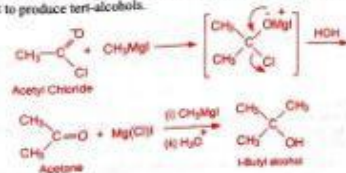
An application of above reaction is the synthesis of 1-methylcyclohexanol from pentamethylene-di-Grignard reagent and methyl acetate.



Such a reaction is possible if the halogen atoms in the dihalo compounds are widely apart. Reactions other than Grignard formation occur if the halogens are close together, e.g., in case of 1,2-dihaloalkanes elimination occurs and 1,3-dihaloalkanes give cyclopropane derivatives.

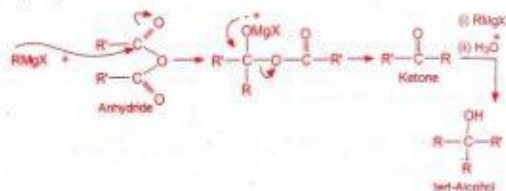
(iv) Reaction with acid chlorides

Acid chlorides react with Grignard reagent to give ketones, which may react with excess of the reagent to produce tert-alcohols.

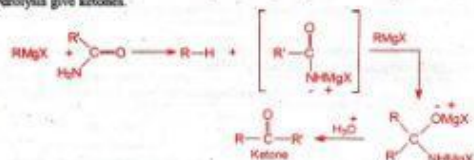


(vi) Reaction with acid anhydrides

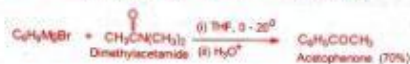
Grignard reagents react with acid anhydrides to give addition products which on hydrolysis give tertiary alcohols.

**(vii) Reaction with amides**

The amides on treatment with Grignard reagent give addition products, which on hydrolysis give ketones.



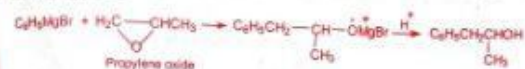
Similarly, dimethylformamide and dimethylacetamide on reaction with a Grignard reagent give corresponding carbonyl compounds in excellent yield.

**3. Reaction with epoxides**

Grignard reagent reacts with an epoxide to give a primary alcohol with the lengthening of the carbon chain by two carbon atoms.



In this case the attack of the Grignard reagent is from the less substituted ring carbon atom of the epoxide.

**4. Reaction with carbon dioxide**

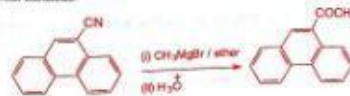
Grignard reagents on treatment with solid carbon dioxide followed by hydrolysis (with dilute acid) yield carboxylic acids. Alternatively, a good yield of carboxylic acid can be obtained by passing the carbon dioxide into the Grignard solution at low temperature (i.f.c.).

**5. Reaction with nitriles**

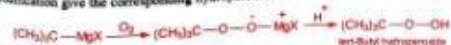
When a Grignard reagent reacts with nitriles (alkyl cyanides), ketones are formed. If HCN (hydrogen cyanide) is used instead of an alkyl cyanide, an aldehyde is obtained.



Since there is no leaving group present, the imine salt is stable until hydrolysis. Thus, the reaction of Grignard reagent with alkyl cyanide yields ketone (see the reactions of Grignard reagents with acid chlorides or esters, which yield alcohols). This method is used for the preparation of keto compounds which are difficult to prepare by conventional methods.

**6. Reaction with oxygen**

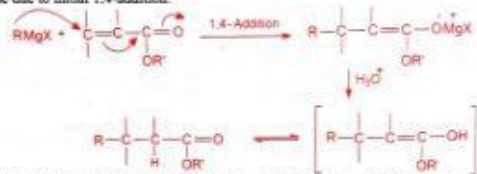
Oxygen reacts with Grignard reagents at low temperature to give an adduct, which on acidification gives the corresponding hydroperoxides.



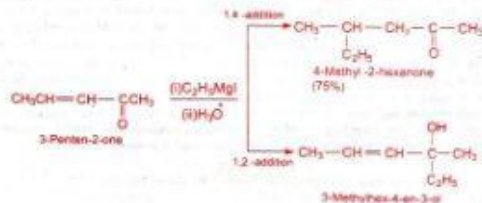
On the other hand an alcohol can also be formed by treating a Grignard reagent with dry oxygen followed by decomposition of the complex. It is a very good method for the preparation of phenols from aryl halides.

13. Addition of Grignard reagent to carbon-carbon double bond

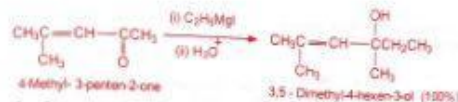
Simple alkenes are not attacked by the nucleophiles (as R^- in case of Grignard reagents). This is attributed to the fact that unlike carbonyl compounds in alkenes there is very little or no electronic polarization. However, if the carbon-carbon double bond is polarized by the presence of a neighbouring electron-withdrawing group, the nucleophilic addition to carbon-carbon double bond is possible (as in **Michael addition**, see sec. 5.63). Thus in the case of α, β -unsaturated esters, the addition of Grignard reagent takes the following course due to initial 1,4-addition.



Similar additions also take place with conjugated aldehydes and ketones. The reaction usually gives a mixture of two products arising from addition to carbon-carbon double bond (1,4-addition) and carbon-oxygen double bond (1,2-addition). Thus, 3-penten-2-one reacts with Grignard reagent ($\text{C}_2\text{H}_5\text{MgI}$) to give a mixture of 4-methyl-2-hexanone (arising from initial 1,4 addition) and 3-methylhex-4-en-3-ol (arising from initial 1,2-addition) in the ratio 3:1.



In the above addition reaction, the ratio of the two products formed depends on the steric hindrance. If a substituent is present at the β -carbon (as in the case of 4-methyl-3-penten-2-one), the attack of the nucleophile (R^- of RMgX) is hindered at the β -carbon due to steric hindrance. In this case the product obtained is exclusively 3,3-dimethyl-4-hexen-3-ol.



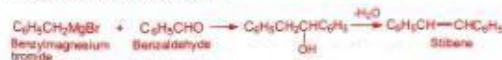
In case of α, β -unsaturated aldehydes (e.g., crotonaldehyde) there is no hindrance at the $\text{C}=\text{O}$ group and the product formed (major) is unsaturated alcohol.



14. Special applications of Grignard reagents

(i) Synthesis of stilbene

It is obtained by the reaction of benzylmagnesium bromide with benzaldehyde, followed by dehydration of the formed alcohol.



(ii) Synthesis of ethers

Grignard reagents react with lower halogenated ethers to produce higher ethers.



(iii) Synthesis of alkyl cyanides

The reaction of Grignard reagents with cyanogen or cyanogen chloride yields alkyl cyanides.



(iv) **Synthesis of primary amines**

Grignard reagents react with chloramine to give primary amines.

(v) **Synthesis of hydrocarbons**

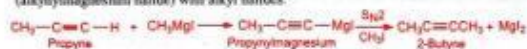
Alkanes are obtained by the reaction of Grignard reagent with compounds containing active hydrogen or with alkyl halides.



Similarly, **alkenes** are obtained by the reaction of Grignard reagents with unsaturated alkyl halides.



Higher alkynes are obtained by the treatment of terminal alkynes with Grignard reagent (alkylmagnesium halide) followed by treatment of the formed Grignard reagent (alkynylmagnesium halide) with alkyl halides.



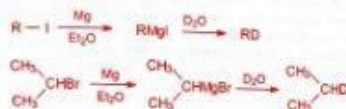
Cycloalkanes are obtained by the treatment of cyclobutylmagnesium bromide with water.



The above method is basically used for the replacement of a halogen with hydrogen in alkyl halides.

(vi) **Synthesis of deuterated hydrocarbons**

The principal use of the above reaction is the synthesis of deuterated hydrocarbons. Some examples are given below:



The table 7.1 gives a summary of different types of compounds which can be synthesised starting from Grignard reagent.

Table 7.1

Compound	Reaction of Grignard reagent with
Alcohols	
Primary alcohols	Formaldehyde Epoxides
Secondary alcohols	Aldehydes other than formaldehyde Cyclic ketones like cyclohexanone Epoxides
Tertiary alcohols	Ketones Acid chloride Isocyanates Acid anhydrides
Carbonyl compounds	
Aldehydes	Ethyl formate Ethyl oxalacetate Diethylformamide
Ketones	Acid anhydrides Diethylformamide Alkyl cyanide Nitriles
Carboxylic acid	Carbon dioxide
Ethers	Methylmethyl chloride
Primary amines	Chloramine
Alkyl cyanide	Cyanogen
Hydrocarbons	
Alkanes	Compounds containing active hydrogen like H_2O , alcohols, ammonia and amines Alkyl halides Unsaturated alkyl halides
Alkenes	Alkynes containing acidic hydrogen
Alkynes	Reaction of cyclic Grignard reagents with water
Cycloalkanes	Reaction of Grignard reagents with D_2O
Unsaturated hydrocarbons	
Alkenes	Sulfur Carbon disulfide
Alkynes	Sulfur dioxide
Isocyanates	Isoles
Alkyl iodides	
Organometallic compounds	PbCl_2 , MgCl_2 , SnCl_4 , PbCl_4 , CBr_4

7.3 Organolithium compounds

The organolithium compounds (or reagents) are characterised by a C-Li bond and are important in organic synthesis. Although organolithium compounds show similar reactivity as Grignard reagents, they are more reactive than the Grignard reagents. However, in certain cases the organolithium compounds are distinctly different from the Grignard reagents. Lithium is less electronegative than carbon, and the C-Li bond is polarized ($C^{\delta-}-Li^{\delta+}$), as in Grignard reagent. The organolithium behaves both as nucleophile and a base.

Preparation

(i) From alkyl or aryl halides

The reaction¹ of lithium metal at low temperature with an alkyl or aryl halide in a hydrocarbon solvent in inert atmosphere (nitrogen or argon) gives an alkyl-lithium.



The yield of the alkyl-lithium is very low if very pure lithium is used. It is believed that lithium must contain at least 0.02% of sodium for the reaction to proceed smoothly. In the above reaction, the reactivity of the halides is: $RI > RBr > RCl$.

(ii) By halogen-metal exchange method

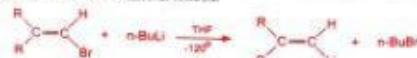
This method is useful for the preparation of those organolithium reagents that cannot be obtained from alkyl halide and metal directly. In this method an organic halide is treated with alkyl-lithiums.



This method is best suited for the preparation of aryl-lithium derivatives. Thus, phenyl-lithium is prepared by treating bromobenzene with *n*-butyl-lithium.



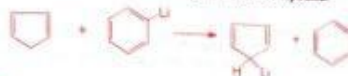
Similarly, vinyl-lithium is obtained as follows.



The special advantage of this method² is that vinyl-lithium can be obtained by retention of configuration.

(iii) By metalation

Compounds containing acidic hydrogen can be easily converted into organolithium compounds by treatment with a suitable organolithium compound.



Properties

Organolithium reagents are very reactive, powerful nucleophiles and strong bases. These find numerous applications in organic synthesis and are better than the Grignard reagents. Synthetic applications of organolithium reagents are given below.

1. Reaction with compounds containing active hydrogen

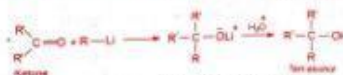
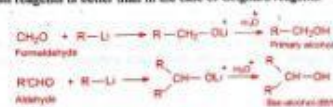
The organolithium reagents react with substrate having active hydrogen such as water, alcohols, amines (primary and secondary) and carboxylic acids to give the corresponding hydrocarbons in quantitative yield.



In this respect the organolithium reagents resemble Grignard reagents.

2. Reaction with carbonyl compounds

As in the case of Grignard reagents, the organolithium reagents react with aldehydes to form secondary alcohols and with ketones to form tertiary alcohols. Primary alcohols are obtained by treatment with formaldehyde. The yields of the alcohols, in case of organolithium reagents is better than in the case of Grignard reagents.



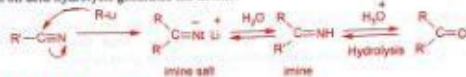
It has been stated that Grignard reagents (e.g., CH_3MgBr) do not react with hindered ketones. However, the organolithium reagents are less susceptible to steric factors and react with hindered ketones giving the corresponding tertiary alcohols.



Organolithium reagents also react with esters to form the tertiary alcohols. The ketones that are the initial products of reactions are more reactive than esters, thus react further with organolithium reagents to yield alcohols.

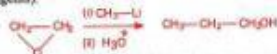
3. Reaction with alkyl cyanide

Like Grignard reagents, the organolithium reagents also react with alkyl cyanides to give imine salts. When the reaction is worked up with water, protonation first gives the imine, which on acid hydrolysis generates the ketone.

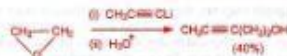


4. Reaction with epoxides

The epoxides react with organolithium reagents to give primary alcohols (as in the case of Grignard reagents).

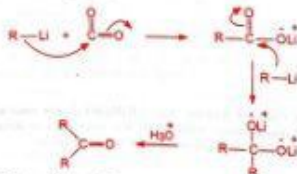


Use of unsaturated organolithium reagent gives unsaturated alcohols.

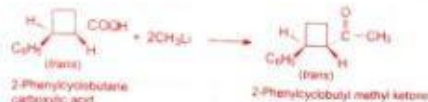


5. Reaction with carbon dioxide

It is known that Grignard reagents on reaction with carbon dioxide give carboxylic acids. However, in case of organolithium reagents, the formed carboxylate anion reacts with a second molecule of the reagent to give a ketone.

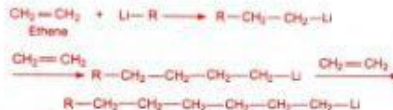


This method finds application in the conversion of carboxylic acids into ketones. A special feature of this reaction is that the original stereochemistry of the carboxylic acid is maintained in the formed ketone.



6. Reaction with alkenes

Organolithium reagents (being more reactive than Grignard reagents) react with alkenes to give alkyl-lithium, which reacts with a second molecule of the alkene to give the corresponding alkyl-lithium. This process continues depending on the relative amount of the alkene.



By properly controlling the amount of the substrate, alkanes of desired chain length can be obtained. It may, however, be stated that Grignard reagents have no action on ethylene.

7. Electrophilic displacement

We have already seen that the reaction of an organic halide with an organometallic compound is known as metal-halogen exchange reaction.



This is an example of electrophilic displacement and finds use in the synthesis of vinyl lithium from vinyl bromide.



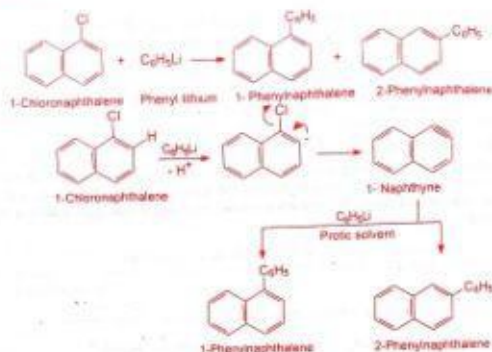
This method is useful for the preparation of phenyl lithium.

8. Nucleophilic displacement

The halogen of the alkyl halides can be substituted with the alkyl group of the organolithium reagent to give hydrocarbons.



This reaction takes place by $\text{S}_{\text{N}}2$ mechanism as in the case of **Wurtz reaction** (see sec. 3.9).



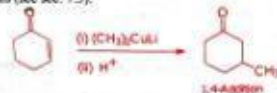
The reaction of aryl halides with phenyl lithium takes place via an elimination-addition pathway and not via the usual aromatic substitution reaction. In this reaction phenyl-lithium acts as a strong base to abstract the α -hydrogen generating a carbanion and also acts as a nucleophile in addition to naphthylene.

9. Reaction with α, β -unsaturated carbonyl compounds

It has been stated that Grignard reagents react with α, β -unsaturated carbonyl compounds giving 1,2- or 1,4-addition product depending on the structure of the carbonyl compound. The main reason is steric hindrance. The organolithium reagents on the other hand give exclusively 1,2-addition products.



Exclusive formation of 1,4-addition product, can however, be achieved by use of lithium dialkylcuprates (see sec. 7.5).

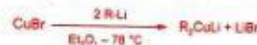


7.4 Organosilicon compounds

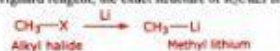
Organosilicon reagents are discussed in chapter 8 (see sec. 8.10).

7.5 Organcopper compounds

The organcopper reagents that are particularly useful, are prepared by transmetalating the Grignard reagent or organolithiums.



The organcopper reagents with the general formula R_2CuLi are called lithium organocuprates or lithium dialkylcuprates. These are prepared from alkyl halides (e.g. CH_3I) by first converting into alkyl lithium (CH_3Li) followed by treatment with Cu(I) salts. Just as with Grignard reagent, the exact structure of R_2CuLi is not clear.



Organcopper reagents are less stable and are prepared *in situ*. Organcopper reagents are highly selective⁴ towards different functional groups and this selectivity is a major factor in determining their usefulness.

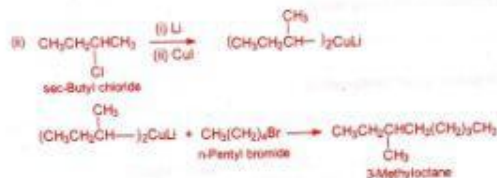
The organcopper reagents are referred to as **Gilman reagents**.^{4,5} The mechanism of the reaction most likely involves an intermediate, transient Cu(III) species and may proceed via one electron transfer.⁶ Besides Gilman reagents, two other organcopper reagents, viz., high order cuprates and copper isonitrile reagents have also been developed. These have been discussed subsequently.

Following are some of the synthetic applications of organcopper reagents.

1. Reaction with alkyl or aryl halides (Coupling reactions)

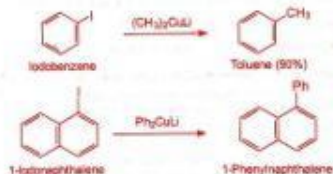
Organocuprates are able to displace halide ion from primary and secondary alkyl halides to give hydrocarbon.



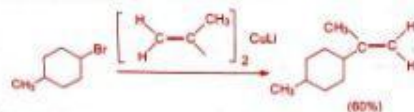


As seen, the alkane is synthesised from two different alkyl halides, which is not possible by the well known **Wurtz reaction** (see. sec. 5.98), in which a number of products are obtained.

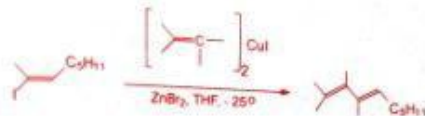
Lithium dimethylcuprate also reacts with aryl halides. In this case the halogen of the aryl halide is replaced by a methyl group or phenyl group depending on the lithium cuprate used.



In place of lithium dimethylcuprate, another reagent, viz., lithium divinylcuprate can also be used. Thus, organocuprates may be used to synthesize alkenes.



Using organolithium reagents, dienes can also be obtained as given below.



The coupling reaction is extremely useful for joining alkyl fragments, alkyl-aryl, aryl-aryl or heterocyclic-aryl fragments. The cuprate derived from 3-lithiofuran, for example, on reaction with 1-bromodecane gives 3-decyfuran.



2. Reaction with epoxides

Organocupper reagents react with the epoxides. The epoxide is attacked at the least substituted carbon atom giving the corresponding alcohol.

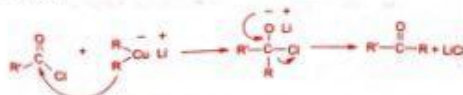


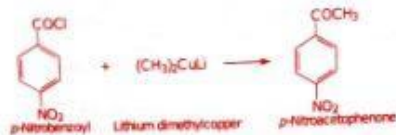
3. Reaction with acid chlorides

The acid chlorides react with organocupper reagents to give the corresponding ketones.

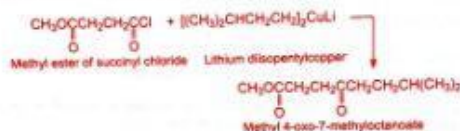


Unlike in the case of Grignard reagents (which react with formed ketone to give 1-alcohols), the ketone formed does not react with more of organocupper. In fact, the low reactivity of organocupper compounds makes the synthesis of ketones possible. Besides, the organocupper reagents do not react with many functional groups (e.g., $-\text{NO}_2$, $-\text{CN}$, $-\text{CO}$, $-\text{COOR}$) with which Grignard reagents and organolithium reagents react, the above method makes it feasible to synthesise ketones having the reactive groups like NO_2 , $-\text{CN}$ etc.



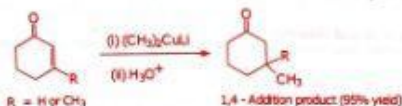


The preparation of an γ -ketoester is given below:

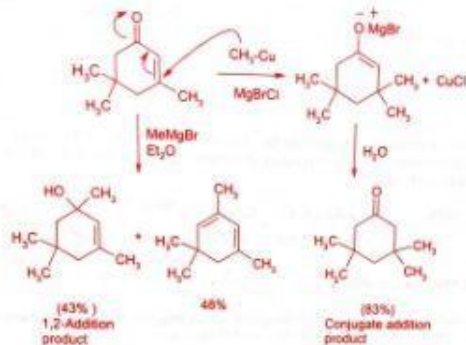


4. Reaction with α, β -unsaturated carbonyl compounds

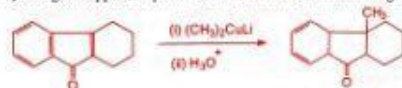
The lithium organocuprates react with α, β -unsaturated carbonyl compounds giving exclusively the 1,4-addition product (conjugate addition).



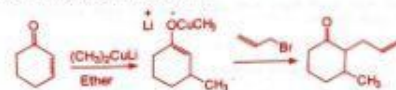
Organocuprate reagents are softer than Grignard reagents (because copper is less electropositive than magnesium), and add in conjugate fashion to the softer C=C double bond. However, Grignard reagents react with α, β -unsaturated ketones mainly by 1,2-addition.



The utility of organocuprate compounds is also illustrated in the following reaction.



In the case of enones, viz., cyclohexenone, consecutive addition of lithium dimethylcuprate and alkyl halides (alkyl halide in the following example), two different alkyl groups can be introduced in one operation.

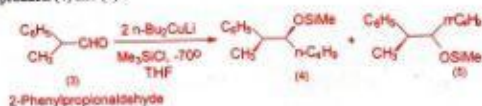


5. Reaction with aldehydes and ketones

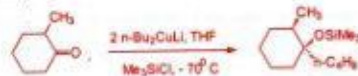
Organocuprates react easily with aldehydes. The reaction of lithium dimethylcuprate, for example, with benzaldehyde (at -92°C) gives phenylethyl alcohol [C6H5CH(OH)CH2CH3]. However, 5-nanonone reacts only at -10°C to give 5-methyl-5-nanol¹. It has been shown² that dimethylcuprate reacts with the aldehyde (1) at -70°C to give the product, (2) (see and eqn. 30.1).



Another interesting example is the reaction of lithium dialkylcuprate with 2-phenylpropionaldehyde (3) in presence of chlorotrimethylsilane to give a 64:1 mixture of the products (4) and (5).



The reaction of ketones with organocuprates is very sluggish. However, the reaction takes place conveniently in presence of chlorotrimethylsilane.



High Order Cuprates

These are represented as $\text{R}_2\text{Cu}(\text{CN})\text{Li}_2$ and are prepared¹⁰ by the reaction of organolithium reagent with cuprous cyanide



These reagents react much faster with alkyl halides or even secondary halides as compared to Gilman reagents.

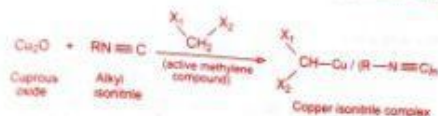


High order cuprates react with chiral halides to give chiral alkane products.

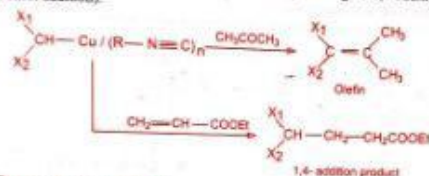


Copper-Isocyanide derivatives

These reagents were developed by Sangusa.¹¹ These are copper-isocyanide complex and are obtained by mixing Cu_2O with an alkylisocyanide and then reacting with an active methylene compound.



The copper-isocyanide complexes on reaction with ketones (e.g. acetone) give Wittig type product. On the other hand, these react with ethyl acrylate to give 1,4-addition product (as in Michael addition).



7.5 Organozinc compounds

Organozinc compounds were the first organometallic compounds to be prepared in the laboratory. Organozinc compounds, R_2Zn , are far less reactive and are not commonly used in organic synthesis. Zinc-copper couple has been used in the **Simmons-Smith reagent** (see sec. 5.84) for the synthesis of cyclopropanes.

Organozinc compounds are prepared by the treatment of alkyl iodides with zinc filings. The alkylzinc iodides initially formed on distillation in carbon dioxide atmosphere give dialkylzinc derivatives. In place of metallic zinc, zinc-copper alloy is also used.



Dialkylaluminum on reaction with zinc chloride also gives dialkylzinc derivatives.



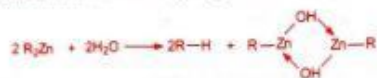
Organozinc compounds are non-polar, low boiling liquids or low melting solids. These are soluble in organic solvents and are inflammable in air. They are used in carbon dioxide atmosphere.

Properties

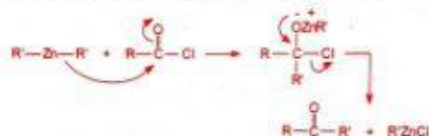
The properties of organozinc compounds are similar to that of Grignard reagents. However, they are much less reactive than the Grignard reagents. They do not react with carbon dioxide (unlike Grignard reagents) and react slowly with ketones, esters and cyanides. Some important reactions of organozinc compounds are given below.

1. Reaction with water

Dialkylzinc on reaction with water gives hydrocarbon.

**2. Reaction with acid chlorides**

Acid chlorides react with organozinc compounds to give ketones.



The reagent viz., organozinc compounds react extremely slowly with ketones. In view of this ketones can be isolated from the reaction mixtures.

3. Reaction with alkyl halides

Primary and secondary alkyl halides show no reaction with organozinc compounds. However, tertiary alkyl halides on reaction with organozinc compounds give hydrocarbons.



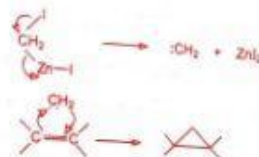
Organozinc compounds are obtained as intermediates in the well known **Reformatsky reaction** (see sec. 5.74). This reaction is used for the preparation of β -hydroxy acids. In this reaction the alkoxyzinc halide is obtained *in situ*.

Iodomethylzinc iodide (ICH₂ZnI)

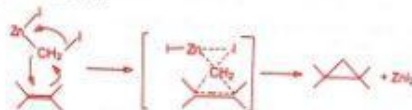
A very useful organozinc compound is iodomethylzinc iodide, ICH₂ZnI. It reacts with olefins to give cyclopropane derivatives.



The reaction was earlier believed to take place by the decomposition of the organozinc compound (ICH₂ZnI) to generate carbene (:CH₂) by an α -elimination process, which could add on to olefinic double bond to give the cyclopropane derivative.



However, it is now believed that the reaction takes place in a concerted manner involving a cyclic transition state.



This reaction is known as **Simmons-Smith reaction** (see sec. 5.84) and the organozinc compound, viz., iodomethylzinc iodide is called **Simmons-Smith reagent**. Iodomethylzinc iodide (the organometallic compound of zinc) is obtained by the reaction of di-iodomethane (methylene di-iodide) and zinc.



This reagent is normally generated *in situ* by the action of di-iodomethane (CH₂I₂) and zinc-copper couple.¹² Thus, the reaction of cyclohexene with di-iodomethane and zinc-copper couple gives bicyclo[4.1.0]heptane (norcaradiene).



For the preparation of organozinc compounds, the zinc must be activated. Alternatively, aluminium is used for the reaction.

7.7 Organoboranes

Organoboranes are discussed in chapter 8, see sec. 8.9.

7.8 Organocadmium compounds

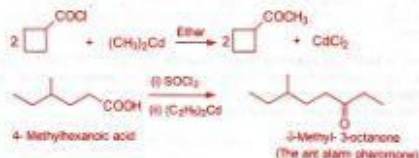
Organocadmium compounds are prepared by the action of cadmium chloride on a Grignard reagent or organolithium.



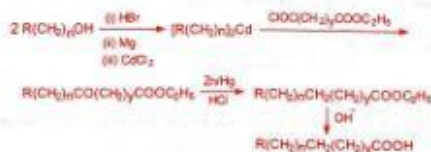
Organocadmium compounds are volatile liquids and are less reactive than the Grignard reagents and organolithium compounds. These do not react with esters or ketones but react with acid chlorides to form ketones.



Since cadmium dialkyls do not react with carbonyl compounds (i.e., esters and ketones), they are especially used for the synthesis of ketones. Some applications of ketone synthesis are given below.

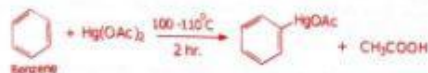


The above procedure for the synthesis of ketones has been used for the synthesis of long chain esters or carboxylic acids.

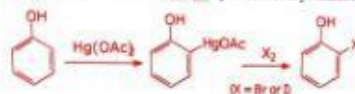


7.9 Organomercury compounds

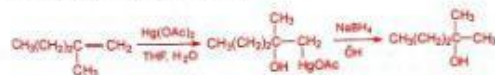
The organomercury compounds are comparatively more stable in air, soluble in non-polar solvents, have low activity and are covalent in nature. The most important organomercury compound is obtained by the reaction of mercuric acetate with benzene. Thus, benzene and its derivatives react with mercuric acetate and undergo mercuration. In this reaction the electrophile $\text{Hg}(\text{OAc})_2$ attacks the ring to produce phenylmercury salts.



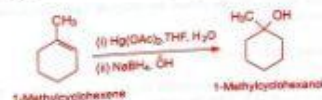
The mercuric salts thus obtained are used for the synthesis of aryl halides.



Mercuric acetate is also used for the preparation of alcohols from olefins. The steps involved are oxymercuration of alkenes with mercuric acetate, followed by *in situ* reduction of the resulting organomercury compound (demercuration) with sodium borohydride in overall yield of 85 to 90%.



The addition of mercuric acetate to the olefin takes place as per Markownikoff rule. In the second step (demercuration), sodium borohydride reduces HgOAc group and replaces it with hydrogen. This method is also helpful to convert 1-methylcyclohexene to 1-methylcyclohexanol.

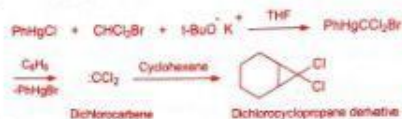


The special features of this procedure¹³ is that there is virtually no rearrangement and that the presence of groups like $-\text{OH}$, $-\text{OCH}_3$, $-\text{X}$, $-\text{OCOCH}_3$ etc. in the substrate molecule has no effect on the reaction. Also, this method can be used for mono, di, tri and tetra-alkyl and phenyl/substituted alkenes.

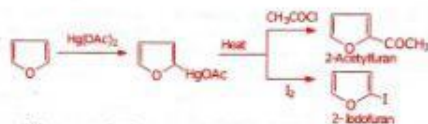
The oxymercuration method is also used for the preparation of ethers. In this procedure alcohol is used as a medium in place of THF/ H_2O mixture.



Organomercuric compound, PhHgCl , on reaction with dichloromethylbromide in presence of $t\text{-BuOK}$ gives dichlorocarbene which can add up to appropriate substrates (e.g., cyclohexene) to give the corresponding dichlorocyclopropane derivatives.



Another important use of organomercury compounds is in the synthesis of 2-iodo and 2-acetylfurans.



Organometallic compounds of mercury like alkylmercuric halides are best prepared from Grignard reagents with mercuric chloride.



Methylmercuric chloride reacts further with mercuric chloride to give dimethylmercury.

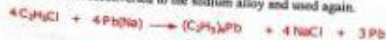


Some alkylmercuric halides like ethylmercuric chloride have fungicidal properties and are used to preserve seeds.

7.10 Organolead compounds

The most important organometallic compound of lead is tetraethyl-lead, $\text{Pb}(\text{C}_2\text{H}_5)_4$. It has been used for a considerable time to improve the antiknock rating of gasoline in concentration of 1-3 ml per gallon. Ethylene dibromide is added to leaded gasoline to convert the formed lead oxide in combustion to volatile lead bromide and thus considerably diminish the deposit formation. Tetramethyl-lead has some advantage over tetraethyl-lead in high performance engines. However, this use has been discontinued due to poisonous nature of the exhaust gases in the automobiles and to reduce the pollution problem. Tetraethyl-lead is prepared as follows:

(i) Tetraethyl-lead is made by the reaction of a lead-sodium alloy with ethyl chloride. The excess of lead is recovered to the sodium alloy and used again.



(ii) On a commercial scale, tetramethyl and tetraethyl-lead are obtained by the electrolysis of an ethereal solution of methyl or ethylmagnesium chloride using lead anode:

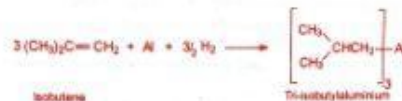


(iii) It is also prepared by treatment of Grignard reagent with lead chloride

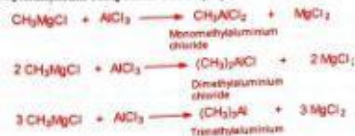


7.11 Organoaluminium compounds

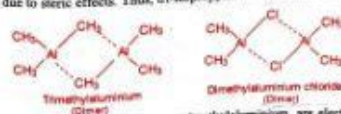
Organoaluminium compounds are prepared by heating an alkene with aluminium powder and hydrogen.



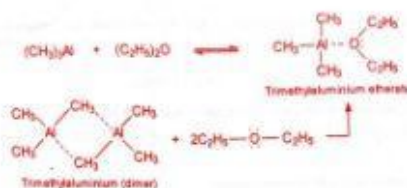
The organoaluminium compounds can also be prepared by treating aluminium trichloride with appropriate Grignard reagent. Depending on the amount of Grignard reagent, mono-, di- and trialkylaluminium compounds can be prepared.



The aluminium n -trialkyls are dimers. However, branched chain compounds are monomers due to steric effects. Thus, tri-isopropylaluminium exists as monomer.



The organometallic compounds, such as dimethylaluminium, are electron deficient and exist as co-ordination compound of the metal with the solvent, like ether. These co-ordination compounds are also obtained by treatment of the dimers with ether.



Trialkylaluminum decomposes on heating to form an alkene and dialkylaluminum hydride.



This is a reversible reaction and is used to prepare other aluminum alkyls by exchange with alkenes.



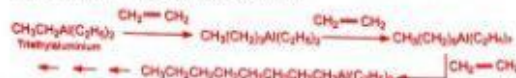
The aluminum trialkyls on treatment with water decompose to form alkanes. Thus, the overall reaction is the reduction of alkenes.



Aldehydes and ketones can be reduced by di-*i*-isobutylaluminum hydride to give alcohols.



The most important use of trialkylaluminum is as a catalyst (Ziegler-Natta type catalyst) for the low temperature polymerization of alkenes.



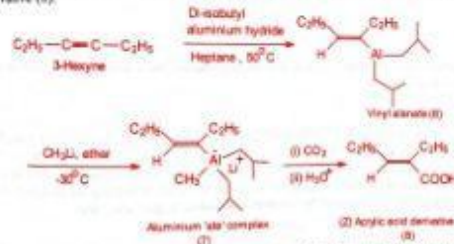
The product with long chain alkyl group undergoes elimination of dialkylaluminum hydride to give alkene. This process is commercially used for the large scale preparation of terminal alkenes.



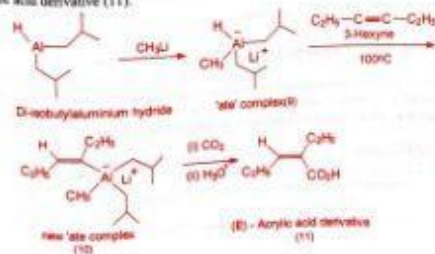
Aluminum trialkyls are also used for the manufacture of long straight chain alcohols as given below.



Another reaction of organoaluminum compounds is with alkynes. Thus, 3-hexyne on reaction with di-*i*-isobutylaluminum hydride gives vinyl alane (6), which on reaction with methyl-lithium gives the aluminium 'ate' complex (7). Subsequent reaction of (7) with an electrophile like CO_2 , followed by hydrolysis gives (Z)-acrylic acid derivative (8).

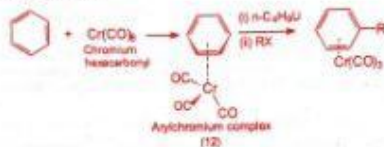


In the above sequence of reactions, the geometry of the intermediate (6) and the final product (8) is changed if the di-*i*-isobutylaluminum hydride first reacts with methyl-lithium to give the aluminane (9) ('ate' complex), which on reaction with 3-hexyne gives a lithium new 'ate' complex (10). Its reaction¹² with CO_2 followed by hydrolysis gives the (E)-acrylic acid derivative (11).



7.12 Organochromium compounds

The reaction of benzene and its derivatives with chromium hexacarbonyl [$\text{Cr}(\text{CO})_6$] gives an arylchromium complex (12)¹⁵. The aryl rings are activated towards nucleophilic attack by metal complexes. For example, the complex (12) can be used for the synthesis of alkyl substituted products by treatment with organolithium reagents, followed by treatment with alkyl halides.



The arylchromium complex (12) can also undergo nucleophilic aromatic substitution with carbon nucleophiles.

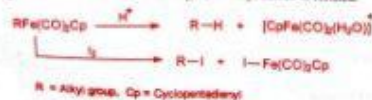
Mechanism

The mechanism involves the addition of the nucleophile (R^-) to the aromatic ring. The resulting anion is stabilized by the chromium atom, which accepts extra electrons. The metal-stabilized anion intermediate is decomposed by the oxidising agent iodine to give aromatic substitution product. The addition can be reversed on heating the complex. Also the complex can be decomposed by reaction with iodine to give alkyl aryl.



7.13 Organoiron compounds

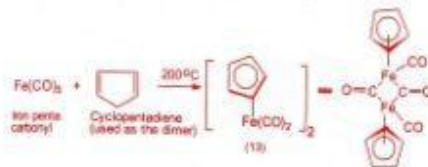
A number of organoiron compounds have been used in organic synthesis. The Fe-C bond can be cleaved by treatment with water, alcohol, acid or an alkyl halide. The reaction with acid gives an alkane while with halogen, an alkyl halide is formed.



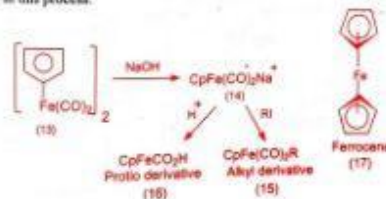
Two most important organoiron reagents which are commonly used are cyclopentadienyliron dicarbonyl (Fp, 14) and sodium tetracarbonyl ferrate (18).

Cyclopentadienyliron dicarbonyl (Fp)

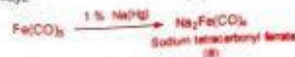
The dimeric species (13) can be prepared by the reaction of iron pentacarbonyl with cyclopentadiene (dimer of cyclopentadiene is used).



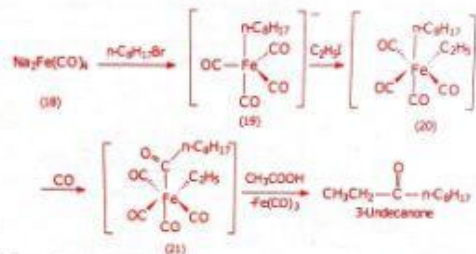
The anionic reagent (14, Fp) is prepared by treatment of (13) with a base. The anionic reagent (14) on reaction with an alkyl halide gives the alkyl derivative (15) and on reaction with acid gives the protio derivative (16). Ferrocene (17) is obtained as a by-product in this process.

**Sodium tetracarbonyl ferrate (18)**

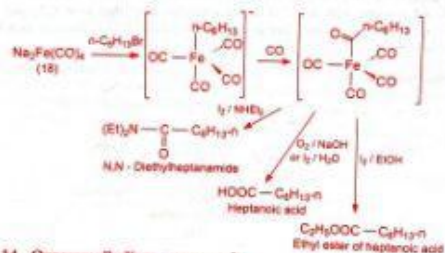
It is an important organoiron reagent and is prepared by the reduction of iron pentacarbonyl.



It reacts with alkyl halides in a stepwise manner. Thus, sodium tetracarbonyl ferrate (18) on reaction with 1-bromooctane gives a trigonal bipyramidal complex (19) which on subsequent treatment with another alkyl halide (viz., ethyl halide) gives an octahedral species (20). Final reaction with carbon monoxide under pressure gives the acyl derivative (21), which on protonolysis with acetic acid gives 3-undecanone.



Another synthetic utility of sodium tetracarbonyl ferrate (18) is given below.

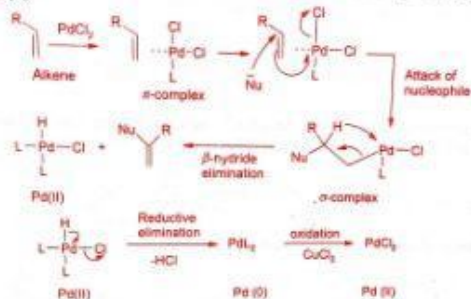


7.14 Organopalladium compounds

Amongst the transition metals (Ni, Cu, Fe, Co, Te, Rh, Pt, Pd), palladium is most exclusively used in organic synthesis. The organopalladium compounds are generated *in situ* for organic synthesis. Palladium chloride is the most commonly used salt of palladium. Though PdCl_2 is insoluble in water but it can be converted into a number of soluble species (e.g., Na_2PdCl_4).

The importance of organopalladium compounds lies in their ability to facilitate reactions that would not occur under normal conditions. For example, a nucleophilic attack on an isolated double bond does not occur. However, when alkene is coordinated to palladium(II), many nucleophiles, such as, water, alcohol and carbonyl compounds, can attack the complexed alkene from side opposite to the palladium. Thus, attack of nucleophile is regioselective for the more substituted position.

A Pd(II) salt adds to an alkene to give π -complex. Attack of nucleophile on complexed alkene yields π -complex, which decomposes by β -hydride elimination to reveal the substituted alkene and palladium (II). Reductive elimination of a proton and an external oxidant is required to convert palladium (0) to palladium(II), so that the cycle can continue. In presence of Cu(II) chloride, oxygen converts palladium (0) to palladium(II).



An industrial process for the manufacture of acetaldehyde from ethylene uses soluble palladium catalyst (**Wacker process**). The method involves the treatment of ethylene with cupric chloride (CuCl_2) and palladium chloride. Water is used as a nucleophile in this reaction.



In the absence of CuCl_2 , Pd(0) is produced which is ineffective for subsequent transformation. Use of catalytic amount of CuCl_2 oxidises Pd(0) to Pd(II) in presence of atmospheric oxygen, which is reused. This method is also useful for the conversion of substituted alkenes into carbonyl compounds.

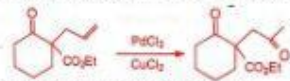


Mechanism

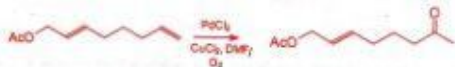
The π complex releases the enol form and β -hydride elimination step, which is converted into the keto form. Overall reaction is hydration of a terminal alkene.



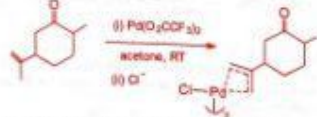
In the reaction of alkenes with $\text{PdCl}_2/\text{CuCl}_2$, the attack is at the more substituted carbon to give the ketones. Another example of this type is given below.



In case of dienes, only the terminal double bond is attacked.



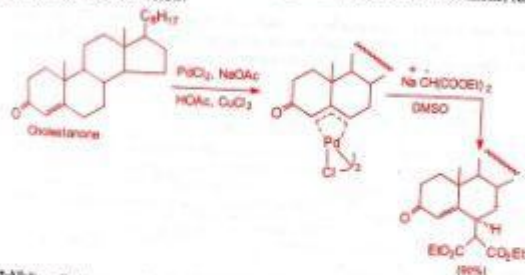
In the Wacker oxidation process, a π-allyl complex (as an intermediate) is involved. The reaction of allylic compounds with highly reactive palladium trifluoroacetate gives the π-allyl complex.



The π-allyl palladium complexes are also obtained by reacting allylic systems with diiodine tetrachloropalladate (Na_2PdCl_4) in the presence of NaOAc / AcOH (Trost's conditions). The formation of π-allyl palladium complexes involves the removal of H and the general order for the removal of allylic protons appears to be $\text{CH}_3 > \text{CH}_2 > \text{CH}$. The presence of CuCl_2 influences the removal of H. The mechanism of the formation of π-allyl palladium complexes was given by Trost and is as follows.



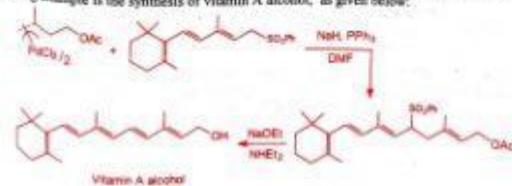
The π-allyl palladium complexes are used for a number of synthesis. For example, π-allyl palladium complexes formed from conjugated alkenes (such as cholestanone) react with carbanion as shown below.



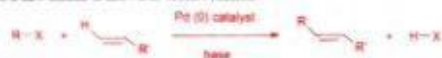
π-Allyl palladium complex formation is facilitated when the allyl moiety carries a good leaving group. This is also made possible by using a catalytic amount of tetrakis(triphenylphosphine)palladium(0).



A variety of carbanion nucleophiles can react with π-allyl palladium complex. A very interesting example is the synthesis of vitamin A alcohol, as given below:

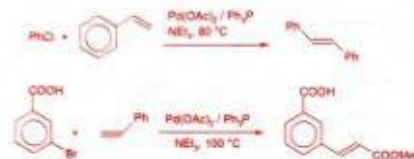


The coupling of an alkene with a halide or triflate in the presence of Pd(0) catalyst to form a new alkene is known as **Heck reaction**.



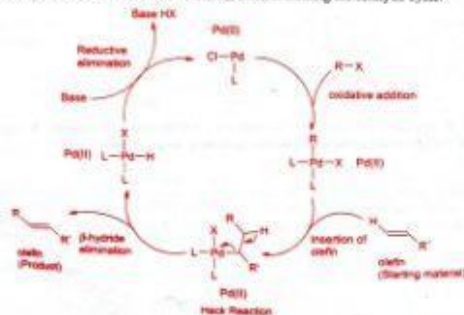
where R = aryl, vinyl or alkyl group without β hydrogens on an sp^2 carbon atom.
X = Halide or triflate (OSO_2CF_3).

The base used in Heck reaction may be mild, such as Et_3N or aqueous Na_2CO_3 . The Heck reaction is one of the most synthetically useful palladium-catalysed reactions. It is used for the arylation of alkenes to give styrene derivatives.



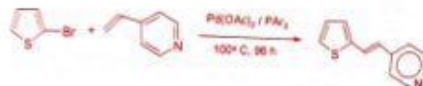
Mechanism

Mechanism involves the oxidative addition of the halide (RX), insertion of the olefin, and elimination of the product by a β -hydride elimination process. The base regenerates the palladium(0) catalyst (π -allyl elimination), thus, continuing the catalytic cycle.



The oxidative addition of RX on Pd(0) complex results in a Pd(II) complex having π alkyl bond. Such complexes are very reactive, especially towards olefins. The role of base is to remove HX from the palladium (II) complex, and the palladium (0) is regenerated.

Heterocyclic halides and alkenes can be coupled by the Heck reaction. Thus, 2-methoxyphenol and 4-vinylpyridine are reacted in presence of 1% $Pd(OAc)_2$ and 2% $Pd(o-Tol)_2$ at $100^\circ C$ to form coupled product.

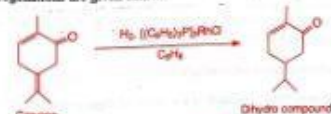


7.15 Organorhodium and ruthenium compounds

The organorhodium and ruthenium compounds are used as soluble catalysts for effecting selective hydrogenation. The rhodium complex, viz., tris(triphenylphosphine)chlororhodium, $[(C_6H_5)_3P]_3RhCl$, is prepared by the reaction of rhodium chloride with excess of triphenylphosphine in boiling ethanol.

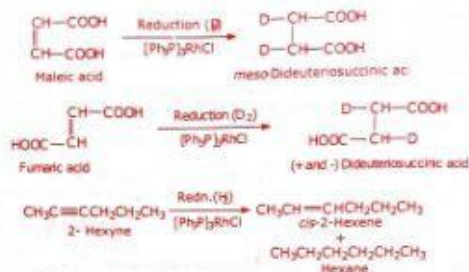


It is an efficient catalyst for the homogeneous hydrogenation of non-conjugated alkenes and alkynes at ordinary temperature and pressure in benzene. Functional groups like oxo, cyano, nitro, chloro and azo are not reduced under these conditions. Some examples of selective hydrogenations are given below.

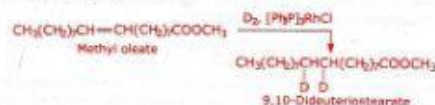


For mechanism of hydrogenation and some more examples see sec. 4.2[B].

It has been shown that hydrogenation takes place by *cis* addition to the double bond. This is shown by catalysed reaction of deuterium with maleic acid which gives *meso*-disubstituted succinic acid while fumaric acid gives the (*±*) compound. Similarly, 2-hexyne gives a mixture of hexane and *cis*-2-hexene.



As seen in the first two examples, deuterium is introduced only at the site of the original double bond. Similarly methyl oleate is converted into 9,10-dideuterioleate.



The ruthenium complex, $[(\text{C}_6\text{H}_5)_3\text{P}]_3\text{RuClH}$, is prepared *in situ* from $[(\text{C}_6\text{H}_5)_3\text{P}]_3\text{RuCl}$ and hydrogen in presence of a base such as triethylamine. It is an efficient catalyst and is specific for hydrogenation of monosubstituted alkenes. $\text{RCH}=\text{CH}_2$. Thus, 1-heptene is converted into heptane but 3-heptene is unaffected.

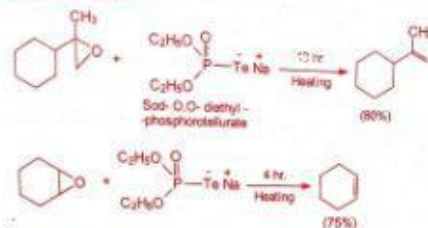
7.16 Organotellurium compounds

Organotellurium reagents have been used in a number of organic syntheses.¹⁸ Following are some of the important applications.

(i) Debromination of vic-dibromides

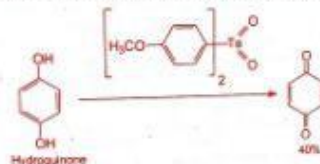


(ii) Deoxygenation of epoxides

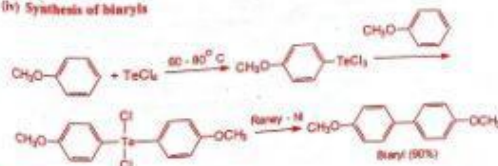


(iii) Oxidation of hydroquinone

Hex-4-methoxyphenyltelluric oxide oxidises hydroquinone to quinone.



(iv) Synthesis of biaryls

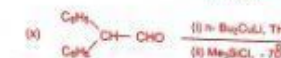
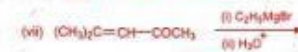
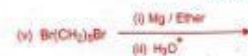


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Problems

- Explain what is an organometallic compound. Give the mechanism of the formation of organometallic compound from an alkyl halide and magnesium.
- Discuss the structure of ethylmagnesium bromide.
- How will you estimate the number of active hydrogens in an organic compound?
- Comment on function of Grignard reagents as carbon nucleophiles.
- How does umplong play a role in the activity of Grignard reagents?
- What happens when methyl cyanide is treated with methylmagnesium iodide and the adduct formed is further treated with H_3O^+ ?
- Starting with Grignard reagents how will you prepare other organometallic compounds containing Pb, Hg, Si, Pd and Cd?
- Starting with a Grignard reagent how will you prepare alkyl cyanide, primary amine and an ether?
- Starting with a Grignard reagent how will you obtain deuterated hydrocarbons?
- How are phenyl-lithium and vinyl-lithium obtained?
- The conversion $RCHO \rightarrow R_2CHOH$ can be brought about by reaction of $RCHO$ with a organometallic compound followed by hydrolysis. Which of the organometallic compounds, CH_3MgBr or CH_3Li will give better yields?
- Starting with trans 2-phenylcyclobutane carboxylic acid how will you obtain trans-2-phenylcyclobutyl methyl ketone?
- Out of CH_3MgBr and CH_3Li which one will react with alkenes and what product will be obtained?
- Starting with pyridine how will you obtain 2-phenylpyridine?
- How will you obtain lithium dimethylcuprate?
- What are Gilman reagents, high order organocopper reagents and copper isonitride reagents? Give one example of each.
- Starting with sec-butyl chloride how will you prepare 3-methyloctane?
- How is isodimethylzinc iodide prepared? How does it react with propene? Give mechanism of the reaction.
- What is a carbenoid?
- How is cyclopentadienyliron carbonyl prepared?
- Describe Wacker process for the manufacture of acetaldehyde.
- Write the product(s) obtained in the following reactions:



23. How will the following conversions be carried out?





24. What happens when

- Di-tert-butyl ketone is made to react with methylmagnesium bromide.
- Methyl isopropyl ketone is made to react with t-butyllmagnesium halide.
- Propene epoxide is treated with organolithium reagent followed by treatment with water.
- What product is obtained by the polymerization of ethylene in presence of triethylaluminium?
- Cinnamaldehyde is reduced in presence of $(\text{Ph}_3\text{P})\text{RhCl}$ catalyst.

8 Reagents

8.1 Aluminium isopropoxide $[(\text{CH}_3)_2\text{CHO}]_3\text{Al}$

8.1.1 Introduction

Aluminium isopropoxide (triisopropoxyaluminium) has specific synthetic uses. It is prepared by reacting isopropyl alcohol with amalgamated aluminium foil in the presence of a small amount of carbon tetrachloride as catalyst. When hydrogen evolution ceases the molten alkoxide is distilled at reduced pressure. Aluminium isopropoxide has been used extensively for the reduction of carbonyl compounds, oxidation of alcohols, hydrolysis of oximes, preparation of ethers and rearrangement of epoxides to allylic ethers.

8.1.2 Reduction of carbonyl compounds

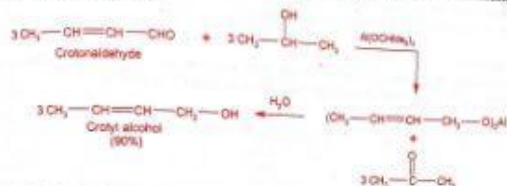
The reduction of aldehydes and ketones takes place by heating the carbonyl compounds with aluminium isopropoxide in the presence of excess isopropyl alcohol. The alcohol, reduction product, is obtained from the reaction mixture after acidification, and acetone is generated from isopropyl alcohol. This is called **Meerwein-Ponndorf-Verley reduction** (also see sec. 5.62).



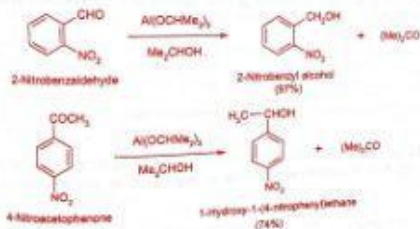
Since the reduction of carbonyl compounds to alcohols with aluminium isopropoxide is a reversible reaction, the reagent can be used for the oxidation of alcohols to carbonyl compounds. The reverse reaction is called **Oppenauer oxidation** (also see sec. 8.1.5). The equilibrium between reactants and products can be shifted in either direction by changing the conditions. For example, oxidation of alcohols to ketone is achieved when excess of acetone is employed. Reduction of carbonyl compounds to alcohols is carried out by distilling the acetone as it forms in the reaction mixture. Aldehydes are esters, β -diketones and other aldehydes and ketones are reduced to secondary alcohols. β -Keto- undergo this reduction.



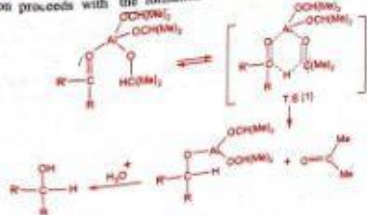
The reagent is specific for the reduction of aldehydes and ketones while olefinic bonds, nitro group, acetals and halogen atoms remain unaffected. For example, crotonaldehyde is reduced to crotyl alcohol.



Similarly, 2-nitrobenzaldehyde and 4-nitroacetophenone are reduced to 2-nitrobenzyl alcohol and 1-hydroxy-1-(4-nitrophenyl)ethane, respectively.



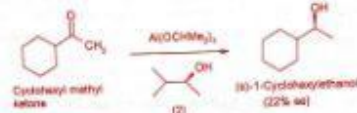
Mechanism
The reaction proceeds with the formation of co-ordination bond between carbonyl



oxygen and aluminum. This is followed by an intramolecular transfer of hydride ion from the carbonyl carbon to the carbonyl carbon, which simultaneously reduces a molecule of the carbonyl compound and oxidises an isopropoxide group to acetone. Thus, the reaction involves a cyclic transition state (1).

Applications

Reduction of cyclohexyl methyl ketone with catalytic amount of Al(OCHMe)_2 and excess of chiral alcohol (2) gives (s)-1-cyclohexylethanol^{1a} in 22% ee.



Cyclohexanones give higher proportion of axial alcohols as a main product by reduction with Al(OCHMe)_2 .



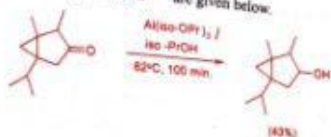
The final step in the synthesis of dihydrocrinine⁷ (4), involves the reduction of carbonyl group in (3) with aluminum isopropoxide in isopropanol to give exclusively the α -alcohol.



Complete reduction of keto group may occur with excess of reagent at high temperature. For example, anthraquinone is reduced to anthracene, when excess of reagent is employed.



Some other important applications^{2a-2c} are given below.

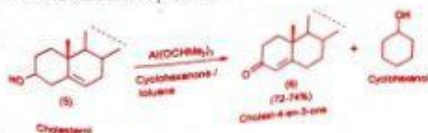


8.1.3 Oxidation of alcohols (Oppenauer oxidation)¹

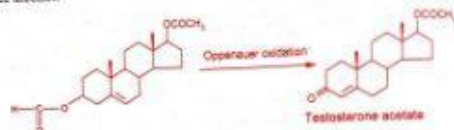
Alcohols on refluxing with $\text{Al(OCMe}_2)_3$ in acetone and benzene or toluene are oxidised to aldehydes or ketones. Acetone acts as hydrogen acceptor, and is converted into isopropyl alcohol. The presence of excess of acetone drives the reaction towards the oxidation product.



The β , γ -double bonds generally migrate into conjugation with the carbonyl group under the reaction conditions. The Oppenauer oxidation method is selective as carbon-carbon double bond is not attacked. For example, oxidation of cholesterol⁴ (5) with aluminium isopropoxide and cyclohexanone as hydrogen acceptor is accompanied by migration of carbon-carbon double bond so that the product cholestenone (6) is α,β -unsaturated. Toluene is often used as a co-solvent to raise the temperature.



Formate unlike an acetate or a benzoate can be oxidised and affords the same product as the free alcohol.



Acetals like olefins are not oxidised.



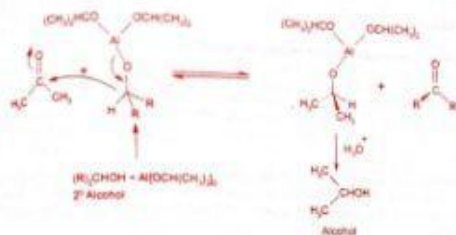
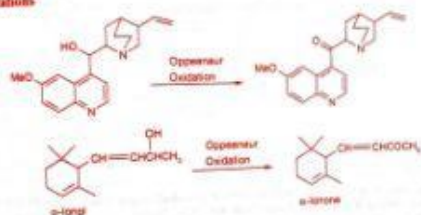
Equatorial hydroxyl groups tend to be oxidised preferentially over axial hydroxyl groups.



Mechanism

The reaction is carried out by refluxing a secondary alcohol with acetone in the presence of aluminium isopropoxide. The aluminium isopropoxide serves only to form the aluminium alkoxide of the alcohol which is then oxidised through a cyclic transition state at the expense of acetone to yield a ketone and isopropyl alcohol. The use of excess acetone shifts the equilibrium to the right. In the above reaction, acetone acts as the hydrogen acceptor within a cyclic complex.

Other ketones, such as 2-butanone and cyclohexanone are also used in place of acetone. The use of inert solvent such as benzene, toluene or dioxane minimises the side products and also reduces the reaction time.

Applications⁸

8.14 Hydrolysis of oximes

Oximes are hydrolyzed to parent carbonyl compounds.



8.15 Preparation of ethers

Ethers⁹ are prepared by the reaction of alkyl halides with $Al(OCHMe)_3$ in DMF.

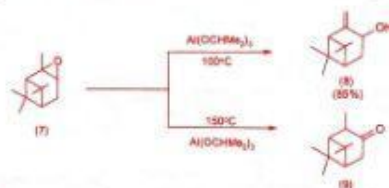


8.1.6 Reaction with epoxides

(a) Regio and chemoselective ring opening of epoxides.



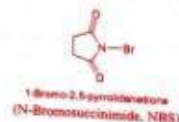
(b) Rearrangement of epoxides to allylic alcohols: α -Pinene oxide (7) rearranges to pinocarvone (8) at 100-120°C in the presence of 1 mol % of $Al(OCHMe)_3$. At higher temperature (140-170°C) and in the presence of 5 mol % of $Al(OCHMe)_3$ pinanone (9) is obtained.



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8.2 N-Bromosuccinimide (NBS)



4.2.1 Introduction

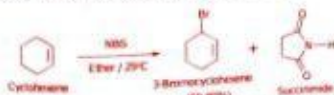
N-bromo-2,5-pyrrolidenedione, commonly known as N-bromosuccinimide (abbreviated as NBS) is a convenient source of bromine for both radical substitution and electrophilic addition reaction. Free radical substitution of allylic or benzylic hydrogen by bromine is accomplished with N-bromosuccinimide in non-polar solvents such as CCl_4 . However, the use of NBS in aqueous solvents (mixture of DMS with water) as a source of electrophilic bromine has found increasing importance in the formation of bromohydrins, the cyclisation of certain aromatic compounds, and in the addition of bromine to alkenes. The oxidation of secondary alcohols to ketones using NBS has been carried out in aqueous solvents.

NBS can be prepared from succinimide and bromine in the presence of sodium hydroxide solution (3 M), the white product obtained is washed with water and recrystallised from hot water or acetic acid. It is stored in a refrigerator and protected from moisture to avoid decomposition. It is easier and safer to handle than bromine.



4.2.2 Allylic and benzylic bromination

Alkenes are brominated at allylic position on refluxing a solution of the alkene and recrystallised NBS in anhydrous CCl_4 . The reaction is initiated by peroxide or light. For example, reaction of NBS with cyclohexene gives 3-bromocyclohexene in the presence of catalytic amount of radical initiator, such as benzoyl peroxide or AIBN. Olefins can be brominated in the allylic position by a number of reagents, but NBS is most common. When this reagent is used, the reaction is known as **Wohl-Ziegler bromination**.



If there are two allylic positions, then two monobromo-derivatives may be obtained. Allylic methylene groups are attacked much more rapidly than allylic methyl groups.
e.g. in 2-hexene, a secondary position is substituted more readily than a primary.



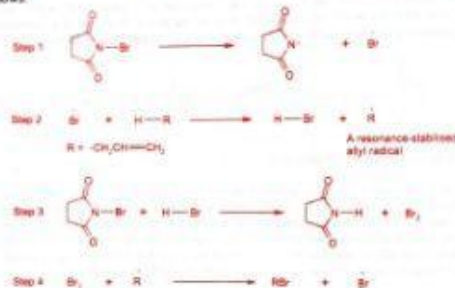
Whenever a structure permits, allylic bromination leads to allylic rearrangement.

1-Butene, for example, on treatment with NBS gives mixture of both possible products,



The action of NBS on di- and poly-olefins often leads to abnormal products by allylic rearrangements. Thus, 1,5-hexadienes give the monobromo-product, 1-bromohepta-2,5-diene, with some of the 3-bromo-isomer and the reaction of 1,5-hexadiene with two moles of NBS give 1,6-dibromohepta-2,4-diene.

Mechanism of allylic bromination which was proposed by Dauben and McCoy¹ is as follows.

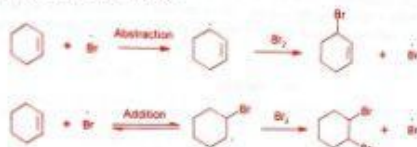


The first step in this reaction is formation of a bromine free radical through dissociation of the nitrogen-bromine bond of NBS. The bromine free radical then abstracts a hydrogen from the allylic position of the alkene to give hydrogen bromide and a resonance stabilised allyl radical (step 2). The allyl radical formed in second step of the reaction abstracts a bromine atom from a bromine molecule to give allyl bromide and a bromine atom (step 4), which starts the cycle all over again.

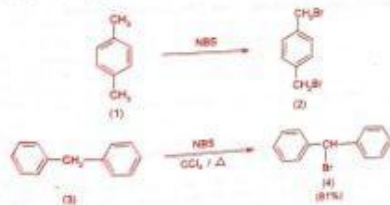
Thus, bromination with NBS is a free radical chain process. The reaction is initiated by small amounts of $\text{Br}^\cdot$. The role of NBS is to provide (step 3) a constant, low concentration of molecular bromine and to use up the HBr liberated in step 2. Thus, NBS is source of bromine in this reaction. Abstraction of an allylic hydrogen by $\text{Br}^\cdot$ gives a resonance stabilised allyl radical. The selective bromination occurs because the intermediate leading to this product is stabilised by resonance. The main evidence for this mechanism is that the reaction is very sensitive to free radical initiators and inhibitors. Ethylbenzene gives 38% yield of the α -bromocompound in the absence of an initiator and 45% yield of the same compound in the presence of an initiator.



The allylic bromination of alkenes occurs in preference to addition to the double bond. The addition of bromine atoms to a double bond is reversible and a low bromine concentration favours hydrogen abstraction. Under certain circumstances di- or poly-bromination has been found to occur.



The bromination of methyl or methylene groups α - to an aromatic ring with NBS has been investigated, both from a synthetic and a mechanistic viewpoint. Reaction of *p*-xylene (1) with NBS yields α, α -dibromo-*p*-xylene (2). Similarly, a benzylic hydrogen atom of methylene group in diphenylmethane (3) is substituted by NBS and the product, bromodiphenylmethane (4) is obtained in 81% yield.



Another example is the conversion of 1-phenylbutane to 1-bromo-1-phenylbutane and 1-methylnaphthalene to 1-bromomethylnaphthalene.



The reaction of heterocyclic compounds with NBS occurs either in a side chain or in the nucleus or a mixture may be formed, depending upon the structure of the compound and on the reaction conditions. The effect of free radical initiators is very well shown in the reaction of NBS with 3-methylthiophene, where nuclear bromination takes place in the absence of an initiator and side chain bromination⁸ occurs in the presence of benzoyl peroxide.



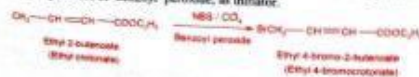
8.2.3 α -Bromination of carbonyl derivatives

Ketones, containing an enolisable hydrogen can be brominated at the α -position with NBS. The reaction probably proceeds via addition of X_2 to the enol form of the carbonyl derivative, and elimination of HX generates the α -bromoketones.⁷ Reaction of cyclohexanone with NBS, for example, gives 2-bromocyclohexanone.

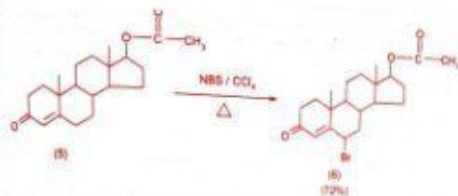


8.2.4 Allylic bromination of unsaturated acids, esters, aldehydes and ketones

NBS reacts with unsaturated fatty acids and their derivatives such as oleic acid⁸ and methyl oleate⁹ to give mixture of monobromo (generally as a major product) and dibromocompounds. The formation of the important 4-bromo esters, used in the Reformatsky reaction, from α, β -unsaturated esters and NBS is a useful synthetic procedure. Thus, ethyl 4-bromocrotonate¹⁰ is readily prepared from ethyl crotonate using NBS in the presence of benzoyl peroxide, as initiator.



Under similar conditions, testosterone acetate (5) is converted into 6- β -testosterone acetate (6) by NBS.



It has been found that unsaturated ketones, having methylene groups in the α -position at both the carbonyl group and the double bond, are preferentially brominated in the methylene α -to the double bond.

12.5 Bromination of aromatic compounds

The aromatic compounds react with NBS under ionic conditions to give nuclear substitution products. The actual brominating agent does not appear to be free halogen but could possibly be the protonated N-bromosuccinimide. Benzene when treated with NBS and mixture of concentrated sulfuric acid and water (1:1, by volume) gives bromobenzene in 95%. However, it is only slightly attacked by NBS under normal Wohl-Ziegler conditions. The reaction of NBS with aromatic compounds containing highly branched chains also appears to give nuclear brominated products.

Phenols, anilines and other electron rich aromatic compounds can be brominated by using NBS in DMF with higher yields and higher levels of *para* selectivity than with bromine. The reaction of tertiary amines with NBS is complex and may involve cleavage of the amine function.

Heterocyclic compounds without alkyl substituents are generally readily brominated by NBS in the hetero-ring. Thiophene is selectively brominated in the 2-position by NBS in acetic acid-chloroform.

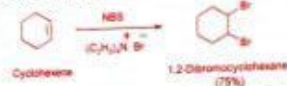


N-substituted pyrroles are brominated with NBS in THF to afford 2-bromopyrroles (with 1-equivalent NBS) or 2,5-dibromopyrroles (with 2-equivalent of NBS) with high selectivity, whereas bromination with bromine affords thermodynamically more stable 3-bromopyrroles.

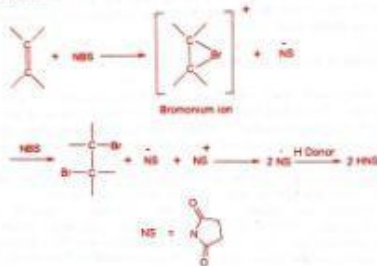
8.2.6 Addition reactions

(a) Formation of dibromocompounds

NBS is often used as the source of electrophilic bromine in polar solvents, thus addition NBS is often used as the source of electrophilic bromine in polar solvents. Braude *et al.* showed that the addition reaction is predominates in polar solvents. Braude *et al.* showed that the addition reaction is predominates in polar solvents. NBS and cyclohexene give 1,2-dibromocyclohexane in the presence of tetraethylammonium bromide.

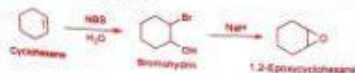


A plausible mechanism for the addition has been suggested by Braude and Waight and is represented as follows.

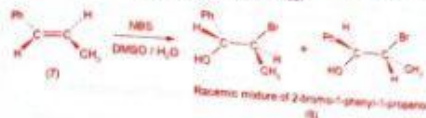


(b) Formation of bromohydrin

Bromohydrins are often formed in fairly high yields when alkenes are treated with NBS in the presence of excess water. The reaction is of great value for the preparation of epoxides by dehydrobromination of the bromohydrins. NBS, for example, reacts with cyclohexene in aqueous medium to form bromohydrin, subsequent treatment with a base, such as sodium hydroxide generates the alkoxide, which is anti to the adjacent bromine. An orientation allows displacement of halide to give cyclohexene oxide (1,2-epoxycyclohexane) via an $\text{S}_{\text{N}}2$ process.



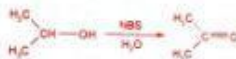
The stereochemistry of the product shows clearly that the *anti* addition takes place at the double bond (i.e., the reaction involves a bromonium ion intermediate). For example (E)-1-phenyl-1-propene (7) gives a racemic mixture of 2-bromo-1-phenyl-1-propanol (8) when treated with NBS in aqueous dimethyl sulfoxide.



8.1.7 Oxidation

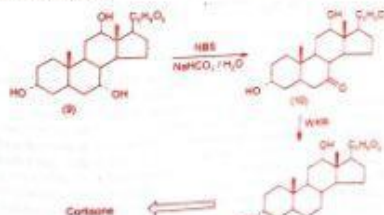
(i) Oxidation of alcohols

NBS in the presence of water is a selective oxidising agent for the oxidation of secondary alcohols to ketones (also see sec. 3.5.22). This procedure has found greatest use in the oxidation of steroidal alcohols¹² to their respective ketones.



Selective oxidation of cholic acid (9) at C-7 with NBS in the presence of water provides an efficient route to deoxycholic acid (10), required as starting material for the synthesis of cortisone.

The mechanism of the oxidation may well involve an ionic process rather than a free radical pathway and the reaction could proceed by substitution of the hydrogen on the carbon bearing the hydroxyl group followed by rapid loss of hydrogen bromide. The exact mechanism is not clear.



(ii) Degradative oxidation of hydroxy-carboxylic acids

NBS has been found to react readily with α -hydroxy acids in hot aqueous solution to give aldehydes or ketones with loss of one carbon atom.¹³ Glycolic acid, lactic acid, and mandelic acid are converted into formaldehyde, acetaldehyde, and benzaldehyde, respectively, in good yields on refluxing with N-bromosuccinimide in water.



Similarly, α -amino acids are decarboxylated with NBS in aqueous medium.



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8.3 Diazomethane (CH₂N₂)

8.3.1 Introduction

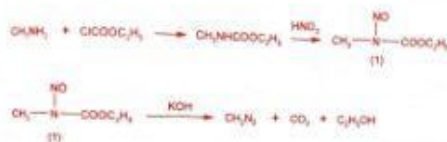
Diazomethane is yellow, toxic and highly reactive gas which is soluble in ether. Liquid diazomethane is explosive but may be handled safely in ethereal solution. It is usually prepared immediately prior to use. Diazomethane has been extensively used for the methylation of compounds containing active hydrogen, i.e., acids, phenols and enols. It can also be used for methylation of compounds containing weak acidic hydrogens such as alcohols and amines. Epoxidation and homologation of aldehydes and ketones can be carried out on reaction with diazomethane. The homologation of carboxylic acids, i.e., the **Arndt-Eistert reaction** (see sec. 5.4), is a particularly valuable synthetic procedure. It is an important precursor for the generation of carbene. Diazomethane is represented by several resonance hybrid structures.



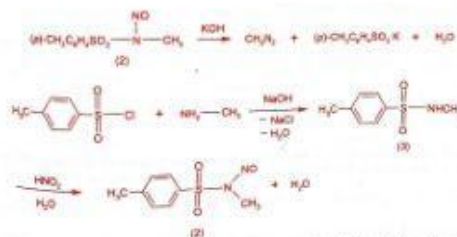
8.3.2 Preparation of diazomethane

The generally used method for the preparation of diazomethane is by the alkaline hydrolysis of N-nitroso compounds $[RN(NO)Me]$.

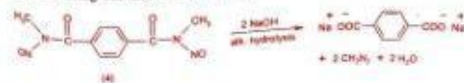
(a) N-Methyl-N-nitrosourethane¹ (1) on warming with methanolic potassium hydroxide undergoes decomposition to give diazomethane. N-Methyl-N-nitrosourethane (1) can be prepared by the reaction of methylamine with ethyl chloroformate, followed by treatment with HNO_2 .



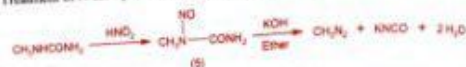
(b) A convenient precursor for the generation of diazomethane is N-methyl-N-nitroso-p-toluenesulfonamide² (2), which is prepared by the action of nitrous acid on N-methyltoluene-p-sulfonamide (3). The latter is formed from toluene-p-sulfonyl chloride and methylamine in alkaline solution.



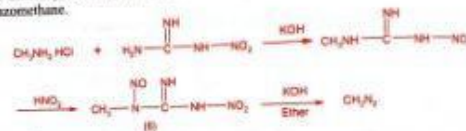
(c) Treatment of N,N'-dimethyl-N,N'-dinitrosocephthalimide³ (4) with base also gives diazomethane along with disodium salt of terephthalic acid.



(d) Treatment of N-methyl-N-nitrosourea⁴ (5) with base gives diazomethane.



(e) Similarly, N-methyl-N'-nitro-N-nitrosoguanidine⁵ (6) on treatment with base gives diazomethane.



8.3.3 Methylation

Diazomethane methylates acidic hydroxy groups, carboxylic acids, sulfonic acids, phenols and enols. Conditions are mild and high yields are obtained. It reacts with carboxylic acid to liberate nitrogen and form methyl ester. Typical examples of methylation with diazomethane are preparation of methyl ester of cinnamic acid from cinnamic acid and anisole from phenol.

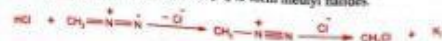


Methyl esters are prepared by treating a solution or suspension of the carboxylic acid with an ether solution of diazomethane. The mechanism of the reaction is given below.

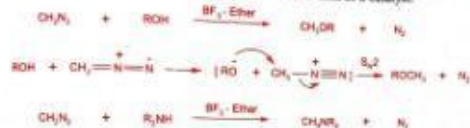


Diazomethane deprotonates the acid forming methyl diazonium ion and weak nucleophile, $RCOO^-$. Although $RCOO^-$ is a weak nucleophile it can displace the excellent leaving group, nitrogen (N_2).

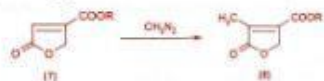
Similarly, halogen acids react with CH_3N_2 to form methyl halides.



Ordinary alcohols and amines, because of the low acidity of the hydroxyl hydrogen, react with CH_2N_2 in the presence of catalyst. Aluminium chloride, boron trifluoride etherate 2° and 3° amines. Methylamine gives a 29% yield of the secondary and 26% yield of the tertiary amine and aniline gives 34% and 38% of the secondary and 26% yield of the dimethylaniline, respectively. Amines are methylated with CH_2N_2 in presence of either boron trifluoride-etherate or cuprous cyanide. In general alcohols are best methylated in the presence of boron trifluoride-etherate or fluoboric acid as a catalyst.

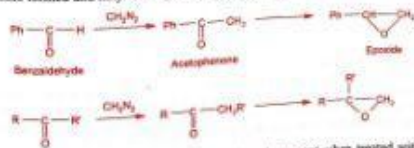


C-Methylation may be seen in the formation of the 3-methyl compound (8) from acetic ester (7) with CH_2N_2 .

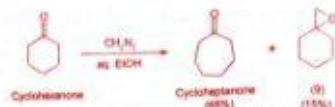


3.3.4 Homologations

(a) Diazomethane reacts with aldehydes to give methyl ketones, as is illustrated by the conversion of benzaldehyde to acetophenone.³ Ketones can be converted to their higher homologues with diazomethane. In both the cases the yields are low as epoxides are sometimes formed and may be the predominant product.



Certain cyclic ketones undergo homologous ring enlargement when treated with CH_2N_2 in the presence of alcoholic solvents. For example, cycloheptanone⁴ is prepared from cyclohexanone on reaction with CH_2N_2 in 65% yield, along with 15% of epoxide (9).

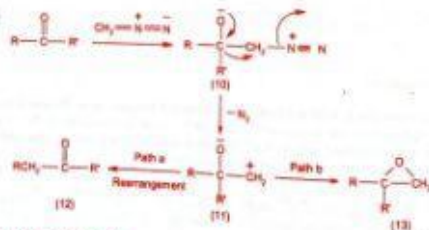


Aliphatic and aryl alkyl ketones react similarly but generally require an acid catalyst. The reaction is catalysed by BF_3 and there is a preference for aryl migration.



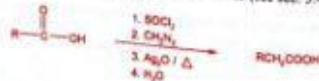
Mechanism

The reaction involves rearmangement and no free carbene is involved. First step is the addition of diazomethane to the carbonyl group of the aldehyde or ketone. The resulting betain (10) loses nitrogen to give (11), which undergoes rearmangement to yield higher ketone (path a) (12) or can also cyclise to give epoxide (path b) (13). Aldehydes give fairly good yields of methyl ketones i.e., hydrogen migrates in preference to alkyl.



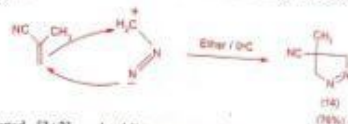
(b) Arndt-Eistert reaction

This reaction is used for converting a carboxylic acid into its next higher homologue. Acid chloride reacts with diazomethane to give α -diazoketone, which rearranges with loss of nitrogen in the presence of excess of colloidal silver to give ketene. The ketene is subsequently converted to carboxylic acid or its derivatives (see sec. 5.4).

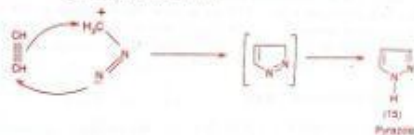


8.3.5 Addition reactions

The 1,3-dipolar addition reactions of CH_2N_2 with a wide variety of compounds containing ethylenic and acetylenic bonds give heterocyclic compounds in high yields. Diazomethane, for example, reacts with α -methyl acrylonitrile to give pyrazoline,⁸ (14) in 76% yield.

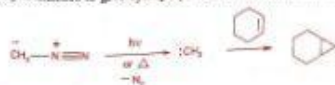


A concerted, [3+2] cycloaddition mechanism for the formation of pyrazolines from diazomethane is suggested and the reaction is stereoselective. Addition of diazomethane to acetylenic compounds gives pyrazole derivatives. Pyrazole (15) itself may be obtained from acetylene and diazomethane.



8.3.6 Miscellaneous reactions

Heat or light generates carbene from diazomethane through loss of nitrogen which can add rapidly to alkenes to give cyclopropane derivatives (for details see sec. 2.5.3).



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8.4 2,3-Dichloro-5,6-dicyano-1,4-benzoquinone (DDQ)

8.4.1 Introduction

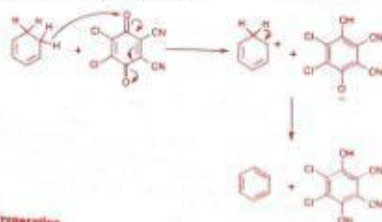
Quinones are generally used for dehydrogenation and are reduced to corresponding hydroquinones. Two important quinones are often used, chloranil and DDQ (also see sec. 3.5.25).



DDQ is very reactive and may be used in cases where the substrate is difficult to dehydrogenate. DDQ is used under anhydrous conditions because it decomposes in presence of water. It is very convenient to handle and the reaction can be carried out in inert solvents such as benzene, toluene, THF and dioxane. Solution of DDQ in benzene is red in color because of formation of charge transfer complex, and after dehydrogenation DDQ is reduced to hydroquinone which is a yellow solid and insoluble in benzene. Thus, the progress of the dehydrogenation can be followed.

8.4.2 Mechanism of dehydrogenation

The mechanism of dehydrogenation with DDQ involves the transfer of hydride ion from hydrocarbon to the quinone oxygen, followed by the transfer of a proton to the phenolate ion. Thus, DDQ is reduced to hydroquinone.

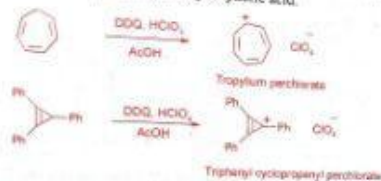


8.4.3 Preparation

DDQ is easily available. Its synthesis has been described by Thiele and Ganther⁹.

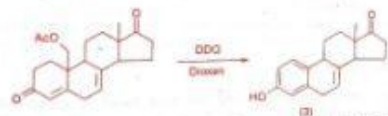
8.4.5 Preparation of salts containing stable aromatic cations

DDQ has been proved to be useful for the preparation of salts of stable aromatic cations. For example, tropylium and triphenylcyclopropenyl cations of stable aromatic cations. In the presence of acids such as perchloric and phosphoric acid.



8.4.6 Useful reagent in steroids

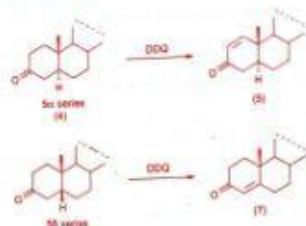
DDQ has found extensive application in the chemistry of steroids. It is frequently used as a reagent in the aromatisation of steroids as illustrated by the synthesis of equilin (3).



In some cases the aromatisation of steroids is accompanied by Wagner-Meerwein rearrangements (section 6.1.1).



DDQ is a versatile reagent for converting keto-steroids into α,β -unsaturated steroidal ketones.¹ 5 α - and the 5 β -series (4 and 6) on dehydrogenation with DDQ are converted into Δ^4 - and $\Delta^4,3$ -keto steroids (5, and 7), respectively.



Dehydrogenation of $\Delta^4,3$ -keto steroids (7) furnishes $\Delta^4,5,3$ -keto steroids (8). The reaction product is obtained in high yield and the advantage of the method is that the substituents commonly encountered in steroids are not effected by DDQ.



8.4.7 Oxidative cyclisation

One particularly important use of DDQ has been found in cyclodehydrogenation reactions of phenolic and carboxylic acids. These reactions lead to oxygen heterocycles such as coumarins, chromones, benzofurans and lactones. For example, 1-diphenylmethyl-1-naphthoic acid (9) on refluxing with DDQ in benzene undergoes oxidative cyclisation to δ -lactone (10).



Similarly, DDQ can be used for the cyclodehydrogenation of following phenols.



8.4.5 Oxidation of phenols

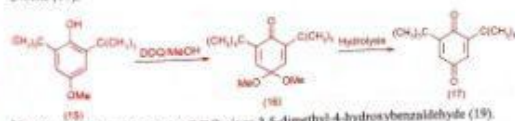
DDQ is a powerful oxidising agent for phenols⁸, usually, the chief product is a dimeric substance formed by either C-C or C-O coupling. 2,6-Dimethoxyphenol (11), for example, with a free *p*-position gives chiefly the diphenoxinone (12), for



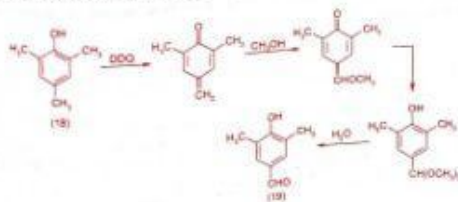
However, the hindered phenol, viz., 2,4,6-tri-*t*-butylphenol (13) affords the C-O dimeric product (14) with DDQ.



2,6-Di-*t*-butyl-4-methoxyphenol (15) gives a yellow oil, which on the basis of IR and NMR spectra is given the dimethylketal structure (16). Hydrolysis of which affords the quinone (17).



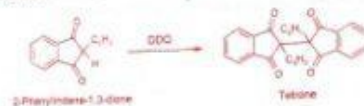
Mesol (18) on oxidation with DDQ gives 3,5-dimethyl-4-hydroxybenzaldehyde (19).



8.4.6 Organic Reaction Mechanisms

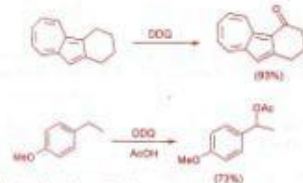
8.4.9 Oxidative dimerization

Enols and enolisable ketones in which α,β -unsaturation is not possible are oxidatively dimerized by DDQ. Thus, 2-phenylindane-1,3-dione is converted into tetrone.



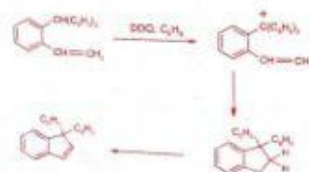
8.4.10 Oxidation of benzylic and allylic alkyl group

DDQ can oxidise benzylic or allylic alkyl group to carbonyl group. Benzylic oxidation by DDQ in aqueous acetic acid proceeds via an intermediate benzylic acetate, which is hydrolyzed under the reaction conditions. In some cases it is possible to isolate intermediate benzylic acetate⁹.



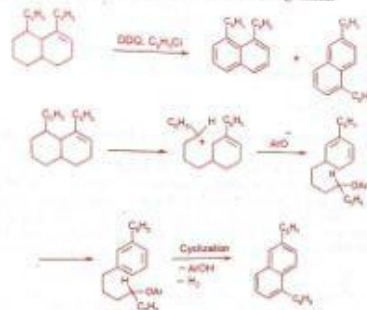
8.4.11 Intramolecular cyclisation

The ability of DDQ to abstract a hydride anion has been applied to the formation of stabilised carbanion ions, some of which have been trapped by intramolecular cyclisation process.



8.1.12 Isomerisation during dehydrogenation

Although dehydrogenation proceeds normally to give aromatic compounds, the compounds which are difficult to dehydrogenate give a mixture of isomeric products. The isomeric product appears to have been formed by fragmentation of intermediate carbonium ion followed by ring closure and further dehydrogenation.



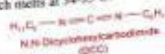
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8.5 N, N-Dicyclohexylcarbodiimide (DCC)

8.5.1 Introduction

DCC is a powerful dehydrating agent and stored under anhydrous conditions. It is a potent skin irritant and should be used carefully. It is commercially available as a waxy low-melting solid, which melts at 34–35°C.



8.5.2 Preparation

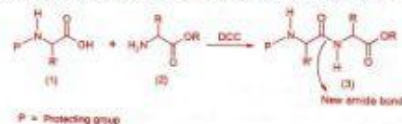
DCC is prepared by oxidation of dicyclohexylurea with *p*-toluenesulfonyl chloride in hot pyridine. It can also be prepared by heating dicyclohexylthiourea with yellow mercuric oxide.



Following are given some important applications of DCC.

8.5.3 Synthesis of peptides¹

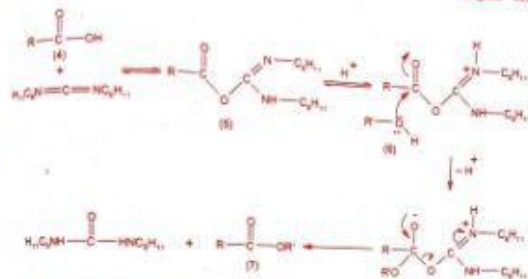
DCC is useful in the coupling of amino acids via the formation of amide bonds. The amino acid monomers should be such that the ends to be attached are activated, or at least available, and other reactive groups blocked, or protected. The protecting groups are deprotected in later steps. DCC is added to activate the carbonyl group of a second amino-protected acid and to promote formation of a new amide linkage during peptide synthesis. For example, for the synthesis of a dipeptide (3) from two α -amino acids (1 and 2), the amino group of one of the amino acids and the carboxylic group of the other must be blocked before the two reagents are brought together in the presence of the DCC.



Phthalic anhydride reacts with an amino acid to form an imide, which effectively blocks the amino group of the first amino acid. The carboxylic acid of the other amino acid is blocked by an ordinary ester function.

8.5.4 Synthesis of esters²

DCC is used for the synthesis of esters (7) from carboxylic acids (4) and alcohols (6). Thus, carboxylic acids can be converted into strong acylating agents (5) by reaction with DCC.



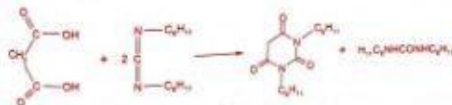
8.5.5 Synthesis of peroxides⁹

Peroxides can be prepared by reaction of carboxylic acid and hydrogen peroxide in the presence of DCC.



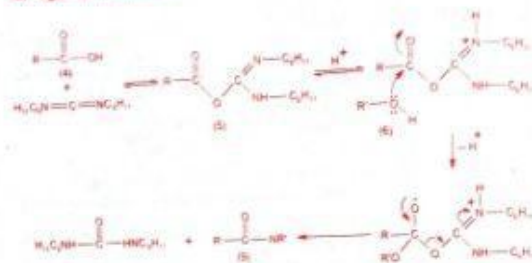
8.5.6 Heterocyclisation reactions⁶

DCC has been used both as reagent as well as reagent in heterocyclisation reactions. For example, barbituric acid and its derivatives can be prepared by the treatment of malonic acid with the DCC.



8.5.7 Synthesis of amides from carboxylic acids and amines

For the formation of amide bond, it is necessary that the poor leaving group, i.e., the hydroxyl group, present in the carboxylic acid function be converted into a better leaving group. DCC is useful in converting the hydroxyl group of the carboxylic acid into a good leaving group. The activated carboxyl group reacts with the amine (8) to give an amide (9). This reaction is used in the synthesis of peptides.



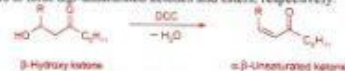
8.5.8 Dehydroxylation of alcohols⁷

The O-acylurea adduct, formed from the reaction of the alcohols or phenols with DCC, can be hydrogenated to yield the corresponding hydrocarbon.



8.5.9 Synthesis of α,β -unsaturated ketones⁸ and esters⁷

DCC is the most effective reagent for the dehydration of β -hydroxy-ketones and β -hydroxy-esters to form α,β -unsaturated ketones and esters, respectively.



8.5.10 Synthesis of ethers⁹ and thioethers⁷

Alcohols and thioalcohols can be converted into ethers and thioethers, respectively, by using DCC.



3.5.11 Synthesis of α -diazoketones

α -Diazoketones¹⁰ can be synthesised by coupling of diazomethane with carboxylic acid in the presence of DCC.



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3.6 Lead tetra-acetate [$\text{Pb}(\text{OCOCH}_3)_4$] or $\text{Pb}(\text{OAc})_4$

3.6.1 Introduction

Lead tetra-acetate $\text{Pb}(\text{OAc})_4$ is a versatile oxidising agent (also see sec. 3.5.7), which has been widely used in organic synthesis. The reagent has also been used as a drying agent for solvents such as benzene, pyridine, chloroform, carbon tetrachloride and ethers. $\text{Pb}(\text{OAc})_4$ is hygroscopic and turns brown due to lead dioxide formation on exposure to air. The reagent is very toxic and may be resorb through the skin. Because of its high toxicity and high vapor pressure it should be handled with extreme care in a chemical fume hood. $\text{Pb}(\text{OAc})_4$ can be readily prepared by slowly adding red lead oxide (Pb_3O_4) to a mixture of acetic acid and acetic anhydride at 60–80°C. The mixture is cooled and the separated lead tetra-acetate filtered. It is recrystallised from acetic acid as white needles.

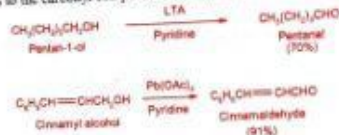
$\text{PbO}_2 + 2 \text{H}_2\text{O} \xrightarrow{\text{Pb}(\text{OAc})_4} \text{PbO}_2 + 4 \text{HOAc}$

For application in organic chemistry, $\text{Pb}(\text{OAc})_4$ is most often used for the oxidative decarboxylation of carboxylic acids, oxidation of alcohols, formation of cyclic ethers. It is also used as a good acetoxylation and methylating reagent.

3.6.2 Reaction of LTA with hydroxycompounds

(a) With monohydric alcohols

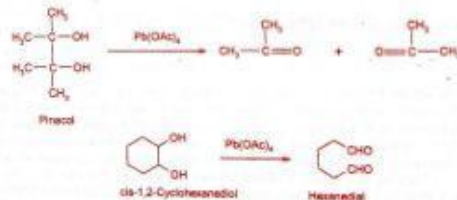
In presence of pyridine solution, $\text{Pb}(\text{OAc})_4$ oxidises a variety of primary and secondary alcohols to the carbonyl compounds at room temperature.



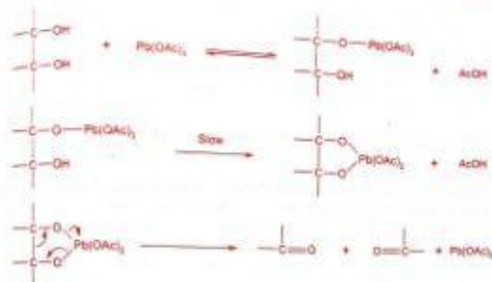
However, primary and secondary alcohols containing δ C-H group give high yields of tetrahydrofuran derivatives when treated with $\text{Pb}(\text{OAc})_4$ in benzene without the presence of pyridine (sec. 3.6.4).

(b) Reaction with 1,2-diols

1,2-Diols are cleaved under mild conditions with lead tetra-acetate to give aldehydes, ketones or both depending upon the structure of the 1,2-diols. The reaction is quantitative and rapid enough to allow titrimetric estimation of glycols. Pinacol, for example, gives two molecules of acetone and 1,2-cyclohexanediol gives hexanedial.

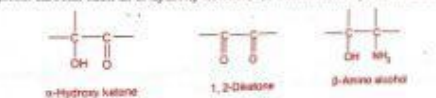


The cleavage of diols proceeds via a cyclic intermediate.¹ Since, cyclic intermediate is formed rapidly with *syn*-diols, therefore, *syn*-diols are oxidised faster than *anti*-diols. Thus, the reaction can be used not only to detect the presence of glycol groups but also by stereochemistry. The mechanism of glycol oxidation with $\text{Pb}(\text{OAc})_4$ was proposed by Criegee².

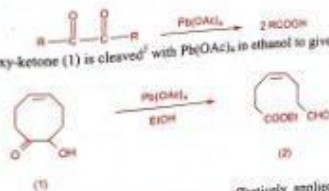


When three or more hydroxy groups are located on adjacent carbon atoms, then the middle one is converted to formic acid.

Similar cleavage is undergone by other compounds that contain oxygen or nitrogen on adjacent carbons such as α -hydroxy-ketones, 1,2-diketones and β -amino alcohols.



Cyclic α -hydroxy-ketone (1) is cleaved with $\text{Pb}(\text{OAc})_2$ in ethanol to give (2).



The reaction of $\text{Pb}(\text{OAc})_2$ with 1,2-diols has been effectively applied in the area of carbohydrates and sugars.



8.6.3 Reaction with carboxylic acids (Oxidative decarboxylation)

(a) Monocarboxylic acids

Monocarboxylic acids on oxidation with $\text{Pb}(\text{OAc})_2$ in the presence of copper (II) salts give mainly alkenes. The free radical mechanism⁸ is generally proposed.

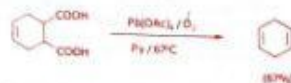


Rosefuran (4) can be obtained by the oxidative decarboxylation of 3-methyl-2-furoic acid derivative (3) with $\text{Pb}(\text{OAc})_2$ in the presence of $\text{Cu}(\text{OAc})_2$.

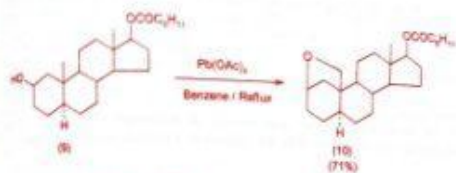


(b) Dicarboxylic acids

Biocarbonylation⁹ of compounds containing carboxyl groups on adjacent carbons can be achieved with $\text{Pb}(\text{OAc})_2$ in the presence of oxygen and pyridine.



Mechanism proposed for this reaction is given below.



(b) Cyclization of carboxylic acids

Usual treatment of carboxylic acids with Pb(OAc)_4 leads to decarboxylation, however, when a double bond is located nearby, lactone is formed.



(i) Dehydrogenation

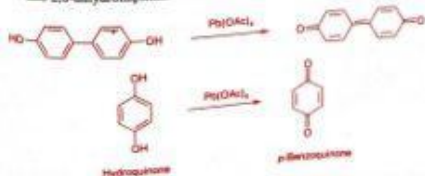
Lead tetra-acetate oxidation of 1° aliphatic amines results in dehydrogenation to nitriles.



N,N-Di-substituted hydrazines are readily dehydrogenated to azo compounds by Pb(OAc)_4 .



Diphenoquinone has been prepared in 45% yield by treating 4,4'-dihydroxybiphenyl with Pb(OAc)_4 in a mixture of dioxane-acetic acid (1:2). Similarly, hydroquinone is converted into p-benzoquinone with Pb(OAc)_4 and 2,6-dihydroxynaphthalene (naphthoquinone) is converted into 2,6-dihydroxynaphthalene-2,6-dione (anthra-naphthoquinone).



8.6.5 Acetoxylation

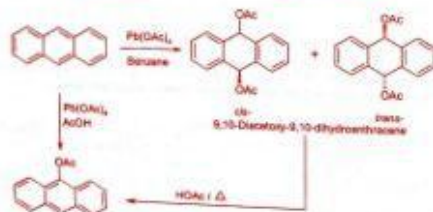
Ketones, in the mol form can be acetoxylation at α -position. The yields of α -acetoxylation product can be improved by the addition of a catalyst, boron trifluoride.



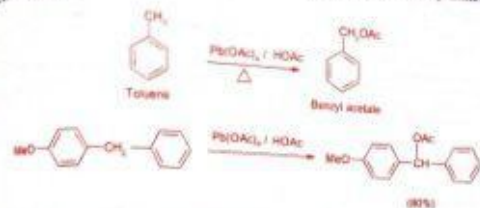
The acetoxylation of unsymmetrical dialkyl ketones usually occurs at the less substituted position. 2-Butanone, for example, gives 1-acetoxy-2-butanone⁸ with Pb(OAc)_4 .



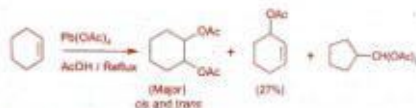
Benzene derivatives, containing electron-donating substituents and the more reactive condensed aromatic hydrocarbons, do undergo acetoxylation on thermal reaction with the Pb(OAc)_4 .



Acylation of alkyl side chains in aromatic compounds can be readily achieved by LTA treatment.

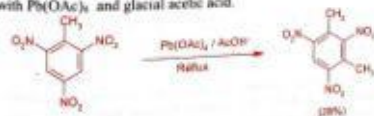


A mixture of products is formed by the oxidation of cyclohexene with Pb(OAc)_4 in acetic acid.

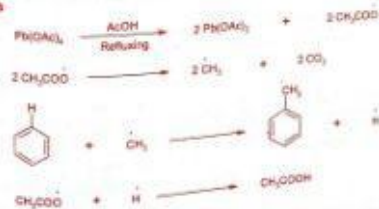


6.6.5 Nuclear methylation⁶

Nuclear methylation of aromatic compounds can be achieved by refluxing the aromatic compound with Pb(OAc)_4 and glacial acetic acid.



Mechanism



References

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2. R. J. Speer, H. R. Mahler, *J. Am. Chem. Soc.*, 1949, 71, 1133.
3. Oregor, Kraft, Rank, *Liebigs Ann. Chem.*, 1933, 509, 159.
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8.7 Lithium aluminium hydride (LiAlH_4)

8.7.1 Introduction

Lithium aluminium hydride (LAH) can be prepared by reaction of lithium hydride (LiH) with aluminium trichloride (AlCl_3) in THF.

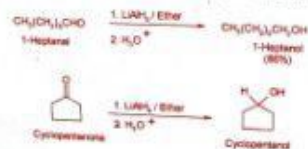


LAH reacts violently with water or protic solvents, resulting in the liberation of hydrogen (also see sec. 4.3.1). The reductions are generally conducted in dry ether, tetrahydrofuran or dioxane. Normally reductions are carried out by adding the compound in ether to the lithium aluminium hydride solution, but in certain cases reverse addition is also done. LAH is more reactive than NaBH_4 and normally reduces various polar functional groups except alkenes and alkynes. It reduces aldehydes, ketones, esters, carboxylic acids, acid anhydrides, acid chlorides and epoxides to the corresponding alcohols. Amides, nitriles, aliphatic nitro compounds, and amils are converted to the corresponding amines.



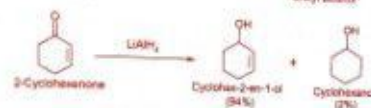
8.7.2 Reduction of carbonyl compounds

LAH reduces aldehydes to primary alcohols, and ketones to secondary alcohols. Reduction of aldehydes is faster than ketones because there is less steric hindrance. Following are given some typical reductions of aldehydes and ketones by LAH.



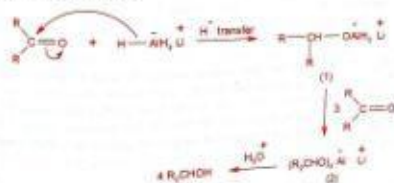


Reduction of α,β -unsaturated carbonyl compounds generally give 1,2-reduction product (i.e. double bond or triple bond is not reduced).



Mechanism

The complex hydride ion, $[\text{AlH}_4]^-$ acts as a carrier of hydride ions and all the four hydrogen atoms of LiAlH_4 are available for transfer to carbonyl groups. The initial transfer of hydride to the carbonyl carbon and co-ordination of aluminium to oxygen generates tetrahedral intermediate (1). Since there are three more active hydrides in (1), three more molecules of carbonyl compounds can react with it to give (2). Hydrolysis of (2) gives the reduced product, alcohol.



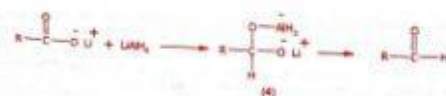
LT3 Reduction of carboxylic acid and its derivatives

Reduction of carboxylic acid and its derivatives, viz., esters, acid anhydrides, and acid chlorides result in the formation of corresponding alcohols. Aromatic anhydrides may undergo partial reduction² with one equivalent of LAH, but diols are the more usual products.³ The order of reactivity of carboxylic acid and its derivatives towards LAH reduction is: $\text{RCOCl} > \text{RCOOR} > \text{RCONR}_2 > \text{RCN} > \text{RCOOH}$.



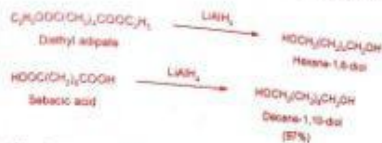
Mechanism

LAH is one of the few reagents that can reduce carboxylic acid to an alcohol. The mechanism of the reaction of carboxylic acid with LAH is not clear. However, it is suggested that carboxylic acid reacts with LAH to first give carboxylate anion (3) and H_2 . This is followed by the addition of hydride ion to the carbonyl group to give tetrahedral intermediate (4). Finally, (4) collapses to give an aldehyde, which is further reduced to primary alcohol.

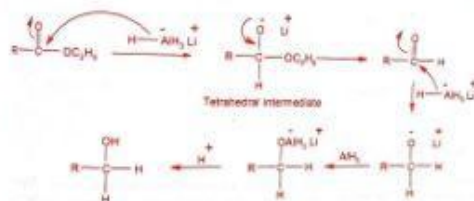


Reduction of diesters to diols with LAH is a very useful reaction, for example, diethyl adipate is reduced to hexane-1,6-diol⁴. Similarly, dicarboxylic acid, sebacic acid is reduced to decane-1,10-diol.

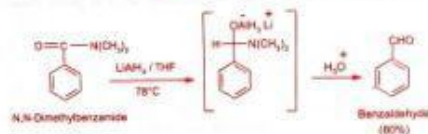
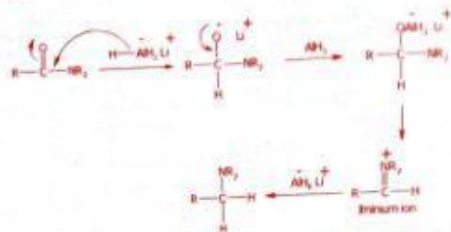
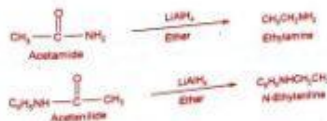
Reagents 353



Many LAH reductions of esters, acids, and acid chlorides are difficult to stop at the intermediate, aldehyde or ketone stage and the usual result is further reduction to the alcohol.

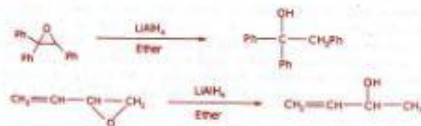


Unsubstituted amides form primary amines, whereas N-substituted amides give secondary amines, and N,N-disubstituted amides form tertiary amines. Reduction of amide with LAH gives aluminium ion as intermediate, which is of course, more electrophilic than the starting amide, so it gets reduced to the amine. When the reaction is carried out at low temperature (-70°C), amides can be reduced to aldehydes. For tetrahedral intermediate is more stable, thus quenching at this stage gives aldehyde. For example, N,N-dimethylbenzamide gives 80% benzaldehyde at -70°C with LAH in THF.



8.7.4 Reduction of cyclic ethers

Epoxides are opened reductively to alcohols. Unsymmetrical epoxide gives highly substituted alcohol. The reaction takes place at less substituted carbon atom by the $\text{S}_\text{N}2$ mechanism.



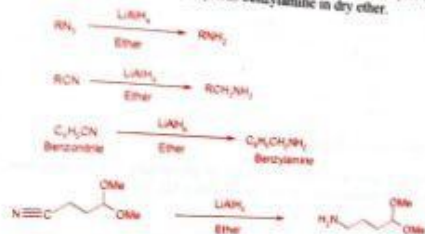
LAH opens the more strained ring in four-membered cyclic ethers, but the five-membered ethers (near strainless) are resistant and can only be cleaved with more vigorous reagent i.e., LAH- AlCl_3 .



8.7.5 Reduction of azides, nitriles, amides, nitroalkanes, imines and oximes

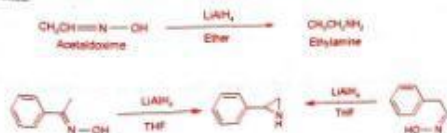
Reagents 513

Reduction of azides and nitriles with LAH give primary amines. For example, reduction of benzonitrile (phenyl cyanide) with LAH yields benzylamine in dry ether.

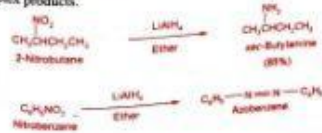


When one equivalent of LAH is added to the nitrile (reverse addition) at low temperature (-50°C), further reduction of the nitrile is avoided and the product formed is aldehyde.

Oximes are reduced to primary amines by LAH, for example, acetaldoxime forms ethylamine. Ketoximes that carry an α - or β -aryl ring, and aldioximes substituted with an aromatic group at the β -carbon, may undergo hydride reduction with ring closure to give aziridines.



Aliphatic nitro compounds give primary amines, however, aromatic nitro compounds give complex products.



8.7.6 Reduction of phosphonium and ammonium salts

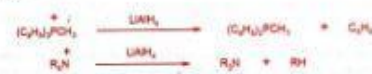
Under similar conditions, $\text{ArCH}=\text{CHNO}_2$ is reduced to $\text{ArCH}_2\text{CH}_2\text{NH}_2$ which is employed in the building up of isoquinoline rings.

Lactams are reduced to cyclic amines by LAH, for example, 2-pyrrolidinone derivative (5) is converted into pyrrolidine derivative (6).



8.7.7 Reduction of sulfur compounds

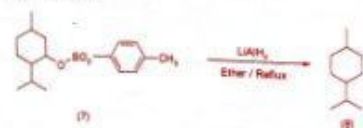
Phosphonium salts are reduced by LAH to phosphines and hydrocarbons. Similarly, quaternary ammonium salts can be cleaved with LAH.



8.7.8 Reduction of sulfur compounds



Sulfonate esters are reduced to the hydrocarbons. Thus, (7) gives *p*-menthane (8) in 60% yield with LAH in dry ether.

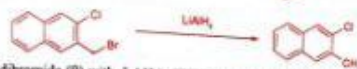


8.7.9 Reduction of alkyl halides and aryl halides

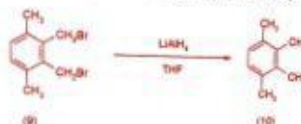
Primary and secondary alkyl halides are reduced to alkanes by LAH.



Alkyl halides are resistant to reduction with LAH, but activated halides can be reduced.

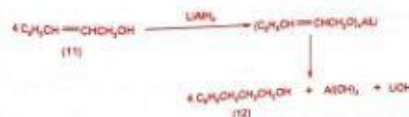


Reduction of dibromide (9) with LAH in THF gives prehnitene (10).



8.1.9 Reduction of allylic and propargylic alcohols

Cinnamyl alcohol (11) is reduced to 3-phenyl-1-propanol (12) with LAH. Similarly, 3-phenylprop-2-ynoic acid (13) is reduced to phenylpropargyl alcohol (14) and cinnamyl alcohol (11) with LAH.



- References**
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8.8 Manganese dioxide (MnO_2)

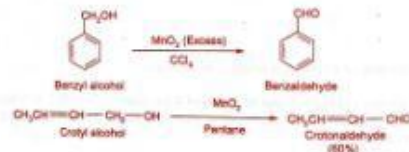
8.8.1 Introduction

MnO_2 is a useful selective oxidising reagent for organic synthesis (also see sec. 3.2.2). The structure and activity of the reagent varies with its method of preparation. MnO_2 is commercially available, and it can also be prepared by the reaction of manganese sulfate tetrahydrate with potassium permanganate in aqueous solution of sodium hydroxide.



8.8.2 Oxidation of alcohols

MnO_2 is capable of oxidising allylic and benzylic alcohols to corresponding carbonyl compounds. The benzyl alcohol, for example, is oxidised to benzaldehyde with MnO_2 at room temperature in 69% yield.¹ Similarly, crotyl alcohol yields crotonaldehyde with MnO_2 .



The advantage of this reagent is that the reaction takes place under mild and neutral conditions, also olefinic and acetylenic bonds are unaffected.



MnO_2 was used as oxidising reagent for the first time by Balf² *et al* to prepare retinol from retinol.



Similarly, secondary alcohols are converted to the corresponding ketones.

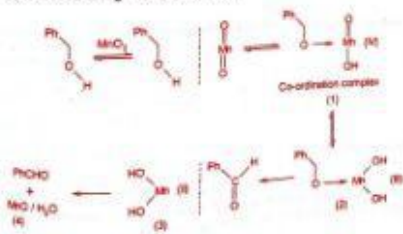


Under ordinary conditions saturated alcohols are not oxidised by MnO_2 , allowing selective oxidation for allylic and benzylic hydroxyl groups as shown below.



Mechanism

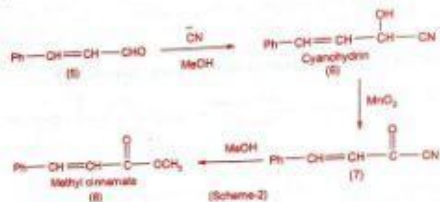
Goldman¹ and Henbest² proposed that the oxidation of alcohols to carbonyl compounds proceeds via a radical intermediate as shown in scheme-1. The alcohol is absorbed on manganese dioxide followed by formation of a co-ordination complex (1). Electron transfer from alcohol to Mn generates a radical (2), further Mn (IV) is reduced to Mn (III) in this process. A second electron transfer generates the carbonyl product and $\text{Mn}(\text{OH})_2$ (3). Finally loss of water molecule and carbonyl desorption results in the formation of carbonyl product and manganese (II) oxide (4).



(Scheme-1)

Although oxidation of allylic alcohols with MnO_2 stops at aldehyde stage and further oxidation to carboxylic acid does not take place. However, in the presence of HCN the formed aldehyde (5) is converted into cyanohydrin (6), which undergoes

further oxidation to acyl cyanide (7). Acyl cyanide (7) on alcoholysis leads to corresponding α,β -unsaturated carboxylic ester³ (8). Thus, cinnamaldehyde (5) is converted into methyl cinnamate (8), as shown in scheme-2.



Another important feature of this transformation is that the reaction proceeds in high yield without *cis-trans* isomerisation of the α,β -olefinic linkage. At higher temperature or using sufficient reagent and pure solvents, active MnO_2 can oxidise even saturated primary and secondary alcohols. Androstane-17-ol (9) in hexane with an excess of active MnO_2 at room temperature gives pure androstane-17-one (10) in quantitative yield.



The reagent is sensitive to steric interactions as shown below



8.8.3 Oxidation of amines

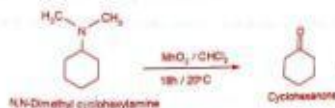
The oxidation of amines by MnO_2 can lead to various products depending on the nature of the starting material. Thus, the formation of imines⁴, amides⁵ and diazo compounds⁶ from amines have been described by the following examples.



N,N-Dimethylaniline on oxidation with MnO_2 in $CHCl_3$ at room temperature affords *N*-acetylformanilide in 78% yield.

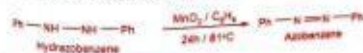


In some cases tertiary amines are cleaved to carbonyl compounds*. For example, *N,N*-dimethylcyclohexylamine is converted into cyclohexanone in 85% yield.



8.8.4 Oxidation of hydrazo compounds

MnO_2 oxidises hydrazobenzene to azobenzene in 97% yield¹⁰.



8.8.5 Oxidation of sulfur compounds

Oxidations of mercaptans and dialkyl sulfides¹¹ with MnO_2 lead to coupled product, disulfides and sulfoxides, respectively.



8.8.6 Oxidative cleavage of 1,2-diols

MnO_2 cleaves 1,2-diols to aldehydes or ketones.



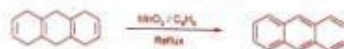
8.8.7 Conversion of nitriles to amides

By treatment with MnO_2 , nitriles are readily converted to amides. Maximum yield of amide is obtained when MnO_2 on silica gel is used.



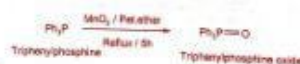
8.8.8 Aromatisation

MnO_2 has been widely used to carry out various dehydrogenation and aromatisation reactions.



8.8.9 Oxidation of phosphines

Triphenylphosphine can be converted into triphenylphosphine oxide by MnO_2 .



References

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8.9 Organoboranes

8.9.1 Introduction

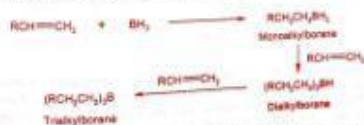
The borane (BH_3) exists as the gaseous dimer, diborane (B_2H_6). Diborane is commercially available in the form of complexes with THF and can be prepared from sodium borohydride and boron trifluoride.



Organoboranes are readily prepared by the addition of borane to olefins¹ and acetylenes. The organoboranes and boranes were introduced as powerful selective reducing agents. Organoboranes are versatile reagents and undergo a wide range of reactions, many of which are of great value in synthesis. The diborane is usually generated *in situ*, and the alkylboranes can be used without isolation.

8.9.2 Hydroboration of olefins

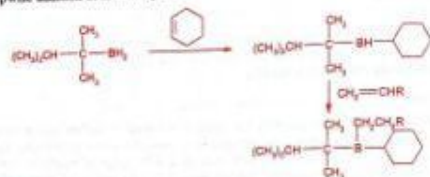
Hydroboration is the process in which alkyl- and alkynyl-boranes are prepared by the addition of borane to olefins and acetylenes. Normally, reaction of borane with olefins does not stop after the addition of one BH_3 molecule, because resulting RBH_2 adds to another molecule of olefin to give R_2BH , which in turn adds to a third olefin molecule, thus the final product is trialkylborane (R_3B).



With simple alkenes, borane reacts with three alkene molecules to form a trialkylborane as shown above. However, hindered alkenes, owing to steric interactions give only partially substituted boranes as addition products.

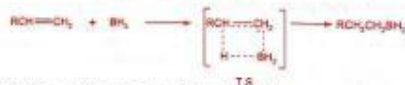


It is also possible to prepare mixed trialkylboranes (with three different alkyl groups) by the stepwise addition of monoalkylborane to two different hindered alkenes.

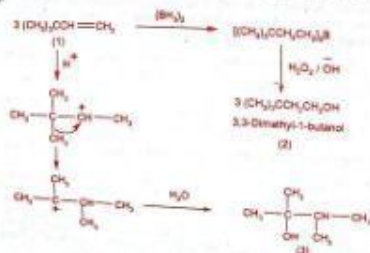


Mechanism

The addition of B-H unit to double bond involves a simple four center transition state. Boron being electron deficient begins to add to the double bonded carbon. The reaction unlike ordinary electrophilic addition, does not proceed to give a carbocation, because the carbon that is losing the π -electrons, begins to take one of the hydrogen attached to boron, with its electron pair. Thus, in the transition state both the boron and hydrogen add to the double bonded carbons as shown below.



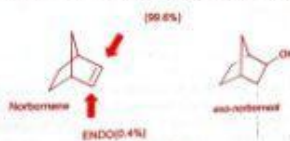
Hydroboration unlike ordinary electrophilic addition, proceeds without skeletal rearrangement at normal temperature because carbocations are not formed as the intermediates. Thus, 3,3-dimethyl-1-butene (1) on hydroboration followed by its oxidation yields the expected 3,3-dimethyl-1-butanol (2) and not the rearranged product (3).



The boron attacks from the less hindered side and overall addition is *cis* and *syn* and *anti* specific. Thus, 1-methylcyclohexene, on hydroboration and oxidation yields *trans*-2-methylcyclohexanol in high yield.



The hydroboration of norbornene, followed by oxidation gives *cis*-norbornanol in 99.6% yield.



Orientation

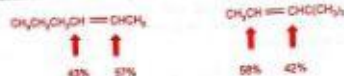
Hydroboration is regioselective. The addition of H-B to alkenes follows **Markovnikov's addition rule**. Since boron is more electropositive than hydrogen therefore attachment of boron takes place readily to the less substituted carbon of the double bond.



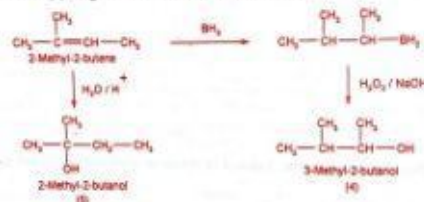
The hydroboration can be performed on alkenes with one to four substituents. Terminal alkenes, such as 1-hexene undergo hydroboration to place 94% of the boron on the terminal position with 6% at the 2-position.



Internal olefins such as 2-hexene and 4,4-dimethyl-2-pentene, show no significant discrimination between the two positions.



Addition of borane to alkenes, followed by oxidation gives alcohol (4) (**anti-Markovnikov's rule**). However, hydration of alkenes in the presence of sulfuric acid yields alcohols (5) in agreement with **Markovnikov's rule**.



8.9.3 Hindered organoboranes

Regioselectivity in the hydroboration of alkenes with borane is very high, however, it is not complete. Also borane is quite unselective and attacks all sorts of double bonds. The greater regioselectivity can be achieved by using sterically hindered, less reactive and more selective organoboranes, such as *tert*-butylborane, 9-BBN and disiamylborane. There are two stereochemical advantages in using hindered alkylboranes as hydroborating agents, increased **anti-Markovnikov's** selectivity and enhanced *cis* selectivity.

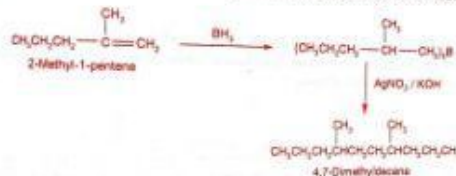


These reagents hydroborate one double bond in a molecule leaving other hindered bonds unaffected or hydroborate one olefin in the presence of a less reactive olefin. In a mixture of *cis* and *trans* isomers, a *cis* olefin can be selectively hydroborated. For example, reaction with hexene-1 gives 94% boron at the terminal carbon with borane, but 99% with tri(1-methylpropyl)borane. Similarly, *trans*-4-methyl-2-pentene shows little selectivity with borane and regioselectivity is almost complete with disiamylborane.



(g) Coupling

Organoboranes on treatment with basic silver nitrate (AgNO_3) lead to coupling¹ of the alkyl groups. This reaction provides a useful method for the formation of carbon-carbon bond. A typical example is synthesis of 4,7-dimethyldecane from 2-methyl-1-pentene upon treatment with BH_3 , followed by reaction with silver nitrate and NaOH .



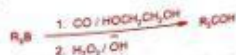
The reaction can be used successfully for unsymmetrical coupling² (coupling of two different alkyl groups) by using an excess of one of the olefins.

(h) Carbonylation (Transformation of organoboranes to alcohols, and carbonyl derivatives)

Organoboranes can be converted into alcohols, aldehydes, and ketones on reaction with carbon monoxide at $100\text{--}125^\circ\text{C}$. This reaction requires high pressure and is known as carbonylation.

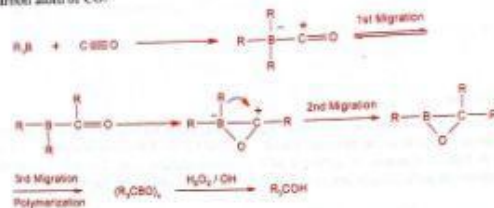
(i) Trialkylcarbinols and dialkyl ketones

The trialkylboranes undergo carbonylation with CO in diglyme solution in the presence of ethylene glycol followed by oxidation with alkaline H_2O_2 to form trialkylcarbinol² in excellent yield.

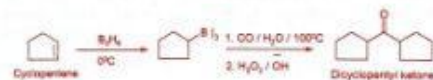


10.1 Organic Reaction Mechanisms

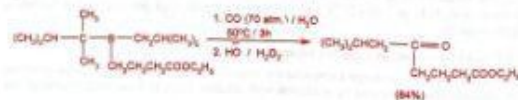
This reaction involves the intramolecular migration of alkyl groups from boron to the carbon atom of CO .



However, when carbonylation is carried out in presence of a small amount of water, migration of third alkyl group from boron to carbon is inhibited and resulting compound is dialkylketone³ and not trialkylcarbinol.

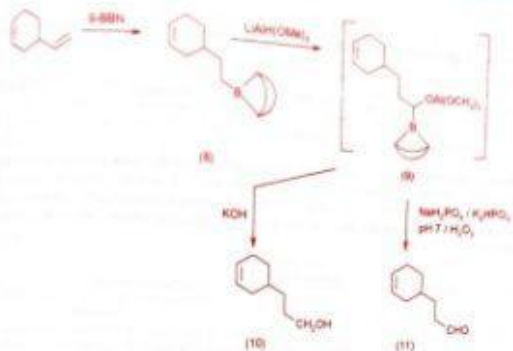


Unsymmetrical ketones can also be prepared by using mixed organoboranes having one bulky group such as t-butyl group. T-butyl group, because of its bulky nature, does not migrate in comparison with other alkyl groups. Thus, mixed trialkylborane containing t-butyl group on carbonylation in presence of a little water, followed by oxidation, leads to unsymmetrical ketone⁴.



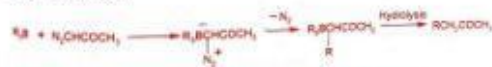
(ii) Primary alcohols and aldehydes

The carbonylation sequence can be modified to produce aldehydes and primary alcohols. Carbonylation of organoborane (8) in the presence of lithium hydrotetramethoxyaluminate, followed by cleavage of (9) with hydronide yields the aldehyde (10). However, oxidation of (9) with buffered hydrogen peroxide yields the alcohol (11).



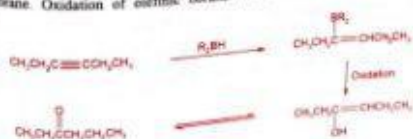
(f) Reaction of trialkylboranes with nucleophiles⁴ and ylides⁵

Another general route for the preparation of ketones from organoboranes depends on the nucleophilic addition of a diazoketone to the organoboranes. The mechanism of this reaction involves the migration of alkyl group from boron to carbon and simultaneous expulsion of nitrogen.

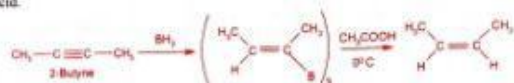


8.5.5 Hydroboration of acetylenes and reactions of alkenylboranes

Terminal alkynes (such as 3-hexyne) on hydroboration with diborane give alkenylboranes. Better yield of alkenylboranes are obtained with disiamylborane or dialkenylboranes. Oxidation of olefinic borane with alkaline hydrogen peroxide affords ketone.



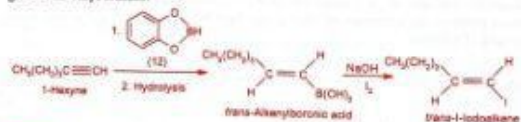
However, high yield of *cis* olefin is obtained by reaction of vinylic boranes with acetic acid.



Terminal alkynes (such as 1-butyne) on hydroboration with diborane give predominantly the dihydroborated products plus unreacted alkyne⁶. But with disiamylborane or trimethylamine-tert-butylborane, high yields of monohydroboration products are obtained. These compounds are synthetically useful because on oxidation they afford aldehydes.



Hydroboration of terminal alkynes with catecholborane (12) yield *trans*-1-alkenylboronic acids, which on hydrolysis followed by reaction with I_2 in the presence of NaOH at $0^\circ C$ give *trans*-vinyl iodides.



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8.10 Organosilicon compounds

8.10.1 Introduction

Silicon is generally employed in organic synthesis in the form of a trialkylsilyl derivatives. The most common reagents having trialkylsilyl functionality are chlorotrialkylsilanes such as chlorotrimethylsilane (Me_3SiCl), chlorotriethylsilane (Et_3SiCl), triisopropylchlorosilane ($\text{isoPr}_3\text{SiCl}$) etc. The usefulness of these reagents is due to their roles as: protecting group, for oxygen capture with elimination to form alkenes, and in the stabilisation of carbanions and carbonium ions.

Silicon hydrides such as triethylsilane (Et_3SiH), Ph_3SiH_2 , $(\text{EtO})_2\text{SiHMe}$ are used for the reduction of alkenes and carbonyls. Trimethylsilyl cyanide is another useful silicon reagent.

8.10.2 Preparation of organosilicon compounds

The organosilicon compounds can be prepared from metallic silicon and silicon halides. Chlorotrimethylsilane (1), a synthetically useful compound, is usually prepared by reaction of methylmagnesium iodide and silicon chloride. Similarly, allylsilanes are prepared by reaction of chlorotrialkylsilanes and allylmagnesium halide (2). This is followed by the preparation of allyltrimethylsilane (3). These involve nucleophilic displacement of halogen from a halosilane by an organometallic reagent.



8.10.3 Chlorotrialkylsilanes

(a) As a protecting group for alcohols (formation of silyl ethers) Chlorotrialkylsilanes are used for the protection of alcohols, amines, thiocarbonyls and other functional groups in the presence of an amine base. Alcohols react with chlorotrialkylsilanes which are important reagents having a primary > secondary > tertiary, in addition, alkyl alcohols are more reactive than phenolic derivatives. The order of reactivity of alcohols towards chlorosilanes is primary > secondary > tertiary, in addition, alkyl alcohols are more reactive than phenolic derivatives. The prototype of this class of protecting groups is the trimethylsilyl ether (4), which is prepared by the reaction of alcohol with chlorotrimethylsilane in the presence of an amine base such as triethylamine (Et_3N) or pyridine.



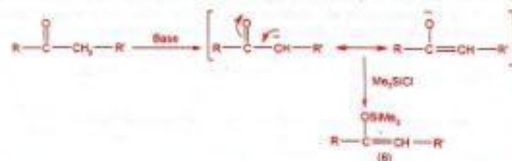
In general silyl ethers can be cleaved with aqueous base or acid, however, trimethylsilyl ethers are very sensitive to many aqueous conditions, and this group is sometimes cleaved during workup procedure. Steric factors play a major role in the cleavage reaction. Thus, more stable silyl ether derivatives such as dimethylisopropylsilyl, tert-butyl dimethylsilyl (5) and triisopropylsilyl ethers, broadly used in synthesis, require dilute acid for hydrolysis. These derivatives are prepared by reaction of alcohols with corresponding chlorosilane and base imidazole.



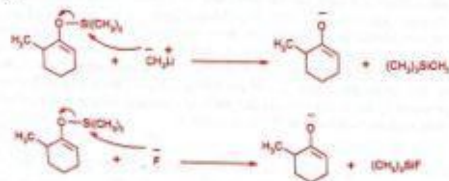
Another common method for the deprotection of silyl ethers is by the use of fluoride ion (tetrabutylammonium fluoride¹, KF , and HF). The fluoride ion readily attacks silicon and cleaves the O-Si bond, because Si-F bond is stronger than Si-O bond. This shows that Si-O bond is readily formed and cleaved equally readily.

(b) Conversion of enolates to silyl enol ethers (6)

Trialkylchlorosilanes can trap the enolate ion, formed by the base treatment of ketones, to give silyl enol ethers (6) which are important reagents with a number of synthetic uses. The silylation occurs exclusively on the oxygen atom of the enolate as the O-Si bond is much stronger than a C-Si bond.



These silyl enol ethers undergo variety of reactions including their cleavage with methylolithium or fluoride ions which regenerate the enolates as illustrated by following examples.

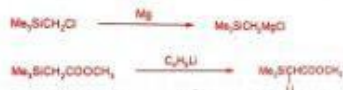


Alkyl silanes also couple with aldehydes in the presence of Lewis acid⁸.

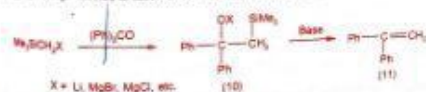


8.10.5 α -Trimethylsilyl substituted carbanions (Peterson reaction)

β -silyl carbanions, negative charge is stabilised with empty 3d orbitals of silicon. Thus, β -silyl carbanions are readily formed from chlorosilanes by reaction with lithium or sodium or by treating weakly acidic silanes (i.e., silanes containing CH group adjacent to both electron-withdrawing group and trimethylsilyl group) with butyllithium.

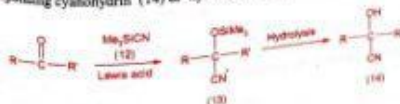


The nucleophilic attack of β -silyl carbanion to an aldehyde or a ketone gives corresponding β -silyl alcohol derivative (10). Subsequent treatment with base induces elimination of the trimethylsilyloxy group to give an alkene (11). This synthesis, a useful alternative to the Wittig olefin synthesis, is known as **Peterson reaction** or **Peterson olefination**.

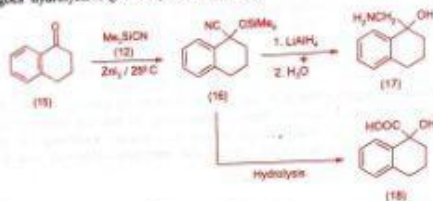


8.10.6 Trimethylsilyl cyanide

Trimethylsilyl cyanide (12) can be prepared by the reaction of chlorotrimethylsilane (11) with metallic cyanides. Trimethylsilyl cyanide (12) reacts with ketones in the presence of Lewis acid to give O-trimethylsilyl cyanohydrin (13), which on further hydrolysis gives the corresponding cyanohydrin (14) or hydroxy acid in good yield.



Reaction of α -tetralone (15) with trimethylsilyl cyanide (12) in ZnI_2 gives trimethylsilyl derivative (16), which can be reduced with LAH to give β -amino alcohol (17), or undergoes hydrolysis to give α -hydroxy acid (18).

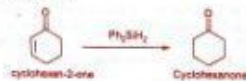


8.10.7 Silanes (Hydrosilation)

Hydrosilation i.e., reduction with silicon hydrides provides a powerful and selective method for the reduction of many functional groups. For example, 1-methylcyclohexene is reduced to methylcyclohexane with triethylsilane in presence of trifluoroacetic acid, in good yield⁹.



Silanes are used for the selective reduction of double bond in the conjugated carbonyls, probably via the formation of a silyl enolates. Thus, Ph_3SiH_2 reduces cyclohexen-2-one to cyclohexanone in 85% yield.



In acidic media, silanes reduce aldehydes and ketones to the corresponding alcohols¹⁰. Selective reduction of aldehyde group is achieved when conjugated aldehyde is treated with $(\text{EtO})_2\text{SiHMe}$ in the presence of K₂F.



Reduction of a number of other functional groups have been reported with silanes, including reductive cleavage of carbonyls or alcohols. These are analogous to the Wolff-Kishner or Clemmensen reduction (see chap. 5). Cyclohexanone, for example, is converted to cyclohexane in 90% yield, using silane-BF₃ complex¹¹.



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III Osmium tetroxide (OsO₄)

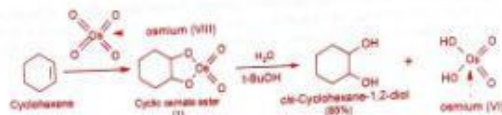
III.1 Introduction

Osmium tetroxide is highly toxic and has high vapor pressure. It should be handled with utmost care in a chemical fume hood. For application to organic chemistry, OsO₄ is most often used for the *syn*-hydroxylation of alkenes (also see sec. 3.5.9). It oxidises ketones to sulfones but does not oxidise sulfides. Ketones and esters can be *α*-hydroxylated by treatment of their enolate forms with osmium tetroxide-N-methylmorpholine-N-oxide.

III.2 Hydroxylation of alkenes

Hydroxylation of alkenes with OsO₄ to vicinal diols proceeds via the formation of five-membered cyclic ester¹ of vicinal diols (osmate ester, 1) as an intermediate, which is then hydrolyzed to yield *cis*-diols. In most of the cases, the osmate ester is not isolated, and the reaction is usually done in the presence of *tert*-butyl alcohol-water mixture, which hydrolyses the osmate ester to the diol. The osmium starts as Os(VIII) and ends up as Os(VI). A variety of reagents can be used to decompose the osmate ester, including sodium sulfite or bisulfite in aqueous ethanol, bisulfite ion in pyridine, mannitol in sodium acetate solution. The reduced osmium species is normally removed by filtration. For example, cyclohexene reacts with osmium tetroxide to give a *cis*-1,2-cyclohexanediol.

III.3 Organic Reaction Mechanisms

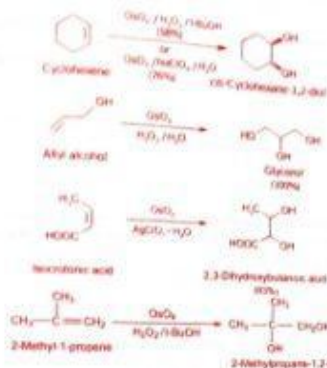


When the reaction is carried out in the presence of pyridine, an ester complex (2), is formed by co-ordination with two equivalents of the ligand (pyridine), and it can sometimes be isolated. The ester is then hydrolyzed to give a *cis*-diol.



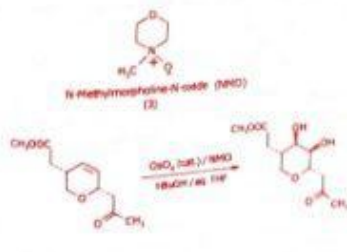
The chief drawback of this reaction is that OsO₄ is expensive and highly toxic. However, *cis* hydroxylation can be performed more economically with a catalytic amount of osmium tetroxide in the presence of oxidising agent which reoxidises hexavalent osmium to octavalent osmium (i.e., regenerates the osmium tetroxide) to continue the catalytic cycle. The common co-oxidants are metal chlorates² (such as barium chlorate or sodium chlorate), hydrogen peroxide³ and *t*-butyl hydroperoxide. This is illustrated by the following examples.



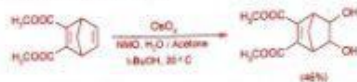


The H₂O₂ or metal chlorate oxidatively cleaves the osmium complex and regenerates the osmium tetroxide by oxidising the reduced form of osmium resulting from the hydroxylation.

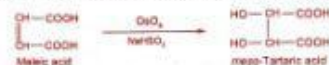
Tertiary amine-oxide, such as N-methylmorpholine-N-oxide (NMO) (3), are very effective catalyst and oxidise Os(VI) back to Os(VIII). In these reactions, where NMO is used as catalyst, only 1 mol % of OsO₄ is required.



Due to electrophilic nature of osmium tetroxide, the presence of electron-withdrawing groups to the alkene double bond retard the hydroxylation. Thus, when more than one double bonds are present, hydroxylation occurs at the most electron-rich double bond as illustrated by the following example.

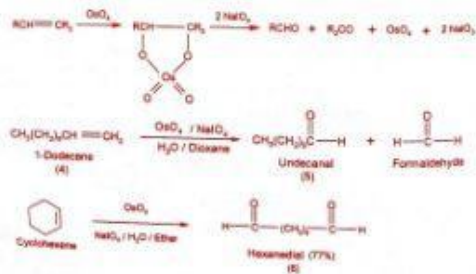


The overall hydroxylation is stereoselectively syn. Thus, *meso* 1,2-diol is obtained from *cis* 2-butene. For example, Maleic acid gives *meso*-tartaric acid with OsO₄ and NaHSO₄.



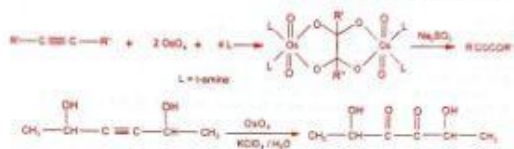
8.11.3 Lemieux-Johnson reagent (OsO₄ + NaIO₄)

When OsO₄ is used in combination with NaIO₄, it is known as Lemieux-Johnson reagent and it gives the same products as is obtained in the ozonolysis procedure. Osmium tetroxide (catalytic amount) reacts with a double bond to give an osmate ester, which then decomposes in the presence of sodium periodate to give cleavage products (aldehydes or ketones) of the diol along with the regenerated osmium tetroxide. For example, 1-dodecene (4) is converted to undecanal (5) and cyclohexene to hexanal (6) by osmium tetroxide and NaIO₄.



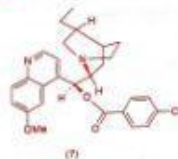
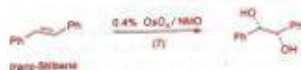
8.11.4 Reaction with alkynes

Acetylenes react with OsO_4 in the presence of tertiary amines, such as pyridine or isoquinoline to give osmium (VI) ester complexes, which on hydrolysis with sodium sulfite yield the corresponding 1,2-diketones from non-terminal alkynes ($R' = R'' = \text{alkyl}$ or aryl), and carboxylic acids with loss of one acetylenic carbon, from terminal alkynes.

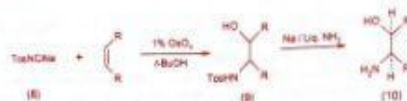


8.11.5 Asymmetric hydroxylation

Osmylation of alkenes with osmium tetroxide yields racemic mixture of 1,2-diols. Sharpless obtained the enantiomeric excess (% ee) of the diol product by adding chiral substrate to the osmylation reagents. For example, *trans*-stilbene with OsO_4 and NMO (3) gives the diol with 99% ee in the presence of cinchona alkaloids, especially esters of dihydroquinidines (7). High diastereoselectivity is obtained only with regiochemically pure alkenes.



α,α -Hydroxyamines are obtained from alkenes by reaction with chloramine-T (8) in the presence of catalytic amount of OsO_4 . The sulfonamides (9), obtained by the reaction of alkenes with (8) in the presence of OsO_4 , are readily converted into the α,α -hydroxyamines (10) by cleavage with sodium in liquid ammonia.



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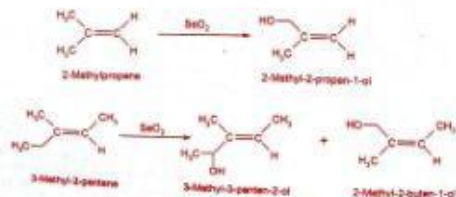
12 Selenium dioxide (SeO_2)

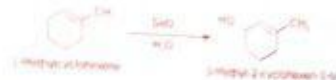
8.12.1 Introduction

Selenium dioxide (SeO_2) is a white crystalline solid. It is soluble in solvents like dioxane, ethanol, acetic acid, acetic anhydride and even in aqueous medium. SeO_2 is extremely poisonous and proper care should be taken while working with it. It is a very selective oxidant (also see sec. 3.5.8).

8.12.2 Oxidation of allylic or benzylic compounds

SeO_2 is used primarily for the oxidation of allylic or benzylic C-H fragments to the corresponding allylic or benzylic alcohols. This reaction has very useful applications as the allylic alcohols can easily be oxidised further to the α,β -unsaturated carbonyl compounds. The order of ease of oxidation is $\text{CH}_3 > \text{CH}_2 > \text{CH}$. The oxidation occurs at the more substituted end of the double bond.



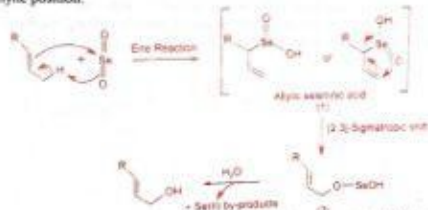


β -Pinene can be converted into *trans*-pinocarveol¹ with selenium dioxide.



Mechanism

The reaction proceeds² via an initial ene reaction of allylic compounds with SeO_2 to give allylic seleninic acid (1), which undergoes a [2,3]-sigmatropic shift to yield (2). Hydrolysis of (2) affords the allylic alcohol. Overall, CH_3 has been replaced by CH_2OH in an allylic position.

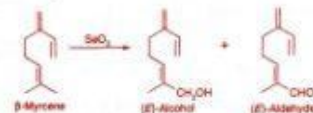


In the presence of *tert*-butyl hydroperoxide, only a catalytic amount of SeO_2 is required, as the peroxide reoxidises the formed Se(II) to give back SeO_2 after each cycle of the reaction. This eliminates the need to get rid of large amounts of selenium-containing products, which are toxic.

In some cases, SeO_2 oxidation continues to give an aldehyde or ketone. The conversion of methylene to carbonyl group is especially easy when methylene group is flanked by two aromatic rings. Thus, diphenylmethane yields benzophenone³ on flanked by two aromatic rings. Thus, diphenylmethane yields benzophenone³ on flanked by two aromatic rings. Thus, diphenylmethane yields benzophenone³ on flanked by two aromatic rings. Thus, diphenylmethane yields benzophenone³ on flanked by two aromatic rings.



The methyl group *trans* to the main chain will react rather than the *cis*, thus, only one (*E*-) isomer is formed. A useful application of this reaction is the oxidation of β -myrcene to give a mixture of the (*E*)-alcohol and the (*E*)-aldehyde.

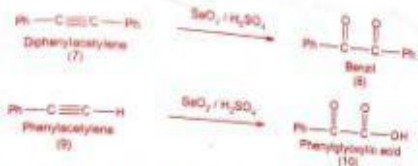


In aromatic heterocycles, the methyl group in α -position with respect to nitrogen are oxidised more easily. Thus, 8-ethyl-2-methylquinoline⁴ (3) gives selective oxidation product, aldehyde derivative (4), when treated with SeO_2 . Similarly, 2,5-dimethylpyridine-N-oxide (5) is converted into 5-methylpyridine-2-aldehyde-N-oxide⁵ (6) on reaction with SeO_2 in the presence of pyridine.



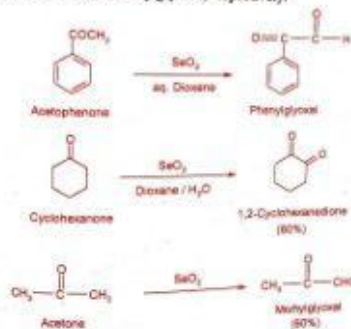
8.12.3 Oxidation of alkynes

SeO_2 is also capable of oxidising alkynes to vicinal dicarbonyl compounds. SeO_2 with a small amount of H_2SO_4 oxidises internal alkynes to α -diketones⁶. Thus, diphenylacetylene (7) is readily oxidised at 110°C in the presence of aqueous acetic acid containing H_2SO_4 to benzil (8) in 84%. Phenylacetylene (9) is oxidised under similar conditions to phenylglyoxylic acid (benzoylformic acid) (10).

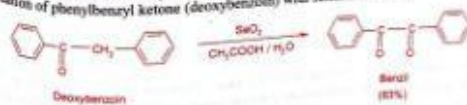


11.14 Oxidation of carbonyl compounds

A useful application of SeO_2 is the oxidation of the methyl or methylene group adjacent to the carbonyl group. Thus, aldehydes and ketones with a methyl or methylene group α to the carbonyl group are oxidised to the 1,2-dicarbonyl compounds. Acetophenone, for example, is converted to phenylglyoxal in 70% yield by warming with SeO_2 in aqueous dioxane. Similarly, cyclohexanone² and acetone³ are converted into cyclohexane-1,2-dione and methylglyoxal, respectively.



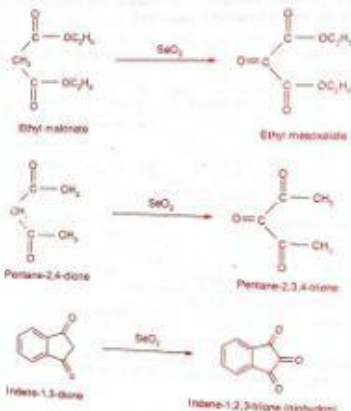
The method is used for the synthesis of benzils. For example, benzil is obtained by the oxidation of phenylbenzyl ketone (deoxybenzoin) with selenium dioxide.



Camphor gives camphorquinone, an intermediate in the preparation of Horner's acid, in about 90% yield with SeO_2 .



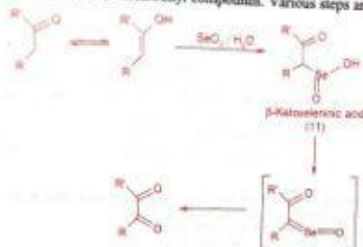
The oxidation of methylene group to carbonyl is easy if it is flanked by two carbonyl groups. Selenium dioxide oxidises ethyl malonate directly to ethyl mesoxalate in 23% yield. Similarly, selenium dioxide oxidises pentane-2,4-dione to pentane-2,3,4-trione. Indane-1,2,3-trione (ninhydrin) may be prepared by the action of SeO_2 on indane-1,3-dione.



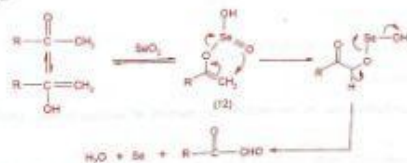
Mechanism

The mechanism of SeO_2 reaction is not yet clear. Sharpless and Goerden⁴ proposed that reaction proceeds via the intermediate β -ketoseleninic acid (11), formed by electrophilic

attack of selenious acid on the enol. β -Ketoselemenic acid (11) undergoes a **Pummerer** like rearrangement to afford 1,2-dicarbonyl compounds. Various steps are shown below.

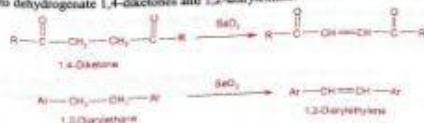


Another mechanism¹⁰ proposed involves a selenate ester intermediate (12), which is formed by the reaction of the enol form of the carbonyl derivative with SeO_2 . Oxidative rearrangement of (12), followed by loss of selenium and water affords the dicarbonyl compound.

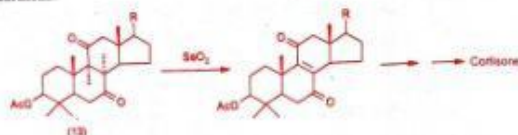


8.12.5 Dehydrogenation

SeO_2 is an oxidising agent but in certain cases it converts carbonyl compounds to α,β -unsaturated carbonyl compounds by removing hydrogen. For example, SeO_2 has been used to dehydrogenate 1,4-diketones and 1,2-diarylethanes.



Another example of dehydrogenation with SeO_2 is found in the case of a 12-ketohylole acid (13), where a 9,11-double bond is introduced. This is the key step in the synthesis of cortisone.



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8.13 Sodium borohydride (NaBH_4)

8.13.1 Introduction

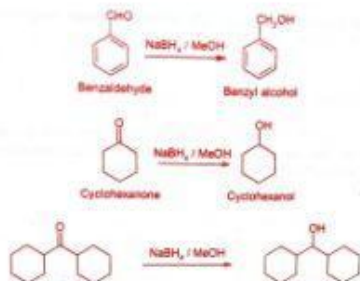
Sodium borohydride can be prepared by the reaction of sodium hydride (NaH) with B(OMe)_3 .



Sodium borohydride, unlike LiAlH_4 (LAH), is insoluble in ether but soluble in water. The reagent is normally used as reducing agent in aqueous (as it reacts slowly with water, while, LAH is a powerful hydride donor and reacts violently with water) or alcoholic solution at room temperature (also see sec. 4.3.2). Sodium borohydride is less reactive than LAH , thus it is a more selective reagent. Like LAH , sodium borohydride also does not usually reduce isolated carbon-carbon double or triple bonds. It reduces aldehydes and ketones to alcohols while the halogen, cyano, nitro, amido, and ester groups remain unaffected. It is also inert towards lactones, epoxides and carboxylic acids.

8.13.2 Reduction of aldehydes and ketones

The aldehyde is reduced to primary alcohol and ketone to secondary alcohol with NaBH_4 . 1° -Alcohols can not be prepared through this kind of reduction. Some typical reductions of this reagent are given below.



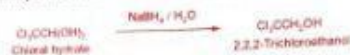
Sodium borohydride reacts with aldehydes much faster than ketones in alcohol. It is a reagent of choice for the reduction of aldehydes and ketones in the presence of a variety of other functional groups as illustrated by the following reactions.



m-Nitrobenzaldehyde is reduced to *m*-nitrobenzyl alcohol in methanolic solution of sodium borohydride. No reaction occurs at the nitro group.



Chloral hydrate is reduced to 2,2,2-trichloroethanol at room temperature in aqueous sodium borohydride solution.

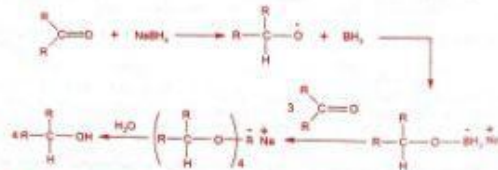


NaBH_4 does not react with less reactive carbonyl compounds such as esters or amides. Thus, when both the ester and aldehyde groups are present in the same molecule, only the aldehyde will be reduced as shown in the following example.



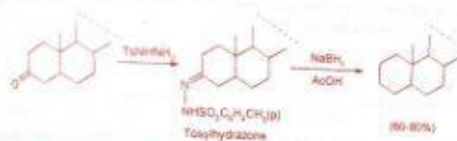
Mechanism

NaBH_4 reacts in a similar manner as LAH. It also delivers hydride ion (H^-), as the powerful nucleophile, to the carbonyl carbon. The alkoxide ion thus formed in the first step can help to stabilise the electron-deficient BH_3 molecule. Now we have again tetravalent boron anion, which could transfer second hydrogen atom to another molecule of carbonyl compound. This process can continue so that, in principle, all four hydrogen atoms could be transferred to molecules of carbonyl compounds. The solvent (such as water or alcohol) provides the proton needed to form the alcohol from the alkoxide. Thus, each molecule of NaBH_4 , like LAH, can reduce four molecules of carbonyl compound.



8.13.3 Reduction of tosylhydrazones

Tosylhydrazones¹ can be reduced to the corresponding methylene compounds in 25-75% yield by NaBH_4 in AcOH.



8.13.4 Reduction of acid derivatives

It does not normally reduce esters, but reduction can be performed by the use of a large excess of reagent in MeOH or EtOH at room temperature or at higher temperatures.



It can reduce selectively one cyano group of 1,1-dicyano epoxide,² which is *trans* to an alkyl or aryl substituent.

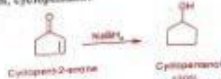


Aldehydes may be reduced to lactones with NaBH_4 . The reaction takes place by first the opening of ring and subsequent ring closure to generate a lactone.³

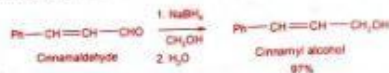


8.13.5 Reduction of α,β -unsaturated carbonyls

The reagent predominantly reduces only carbonyl group (1,2-reduction) of α,β -unsaturated carbonyl compounds in most cases, though substantial amounts of fully saturated alcohols are also obtained in some cases. For example, cyclopent-2-enone gives fully saturated alcohol, cyclopentanol.



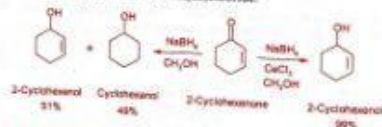
However, β -aryl- α,β -unsaturated aldehydes give more 1,2-reduction product than the corresponding α,β -unsaturated ketones.



The reduction of adjacent double bond to carbonyl group (1,4-reduction) depends upon the conditions such as temperature, solvent, amount of hydride used and the presence of catalyst. For example, the use of pyridine as solvent increases the selectivity for 1,4-reduction, as exemplified by the reduction of (R)-carvone¹ (1) to dihydrocarvone (2) in 75% yield.

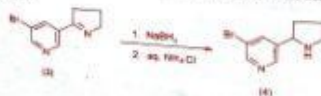


The presence of metal ions in the reaction mixture greatly increases the 1,2-reduction product. For example, 2-cyclohexenone yields both 2-cyclohexenol (1,2-reduction product) and cyclohexanol (1,4-reduction product) with NaBH_4 . However, more than 99% 2-cyclohexenol (1,2-reduction product) was formed when reduction was carried out with NaBH_4 in the presence of cerium(III)chloride.



8.13.6 Reduction of C=N bond in enamines, imines and iminium salts

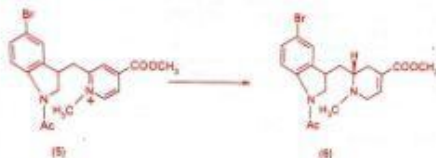
Imines can be reduced to amines with NaBH_4 in alcoholic solvent under neutral conditions, however, protonation of the amino nitrogen dramatically increases the rate of reduction. The mechanism of reduction is same as the reduction of carbonyl group. An example of such a reaction is the reduction of imine (3) to the nicotine derivative⁴ (4) in good yield.



Another example is the reduction benzalaniline to N-benzylaniline.

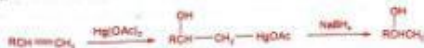


Julia *et al.* used NaBH_4 in the synthesis of lysergic acid⁶ for the reduction of pyridinium salt (5) to tetrahydropyridine (6).



8.13.7 Reduction of organometallic compounds

Sodium borohydride is used in the two-step hydration of alkenes (i.e., oxymercuration-demercuration). An alkene is first treated with mercuric acetate and the process is called oxymercuration, which is followed by reduction with sodium borohydride to generate alcohol. In the second step, sodium borohydride efficiently replaces the mercury with hydrogen and the process is called demercuration. The two-step hydration is of great advantage as it gives the product of Markovnikov's addition, and no rearrangement takes place.



8.13.8 Reduction of alkyl halides

Reductive fusion of alkyl halides can be carried out with NaBH_4 in the presence of dimethyl sulfoxide.



8.13.9 NaBH_4 -Lewis acid complexes

$\text{NaBH}_4\text{-AlCl}_3$ complex⁷ is a more powerful reducing agent and converts nitriles to primary amines and amides to amines. $\text{NaBH}_4\text{-BF}_3$ complex⁸ reduces lactones to cyclic ethers. The actual reducing agent in this reduction is diborane, B_2H_6 , formed by reaction of sodium borohydride and boron trifluoride.

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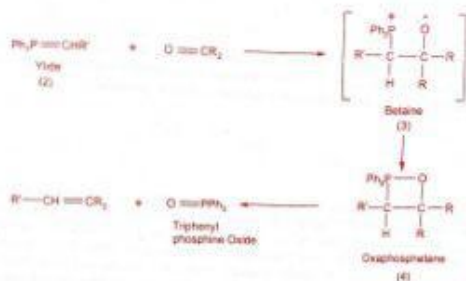
8.14 Wittig reagent

8.14.1 Introduction

Phosphonium salt (1) is formed when triphenylphosphine reacts with an alkyl halide. The reaction involves the nucleophilic displacement ($\text{S}_{\text{N}}2$) of halide by the nucleophilic phosphorus atom of triphenylphosphine. The phosphonium salt (1) contains acidic hydrogen that can be removed by a moderately strong base (such as, phenyl-lithium or NaH) to give phosphorus ylide (2), commonly known as **Wittig reagent**. These phosphorus ylides (also discussed in chap. 2, sec. 2.8) carry a positive and a negative charge on adjacent atoms and can be represented as doubly bonded species, called phosphoranes. Phosphorus ylides, because of negative charge on carbon atom, are strong nucleophiles, and add to carbon-oxygen double bond of aldehydes or ketones to form betan (3), which collapses to a four-membered ring called oxaphosphetane (4).

It is postulated that either of the intermediate i.e., betan or oxaphosphetane can decompose to give the products, an alkene and triphenylphosphine oxide. Thus, this reaction provides versatile means of synthesising alkenes from aldehydes or ketones and is known as **Wittig reaction**. The Wittig reaction is named after its discoverer, Georg Wittig, who was awarded the Nobel Prize in 1979.



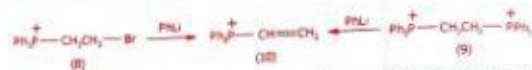


The ylides used in Wittig reaction may contain a wide variety of substituents which will not interfere in the reactions of ylides with other compounds. Simple ylides (5, R', R'' = H, Alkyl) are highly reactive. If R' or R'' is an electron-withdrawing group (COR, CN, CHO, COOR), the ylide becomes stable because of resonance and their reactivity towards carbonyl group is decreased. For example, (6) is more stable because negative charge is delocalised by the ester group. Such ylides, called stabilised ylides, react with aldehydes but not with ketones. In extreme cases the ylide (such as 7) does not react with aldehydes and ketones.



Strength of the base used for deprotonation of the phosphonium salt depends on the alkyl (R', R'') groups and also on the nature of groups on phosphorus. More commonly used bases are butyllithium, sodamide, sodium hydride, or a sodium alkoxide. But, if the α -hydrogen is acidic enough, for example in $\text{Ph}_3\text{P}^+\text{CH}_2\text{P}^-\text{Ph}_3$, the sodium carbonate is a strong enough base to pull the proton. If the phosphonium salt contains a leaving group such as Br, OMe or PPh₃ in the β -position, treatment with base gives elimination product and not the ylide. For instance (8) and (9) (bis-phosphonium salt) on treatment with phenyllithium, decomposed to vinylphosphonium salt (10).¹

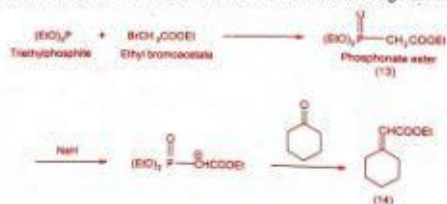
10 Organic Reaction Mechanism



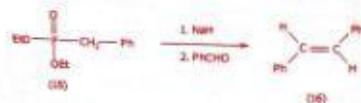
Another side reaction of phosphonium salt bearing a hetero substituent is intramolecular displacement of heteroatom to form triphenylcyclobutylphosphonium salt. Thus, phosphonium salt (11), for example, on treatment with base gives (12).¹



The R group on phosphorus should not contain α -protons, since deprotonation would lead to mixture of ylides. Typically triphenyl or trialkylphosphines are used in Wittig reaction. Several modification of the Wittig reagent has been made to improve the reactivity of the ylides. The most important is preparation of ylides from phosphonate esters, which themselves are readily available from alkyl halides and triethylphosphite via an **Arbuzov rearrangement**.⁴ These ylides are more reactive than the corresponding phosphoranes and often react with ketones that are inert to phosphoranes. Thus, reaction of ethyl bromoacetate with triethylphosphite gives phosphonate ester, (13), which on treatment with base (NaH) and reaction with cyclohexanone gives α,β -unsaturated ester, ethyl cyclohexylideneacetate (14) in 70% yield (with triphenylphosphorane (2) only 25% yield is obtained). This method is most useful for the preparation of unsaturated esters, and called the **Horner-Wadsworth-Emmons modification**⁵ of the Wittig reaction.

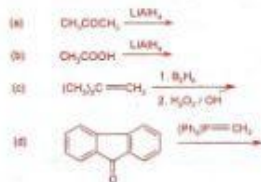


Similar reaction of phosphonate ester derivative (15) with benzaldehyde in presence of NaH gives trans stilbene (16) in 84% yield.

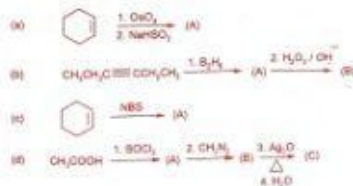


Problems

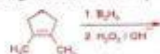
- How can you prepare cinnamic acid by the Wittig reaction starting from Benzaldehyde?
- Write resonance forms of diazomethane.
- Write structural formula(s) for the product(s) formed when propanal reacts with each of the following reagents.
 - NaBH_4 in aqueous NaOH
 - LiAlH_4 then water
 - $\text{CH}_3\text{CH}=\text{P}(\text{Ph})_3$
 - SeO_2
- Write the product(s) of the reactions given below.



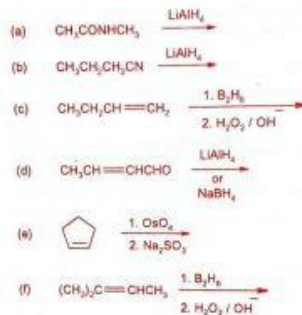
- Complete the following reactions.



- For the reaction given below write the product along with the stereochemistry.



- Complete each of the following equations by writing the correct structural formula(s) of the product(s) formed.



- Which reagent will yield *cis*-1,2-cyclopentanediol from cyclopentene?

9 Pericyclic Reactions

9.1 Introduction

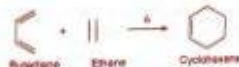
Most of the organic reactions proceed in a stepwise manner, the exceptions being S_N2 (section 1.3.2) and E2 type (section 1.5.1). However, there are certain reactions, which proceed in a single concerted step via the formation of a cyclic transition state involving six π -electrons. Such reactions are called pericyclic reactions. The energy for pericyclic reactions is supplied by heat in a thermally induced reaction or by ultraviolet light in a photo-induced reaction. Pericyclic reactions are highly stereospecific. Thermal and photochemical processes give products with different but specific stereochemistry. Pericyclic reactions do not involve ionic or free radical intermediates and so solvents and reagents (electrophilic or nucleophilic) have no effect on the course of the reaction.

9.1.1 Types of pericyclic reactions

In this chapter we will discuss only the three most common types of pericyclic reactions.

1. Cycloaddition reactions

In these reactions two molecules combine to form a ring. The reaction involves conversion of two π -bonds into two sigma bonds. An example of cycloaddition reaction is the well known Diels-Alder reaction (also see section 5.29).



2. Electrocyclic reactions

These are reversible reactions in which a compound with conjugated double bonds undergoes cyclisation. In this process two π -electrons are used to form a σ -bond. Thus, 1,3,5-hexatriene on heating gives 1,3-cyclohexadiene.



9.1.2 Organic Reaction Mechanisms



In the above illustration, an electrocyclic ring closure takes place. The reverse of this process is an electrocyclic ring opening.

3. Sigmatropic rearrangements

These are concerted intramolecular rearrangements. In these rearrangements, an atom (or a group of atoms) shifts from one position to another. The process involves breaking of a bond and forming of a new bond. Thus, 3-methyl-1,5-hexadiene on heating gives 1,5-heptadiene.

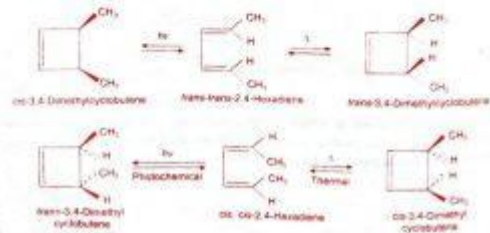


Another common example of sigmatropic rearrangement is Claisen rearrangement (see section 6.5.12).

9.1.2 Stereochemistry of pericyclic reactions

The pericyclic reactions are highly stereospecific and very often different (isomeric) products are formed by thermal and photochemical pathways. For example electrocyclic reactions in which a cyclobutene system opens to a 1,3-butadiene and vice-versa are highly stereospecific.

When ring closure of *trans,trans*-2,4-hexadiene is carried out under thermal conditions the only product formed is *trans*-3,4-dimethylcyclobutene. However, when the same reaction is performed photochemically, *cis*-3,4-dimethylcyclobutene is obtained. In contrast to above, the ring closure reaction of *cis, cis*-2,4-hexadiene under the thermal and photochemical conditions gives cyclobutene with opposite stereochemistry.



The understanding of these reactions relies on the principle of conservation of orbital symmetry.

4.2 Theoretical basis of pericyclic reactions

Several theories have been formulated to understand a rational explanation of pericyclic reactions. Woodward and Hoffmann² (1965) proposed the **principle of conservation of orbital symmetry** theory as a basis for explaining pericyclic reactions. According to this principle, the symmetries of orbitals at both the reactants and the product should correlate or be the same. Thus, in a reaction involving a cyclic transition state (i.e., pericyclic reactions) orbitals in the reactants can only transform into orbitals in the product which have the same symmetry properties. If the symmetries correlate, the reaction is **symmetry allowed**, failing which it is **symmetry forbidden**. The former (ψ -symmetry allowed) reactions require mild conditions. The symmetry forbidden reactions may occur in a non-concerted way.

An alternative approach, viz. **Frontier orbital theory** was described by Kenichi Fukui³ in the late 1960s. It is based on only two molecular orbitals, called the frontier molecular orbitals (FMO) which include the highest occupied molecular orbital (HOMO) and the lowest unoccupied molecular orbital (LUMO).

Another theory named aromatic transition state theory is also used for the interpretations of pericyclic reactions.

All of these theories are based on molecular orbital theory. Out of all the approaches to pericyclic reactions, the FMO approach is simpler and a detailed understanding of molecular orbital theory and symmetry is not required.

Before discussing pericyclic reactions, one must understand the basic features of molecular orbital theory and symmetry properties of reactant and product molecular orbitals.

4.2.1 Molecular orbital theory

According to the molecular orbital theory, molecular orbitals result by the linear combinations of atomic orbitals (LCAO). It is well known that in the saturated hydrocarbons like methane or ethane, the carbon atoms are sp^3 hybridized. There are two types of σ -bonds in them, between carbon atoms as well as between carbon and hydrogen atoms, formed by the overlap of sp^3 - sp^3 or sp^3 - $1s$ atomic orbitals, respectively. Each of these σ -bonds will have a bonding orbital and the corresponding anti bonding orbital.

In the formation of a σ -bond between carbon and carbon, the sp^3 hybrid orbitals of two carbon atoms combine. There are two possibilities when two sp^3 hybridized orbitals come close and interact with each other. Orbitals of the same phase can interact with each other to form bonding molecular orbital (σ -molecular orbital in this case). When orbitals of opposite phase interact, the antibonding orbital (σ^* -molecular orbital in this case) is formed. The phase may be indicated by shading or by labeling one to be of an orbital sign (+) and the other sign (-).

The bonding orbitals is lower in energy than the separate atomic orbitals and

antibonding orbitals. The antibonding orbital which does not contribute to the bond formation between the atoms is of higher energy. This is shown in Fig. 1

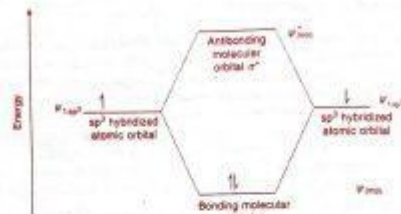


Fig. 1 Energy diagram (ψ_{bond} and ψ_{antibond} represent wave functions for bonding and antibonding molecular orbitals.

The bonding molecular orbital (ψ_{bond}) contains both the electrons in the lowest energy state (ground state) and is formed when the atomic orbitals combine in the way shown in Fig. 2. In this case, the atomic orbitals combine by addition; this means that the atomic orbitals of the same phase sign overlap. Such overlapping leads to reinforcement of the wave function in the region between the two nuclei.

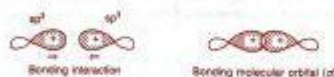


Fig. 2 Bonding orbitals

The antibonding orbital (ψ_{antibond}) does not contain any electron in the ground state of the molecule and is formed by subtraction in the way shown in Fig. 3; subtraction means that the phase sign of one orbital has been changed from (+) to (-). In this case, the orbitals of opposite phase overlap and so the wave functions interfere with each other in the region between the two nuclei and a node is produced (at the node, $\psi = 0$, and on either side of the node ψ is small). Having electrons in the anti bonding orbitals would not tend to hold the atoms together.



Fig. 3 Antibonding orbitals

Molecular orbitals of ethene

However, in alkenes molecular orbitals of ethene (for example, ethene) the carbon atoms are sp^2 hybridised. The double bond between two carbon atoms is comprised of a σ - and a π -bond. The former ($C-C$ σ -bond) is formed by the overlap of two sp^2 orbitals. The overlapping is discussed in saturated hydrocarbons, i.e. of the overlapping of sp^3 - sp^3 hybrid orbitals. The π bond is formed by sideways overlap of p -orbitals resulting in two π -molecular orbitals. In the above case, the bonding π -orbital is formed by the overlap of in-phase p -orbitals, and the other antibonding π^* -orbital arises from the interference between two p -orbitals of opposite phases. These orbitals are designated as ψ_1 and ψ_2 respectively.

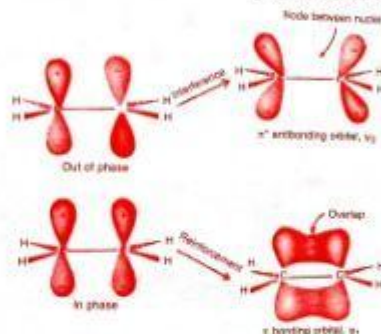
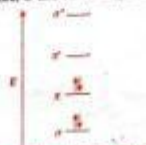


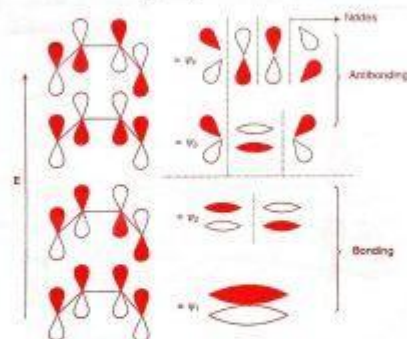
Fig. 4 Bonding and antibonding orbitals of ethene.

In the Fig. 4 representation of π and π^* -orbitals of ethene are shown. The π^* -orbital is formed by interference between the out of phase p -orbitals and has a node (or a region of minimum electron density between the nuclei). The comparison of the energies of σ , π , π^* and σ^* -orbitals is shown in the Fig. 5. The bonding electrons, as expected, are in the two orbitals with lowest energies, σ and π , in the ground state of ethene.

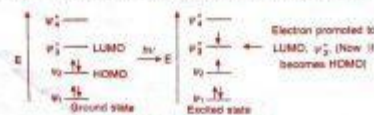

 Fig. 5. Ground state of C_2C in ethene.

Molecular orbitals of butadiene

A study of molecular orbitals of butadiene is important for the discussion of pericyclic reactions. In butadiene there are four p orbitals and their combination gives four molecular orbitals having wave functions ψ_1 , ψ_2 , ψ_3 and ψ_4 with different energies. Of these ψ_1 and ψ_2 π -molecular orbitals are bonding and ψ_3 and ψ_4 are anti-bonding orbitals. Molecular orbital is bonding if the number of bonding interactions is greater than the number of nodes between the nuclei, and a molecular orbital is antibonding if the number of bonding interactions is less than the number of nodes between the nuclei. Fig. 6 depicts these orbitals in terms of increasing energy.


 Fig. 6. Four π molecular orbitals of butadiene, ψ_1 to ψ_4 .

In the case of butadiene out of the four molecular orbitals in ground state, two, viz. ψ_1 and ψ_2 are of lowest energy; ψ_2 is the highest occupied molecular orbital (HOMO) and ψ_3 is the lowest unoccupied molecular orbital (LUMO). Both HOMO and LUMO are referred to as frontier orbitals and are used in analysing pericyclic reactions. On absorption of a photon of proper wave length (in the uv range), an electron is promoted from ψ_2 to ψ_3 ($\psi_2 \rightarrow \psi_3$) which then becomes a new HOMO, see Fig. 7.


 Fig. 7. Promotion of ψ_2 to ψ_3 .

Molecular orbitals of 1,3,5-hexatriene

As in the case of butadiene, the six p -electrons of 1,3,5-hexatriene are accommodated in the first three molecular π -orbitals, ψ_1 , ψ_2 , ψ_3 which are bonding orbitals and the remaining three higher energy molecular π -orbitals (ψ_4 , ψ_5 , ψ_6) are antibonding orbitals, which remain unoccupied in the ground state, see Fig. 8. Thus, six π -electrons are accommodated in ψ_1 , ψ_2 and ψ_3 , the bonding orbitals.

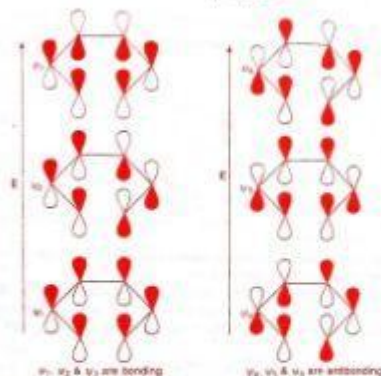


Fig. 8 Six molecular orbitals of 1,3,5-hexatriene, ψ_1 to ψ_6 (shown in a simplified manner).

The bonding or antibonding interactions of the frontier molecular orbital(s) determine whether the reactions are thermally or photochemically allowed or forbidden.

5.2.2 Symmetry properties of reactant and product orbitals

Molecular orbitals (of reactants and products) are classified according to two independent symmetry operations, either a plane of symmetry (m) or a axis of symmetry (c_2). For example, the symmetry properties of π -orbitals (bonding and antibonding) of ethene are classified in terms of whether they are symmetric (S) or antisymmetric (A) with respect to both the mirror plane and the c_2 axis. This is shown in Fig. 9.



Fig. 9 Mirror plane (m) and C_2 of ethene π molecular orbitals

The π (bonding orbital) is symmetric (S) with respect to the mirror plane (m) (which bisects the π -orbital, see Fig. 10.) but antisymmetric (A) with respect to the rotation axis, c_2 .



Fig. 10. Mirror bisects the π orbital, therefore π orbital possesses m symmetry.

Antibonding orbital, π^* , of ethene is antisymmetric with respect to m (Fig. 11) and symmetric with respect to c_2 axis.



Fig. 11 The rotation of the π^* -orbital around the axis, c_2 , results in a molecular orbital identical with the original. Therefore, π^* possesses c_2 symmetry.

Two electrocyclic reactions are very common i.e., interconversion of butadiene to cyclobutene and hexatriene to cyclohexadiene.

Symmetry of the orbitals of the butadiene and the orbitals of the cyclobutene are described as given below (Fig. 12) in terms of whether they are symmetric (S) or antisymmetric (A) with respect to both the m (mirror plane) and the c_2 axis.

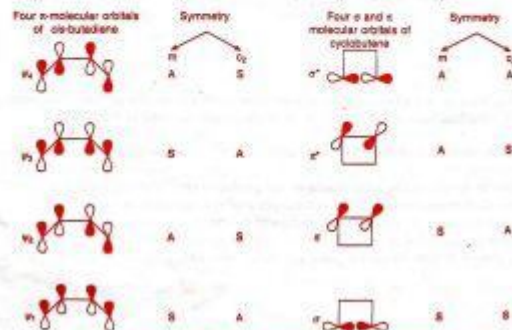


Fig. 12 Symmetry properties of butadiene and cyclobutene molecular orbitals

Symmetry properties of all the π -molecular orbitals of hexatriene (ψ_1 to ψ_6) and cyclohexadiene (two σ and four π) are described in Fig. 13.

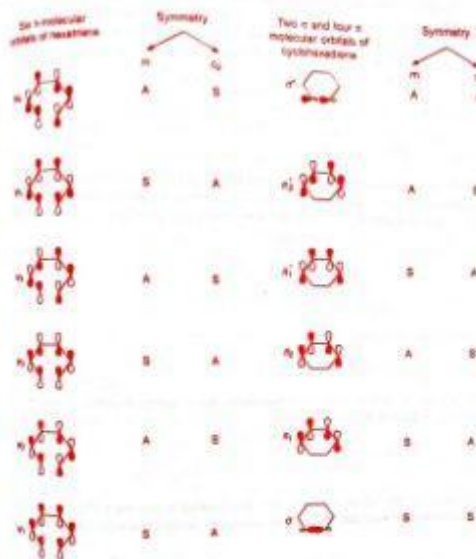
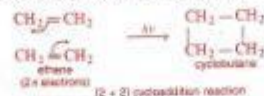


Fig. 13 Symmetry properties of hexatriene and cyclohexadiene molecular orbitals.

Once these symmetries are noted, correlations of reactant and product orbitals may be drawn so that orbitals of like symmetry are connected. If there is a correlation between an orbital of reactant in the ground state with one orbital of product in the excited state, then this reaction will involve a photochemical excitation. But if there is correlation between the ground state orbital(s) of reactant and product then the reaction is thermally allowed.

9.3 Cycloaddition reactions

Cycloaddition reactions are concerted and stereospecific. These reactions can be either thermal or photo induced but not both. In these reactions two unsaturated molecules undergo addition to give a cyclic product. Thus, cycloaddition of two molecules of ethene (two π -electron system) gives cyclobutane on irradiation with uv light.



The above cycloaddition reaction of ethene is known as [2 + 2] cycloaddition reaction and in this case 2π -electrons + 2π -electron are involved. However, the cycloaddition of butadiene (4π -electrons) and ethene (2π -electrons) is an example of [4 + 2] cycloaddition reaction.



A. Frontier orbital theory

9.3.1 [2 + 2] Cycloadditions

As already stated the combination of two molecules of ethene to give cyclobutane is the simplest [2 + 2] cycloaddition reaction.



In this case, the orbitals of two molecules may overlap in two ways (Fig. 14). When the bond is formed between the two reactant molecules on the same side of the π -orbital, the

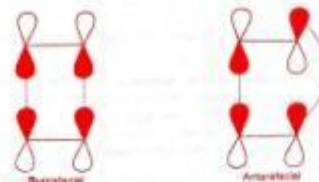


Fig. 14 Suprafacial and antarafacial interactions

addition is known as **suprafacial**. However, it is known as **antarafacial** if the bond is formed from the opposite side of the π -orbital.

[2 + 2] Cycloaddition reaction takes place only photochemically but not thermally. According to frontier orbital theory, the cycloaddition can be explained by assuming that the flow of electrons takes place from the HOMO of one molecule to LUMO of the other molecule. Thus, the HOMO of one molecule must overlap with the LUMO of the other molecule. According to FO theory, a pericyclic reaction is allowed when the HOMO of one reactant has the same symmetry as the LUMO of the other.

We know that ethene has two π -molecular orbitals π and π^* with wave functions, ψ_1 and ψ_2 , respectively. In its ground state, π , bonding orbital, is HOMO while π^* , antibonding orbital, is LUMO. (Fig. 15).

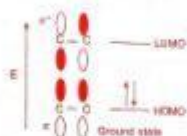


Fig. 15 Two π -orbitals of ethene in-bonding and π^* -antibonding.

Under thermal conditions, when ethene is heated, the π -electrons are not promoted and remain in the ground state. This is simply clear by examining the HOMO of ethene molecule and LUMO of another ethene molecule. This explains that there is no reaction under thermal conditions. Thus, this reaction is **symmetry forbidden**, see Fig. 16.

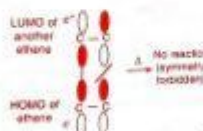


Fig. 16 Thermal conditions [2 + 2] cycloaddition, thermally symmetry forbidden

A symmetry forbidden reaction, may take place under different conditions (the energy of activation is very high) but the reaction will not take place in a concerted manner and may involve stepwise reaction via radical intermediates.

The photochemical suprafacial mode of cycloaddition is **symmetry-allowed**. This is because irradiation of ethene promotes an electron to the anti-bonding orbital, π^* ($\pi \xrightarrow{h\nu} \pi^*$), which now becomes HOMO. Since, the symmetry of HOMO (π^*) of one ethene corresponds with LUMO (π^*) of another ethene molecule, therefore, the cycloaddition is **photochemically allowed**, see Fig. 17.

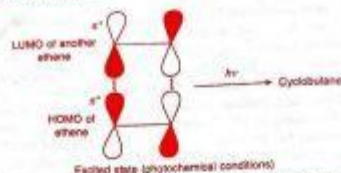
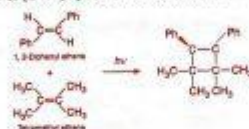


Fig. 17 [2 + 2] Cycloaddition reaction, photochemically symmetry allowed

Another example of [2 + 2] cycloaddition reaction is shown below.



9.3.2 [4 + 2] Cycloadditions

The most well known Diels-Alder reaction (section 5.29) is the thermal [4 + 2] cycloaddition reaction. It proceeds stereospecifically and smoothly. In Diels-Alder reaction the diene must have a *cisoid* conformation. Thus, *cisoid* butadiene adds on to ethene in a *cis* or *syn* manner to give cyclohexene.



In *cisoid*-butadiene, *cisoid* refers to the geometry around the single bond, which determines the conformation. The two conformations of 1,3-butadiene are:



As already stated, the [4+2] cycloaddition of 1,3-butadiene is thermally allowed; such addition is not possible photochemically. This can be understood on the basis of the following considerations. Let us examine the HOMO-LUMO interactions of the p -orbitals which is responsible for forming a new sigma bond in [4 + 2] cycloaddition. In the thermally included cycloaddition between 1,3-butadiene and ethene, one can visualise the π -electrons flowing from HOMO, ψ_2 , of the diene to LUMO, ψ_2 , of the dienophile (ethene). This reaction is (therefore) symmetrically allowed (Fig. 18).

However, in case of photochemical induced Diels-Alder reaction, the diene (butadiene) on excitation by light, its HOMO becomes the π_3^* -orbital (Fig. 19), which cannot

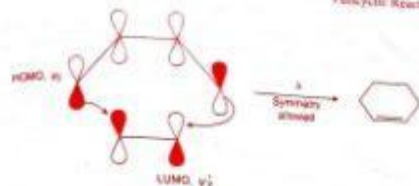


Fig. 18 Thermal Diels-Alder reaction, symmetry allowed

overlap with the LUMO of the dienophile (ethene) since the two are not in phase. In view of this, the photo-induced $[4 + 2]$ cycloaddition is symmetry forbidden.

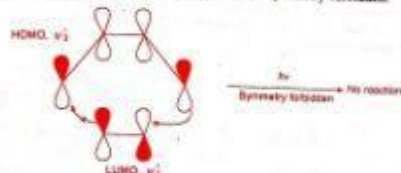


Fig. 19 Photochemical Diels-Alder reaction, symmetry forbidden

3. Correlation diagrams

Cycloaddition reactions can also be explained using correlation diagrams. The term orbital correlation diagram describes the theoretical device, developed by Woodward and Hoffmann to interpret pericyclic reactions. According to orbital symmetry theory the symmetry of the orbitals of the reactants must be conserved as they are transformed into the orbitals of the product.

Consider a simple example of cycloaddition reaction of two molecules of ethene to form cyclobutane



Let us classify all the molecular orbitals of reactants and the products as symmetric (S) or anti-symmetric (A) with respect to symmetry plane. Once these symmetries are noted, correlations of reactants and product orbitals may be drawn so that orbitals of like symmetry are connected.

In a $[2 + 2]$ cycloaddition reaction of the ethene molecules to form cyclobutane, it is assumed that ethene molecules attack each other in parallel planes (i.e., vertically). Thus are two symmetry planes (the mirror planes), one bisecting the π -system of the molecules (plane 1, vertical) and other between the interacting molecules (plane 2, horizontal) as shown in Fig. 20.

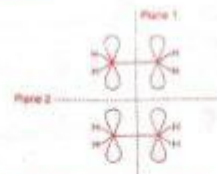


Fig. 20 Two symmetry planes (1 and 2)

There are two π -orbitals of each ethene molecule, π and π^* (bonding and anti-bonding, respectively). The ethene orbitals can interact with another ethene orbitals in four ways to give four π -orbitals i.e. π_1 , π_2 , π_3 and π_4 .

Fig. 21 shows the possible interactions of the orbitals of the two ethene with respect to two symmetry planes (1 and 2).

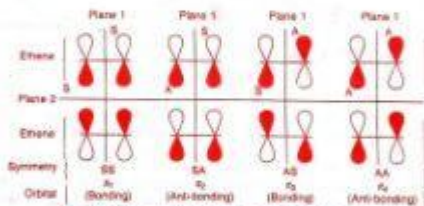
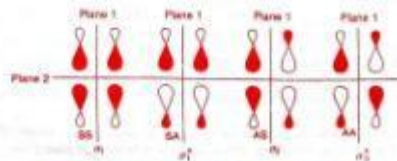


Fig. 21 Symmetry properties of interacting ethene p-orbitals

Let us consider the σ -orbitals of the cyclobutane (product) and analyse them with respect to same planes used for the ethene interaction. This is shown in Fig. 22.


 Fig. 22 Symmetry properties for cyclobutane σ -orbitals

After discussing symmetry properties of the orbitals of ethene and cyclobutene a correlation diagram can be constructed for the ethene-cyclobutene conversion, as shown in Fig. 23. This is the central postulate of orbital symmetry theory: orbitals in the reactants must transform into product orbitals that have the same symmetry. Since the σ_1^* orbital in the product is a high energy orbital, there must be a high activation energy for the formation of the product.

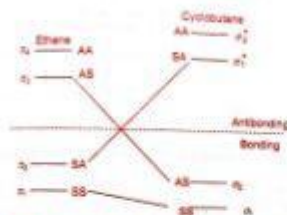
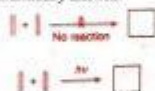


Fig. 23 Correlation diagram for the $[2+2]$ cycloaddition.

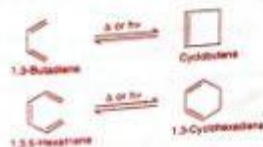
The correlation diagram clearly illustrates that $[2+2]$ cycloaddition reaction is formally forbidden but photochemically allowed.



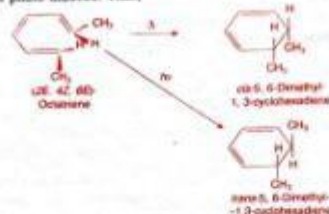
Since orbital correlations diagrams for more cycloaddition reactions involving more than two reactants are necessarily more complex, we will not deal further with this approach.

9.4 Electrocyclic reactions

Electrocyclic reactions can take place either thermally or photochemically. Some of the examples are:



The reverse reaction involving ring opening also proceeds by similar mechanism. The stereochemistry of the formed product is dependent on whether the reaction is thermal or photo-induced. Thus,



Let us consider electrocyclic cyclisation of $4n$ systems and $[4n+2]$ systems.

9.4.1 Cyclisation of $4n$ systems

The simplest example of a polyene with $4n$ electrons is 1,3-butadiene. It cyclises to give cyclobutene. The cyclisation takes place by the end-to-end overlap of its p-orbitals and is accompanied by rehybridisation of the carbon atoms involved in bond formation. The cyclisation can be either in phase or out of phase with each other as shown in Fig. 24.



Fig. 24 In phase & out of phase cyclisation

For the cyclisation involving the formation of a new sigma bond, the existing C-C sigma bonds must rotate so that the p-orbitals undergo in-to-end overlap; the energy required for rotation comes either by heat or by ultraviolet. The existing C-C sigma bonds can rotate (to bring the p-orbitals in phase for overlap) in two ways (Fig. 25).

- The two C-C sigma bonds can rotate in the same direction, either clockwise or anticlockwise. The type of rotation is called **conrotatory**.
- The two sigma bonds can rotate in opposite directions. This type of rotation is called **disrotatory**.

In the first example, the phases of p-orbitals in the starting diene are different. Though the phases of p-orbitals are out of phase in the starting diene, the conrotating motion brings them into phase for symmetry allowed overlap. However in the second example, the p-orbitals are in phase before rotation, disrotatory motion is required to bring them

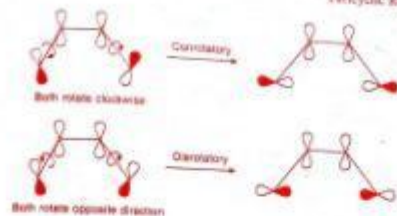


Fig. 25 Corrotatory and disrotatory

in phase for symmetry allowed overlap prior to cyclisation. The phases of p -orbitals of the starting diene depends on whether the molecule is in the ground state or in the excited state.

Thus, 1,3-butadiene on heating cyclises from the ground state. In this case the electrons that are used for sigma bond formation are in the HOMO, ψ_2 . The p -orbitals, which are required for the σ -bond formation are out of phase with each other. For the reaction to take place, only corrotatory motion is necessary. Disrotatory motion would not bring lobes of p -orbitals in phase for overlap, see Fig. 26.

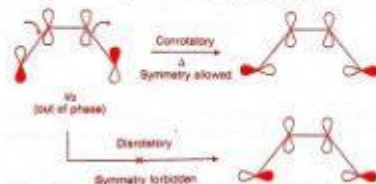


Fig. 26 Thermal reaction of 1,3-butadiene is symmetry allowed.

The photocyclisation takes place in the excited state. In this case HOMO is ψ_3^* in which phases of p -orbitals are in phase and so the rotation of C-C sigma bond has to be disrotatory for a symmetry allowed reaction to occur, see Fig. 27.

Stereochemistry

As seen in the cyclisation of butadiene to cyclobutene, the reaction can be performed both thermally or photochemically. The reaction is strictly stereospecific. However, the stereochemistry of products formed when the reaction is performed under thermal conditions is different than the stereochemistry of the product obtained when reaction is

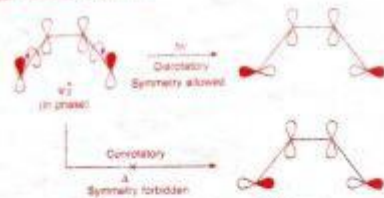


Fig. 27 Photochemical cyclisation of 1,3-butadiene

performed under photochemical condition. Thus, the stereochemistry of the product in 4π cyclisation depends on the reaction conditions; thermal or photoinduced. This can be well understood if we consider the cyclisation of (2E, 4Z)-hexadiene. The product obtained is *cis*-3,4-dimethylcyclobutene under thermal conditions and *trans*-3,4-dimethylcyclobutene under photochemical conditions. In the former case, corrotatory motion is a must for bond formation, i.e., both the methyl groups rotate in the same direction forming *cis* product (Fig. 28).

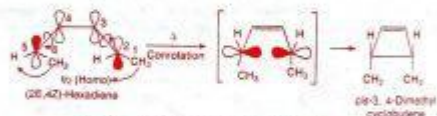


Fig. 28 Thermal cyclisation of (2E, 4Z)-hexadiene

However, under photochemical conditions, disrotatory motion is a must for bond formation, i.e., two methyl groups rotate in opposite direction giving rise to *trans* product (Fig. 29).

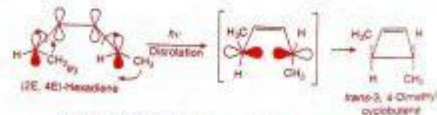


Fig. 29 Photochemical cyclisation of (2E, 4Z)-hexadiene

9.4.2 Cyclisation of $[4n+2]$ systems

A typical example of electrocyclic reaction of $[4n+2]$ system is the cyclisation of 1,3,5-hexatriene to 1,3-cyclohexadiene. The HOMO of 1,3,5-hexatriene in the ground state is ψ_3 . The p -orbitals that form sigma bond are in phase and so thermal cyclisation would require disrotatory motion (Fig. 30).

of reactant does not correlate with ground state orbitals of product. Thus, thermally disrotatory process is **symmetry-forbidden**.

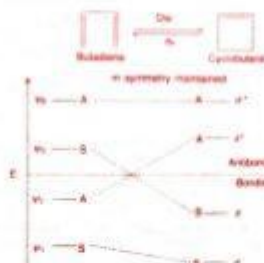


Fig. 34 Correlation diagram for disrotatory cyclization (photochemically allowed)



After studying the correlation diagrams for both conrotatory and disrotatory processes, it is concluded that the interconversion of butadiene to cyclobutene thermally proceeds in a conrotatory way while photochemically proceeds in a disrotatory way.

Working on similar lines, one can draw correlation diagram for $[4n+2]\pi$ -electron system. A example of $[4n+2]\pi$ -electrons system is interconversion of hexatriene to cyclohexadiene. It is concluded from correlation diagrams that the interconversion of hexatriene to cyclohexadiene in a disrotatory mode is thermally allowed (Fig. 35). Whereas, photochemically, the above reaction occurs in a conrotatory mode (Fig. 36).

In the disrotatory process, m symmetry is maintained. The correlation diagram for disrotatory process clearly indicates that the bonding orbitals of reactant correlates with the bonding orbitals of products



Thus, this process is **thermally allowed**. On the other hand in a conrotatory process c_2 axis symmetry is maintained. The correlation diagram for this process indicates that this process is thermally not allowed as bonding orbitals (in ground state) of hexatriene do not correlate with bonding orbitals (in ground state) or cyclohexadiene



However on irradiation (i.e., photochemically) an electron is promoted from Ψ_3 to Ψ_6 in hexatriene. Now all the orbitals of hexatriene (in excited state) correlates with orbitals

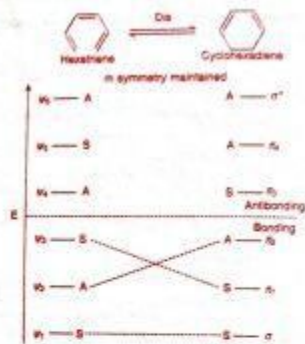


Fig. 35 Correlation diagram for disrotatory cyclization of hexatriene to cyclohexadiene (thermally allowed)

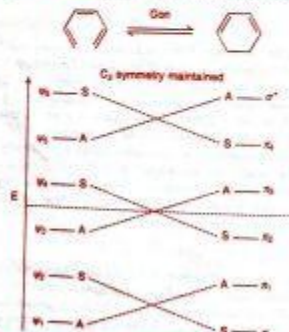


Fig. 36 Correlation diagram for conrotatory cyclization of hexatriene to cyclohexadiene (photochemically allowed). (In excited state) of cyclohexadiene. Thus, conrotatory process for this reaction is photochemically allowed.



Thus, Woodward and Hoffmann selection rules for electrocyclic reactions of $4n$ and $[4n + 2]$ π -electron system is summed up in the form of table 2.

Table 2. Selection rules for electrocyclic reactions

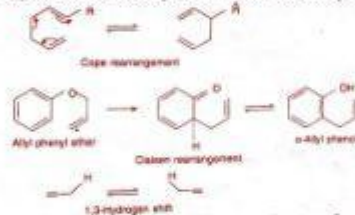
Number of π electrons	Thermal (Δ)	Photochemical ($h\nu$)
$4n$	Con	Dis
$4n + 2$	Dis	Con

9.5 Sigmatropic rearrangements

Molecular rearrangements in which a σ -bonded atom or group, flanked by one or more π -electron systems, shift to a new position with a corresponding reorganization of the π -bonds are called sigmatropic reactions. The total number of σ -bonds and π -bonds remain same in starting and final product. Cope and Claisen rearrangements are among the most commonly studied sigmatropic rearrangements.

Few examples of sigmatropic rearrangements are:

These rearrangements are described by two numbers set in brackets [i , j] that refers to

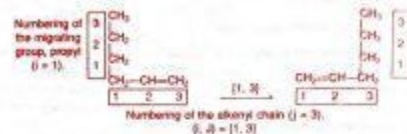


the relative position of the atoms involved in migration. Few examples of sigmatropic rearrangements involving shift of hydrogen atom are [1,3], [1,5] and [1,7] rearrangements as described below:

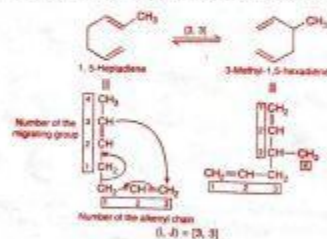


The numbering of the alkenyl chain given in the above examples is not related to nomenclature numbers. In the first-example, the H atom ($i = 1$) is migrating on atom 3 ($j = 3$) of the alkenyl chain, thus, this rearrangement is known as [1, 3] sigmatropic rearrangement. Similarly, in [1, 5] and [1, 7] sigmatropic rearrangements, the H atom ($i = 1$) migrates to carbon atom 5 and 7, ($j = 5$ or 7), respectively.

However, when the migrating group is other than H atom, then the migrating group is also numbered starting at the position of its original attachment



The Cope rearrangement is an example of [3, 3] sigmatropic rearrangement. In this case the first atom of the migrating group is not bonded to the alkenyl chain.



It is atom 3 ($j = 3$) of the migrating group which become bonded to atom 3 ($j = 3$) of the alkenyl chain. Thus, this is an example of [3, 3] sigmatropic rearrangement.

Analysis of sigmatropic rearrangement

Let us consider the sigmatropic rearrangements in which H-atom shift takes place. There are two possible modes for H shift. If all the bonding events take place on the same side of the alkenyl chain (π -system), the rearrangement is called **suprafacial**. If the bonding events occur on opposite side of the π -system, the process is known as **antarafacial**. In a symmetrical π -molecular orbitals the suprafacial migration (i.e., top to top) occurs and in an antisymmetrical π -molecular orbitals the antarafacial migration (i.e., top to bottom) occurs. The following diagrams (Fig. 37) illustrate both these processes.

The most easy way to analyze these rearrangements is to assume that the migrating σ -bond undergoes homolytic cleavage to yield a pair of radicals. For example, in the

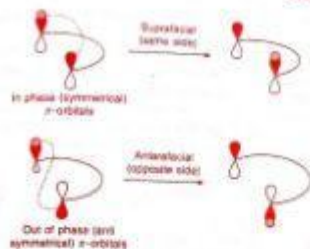
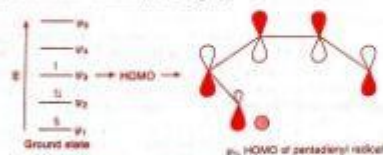


Fig. 37 Suprafacial and antarafacial H migration.

use of a [1, 5] sigmatropic rearrangement, the products of hypothetical cleavage are a hydrogen atom and pentadienyl radical. The latter contains five π -electrons and therefore there are five π -molecular orbitals, as in Fig. 38.


 Fig. 38 π -Orbitals of pentadienyl radical

Because in the ground state the HOMO is ψ_3 hence the hydrogen shift is controlled by the symmetry of the ψ_3 of pentadienyl radical. The ψ_3 has similar sign on the terminal lobes i.e., it is symmetrical. Thus, the 1,5 hydrogen shift is **thermally allowed** and occurs in a **suprafacial process**. This involves a transition state in which the C_1 and C_5 orbitals overlap with $1s$ hydrogen orbital. This shift is both symmetry allowed and geometrically favourable, as shown in Fig. 39.



Fig. 39. [1,5] Suprafacial shift is thermally allowed

In an excited state (i.e. photochemically) the HOMO is now ψ_4 and it is antisymmetrical. Therefore, [1,5] suprafacial migration is no longer possible i.e., is symmetry forbidden. The photochemical reaction will follow the **antarafacial route**, which is **symmetry allowed** (Fig. 40). However, this cannot be accomplished due to steric problem in this type of system. Sigmatropic rearrangements involve cyclic transition states. If the transition state has six or fewer atoms in the ring, the migration must be suprafacial because of the geometric constraints of small rings. The antarafacial shift can occur only with large rings. Therefore photochemically this reaction does not occur.



Fig. 40 1,5-Antarafacial shift is photochemically allowed but geometrically unfavourable

In contrast to [1, 5] H shift, in a suprafacial [1, 3] H shift, the $1s$ orbital of the H atom cannot bond simultaneously to both terminals of the allyl radical. This is because the HOMO for a thermal reaction (i.e. in a ground state) of allyl radical is ψ_2 (Fig. 41), which is antisymmetrical, thus, [1,3] suprafacial migration is **symmetry forbidden**. The $1s$ hydrogen atom must be transferred from one end of HOMO to the other by overlap between like signs, if bonding is to result. However, for this shift to be accomplished in allyl system the H-atom must be transferred from the top face to the bottom face of HOMO i.e., by **antarafacial process**. The antarafacial [1,3] H-atom shift is symmetry allowed but geometrically unfavourable, hence reaction fails, see Fig. 42.

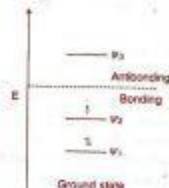

 Fig. 41 HOMO, ψ_1 for a thermal reaction of allyl radical.


Fig. 42 [1,3] Suprafacial shift is symmetry forbidden. However, antarafacial shift is symmetry allowed but geometrically unfavourable.

Thus, the [1,3] sigmatropic rearrangement is thermally not allowed and does not take place.

However, [1,3] H-atom shift will take place photochemically. The HOMO of allyl system for a excited state is Ψ_2 ($\Psi_1^2, \Psi_2^2, \Psi_3^2 \rightarrow \Psi_1^2, \Psi_2^2, \Psi_3^2$). The Ψ_2 is symmetrical i.e. now it has terminal lobes of the same phase. Therefore, [1,3] H-shift is photochemically symmetry allowed and occurs in a suprafacial process (Fig. 43).



Fig. 43 Photochemically symmetry allowed

The general rules for migration of hydrogen is given in Table 3.

Table 3. Selection rules for sigmatropic reaction

Number of electrons ($\pi + \sigma$)	Ground state (Thermally allowed)	Excited state (Photochemically allowed)
$4n$ $4n + 2$	Antarafacial suprafacial	Suprafacial Antarafacial

For [1,3] shift in $4n$ electrons, $n = 1$ i.e., total 4 electrons, $4n + 2\pi$

For [1,7] shift in $4n$ electrons, $n = 2$ i.e., total 8 electrons, $4n + 2\pi$

For [1,5] shift in $4n + 2$ electrons, $n = 1$ i.e., total 6 electrons, $4n + 2\pi$

Unlike [1,3] sigmatropic migrations of H, which cannot occur under thermal conditions, the [1,3] sigmatropic migrations of carbon can occur under thermal conditions. This is because carbon has a two lobed p -orbital. Therefore, carbon can simultaneously interact with the migrating source and the migrating terminus using either one of its lobes or both of its lobes, as shown in Fig. 44.

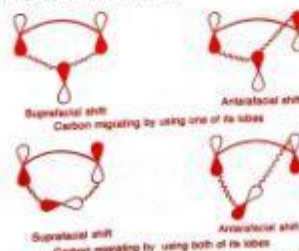


Fig. 44 Sigmatropic rearrangements involving carbon shift

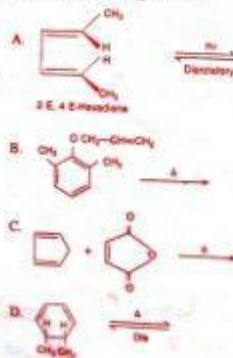
Thus, in a suprafacial carbon shift if the HOMO is symmetrical, carbon will migrate using one of its lobes, but if the HOMO is antisymmetric, it will migrate using both of its lobes. However, when carbon uses only one of its lobes, the migrating group retains its configuration. When carbon migrates by using both of its lobes, there is inversion of configuration. In case of [1,3] carbon shift, the HOMO is antisymmetrical (see Fig. 42). Therefore, carbon can migrate using both of its lobes in a suprafacial process.

References

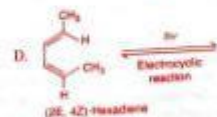
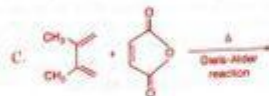
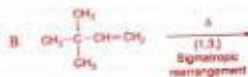
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Problems

1. What are pericyclic reactions?
2. Explain the terms: (A) Suprafacial and antarafacial (B) Conrotatory and disrotatory processes (C) HOMO and LUMO.
3. Explain the frontier molecular orbital method for analyzing an electrocyclic reaction by taking one example.
4. Draw the π orbital diagrams for the ground state and the lowest energy excited state of 1,3-butadiene and indicate the HOMO in each case.
5. With the help of correlation diagram, show that cyclisation of hexatriene to cyclohexadiene on heating proceeds by disrotatory mode.
6. Define Woodward-Hoffmann selection rule for electrocyclic reactions.
7. Explain Diels - Alder reaction.
8. Complete the following reactions:



9. Explain with the help of FMO theory that [1,3] sigmatropic shift of hydrogen is thermally forbidden.
10. Draw correlation diagram for [4n + 2] cycloaddition reaction and explain why it is thermally allowed and photochemically symmetry forbidden.
11. Give the product of the following reactions:



10 Photochemical Reactions

10.1 Introduction

For any chemical reaction (or chemical transformation), certain amount of energy, known as activation energy has to be supplied to the molecules of the reactants. Generally, this energy is supplied by increasing the temperature. By this process, the molecules of the reactants remain in their ground state with vibrational, rotational and translational energies at a higher level than described by Maxwell-Boltzmann law. At higher temperatures, the molecules which have acquired sufficient energy lead to formation of the product.

Alternatively, the energy for a chemical reaction can be supplied photochemically. This involves absorption of electromagnetic radiation in the visible or ultraviolet region. Under these conditions, a molecule absorbs a quantum of light, the energy of which depends on the frequency of the radiation as expressed by the equation

$$E = h\nu = \frac{hc}{\lambda}$$

where h is the Planck's constant and c is the velocity of light. This energy is greater than the bond dissociation energy of a carbon-carbon σ bond (347 kJ mol^{-1}). Unlike thermal reaction, in photochemical reactions the absorption of light raises an individual molecule to an excited electronic state. In fact, the selective excitation of individual molecules is a special character of photochemical reactions. The chemistry of the excited molecules (in photochemical reactions) is quite different from the chemistry of the molecules in the ground state (in thermal reactions), even though the total energy supplied thermally is much more than what is introduced in photochemical process. Photochemical reactions, as we will see subsequently, have been used for synthesising highly strained, thermodynamically unstable compounds. Also the photochemical reactions are highly stereospecific. The products obtained by thermal and photochemical process normally differ in stereochemistry.

10.2 Basic laws of photochemistry

Photochemistry is the study of the interaction of light and chemicals. Organic photochemistry is a branch of organic chemistry that studies light-induced chemical reactions of organic compounds.

10.2.1 Grothues-Draper Law

The first law of photochemistry, known as the Grothues-Draper law, states that light must be absorbed by a chemical substance in order for a photochemical reaction to take place.

This law was modified by Stark and Einstein. The Stark-Einstein law states that for each photon of light absorbed by a chemical system, only one molecule is activated for photochemical reaction. This is also known as the photoequivalence law or i.e. only one excited molecule per photon absorbed.

10.2.2 Beer Lambert law

This law is named after the scientists Johann Heinrich Lambert and August Beer. The Beer-Lambert law is the linear relationship between absorbance and concentration of an absorber of electromagnetic radiation. Lambert observed that the absorption of light of a single wavelength (monochromatic radiation) passing through homogeneous solutions of equal concentration is proportional to the pathlength.

$$A = k \cdot l$$

where l is path length and k is constant

When a beam of light is passed through a transparent medium the rate of decrease of intensity with the thickness of medium is directly proportional to the intensity of the light. Thus, transmittance of a solution is an exponential function of the thickness of the layer.

$$-\frac{dI}{dx} = I = -\frac{dI}{dx} = kI$$

$$\ln \frac{I_0}{I_t} = kx \text{ or } I_t = I_0 \cdot e^{-kx}$$

where, I = intensity of incident light

I_t = the transmitted light intensity

x = the thickness of the layer of absorbing material

k = a proportionality factor depends upon the wavelength and absorbing medium used.

Beer's law states that the absorption of light of a single wavelength (monochromatic radiation) passing through homogeneous solution of equal pathlength is proportional to the concentration.

$$A = k' \cdot c$$

where, c is concentration and k' is constant. The combination of these two laws gives the Beer-Lambert's law:

$$A = k'' \cdot c \cdot l$$

Beer-Lambert law states that the quantity of light absorbed by a substance dissolved in a nonabsorbing solvent is directly proportional to the concentration of the substance and the path length of the light through the solution.

Beer-Lambert law is commonly written as:

$$A = \epsilon \cdot c \cdot l$$

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where, A = absorbance (no units)

c = concentration of the compound in solution in moles per liter

l = path length of the sample in centimeters

ϵ = constant of proportionality known as the molar extinction coefficient with units of $\text{Lm}^{-1}\text{cm}^{-1}$. The value of constant depends on the substance, the solvent, the wavelength and units used for the concentration and pathlength.

The amount of radiation absorbed (or intensity of absorption) can be measured in a number of ways. Experimental measurements are usually made in terms of transmittance (T), which is defined as the ratio of the intensity of the radiation transmitted (I) to that of the incident radiation (I_0), i.e.,

$$T = I/I_0$$

$$\% \text{ transmittance } (\%T) = 100 T \text{ or } \% T = 100 \times \frac{I}{I_0}$$

Intensity of absorption is more conveniently expressed in terms of absorbance (A), which is the logarithm of reciprocal of transmittance (T), i.e.,

$$A = \log_{10} \left(\frac{1}{T} \right)$$

or

$$A = \log_{10} I_0/I$$

Thus, the Beer-Lambert law of light absorption is formulated as

$$A = \log_{10} I_0/I = \epsilon \cdot c \cdot l$$

absorbance is dimensionless quantity. In SI units,

$$c = \text{mol m}^{-3}$$

$$l = \text{m}$$

$$\epsilon = \text{m}^2 \text{mol}^{-1}$$

Problem

A $2 \times 10^{-3} M$ solution [A] of a compound has an absorbance of .15 at 550 nm. Another solution [B] of unknown concentration of the same compound has an absorbance of .06 at the same wavelength what is the concentration (c) of this solution? (the same cuvette was used for the two experiments).

solution:

$$c_1 = \text{concentration of solution [A]} = 2 \times 10^{-3} M$$

$$c_2 = \text{concentration of solution [B]} = ?$$

$$l_1 = l_2 = \text{path length (constant)}$$

$$A_1 = \text{absorbance of solution A} = .15 \text{ at } 550 \text{ nm}$$

$$A_2 = \text{absorbance of solution B} = .06 \text{ at } 550 \text{ nm}$$

According to Beer-Lambert's law:

$$A = \epsilon \cdot c \cdot l$$

ϵ is constant for a given wavelength, solute and solvent and l is also unchanged.
Thus $\epsilon \cdot l = \text{constant}$

$$\text{Therefore, } \frac{A_2}{c_2} = \frac{A_1}{c_1} \text{ or } c = \frac{A_2}{A_1} \times \frac{c_1}{c} = \frac{0.6}{1.5} \times 2 \times 10^{-3} = .0008M$$

The Beer-Lambert law is accurate only for dilute solutions. Deviation from the law occurs in concentrated solution because of interactions between molecules of the solute, the substance dissolved in the solvent. The concentration of a substance dissolved in liquids or gases can be determined by measuring the absorbance A .

$$A = \log_{10} I_0/I = \log_{10} \frac{1}{T}$$

The equation $A = 2 - \log \% T$ can be used to easily calculate absorbance from percentage transmittance data. So, if all the light passes through a solution without any absorption, then absorbance is zero, and $\% T$ is 100%. If all the light is absorbed, then $\% T$ is zero, and absorption is infinite.

10.3 Basis of photochemistry

Photochemical reactions occur by absorption of electromagnetic radiation to produce electronically excited states. It is the electronically excited molecules which gives the products of reactions. The process of raising molecules from ground state of minimum energy to an excited state of higher energy is called excitation. Excitation in the rotational, vibrational or electronic energy levels of molecules result from absorption in microwave, infrared and ultraviolet region of the electromagnetic spectrum. The effects of various kinds of radiation on the molecules is given below.

	Type of radiation	Effect on absorbing molecule
Increasing energy ↑	Ultraviolet	Electronic excitation
	Visible	Vibrational excitation
	Infrared	Rotational
	Microwaves and Radiowaves	

The ultraviolet radiation causes high energy electronic transitions in molecules. The resulting photo excited species can relax (react) via a variety of pathways. Traditionally, most photo reactions have been performed with UV lamp sources.

The electronic excitation is of great importance in organic photochemistry, although, it is also accompanied by increase in vibrational and rotational energies.

10.3.1 Electronic excitation

According to molecular orbital theory, overlapping of two atomic orbitals produces two molecular orbitals. One of them is a low energy (E_1) orbital referred as bonding orbital and accommodates both the electrons in the ground state of the molecule. The other orbital is called antibonding orbital which has higher energy (E_2) than either of the atomic orbitals and remains vacant in the ground state. The $E_2 > E_1$. The relative energies of atomic and molecular orbitals are shown below in Fig. 10.1.

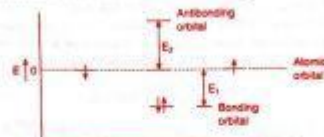


Fig. 10.1 Relative energies of atomic and molecular orbitals.

When excitation takes place, electrons from one of the filled orbitals (σ , π or n) gets excited to one of the vacant antibonding orbitals (σ^* or π^*). Various types of absorptions are:



The relative energies of σ , π and n MOs are shown below in Fig. 10.2.



Fig. 10.2 Relative energies of σ , π and n MOs.

As expected, the electron requires a high energy for excitation to σ^* level. The order of decreasing energy for the absorption are as follows:



Of all the possible transitions, the last three account for absorption in the region 200 - 800 nm, while others demand much higher energy. The last three transitions are also responsible for majority of the organic photochemical reactions.

10.3.2 Excited states

According to **Pauli exclusion principle**, when two electrons are accommodated in the same orbital, their spins must be opposite, i.e., they are paired. A molecule is said to be

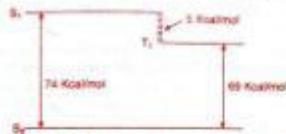


Fig. 10.5 Intersystem crossing in benzophenone

- (iv) S_1 can undergo chemical transformation such as decomposition, isomerisation or other chemical reactions with surrounding molecules leading to new products this process is the basis of organic photochemistry, which will be discussed subsequently.
- (v) S_1 can transfer its excess electronic energy to other molecules and may be converted to S_0 . This process is called **singlet energy transfer (photosensitisation)** and is symbolised as $S_1 + S_0^{\text{(acceptor)}} \rightarrow S_0 + S_1^{\text{(acceptor)}}$. This kind of energy transfer is also very important aspect of photochemistry.
- A molecule in the triplet state has a longer life time (10^{-2} to 10^{-3} sec) and behaves like a radical and participates in bimolecular reactions by photosensitisation, which will be discussed subsequently.
- (vi) T_1 state may be converted to S_1 since T_1 is of lower energy. However, it may either undergoes chemical reaction or may return to the ground state (S_0) by emission of a photon, a process known as **phosphorescence**. As in the case of fluorescence, the wavelength of the phosphorescent light is longer than that of the initially exciting light.
- (vii) T_1 can transfer its electronic spin to another molecule and become converted to S_0 . This process is called **triplet energy transfer (photosensitisation)** and is symbolised as



This transformation is also very important aspect of photochemistry.

A summary of various processes undergone by excited molecules are given below (also represented by Fig. 10.6).

$S_0 + h\nu \rightarrow S_1$	Excitation
$S_1 \rightarrow S_1 + \text{heat}$	Vibrational relaxation
$S_1 \rightarrow S_0 + h\nu$	Fluorescence
$S_1 \rightarrow S_0 + \text{heat}$	Internal conversion
$S_1 \rightarrow T_1$	Intersystem crossing
$T_1 \rightarrow T_1 + \text{heat}$	Vibrational relaxation
$T_1 \rightarrow S_0 + h\nu$	Phosphorescence
$T_1 \rightarrow S_0 + \text{heat}$	Intersystem crossing
$S_1 + S_0^{\text{(acceptor)}} \rightarrow S_0 + S_1^{\text{(acceptor)}}$	Singlet-singlet transfer (photosensitisation)
$T_1 + S_0^{\text{(acceptor)}} \rightarrow S_0 + T_1^{\text{(acceptor)}}$	Triplet-triplet transfer (photosensitisation)

Jablonskii diagram

Several paths by which a molecule in excited state dissipate its energy are best shown diagrammatically and the diagram is known as Jablonskii diagram. (Fig. 10.6) Prior to the excitation, the electronic configuration of the molecule is described as being in the general state. Absorption of UV radiation by a molecule excites it from a lower vibrational level in the electronic ground state to one of the many vibrational levels in the electronic excited state. The electronic excited state is usually the singlet state. The typical Jablonskii diagram illustrated a singlet ground electronic state (the parallel bars labeled S_0) as well as singlet first (S_1 , upper set of parallel bars) and sometimes a second electronic excited state (S_2). The multiple lines in each electronic state representing the vibrational energy levels.

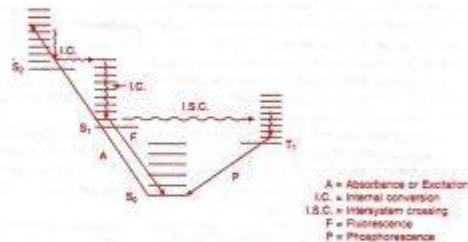


Fig. 10.6 Jablonskii diagram

The molecules in the excited state are considerably more reactive and the excess energy possessed in the excited state can be dissipated by one or more of the following ways.

1. Non-reactive processes between states
2. Radiative processes between states
3. Loss of energy by intermolecular energy transfer
4. Chemical reaction

Usually radiationless transfer of energy can occur before any radiative processes or chemical reactions can occur due to the rapidity of the process. The excess vibrational energy is lost by collision with other molecules i.e., **Vibrational relaxation**. The molecules cross the state to another, e.g., from S_2 to S_1 by a process called **internal conversion**. The excess energy in internal conversion is converted into vibrational energy. This excess vibrational energy is again lost by a **vibrational relaxation**.

In the liquid state, the excited state species may be quenched in which the energy of the excited state species is converted into vibrational energy (heat).



Vibrational energy within a state is usually lost (deactivation process) within 10^{-13} sec and between S_1 and S_0 within $10^{-10} - 10^{-12}$ sec. Thus the vibrational relaxation or internal conversion occurs in about a picosecond or less. The intersystem crossing ($S_1 \rightarrow T_1$) and the decay by radiative processes ($S_1 \rightarrow S_0$) take place relatively slowly compared to internal conversions. Excited state species can emit light (Radiative processes) in a process called **luminescence**. If the process is quick, it is known as fluorescence and if it is delayed, it is known as phosphorescence. Fluorescence ($S_1 \rightarrow S_0$) lifetime is typically four orders of magnitude slower than vibrational relaxation, giving the molecules sufficient time to achieve a thermally equilibrated lowest energy excited state prior to fluorescence emission.

Phosphorescence decay is similar to fluorescence, except the electron undergoes a spin conversion into a forbidden triplet state T_1 (intersystem crossing). There is no intersystem crossing until the lowest level of the excited state is reached. Usually the rate constants for intersystem crossing are in the range of 10^{-5} to 10^{-3} sec^{-1} . Emission from the triplet state occurs with lower energy relative to fluorescence, hence emitted photons have longer wavelength, with delayed fluorescence, the electron first decays into the triplet state, and then crosses back over into the lowest singlet excited state before returning of the ground state.

Many molecules do not have any photoluminescence even though they can absorb UV light. The return to the ground state in these molecules occurs through the internal conversions of the excitation energy into vibrational energy the result is heat rather than photoluminescence.

Fluorescence

The emission of light energy (radiative transitions) when the molecules returns from the excited singlet state in their lowest vibrational levels to the several levels of the ground-state singlet is known as fluorescence. If a molecule which absorbs UV radiation does not fluoresce it means that it must have lost its energy some other way. The electronic transitions are almost instantaneous in nature often occurring in time frames ranging from nano to sub-pico seconds (approximately 10^{-13} sec), which are far too short to observe significant lateral displacement of nuclei during fluorescence and phosphorescent events. Thus, if the geometry of the nucleus and the vibrational spacings in the excited singlet state and ground state are similar then the fluorescence spectrum ($S_1 \rightarrow S_0$) is typically a mirror image of the absorption spectrum ($S_0 \rightarrow S_1$). For example, the fluorescence and absorption spectra of anthracene in ethanol (Fig. 10.7) is similar but reversed.

However, when there is differences in dipole orientations by hydrogen bonding and there is difference in geometry between the ground and the fluorescent state (excited state) the mirror relationship can be distorted.

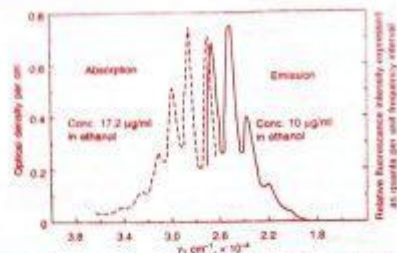


Fig. 10.7 Fluorescence and absorption spectra of anthracene in ethanol. (Reproduced from C.A. Parker and W.T. Rees, *Analyst*, 1960, 85, 587)

According to Stokes's law the wavelength of light absorbed for excitation will be shorter than the wavelength emitted during de-excitation. Thus, the fluorescent light is of slightly lower energy (longer wavelength) than the absorbed light Fig. 10.8. The red-shift (longer wavelength in the emission band relative the absorption band) is known as "Stokes shift".

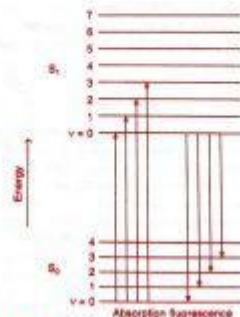


Fig. 10.8 Red shift in the emission band (Fluorescence)

The loss in energy between the absorption and the emission processes can be calculated from the equation:

$$\Delta \bar{\nu} = (\bar{\nu}_a - \bar{\nu}_f)$$

where $\Delta \bar{\nu}$ = loss in energy

$\bar{\nu}_a$ = position of the line of symmetry between absorption and fluorescence

$\bar{\nu}_f$ = position of the centre of gravity of the fluorescence curve all measured in cm^{-1}

The excited states decay exponentially with time when illuminations is withdrawn and can be given by a simple relationship:

$$I = I_0 e^{-t/\tau} \text{ or } \log \frac{I}{I_0} = \frac{-t}{\tau}$$

where

I_0 = Initial intensity at time zero,

I = Intensity at some later time t ,

τ = constant can be defined as lifetime of the excited state emission or mean decay time for the fluorescence,

$1/\tau = k_f$ = the rate constant for fluorescence

Prompt and delayed fluorescence

If a state is populated by way of a strongly allowed transition (readily) then the reverse emission process will be very short-lived. Such type of fluorescence is known as prompt fluorescence and can be given by equation:

$$\tau_0 = \frac{10^{-8}}{f_{\text{max}}} \text{ sec.}$$

where, τ_0 is the inherent radiative lifetime, f_{max}

A strongly absorbing compound with an f_{max} of 10^5 would have a lifetime of 10^{-9} sec.

The prompt fluorescence can be observed either when fluorescence is exhibited by a molecule in its unimolecular decay to the ground state,



or when the molecule in its excited singlet state collides with a molecule of the same substance in the ground state and fluorescence is emitted by the complex.



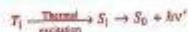
Molecules like benzene, naphthalene, Excimer anthracene, phenanthrene or pyrene also show prompt fluorescence only at high concentrations by a mechanism in which excimer is formed. Excimer is a complex formed by the interaction of an S_1 state of one molecule with an S_0 state of another.

The delayed fluorescence though have similar spectrum to prompt fluorescence but has a larger lifetime (10^{-3} sec). The mechanism of delayed fluorescence is given below:



i.e., the molecules are excited to the first excited state followed by intersystem crossing to the lowest triplet state. Two molecules in the triplet state undergo annihilation to give one ground state molecule and another molecule in the first excited singlet state. Then the molecule in excited singlet state (S_1) emits fluorescence. The delay in the emission is because of several steps before fluorescence.

Another mechanism is possible for delay fluorescence involves only one molecule in triplet state which undergoes reverse intersystem crossing ($T_1 \rightarrow S_1$).



$$h\nu' < h\nu$$

Phosphorescence

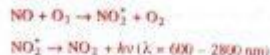
The emission of light energy when the molecules return from their lowest vibration levels in the excited triplet state (T_1) to the several levels of the ground-state singlet, is known as phosphorescence. A triplet to singlet transition is much less probable than a singlet to singlet transition. The emission in case of phosphorescence from the T_1 state is of lower energy (longer wavelength) than fluorescence from the S_1 state and still persists when the illumination is removed. Unlike fluorescence, in which the absorbed light is emitted about 10^{-8} second after excitation, in phosphorescence the extra energy absorbed is stored in metastable states and reemitted later. Phosphorescence may last from about 10^{-3} second to days or even years. In intersystem crossing the spin of an excited electron is reversed, leaving the molecule in an excited triplet state. For example, the S_1 (excited singlet) state of naphthalene can convert into the T_1 (excited triplet) state.



A molecule in a high vibrational level of the excited triplet state can lose energy by vibrational relaxation (by collision with solvent molecules), leaving it at the lowest vibrational level of the triplet state. It can then either undergo a second intersystem crossing to a high vibrational level of the electronic ground state or emit a photon and return to the ground state (phosphorescence) (Fig. 10.6). From high vibrational level of the electronic ground state the molecule returns to the lowest vibrational level of the electronic ground state by vibrational relaxation. Phosphorescence requires low temperatures, because at higher temperatures, triplet state is de-activated by quenching.

Chemiluminescence

A chemical reaction produces an electronically excited species which emits a photon in order to reach to ground state, the phenomenon is known as chemiluminescence. When these type of reactions are encountered in biological system and the phenomenon is known as **bioluminescence**. The chemiluminescence is a rare phenomenon. An example of chemiluminescence is given below:



10.4 Difference between photochemical and thermal reactions

On the basis of what has been stated so far it can be said that thermal reactions occur through higher vibrational levels of the ground state, whereas, photochemical reactions take place through electronic excited states (singlet or triplet). Thermal reactions require less energy ($63-209 \text{ kJ mol}^{-1}$) compared to photochemical reactions ($200-627 \text{ kJ mol}^{-1}$). So light-induced or photochemical reactions are comparatively high energy processes. In photochemical reactions the light energy is absorbed by the reactants at room temperature (or even below room temperature). In case photochemical reactions lead to polymeric products due to high concentration of substrate, in such cases low concentration of substrate is used.

In our discussion of pericyclic reaction (chapter 9) the relationship between thermal and photochemical reactions have been discussed and have used frontier orbital method for analysing the mechanism of both thermal and photoinduced reactions. We have also discussed how forbidden thermal reaction is symmetrically allowed in photo induced conditions.

10.5 Photochemical reactions

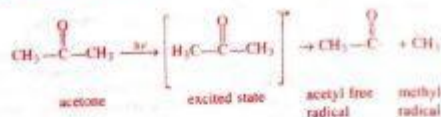
Because the energy of visible and ultraviolet light is of the same order of magnitude as that of covalent bond, a molecule on absorbing a photon of light may cleave into two parts. This process is known as photolysis.

10.5.1 Photochemical reactions of some carbonyl compounds

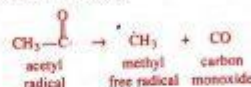
Carbonyl compounds, particularly ketones undergo very interesting photochemical reactions. Some of these are discussed below:

10.5.1.1 Photolysis of acetone (Propanone)

The term photolysis is used when light absorption of molecules leads to cleavage of the bond. Absorption of light by acetone leads to the formation of an excited state, which has sufficient energy to undergo cleavage of a C—C bond (the weakest bond in the molecule) and forms a methyl free radical and an acetyl free radical.



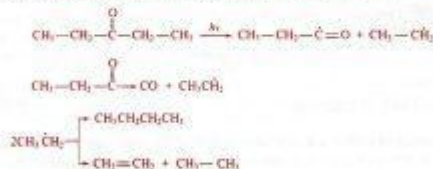
At temperature much above room temperature the acetyl radical breaks down to give another methyl radical and carbon monoxide.



The products obtained on completion of the reaction are ethane and carbon monoxide.



In case of photolysis of 2-pentanone ($\text{CH}_3\text{CH}_2-\overset{\text{O}}{\underset{\text{||}}{\text{C}}}-\text{CH}_2\text{CH}_3$) the $\text{CH}_3\dot{\text{C}}\text{H}_2$ radical forms, which can also undergo disproportionation in addition dimerization.



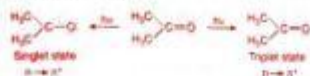
In photolysis, vapours of acetone undergo photodissociation reaction with 313 nm light with quantum yield (ϕ) about 1. In fact, the efficiency of a photochemical reaction is usually expressed in terms of quantum yield, ϕ which is defined as

$$\phi = \frac{\text{Number of molecules reacting or formed in unit time}}{\text{Number of quanta absorbed in unit time}}$$

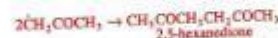
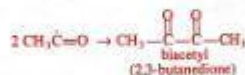
If each quantum of light absorbed leads to the formation of product molecule, the ϕ will be 1.0, but in practice it is usually less than 1 due to decay of same light energy by fluorescence, phosphorescence or radiationless processes.

As already stated, acetone absorbs light to give an excited state ($n \rightarrow \pi^*$ transition), which can be either a singlet or a triplet state. It has been shown that the above reaction

occurs efficiently through the triplet state. The carbon-carbon bond (generally the one α to the C=O group), being weaker as compared to carbon-oxygen double bond, breaks in the first two steps. It is not possible to draw an explicit structure for the excited state, however, it is sometimes represented as

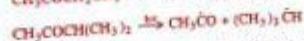
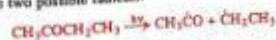


At room temperature, photolysis of acetone gives biacetyl (2,3-butanedione), ethanal (acetaldehyde), methane and 2,5-hexanedione as shown below:

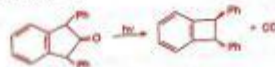


Photochemical reactions of ketones and also of aldehydes by fission of carbon-carbon bond adjacent to carbonyl group and elimination of carbon monoxide are termed as **Norrish type I** processes or cleavage (also see section 5.67).

In case of unsymmetrical ketones, splitting takes place in a way as to generate the more stable of the two possible radicals.



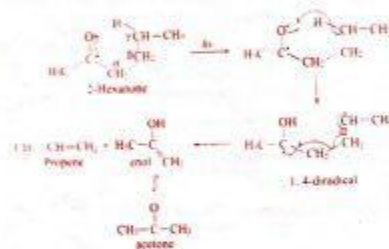
Photolytic decarbonylation of cyclic ketones produces cyclic hydrocarbons.



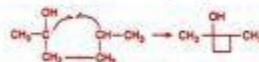
10.5.1.2 Photolysis to 2-hexanone

Ketone possessing a γ -hydrogen atom (as in the case of a 2-hexanone,

$\text{CH}_3-\overset{\alpha}{\text{C}}(\text{O})-\overset{\beta}{\text{CH}_2}-\overset{\gamma}{\text{CH}_2}-\text{CH}_2-\text{CH}_3$) undergoes an interesting photochemical reaction, the course of which is different than that described above. In this case, the excited state of 2-hexanone undergoes an intramolecular hydrogen transfer (from γ -carbon to the oxygen of the carbonyl group) with simultaneous fission of α - β carbon-carbon bond in the alkyl group. The products of this reaction is an alkene and a simpler ketone (in its enolic form). This process is known as **Norrish type II reaction** (see also section 5.67). This reaction proceeds by an initial γ -hydrogen abstraction by the oxygen atom yielding a 1,4-biradical, which subsequently gives an olefin and an enol.



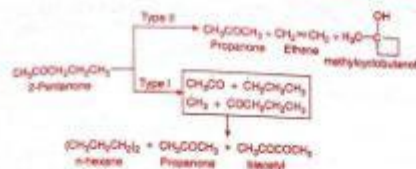
The 1,4-diradical can undergo ring closure to give cyclobutane derivative.



In the photolysis of 2-hexanone, Norrish type II cleavage is often accompanied by a Norrish type I process though to a lesser extent. Propanone, the product of photolysis of 2-hexanone can undergo Norrish type I reaction and finally a complex mixture of products consisting of propene, propanone, ethane and carbon monoxide are formed.

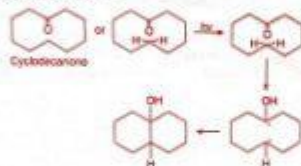


Similarly, irradiation of 2-pentanone yields the following products:



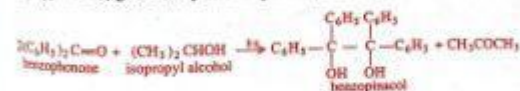
Problem: What product would be formed by ultraviolet irradiation of cyclohexanone?

Solution: The cyclic ketones with larger rings on irradiation undergo Norrish type II process to give the cyclic compound.

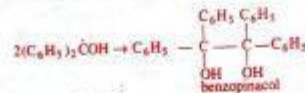
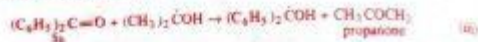
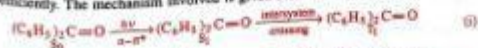


10.5.1.3 Photolysis of benzophenone (Diphenyl methanone)

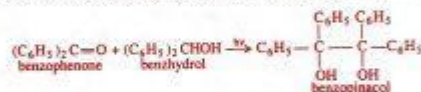
Photolysis of benzophenone (in sunlight) in presence of an alcoholic solvent (preferably isopropyl alcohol) gives benzopinacol in quantum yield unity.



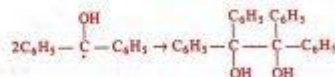
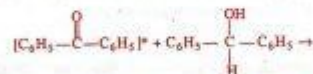
It is well known that benzophenone by reduction with zinc and acetic acid gives benzopinacol. The photolysis reaction of benzophenone is known as **photoreductive dimerization**. In the above reaction since the quantum yield is unity, it implies that each molecule of excited benzophenone gives rise to one molecule of benzopinacol. Also no fluorescence is observed, so a triplet excited state is most likely involved in the above reaction. It is believed that a $\pi \rightarrow \pi^*$ triplet excited state abstracts a hydrogen atom from isopropanol more efficiently. The mechanism involved is given below:



As seen, benzhydrol radicals are formed by the abstraction of hydrogen from isopropyl alcohol by a triplet excited benzophenone (equation ii) and also by abstraction of a hydrogen from isopropanol radical (2-hydroxy-2-propyl radical) by benzophenone in ground state (equation iii). The 2-hydroxy-2-propyl radical has a very short life time, so it transfers its hydroxylic hydrogen too rapidly (equation iii) and gets converted to propanone rather than undergoes dimerization to pinacol $[(\text{CH}_3)_2\text{C}(\text{OH})\text{C}(\text{OH})(\text{CH}_3)_2]$. The step (iii) is energetically favourable due to the greater possibility for delocalisation of the odd electron in benzhydrol radical than the 2-hydroxy-2-propyl radical. The coupling reaction of benzophenone to benzopinacol is more efficient when the hydrogen donor is benzhydrol, the reduction product of the carbonyl compound (benzophenone).



The mechanism of above reaction is similar to that for isopropyl alcohol as the reducing agent.



Calculations have shown that the singlet excited state of benzophenone undergoes intersystem crossing to triplet state very rapidly (equation i). So it is the triplet state that is involved in this reaction.

10.5.2 Photochemical reactions of olefins

In case of olefins, photochemical reactions involve two types of electronic absorption (i) $\sigma \rightarrow \pi^*$ excitation (requires more energy and is available only from light of wavelength lower than 150 nm and so it is difficult to achieve under usual experimental conditions) and (ii) $\pi \rightarrow \pi^*$ excitation (requires the absorption of light of about 180-210 nm for

nonconjugated olefins and above 220 nm for conjugated olefins). Most of the photochemical reactions of olefins involve $\pi \rightarrow \pi^*$ excitation. The initial excitation generally occurs with no change in multiplicity and so a first singlet excited state is obtained. Also, this transition ($\pi \rightarrow \pi^*$) is symmetry allowed. The singlet excited states of olefins have less tendency for intersystem crossing and are capable of initiating many photochemical reactions. However, the T_1 states of olefins are generated conveniently by intermolecular energy transfer from a triplet donor to an olefin molecule. The photochemistry of singlet excited state of an olefin differs from that of its triplet state.

16.5.2.1 Isomerization of olefins

On irradiation with UV light, olefins undergo isomerization. This can be effected by irradiation of the olefin as such or in presence a sensitizer and it may take place through a singlet or triplet excited state.

In simple olefins, *E*-isomers absorb energy more effectively and at a slightly different wavelength than the *Z*-isomer. Usually, an *E*-isomer is partially converted into its thermodynamically less stable *Z*-isomer. An example is the interconversion of fumaric and maleic acids.

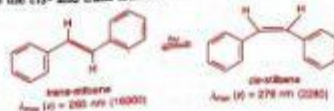


In presence of a sensitizer, many olefins are excited to a common triplet state which then decays at different rates to the *E* & *Z*-isomers. The ratio of the products formed depends on the substrate and sensitizer triplet energies as well as the nature of the alkene.

A most commonly studied is the photoisomerization of stilbene (discussed in detail below).

16.5.2.2 Photoisomerization of *cis* and *trans*-stilbenes

Olefins are known to exhibit geometrical isomerism. The photochemical *cis-trans* isomerization of stilbenes (1,2-diphenylethenes) provides the simplest case of light-induced geometrical isomerization. It is found that irradiation of *trans* stilbene in hexane in UV light results in the formation of the *cis* isomer. After some time the *cis-trans* ratio in UV light results in the formation of the *cis* isomer. After some time the *cis-trans* ratio becomes constant and does not change if irradiation is continued. This condition is called a **photostationary state** and is also reached on irradiation of the *cis*-isomer. The equilibrium favours the formation of thermodynamically less stable *cis* form. The *trans*-stilbene gives the *cis*- and *trans* isomers in relative amounts of 10:1.

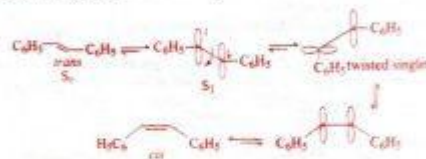


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The *trans* isomer is more stable than the *cis*, since *cis* is distorted from planarity due to the non-bonded interaction between the ortho hydrogens in the benzene ring. This explains why thermal equilibrium favours the conversion of *cis* stilbene to the *trans* isomer.

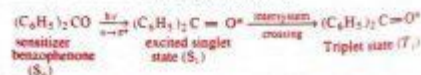
The photoequilibrium favours the formation of the *cis*-isomer (contrary to the thermal equilibrium). This can be explained as follows:

Both isomers (*cis* and *trans*) of stilbene absorb light, but the *trans* isomer gets excited a much more frequently (since it has a higher extinction coefficient and absorbs at a higher wave length) than the *cis* isomer. The rotation about C—C bond occurs because the π -bond, which normally prevents it, is lost in excited state. Rotation about carbon-carbon bond relieves the unfavourable interaction between the singly filled orbitals of carbon atoms and gives a twisted or non-planar state as shown below:

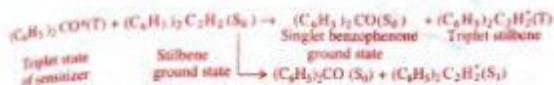


However, when the molecules returns to the ground state it can give both *cis*- and *trans*-isomers.

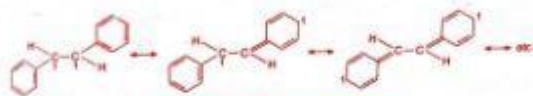
The above conversion (i.e., conversion of *trans* into *cis* stilbene) can be conveniently achieved by photoreaction in presence of a suitable photosensitizer. Such a reaction is called a **sensitized reaction** and its pathways is different from the unsensitized reaction. This process does not contravene the laws of thermodynamics, since the input of radiant energy permits equilibrium point to be shifted from what it would be normally. Photoisomerisation in presence of a sensitizer occurs by the following sequence. The sensitizer, usually a ketone such as benzophenone, acetophenone or β -acetosaphenone, is raised by an $n \rightarrow \pi^*$ transition from the singlet ground state (S_0) to an excited state (S_1) by absorption of light. Intercrossing then occurs to give triplet state (T_1) of the sensitizer as shown below in the case of benzophenone.



The next step is energy transfer from the triplet state of the sensitizer to the alkene (stilbene). This means that triplet (T_1) benzophenone plus singlet (S_0) stilbene produces singlet (S_0) benzophenone and triplet (T_1) stilbene.



In the above process, the triplet state of benzophenone (sensitizer) acts as a donor and *trans* stilbene in its ground state (S_0) as an acceptor of the excitation energy. In this process the total spins are conserved i.e., a triplet and singlet give rise to a new triplet and new singlet species. The triplet state of *trans* stilbene is stabilised by resonance.

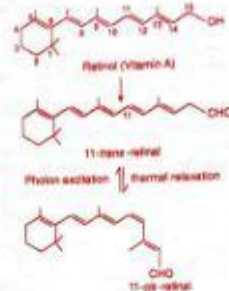
Resonance stabilisation of triplet *trans* stilbene

As noted from the above resonance structures of triplet *trans* stilbene, it is expected that there will not be much double-bond character between the ethylenic carbons and so lesser energy would be required to effect a rotation about the central C—C bond. So the *cis* and *trans* triplet states of stilbenes should be rapidly interconverted.

(Interconversion of triplet states of *cis* and *trans* stilbenes)

In fact, the *trans*-triplet state is expected to be more stable because like *trans* stilbene itself it will have less steric hindrance between the phenyl groups. It is expected that *trans*-triplet stilbene can be converted by phosphorescence to the ground electronic state or to a vibrationally excited form of the *trans*-ground singlet state by intersystem crossing. This excited state will have more than enough energy to have rapid rotation around the C—C central bond and so can lead to both the *cis* and *trans* isomers. If we start with either *cis*- or *trans*-stilbene a mixture of both isomers is formed.

The photo induced *trans*-to-*cis* isomerism exploited in the visual system where the conversion of 11-*trans*-retinal to 11-*cis*-retinal is the main photon detector. With time, the 11-*cis*-retinal thermally relaxes back to the 11-*trans*-retinal configuration. Retinal is derived from retinol, also known as Vitamin A.

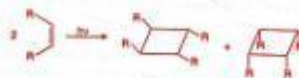


10.5.3 Photochemical cycloaddition reactions

We know that 1,2- and 1,4-cycloaddition reaction can take place thermally. The [4+2] cycloaddition reaction have been discussed earlier (see Diels-Alder reaction section 5.29). 1,2- and 1,4-cycloadditions also occur photochemically with or without sensitizers. In many cases highly unusual products are obtained.

The photodimerization process occurs with alkenes, conjugated alkenes and aromatic compounds. The photodimerization reaction of an excited state of one molecule of a reactant with another molecule of the same reactant in its ground state gives the 1:1 adduct. The excited state of one molecule of a reactant may be a singlet or triplet depending on the structure of the reactant and the conditions of excitation.

For examples, non-conjugated alkenes reacts through the excited singlet S_1 and addition is concerted. The photochemical [2 + 2] π cycloaddition is **symmetry-allowed** and discussed in chapter 9, pericyclic reactions.



However when photodimerization is accomplished with a photosensitizer it occurs through the triplet state. For example, photodimerization of alkenes in the presence of a sensitizer such as acetophenone occurs through the excited triplet alkene molecule Fig. 10.10. The acetophenone (sensitizer) absorbs at λ_{max} 270 nm and excited to S_1 state, which undergoes intersystem crossing to T_1 . Now interaction of T_1 excited state of acetophenone with the alkene converts alkene molecule into a triplet state.

The alkene molecule in its triplet state reacts with second molecule of alkene in its

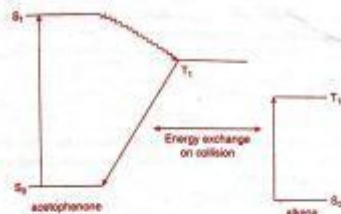
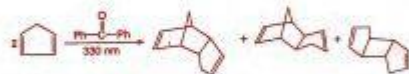


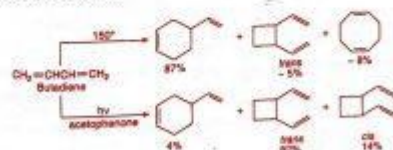
Fig. 10.10

ground state to give ring in two stages (after a spin-inversion). Thus, this cycloaddition is not concerted.

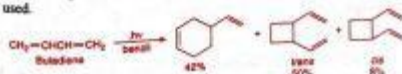
Similarly, photodimerization of conjugated alkenes occurs through the excited triplet sensitization. For example, photodimerization of cyclopentadiene in the presence of benzophenone (sensitizer) gives mixture of products.



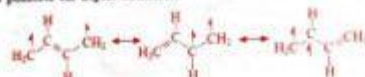
Butadiene provides an excellent example of the difference between thermal and photochemical cycloadditions.



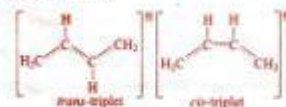
It is found that the photochemical cycloaddition products of butadiene depend on the sensitizer used.



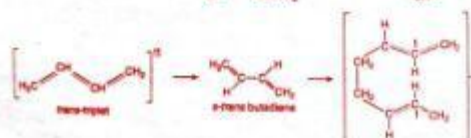
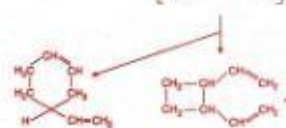
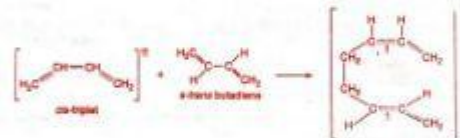
A possible explanation of this behaviour can be seen from the three resonance structures that may be possible for triplet butadiene.



As seen, the 2-3-double bond has one-third double bond character. So it is unlikely that there will be free rotation around the 2,3 bond. The result is that separate *cis* and *trans* triplet butadienes are possible.

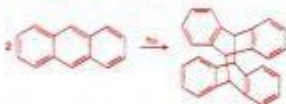
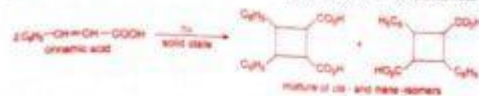


The *cis*-triplet can react with butadiene in the *s-trans* configuration to give either 1,2 or 1,4-cycloaddition. The triplet-*trans* can give only 1,2-cycloaddition.

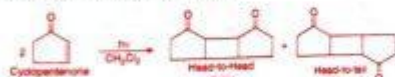


The difference between various sensitizers in influencing the ratios of the products depend on the ease with which they transfer energy to *s-cis* and *s-trans*-butadiene to give

either the *cis*- or the *trans*-triplet state. Low energy sensitizers tend to give the *cis*-triplet, while the high energy sensitizers favor the formation of the *trans* triplet. Following are given examples of a number of photochemical dimerization reactions.

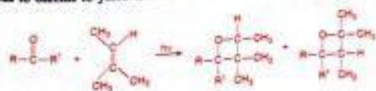


Photodimerization of cyclopentenone on irradiation with light in dichloromethane solution gives a mixture of 'head to head' and 'head to tail' dimers. These may be formed via an excimer (excited dimer) derived from ($\pi \rightarrow \pi^*$) from the cyclopentenone and a molecule of ground state cyclopentenone.

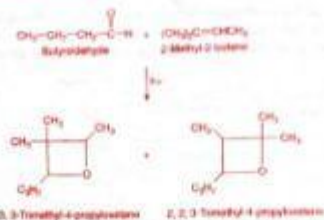


Photocycloaddition may occur between an alkene or alkyne with carbonyl or aromatic compounds.

A very interesting photochemical cycloaddition reaction is the addition of carbonyl compounds to olefins to yield oxetanes (oxa-cyclobutanes).

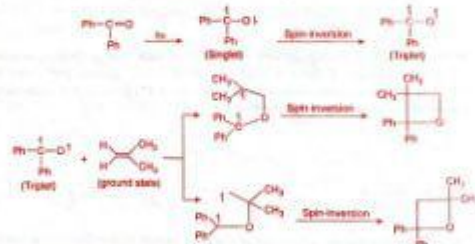


This reaction is known as **Paterno-Büchi reactions**. For example, photocycloaddition of butyraldehyde to 2-methyl-2-butene yields mixture of 2,3,3-trimethyl-4-propyloxetane and 2,2,3-trimethyl-4-propyloxetane.

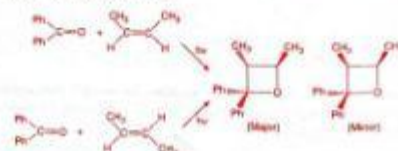


The Paterno-Büchi reaction normally occurs by the cycloaddition of the triplet state of the carbonyl compound with the ground state of an alkene.

The oxetane ring is formed in two steps. The carbonyl compound (triplet state) adds through its oxygen atom to alkene to give the more stable diradicals. In next step the spin-inversion occurs and then bond is formed to give the oxetane.

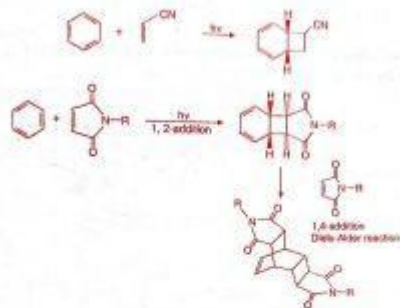


The photocycloaddition of benzophenone with *cis*- and *trans*-2-butene gives the same mixture of *cis*- and *trans*-oxetanes. This shows that the reaction is not stereospecific. The lack of stereochemical discrimination clearly shows that the reaction is not concerted and the ring is formed in two stages.

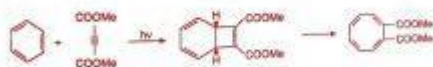


The formation of mixture in both the cases (i.e., reaction of benzophenone with *cis*- and *trans*-2-butene) indicates that the time lag before the final spin-inversion is more than enough for rotation to occur about single bonds.

Examples of photochemical addition of alkene and alkynes with benzene are given below:



1,2-Cycloaddition of alkyne with benzene gives strained cyclobutene, which undergoes a spontaneous electrocyclic ring-opening reaction.



The cycloaddition could also proceed in an intramolecular fashion. For example, irradiation of *trans*, *trans*-1, 4-dimethyl-1,3-butadiene undergoes ring closure to give *cis*-3,4-dimethyl cyclobutene.

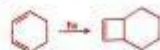


Similarly, *trans*, *trans*-1, 6-dimethyl-2,4, 6-hexatriene cyclizes to give *trans*-5,6-dimethylcyclohexadiene.

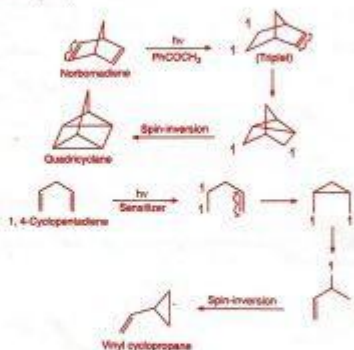


Both the reactions are concerted and are electrocyclic type as discussed in chapter 9, pericyclic reactions.

The intramolecular photocyclization reaction of 1,3-cyclooctadiene gives bicyclo [4.2.0] oct-7-ene.



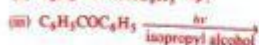
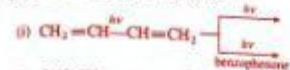
However, when diene is not conjugated then a triplet sensitization is required as shown in the examples given below:



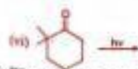
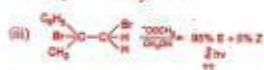
Problems

1. What are photochemical reactions? How do they differ from thermal reactions?
2. Explain the following terms:
 - (i) Fluorescence
 - (ii) Phosphorescence
 - (iii) Photosensitization
 - (iv) Internal conversion
 - (v) Intersystem crossing
3. Write notes on:
 - (i) Norrish type I reaction
 - (ii) Norrish type II reaction
 - (iii) Paterno-Büchi reaction
4. What do you understand by quantum yield?

5. Discuss the chemistry of excited molecules.
6. Indicate the products that could be formed in the following photochemical reactions and give mechanism of each reaction:



7. Complete the following photochemical reaction:



8. What products can be obtained by photolysis of 2-hexanone? Give mechanisms.
9. Discuss photolysis of benzophenone in detail.
10. Write a note as photoisomerization of *cis* and *trans* stilbenes.

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