UNIT-I

LESSON: 1 – AROMATICITY

CONTENTS

1.0. AIMS AND OBJECTIVES

The aim is to motivate and enable a comprehensive knowledge on configurational and conformational analysis to the students.

On successful completion of this lesson the student should have:

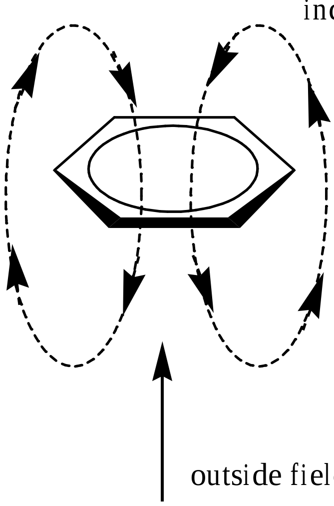
* Understand the aromaticity, anti-aromaticity and non-aromaticity in organic compounds.

1.1. INTRODUCTION

Aromaticity can now be defined as the ability to sustain an induced ring current. A compound with this ability is called diatropic.There are several methods of determining whether a compound can sustain a ring current, but the most important one is based on NMR chemical shifts. In order to understand this, it is necessary to remember that, as a general rule, the value of the chemical shift of a proton in NMR spectrum depends on the electron density of its bond, the greater the density of the electron cloud surrounding or partially surrounding a proton, the more up field is its chemical shift.

This rule has several exceptions; one is for proton in the vicinity of an aromatic ring. When an external magnetic field is impulsed upon an aromatic ring the closed loop of aromatic electrons circulates in a diamagnetic ring current, which sends out a field of its own.

As can be seen in the diagram, this induced field curves around and in the area of the proton is parallel to the external field, so that the field felt by the aromatic proton is greater than it would have been in the absence of the diamagnetic ring current. The protons are moved downfield compared to where they would be if electron density were the only factor. The ordinary olefinic hydrogens are found at 5 to 6δ, while the hydrogens of benzene rings are located at about 7 to 8δ.



If the proton attached to the ring are shifted downfield from the normal olefinic region, we can conclude that the molecule is diatropic and hence aromatic. In addition, if the compound is diatropic, these will be shifted up field. This method cannot be applied to compounds that have no protons in either category e.g. the dianion of squaric acid.

1.2. CONDITIONS FOR AROMATICITY

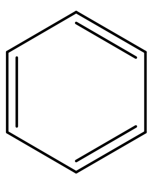
For a compound to be aromatic one looks for diamagnetic ring current, equal or approximately equal bond distances, planarity, chemical stability and the ability to undergo aromatic substitution.

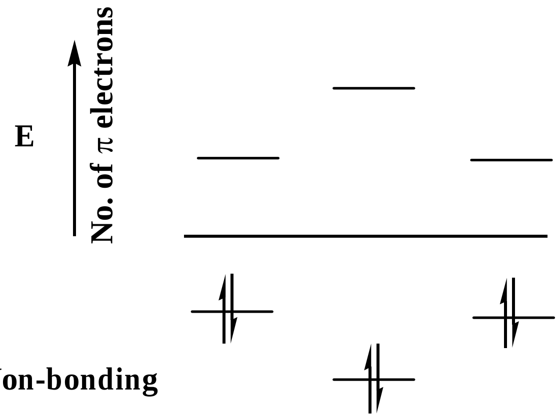
1. The structure must be cyclic.
2. The ring must be planar.
3. Each of the rings must be SP^2 hybridized (or occasionally SP hybridized) and have an unhybridized p-orbital.
4. The total number of π electrons in the molecule or ion should be $(4n+2)$ where $n = 0,1,2,3,......$
5. The unhybridized p-orbital must overlap to give a continuous ring of parallel orbital (the condition of planarity is for effective overlap).
6. This delocalization of π electrons over the ring result in the lowering of the electronic energy

1.3. HUCKEL (4n+2) RULE FOR AROMATICITY

Huckel carried out molecular orbital calculation on monocyclic systems C_nH_n containing n π electrons and each carbon atom providing one π electrons and as a result connected aromatic stability (high delocalization energy or high resonance energy) with the presence of $(4n+2)$ π electrons in a closed shell.

To be aromatic, a molecule must have 2(n=0), 6(n=1), 10(n=2)…….. π electrons. In this description of aromaticity, no mention is made of the number of carbon atom in the ring; the essential requirement is the presence of $(4n+2)$ π electrons. Another requirement, for Aromaticity is planarity of the ring. If the ring is not planar, overlap of the p-orbital is diminished or absent. Thus if a molecule is a monocyclic planar system and contains (4n+2) π electrons that molecule will exhibit aromatic character (i.e.) will have unusual stability. For benzene ring or shell of six π electrons (i.e.) bonding molecular orbital are doubly filled.



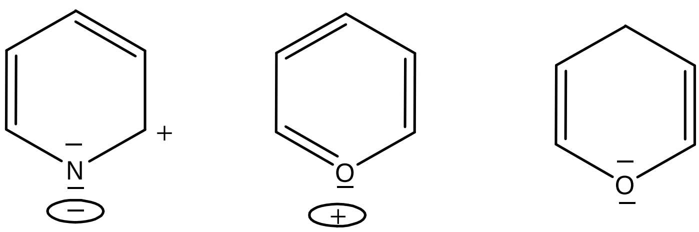


4n + 2 **Non-bonding**

1.4. AROMATICITY OF BENZENOID AND HETEROCYCLIC COMPOUNDS
1.4.1. BENZENOID COMPOUNDS
1.4.1.1. Six-membered rings

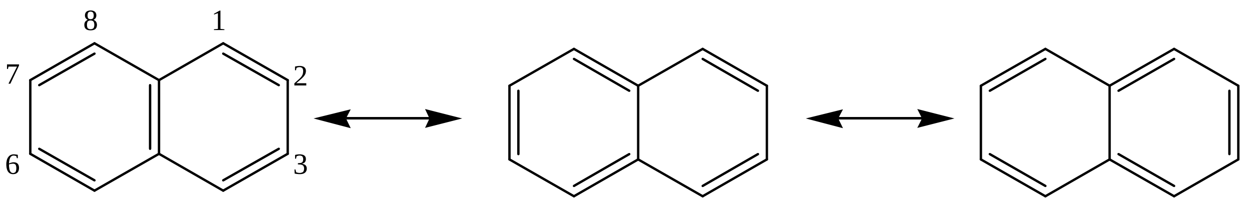
Not only is the benzene ring aromatic but so many heterocyclic analogs in which one or more hetero atoms replace carbon in the ring. When nitrogen is the hetero atom, little difference is made in the sextet and unshared pair of the nitrogen does not participate in the Aromaticity or pyridinium ions are still aromatic.

However for nitrogen heterocycles there are more significant canonical forms than for benzene. (Eg: 1)



(1) (2) (3)

Where oxygen or sulphur is the hetero atom, it must be present in its ionic form (2) in order to possess the valence of (3) that participation in such a system demands. Thus, pyran (3) is not aromatic but the pyridinium ion is. (2)In systems of fused six-membered aromatic rings, the principal canonical forms are usually not all equivalent. (4) has a central double bond and thus different from the other two canonical forms of naphthalene, which are equivalent to each other.



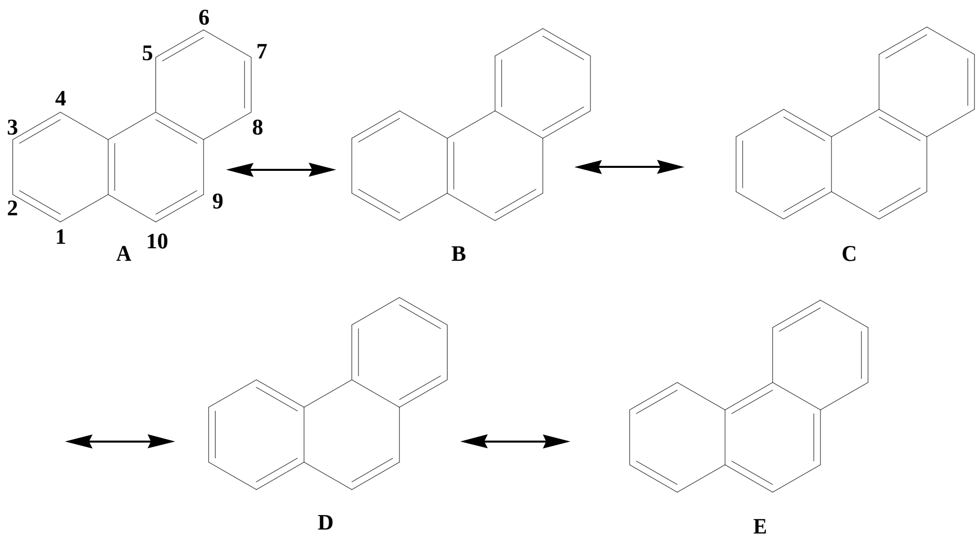
Naphthalene

(4)

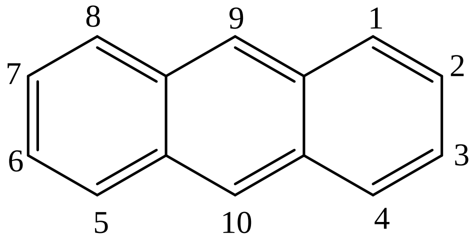
If we assume that three forms contribute equally, the 1, 2 bonds have more double bond character than 2, 3 bonds. Molecular orbital calculations shows bond order of 1.724 and 1.603 respectively (compare benzene 1.667). in agreement with these predictions the 1,2 and 2,3 bond distances are 1.36 and 1.415Å respectively and ozone preferentially attacks the 1,2 bond. This non equivalency of bonds, called partial bond fixation is found in nearly all fused aromatic systems.

1.4.1.2. Phenanthrene and anthracene

In phenanthrene, where the 9,10 bond is a single bond in only one of five forms, bond fixation becomes extreme and this bond is readily attacked by many reagents.



The resonance energies of fused systems increase as the number of principal canonical forms increases, thus for benzene, naphthalene, anthracene and phenanthracene, for which we can draw, respectively. Two, three, four and five principal canonical forms, the resonance energies are respectively 36, 61, 84 and 92 $KCal/Mol$,calculated from heat of combustion data.

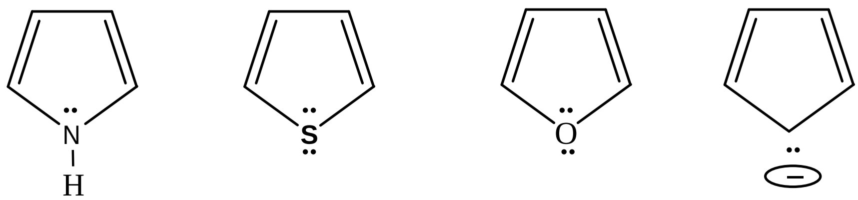


Anthracene

1.4.1.3. Heterocyclic compounds

Heterocyclic compounds can also be aromatic since for the application of Huckel's rule what one needs is a ring of atoms, all with unhybridized 'p' orbital in a planar arrangement in order that the 'p' orbital overlaps in a continuous ring. Thus the heterocyclic compounds are all aromatic.

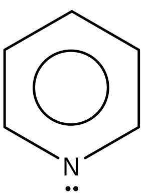
(1) Pyrrole, furan and thiophene in fact represent 1-hetero 2, 4-cyclopentadiene and a butadiene unit bridged by a hetero atom bearing lone pairs. In electronic structure these three compounds are similar to cyclopentadienyl anion.



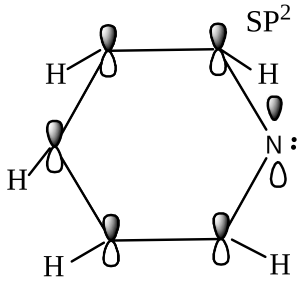
Pyrrole Thiophene Furan cyclopentadienyl anion(6πelectrons)

Pyridine

Both benzene and pyridine have a similar Kekule structure. Pyridine with resonance energy of $27 KCal (113 KJ)$ per mole shows typical characters of aromatic compound. The nitrogen atom in pyridine is SP^2 hybridized nitrogen donates one electron to the π system and this along with one each from the five carbon atoms give pyridine a sextet of π electrons similar



Pyridine



Pyridine

to that in benzene. The non-bonding electrons of nitrogen are in an SP^2 orbital which lies in the plane of the ring and these electrons do not interact with the π system of the ring.

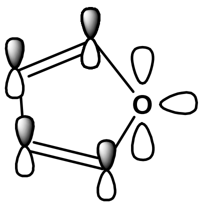
The unshared pair of non-bonding electrons confers on pyridine the properties of a weak base. Thus pyridine protonates to yield the pyridinium ion which retains its aromatic character since the process does not disturb the electrons of the aromatic sextet.

Pyrrole

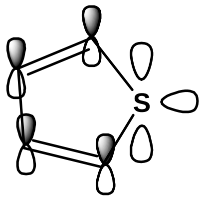
In pyrrole only four π electrons are contributed by the carbon atoms of the ring. To make an aromatic sextet the SP^2 hybridized nitrogen then contributes two electrons. Pyrrole is far less basic than pyridine because these apparently unshared electrons are in the aromatic π cloud. These are not readily available for bonding with proton (protonation).

Furan and thiophene

Both furan and thiophene have two pairs of electrons on the hetero atoms and therefore, combine the structural features of pyrrole and pyridine. One pair of electrons is in the six-electron π system and other lies in the plane of the ring.



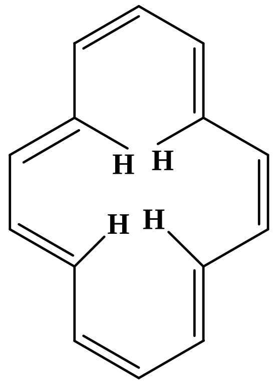
Furan



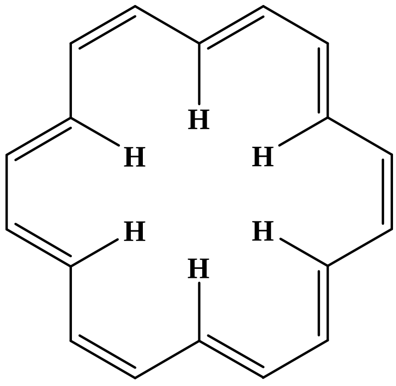
Thiophene

1.4.2. NON-BENZENOID AROMATIC COMPOUNDS
1.4.2.1. Annulenes

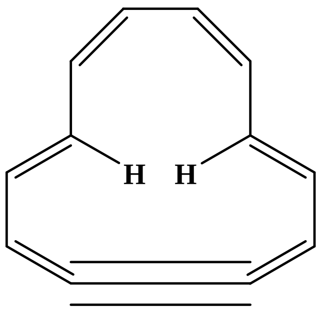
Conjugated monocyclic polyenes, C_nH_n in which $n \geq 10$ are usually called annulenes, and were prepared by sondheimer et al (1962) to test the Huckel's rule. The annulenes prepared have n= 12, 14, 16, 18, 20, 24, 30. Out of these only [14], [18], [30] annulenes are $(4n+2)$ π electrons molecules, whereas the rest are 4n molecules, some examples are



[14] annulene



[18] annulene

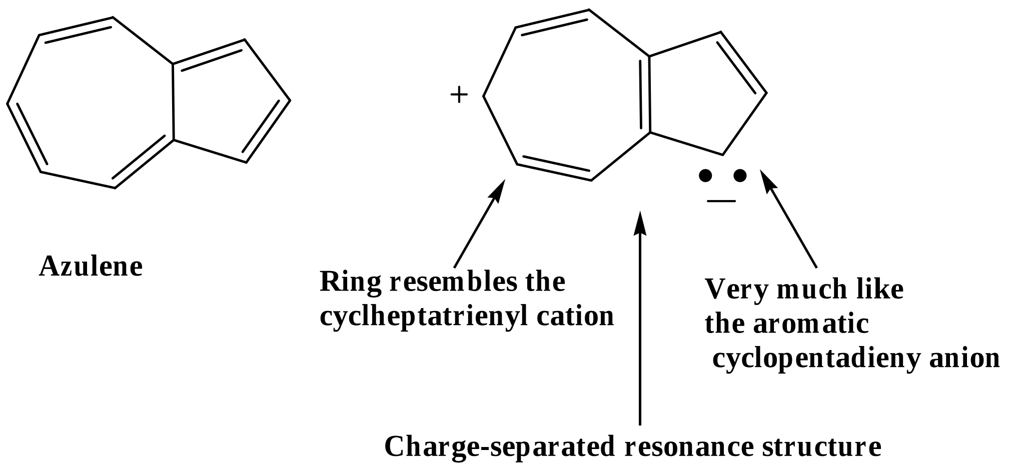


dehydro [14] annulene

1.4.2.2. Azulenes

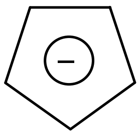
Azulene is one of the few completely conjugated non-benzenoid hydrocarbons that appear to have appreciable aromatic stabilization. The parent hydrocarbon and many of its derivatives have been well characterized and are stable compounds. The structure of azulene itself has been determined by both X-ray and electron-diffraction measurements. The peripheral bond lengths are in the aromatic range and show no regular alteration. The bond shared by the two rings is significantly longer, indicating dominant single-bond character.

Azulene has resonance energy of 49 kcal/mol. It has a substantial dipole moment (1.0 D) while the dipole moment of the isomeric compound naphthalene is 0. That presence of dipole moment in azulene suggests that charge separation exists in the molecule and that each ring approximates to six π-electron system. Azulene may be regarded as a combination of aromatic cyclopentadienyl anion and aromatic cycloheptatrienyl cation. Thus in valence bond terms, the ionic structure of azulene (a non-benzenoid aromatic compound) is an important contributor to the resonance bond.



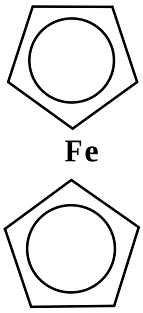
1.4.2.3. Ferrocene

Ferrocene is an aromatic compound (non-benzenoid) which is highly stable and undergoes a number of electrophilic aromatic substitutions. The carbon-carbon bond distances are also 1.40 Å and carbon-iron bond distances are all 2.04 Å. Due to these structural features the compounds like Ferrocene they are called "Sandwich" compounds. The carbon iron bonding in Ferrocene may be looked upon as a result from overlap between the inner lobes of the '*p*' orbital of the cyclopentadienyl anions and 3d orbital of the iron atoms. A noteworthy feature of many organic derivatives of transition metals is that the organic group is bonded to the metal through the π system rather than by a 'σ'bond as in (benzene/tricarbonyl chromium).



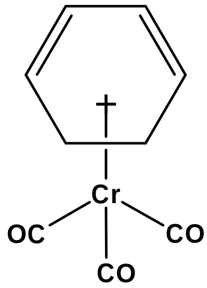
+ Fe^{+2}

Cyclopentadienyl anion(6πelectrons) aromatic



Dicyclopentadienyl iron (ferrocene)

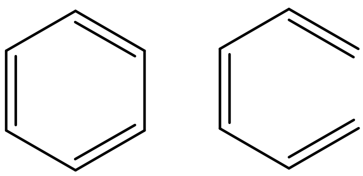
$[(C_5H_5)^-]_2Fe^{+2}$



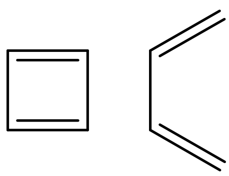
(Benzene) tricarbonyl chromium

1.5. AROMATIC, ANTIAROMATIC AND NON-AROMATIC COMPOUNDS

Cyclic conjugated polyenes can be aromatic (Eg: benzene) provided they contain $(4n+2)$ electrons (n=0, 1, 3…). Aromatic structures are more stable when compared with their open chain counter parts. In contrast, a conjugated cyclic system with $4n\pi$ electrons is called anti aromatic since in it π electron delocalization results in increase in energy (destabilization). Cyclobutadiene is thus an antiaromatic compound. Since the delocalization of the π electrons results in an increase in the electronic energy. Cyclobutadiene is less stable than its open chain counterpart (1, 3, butadiene).

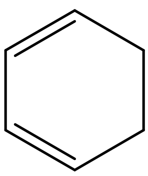


Aromatic

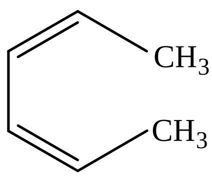


Anti Aromatic

A cyclic compound in which continuous overlapping ring of p- orbital is disrupted sufficiently cannot be aromatic or anti aromatic (both require overlap of parallel p-orbital. It is termed non-aromatic or aliphatic.



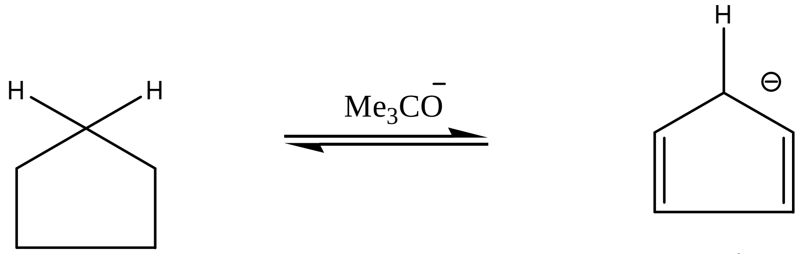
← **Similar Stabilities** →



Non Aromatic (1,3-cyclohexadiene)

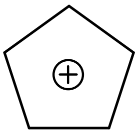
(*cis*-C-2,4-hexadiene)

1.5.1. Cyclopentadiene

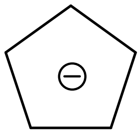


Aromatic anion

Cyclopentadiene is not aromatic, 5π electrons (n=1) (4n+1) molecules do not obey Huckel's rule. Number of π electrons 4 (n=1). 4n molecule does not satisfy Huckel's rule.



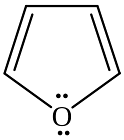
Cyclopentadienyl cation



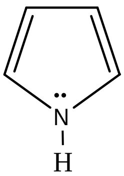
Cyclopentadienyl anion

Number of π electrons 6 (n=1). (4n+2) molecule. Satisfy Huckel's rule. It is aromatic.

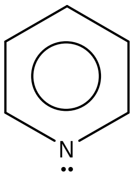
1.5.2. Furan



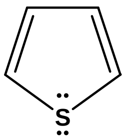
Furan



Pyrrole



Pyridine

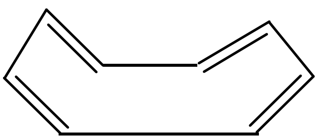


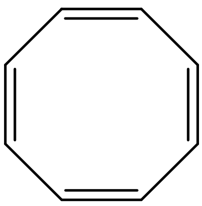
Thiophene

In this heterocyclic compound can also be aromatic. It obeys Huckel's rule.Unhybridized *p*-orbital overlap in a continuous ring. Furan-6 electrons, n = 2, (4n+2) molecule; Pyrrole-6 electrons, n = 2, (4n+2) molecule and Pyridine and thiophene-6 electrons, n =2, (4n+2) molecule.

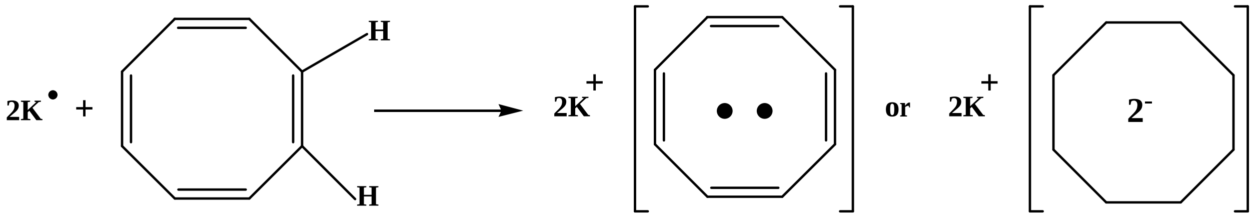
1.5.3. Cyclooctatetraene

8 electrons (n = 2) (4n) molecules. It is a non-aromatic. Do not obey the Huckel's rule. Molecules do not possess a closed shell planar configuration in the ground state. This is the reason for the instability or reactivity of these compounds. Monocyclic (4n) π electrons molecules are less stable than acyclic. This decreased stability of 4n molecules has been attributed to anti-aromaticity.



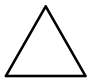


The metal acts as an electronic source, supplying two electrons to the cyclooctatetraene. The resulting dianion has ten electrons (a Huckel's number) and by planar configuration becomes aromatic and therefore, more stable.



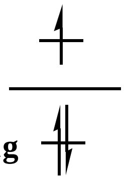
1.5.4. Cyclopropenium salts

1.5.4.1. Cyclopropene

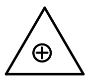


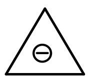
Cyclopropene

Non-bonding

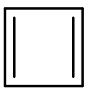


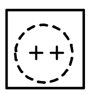
3 electrons, n = 0; (4n + 3) molecule. Do not obey the Huckel's rule.

1.5.4.2. Cyclopropenyl Cation  It becomes a closed-shell (4n+2) π electron molecule (n = 0). It represented as a resonance hybrid.

1.5.4.3. Cyclopropenyl anion  (4n) molecule (n = 1).

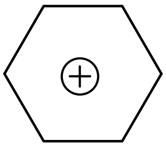
1.5.5. Cyclobutenium salts

 (4n) π electron molecule, and is in the triplet state. This is the ground state of Cyclobutadiene and accounts for its high instability. Other hand, loss of 2 π electrons in the separate non-bonding molecular orbitals produces the closed shell (4n+2) π electron molecule (n=0) (i.e.) cyclobutenyl di-cation.



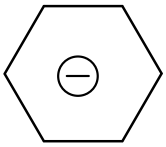
1.5.6. Tropylium salts

By loss of the single π electron in the anti bonding molecular orbital gives the Tropylium Cation.



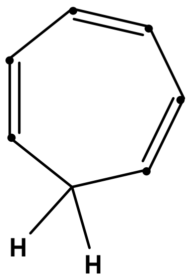
6 π electrons (4n+2) (n=1) obeys the Huckel's rule.

Tropylium anion



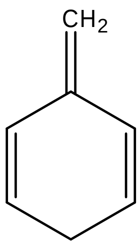
8 π electrons (4n) n = 2. It does not obey the Huckel's rule.

1.5.7. Aromatic or Non aromatic



Cycloheptatriene

Non aromatic, 6 π electrons (4n) – n = 2. It does not obey the Huckel's rule. Here one of the C is SP^3 hybridized there by preventing a completed cyclic overlapping π system.



3-Methylene-1,4 Cyclohexadiene
Non aromatic 6 electrons

Here the methylene C is not part of the ring which has one SP^3 hybridized C.

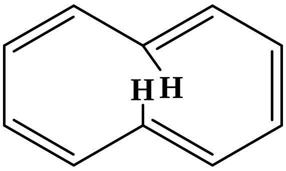
1.6. LET US SUM UP

In this lesson, we:

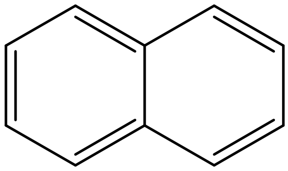
* Explained the conditions for aromaticity
* Pointed out the Huckel (4n+2) rule for aromaticity
* Explained the aromaticity of benzenoid and heterocyclic compounds
* Discussed the non-benzenoid aromatic compounds
* Explained the aromatic, antiaromatic and non-aromatic compounds

1.7. CHECK YOUR PROGRESS

1. Comment on the aromaticity of the compound (1) and (2).

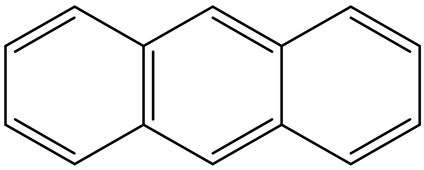


(1)



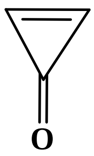
(2)

2. On hydrogenation anthracene liberates 116.2Kcal/mol. What is the resonance energy of anthracene?

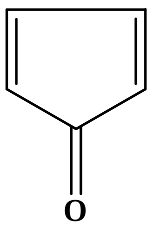


1.8. POINT FOR DISCUSSION

1. Why compared to [14] annulenes, [18] annulenes is more stable?
2. Why cyclopropenone is a stable compound while Cyclopentadiene has not been prepared



Cyclopropenone



Cyclopentadienone

1.9. REFERENCES

1. Jerry march, Advanced Organic Chemistry, Fourth edition, Wiley India edition.

2. P.S. Kalsi, Organic reactions and their mechanisms, Second edition, New age international publishers.

LESSON: 2 – KINETIC AND NON-KINETIC METHODS OF STUDY OF REACTION MECHANISMS

CONTENTS

2.0. AIMS AND OBJECTIVES

The aim is to motivate and enable a comprehensive knowledge on kinetic and non-kinetic methods of study of reaction mechanisms to the students.

On successful completion of this lesson the student should have:

* Understood the kinetic and non-kinetic methods of study of reaction mechanisms

2.1. INTRODUCTION

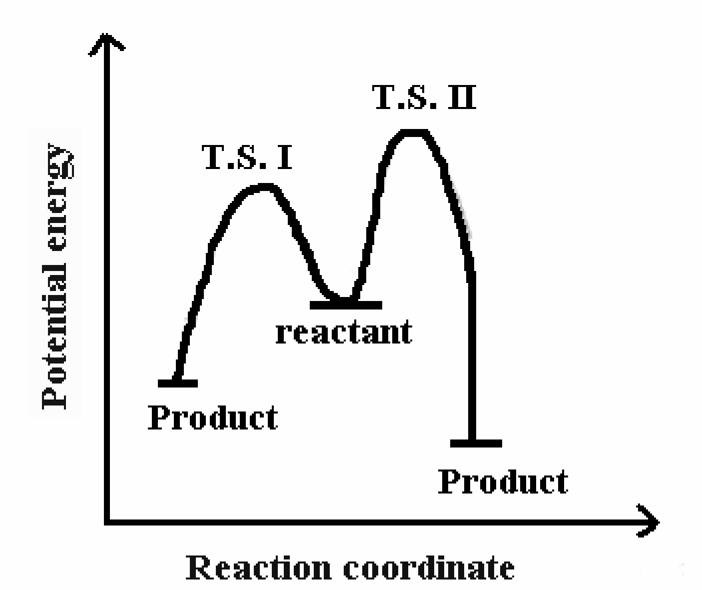
Under reversible reaction conditions the ratio of possible products is determined by the relative stability of each product, measured by its standard free energy (ΔG^0). The composition of the equilibrium mixture does not depend on how fast ($\Delta G^\ddagger$) each product is formed in the reaction. This is termed thermodynamic (or equilibrium) control. On the other hand when the quantity of each product is formed and is not a function of the relative stability (ΔG^0) of each product, one calls it kinetic control reaction.

2.2. KINETIC AND THERMODYNAMICS CONTROL OF A REACTION

A given set of the reaction at the given condition, some times two products may formed i.e., two isomeric products. As a mixture in such a reaction one product is called kinetically controlled and the other one is called thermodynamically controlled product.

$$A \longrightarrow B + C$$

B and C are two isomeric products.



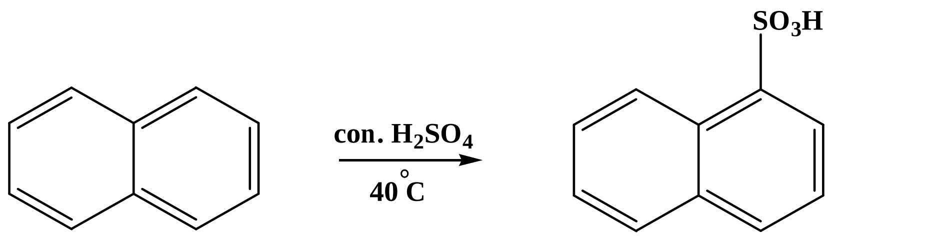
The one which has high activation energy is more stable product and this product is thermodynamically controlled product. The one has low activation energy is less stable product this product is kinetically controlled products.

(i). Both the steps are irreversible then the product will contain more C.

(ii). If both the steps are reversible and if the reaction is stopped before the equilibrium attain then also we get more kinetic controlled product C.

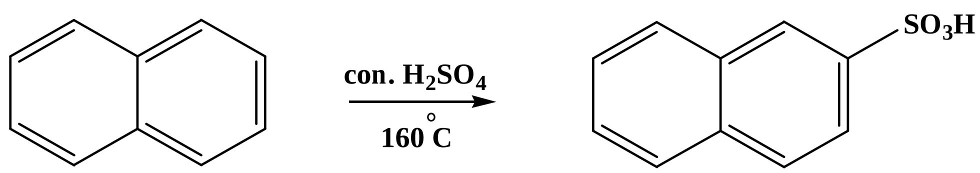
(iii). If both the steps are reversible and the equilibrium is reached, then we get the B which is thermodynamic controlled product is formed.

Example:



Naphthalene-1-sulphonicacid

Kinetically controlled product



Naphthalene-2-sulphonicacid

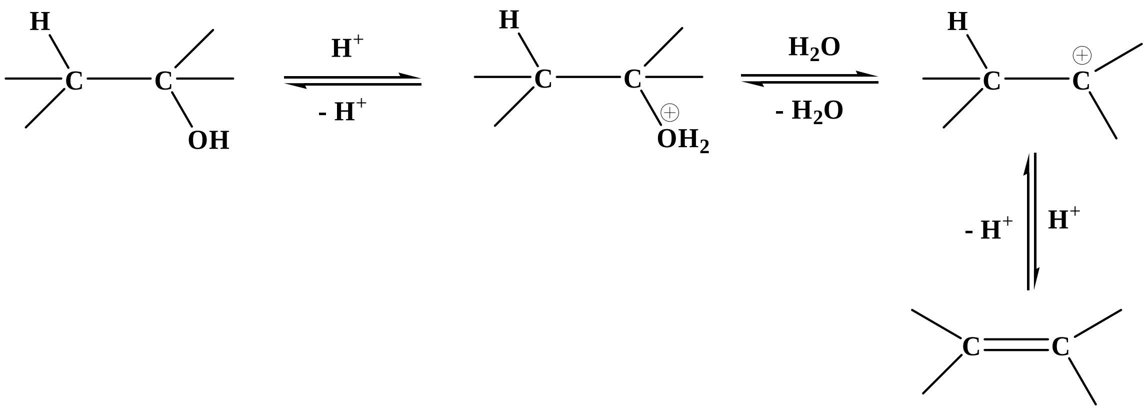
Thermodynamically controlled product

2.3. MICROSCOPIC REVERSIBILITY

In a reversible reaction the forward and reverse reactions must follow the same mechanism. This phenomenon is called the principle of microscopic reversibility.

Example:

In the dehydration of an alcohol, an olefin is format via. a carbonium ion intermediate, as a consequence of the principle of the microscopic reversibility, the reverse reaction i.e., the acid catalyzed hydration of olefin to alcohol, must involve the same carbonium ion.

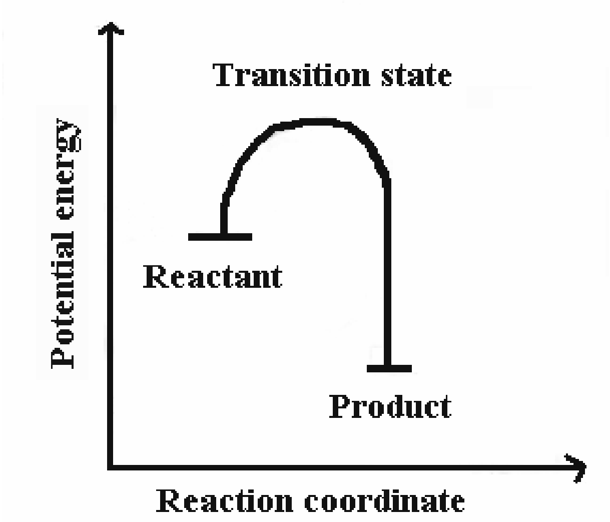


2.4. HAMMOND'S POSTULATE

For any single reaction step, the geometry of the transition state resembles to the side to which it is closer in energy.

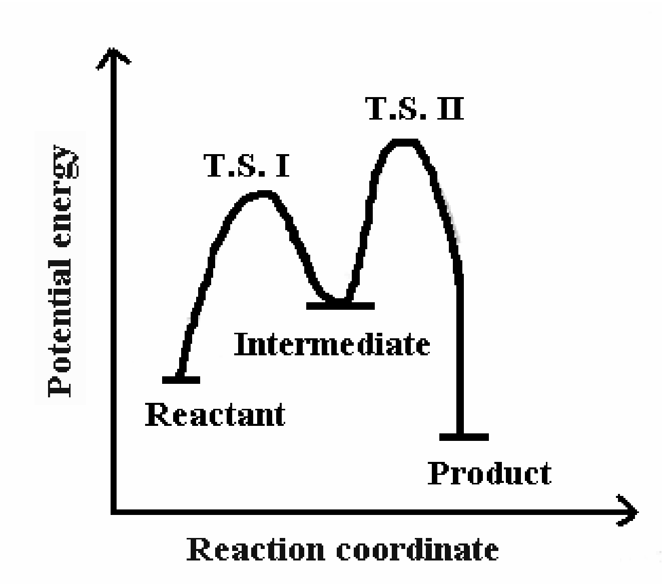
Example (i):

In the exothermic reaction the energy of transition state is closer to reactant. So the geometry of transition state resembles as reactant.



Example (ii):

In S_N1 reaction, there will be two transition state, energy of these transition state are closer to intermediate so the geometry of transition state resembles as intermediate.



Methods that are used to determine to Reaction Mechanism:

(i) Kinetic Methods
(ii) Non-Kinetic Methods

2.5. K INETIC AND NON-KINETIC METHODS OF STUDY OF REACTION MECHANISMS

2.5.1. KINETIC METHODS

2.5.1.1. PRIMARY AND SECONDARY KINETIC ISOTOPIC EFFECT

This will observed if the C-H bond cleavage takes place in a slow step mechanism. Isotopic substitution will give acceptable charges, i.e., the rate of the reaction.

$$CH_3-\overset{O}{\overset{\parallel}{C}}-CH_3 \quad + \quad Br_2 \xrightarrow{H^+ \text{ or } OH^-} CH_3-\overset{O}{\overset{\parallel}{C}}-CH_2Br \quad + \quad HBr$$

This reaction can be catalyzed by both an acid and a base.

The rate of the reaction depend on,
(i) Catalyst (ii) Reactant (iii) Independent of Br_2

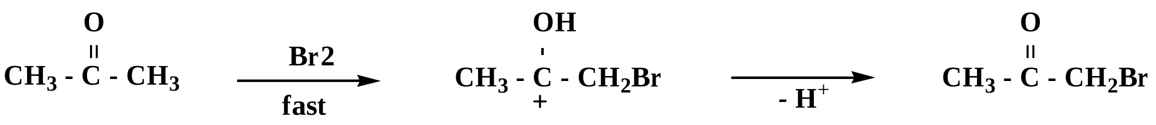
$$CH_3-\overset{O}{\overset{\parallel}{C}}-CH_3 \quad + \quad Br_2 \xrightarrow{H^+ \text{ or } OH^-} CH_3-\overset{O}{\overset{\parallel}{C}}-CH_2Br$$

The acid or base reacts with the ketone means, the α-hydrogen is reacted and forms the enol.

$$CH_3-\overset{O}{\overset{\parallel}{C}}-CH_3 \xrightarrow[H^+ \text{ slow}]{OH^-} CH_3-\overset{OH}{\overset{|}{C}}=CH_2Br$$

Enolisation involves the C-H bond cleavage.

The C-H bond cleavage taking place in the reaction mechanism:



In the case of CH_3-CO-CH_3, the energy for C-O bond cleavage is high i.e., energy increases means rate decreases.

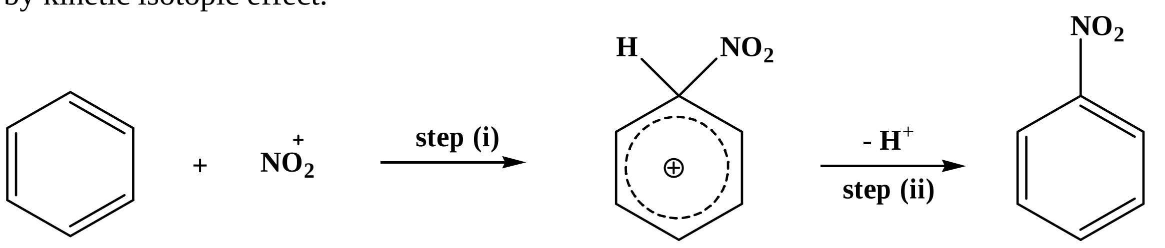
CH_3-CO-CH_3 - Rate of the reaction for normal ketone is K_H.
CH_3-CO-CH_3 - Rate of the reaction for isotopic hydrogen presence in the ketone is K_D.

In the case of heavier isotope has lower zero point vibrational energy by giving kinetic energy by means of thermal energy, the energy is increased of one stage, bond is cleaved so the energy is increased and the rate is decreased.

$\frac{K_H}{K_D} = 7$. If $\frac{K_H}{K_D}$ is 7 or around 7 means the mechanism is correct.

Example:

Consider the nitration of benzene, the mechanism of nitration of benzene was established by kinetic isotopic effect.



The above nitration involves two different steps and any one of the two steps may be rate determining there are two possibilities.

(i) Step (i) slow and step (ii) fast.
(ii) Step (i) fast and step (ii) slow.

First let us assume step (i) is slow and step (ii) is fast. The rate constant for the nitration of benzene is K_H. The rate constant for the nitration of benzene is K_H. The rate constant for the nitration of deuterated benzene is K_D. The step (ii) alone involves the C-H bond breaking. Here in this case K_H=K_D there is kinetic isotopic effect.

If we consider the (ii), i.e., step (ii) as fast and (ii) as rate determining then K_H is not equal to K_D. But the experimental result shows that $K_H/K_D = 1$. There is no isotopic effect.

The kinetic isotopic effect shows that the first step is the rate determining step and it does not involve the C-H bond breaking. In some of the reaction the C-H bond breaking is not the rate determining step. But there will be isotopic effect, even though the C-H bond breaking is not involved in the determining step. This effect is called the secondary kinetic isotopic effect.

2.5.2. NON-KINETIC METHODS OF STUDY OF REACTIONMECHANISM

Non-Kinetic method involves the following steps.

a) Identification of product
b) Identification of intermediate
c) Isotopic labeling
d) Stereo chemical evidences:

2.5.2.1. Identification of products

The most fundamental basis for mechanistic speculation i.e., the identification of the products, without such intermediate we can’t be sure which reaction actually occurs under the given conditions.

This should account for all the products, relative proportion of the product and also the product formed by the side reaction.

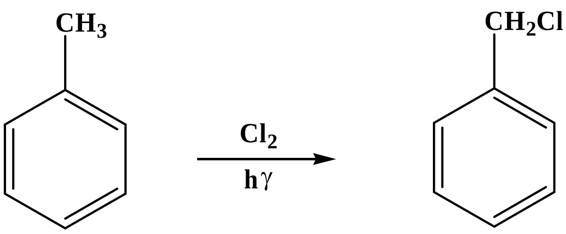
Example (i):

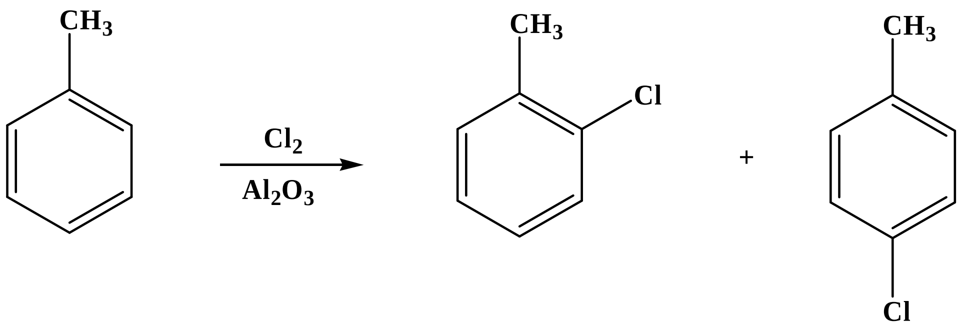
$$CH_4 + Cl_2 \longrightarrow CH_3Cl + CH_2Cl_2 + CHCl_3 + CCl_4$$

There will be small amount of CH_3-CH_3 (ethane) i.e., the $^{\bullet}CH_3$ is formed.

Example (ii):

Chlorination of toluene yields benzyl chloride in vapor phase but if the chlorination is carried out in the liquid phase in the presence of $AlCl_3$ *o*-chlorotoluene and *p*-chlorotoluene result.





Therefore the identification of products suggests that two different chlorination mechanisms operate depending upon the conditions.

2.5.2.2. Identification of the intermediate

Among the most concrete evidence obtained about the mechanism of the reaction is that provided by the actual isolation and identification of one or more intermediates from the reactions mixtures.

(i) Isolation of an intermediate

It is sometimes possible to isolate an intermediate from a reaction mixture by stopping the reaction after a short time or by use of very mild conditions.

Eg: Hofmann rearrangement reaction.

$$\underset{\text{Amide}}{RCONH_2} \xrightarrow{NaOBr} \underset{\text{Amine}}{RNH_2}$$

In these reaction three intermediates namely N-bromamide, its anion and an isocyanate have been isolated.

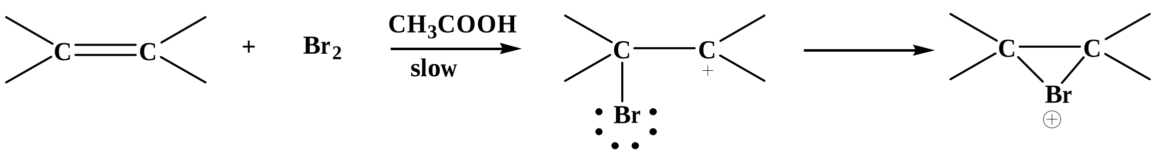
$$RCONH_2 \xrightarrow{OBr^-} RCONHBr \xrightarrow{OH^-} R\overset{O}{\overset{\|}{C}}\overset{\ominus}{N}Br \xrightarrow{OBr^-} R-N=C=O$$

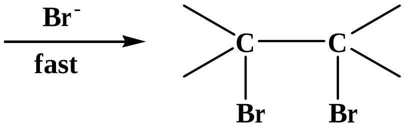
$$\xrightarrow{H_2O} RNH_2 + CO$$

(ii) Trapping of intermediate

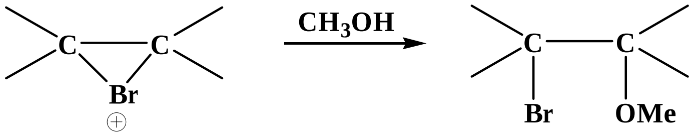
Some times an intermediate may be detected but cannot be isolated in such cases the trapping reagent is added to react with the intermediate from the nature of the product the intermediate could be identified.

Eg: Bromination of olefins:

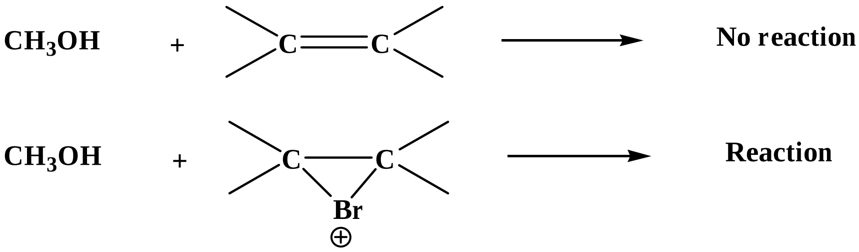




If we add the external nucleophile along with the bromonium ion the external nucleophile is also attached CH_3OH is the trapping agent.

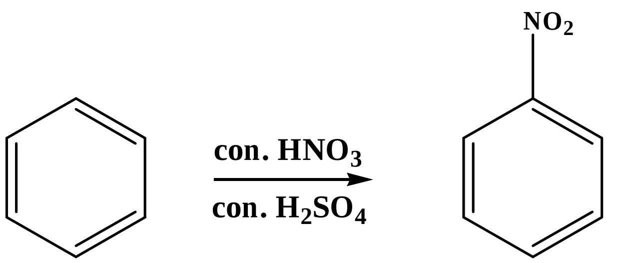


dibromo compound + bromoester → No reaction.



(iii) Detection of an intermediate

In many cases an intermediate can't be isolated but can be detected.



Nitrobenzene

The NO_2^+, the electrophile is detected by Raman spectroscopy. In the free radical the unpaired electron is observed by ESR or EPR. So the formation of the radical intermediate is detected.

2.5.2.3. Isotopic labeling

This is an effective method of determining specific information about the bonds that are involved in a reaction.

$$R^{14}COO^- + BrCN \longrightarrow R^{14}CN + CO_2 + Br^-$$

Carbon has two isotopes C^{14} is the radio active so we label the C in $RCOO^-$ is $RC^{14}OO$ but in the product C^{14} is present in alkylcyanide.

Eg:

Ester hydrolysis whether it is acid catalysis and basic catalysis in involves two types cleavage.

$$\mathrm{R - \overset{\displaystyle O}{\overset{\|}{C}} - OR'} \xrightarrow{\mathrm{H_2O^{18}}} \mathrm{RCO\overset{18}{O}H + R'OH}$$

Mostly acyloxygen cleavage takes place.

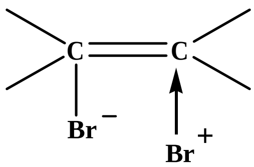
$$\mathrm{R - \overset{\displaystyle O}{\overset{\|}{C}} - OR'} \xrightarrow{\mathrm{H_2O^{18}}} \mathrm{RCO\overset{18}{O}H + R'OH}$$

O^{18} in the products is found out by the help of mass spectrum i.e., the acid and the alcohol are analysed and the heavy isotope O^{18} is present in the acid i.e., confirms the acyloxygen cleavage present.

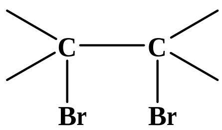
2.5.2.4. Stereo Chemical evidences

Olefins undergo addition because the double bond is rich in electron. It is a univalence atom so we add 2 atoms.

(i) Two atoms are added simultaneously this is called constructed mechanism.

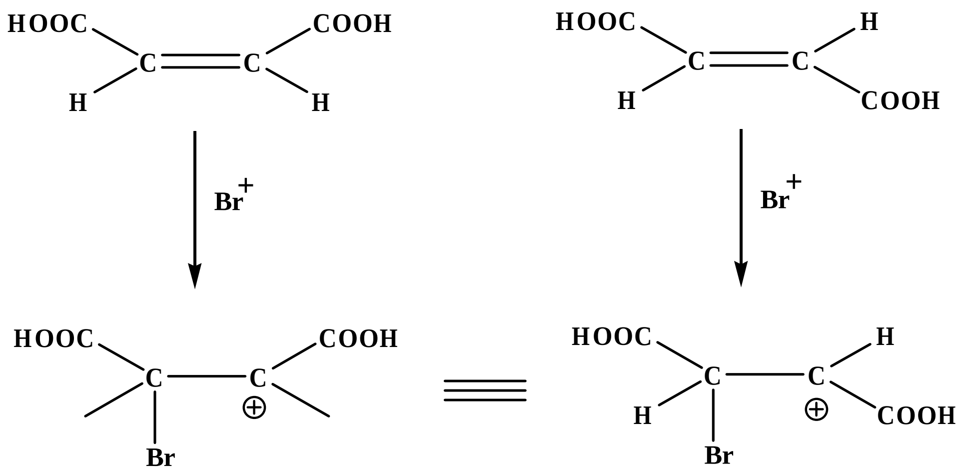


If the two new bonds can add from the same side then the mechanism is called *cis* or *syn* addition.



First the bromonium ion forms a cyclic intermediate, the second Br^- goes to the other side i.e, the two Bromine atoms add from the opposite side then the mechanism is called *trans* addition.

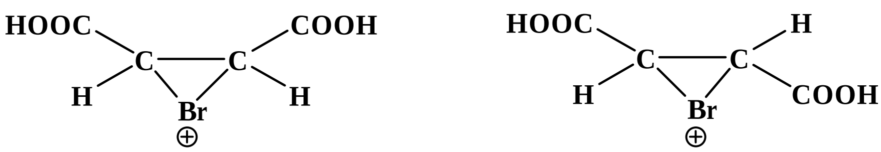
(i). Addition of Bromine in olefins



Whether *cis* or *trans* isomer, carbonium ion intermediate is formed means because of single bond is capable of free rotation and the two acids i.e., maleic and fumaric acid leads to the same product because the bulky –COOH groups in the maleic acid intermediate and hindrance and it forms the intermediate of trans isomer.

If it is bromium ion intermediate means the rotation is not possible.

If it is cyclic bromonium ion intermediate means the intermediate obtained by *cis* and *trans* isomers are not identical. So the products are different i.e., it retained the stereo chemistry of the reactant.



2.5.2.5. Stereo Chemical Method

Organic substance exhibits in stereo isomerism i.e., geometrical isomerism and optical isomerism in the case of optical isomerism the starting material is in *meso* active or *racemic* form, after the reaction is completed then also we have to see the nature or seterochemistry of the product.

$$\left.\begin{array}{l} R \longrightarrow S \\ S \longrightarrow R \end{array}\right\} \quad \textbf{Inversion of configuration}$$

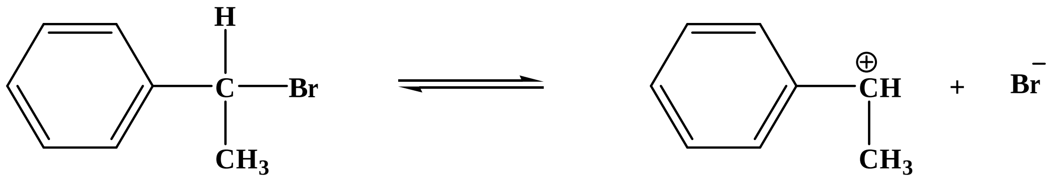
$$\left.\begin{array}{l} R \longrightarrow R + S \\ S \longrightarrow R + S \end{array}\right\} \quad \textbf{Racemisation}$$

$$\left.\begin{array}{l} R \longrightarrow R \\ S \longrightarrow S \end{array}\right\} \quad \textbf{Retention of configuration}$$

Eg: S_N^1 reaction.

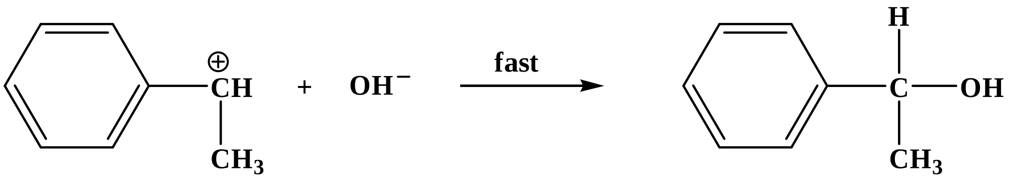
Kinetics of this mechanism shows that it is first order mechanism and the nucleophile is not involved the rate determining step.

I step: Formation of the carbocation



The carbocation S_N^1 reaction is a symmetry reaction.

II step: Attacks of nucleophile:

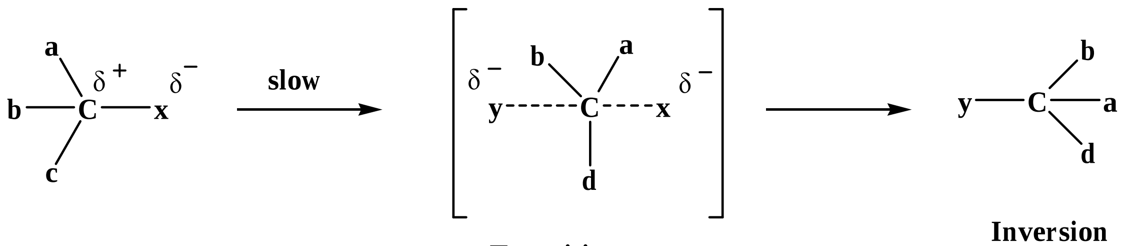


Racemic mixture

Saturated carbon means its geometry is tetrahedral, for carbocation the geometry is planar. The starting compound is a asymmetric compound but the carbocation i.e., symmetric to the product is always racemic mixture.

Eg: S_N^2 reaction:

Kinetic observed is second order.



Transition state

Inversion configuration

The nucleophilic attack takes place from the side remote to that of the leaving group.

The transition state is also the asymmetric compound. The reaction with the formation of the transition state is always leads to the product i.e., leads to inversion of configuration. By using polarimeter the optical activity is measured.

2.6. LET US SUM UP

In this lesson, we:

* Described that the kinetic and thermodynamic control of a reactions and microscopic reversibility
* Explained the aromaticity of benzenoid and heterocyclic compounds
* Discussed the Hammond's postulate, primary and secondary kinetic isotopic effect
* Pointed out the identification of product and intermediate, isotropic labeling and stereo chemical evidences

2.7. CHECK YOUR PROGRESS

1. What is isotopic effect? How does isotopic labeling help in establishing the mechanism of a reaction?
2. Discuss the importance of kinetic evidence in establishing the mechanism of a reaction.

2.8. POINT FOR DISCUSSION

1. State Hammond's postulate. Explain with a suitable example the application of Hammond's postulate in determining the shape and geometry of transition state.
2. Explain non-kinetic methods of study of reaction mechanism.

2.9. REFERENCES

1. Jerry march, Advanced Organic Chemistry, Fourth edition, Wiley India edition.

2. P.S. Kalsi, Organic reactions and their mechanisms, Second edition, New age international publishers.

LESSON: 3 – LINEAR FREE ENERGY RELATIONSHIP

CONTENTS

3.0. AIMS AND OBJECTIVES

The aim is to motivate and enable a broad knowledge on linear free energy relationship to the students.

On successful completion of this lesson the student should have:

* Understood the linear free energy relationship.

3.1. INTRODUCTION

For the study of reaction mechanism, one has to collect several evidences which point to the mechanism of the reaction. An important concept is that a given structural feature will effect related reactions in generally the same way. Thus if replacement of a hydrogen by chlorine makes acetic acid to become a strong acid, then introduction of a chlorine at the α-position of propanoic acid will also result in an increase in acidity. A linear free energy relationship is simply a quantization of this concept.

3.2. THE HAMMETT EQUATION

The first and most important linear free energy relationship is the Hammett $\sigma\rho$ equation which is based on the acidities of aromatic carboxylic acids.

Acidities of benzoic and phenylacetic acids were measured by changing substituent group on the aromatic ring. In these experiments the positions of acid base equilibria were measured as functions of the substituent groups. In case the different acidity values for each series of compounds are due only to the influence of the substituents, then a relation between the sets of data should exist. When the pK_a values obtained from the two series of compounds were plotted against each other (Fig. I), a linear relation (Equation *I*) was obtained.

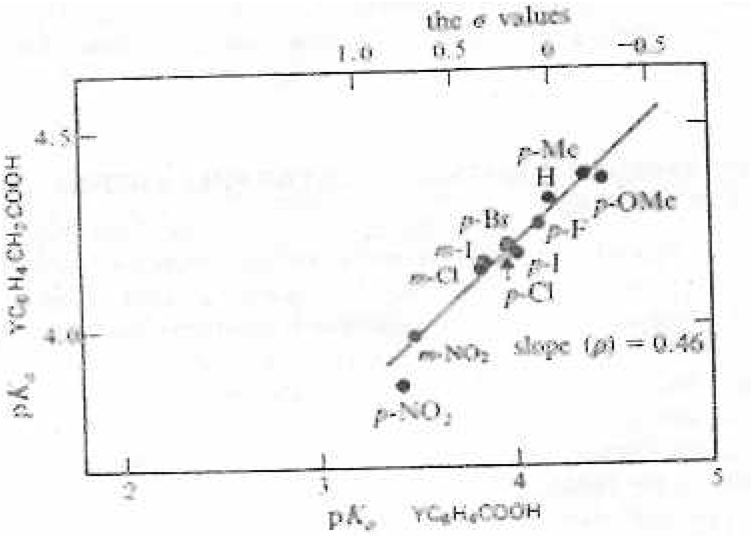


Fig. I. Hammett plot.

[Fig. I. is a Hammett plot with ρ = 0.46. The value of ρ indicates the sensitivity of a reaction or equilibrium to particular substituents. A positive ρ-value shows that the reaction or equilibrium is aided by electron attracting substituents (withdrawl of electrons from the reaction site). In case of phenylacetic acids, for ionization, the ρ of + 0.46 points that a given electron attracting substituent facilitates ionization but has only 0.46 of the effect that the same substituent has in facilitating ionization of benzoic acid]

The pK_a values for phenylacetic and benzoic acids

$$pK_{PA} = \rho(pK_B) + C \qquad \text{------ (I)}$$

ρ (rho) = a proportionality constant – is the slope of the line (or)

$$\log K_{PA} = \rho \log K_B + C'$$

C or C' = the intercept of the straight line.

The acidity values of un-substituted carboxylic acids pK_0 (substituent = H) are taken as standards with which the effect of a substituent is compared and the equation *II* is for this standard. An expression *III* is obtained on subtracting one equation from the other, and this expression relates the substituent effects on the two series of compounds (the K and K_0 represent the equilibrium constants for substituted and un-substituted compounds.

$$\log K_{oPA} = \rho \log K_{0B} + C' \qquad \text{------ (II)}$$

$$\log \frac{K_{PA}}{K_{0PA}} = \rho \log \frac{K_B}{K_{0B}} \qquad \text{------ (III)}$$

The acidities of different benzoic acids in equation media (25°C) are the standard measure of the effect of each substituent group and the substituent constant sigma (σ) for every substituent group is defined in the expression *IV*. The Hammett equation-the linear relation is thus expressed as in equation *V*. Sigma (σ), the substituent constant is a measure of the effect of a substituent on the acidity of benzoic acid. Those substituents which enhance the acidity relative to unsaturated benzoic acid will show positive values (σ > 0), the hydrogen atom having a sigma value of zero.

$$\sigma = \log \frac{K_B}{K_{0B}} \qquad \text{------ (IV)} \qquad (\sigma - \text{substituent constant})$$

$$\log \frac{K_{PA}}{K_{0PA}} = \sigma\rho \qquad \text{------ (V)}$$

The Hammett equation can thus be used:

1. To account for the influence of substituents on molecular reactivity.

2. It explains the influence of polar *meta- or para*-substituents on the side chain reactions of benzene derivatives. Table.1. summarizes σ values for different *meta* and *para* substituents. The s constant is generally independent of the nature of the reaction by *m-or p*-substituent relative to hydrogen. A negative σ value signifies an electron attracting group. The large the magnitude of σ, the greater is the effect of the substituent. The ρ constant (ρ is the reaction constant) is dependent on the nature of the reaction and on conditions. It is a measure of the sensitivity of a given reaction series to the polar effect of ring substituents i.e., to changes in the s values of the substituent.

Substituent	σ_m	σ_p
NH_2	-0.16	-0.66
CH_3	-0.07	-0.17
OH	0.12	-0.37
C_6H_5	0.06	-0.01
OCH_3	0.12	-0.27
SCH_3	0.15	-0.0
F	0.34	0.06
I	0.35	0.18
Cl	0.37	0.23
Br	0.39	0.23
CF_3	0.43	0.54
CN	0.56	0.66
NO_2	0.71	0.78

Table. 1. Hammett substituent constant values of common groups.

3. Reactions that are assisted by high electron density at the reaction site have negative ρ values.
4. The Hammett equation is however, not applicable to the influence of *ortho* substituents, since these exert steric effects.

When one considers the rates of hydrolysis of substituted benzoates with hydroxide ion (in aqueous acetone), one observes a straight line on plotting against the Hammett σ-constants with a slope (ρ) of 2.23. These data show that the substituent groups which facilitate ionization of benzoic acid, facilitate the hydrolysis of benzoate as well. For ester hydrolysis the transition state (Scheme I, the reaction involves nucleophilic attack by the hydroxide ion on the carbon atom of the carbonyl group), has considerable negative charge, since positive ρ indicates stabilization by electron attracting group. Indeed, in keeping with this observation the mechanism of ester hydrolysis which proceeds through an anionic tetrahedral intermediate gets support. Moreover, this hydrolysis will be further facilitated when electron withdrawing group (σ is positive, Table. 1) is attached to the aromatic ring. With an electron releasing group (σ is negative) the reaction will be retarted.

$$\mathrm{Ar\text{-}\overset{\overset{\large O}{\|}}{C}OCH_3} + \mathrm{OH^{\ominus}} \longrightarrow \left[\mathrm{Ar\text{-}\overset{\overset{O^{\ominus}}{|}}{\underset{\underset{OCH_3}{|}}{C}}\text{-}OH}\right] \longrightarrow \mathrm{ArCO_2^{\ominus}} + \mathrm{CH_3OH}$$

Scheme I

Hydration of styrenes ($HClO_4$, 25°C) shows a –ρ value, to show that the transition state of the reaction is like a carbocation intermediate.

3.3. LET US SUM UP

In this lesson, we:

* Explained the Hammett equation

3.4. CHECK YOUR PROGRESS

1. What is Hammett constant σ ? Predict the sign of Hammett σ constant for the following substituents giving a proper reason: m-NO_2, p-MeO, p-CO_2H, m-OH, and p-OH.
2. Predict the sign of ρ for the following reactions.

(a) $\mathbf{ArH + \overset{+}{N}O_2 \longrightarrow ArNO_2 + \overset{+}{H}}$

(b) $\mathbf{ArCOCl + EtOH \longrightarrow ArCO_2Et + HCl}$

3.5. POINT FOR DISCUSSION

1. Derive Hammett equation and explain its applications.
2. Explain quantitative treatment of the effect of structure on reactivity (Using LFER).

3.6. REFERENCES

1. Jerry march, Advanced Organic Chemistry, Fourth edition, Wiley India edition.

2. P.S. Kalsi, Organic reactions and their mechanisms, Second edition, New age international publishers.

UNIT-II

LESSON: 4 – AROMATIC ELECTROPHILIC SUBSTITUTION REACTIONS

CONTENTS

4.0. AIMS AND OBJECTIVES

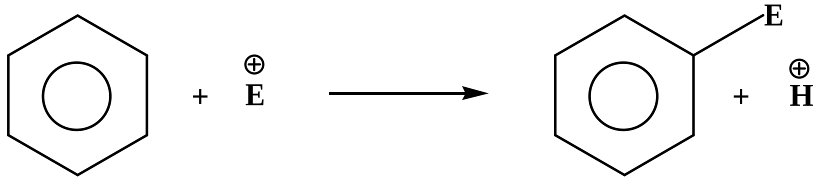
The aim is to motivate and enable the student to comprehend the possible chemical route by which the aromatic electrophilic substitution reactions may proceed.

On successful completion of this lesson the student should have:

* learnt possible reaction pathways in aromatic electrophilic substitution reactions.

4.1. INTRODUCTION

The benzene is a resonance hybrid which is a flat ring with a cyclic cloud of negative charge above and below the plane of the ring. Benzene ring therefore discourages nucleophilic attack and encourages electrophilic attack only.



The typical reaction of benzene and its derivations are electrophilic substitution. Aromatic electrophilic substitution includes a wide variety of reactions such as nitration, sulphonation, halogenation, Friedel-crafts reactions etc. the reaction permits the direct introduction of groups to the ring and their subsequent transformation to various products.

$$ArH + HNO_3 \xrightarrow{H_2SO_4} ArNO_2 + H_2O$$

$$ArH + Cl_2 \xrightarrow{AlCl_3} ArCl + HCl$$

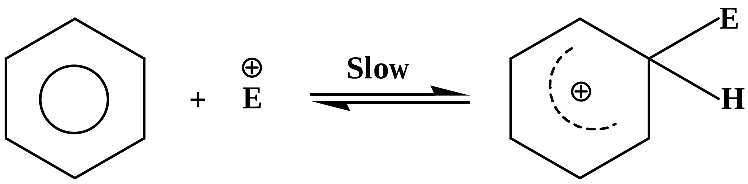
$$ArH + H_2SO_4 \xrightarrow{SO_3} ArSO_3H + H_2O$$

$$ArH + RCl \xrightarrow{AlCl_3} ArR + HCl$$

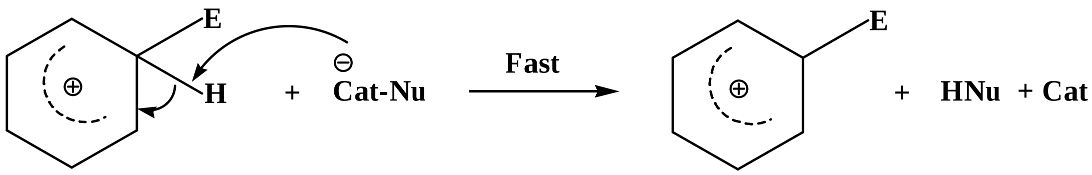
4.1.1. MECHANISM OF ELECTROPHILIC SUBSTITUTION

The reagent and catalyst undergo acid-base reaction to produce the attacking electrophilic which then attacks the ring to form a carbocation (σ complex) in the first slow step. In the second step the proton from the site of attack is rapidly removed by the base to complete the reaction.

$$E - Nu + cat \rightarrow E^+ + Nu - cat^- \qquad \text{------ (i)}$$



σ − complex



------ (ii)

The energy gained in passing from the σ complex to the product provides the energy for breaking the strong $C - H$ bond. It may be seen that the formation of σ complex would involve high energy. This is however, not so because the energy liberated by the formation of $C - E$ bond and the delocalization of the positive charge lowers the energy of the σ complex.

The rate of reaction does not involve the breaking of the $C - H$ bond. This has been established by isotope effect. The rates of reaction are the same on replacement of hydrogen by deuterium or tritium. Hence, the rate of the substitution reaction is determined by the slow attachment of the electrophile to the ring in the first step.

4.2. NITRATION

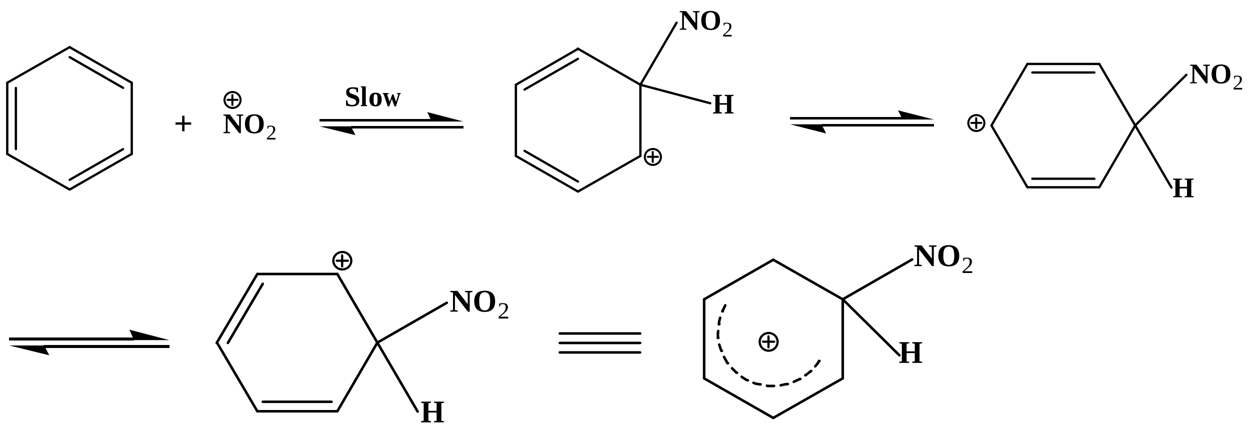
Nitration of benzene is effected with a mixture of concentrated nitric and sulphuric acids. In the absence of sulphuric acid the reaction is slow. It is suggested that H_2SO_4 acts as a strong acid protonates. HNO_3 to generate nitronium ion, $\overset{+}{N}O_2$. This has been confirmed by various methods.

$$HO - NO_2 + H_2SO_4 \rightleftharpoons \overset{\oplus}{H_2O} - NO_2 + HSO_4^- \underset{}{\overset{H_2SO_4^-}{\rightleftharpoons}} HNO_3 + H_2SO_4$$

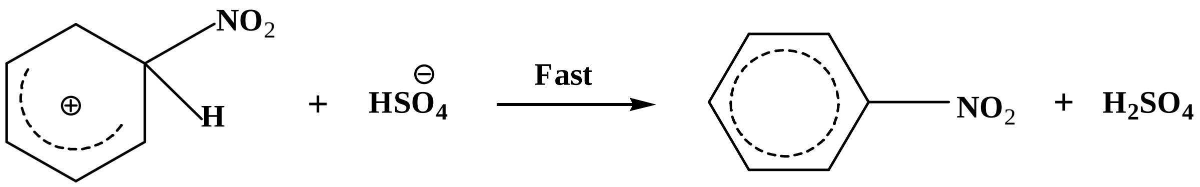
Overall reaction is

$$HNO_3 + 2H_2SO_4 \rightleftharpoons \overset{\oplus}{NO_2} + 2HSO_4^- + H_3O^+$$

The nitronium ion then attacks the benzene ring to form a carbocation in the first step.



In the second step, a fast abstraction of hydrogen from the site of attack by the base (HSO_4^-) completes the reaction.

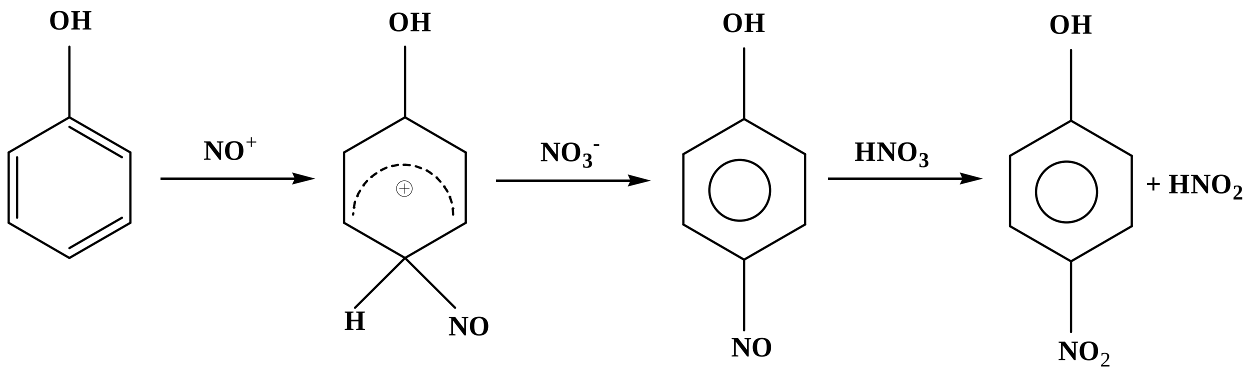


The presence of appreciable amount of water in the acid mixture is not desirable since it reduces the nitronium ion, hence the use of concentrated acid mixture.

$$\overset{+}{NO_2} + H_2O \rightleftharpoons H_2NO_3^+ \overset{HSO_4^-}{\rightleftharpoons} H_3O^+ + NO_2^+ + 2HSO_4^-$$

Phenol, which is highly reactive due to the mesomeric effect of the OH group, is nitrated even with dilute HNO_3. A small amount of phenol is oxidized to produce HNO_2 which with HNO_3 gives nitrosonium ion, $\overset{+}{NO}$. The latter nitrosates the reactive phenol to yield nitrosophenol which is rapidly oxidized to nitrophenol with HNO_3 and nitrous acid is produced by reaction of HNO_3. With the progress of the reaction more and more nitrous acid is produced and the reaction rate is increased.

$$HNO_2 + 2HNO_3 \rightleftharpoons H_3O^+ + 2NO_3^- + NO^+$$



p-nitrosophenol *p*-nitrophenol

4.3. SULPHONATION

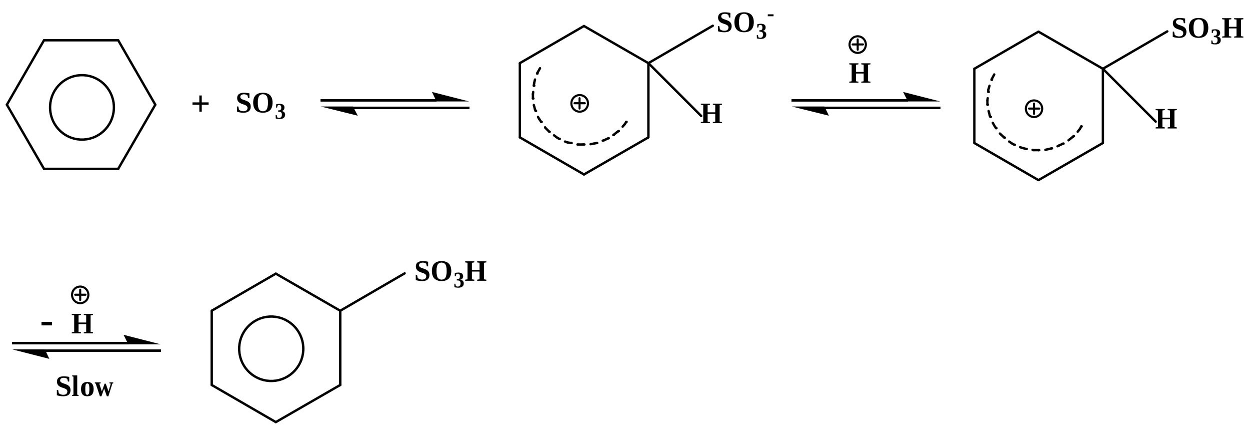
Benzene on heating with concentrated or better with fuming sulphuric acid gives benzene sulphonic acid, $C_6H_6SO_3H$. Sulphonation can also be affected with $ClSO_3H$.

$$C_6H_6 + H_2SO_4 \rightleftharpoons C_6H_5SO_3H + H_2O$$

The reaction is slow with conc. H_2SO_4 but rapid with oleum or SO_3 in inert solvent. The electrophile is SO_3 which is present in small amount in H_2SO_4 .

$$2H_2SO_4 \rightleftharpoons SO_3 + HSO_4^{\ominus} + H_3O^{\oplus}$$

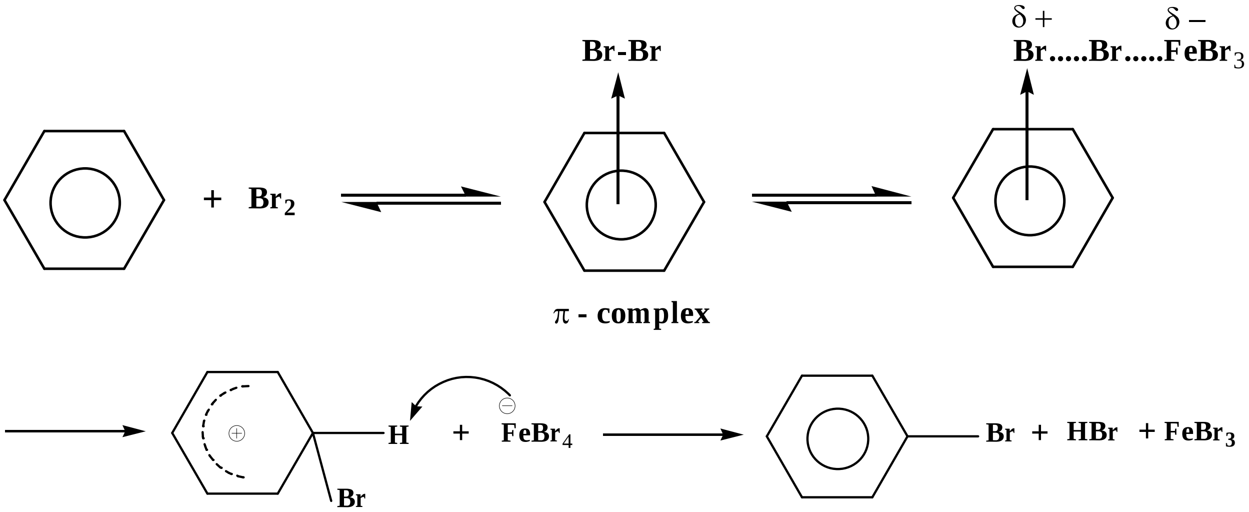
The electrophile SO_3 is neutral but has powerful electrophilic sulphur which attacks the ring.



The rate determining step involves the breaking of $C-H$ bond. Since deuterated benzene is sulphonated more slowly. The reaction is reversible on treatment with steam. SO_3H group is replaced by hydrogen. The reversibility of the reaction has practical utility.

4.4. HALOGENATION

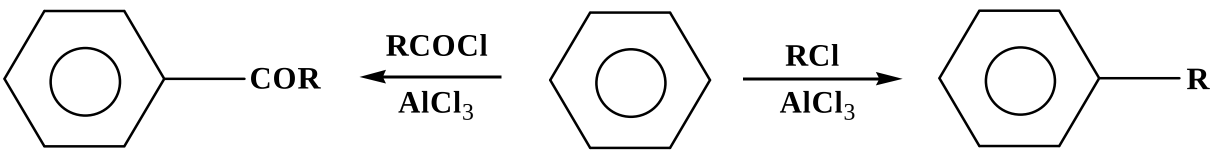
Free halogens can attack activated benzene rings but lewis acid catalyst is required for benzene ring. It is suggested that probably benzene first forms a π complex with the halogen molecule. (Eg) Br_2. The lewis acid ($FeBr_3$) then polarizes the $Br-Br$ bond and helps in the formation of a σ complex between benzene carbon and the electrophilic end of the polarized bromine by removing the incipient bromide ion. Subsequent abstraction of hydrogen in the second step completes the reaction.



The order of reactivity of the halogen is $F_2 > Cl_2 > Br_2 > I_2$. Fluorine is too reactive for practical use. Under ordinary condition, ionization fails. In the presence of HNO_3 direct iodination has been affected. The attacking electrophile I^+ is produced by HNO_3.

4.5. FRIEDEL CRAFTS REACTIONS

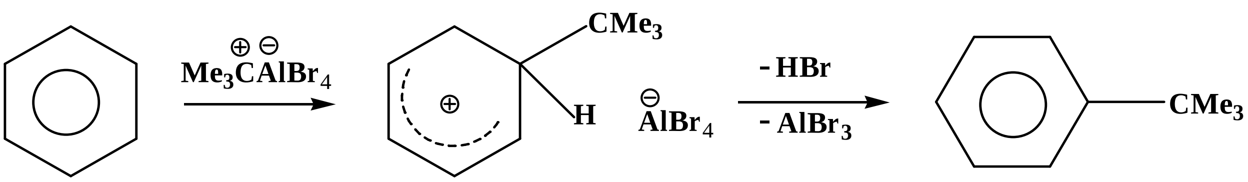
Alkylation and acylation of aromatic rings with alkyl halides and acid chlorides or anhydrides respectively in the presence of lewis acids, E.g. $AlCl_3, FeBr_3, BF_3, BCl_3$, etc is known as friedel crafts reaction.



4.5.1. ALKYLATION

The function of the catalyst is to provide a real or potential carbocation for the electrophilic attack. When the alkyl group can form a stable carbocation as in the case of tertiary halides, the attacking species is the real carbocation which forms as ion pair.

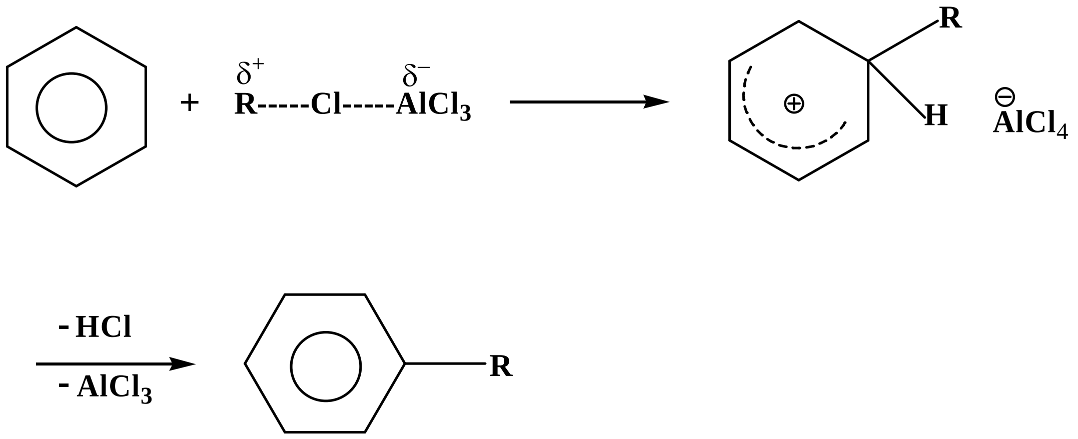
$$Me_3CBr + AlBr_3 \rightleftharpoons Me_3C^+Al^-Br_4$$



(1)

In other cases a polarized complex with a potential carbocation is the attacking species.

$$R\text{-}Cl + AlCl_3 \rightleftharpoons \overset{\delta^+}{R}\text{-----}Cl\text{-----}\overset{\delta^-}{AlCl_3}$$



(2)

The intermediates (1) and (2) have been isolated in some cases. It has been observed that the sane alkyl halide gives a rearranged and unrearranged product with different lewis acid catalysts.

$$C_6H_6 + Me_3C.CH_2Cl \xrightarrow{AlCl_3} \underset{\textbf{Rearranged}}{C_6H_5CMe_2CH_2Me}$$

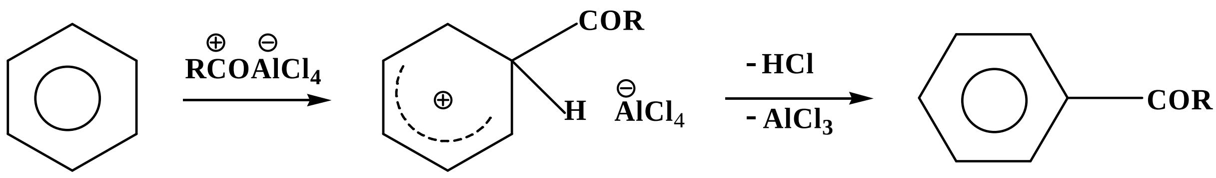
$$C_6H_6 + Me_3C.CH_2Cl \xrightarrow{FeCl_3} \underset{\textbf{Unrearranged}}{C_6H_5CH_2CMe_3}$$

Since $AlCl_3$ is a stronger lewis acid than $(FeCl_3)$. It is presumed that the complex with $AlCl_3$ is so strongly polarized that the alkyl group attains almost a free carbocation character to undergo rearrangement. The alkylating reagent besides alkyl halides may be aliphatic alcohols, alkenes, ethers, etc in the presence of strong proton acids which generate the carbocation for the electrophilic attack.

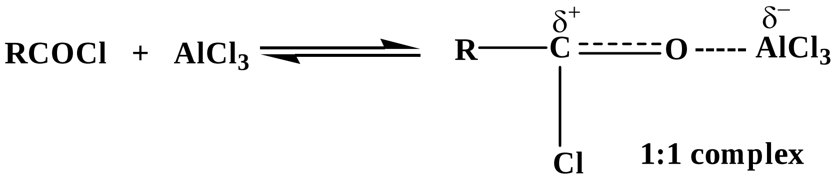
4.5.2. ACYLATION

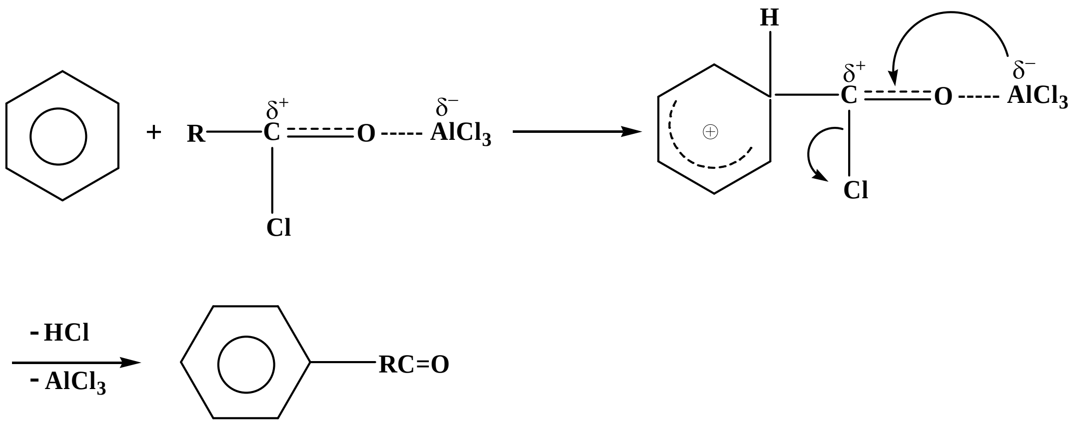
Acylating reagents are acid chlorides or acid anhydrides in the presence of lewis acid. The electrophilic species may be (a) acylcation as an ion pair or (b) a polarized 1:1 complex. Probably both mechanisms operate depending on conditions.

$$\text{(i)} \quad RCOCl + AlCl_3 \longrightarrow \overset{\oplus}{RCO} + \overset{\ominus}{AlCl_4} \quad \text{or} \quad \underset{\textbf{Ion pair}}{\overset{\oplus}{RCO}\overset{\ominus}{AlCl_4}}$$



(ii)





In both cases, one mole of the catalyst remains complexed with the product, ketone. Hence slightly more than one mole of lewis acid is required for acylation. Acylation may be affected with acid anhydride also. The attacking species in this case may be a free RCO^+ or $RCOCl$.

4.5.3. APPLICATIONS

The reaction is very useful for the synthesis of many classes of organic compounds.

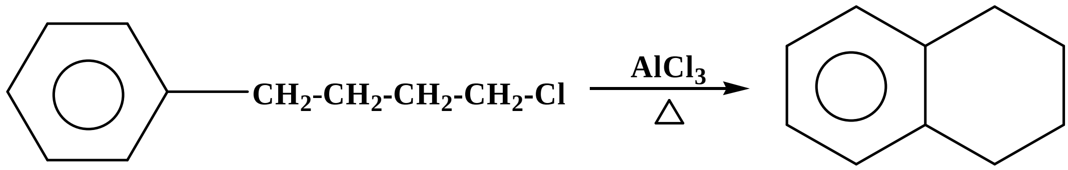
(a). Hydrocarbons:

$$C_6H_6 + C_6H_5CH_2Cl \xrightarrow{AlCl_3} \underset{\text{Diphenyl methane}}{C_6H_5CH_2C_6H_5}$$

(b). Ketones:

$$C_6H_6 + RCOCl \xrightarrow[PhNO_2]{AlCl_3} C_6H_5COR + HCl$$

(c). Poly-nuclear hydrocarbons:



Tetralin

4.6. LET US SUM UP

In this lesson, we:

* Pointed out the mechanism of electrophilic substitution such as nitration, sulphonation, halogenation, Friedel crafts reactions (alkylation and acylation) and its applications

4.7. CHECK YOUR PROGRESS

1. It is known that the aromatic electrophilic substitution is a two step process. What are the arguments which can be advanced in support of this statement?
2. Name the electrophile and show with the chemical equation how it is produced in the reaction, bromination with bromine in presence of $FeBr_3$.

4.8. POINT FOR DISCUSSION

1. Give the mechanism for following reactions.
   (a) Nitration
   (b) Sulphonation
2. Differentiate Friedel Craft Alkylation and Acylation with mechanism and applications.

4.9. REFERENCES

1. Jerry march, Advanced Organic Chemistry, Fourth edition, Wiley India edition.

2. P.S. Kalsi, Organic reactions and their mechanisms, Second edition, New age international publishers**.**

LESSON: 5 - ORIENTATION AND REACTIVITY: ELECTOPHILIC SUBSTITUTION ON MONOSUBSTITUTED AND DISUBSTITUTED BENZENES

CONTENTS

5.0. AIMS AND OBJECTIVES

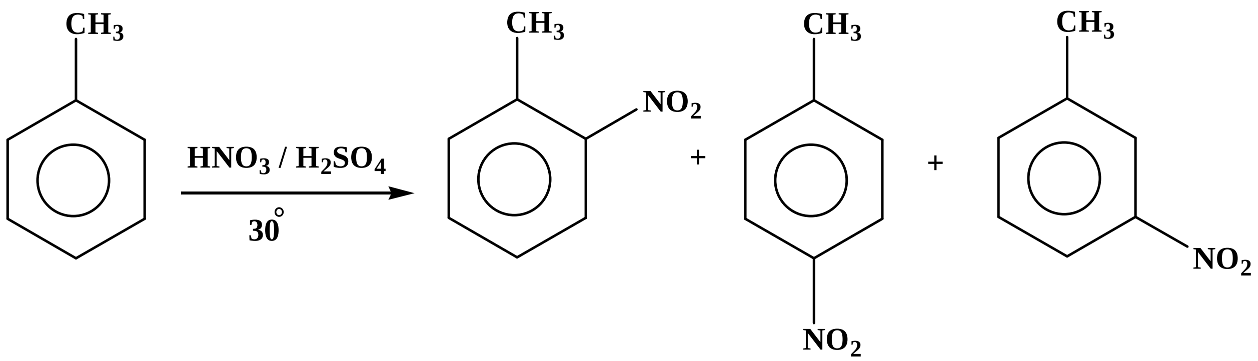
The aim is to motivate and enable a comprehensive knowledge on orientation and reactivity of electophilic substitution on monosubstituted and disubstituted benzenes to the students.

On successful completion of this lesson the student should have:

* Understood the orientation and reactivity of electophilic substitution on monosubstituted and disubstituted benzenes.

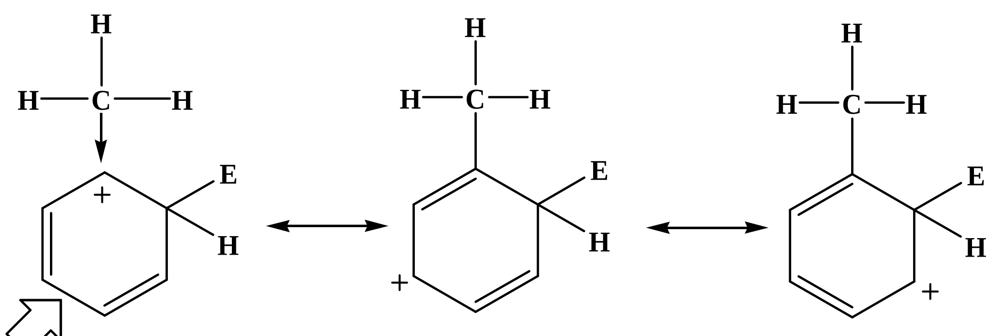
5.1. INTRODUCTION

Since each product i.e. *ortho, para* or *meta* originates from the same starting materials, the partitioning to different products must relate to the relative activation energies of each reaction. Although the cyclohexadienyl cation produced in each case is stabilized by resonance, there are important differences. An analysis of these differences helps to explain the orientation. It must be remembered that a more stable intermediate is associated with a more stable transition state and lower activation energy in the rate determining step. The more stable a reaction intermediate, the greater is the proportion of product derived from that intermediate. As an example electrophilic substitution on toluene may be considered eg. Nitration of toluene gives essentially *ortho* and *para* substitution products as the major product and only 4% of the *meta* product.



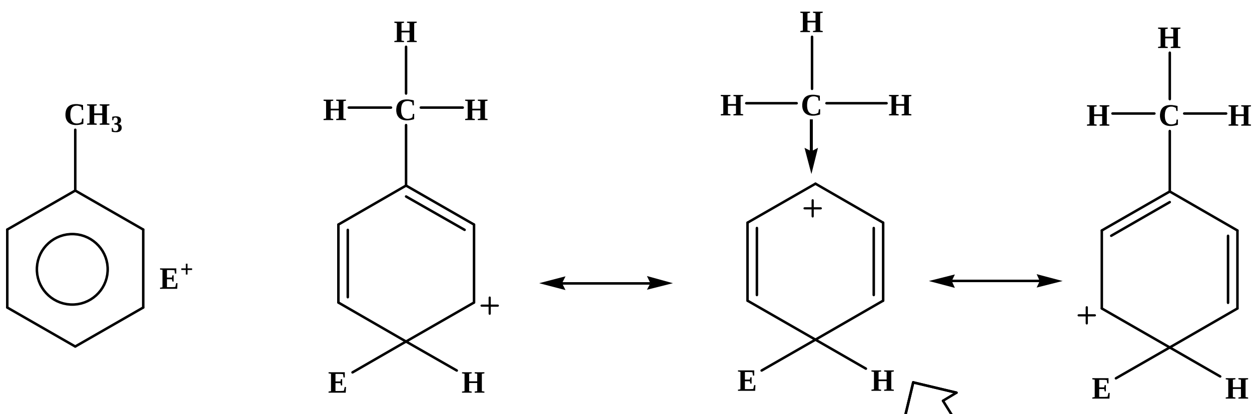
***o*-Nitrotoluene** **(59%)** ***p*-Nitrotoluene** **(37%)** ***m*-Nitrotoluene** **(4%)**

Compare the carbocations formed by the attack of the electrophile (E^+) at the *ortho*, *para* and *meta* position of toluene. Reaction at the *ortho* and *para* positions gives two of the structures, in each case, which are those of secondary carbocation, but the third structure corresponds to a more stable tertiary carbocation. Although, the methyl group releases electrons to all the position in the ring, it does so more effectively to the carbon atom nearest to it. Therefore structures (I and II) are particularly more stable and because of contributions from these structures ,the hybrid carbocation as a result of attack at the *ortho* and *para* positions is more stable than the carbocation resulting from the attack at the *meta* position. The sigma complex for the *ortho* and *para* substitution has its positive charge spread over two 2° carbons and one 3° carbon. When substitution occurs at the *meta* position the positive charge is not delocalized onto the tertiary carbon. As a consequence, the methyl group has a much smaller effect on the stability of the sigma complex.

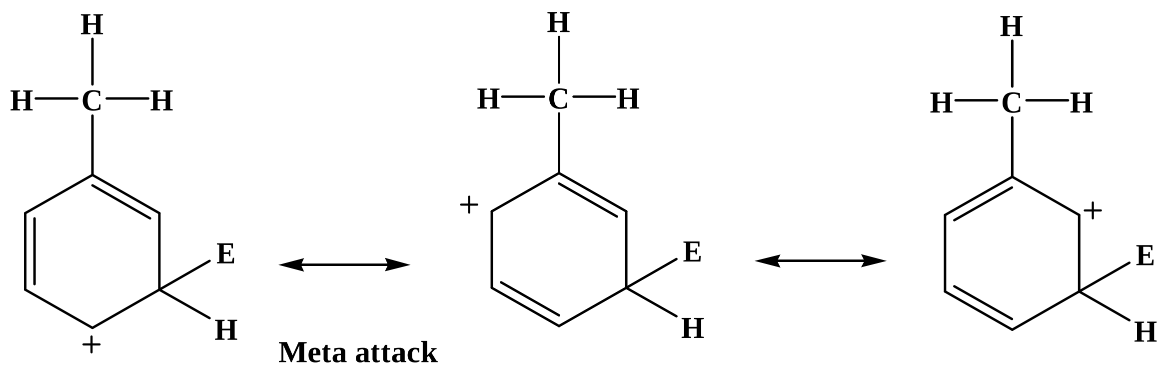


(I)

Ortho attack



Para attack **(II)**



In summary, therefore, an alkyl group stabilizes the sigma complexes and the transition states leading to these. This stabilization is, however, most effective when the alkyl group is *ortho* (or) *para* to the site of substitution. Steric factors may be involved in the attacking electrophile. Thus, the chlorination to chlorobenzene (Cl^+ is the electrophile) gives a mixture of dichlorobenzenes in which the *ortho*/*para* ratio is about 0.7 whereas nitration of chlorobenzene (the electrophile is the more bulky nitronium ion, NO_2^+) gives an *ortho/para* ration of about 0.4. The net result is, therefore, *ortho* and *para* orientation.

5.2. ELECTOPHILIC SUBSTITUTION ON MONOSUBSTITUTED BENZENES – ORIENTATION AND REACTIVITY

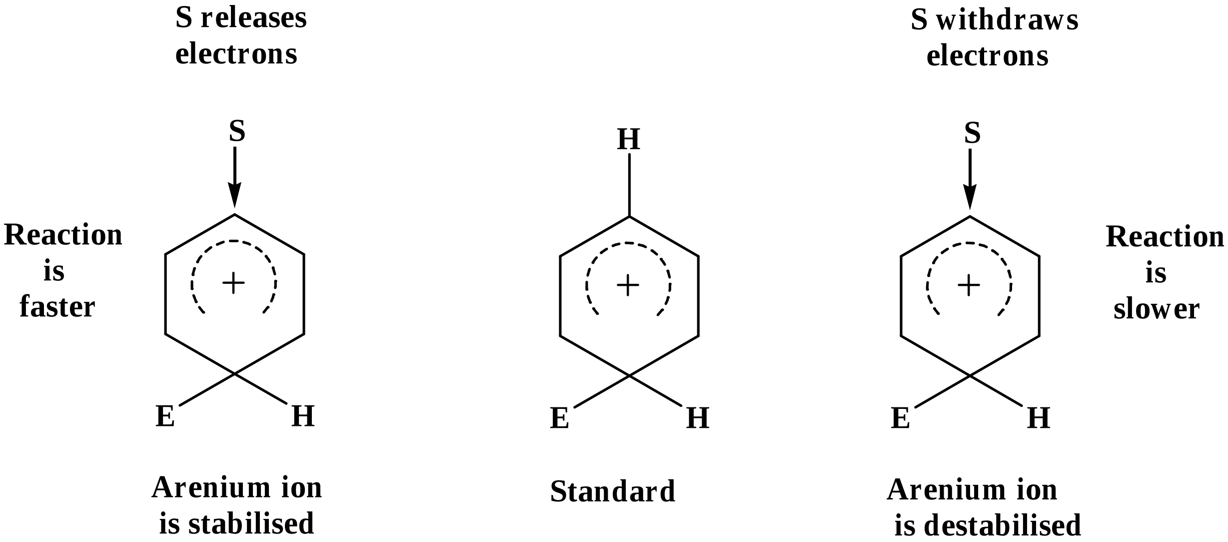
The reactivity of mono-substituted benzene (C_6H_5-S) and the orientation of incoming substituent depend on the nature of the substituent (S) already present on the ring. A mono-substituted benzene on electrophilic substitution may give three possible di-substituted products (*ortho, meta and para* isomers).

From the yields of these isomers, it is possible to separate the substituents into two groups the *o, p*-directors which give predominantly *o, p* products and the *m*-directors which mainly give mainly the *meta* products.

The following points will help to understand both the reactivity i.e., if the reaction will be slower or faster than with benzene and orientation of the incoming group in a mono-substituted benzene derivative, i.e., the position (*o, p or m*) which the new group will take.

5.2.1. ACTIVATION AND DEACTIVATION

The term activation or deactivation is applied when the reactivity of mono-substituted benzene (C_6H_5-S) in electrophilic substitution reaction is compared with benzene (C_6H_6) under the identical conditions. An electron-releasing group i.e., +*I* effect of the substituent helps to



stabilize the positive charge of the reaction intermediate (σ complex) produced in the rate-determining step by furthering the delocalization of the charge. This will serve to lower the activation energy in the rate determining step relative to that of benzene. Thus, the compound (C_6H_5-S) where S has +*I* effect will undergo electrophilic substitution reactions more readily than benzene itself (i.e., faster rate or milder conditions). Such a group is said to be an activating group (Table II.5.1).

Table II.5.1.

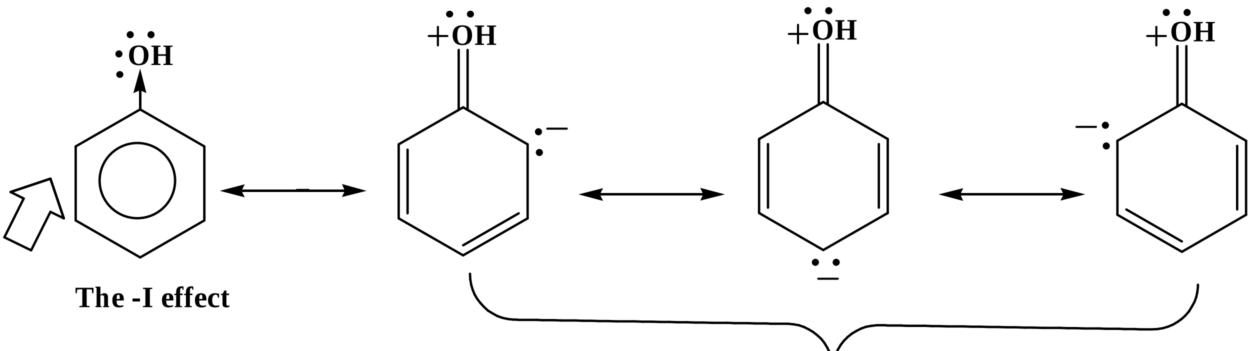
Substituents	Reactivity	Orientation
$-\ddot{N}R_2$, $-\ddot{N}H_2$, $-\ddot{O}H$, $-\ddot{O}:^{\ominus}$	**Strongly activating**	**ORTHO- PARA DIRECTORS**
$-\ddot{N}-\overset{O}{\overset{\parallel}{C}}-R$, $-\ddot{O}-\overset{O}{\overset{\parallel}{C}}-R$, $-\ddot{O}R$	**Activating**	
-R,-Ar	**Weakly activating**	
-H	**(Standard for comparision)**	
$-\ddot{X}:^{\ominus}$, $-CH_2X$	**Weakly deactivating**	
$-NO_2$, $-SO_3H$, $-\overset{\vert}{C}=O$, $C\equiv N$, $-\overset{+}{N}R_3$, $-\overset{+}{S}R_2$, $-CF_3$	**Strongly deactivating META DIRECTORS**	

Effect of substituents on electrophilic aromatic substitution

On the other hand, an electron-withdrawing group, (-*I* effect) will exert the opposite effect. It destabilizes the positive charge of the reaction intermediate (the σ complex) in the rate determining step by developing electron density away from the ring, thus intensifying the positive character of the ring carbons compared with benzene to raise the activation energy of its rate-determining step, thus rendering the compound C_6H_5-S less reactive than benzene in electrophilic substitution reactions. Such a group is called a deactivating group (Table II.5.1), and an example is of $-N^+Me_3$ group which with its –*I* effect is deactivating.

A substituent however, releases electron density to the aromatic ring or depletes electron density from it via both inductive (*I*) and resonance (*R*) effects. This is explained by taking, phenol, toluene, chlorobenzene and an aryl ketone as examples.

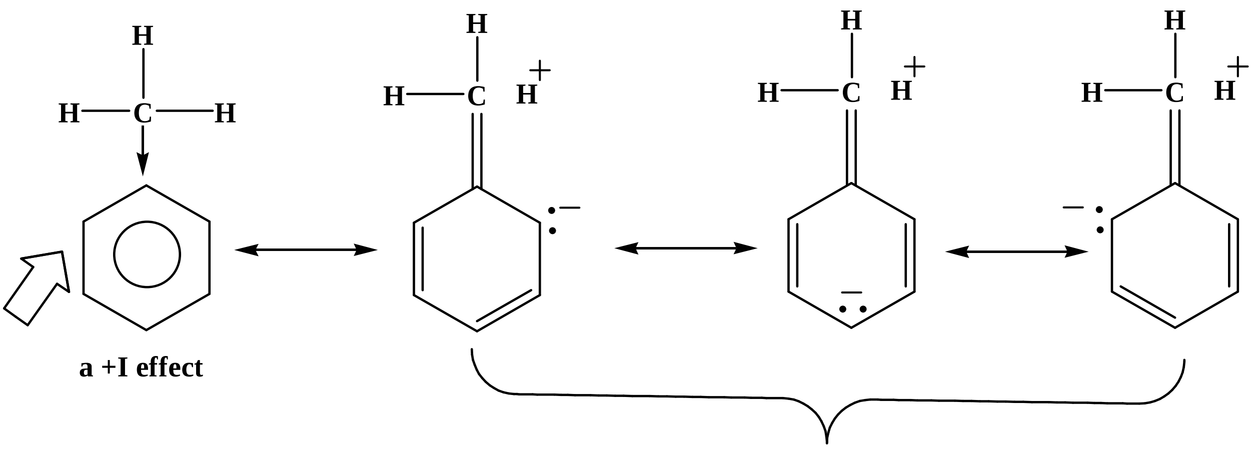
(i). Phenol: The OH group is activating +*R* effect > -*I* effect. Electrons are therefore, released from this group into the ring making the ring positions in phenol more electron-rich than those of (*o* and *p*) benzene (Fig) it, therefore, is more susceptible to electrophilic attack than benzene.



The -I effect

a +R effect

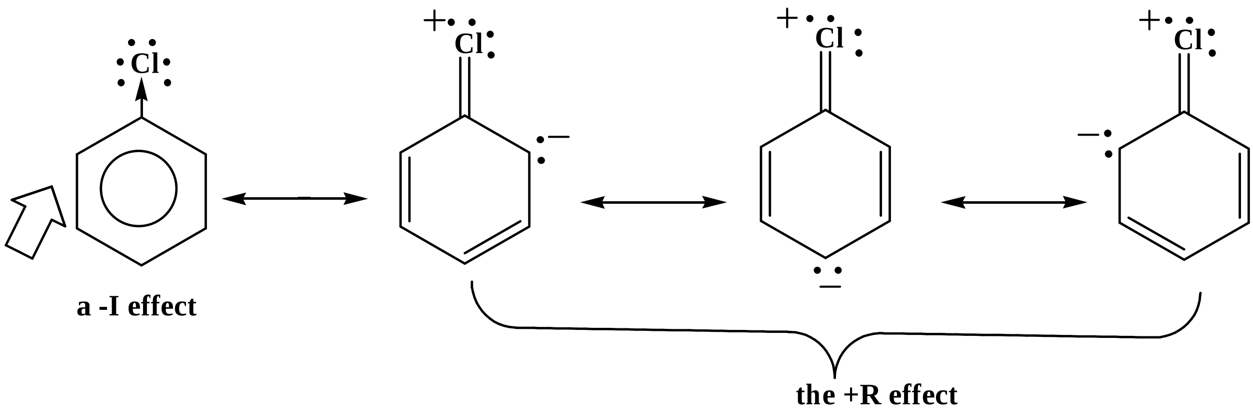
(ii). Toluene: The CH_3 group is activating +*I* and +*R* effects (caused by hyperconjugation) work together to push electron density into the ring (Fig) and like phenol, therefore, toluene is more susceptible to electrophilic attack than benzene.



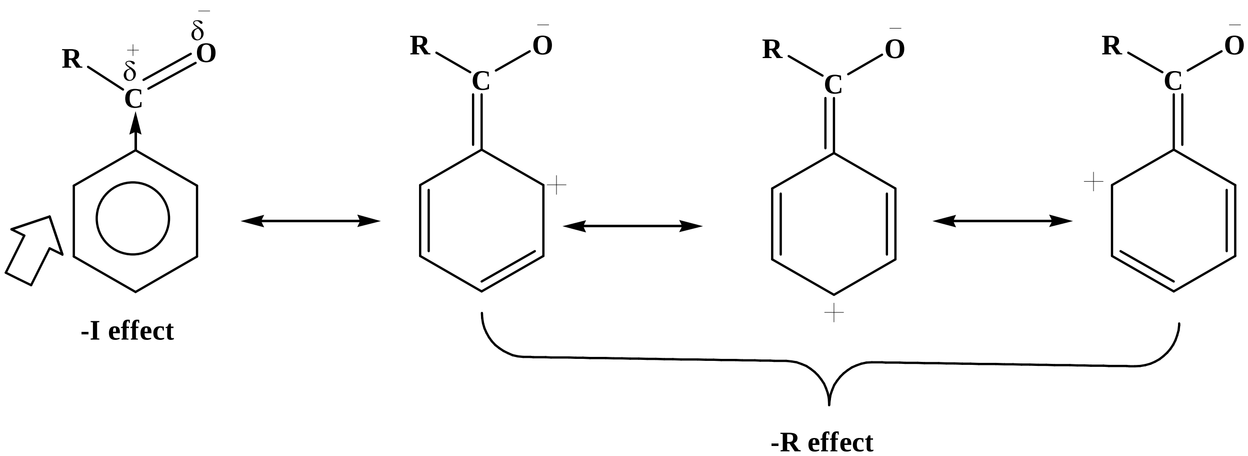
a +I effect

+R effect (hyperconjugation)

(iii). Chlorobenzene: The Cl atom on the other hand is deactivating because –*I* effect > +*R* effect. There is a slight drain of electron density away from the ring positions of this compound so that they are comparatively less electron-rich than those of benzene (Fig). The compound thus is less susceptible electrophilic attack than benzene.

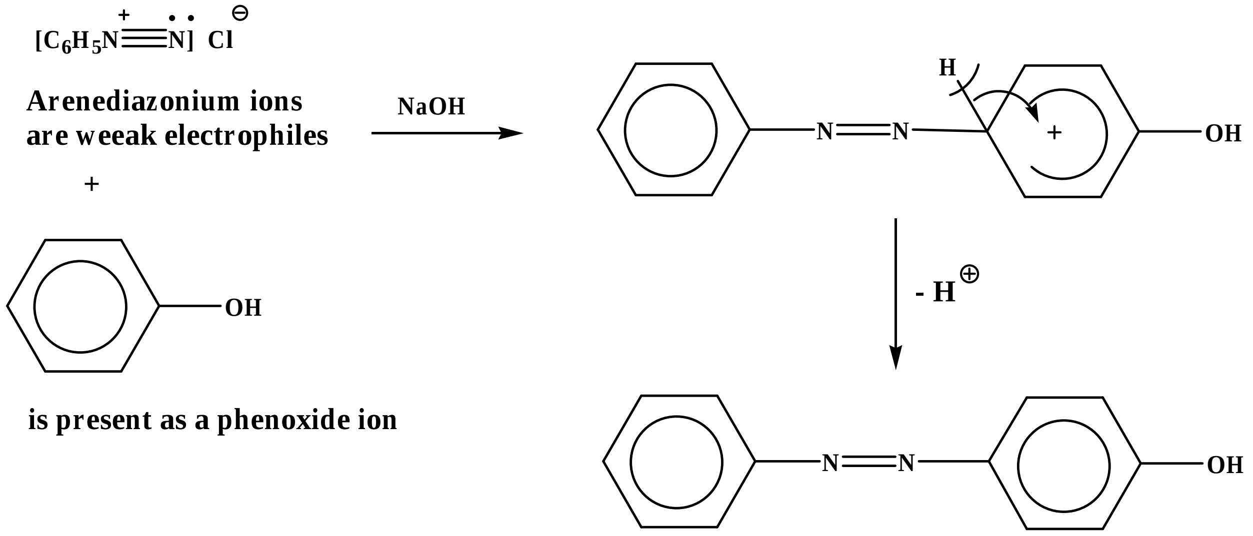


(iv). Aryl-ketones: The RCO-group is deactivating, since –*I* effect and –*R* effect now work hand in hand together to draw electron density away from the ring, to make ring positions less electron-rich compared to those of benzene. The compound is, thus, less susceptible to electrophilic attack than benzene.



(v). Summary: Substituents with –*I* and –*R* effects e.g., NO_2, COR, CO_2R, CN are deactivating and *meta* directing, however, their deactivating influence is less than the positively charged $-N^+Me_3$ group.

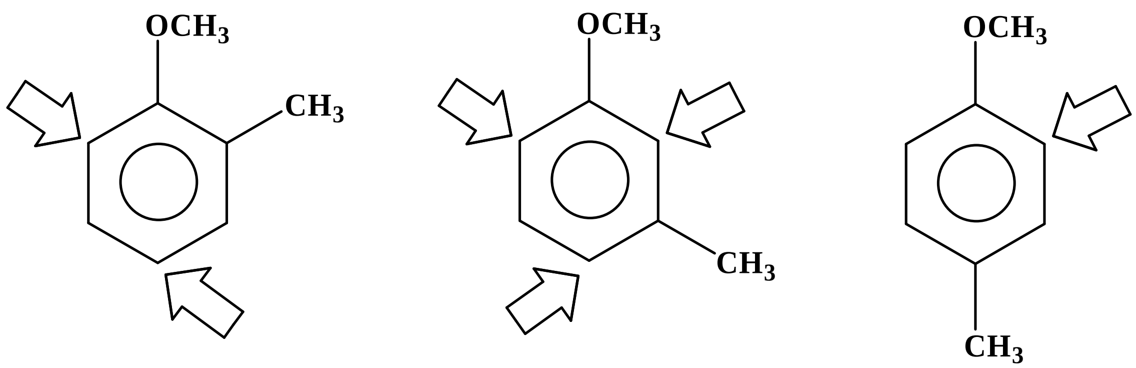
Substituents with +*I* and +*R* effects like alkyl groups are activating and *ortho, para*-directing. The $-O^-$ substituent e.g., in a phenoxide ion ArO^-, is also of +*I* and +*R* type and these effects are much stronger compared with those in an alkyl group. For this reason, the phenoxide ions are even more reactive toward electrophilic substitution than are phenols themselves. Thus the weak electrophiles like phenols in electrophilic aromatic substitution (a diazo coupling reaction). The diazo coupling with phenols occurs most readily in slightly alkaline solution, when an appreciable amount of the phenol is present as its more reactive phenoxide ion. In case the *p*-position is not open then coupling takes place in the *o*-position as is so in 4-methylphenol (*p*-cresol).

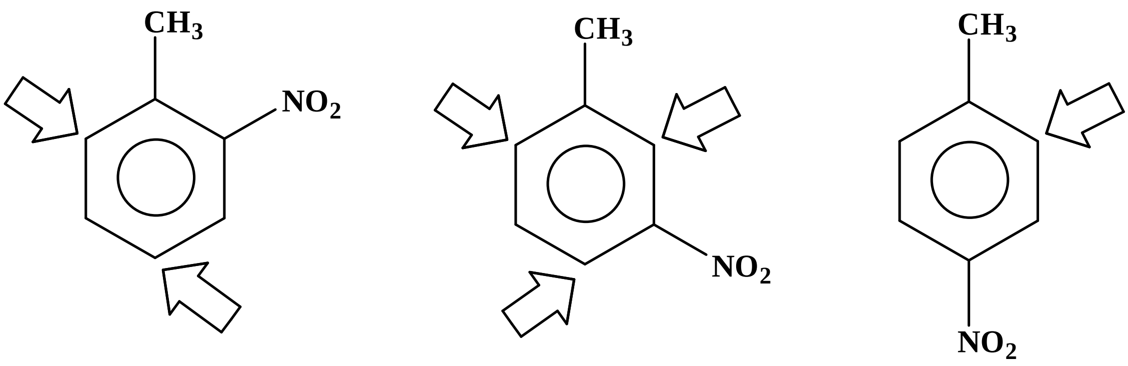


An azo compound
(*p*-hydroxyazobenzene)

5.3. ELECTROPHILIC SUBSTITUTION OF DISUBSTITUTED BENZENES

Aromatic substitution reactions of disubstituted benzenes usually lead to a mixture of products because of competing orientation influences of two substituents to afford a mixture of products. If both substituents are activating groups, the position of the incoming electrophile is primarily governed by the orientation influence of the stronger of the two activating groups. If one substituent is activating while the other is deactivating, the position of the entering group will be dictated mainly by the activating group (FIG). The position between the two *meta* substituents is least attacked by the incoming electrophile due to the steric hindrance.





5.4. LET US SUM UP

In this lesson, we:

* Pointed out the orientation and reactivity of electophilic substitution on monosubstituted and disubstituted benzenes

5.5. CHECK YOUR PROGRESS

1. Explain the effect of substituents on electrophilic aromatic substitution reactions.
2. Explain the electrophilic substitution of disubstituted benzene.

5.6. POINT FOR DISCUSSION

1. Briefly explain the theory of orientation in electrophilic aromatic substitution.
2. "A substituent releases or depletes electron density to the aromatic ring". Explain the statement with examples.

5.7. REFERENCES

1. Jerry march, Advanced Organic Chemistry, Fourth edition, Wiley India edition.

2. P.S. Kalsi, Organic reactions and their mechanisms, Second edition, New age international publishers.

LESSON: 6 – TYPICAL AROMATIC ELECTROPHILIC SUBSTITUTION REACTIONS

CONTENTS

6.0. AIMS AND OBJECTIVES

The aim is to motivate and enable the student to comprehend the possible chemical route by which the aromatic electrophilic substitution reactions may proceed.

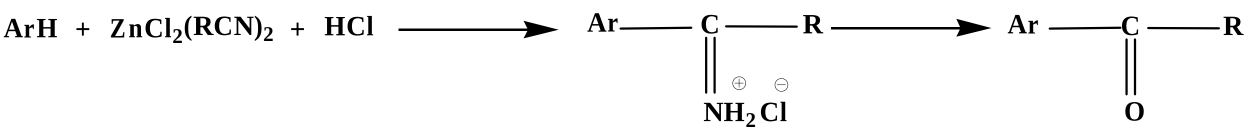
On successful completion of this lesson the student should have:

* learnt possible reaction pathways in typical aromatic electrophilic substitution reactions.

6.1. GATTERMAN REACTION

$$\mathbf{ArH + Zn(CN)_2 \xrightarrow{HCl} ArCH{=}\overset{\oplus}{N}H_2\,\overset{\ominus}{Cl} \xrightarrow{H_2O} ArCHO}$$

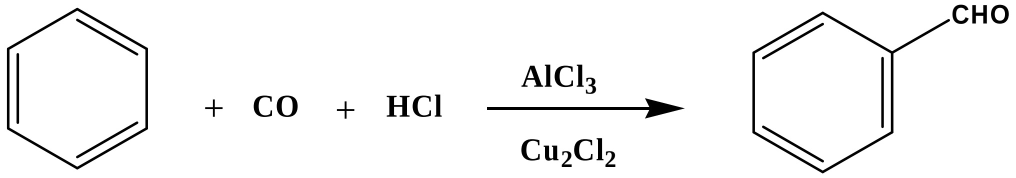
Formylation with $(Zn(CN)_2)$ and HCl is called the Gattermann reaction. In contrast to reaction this method can be successfully applied to phenols and their ethers and to many heterocyclic compounds. However it cannot be applied to aromatic amines. In the original version of this reaction the substrate was treated with $HCl, HCN, ZnCl_2$ but the use of $(Zn(CN)_2)$ and HCl makes the reaction more convenient to carry out and does not reduce yields. The mechanism of the Gattermann reaction has not been investigated very much, but there is an initial nitrogen containing product that is normally not isolated but is hydrolyzed to aldehyde.



The first stage consists of an attack on the substrate by species containing the nitrile and HCl to give an imine salt. In the second stage the salts are hydrolyzed to the products.

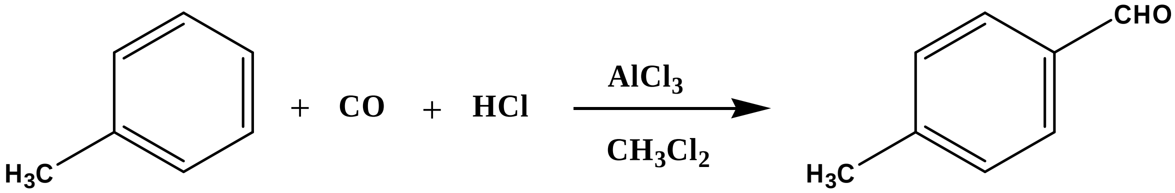
6.2. GATTERMANN-KOCH REACTION

The formylation of benzene and alkylbenzene using carbonmonoxide and hydrogen chloride in the presence of aluminium chloride (catalyst) and a small amount of cuprous chloride (co-catalyst) under high pressure is known as Gattermann-Koch reaction.



Benzene **Benzaldehyde**

Usually, nitrobenzene or ether is used as solvent. In the case of alkylbenzene, the aldehyde group is introduced into the para position only. This method is used industrially to prepare arylaldehdes.

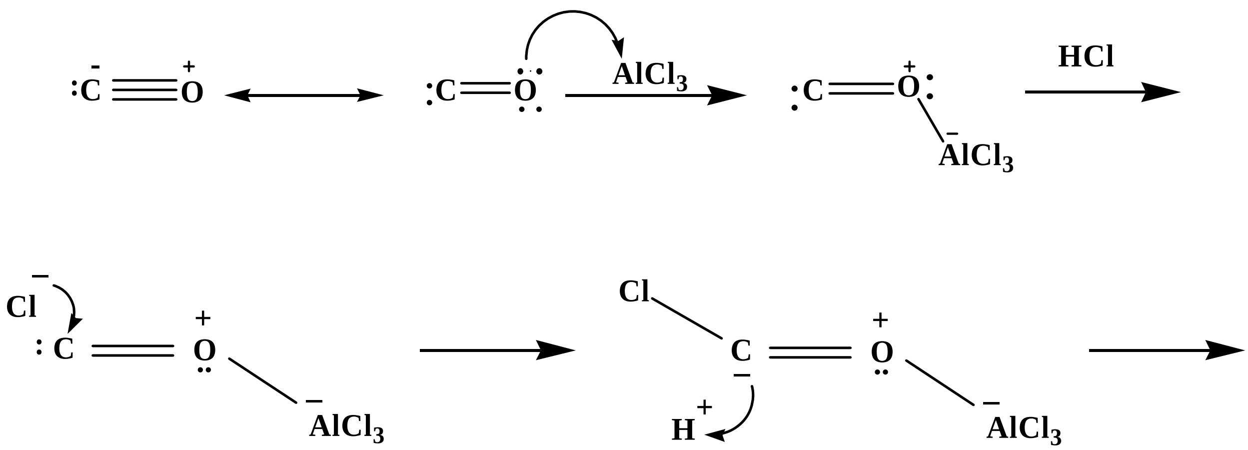


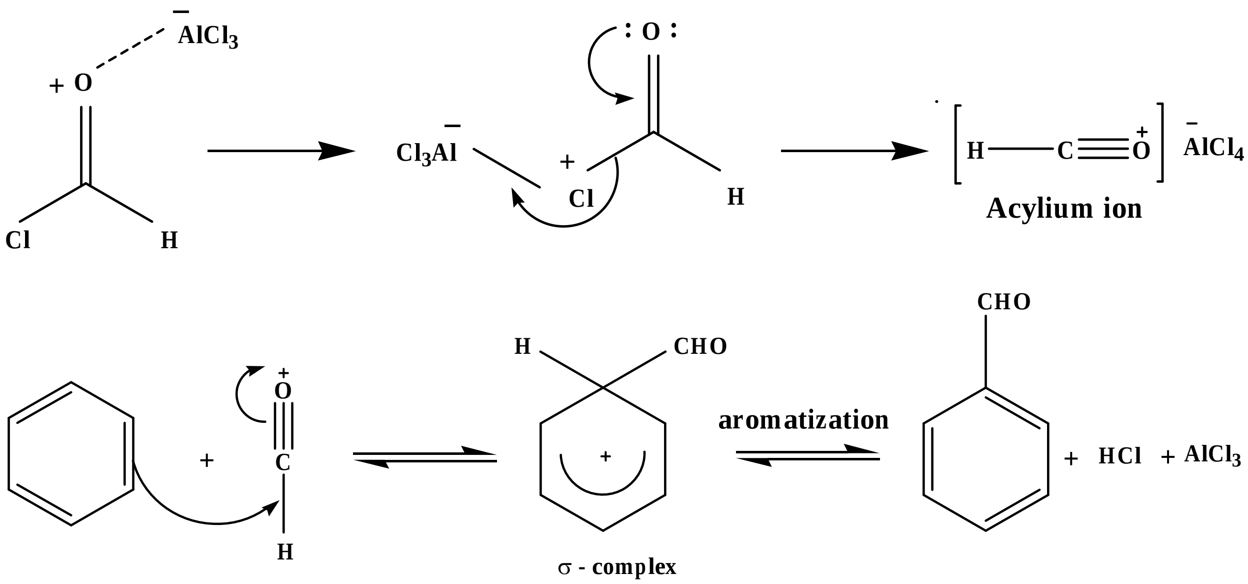
Toulene ***p*-tolualdehyde -50%**

The Gattermann-Koch aldehyde synthesis is not applicable to phenols o their ethers, amino aromatic species and also when the aromatic ring is strongly deactivated. (Nitrobenzene)

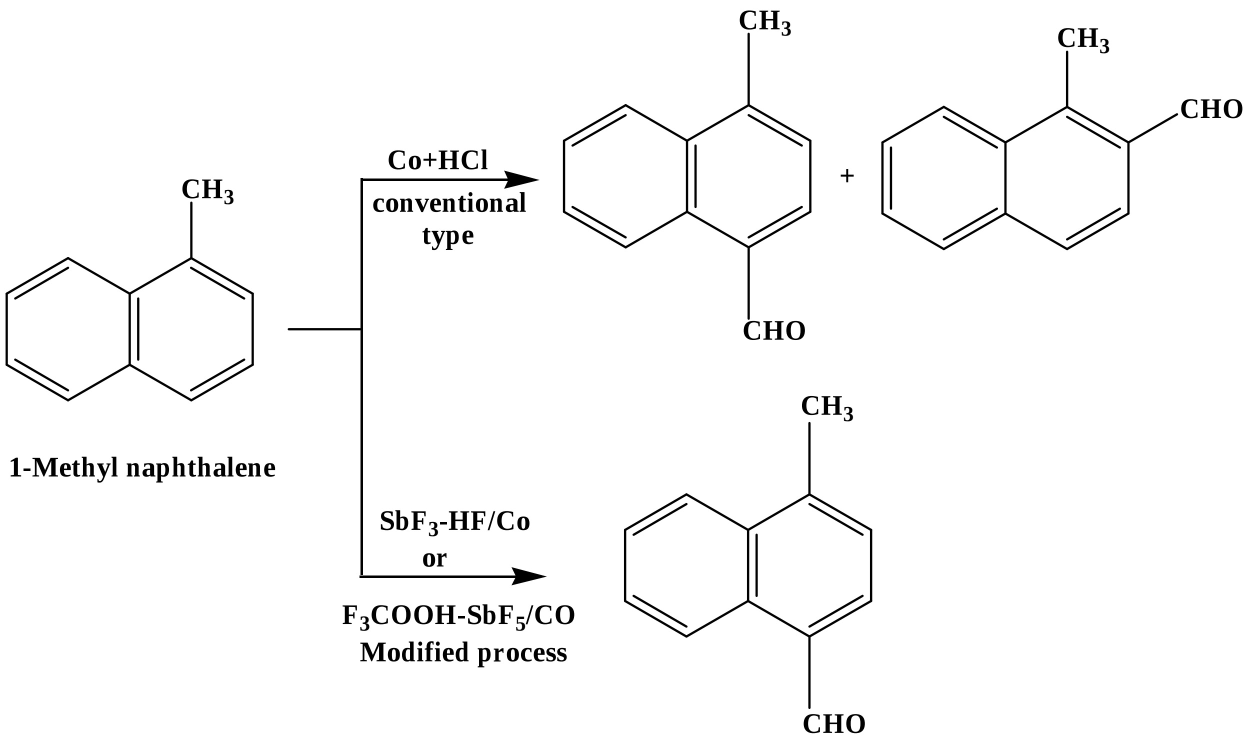
Mechanism:

The Gattermann-Koch formylation is considered as a typical electrophilic aromatic substitution with high para regioselectivity. The most likely electrophile is the acylium ion $[HCO^{+}]^{+}$ in the ion pair $[HCO]^{+}[AlCl_{4}]^{-}$. Common factors such as electron density of the aromatic substrate, reactivity of electrophile, stability of reaction intermediates, and steric factors may influence the regioselectivity.



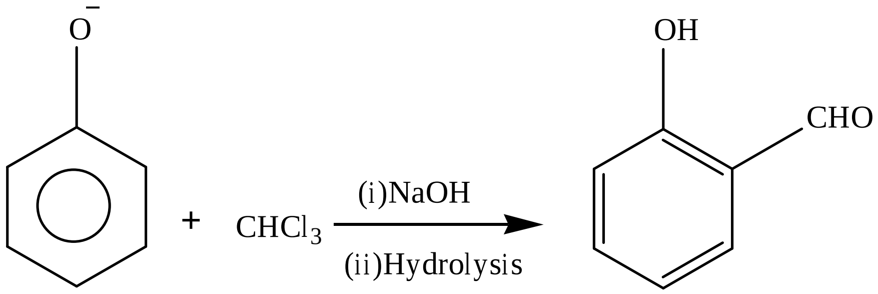


Application:

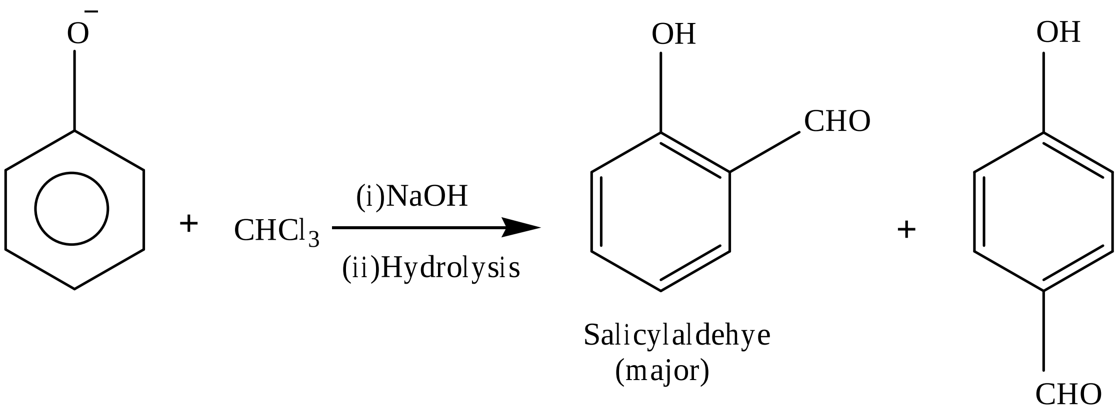


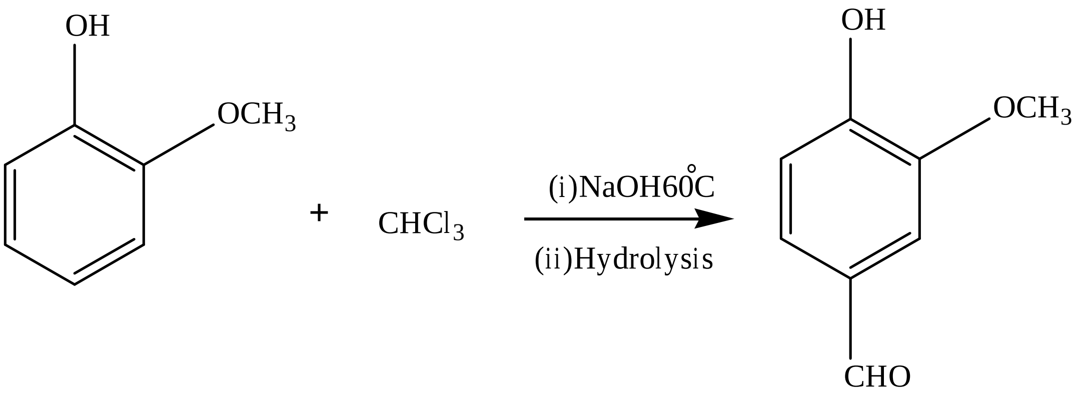
6.3. THE REIMER-TIEMANN REACTION

The formylation of activated aromatic ring compound with chloroform in alkaline solution is known as Reimer-Tiemann reaction. The method is useful only for phenols and certain heterocyclic compounds such as pyrroles and indoles. It leads preferentially to the formation of an *ortho* formylated product; when both the *ortho* positions are blocked, the incoming group occupies the *para* position.



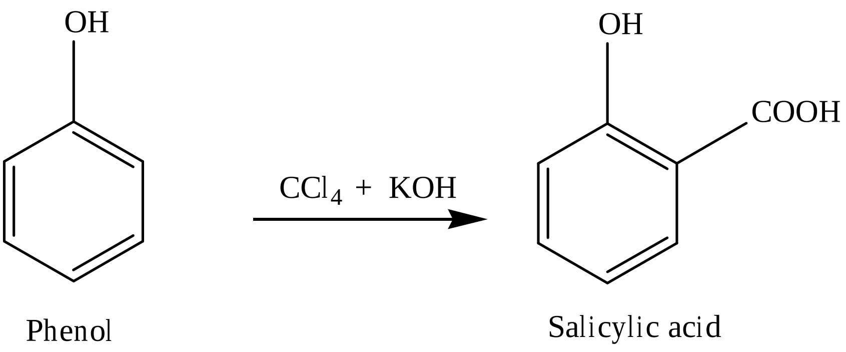
Salicylaldehye





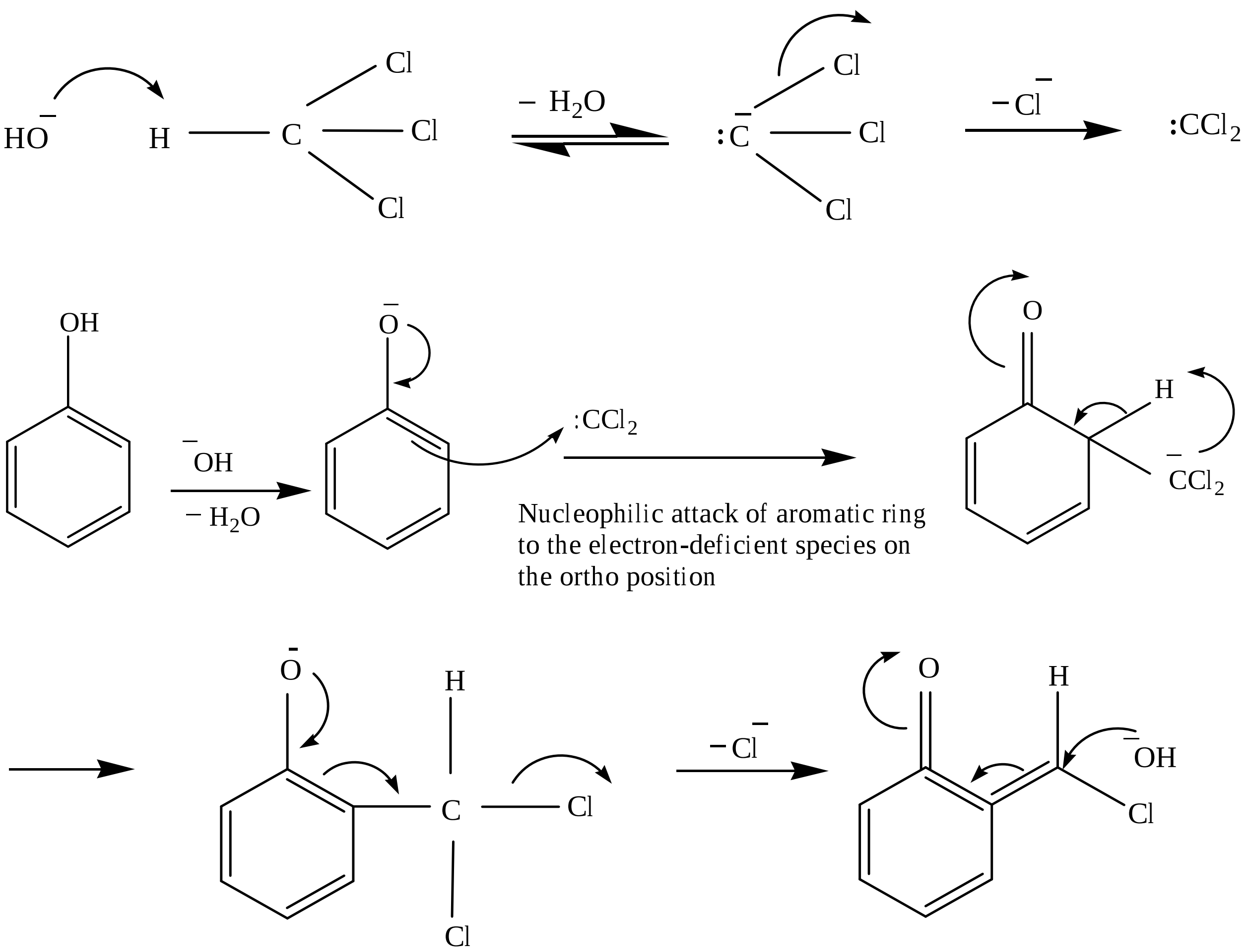
Vanillin

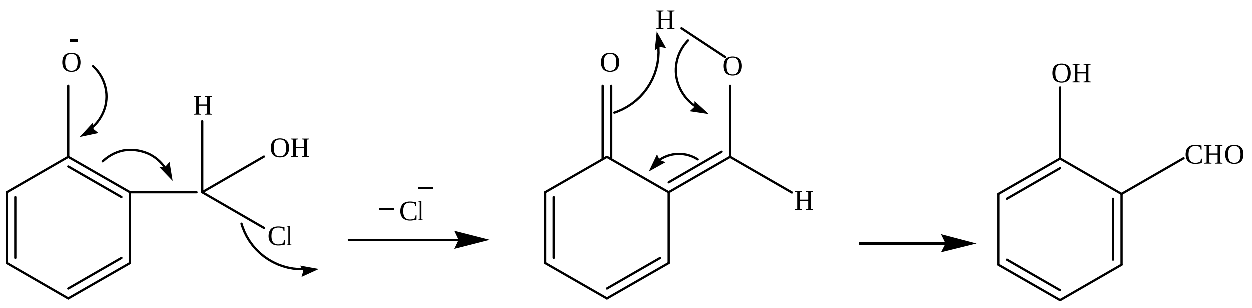
The Riemer-Tiemann reaction is mainly used for the synthesis of ortho-hydroxy aromatic aldehydes. Yields are generally low. However it has been reported that application of ultrasound leads to shorter reaction times and improved yields. If CCl_4 is used instead of $CHCl_3$, carboxylation occurs under the reaction conditions.



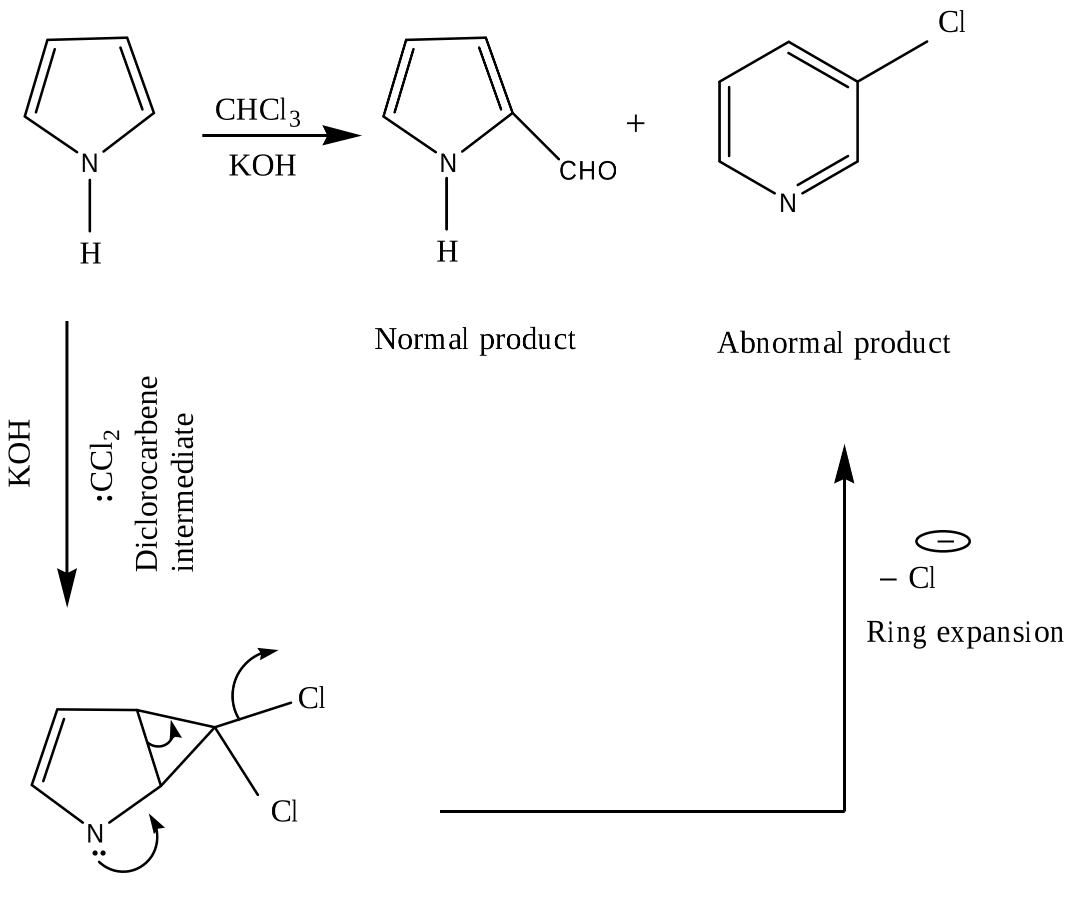
Mechanism

The reaction is believed to proceed in the following manner. Firstly the dichlorocarbene $(:CCl_2)$ an electron-deficient reactive species is formed by the reaction of chloroform with strong alkali. In the second step, it attacks the electron rich ortho position of the aromatic ring to form orhtodichloromethylphenolate, which hydolysis to give hydroxyarylaldehyde.



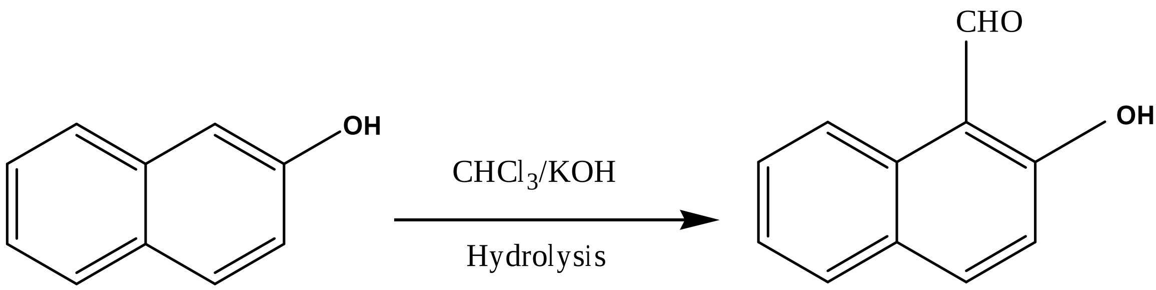


The involvement of dichlorocarbene as the reaction intermediate receives support from the fact that certain substrates (Eg) pyrrole under the reaction condition gave side products (called as abnormal product) along with the normal products or instead of these.



Application

The reaction offers a useful method for introducing formyl group in phenolic compound as well as certain heterocycles. For (Eg).



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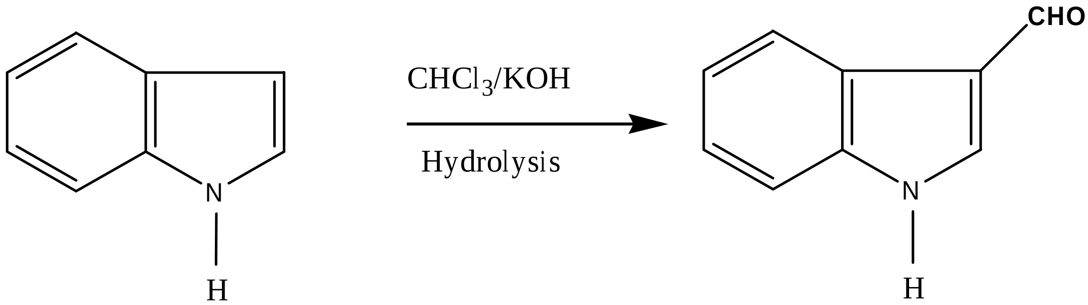


(ii)

6.4. KOLBE REACTION

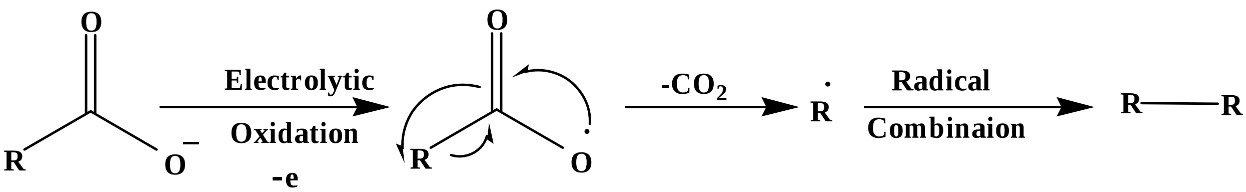
Decarboxylative dimerization

$$2RCOO^{\ominus} \xrightarrow{\text{Electrol}} R-R$$

Electrolysis of carboxylate ions, which results in decarboxylation and combination of the resulting radicals, is called the Kolbe reaction. it is used to prepare symmetrical $R-R$ where R is straight or branched chained, except that little or no yield is obtained when there is α branching. when R is aryl , the reaction fails. Many functional groups may be present, though many others inhibit the reaction. Unsymmetrical $R-R'$ have been made by coupling mixtures of acid salts. A free radical mechanism is involved.

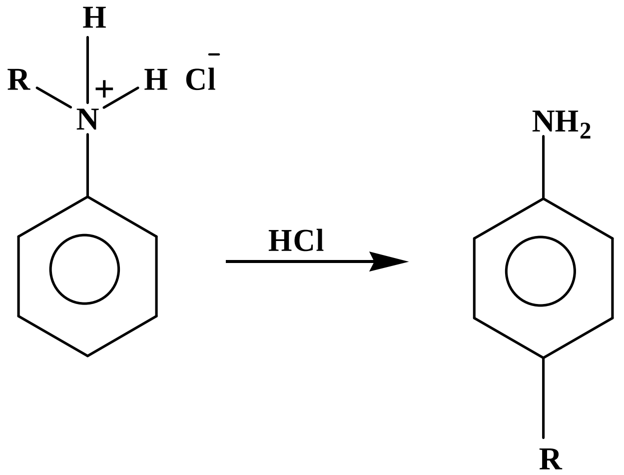
$$RCOO^{\ominus} \xrightarrow[\text{Oxidation}]{\text{Electrolytic}} RCO\dot{O} \xrightarrow{-CO_2} R-R$$

Mechanism



6.5. HOFFMANN-MARITUS REACTION

When *HCl* salts of aryl alkyl amines are heated at about 200 to 300 migration occurs. This is called the Hofmann- Maritus reaction. it is an intermolecular reaction, since crossing is found. For example methyl anilinium bromide gave not only the normal products *o* and *p*-toluidine but also aniline and di and trimethylanilines. As would be expected for an intermolecular process, there is ionization when *R* is primary. With primary *R*, the reaction probably goes through the alkyl halide formed initially in an S_N2 reaction.

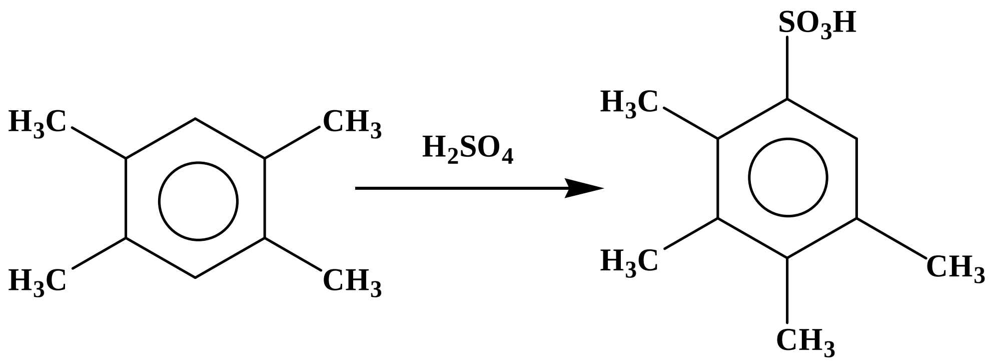


$$R\overset{\oplus}{N}H_2Ar \;+\; Cl^{\ominus} \longrightarrow RCl \;+\; ArNH_2$$

Evidence for this view is that alkyl halides have been isolated from the reaction mixture and that Br^-, Cl^-, I^- gave different ortho/para ratios, which indicates that the halogen is involved in the reaction. Further evidence is that the alkyl halides isolated are rearranged even though the alkyl groups in the ring are rearranged. Once the alkyl halides are formed, it reacts with the substrate by a normal friedel-crafts Alkylation process, accounting for the rearrangement. When *R* is secondary or tertiary carbocation may be directly formed so that the reaction does not go through the alkyl halides.

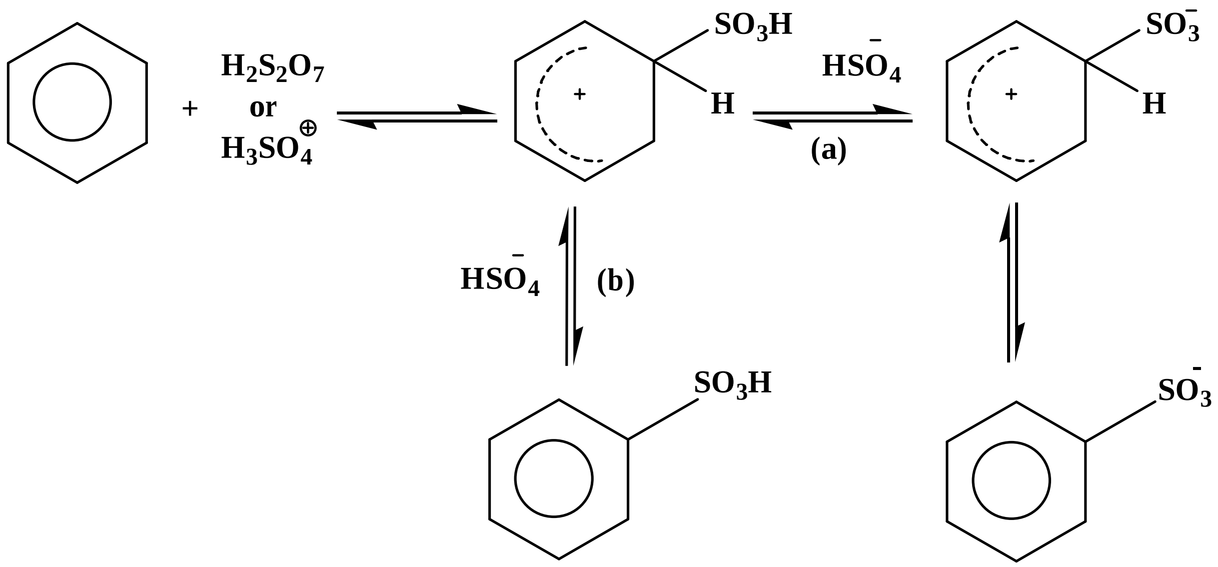
6.6. JACOBSEN REACTION

When polyalkyl or polyhalobenzenes are treated with sulphuric acid, the ring is sulphonated, but rearrangement also takes place. The reaction, known as Jacobsen reaction, is limited to benzene rings that have at least four substituents, which may be any combination of alkyl and halogen groups, where the alkyl groups may be ethyl or methyl and the halogen iodo, chloro, bromo. When isopropyl or t-butyl groups are on the ring, these groups are cleaved to give olefins. Since a sulpho group can later be removed. The Jacobsen reaction can be used as a means of rearranging polyalkylbenzenes. The rearrangement always brings the alkyl or halo



groups closer together than they were originally. Side products in the case illustrated above are pentamethylbenzenesulphonic acid, 2, 4, 5 trimethyl benzenesulphonic acid, etc., indicating an intermolecular process, at least partially.

The mechanism of the Jacobsen reaction is not established, but a likely possibility or attack by a sulphonating species at an ipso position .with the alkyl group thus freed migrating inter or intramolecularly by another position.



Path ‘a’ is the principal route, except at very high H_2SO_4 concentrations, when path ‘b’ becomes important. With $H_3SO_4^+$ the first step is rate determining under all conditions, but in $H_2S_2O_7$ the first step is the flow step only upto about 96% H_2SO_4, when a subsequent proton transfer becomes partially rate determining step.

6.7. LET US SUM UP

In this lesson, we:

- pointed out the typical aromatic electrophilic substitution reactions such as
- Gattermann reaction
- Gattermann-Koch reaction
- the Reimer-Tiemann reaction

- Kolbe reaction
- Hoffmann-Maritus reaction and
- Jacobsen reaction

6.8. LESSON END ACTIVITIES

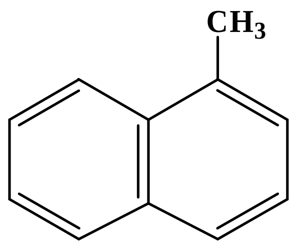
1. The Gattermann Koch reaction for the formulation of an aromatic ring is regarded as aromatic electrophilic substitution reaction. Consider the following reaction sequence for the synthesis of benzaldehyde.

$$C_6H_6 + CO + HCl \longrightarrow C_6H_5CHO + HCl$$

If we use DCl in place of HCl, shall we get C_6H_5CHO or C_6H_5CDO, Give reason?

2. Predict the product for the following reaction.

(a) $ArH + Zn(CN)_2 \xrightarrow[\text{Hydrolysis}]{HCl}$

(b)  $\xrightarrow{CO + HCl}$

6.9. POINT FOR DISCUSSION

1. Briefly explain the mechanism and applications of Reimer-Tiemann reaction.
2. Write notes on
   (a) Kolbe reaction
   (b) Hoffmann-Martius reaction
   (c) Jacobson's reaction

6.10. REFERENCES

1. Jerry march, Advanced Organic Chemistry, Fourth edition, Wiley India edition.

2. P.S. Kalsi, Organic reactions and their mechanisms, Second edition, New age international publishers.

UNIT-III

LESSON: 7 – ALIPHATIC NUCLEOPHILIC SUBSTITUTION

CONTENTS

7.0. AIMS AND OBJECTIVES

The aim is to motivate and enable the student to comprehend the possible chemical route by which the aliphatic nucleophilic substitution reactions may proceed.

On successful completion of this lesson the student should have:

* learnt possible reaction pathways in aliphatic nucleophilic substitution reactions.

7.1. INTRODUCTION

Nucleophilic substitution reaction involves the displacement of a nucleophile by another. These reactions have great synthetic importance. A classic example is the hydrolysis of alkyl halides.

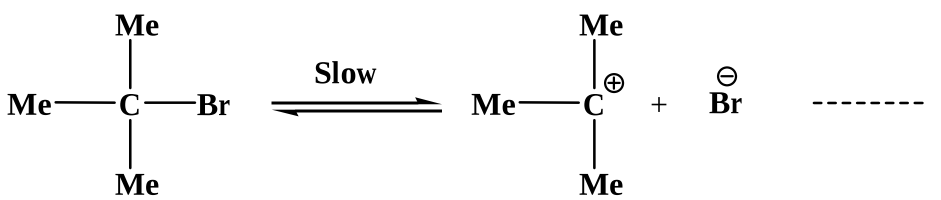
$$\overset{\ominus}{HO:} \;+\; R:X \longrightarrow HO:R \;+\; \overset{\ominus}{:X}$$

The nucleophile furnishes an electron pair to the carbon from which the leaving group departs with the bonding pair of electrons. Investigations by Ingold and co-workers indicate that nucleophilic substitution reaction can proceed by two different paths which have been designated by Ingold's as S_N1 and S_N2 depending on the nature of the substrate, the nucleophile, the leaving group and the solvent.

7.2. S_N1 MECHANISM

Kinetic studies of the hydrolysis of t-Butyl bromide indicate that the rate of the reaction is proportional to the concentration of the alkyl halide. (i.e.) rate $\propto$ [R_3CX].
Since the rate of the reaction is dependent on one of the reactants, the reaction is a first order reaction. Nucleophilic substitution reaction which follows first order kinetics is designated S_N1 (substitution nucleophilic unimolecular).

As the rate of the reaction is independent of $[\overset{\ominus}{OH}]$, it is interpreted that the halide undergoes slow ionization in the first step producing carbocation intermediate. In the second step a rapid attack of $\overset{\ominus}{OH}$ on the carbocation completes the hydrolysis.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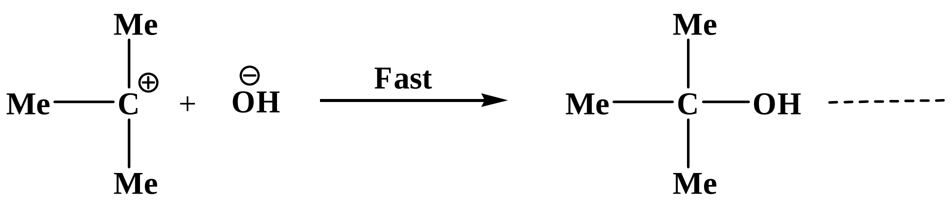
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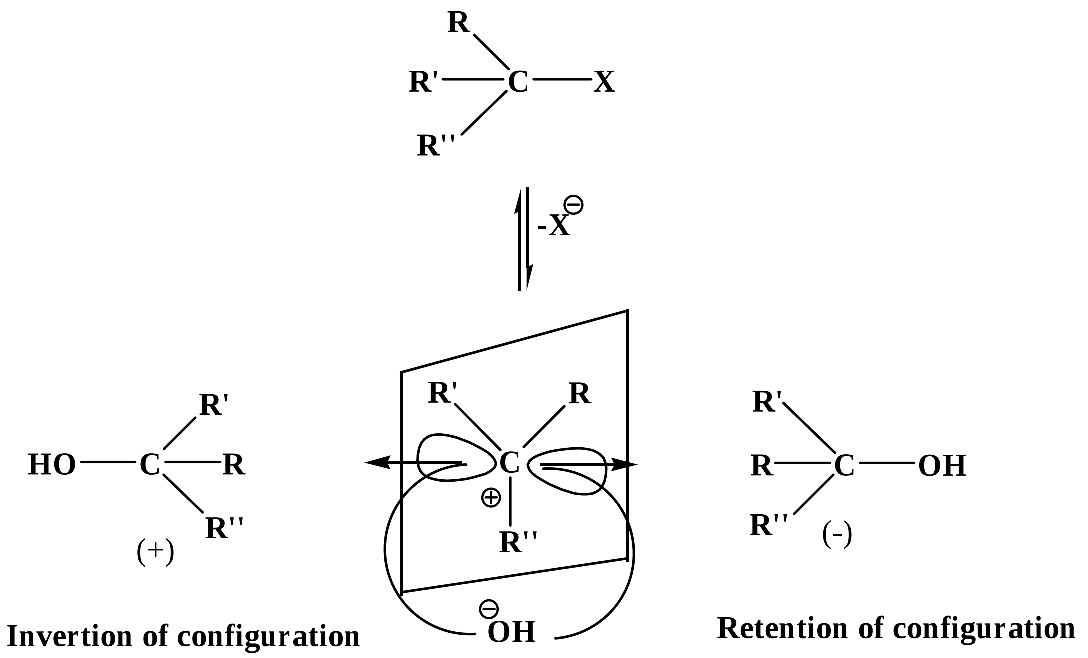
The energy required for the ionization of the halide is supplied by the energy of salvation of the ions. Since a carbocation is formed in the slowest step, the alkyl halide which can most easily form a stable carbocation will favor hydrolysis by S_N1 path. Hence, the order of hydrolysis of alkyl halides by S_N1 path is:

$$\text{Allyl, Benzyl} > 3^0 > 2^0 > 1^0 > CH_3X$$

7.2.1. STEREOCHEMISTRY OF S_N1 REACTION

Since a carbocation is flat (SP^2, trigonal planar) with the vacant 2P orbital vertical to the plane bearing the three groups, the attack o the reagent can occur from either side of the plane with equal probability, i.e. a racemic product should result if the alkyl halide is chiral.



Pure racemisation (50/50 mixture) is rarely observed. This is because the leaving group lies close to the carbocation shielding the side from the attack till it has sufficiently moved away. Thus, more attack of the reagent occurs from the opposite side to the leaving group. This causes more inversion than retention of configuration. Stable carbocations have longer life to permit salvation from either side of the plane of the carbocation resulting in greater proportion of racemisation. Greater proportion of inversion is observed with more nucleophilic solvent due to faster attack from the opposite side to the leaving group.

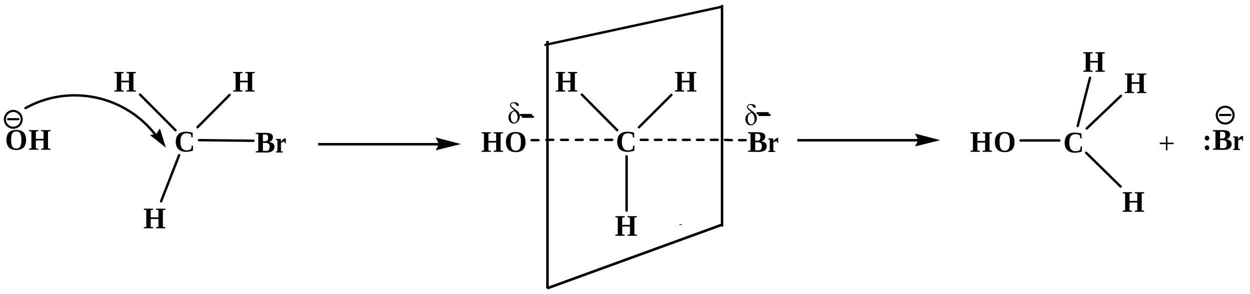
7.3. S_N2 MECHANISM

Nucleophilic substitution reactions which follow second-order kinetics are called S_N2 (substitution nucleophilic reactions which follow second-order kinetics depending upon the concentrations of both the reactants. Thus, the rate of hydrolysis of methyl bromide with NaOH has been found to be of second order, i.e.,

$$\text{the rate} \propto [CH_3Br]\,[OH^-]$$

Since the rate determining step involves both CH_3Br and OH^-, a collision between the two reactants resulting in the direct displacement of Br^- by OH^- occurs in such a way that while a new C-OH bond is being formed, the C-Br bond starts breaking, i.e. the bond formation and the bond breaking are simultaneous. Hence, the reaction is a concerted one step reaction without any intermediate.

During the collision an energetic hydroxide ion approaches the methyl bromide molecule from the side opposite to bromine to avoid repulsion, i.e. at 180° to the leaving group- a back-side attack. When the OH^- is sufficiently near the electron-deficient carbon of the substrate, it begins to form a bond with it and the C-Br bond starts stretching. At one stage of the reaction, a state is reached when the OH and Br are partially bonded to the central carbon and the non-participating groups lying in a plane perpendicular to the line HO….C….Br. This state is called the transition state. In the transition state partial negative charge of the hydroxide ion is transferred to bromine via the carbon atom. With further approach of hydroxide, a complete C-OH bond is formed and bromine departs with the bonding pair of electrons.



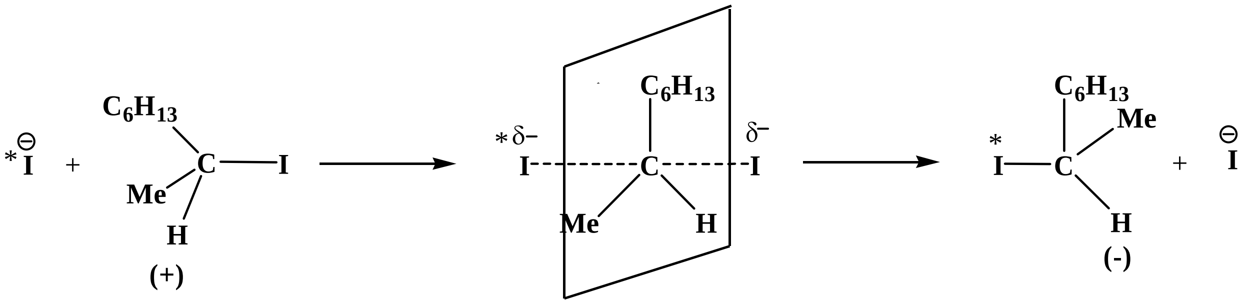
Transition state

In the transition state five groups or atoms are bonded to the α-carbon. As we go along the series from methyl bromide to t-butyl bromide, the increasing crowding of the carbon bearing the bromine atom progressively decreases the nucleophilic attack. Also, the increasing +1 effect along the series makes the carbon bearing the bromine progressively less positively polarized and consequently less readily attacked by the nucleophile. The steric factor is, however, more important than the electronic factor. Hence, the E_{act} for the formation of the transition state will be highest for 3° halides and least for methyl halides. Therefore, the rate of hydrolysis of alkyl halides by S_N2 path is CH_3X >1° > 2° > 3°, reverse of S_N1 path.

7.3.1. STEREOCHEMISTRY OF S_N2 REACTION

From the course of the direct displacement reaction as shown above, it is seen that the molecule is turned inside out. A Walden inversion is therefore expected to take place. An optically active halide on hydrolysis by S_N2 path, therefore, should give an alcohol with inversion of configuration. The change of configuration can be established by observing the directions of optical rotation. In this case, however the substrate (bromide) and the product (alcohol) are two different compounds. The directions of rotation and the configurations of two different compounds are not usually related. Hence, the configurations of the substrate and the product should be related to arrive at the conclusion.

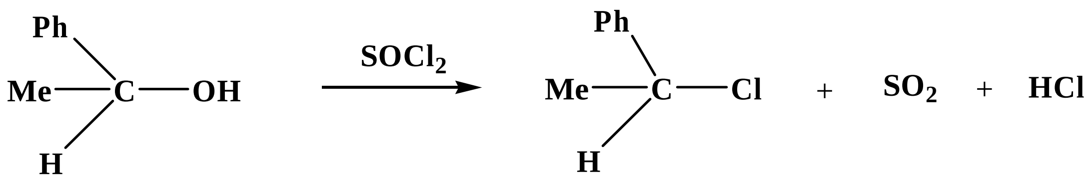
An elegant method has been suggested (Huges and Ingold) to establish the inversion of configuration in S_N2 reaction. The method involves the conversion of (+2) iodooctane with potassium radioiodide ($K^{128}I$) in acetone to (-) 2-iodooctane. The reaction was found to be bimolecular (S_N2), i.e. rate $\propto$ [$C_6H_{13}CHICH_3$] [I*].The exchange of ordinary iodide with the radioactive iodide was accompanied by the loss of optical activity. This indicates the formation of (-) isomer from the (+) isomer to result in racemisation.



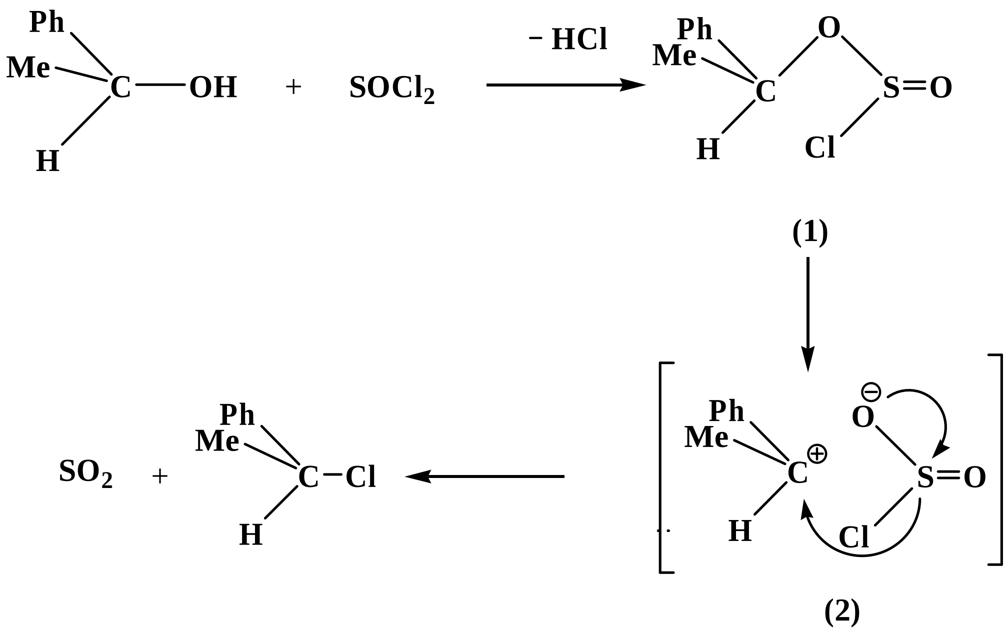
The rate of loss of optical activity (i.e. racemisation) was found to be twice the rate of iodine exchange (i.e. inversion) - one (+) molecule is inverted and another (+) molecule pairs with it to form a (±) modification. The above formulated mechanism of S_N2 reaction is therefore established. Inversion of configuration is always indicative of S_N2 reaction.

7.4. S_N i MECHANISM

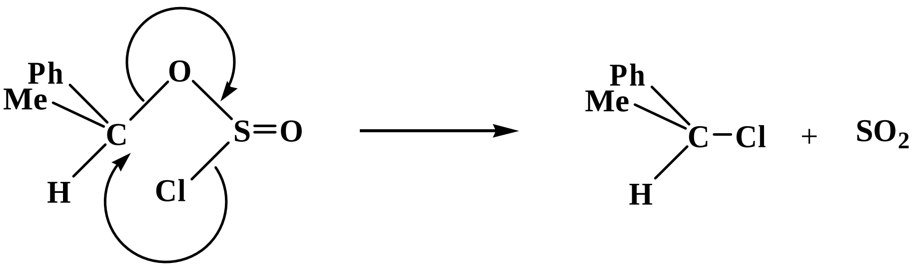
It means Substitution Nucleophilic Internal mechanism. This follows second-order kinetics and yet with no change in the configuration of the product is identified as S_Ni. Thus, the esterification of chiral alcohols with thionyl chloride results in the retention of configuration of the product.



The rate of the reaction is found to be dependent on both the reactants, i.e., rate $\propto$ [PhCH(Me)OH] [$SOCl_2$]. Thionyl chloride reacts with alcohol to furnish alkyl chlorosulphite (1) which has the same configuration as the alcohol. There is evidence to show that the transformation of (1) to product involves an ion pair (2). The chloride ion is then supplied by the chlorosulphite anion for attack. The attack occurs from the front side since the chlorosulphite anion is held from the front side. Hence, no inversion of configuration is observed.

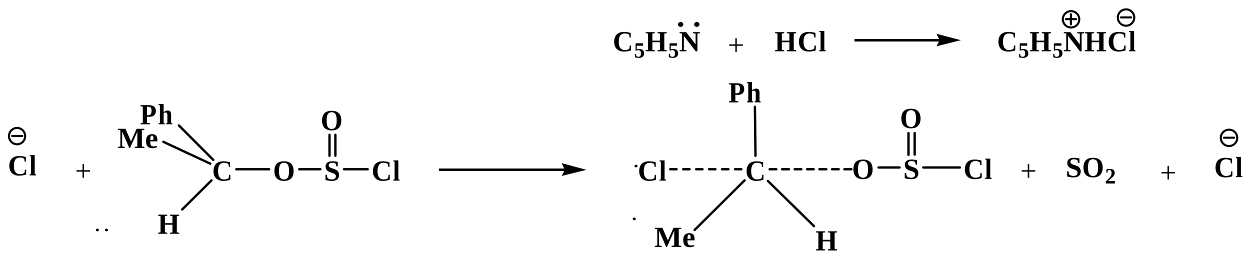


The overall reaction may be considered as an internal attack.



Hence the reaction is designated S_Ni as to distinguish it from S_N2.

When the reaction is carried out in the presence of pyridine, the pyridine hydroxide formed in the reaction supplies the effective nucleophile, Cl^-, for a back-side attack as in normal S_N2 reaction with inversion of configuration.



7.5. FACTORS AFFECTING NUCLEOPHILIC SUBSTITUTION

7.5.1. SOLVENT

Polar solvents help in the separation and stabilization of unlike charges, i.e. aid ionization. In S_N1 reaction ionization occurs in the rate determining step. Hence, polar solvents promote S_N1 reaction. In S_N2 reaction, the charge brought in by the nucleophile is spread over a large part in the transition state. Hence polar solvents have little effect on the transition state. However, highly polar solvents form strong solvent layer around the nucleophile. Therefore, extra energy is required to break the solvent layer for the attack. Hence strongly polar solvents slightly slow down the S_N2 reaction.

7.5.2. NUCLEOPHILE

In S_N1 reaction a carbocation is attacked by the nucleophile. Hence, a low concentration of weak nucleophiles is sufficient for S_N1 reaction. A high concentration of strong nucleophile may act as a base by accepting proton from suitable carbocation resulting in the formation of alkenes. In, S_N2 reaction a high-energy transition state has to be formed. Therefore, a high concentration of strong nucleophile is required for S_N2 reaction.

7.5.3. LEAVING GROUP

Less basic groups are better leaving groups because a strong base has a greater tendency for a backward direction in the reversible reaction

$$HA \rightleftharpoons H^+ + A^-$$

Strong bases such as $\overset{\ominus}{\mathbf{OH}}$, $\overset{\ominus}{\mathbf{OR}}$, $\mathbf{R_2\overset{\ominus}{N}}$, etc., are not good leaving groups. Thus alcohols are resistant to substitution in non – acidic medium. In acidic medium, however, the hydroxyl group leaves as H_2O which is a weak base.

$$\mathbf{R\text{-}OH} \xrightarrow{\overset{\oplus}{\mathbf{H}}} \mathbf{R\text{-}\overset{\oplus}{O}H_2} \xrightarrow{\overset{\ominus}{\mathbf{Br}}} \mathbf{R\text{-}Br} + \mathbf{H_2O}$$

Increase in the ionic size of the elements of the same group in the periodic table causes decrease in the basicity as the charge to size ratio decreases. The basicity order of the halogens is $\overset{\ominus}{\mathbf{I}} < \overset{\ominus}{\mathbf{Br}} < \overset{\ominus}{\mathbf{Cl}} < \overset{\ominus}{\mathbf{F}}$. Therefore, the rate of hydrolysis of the alkyl halides is RI > RBr > RCl by either S_N2 path.

7.5.4. SUBSTRATE

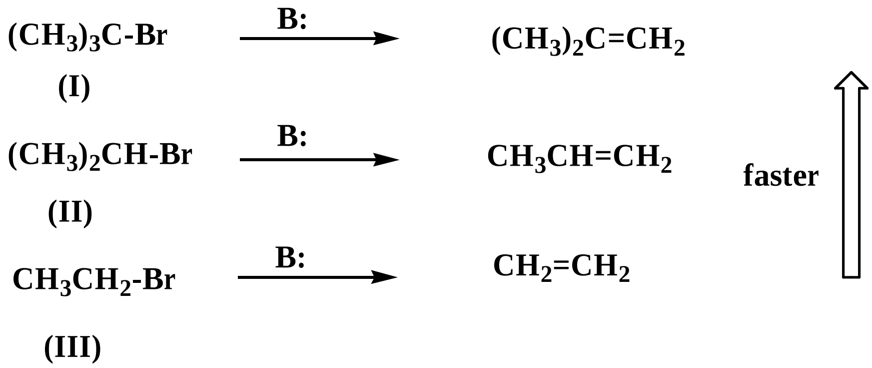
(a) For S_N2 reactions

The rate of direct displacement i.e., an S_N2 reaction is very sensitive to the steric bulk of the substituents present on the carbon undergoing such as reaction. Thus is expected since the degree of coordination increases at the reacting carbon atom. Thus from the steric point of view, the optimum substrate would be CH_3-X. Each replacement of hydrogen by a more bulky alkyl group should decrease the rate of reaction. Consequently, the order of reactivity of alkyl groups is expected to be methyl > primary > secondary > tertiary and this is observed. Table 7.5.4.1 gives the relative rates of typical S_N2 reactions. Methyl halides react most rapidly and tertiary halides react so slowly as to be unreactive by the S_N2 mechanism.

It may be noted that in E2 reactions the order of reactivities (see Scheme 7.5.4.1.) is the opposite to this, therefore, the S_N2 / E2 ratio is largest for a primary halide while it is least for a tertiary halide and this is seen during the reactions of alkyl bromides with ethoxide ion in ethanol at 55^{0}C (Scheme 7.5.4.2.). Thus tertiary halides do not give any significant yield in the S_N2 reactions. One may fail to prepare e.g., t-butyl cyanide from t-butyl chloride and cyanide ion, the product being the one derived from elimination, $(CH_3)_2C = CH_2$.

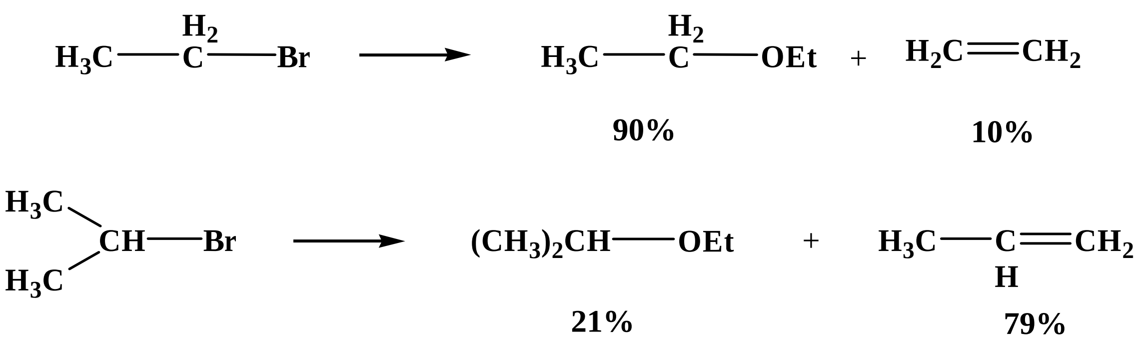
Table 7.5.4.1: Relative rates of reactions of alkyl halides in S_N2 reactions

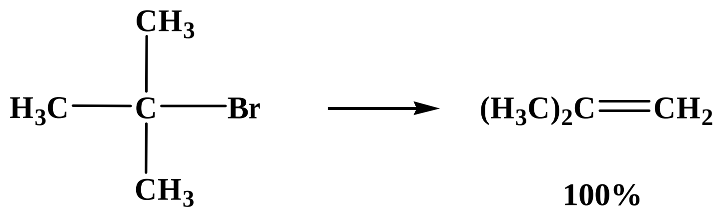
Substituent	Compound	Relative rate
Methyl	CH_3-X	30
1°	CH_3-CH_2-X	1
2°	$(CH_3)_2$-CH-X	0.02
3°	$(CH_3)_3$-C-X	0



Scheme 7.5.4.1

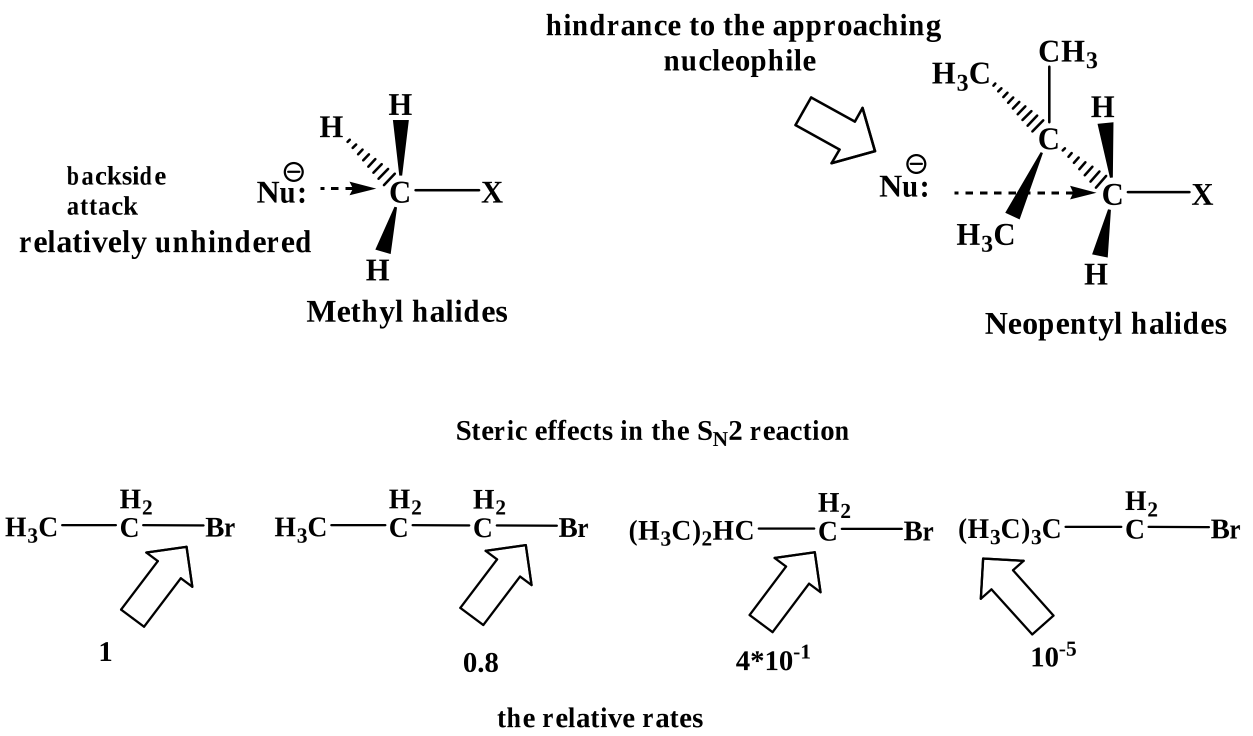
Neopentyl halides are primary halides and even then these are unreactive in S_N2 reactions. This situation shows that steric hindrance effects are operative even if the β-carbon is substituted by alkyl groups. A general statement is therefore, that S_N2 type displacements are retarted by increased steric repulsions at the transition state. In substrates of the type R-CH_2-X, where X is a leaving group, showed that steric effects of R are the dominant factor in determining rates. For the reaction with iodide ion in acetone the relative reactivities of alkyl bromides were as shown (Scheme 7.5.4.3., good yields of neopentyl iodide can be obtained via Grignard reagent, see Scheme 7.5.4.4.). The bulky substituents on or near the carbon atom undergoing S_N2 reaction hinder the approach of the nucleophile to a distance within bonding range.



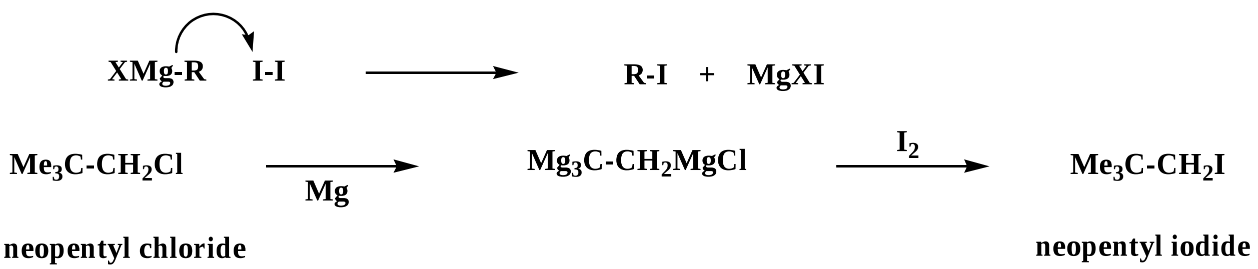


Scheme 7.5.4.2

In an extreme case within the series i.e., in neopentyl system (compared to methyl), the approach of the nucleophile along the line of the C-X bond is hindered by a methyl group, whatever geometry is attained by rotation about the single bonds (Scheme 7.5.4.3).



Scheme 7.5.4.3

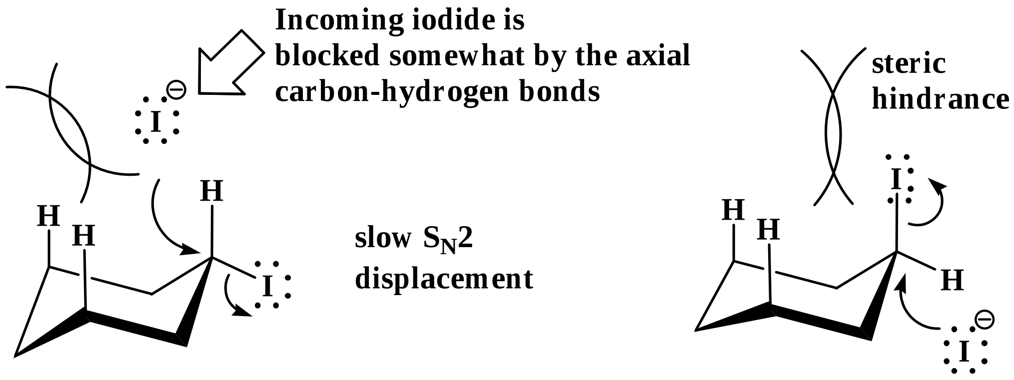


Scheme 7.5.4.4

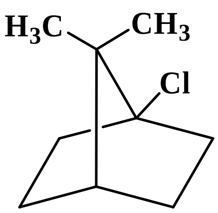
The halocycloalkanes display significant rate differences during S_N2 reactions depending on the size of the ring. Halocyclohexanes although seemingly more capable of attaining sp^2 hybridization at the reacting carbon are somewhat slower in S_N2 reaction (see Table 7.5.4.2). When a nucleophile approaches an equatorial halide, it faces an inhibiting effect i.e., steric hindrance by the two axial hydrogens at C-3 and C-5 carbons (Scheme 7.5.4.5). In a conformation where the leaving group is axial, then its exit its encounters steric hindrance.

Table 7.5.4.2: Relative rates of reaction of alkyl bromides with lithium iodide in acetone

Alkyl group	Relative rate
Isopropyl	1.0
Cyclopropyl	<0.0001
Cyclobutyl	0.008
Cyclopentyl	1.6
Cyclohexyl	0.01
Cycloheptyl	1.0
Cyclooctyl	0.2



Scheme 7.5.4.5



(apocamphyl chloride)

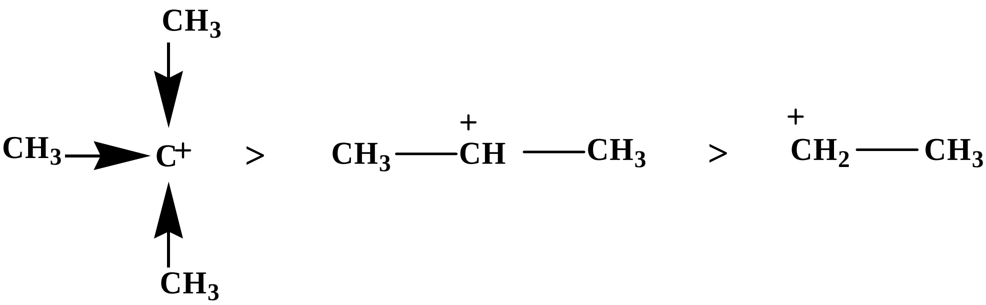
1-chloro-7,7-dimethylbicyclo[2.21]heptane

Scheme 7.5.4.6

A bridgehead halide (Scheme 7.5.4.6.) is inert since the three bridges prevent the backside attack necessary for S_N2 reaction. Moreover, inversion of such a system is impossible.

(a) For S_N1 reactions

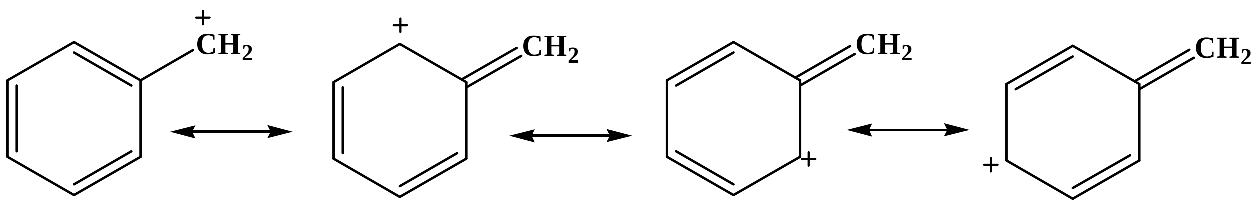
The major structural features necessary for a substrate to undergo S_N1 substitution is the presence of substituents which stabilize the carbocation derived from it. These are the substituents which have *+I* and or *+M* effects. Among alkyl halides, for all practical purposes only tertiary halides react by S_N1 mechanism. A tertiary carbocation being stabilized by three electron releasing groups (see, Scheme 7.5.4.7). Allylic and benzylic halides can also react by an S_N1 mechanism since these substrates can form relatively stable carbocations (see e.g., Scheme 7.5.4.8).



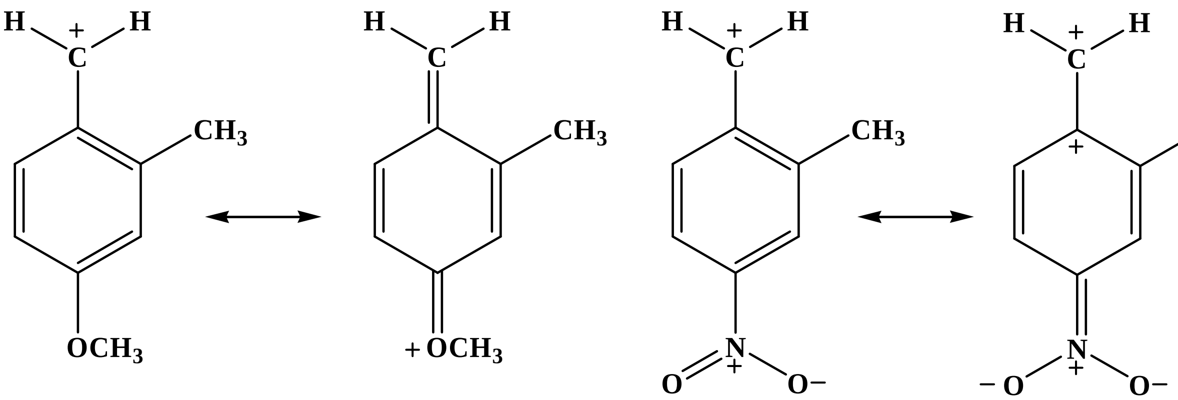
Stability of carbocations $3^\circ > 2^\circ > 1^\circ > \overset{+}{C}H_3$

Electron release: Disperses charge, stabilizes ion

Scheme 7.5.4.7

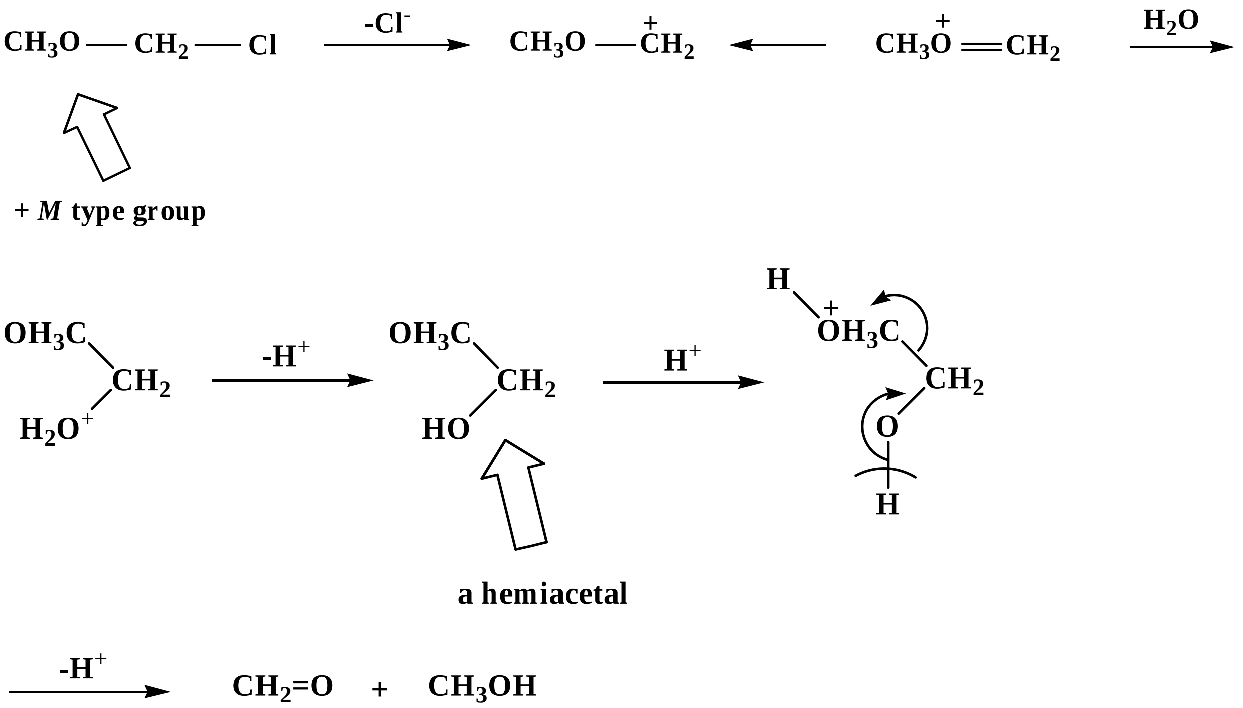


benzylic cation
greater stability
positive carbon is in conjugation with a double bond positive charge is spead over due to resonance



Scheme 7.5.4.8

Methyl chloromethyl ether, with ether group of $+M$ type is hydrolyzed fast in water. The intermediate formed after heterolytic dissociation being the delocalized carbocation (oxonium ion, Scheme 7.5.4.9).

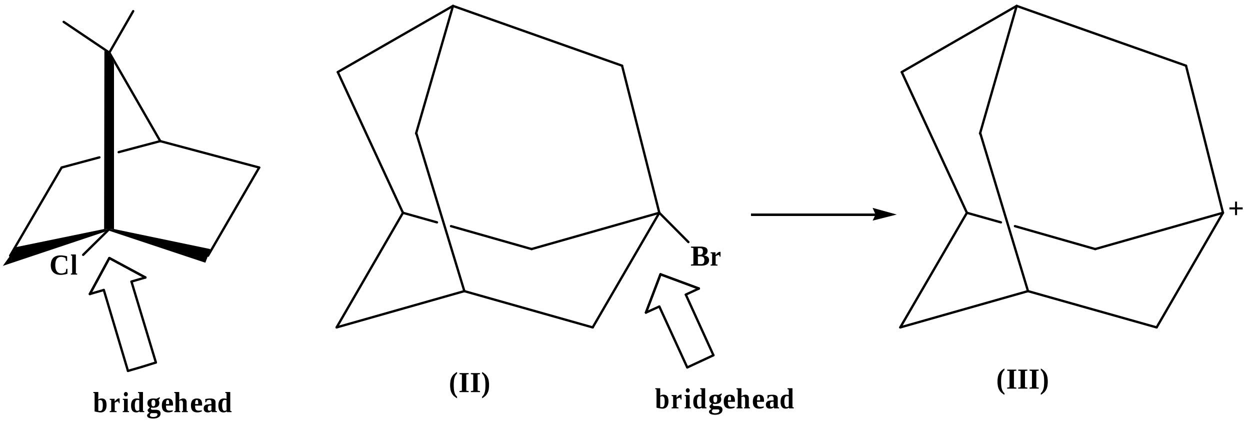


Scheme 7.5.4.9

B strain and I strain effects are observed in many substrates and these effect the rate of S_N1 reactions. When e.g., in a tertiary alkyl halide (R_3Cl), one or more R groups are highly branched like e.g., t-butyl, the ionization is facilitated by relief of steric crowding in going from the tetrahedral ground state to the transition state for ionization and finally to the carbocation. This strain which may be present in a suitable substrate is called B strain.

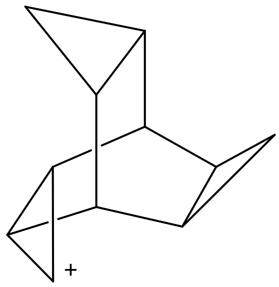
Similarly *I strain* effects S_N1 solvolysis rates in some cyclic compounds.

Nucleophilic S_N1 substitutions at bridgeheads are impossible or very slow, since a rigid bridged system prevents rehybridization to a planar sp^2 carbon. However, when such a structure is flexible the S_N1 reactions can take place, since now the bridgehead carbocation can be generated. (see, Scheme 7.5.4.10).



(II)

(III)

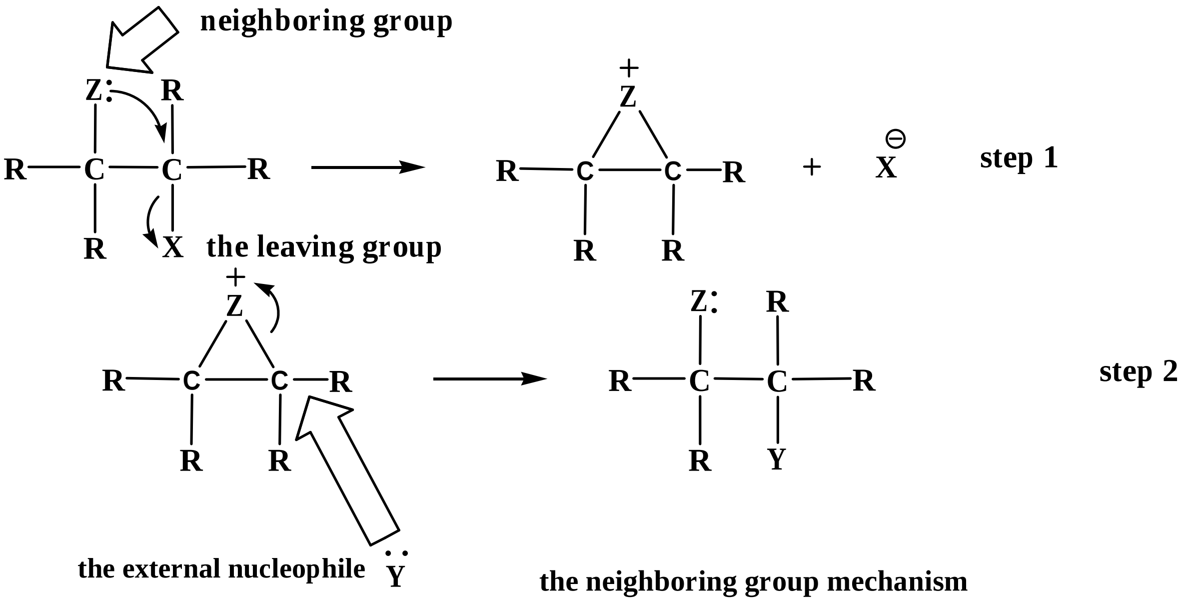


the 1-trishomobarrelyl cation (IV)

Scheme 7.5.4.10

7.6. NEIGHBORING GROUP PARTICIPATION

One has seen that nucleophilic substitutions take place with recemization or with inversion of configuration. However, in several cases such reactions occur with overall retention of configuration. One factor which leads to retention of configuration during a nucleophilic substitution is neighboring group participation. The neighboring group is an electron rich (Z:, Scheme 7.6.1) substituent present in the proper position for backside attack i.e.. anti attack to the leaving group (X). The process infact is a two step process. In the first step (Scheme 7.6.1) the neighboring group (acting as an internal nucleophile) attacks carbon at the reaction center (S_N2 attack) and the leaving group is lost to give a bridged intermediate. This is then attacked in the second step by an external nucleophile (Y:, another S_N2 attack) and the internal nucleophile goes back to where it came from, the net result is two consecutive S_N2 reactions leading to retention of configuration at the reacting carbon.

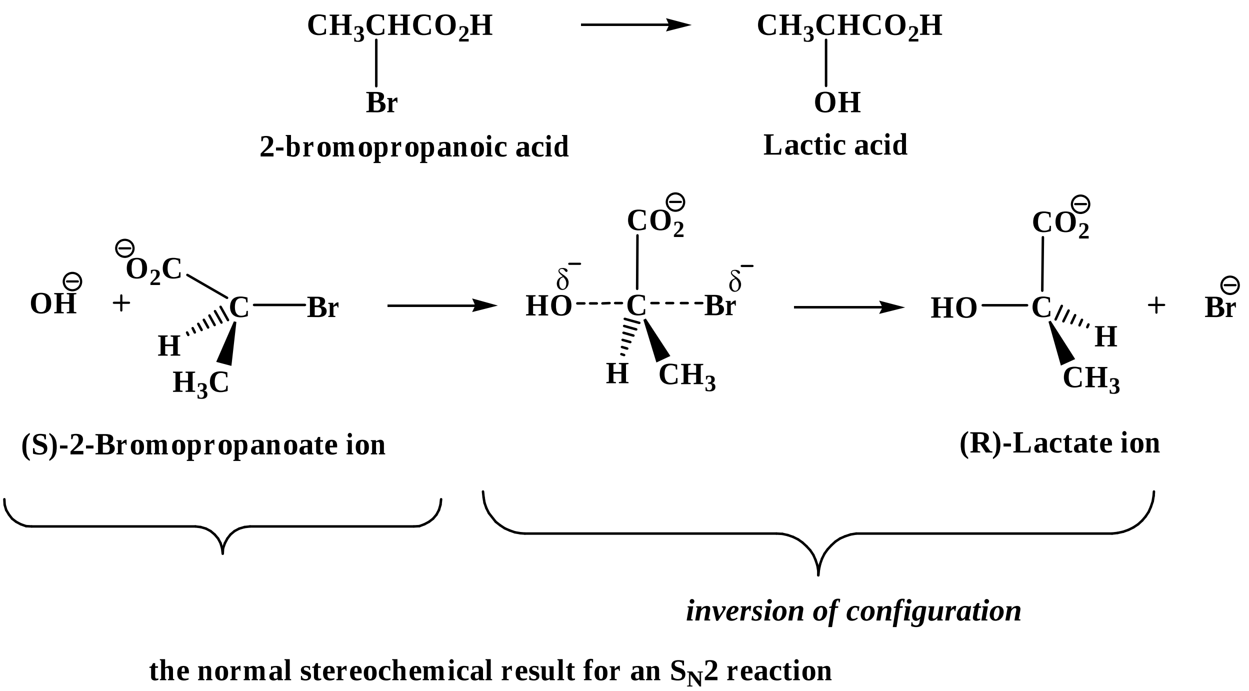


the neighboring group mechanism
two S_N2 substitutions, each causing an inversion
the configuration at a chiral carbon is retained
and not inverted or racemized

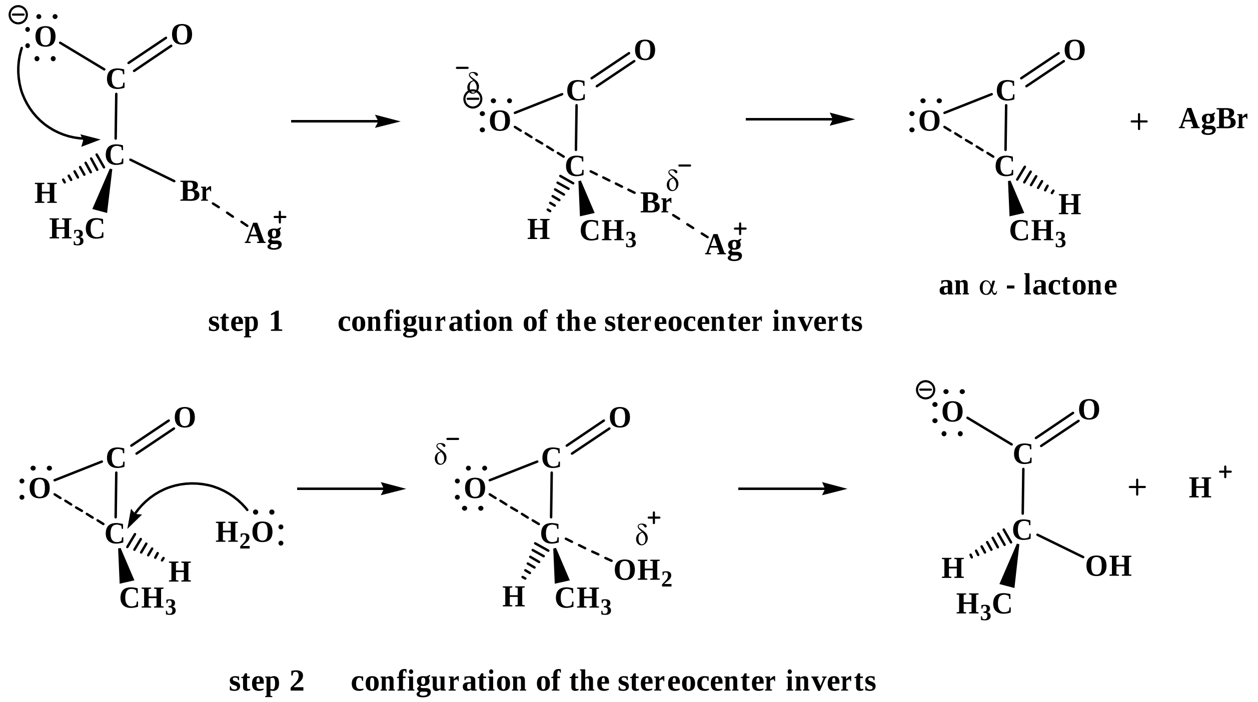
Scheme 7.6.1

A graphic example of neighboring group participation is found in the conversion of 2-bromopropanoic acid into lactic acid (Scheme 7.6.2). In the presence of concentrated sodium hydroxide, (S)-2-bromopropanoic acid (shown as its ion, Scheme 7.6.2) undergoes a bimolecular displacement with inversion of configuration as expected from the normal S_N2 reaction. The same reaction when carried out in the presence of Ag_2O and a low concentration of hydroxide ion, however, occurs with retention of configuration (Scheme 7.6.3).

The reaction now involves two steps, in the first step the carboxylate group acts as a neighboring group to displace bromide ion via backside attack on the chiral center. The silver ion here acts as an electrophilic catalyst and aids the removal of bromine. In the second step, the α–lactone is attacked by a water molecule. Both the steps involve an inversion of configuration on the attacked carbon. Thus, the net result of two inversions in two steps is an overall retention of configuration.

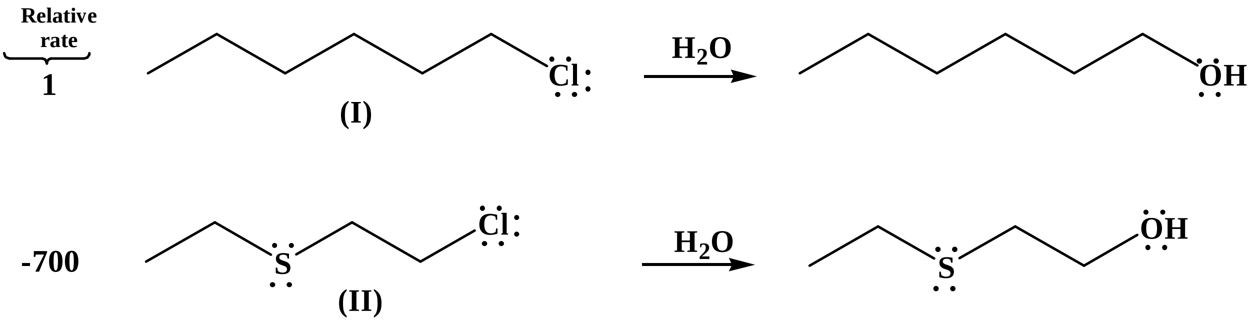


Scheme 7.6.2



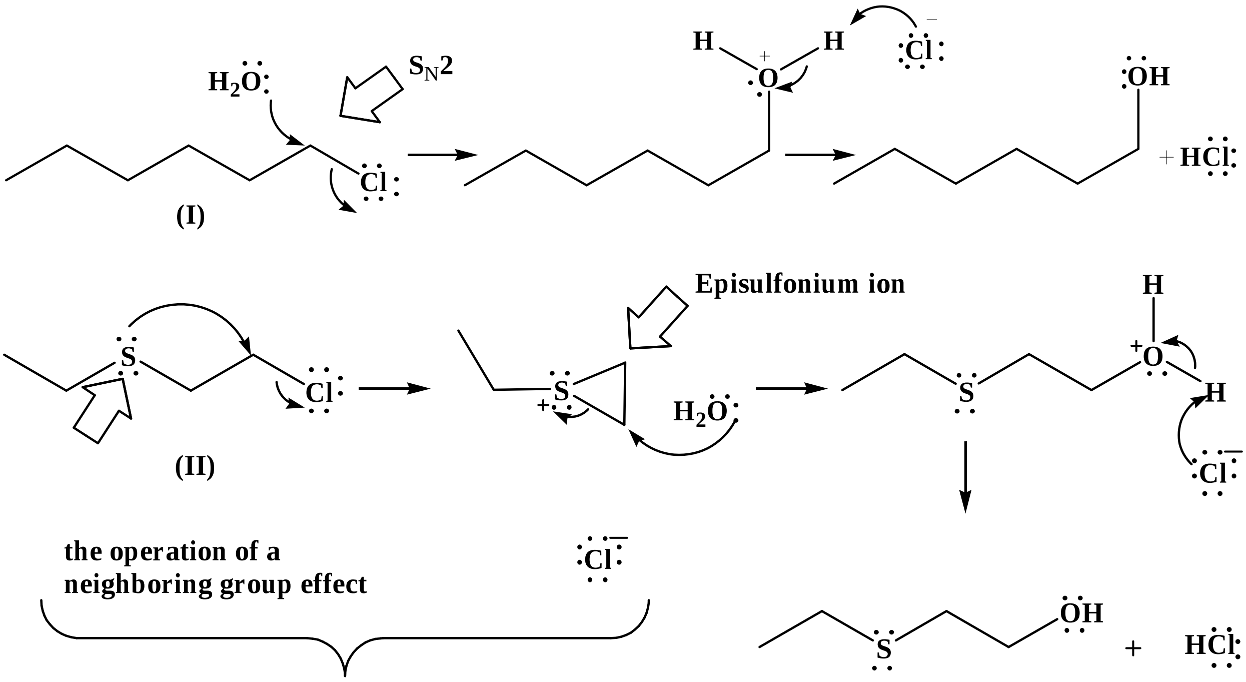
Scheme 7.6.3

When the neighboring group participation operates during the rate determinating step of a reaction, the reaction rate is usually markedly increased. This effect is then termed anchimeric assistance. Sulfur atoms act as powerful nucleophiles and the participation of sulfur as a neighboring group is common. On reaction with water both hexyl chloride (I,Scheme 7.6.4) and 2-chloroethyl-ethylsulfide (II) give their corresponding alcohols.



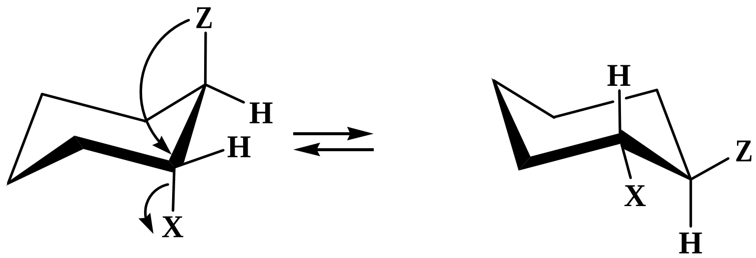
Scheme 7.6.4

However the rate of reaction of sulfur containing compound (II) is much greater than that of the alkyl chloride. The reaction in the case of (I) is a simple S_N2 displacement of chloride with water, while in the case of sulfide, it is the sulfur atom, which displaces the leaving group and acts as a neighboring group. The intramolecular reaction (as expected) is much faster than the intermolecular reaction. The initial product from (II) is an episulfonium ion which is then opened by second S_N2 displacement (now intermolecular) to give the product (Scheme 7.6.5).

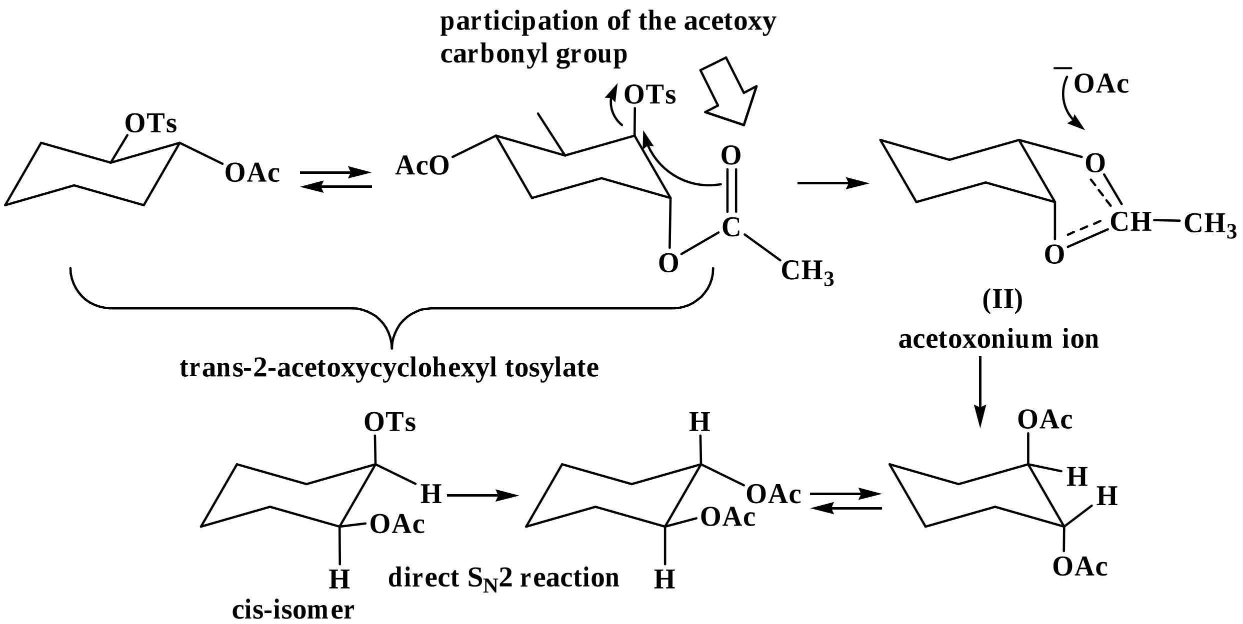


Scheme 7.6.5

In a 1,2-disubstituted cyclohexane derivative, for the neighboring group participation to be operative the groups have to be anti to each other i.e., diaxial as in (I, Scheme 7.6.6). A ring flip may be necessary to bring about such an arrangement of the groups. Consider the acetolysis of cis and trans isomers of 2-acetoxycyclohexyl tosylate (Scheme 7.6.7) which give the same product I.

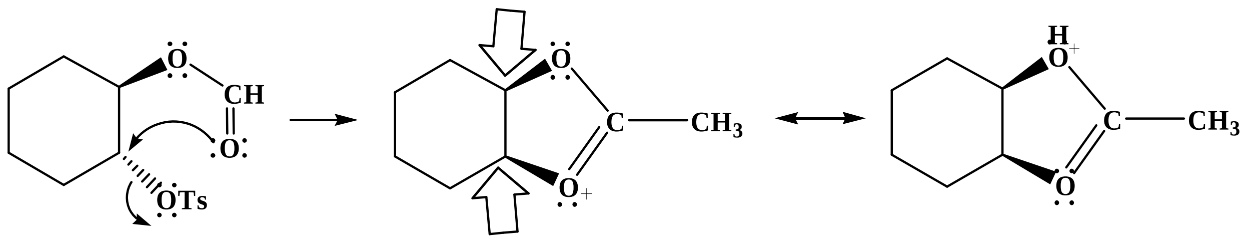


Scheme 7.6.6



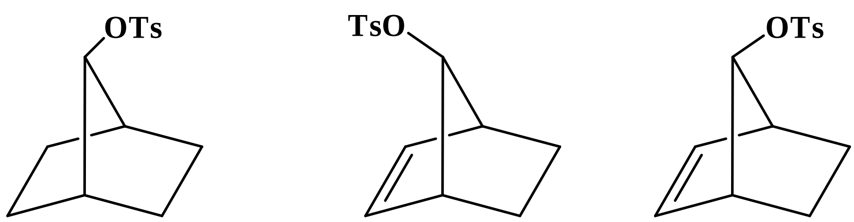
Scheme 7.6.7

The *cis* isomer reacts via a direct S_N2 mechanism and the trans isomer reacts (about 700 times faster) via neighboring group participation by involving an acetoxonium ion (II, Scheme 7.6.7).The acetoxonium ion (the resonance hybrid structure) from the trans isomer is, symmetrical achiral (Scheme 7.6.8) and can be attacked by the acetate ion at either of the two equivalent carbons shown by arrows. Thus, if one starts with an optically active trans isomer, the net result is the formation of a racemic mixture of diacetates.



Scheme 7.6.8

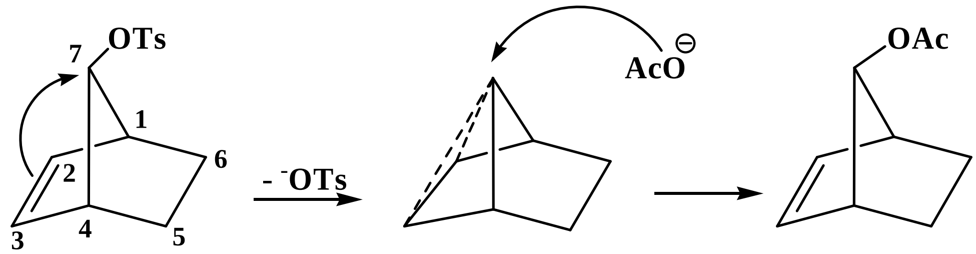
Among the norbornyl derivatives (on acetolysis) the anti tosylate (III,Scheme 7.6.9) reacts 10^{11} times faster than (I) while (II) has 10^4 times reactivity compared to (I).



(I) (II) (III)

Scheme 7.6.9

The fastest rate of acetolysis of anti-tosylate (III) compared to (I, Scheme 7.6.9) proves the removal of the tosyl group (the rate determining step) with strong anchimeric assistance by the double bond. The resulting non-classical carbocation i.e., bridged ion can only react with acetate ion from the side opposite to the neighboring group, with retention of configuration (Scheme 7.6.10). In the syn-isomer (II, Scheme 7.6.9) the rate is slower because the double bond is not properly situated for participation. Thus this isomer dissociates without anchimeric assistance to give a homoallylic carbocation which rearranges to allylic carbocation (V, Scheme 7.6.11) and this reacts to give an acetate. The high reactivity of (II) than (I) may be because of participation of σ electrons of two allylic 1, 6 and 4, 5 bonds.

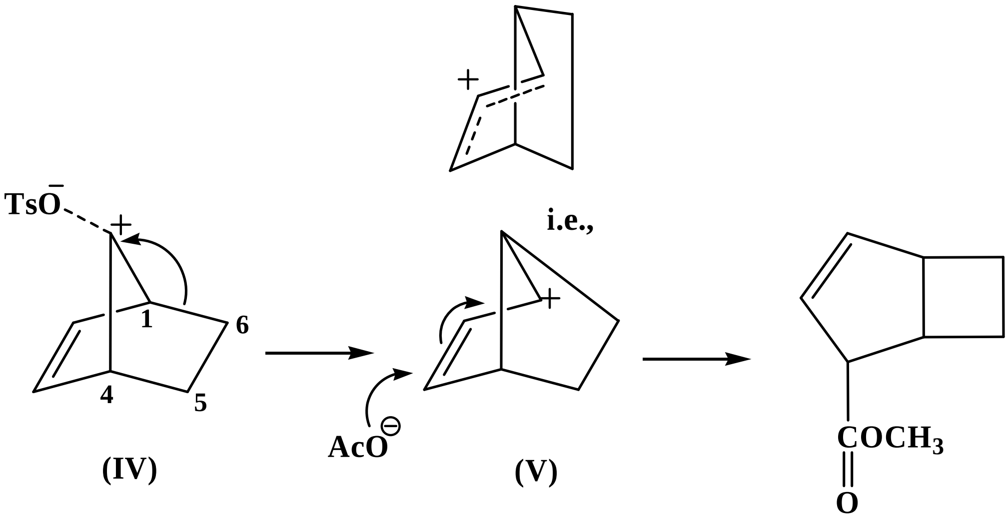


***anti*-7-Norbornenyl tosylate (III)**

Bridged cation

***anti*-Acetate**

Scheme 7.6.10



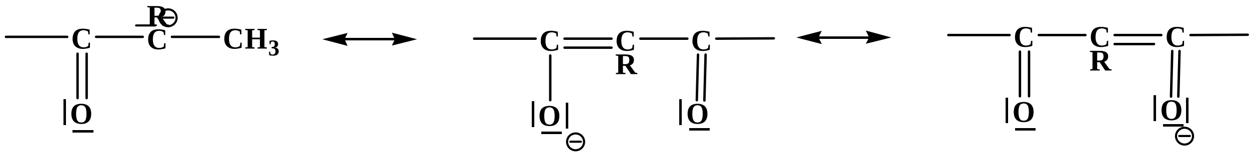
Scheme 7.6.11

7.7. AMBIDENT NUCLEOPHILE

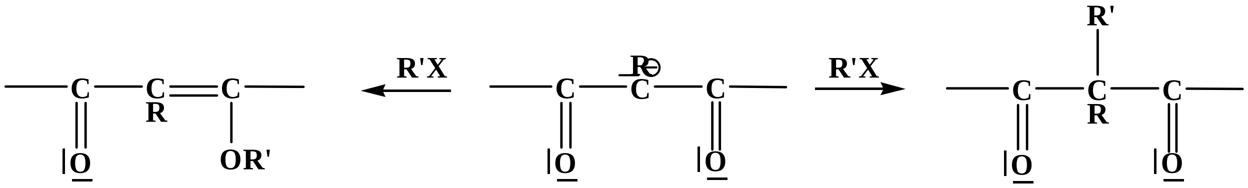
Some nucleophiles have a pair of electrons on each of two or more atoms, or canonical forms can be drawn in which two or more atoms bear an unshared pair. In these cases the nucleophile may attack in two or more ways to give different products. Such reagents are called ambident nucleophiles.

Some important ambident nucleophiles are:

1. Ions of the type $\text{-CO-}\overset{\ominus}{\bar{\text{C}}}\text{R-CO-}$. These ions, which are derived by removal of a proton from malonic esters, β–keto esters, β–diketones, etc., are resonance hybrids:

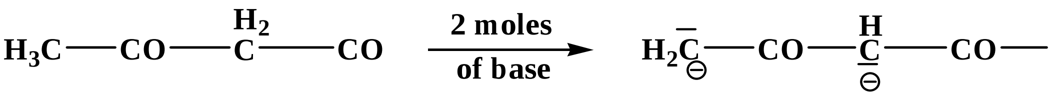


They can thus attack a saturated carbon with their carbon atoms (C-alkylation) or with their oxygen atoms (O-alkylation):



With unsymmetrical ions, three products are possible, since either oxygen can attack. With a carbonyl substrate the ion can analogously undergo C-acylation or O-acylation.

2. Compounds of the type $CH_3CO\text{-}CH_2\text{-}CO\text{-}$ can give up two protons, if treated with two moles of a strong enough base, to give dicarbanions:



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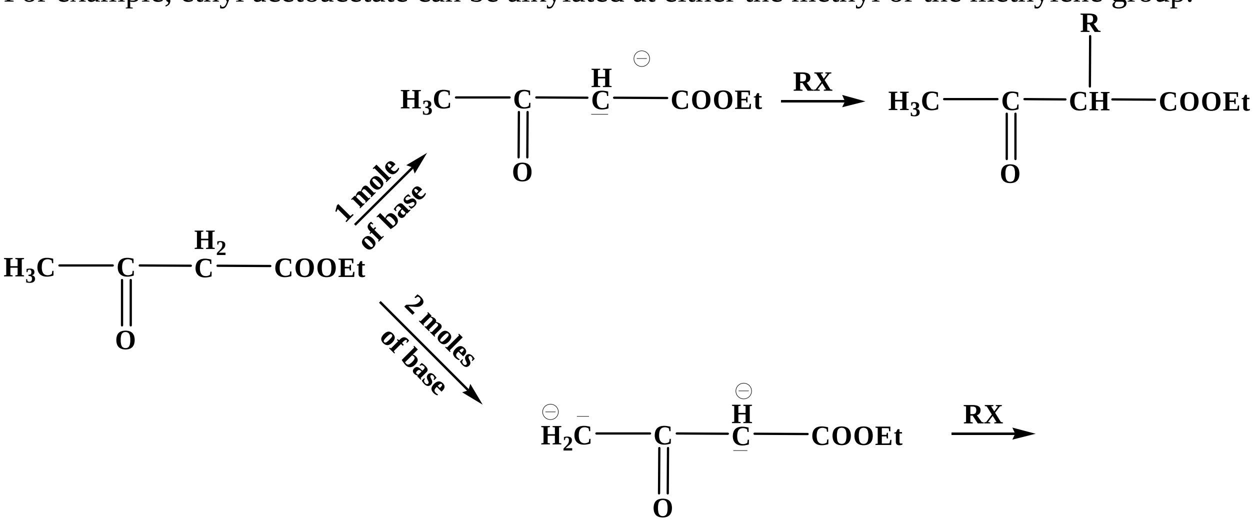
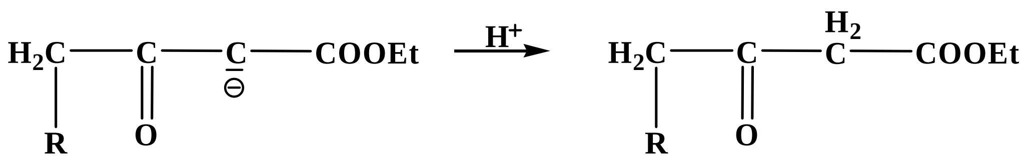
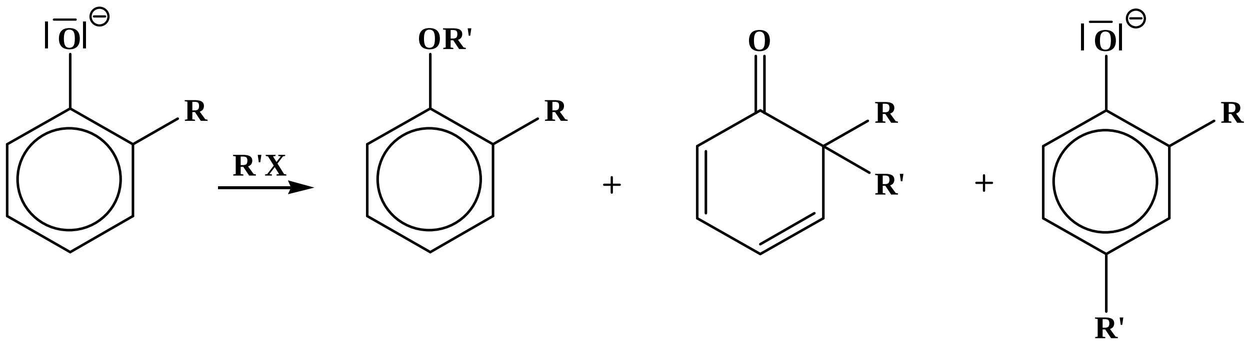
Such ions are ambident nucleophiles, since they have two possible attacking carbon atoms, aside from the possibility of attack by oxygen. In such cases, the attack is virtually always by the more basic carbon. Since the hydrogen of a carbon bonded to two carbonyl groups is more acidic than that of a carbon bonded to just one, the CH group of **1** is less basic than the CH_2 group, so the latter attacks the substrate. This gives rise to a useful general principle: whenever we desire to remove a proton at a given position for use as a nucleophile but there is a stronger acidic group in the molecule, it may be possible to take off both protons; if it is, then attack is always by the desired position since it is the ion of the weaker acid. On the other hand, if it is desired to attack with the more acidic position, all that is necessary is to remove just one proton. For example, ethyl acetoacetate can be alkylated at either the methyl or the methylene group.

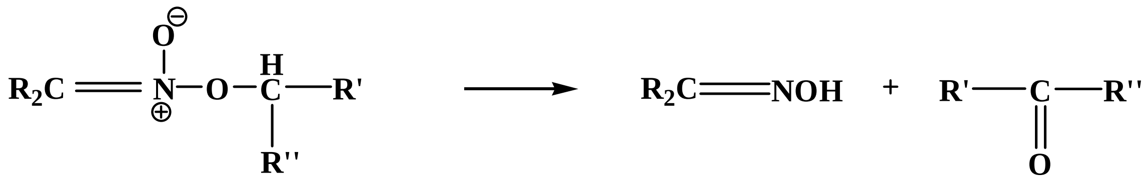




3. The CN⁻ ion. This nucleophile can give nitrites **RCN** or isocyanides **RN≡C.**
4. The nitrite ion. This ion can give nitrite esters R-O-N=O or nitro compounds RNO_2, which are not esters.
5. Phenoxide ions (which are analogous to enolate ions) can undergo C-alkylation or O-alkylation:



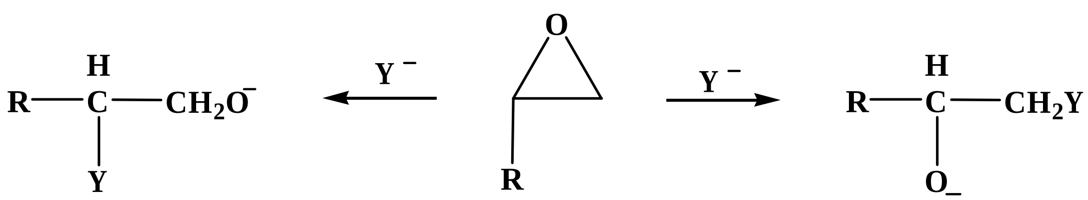
6. Removal of a proton from an aliphatic nitro compound gives a carbanion $\mathbf{R_2\overset{\ominus}{C}-NO_2}$ that can be alkylated at oxygen or carbon. O-alkylation gives nitronic esters, which are generally unstable to heat but break down to give an oxime and an aldehyde or ketone.



There are many other ambident nucleophiles.

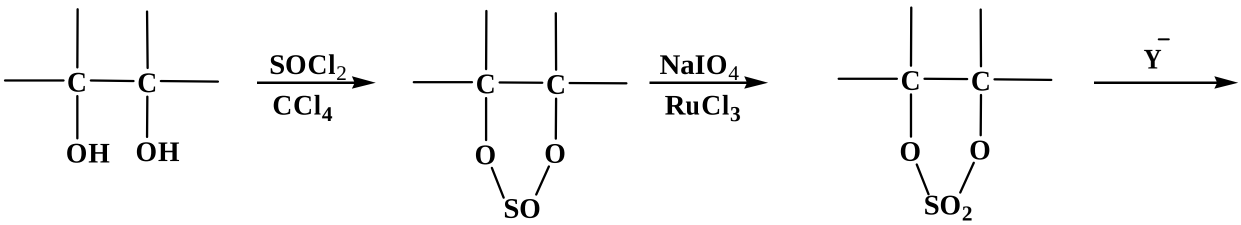
7.8. AMBIDENT SUBSTRATES

Some substrates (e.g., 1,3-dichlorobutane) can be attacked at two or more positions. We may call these *ambident substrates*. In the example given, there happen to be two leaving groups in the molecule, but there are two kinds of substrates that are inherently ambident (unless symmetrical). One of these, the allylic type, has already been discussed. The other is the epoxy (or the similar aziridine or episulfide) substrate.

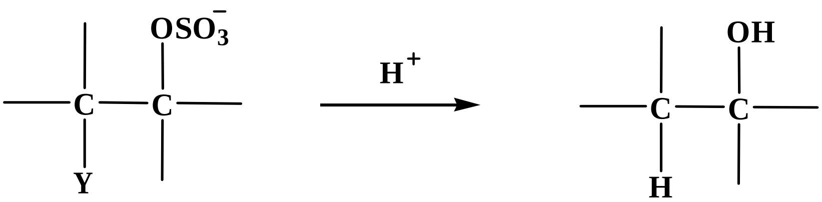


Substitution of the free epoxide, which generally occurs under basic or neutral conditions, usually involves an S_N2 mechanism. Since primary substrates undergo S_N2 attack more readily than secondary, unsymmetrical epoxides are attacked in neutral or basic solution at the less highly substituted carbon, and stereospecifically, with inversion at that carbon. Under acidic conditions, it is the protonated epoxide that undergoes the reaction. Under these conditions the mechanism can be either S_N1 or S_N2. In S_N1 mechanisms, which favor tertiary carbons, we might expect that attack would be at the more highly substituted carbon, and this is indeed the case. However, even when protonated epoxides react by the S_N2 mechanism, attack is usually at the more highly substituted position. Thus, it is often possible to change the direction of ring opening by changing the conditions from basic to acidic or vice versa. In the ring opening of 2,3-epoxy alcohols, the presence of Ti(O-i-Pr)$_4$ increases both the rate and the regioselectivity, favoring attack at C-3 rather than C-2. When an epoxide ring is fused to a cyclohexane ring, S_N2 ring opening invariably gives diaxial rather than diequatorial ring opening.

Cyclic sulfates (**2**), prepared from 1, 2-diols, react in the same manner as epoxides, but usually more rapidly:



(2)



7.9. LET US SUM UP

In this lesson, we:

Pointed out

- S_N1 mechanism
- Stereochemistry of S_N1 reaction
- S_N2 mechanism
- Stereochemistry of S_N2 reaction
- S_N i mechanism
- Factors affecting nucleophilic substitution
- Neighboring group participation
- Ambident nucleophile
- Ambident substrates

7.10. CHECK YOUR PROGRESS

1. What are the evidences for the intermediacy of carbonium ion in S_N1 reactions?
2. Why CH_3OCH_2Cl reacts with iodide ion in acetone several thousand times faster than CH_3Cl?

3. What is neighboring group participation?
4. Why the reaction of α bromo propionate (optically active) in methyl alcohol gives a product with retention of configuration?

7.11. POINT FOR DISCUSSION

1. Define S_Ni reaction. Discuss cyclic as well as ion pair mechanism for S_Ni reaction. How do both the mechanisms explain the observed results of these reactions including stereochemistry?
2. Briefly explain the various factors affecting the Nucleophilic Substitution Reaction.
3. Write notes on
   (a) Ambident nucleophile
   (b) Ambident substrate

7.12. REFERENCES

1. Jerry march, Advanced Organic Chemistry, Fourth edition, Wiley India edition.

2. P.S. Kalsi, Organic reactions and their mechanisms, Second edition, New age international publishers**.**

3. S.N. Sanyal, Reactions, rearrangements and reagents, Bharati Bhavan (P&D), Patna.

LESSON: 8 – NUCLEOPHILIC SUBSTITUTION AT ALLYLIC AND VINYLIC CARBON

CONTENTS

8.0. AIMS AND OBJECTIVES

The aim is to motivate and enable the student to comprehend the possible chemical route by which the nucleophilic substitution reactions at allylic and vinylic carbon compounds may proceed.

On successful completion of this lesson the student should have:

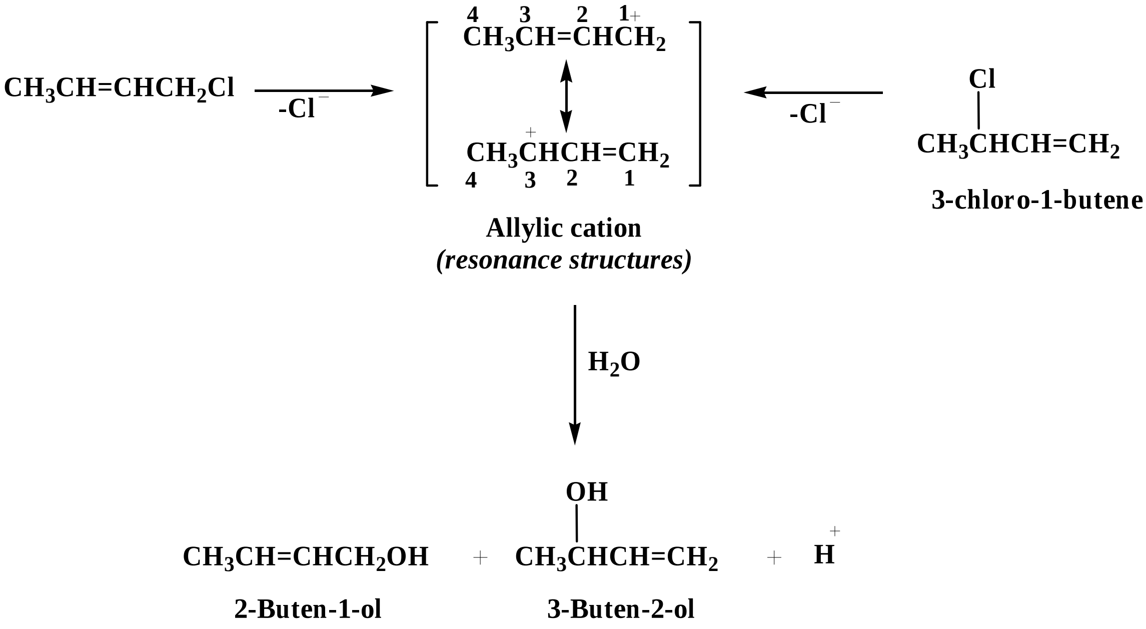
* learnt possible reaction pathways in nucleophilic substitution reactions at allylic and Vinylic carbon compounds.

8.1. INTRODUCTION

Allylic substrates e.g., allylic halides undergo nucleophilic substitution reactions especially rapidly and are usually accompanied by a rearrangement known as an allylic rearrangement (allylic shift).

8.2. ALLYLIC REARRANGEMENT (ALLYLIC SHIFT)

When allylic substrates are treated with nucleophiles under S_N1 conditions two products are usually obtained, one is normal and the other is rearranged. This is seen in the case of either 1-chloro-2-butene or 3-chloro-1-butene (Scheme 8.2.1). Two products are formed since the intermediate carbocation which is formed is a resonance hybrid, and consequently C1 and C3 each carry a partial positive charge and both are attacked by the

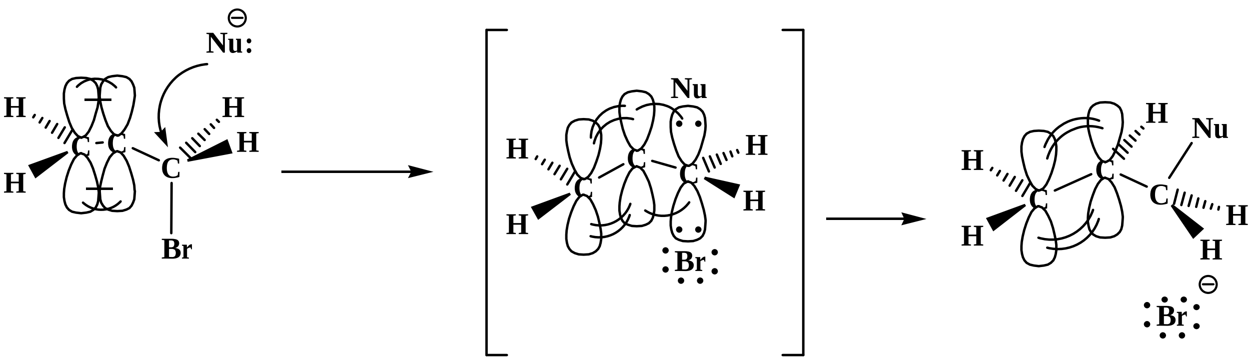


Scheme 8.2.1

nucleophile (OH-). An allylic rearrangement cannot, however be detected in the case of symmetrical allylic cations. Moreover, different allylic halides may give identical products upon solvolysis, if they, dissociate to the same allylic cation (Scheme 8.2.1). This mechanism has been called S_N1' mechanism (i.e., substitution unimolecular with rearrangement).

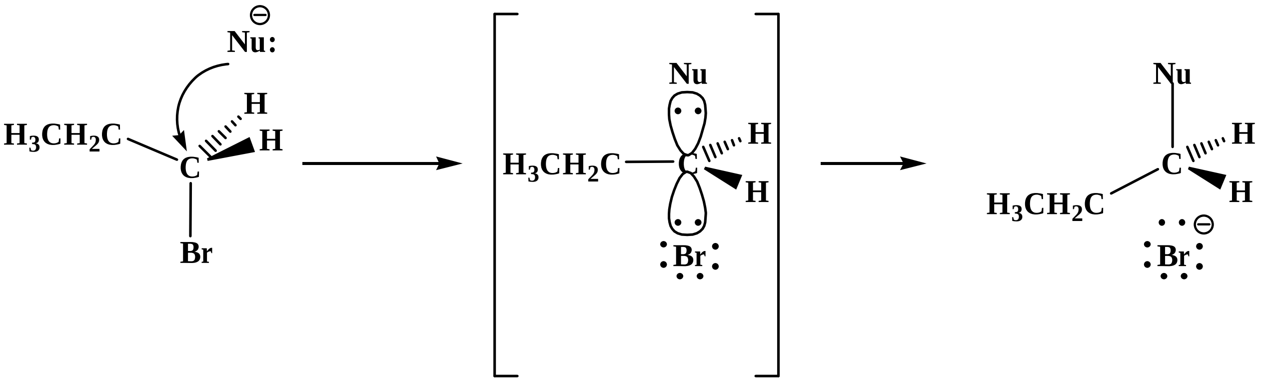
8.3. S_N2 REACTIONS WITH ALLYLIC AND VINYLIC SYSTEMS

The allylic systems are prone to react by S_N1 mechanism since these form delocalized allylic carbocations easily. However, the synthetic utility of these reactions is limited due to the allylic shift of the double bond. It is possible to have suitable reaction conditions under which allylic bromides react cleanly (without rearrangement) by way of the S_N2 mechanism. Thus allyl bromide undergoes bimolecular substitution about 40 times faster than n-propyl bromide. In the case of allylic system, the transition state receives resonance stabilization through conjugation with the p orbitals of the pi bond, (Scheme 8.3.1). The electronic structure of this transition state resembles the structure of the allyl anion. The stabilization of the transition state via the conjugation with the p orbital which is momentarily generated on the reacting carbon atom lowers the activation energy of the system, increasing the reaction rate.



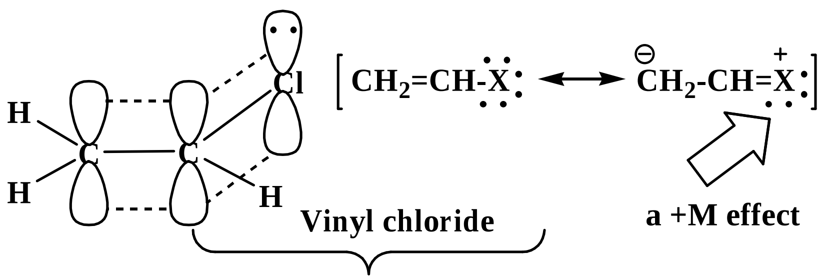
transition state

S_N2 reaction on allyl bromide



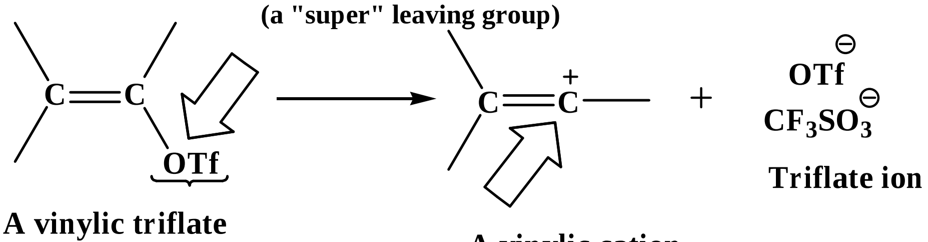
transition state
S_N2 reaction on propyl bromide
(Scheme 8.3.1)

Haloalkenes, in which the halogen is directly attached to the unsaturated carbon and phenyl halides, display exceptionally low reactivity either by S_N1 or S_N2 mechanism. Thus while n-propyl chloride ($CH_3CH_2CH_2Cl$) undergoes rapid substitution with potassium iodide in acetone 1-chloropropene ($CH_3CH{=}CHCl$) is inert. Simple alkenyl halides e.g., vinyl chloride ($CH_2{=}CHCl$) also do not form carbocations readily. This is due to increased strength of the vinyl halogen bond (see, Scheme 8.3.2) in Vinylic and phenyl halides. Moreover, the electrons of the double bond of benzene ring repel the approach of the nucleophile from the backside to be unreactive by S_N2 mechanism, S_N1 reaction is also retarded due to the instability of phenyl cation.



(Scheme 8.3.2)

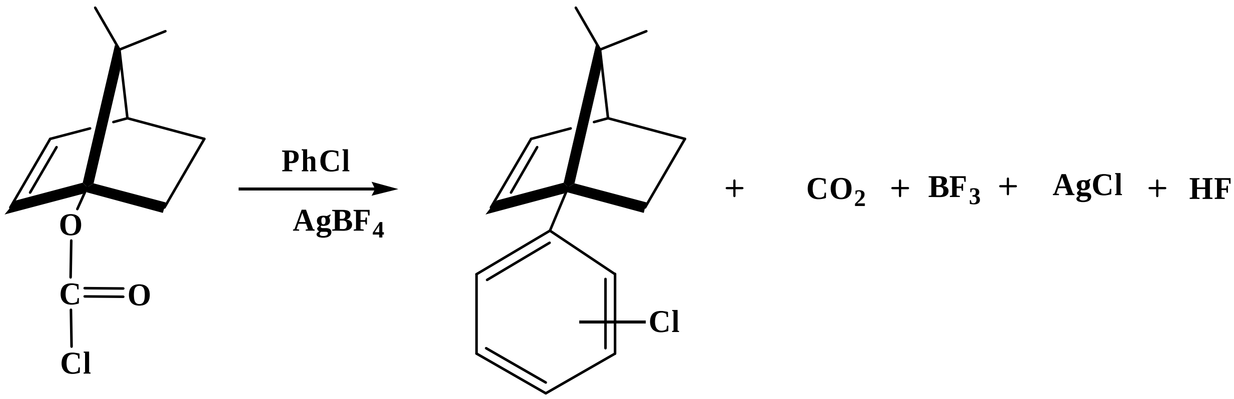
S_N1 type of solvolysis leading to Vinylic cations can however, be carried out on suitable substrates provided one has an efficient leaving group) and the Vinylic group contains electron releasing groups (Scheme 8.3.3, see also Scheme 8.3.2).



(Scheme 8.3.3)

8.4. NUCLEOPHILIC SUBSTITUTION AT A BRIDGEHEAD CARBON

When the leaving group e.g., at [2.2.1] bridgehead is such that it cannot function as a nucleophile i.e., to come back once it has gone, then a nucleophilic substitution can occur. Thus (I) undergoes substitution with chlorobenzene as the nucleophile to give (II).



(I) (II)

8.5. LET US SUM UP

In this lesson, we:

Pointed out

- S_N1 reactions with allylic and vinylic systems
- S_N2 reactions with allylic and vinylic systems
- Nucleophilic substitution at a bridgehead carbon

8.6. CHECK YOUR PROGRESS

1. Why the allylic systems are prone to react with S_N1 mechanism?
2. Write short notes on nucleophilic substitution at a bridgehead carbon.

8.7. POINT FOR DISCUSSION

1. Comment upon the nucleophilic substitution reactions of allylic and Vinylic carbon compounds.

8.8. REFERENCES

1. P.S. Kalsi, Organic reactions and their mechanisms, Second edition, New age international publishers.

LESSON: 9 – TYPICAL ALIPHATIC NUCLEOPHILIC SUBSTITUTION REACTIONS

CONTENTS

9.0. AIMS AND OBJECTIVES

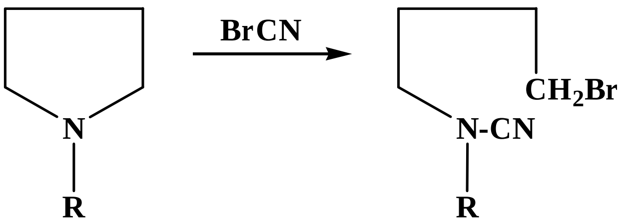
The aim is to motivate and enable the student to comprehend the possible chemical route by which the aliphatic nucleophilic substitution reactions may proceed.

On successful completion of this lesson the student should have learnt possible reaction pathways in typical aliphatic nucleophilic substitution reactions.

9.1. VON BRAUN REACTION

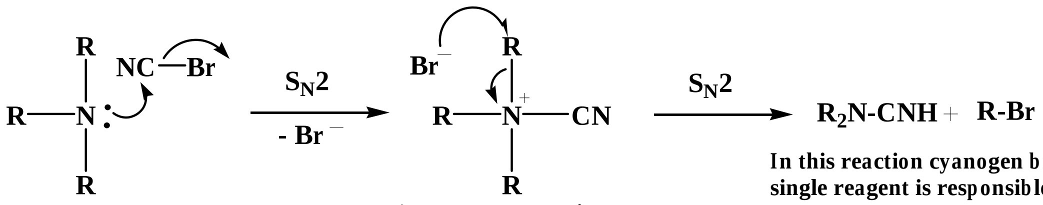
The von Braun reaction involves the cleavage of tertiary amines by cyanogen bromide to afford an alkyl bromide and a disubstituted cyanamide. Cyanogen bromide reacts with tertiary nitrogen compounds to break one carbon to nitrogen linkage.

$$\mathbf{R_3N + BrCN \rightarrow R_2N\text{-}CN + R\text{-}Br}$$



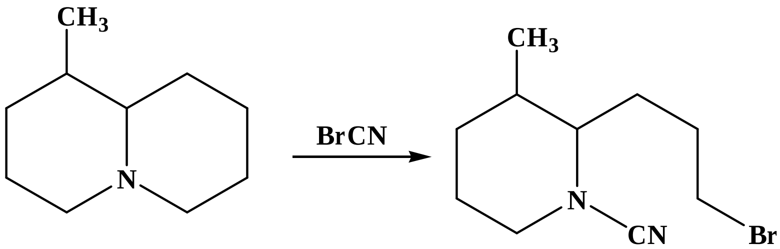
Usually, the smallest alkyl group or that would furnish the most reactive halide (e.g. benzyl or allyl) is cleaved. The reaction can also be run on secondary amines, but the yields have been found to be poor.

Mechanism



(N-cyanoammonium bromide intermediate)

In this reaction cyanogen bromide, a single reagent is responsible for two transformations in one reaction vessel; hence NC-Br is called a counterattack reagent

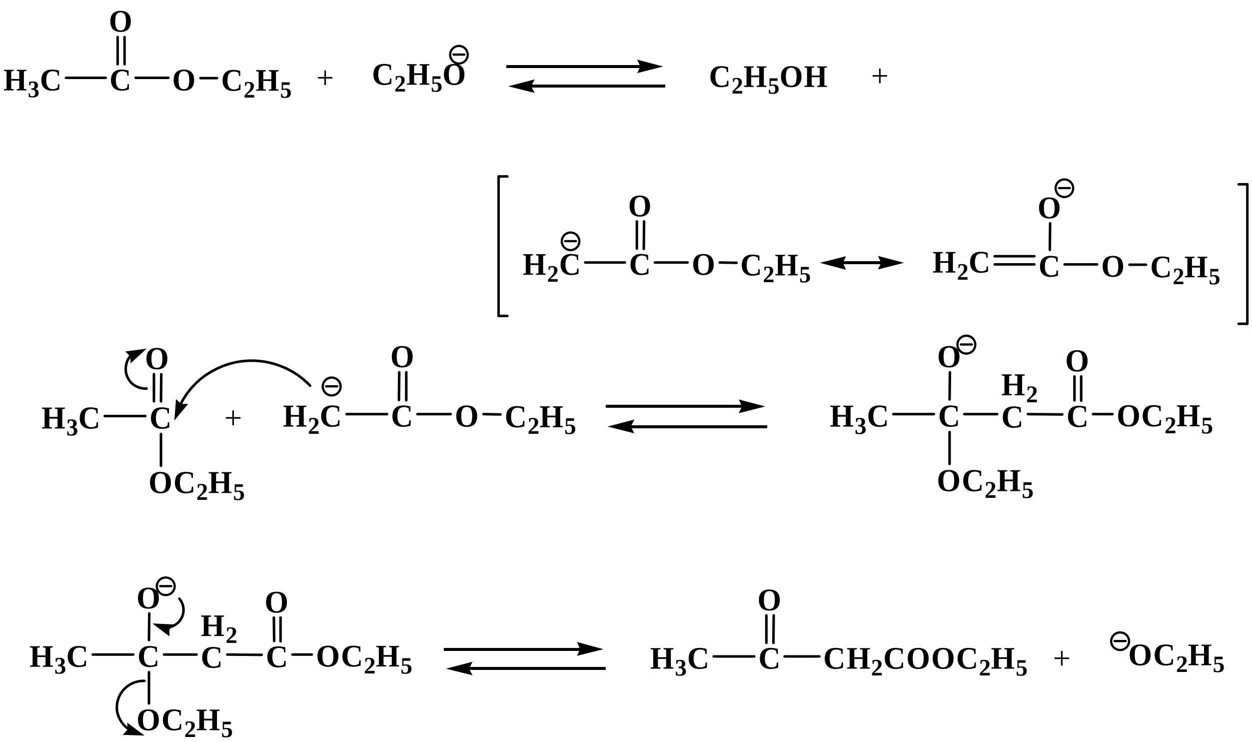


9.2. THE CLAISEN CONDENSATION

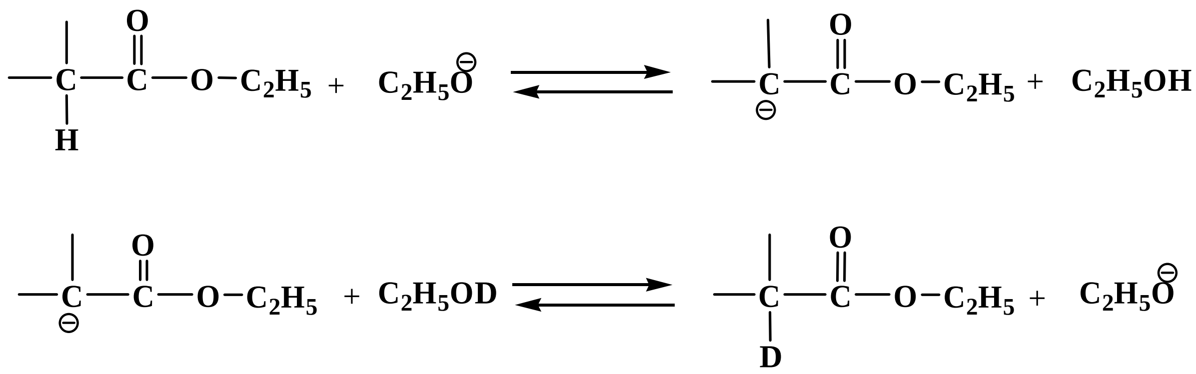
Ethyl acetate can be converted to ethyl acetoacetate.

$$2\ CH_3COOC_2H_5 \longrightarrow CH_3COCH_2COOC_2H_5$$

The reaction is known as Claisen condensation and it covers various condensations between a carboxylic ester and an α–hydrogen containing ester, ketone or nitrile, yielding a β-ketoester, ketone or nitrile, respectively. These reactions are usually carried out by means of sodium ethoxide in ethanol solution. Claisen condensation resembles aldol condensation in the sense that it involves the attack of a carbanion, generated by the removal of acidic hydrogen, on the carbonyl carbon of the ester. Expulsion of the ethoxide ion then yields the product.

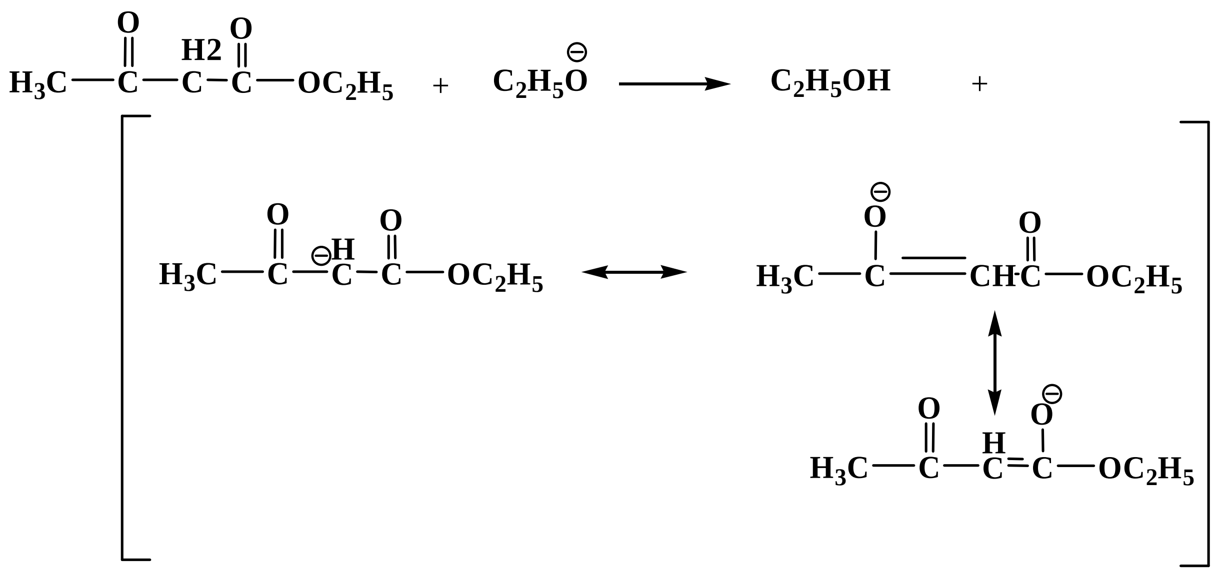


The reversible formation of carbanions in the above sequence has been demonstrated by treating ester with C_2H_5OD containing sodium ethoxide whereby these esters underwent hydrogen exchange at the α-position.

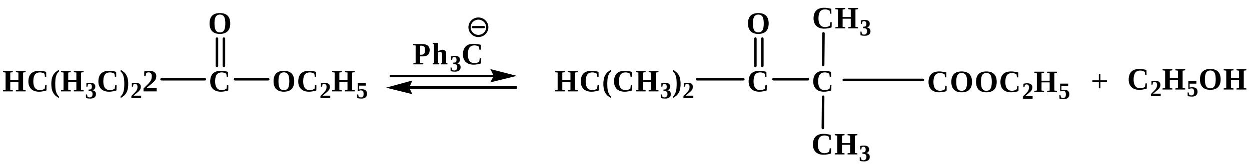


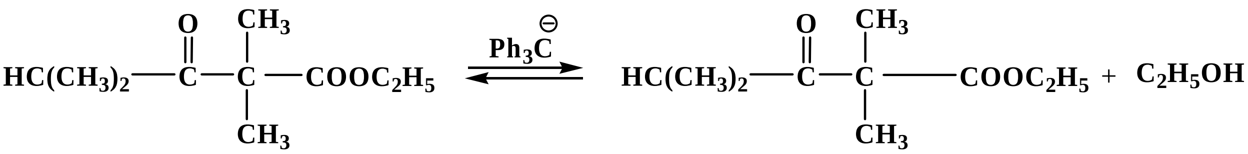
It was also observed that the rates of exchange of these hydrogens parallel the reactivity of these esters in Claisen condensation. The same conclusion was reached by the observation that optically active esters containing an α-hydrogen racemize in the presence of sodium ethoxide.

Since these steps are reversible, the success of Claisen condensation depends upon the removal of the final product from the reaction site and thus forcing the equilibrium to the right. Usually this is done by converting the product ester into an enolate anion which is stabilized by resonance.



It follows that when the product β-ketoester does not have an α-hydrogen, the equilibrium of the condensation cannot be shifted to the right and hence esters without two a α-hydrogens do not undergo Claisen condensation in the presence of sodium ethoxide. The equilibrium in such reactions, however, may be forced to the right by the use of more strongly basic catalysts, such as sodium triphenylmethide and sodium amide which are capable of bringing about the formation of β–ketoesters that contain no α-hydrogen atoms.

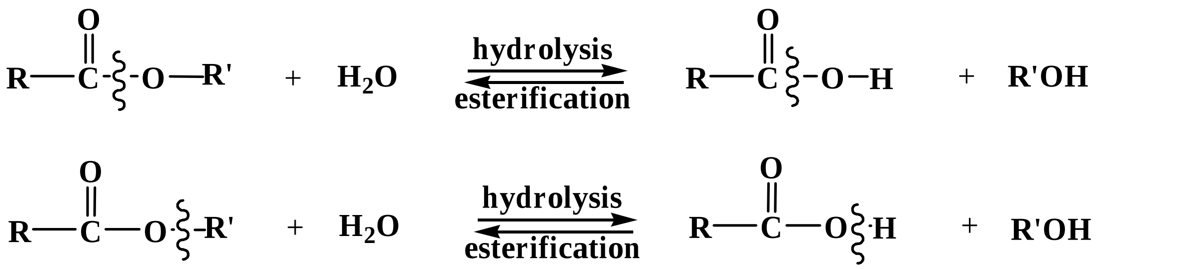




9.3. HYDROLYSIS OF ESTERS

There are a number of distinct mechanisms by which esterification of an acid and the hydrolysis of an ester may proceed. This plurality of mechanisms is due to the following three reasons:

(i) Esterification and hydrolysis may proceed either through an acyl-oxygen bond cleavage (A) or an alkyl-oxygen bond cleavage (B).



A

B

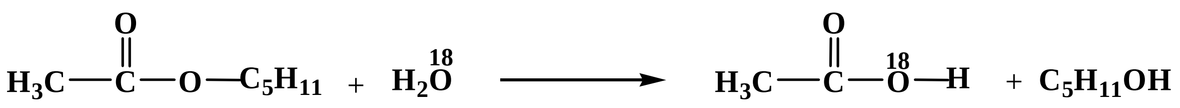
(ii) Hydrolysis of an ester may be accomplished either by acids or alkalis and depending upon the reagent, the species undergoing hydrolysis may be a neutral ester molecule (R-COOR') or an ionic conjugate acid $(RCOOHR)^+$.

(iii) The esterification and hydrolysis may proceed either by a unimolecular or a bimolecular mechanism.

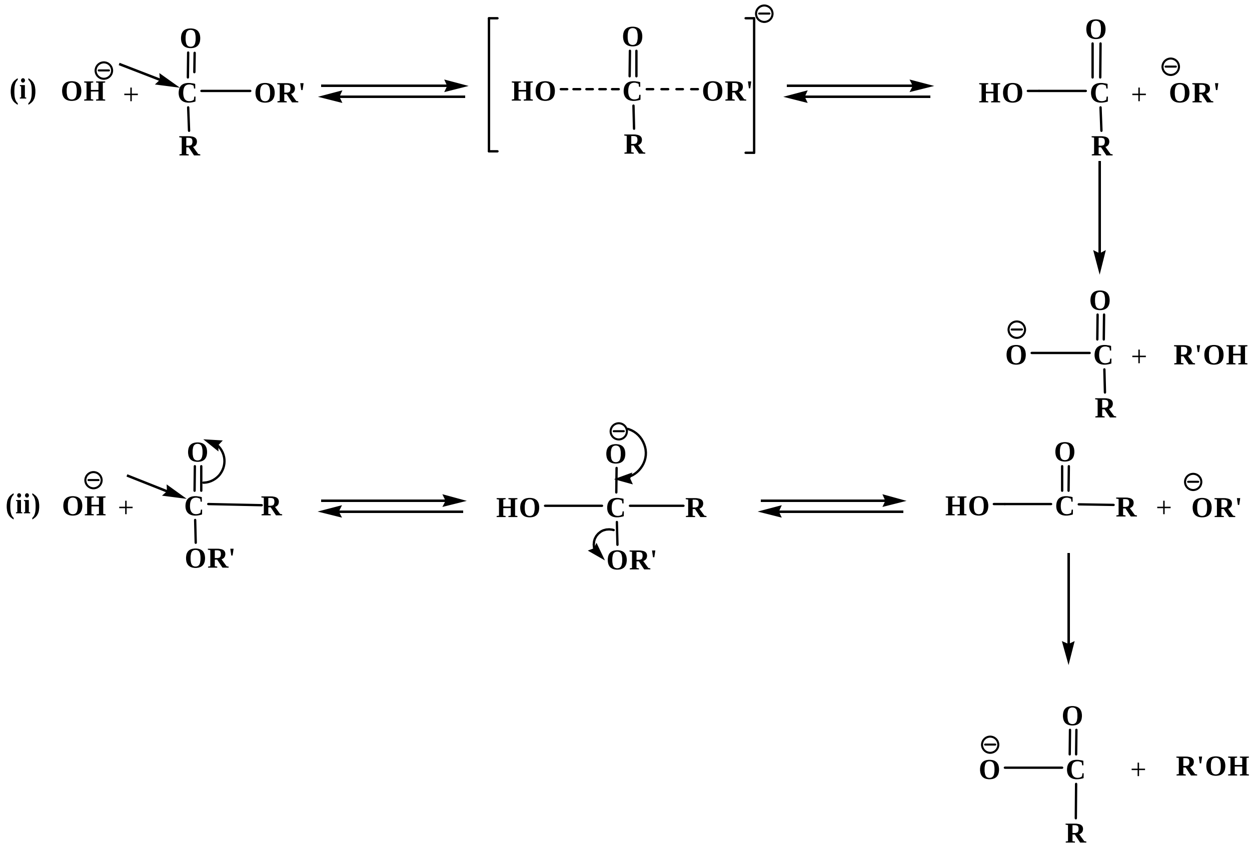
Since esterification in basic medium is not possible because of the conversion of carboxylic acid to a resonance-stabilized carboxylate anion, depending upon the above three factors, there are four possible mechanisms by which esterification may proceed. Similar considerations visualize eight mechanisms for ester hydrolysis. Ingold has suggested a shorthand notation to describe these bewildering number of mechanisms in which A or B refers to the acidic or basic (and neutral) medium; acyl-oxygen or alkyl-oxygen cleavage is symbolized by AC or AL, respectively and molecularity of the reaction is indicated by the usual numbers 1 or 2. Thus by a $B_{AC}2$ hydrolysis we mean a bimolecular basic hydrolysis of an ester proceeding through the acyl-oxygen bond cleavage. In the following pages we shall exemplify a few of the relatively more common mechanisms.

9.3.1. BASIC HYDROLYSIS (the $B_{AC}2$ Mechanism)

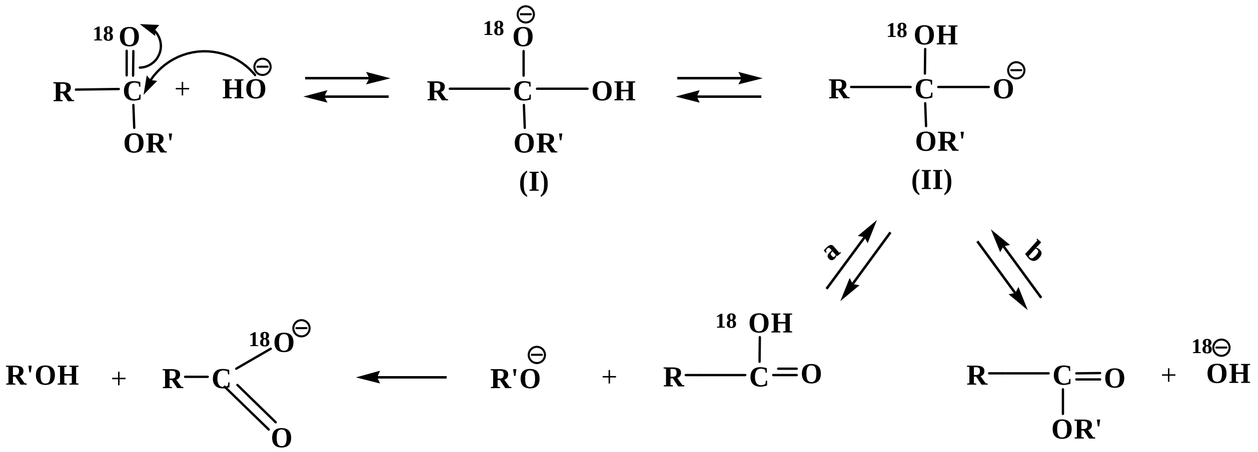
The hydrolysis of esters by hydroxide ions in aqueous solution is kinetically a second-order reaction, first order in ester and first order in hydroxide ion. It is, therefore, a bimolecular reaction. The evidence for the acyl-oxygen bond fission is provided by carrying out the hydrolysis of n-amyl acetate in water enriched in ^{18}O and then isolating n-amyl alcohol without ^{18}O.



The hydrolysis can thus be depicted as involving a $B_{AC}2$ reaction for which two mechanisms are consistent with the above data.



In the first of these two mechanisms there is a transition state (S_N2 reaction) with an energy maximum in the reaction coordinate whereas the second mechanism postulates a true intermediate with energy minimum. Bender solved the problem of deciding between these two mechanisms by hydrolyzing esters (ethyl, isopropyl and t-butyl benzoates) labeled in the carbonyl group with ^{18}O in ordinary water containing hydroxide ions. When the hydrolysis was stopped before completion, unreacted esters were found to contain less ^{18}O content. This decrease in ^{18}O content of the ester cannot be explained by the first mechanism as it is a concerted process. But if we assume that the proposed tetrahedral intermediate (I) of the second mechanism lives long enough to survive a proton shift and establish an equilibrium with another intermediate (II) then the two oxygen atoms become equivalent. Since the basicities of alkoxide and hydroxide ions are comparable, the two intermediates may lose these ions at comparable rates (paths a and b, respectively) and then it appears quite reasonable to expect unlabelled ester to be formed in the process.



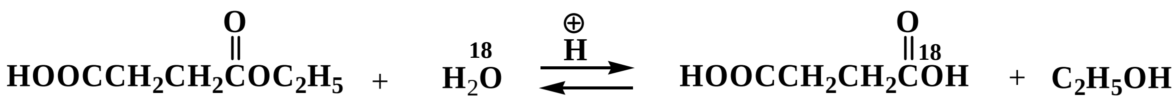
Electron-withdrawing substituents in either the acyl or alkyl part of the ester facilitate attack by hydroxide ions.

The effects of substituents on $B_{AC}2$ hydrolysis of aromatic esters fall in line with the above conclusions. It was observed that the substituents Cl, Br and NO_2 group accelerate the reaction while CH_3, p-OCH_3 and NH_3 groups retard it.

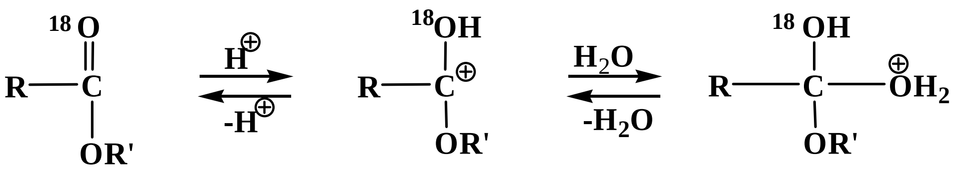
9.3.2. ACIDIC HYDROLYSIS (The $A_{AC}2$ Mechanism)

Acid-catalyzed hydrolysis of esters is a reversible reaction unlike base-catalyzed hydrolysis. The principle of microscopic reversibility tells us that the mechanism of the reverse reaction is known with as much certainty as is the mechanism of the forward reaction. This means that a study of the mechanism of acid-catalyzed hydrolysis will automatically establish the mechanism for acid-catalyzed esterification.

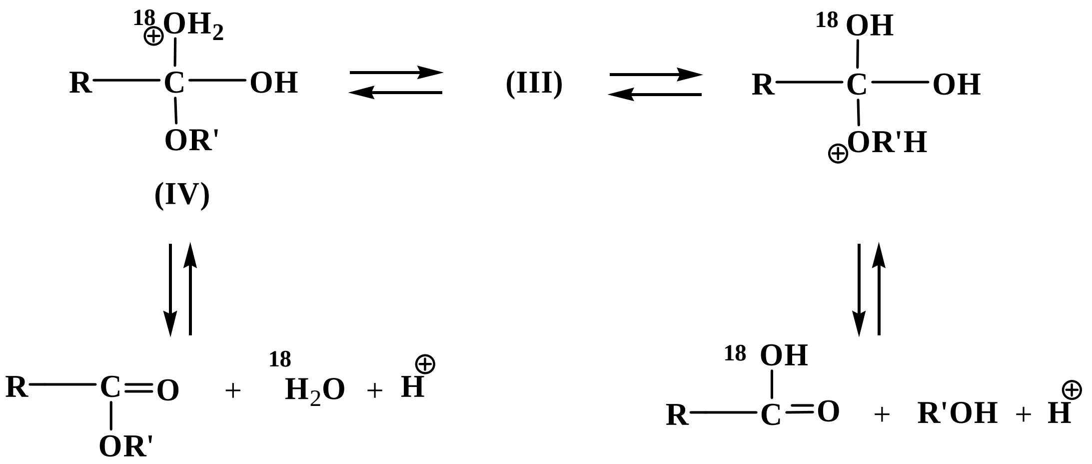
The rate of acid-catalyzed hydrolysis of common esters is found to be proportional to both H^+ and the ester and when the hydrolysis is carried out in the presence of $H_2{}^{18}O$, the product alcohol has no ^{18}O content. Thus, it is an $A_{AC}2$ reaction.



Again Bender observed the loss of ^{18}O content in the unreacted ethylbenzoate when the hydrolysis was stopped before completion. This loss can only be explained by assuming two intermediates III and IV whose life is long enough to permit proton exchange thus making the two oxygen atoms equivalent.



(III)

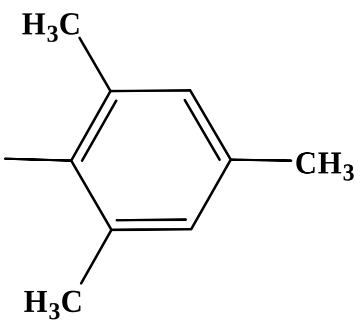


In contrast to basic hydrolysis, acidic hydrolysis (and esterification) is rather insensitive to polar effects. This appears quite reasonable as the two parts of the process, protonation and subsequent nucleophilic attack by water, require two opposing electronic influences. Electron-donating groups accelerate protonation, but they inhibit the subsequent attack by a nucleophile. On the other hand, electron-withdrawing substituents repress protonation but they accelerate the nucleophilic attack. These reactions, however, are subject to steric effects; for instance, esterification of 2-methyl benzoic acid is retarded while that of 2, 6-dimethylbenzoic acid is completely prevented.

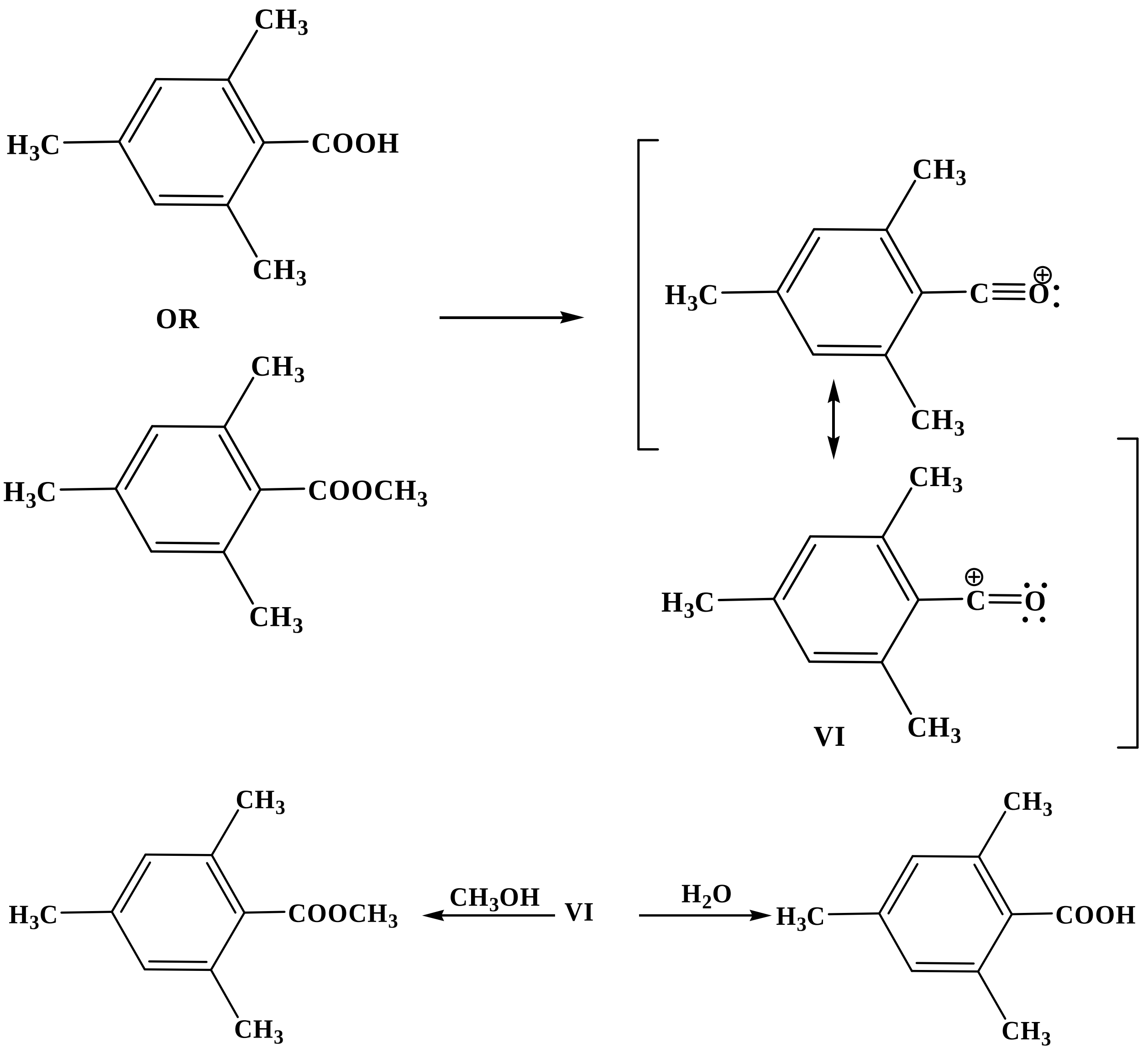
9.3.3. THE ACYLIUM ION MECHANISM (The $A_{AC}1$ Mechanism)

Hydrolysis and esterification of sterically hindered compounds, such as derivatives of trialkylacetic acids and ortho disubstituted benzoic acids, are carried out by dissolving them in concentrated sulphuric acid and then pouring this solution into cold water (for hydrolysis) or into an alcohol (for esterification). Mesitoic acid (2,4,6-trimethylbenzoic acid; (V) provides a good example of this type whose solution in concentrated sulphuric acid indicates the presence of four particles. The available evidence indicates that like $A_{AC}2$ mechanism, there is an initial formation of an oxonium ion by the addition of a proton to the substrate which then undergoes a rate-controlling heterolytic fission to yield an acylium ion (VI).

$$\underset{\textbf{V}}{R\text{—}COOH} + 2H_2SO_4 \longrightarrow \underset{\textbf{VI}}{RC\overset{\oplus}{O}} + H_3\overset{\oplus}{O} + 2HS\overset{\ominus}{O}_4$$

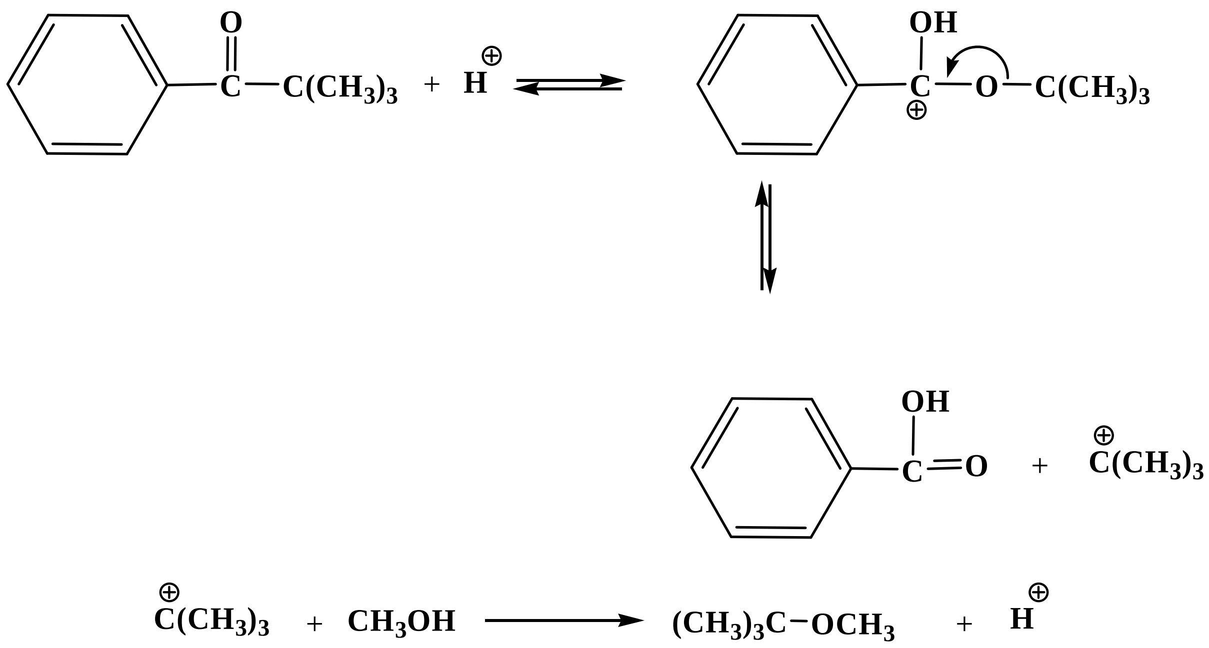
R = 

The acylium ions are linear and their formation is favored primarily because of relief in the steric strains of the sterically hindered compounds. Another factor that favors their formation is the conjugation of the $-C\equiv O^{+}$ group with the unsaturated system thus delocalizing the positive charge over the whole ion VI. A rapid attack by water or alcohol on this ion results in the formation of acid or ester, respectively. Thus esterification (or hydrolysis of methyl ester) of mesitoic acid proceeds as follows:

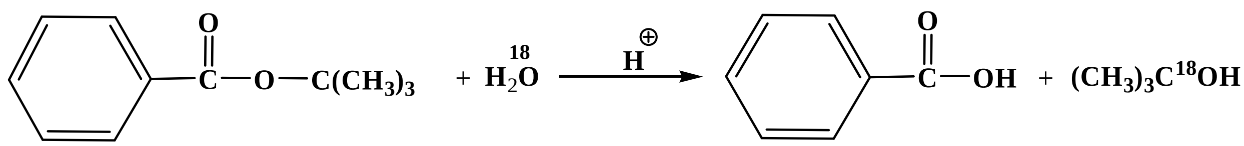


9.3.4. THE CARBONIUM ION MECHANISM (The $A_{AL}1$ Mechanism)

When groups such as tert-alkyl, benzyl, etc., capable of forming stable carbonium ions are the alkyl moiety in the substrate, hydrolysis and esterification may place by an alkyl-oxygen bond cleavage. A mechanism of this type occurs in the solvolysis of tert-butyl benzoate which on treatment with methanol and acid gives tert-butyl methyl ether and benzoic acid, rather than tert-butyl alcohol and methyl benzoate, the products of normal solvolysis. The following mechanism is consistent with the product analysis.



Conformation of this mechanism is provided by carrying out the hydrolysis in $H_2{}^{18}O$.



This type of mechanism has been labeled as $A_{AL}1$ mechanism. The intermediate has features so characteristic of a free carbonium ion, i.e., its recemization and rearrangement, if the structure permits.

9.4. LET US SUM UP

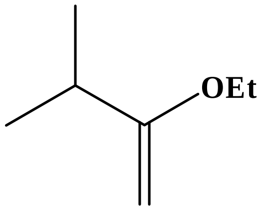
In this lesson, we:

Pointed out

- Vonbraun reaction
- The Claisen condensation
- Hydrolysis of esters

9.5. CHECK YOUR PROGRESS

1. Explain Vonbraun reaction with mechanism.
2. Ethyl 2-methyl propionate (I) fails to undergo the Claisen reaction with sodium ethoxide in ethanol and the possible product (II) is not isolated. Explain.



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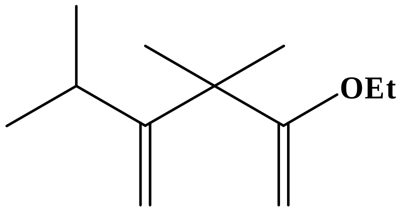


(II)

9.6. POINT FOR DISCUSSION

3. Discuss the mechanism of Claisen Condensation. How will you synthesize a β-ketoester without α-hydrogen atoms?
4. Classify the various mechanisms by which esterification of an acid and the hydrolysis of an ester may proceed. Discuss their mechanism.

9.7. REFERENCES

1. Goutam Brahmachari, Organic name reactions, Narosa publishing house, New Delhi.

2. S.M. Mukherji and S.P. Singh, Reaction mechanism in Organic Chemistry.

UNIT-IV

LESSON: 10 – ELIMINATION REACTION

CONTENTS

10.0. AIMS AND OBJECTIVES

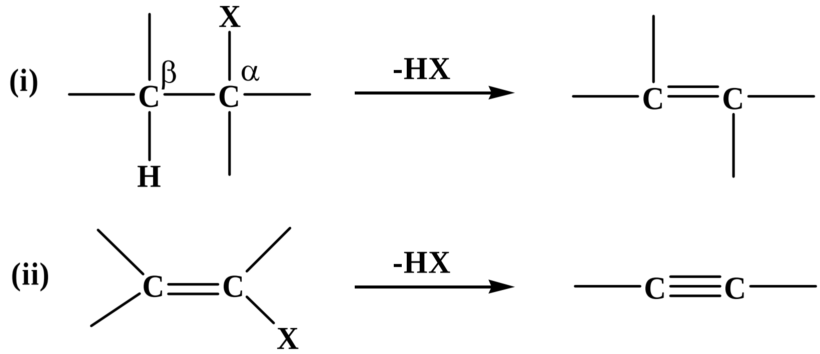
The aim is to motivate and enable the student to comprehend the possible chemical route by which the elimination reactions may proceed.

On successful completion of this lesson the student should have:

* learnt possible reaction pathways in elimination reactions.

10.1. INTRODUCTION

When two groups or atoms from adjacent carbons are eliminated with the formation of unsaturated compounds the reaction is called elimination reaction. Most commonly a nucleophile and a proton from the β−carbon are eliminated. Hence the reaction is known as 1,2- or α,β-elimination or β-elimination.



Some similar elimination reactions are

(1) Dehydrohalogenation of alkyl halide by base.

$$\mathbf{RCH_2CH_2{-}X \xrightarrow{\overset{\ominus}{OH}} RCH{=}CH_2 \quad H_2O + \overset{\ominus}{X}}$$

(2) Dehydration of alcohols by acids.

$$\mathbf{RCH_2CH_2{-}OH \xrightarrow{\overset{\oplus}{H}} RCH{=}CH_2 + H_2O + \overset{\oplus}{H}}$$

(3) Hofmann's degradation of quaternary bases by heat.

$$\mathbf{RCH_2CH_2{-}\overset{\oplus}{N}R_3\overset{\ominus}{O}H \xrightarrow{\Delta} RCH{=}CH_2 + R_3N + H_2O}$$

The presence of at least one hydrogen atom on the β carbon is necessary for elimination. The driving forces for elimination are

(a) Stability of the olefin formed

(b) The relief from steric strain due to crowding in the substrate.

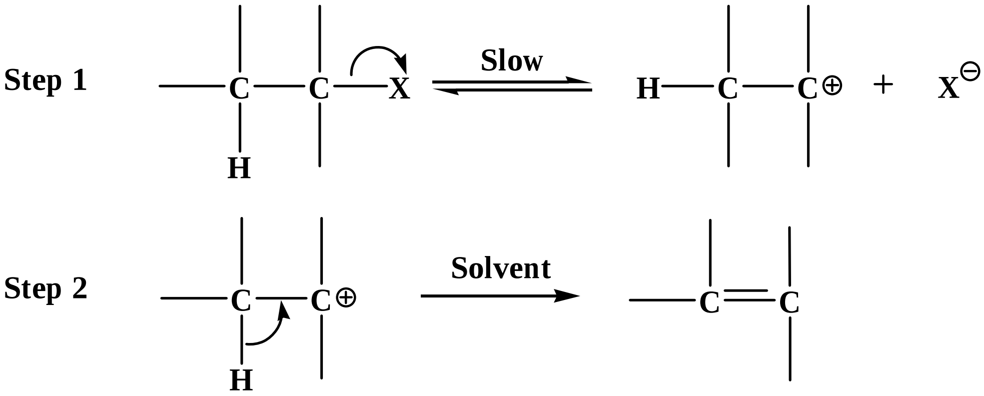
Branching at the β carbon of the substrate produces substituted olefins stabilized by hyperconjugation and hence favors elimination.

Strain in the substrate due to crowding by the substituents can be relieved on the formation of olefin since the bond angles increase from 109.5^0 in the substrate (sp^3 hybridized) to 120^0 in the product (Sp^2 hybridized). Hence 3^0 halides favor elimination most and 1^0 halides the least. i.e., the order of the elimination in halide is $3^0>2^0>1^0$.

The elimination reaction may proceed by either unimolecular or bimolecular mechanism.

10.2. E1 MECHANISM

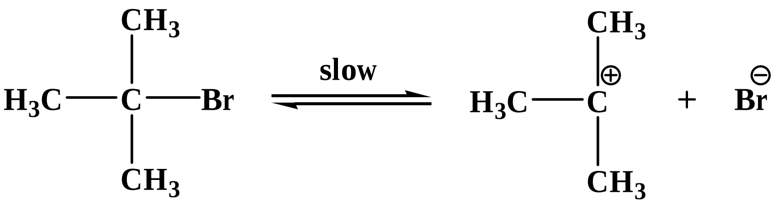
The E1 mechanism is a two step process in which the rate determining step is ionization of the substrate to give a carbocation that rapidly loses a β-proton to a base.



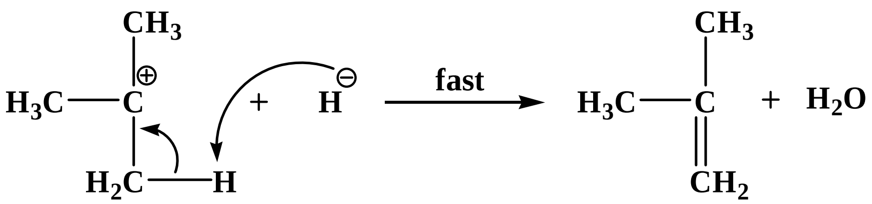
E1 mechanism reaction the product should be completely nonstereospecific, since the carbocation is free to adopt its most stable conformation.

10.2.1. DEHYDROHALOGENATION OF ALKYL HALIDES

The rate of elimination of a halo acid from t-butyl bromide in basic medium is found to be proportional to [Me_3CBr]. Therefore, the halide undergoes slow ionization in the first step. This is followed by a rapid extraction of a proton from the carbocation by the base or solvent in the second step.

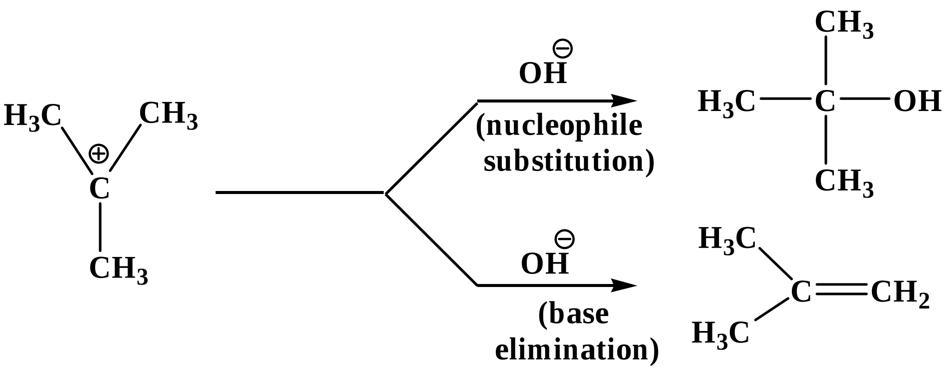


-------- (i)

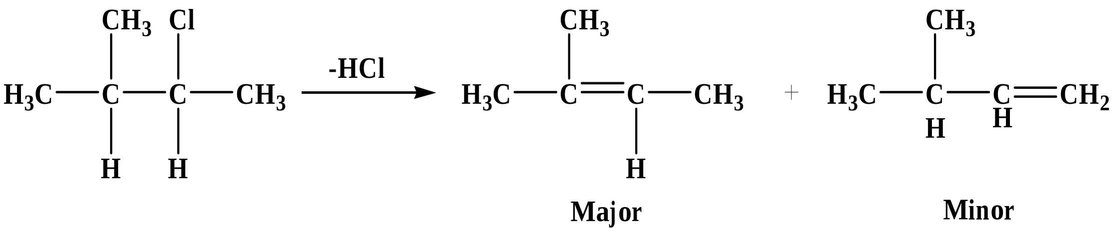


-------- (ii)

The carbocation is formed in the first step in E_1 reaction. Hence the reagent can attack the carbon to give substitution product and also can accept a proton to give elimination product. In practice both alcohol and alkene are obtained on hydrolysis of Me_3CBr.



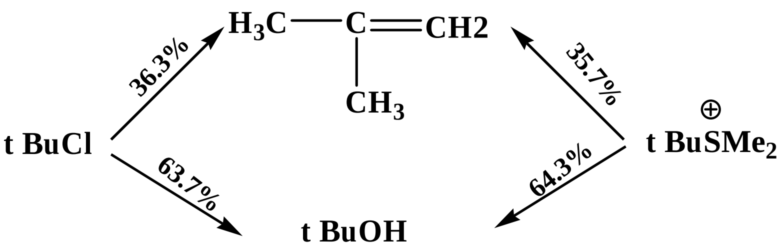
When more than one alkene can be formed, the alkene will predominate which has large number of alkyl groups on the double-bonded carbons – this is Saytzev's rule. This is understandable since the substituted alkyl groups will stabilize the alkene by hyperconjugation.



10.2.2. EVIDENCE FOR E1 MECHANISM

1. The reaction exhibits first order kinetics as expected. Solvent does not appear in the rate equation, even if it were involved in the rate determining step, but this point can be checked by adding a small amount of the conjugate base of the solvent. This addition does not increase the rate of the reaction. An example of an E1 mechanism with a rate determining second step has been reported.

2. If the reaction is performed on two molecules that differ in the leaving group the rates should obviously be different. Since, they depend on the ionizing ability of the molecule.



3. If carbocations are intermediates, we expect rearrangements with suitable substrates. These have often been found in elimination reaction performed under E conditions.
E1 reactions can involve ion pair. This effect is naturally greatest for nondissociating solvents.

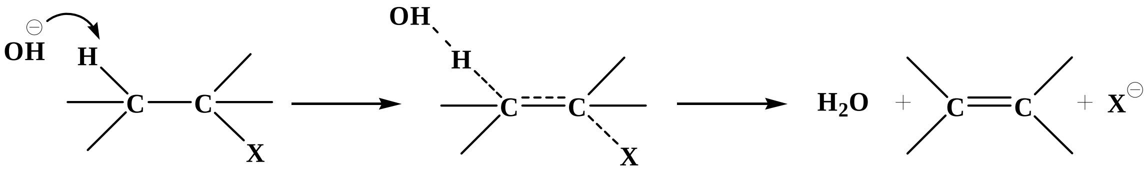
E_1 reaction is facilitated by:

(i) Branching at the α and β carbons of the substrate – for the stability of the olefin.

(ii) Strong polar solvent – to acid ionization.
(iii) Low concentration of base–the greater stability of the alkene over the carbocation makes the extraction of proton easy.

10.3. E2 MECHANISM

When the rate of elimination reaction is dependent on both the substrate and the reagent the reaction is kinetically second order or bimolecular.

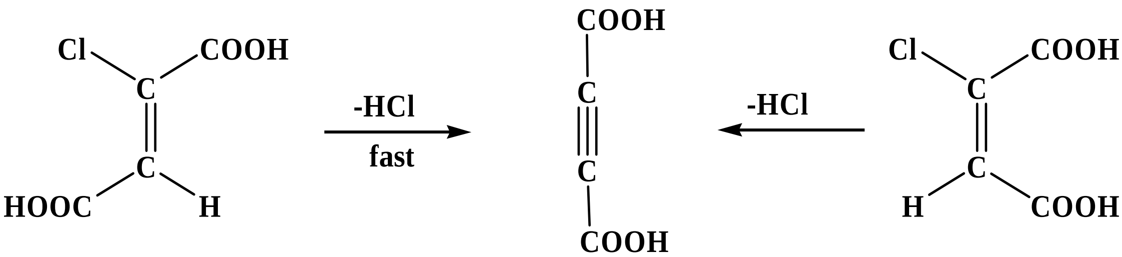


Transition state

The base abstracts a proton from the β-carbon; simultaneous departure of the nucleophile takes place from the α-carbon. In the transition state the β-C-H and α–C-X bonds are stretched on the attack of the reagent with incipient π-bond formation.

The energy of the transition state will be least when two leaving groups, the α and β carbons and the attacking base are coplanar in the transition state. Also, the two leaving groups (H and X) should be trans to each other to effect π bond.

The two leaving groups orient themselves in the trans position when a σ bond exists between the α and β carbons. However, free rotation is not allowed as in the case of double bond, the elimination is difficult when two leaving groups are cis to each other. Thus, acetylene dicarboxylic acid is more easily formed from chlorofumaric acid (1) than from chloromaleic acid (2).



Leaving groups trans (1)

Leaving groups cis (2)

10.3.1. EVIDENCES FOR THE EXISTENCE OF E2 MECHANISM

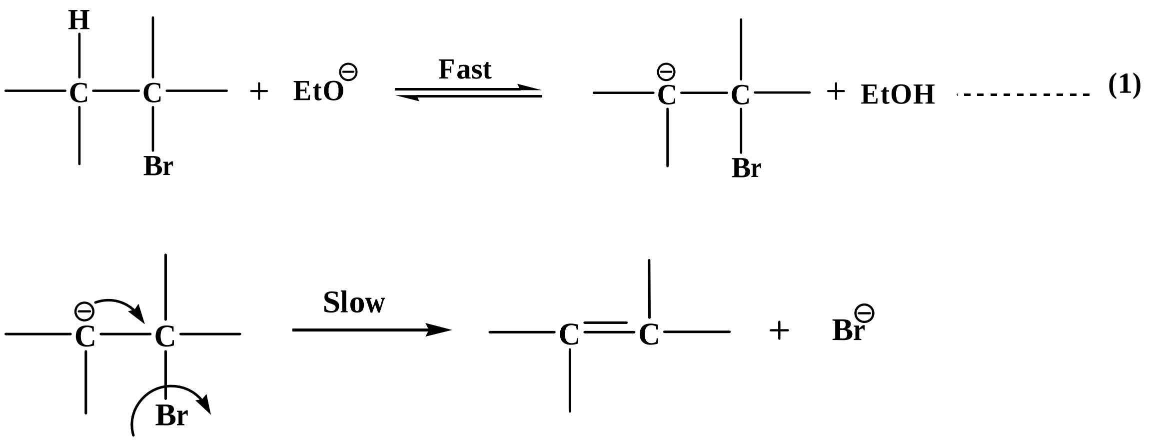
1. The reaction displays the proper second-order kinetics.
2. When the leaving hydrogen is replaced by deuterium in second order elimination there is an isotope effect with breaking of cis bond in the rate determining step. This result proves that E_2 mechanism. E_2 is stereospecific it is found from stereochemical studies.

E2 reaction is facilitated by:

1. branching at α and β carbons since more stable olefins is formed.
2. Strong base of high concentration since a strong C-H bond has to break.
3. Solvent of low polarity.

10.4. E1CB MECHANISM

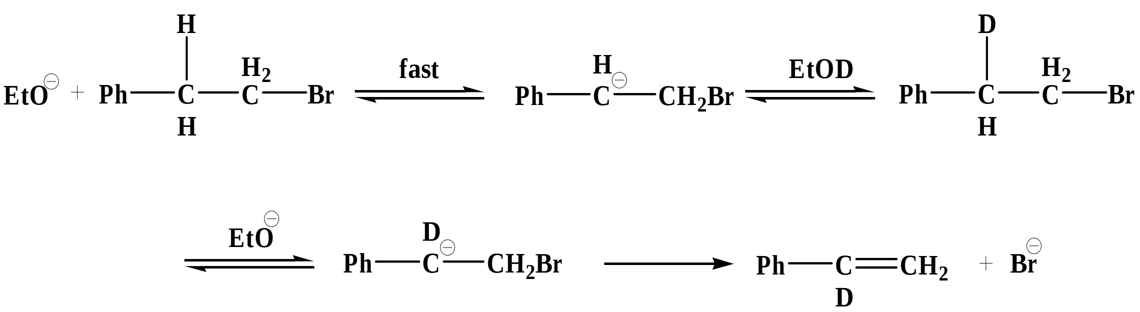
The second-order elimination reaction may as well proceed in two steps as on E1 reaction. The first step involved a fast and reversible removal of a proton from the β-carbon with the formation of a carbon ion which then loses the leaving grouping in the second slow rate determining step.



The overall rate of this reaction is thus dependent on the concentration of the conjugate base of the substrate. Hence this designated as E1CB.

To distinguish between E_2 and E1CB mechanism, deuterium exchange experiment was performed.

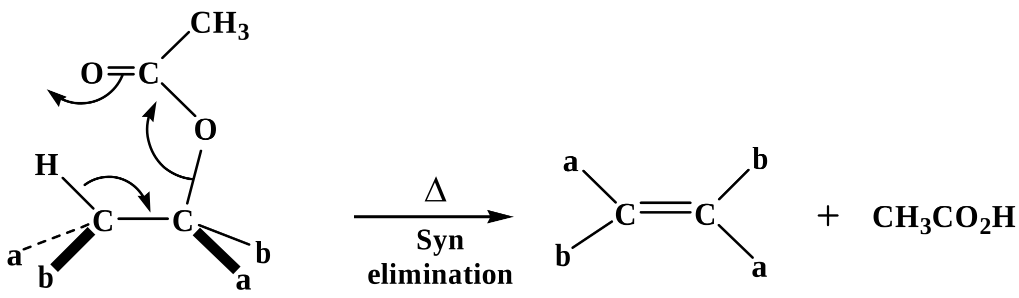
For this 2-phenyl ethyl bromide was treated with sodium ethoxide in EtOD. This substrate was selected because the Ph group is expected to increase the acidity of β– hydrogen and also to stabilize the carbanion to exist long enough for the incorporation of deuterium in the starting from the solvent EtOD.



The reaction was interrupted before completion and analysed for deuterium content. No deuterium incorporation was found either in the substrate or in the styrene. Hence no reversible carbanion was formed. The reaction followed E_2 path. However, the E1CB mechanism does operate in substrates having strong electron- withdrawing groups, e.g., chlorine on β carbon and poor leaving groups e.g., fluorine as in $Cl_2CH\text{-}CF_3$.

10.5. INTRAMOLECULAR ELIMINATION (Ei)

Concerted 1,2-elimination the base is actually part of the substrate molecule. Such elimination can be described as intramolecular. The two groups leave at about the same time and bond to each other as they are doing so. The elimination must be syn, for the four and five membered transition states, the four or five atoms making up the ring must be coplanar.



10.5.1. EVIDENCE FOR THE EXISTENCE OF THE Ei MECHANISM

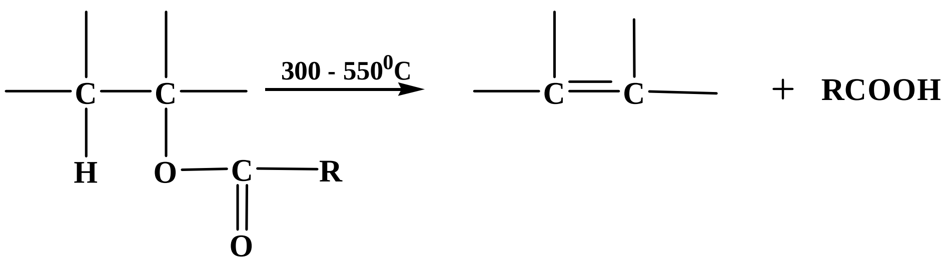
1. The kinetics is first order, so that only one molecule of the substrate is involved in the reaction.
2. Free-radical inhibitors do not show the reaction. So that, no free-radical mechanism is involved.
3. The mechanism predicts exclusive syn elimination, and this behavior has been found in many cases. The evidence is inverse to that for the anti E2mechanism.
4. ^{14}C isotope effects for the cope elimination show that both the $C-H$ and $C-N$ bonds have been exclusively broken in the transition state.
5. Some of these reactions have been shown to exhibit negative entropies of activation, indicating that the molecules are more restricted on geometry in the transition state.

Examples for Ei Mechanism

Acetate esters bearing β, hydrogen's often eliminate acetic acid when pyrolyzed giving the corresponding alkenes. This reaction is found to follow a syn stereo chemical course rather than anti because the eliminated H must be near double bonded O.

For this mechanism to operate, the substrate molecule must be able to adopt a cyclic conformation (usually five or six), so that the basic atom can approach the β-hydrogen within bonding distance because the concerted syn elimination involves a cyclic rearrangement of electrons.

10.5.2. HYDROACYLOXY ELIMINATION



Ester in which the alkyl group has a β-hydrogen can be pyrolyzed. Most often in the gas phase to give the corresponding acid an olefin.

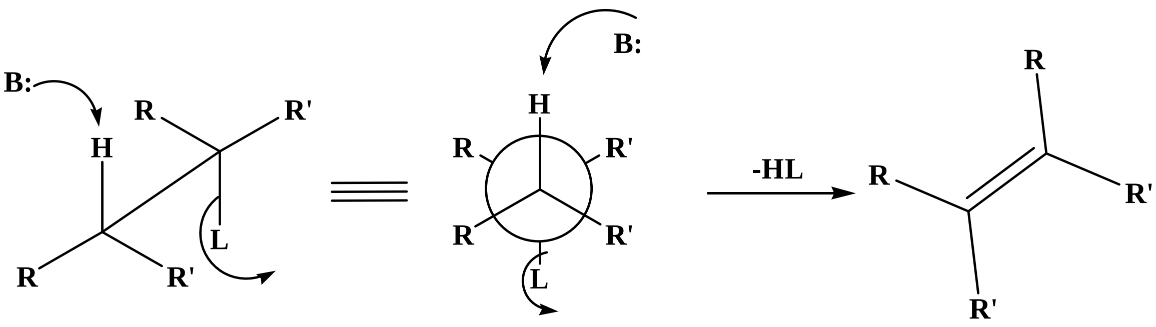
No solvent is required. For higher olefins a better method is to pyrolyze the alcohol in the presence of acetic anhydride.

The mechanism is E_i. Lactones can be pyrolyzed to give unsaturated acids, provided that six membered transition state required for E_i is available. Amides give a similar reaction but require higher temperatures.

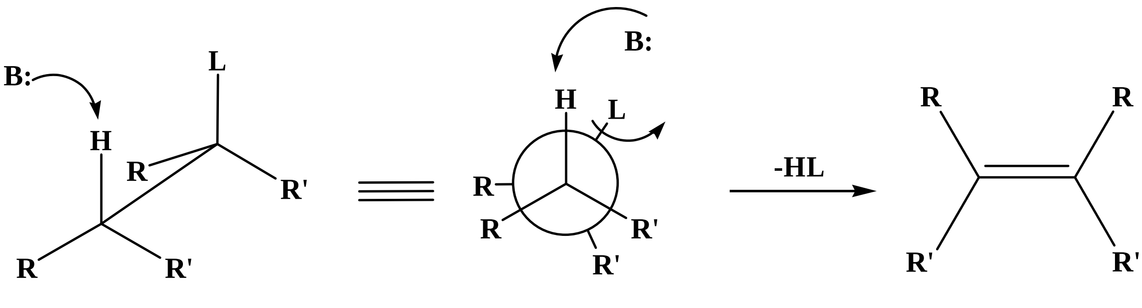
10.6. STEREOCHEMISTRY OF ELIMINATION REACTIONS

Eliminations results in π bond formation. In E2 reaction the *p*-orbital which develops on the α and β carbons with the departure of the leaving group should be parallel for maximum overlap, for this both the leaving groups and carbons bearing them should be in one plane.

When the two leaving groups are planar there are two extreme conformations. Anti-periplanar (i.e.) two groups in *trans* position, syn-periplanar (i.e.) two groups in *cis* position. The elimination then may proceed as given below:



(1) (1a)



(2) (2a)

From the Newman projection of the *trans* and *cis* conformations the elimination is expected to be more facile from the trans conformation 1(a) than from the cis conformation 2(a). This is because in 1(a) the attacking base approaches from the farthest side o the leaving group, while in 2(a) the attack is from the same side which causes repulsion. The developing charge on the β -carbon displaces the leaving group with its bonding pair from the backside a path of least energy. The elimination occurs from the lower energy staggered conformation than from the high energy eclipsed conformation.

10.7. ELIMINATION *VS* SUBSTITUTION

Elimination reactions are usually accompanied by substitution reaction. When the reagent is a good base it accepts a proton to yield elimination product and if it is a good nucleophile then it attacks the carbon to give substitution product.

The proportion of elimination and substitution depends upon the following:

10.7.1. STRUCTURE OF THE SUBSTRATE

The proportion of elimination increases from $1^0 \longrightarrow 2^0 \longrightarrow 3^0$ substrates. The reason is that alkenes formed on elimination are stabilized by hyperconjucation. The steric strain is relieved on the formation of alkene, whereas on substitution the strain is reintroduced.

10.7.2. NATURE OF THE BASE

Strong base promotes elimination over substitution and in particular E2 over E1. Alcoholic KOH favors elimination and aqueous KOH favors substitution. Strong nucleophiles but weak bases promote substitution over elimination whereas strong base but weak nucleophile promotes elimination over substitution. Though pyridine and R_3N are not strong bases they are poor nucleophile because the branching at the nitrogen atom causes steric hindrance to nucleophilic attack on carbon. Hence, they act as base to accept the more exposed hydrogens of the substituent groups to afford alkene. A similar steric effect is observed with the size of the base or nucleophile. Elimination increases with increase in the size of the nucleophile.

10.7.3. NATURE OF SOLVENT

A less polar solvent not only favors bimolecular reaction but also E2 over SN2. Change of hydroxylic solvents to aprotic solvents increases the base strength as the solvents layer around the base by hydrogen bonding is absent. Thus Cl^-, OH^-, OR^- etc., are very strong bases in DMF or DMSO. The use of aprotic solvent may change the pathway from E1 to E2.

10.7.4. EFFECT OF TEMPERATURE

In elimination reaction a strong C-H bond has to break, hence a high activation energy is required for elimination reaction rather than for substitution reaction. In general, the proportion of elimination increases on using a strong base of high concentration and a solvent of low polarity. On the other hand the proportional substitution increases by using a weak base of low concentration and a solvent of high polarity.

10.8. LET US SUM UP

In this lesson, we:

Pointed out

- E1 mechanism
- E2 mechanism
- E1CB mechanism
- Ei mechanism

- Stereochemistry of elimination reaction
- Elimination *vs* substitution reaction

10.9. CHECK YOUR PROGRESS

1. How can you distinguish between E1 and E1CB reactions by labeling experiments?
2. Differentiate E2 and Ei reactions with examples.

10.10. POINT FOR DISCUSSION

1. With suitable examples, illustrate E1,E2, and E1CB reactions. Outline conditions for each of these mechanisms to operate.
2. What are the stereochemical preferences in elimination reactions? Comment on the statement that in contrast to E2 reactions E1 reactions are not stereospecific.

10.11. REFERENCES

1. Jerry march, Advanced Organic Chemistry, Fourth edition, Wiley India edition.
2. P.S. Kalsi, Organic reactions and their mechanisms, Second edition, New age international publishers.

LESSON: 11 – TYPICAL ELIMINATION REACTIONS

CONTENTS

11.0. AIMS AND OBJECTIVES

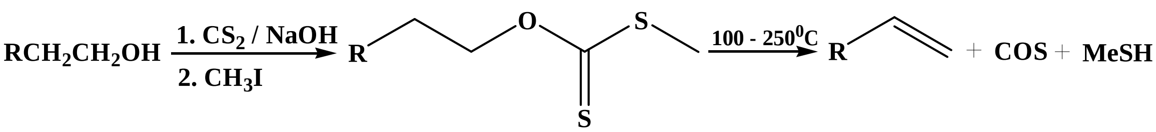
The aim is to motivate and enable the student to comprehend the possible chemical route by which the elimination reactions may proceed.

On successful completion of this lesson the student should have:

* learnt possible reaction pathways in typical elimination reactions.

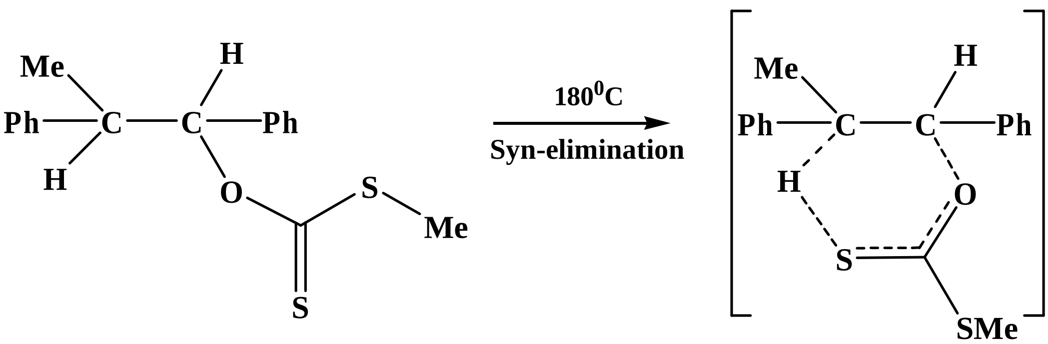
11.1. CHUGAEV REACTION

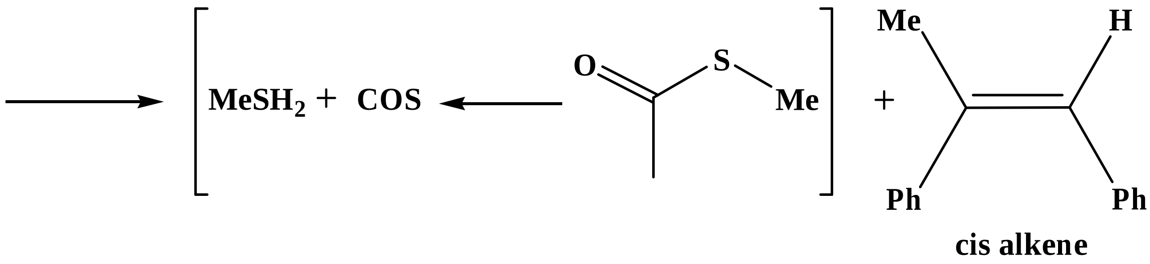
The thermal decomposition of xanthates prepared from alcohols involving stereo specific elimination to yield alkenes is called the Chugaev reaction. The reaction is advantageous because it requires relatively lower temperature and leads to the predominant formation of unrearranged terminal alkenes.



Mechanism:

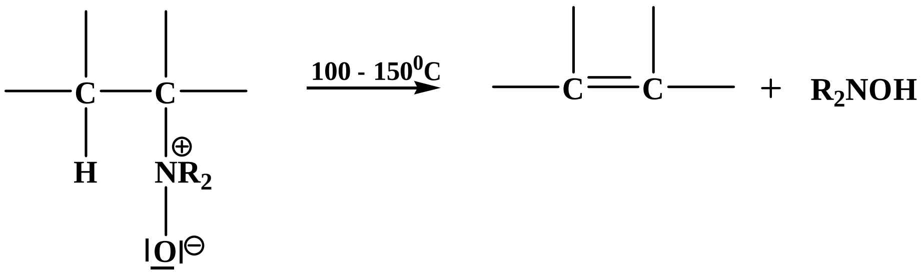
The reaction involves a six membered cyclic transition state, and proceeds through Ei mechanistic pathway.





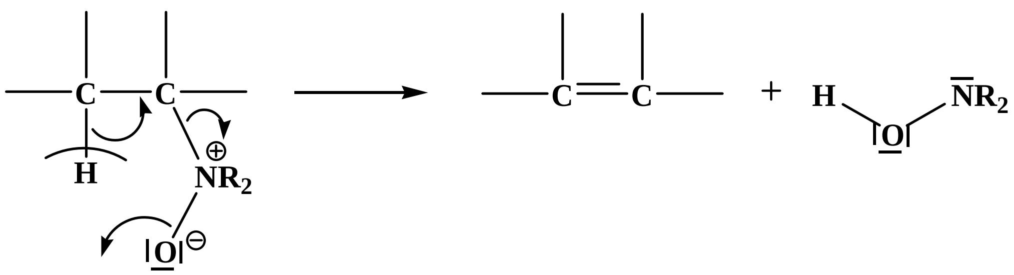
11.2. COPE REACTION

The cleavage of amine oxides to produce an alkene and a hydroxylamine is called cope reaction.



The reaction is usually performed with a mixture of amine and oxidizing agent without isolation of the amine oxide.

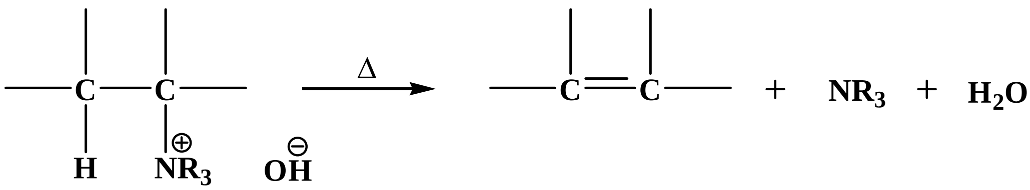
The reaction is thus useful for preparation of many olefins. The elimination is a stereo selective syn process and the five membered Ei mechanisms operate.



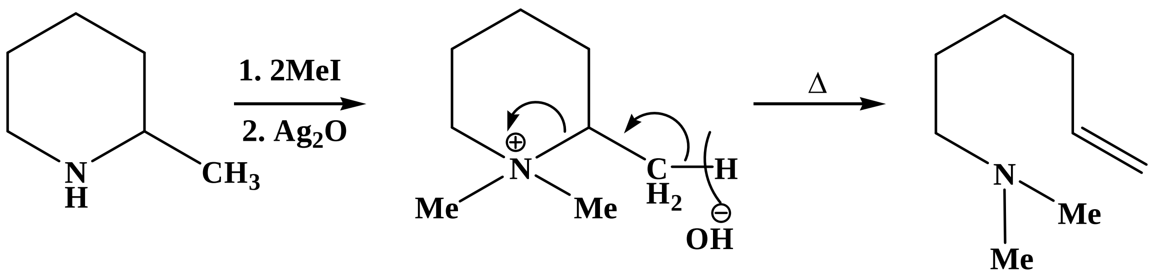
Evidences indicate that the transition state must be planar. The stereoselectivity of this reaction and lack of rearrangement of the product, it is useful for the formation of trans-cycloolefins.

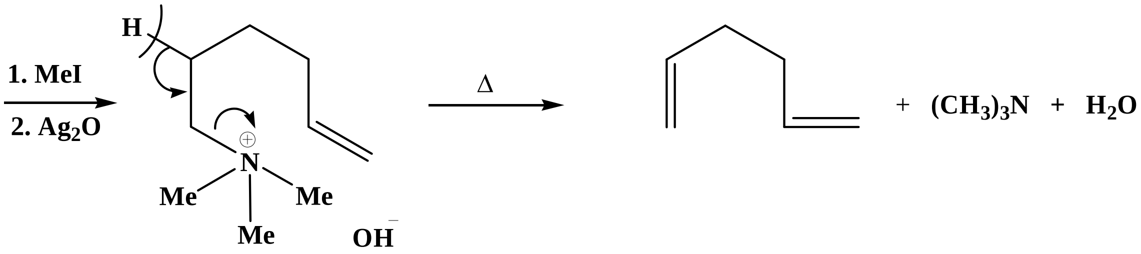
11.3. HOFMANN DEGRADATION

Cleavage of quaternary ammonium hydroxide is the final step of the process known as Hofmann degradation.

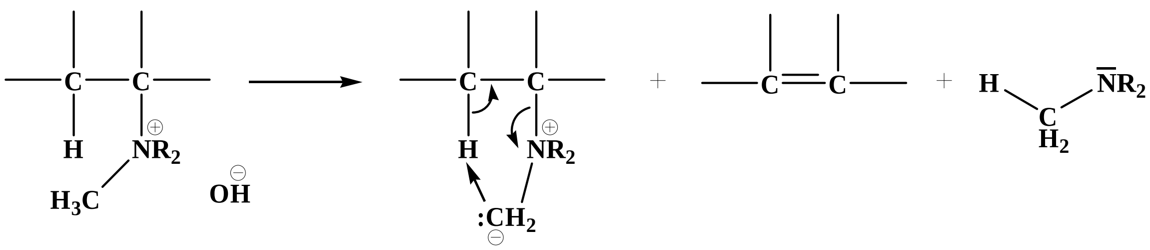


The reaction is used for synthesizing olefins and some cyclic olefins.





The mechanism is usually E2. Hofmann's rule is generally obeyed by acyclic and Zaitsev's rule by cyclohexyl substrates. Some cases, where the molecules are highly hindered a five membered Ei mechanism.



E1and E2mechanisms are distinguished by the use of deuterium labeling. For example, if the reaction is carried out on a quaternary hydroxide deuterated on the β-carbon then the rate of deuterium indicates the mechanism. If the E2 mechanism is in operation, the trimethylamine produced would contain no deuterium. But if the mechanism is Ei the amine would contain deuterium.

11.4. LET US SUM UP

In this lesson, we:

Pointed out

- Chugaev reaction
- Cope reaction
- Hofmann degradation

11.5. CHECK YOUR PROGRESS

1. Illustrate the mechanism of chugaev reactions with examples.
2. Explain Cope reaction.

11.6. POINT FOR DISCUSSION

1. Discuss various factors which influence the extent of elimination and substitution.
2. Explain the mechanism of Hoffmann degradation.

11.7. REFERENCES

1. Jerry march, Advanced Organic Chemistry, Fourth edition, Wiley India edition.

2. P.S. Kalsi, Organic reactions and their mechanisms, Second edition, New age international publishers**.**

LESSON: 12 – CARBENES AND NITRENES

CONTENTS

12.0. AIMS AND OBJECTIVES

The aim is to motivate and enable a comprehensive knowledge on carbenes and nitrenes.

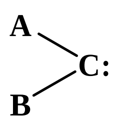
On successful completion of this lesson the student should have:

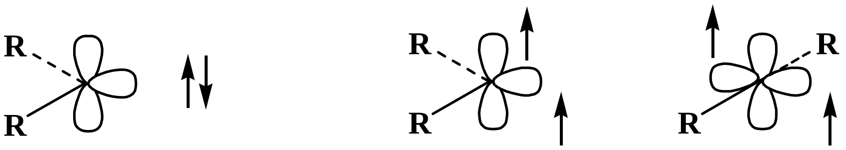
* Understood the structure, generation and reactions of carbenes and nitrenes.

12.1. INTRODUCTION

Carbenes are neutral intermediates having bivalent carbon, in which a carbon atom is covalently bonded to two other groups and has two valence electrons distributed between two non bonding orbital.

When the two electrons are spin paired the carbons is a singlet, if the spins of the electrons are parallel it is a triplet.





Singlet Triplet

The nitrenes $R-N$ represent the nitrogen analogs of carbenes and may be generated in the singlet $(R-\ddot{N}$ or triplet $R-N\cdot)$

12.2. CARBENES

12.2.1. STRUCTURE

A singlet carbene is thought to possess a bent SP^2 hybrid structure in which the paired electrons occupy the vacant SP^2 orbital.

A triplet carbene can be either bent SP^2 hybrid with an electron in each unoccupied orbital or a linear SP hybrid with an electron in each of the unoccupied P-orbital. The singlet and triplet state of a carbene display different chemical behavior. Thus addition of singlet carbene to olefinic double bonds to form cyclopropane derivatives is much more stereo selective than addition of triplet carbenes.

12.2.2. GENERATION

Carbenes are obtained by thermal or photochemical decomposition of diazoalkanes. These can also be obtained by α-elimination of a hydrogen halide from a halo form with base, or of a halogen from a gem dihalide with a metal.

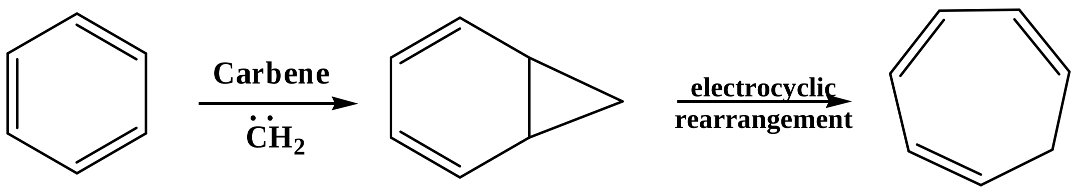
$$\mathbf{RCHN_2} \xrightarrow{h\nu} [\mathbf{RCH:}] + \mathbf{N_2}$$

$$\mathbf{N_2CHCO_2C_2H_5} \xrightarrow{\Delta} [\mathbf{:CHCO_2C_2H_5}]$$

$$\mathbf{CHCl_3} \xrightarrow{\bar{B}:} \mathbf{BH} + \mathbf{:CCl_3^-} \longrightarrow \mathbf{:CCl_2} + \mathbf{Cl^-} + \mathbf{BH}$$

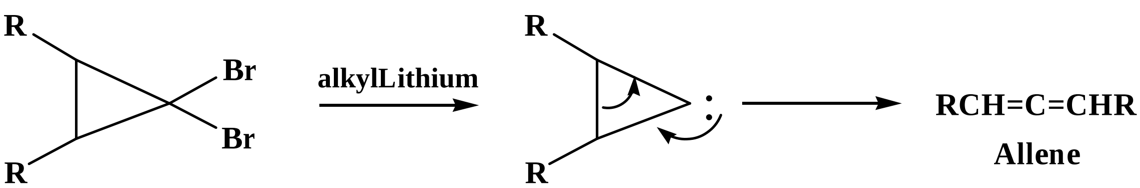
12.2.3. REACTIONS

These add to carbon double bonds and also to aromatic system and later case the initial product rearranges to give ring enlargement products.



Cycloheptatriene

When a carbene is generated in a three membered ring allenes are formed by rearrangement.



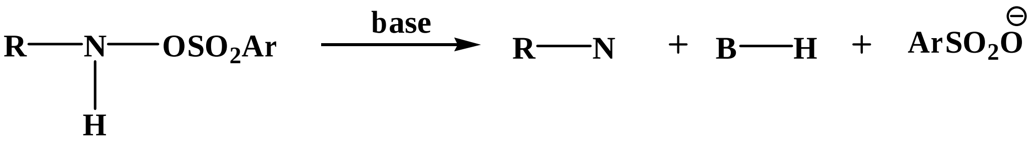
12.3. NITRENES

12.3.1. STRUCTURE

The nitrenes $R-N$ represent the nitrogen analogs of carbenes and may be generated in the singlet $(R-\ddot{N}$ or triplet $R-N\cdot)$

12.3.2. GENERATION

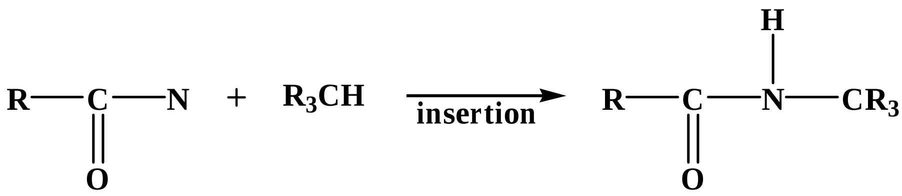
A nitrene can be generated via elimination or by the thermal decomposition of oxides $(R-N=\overset{+}{N}=\overset{-}{N}\longrightarrow RN+N_2)$



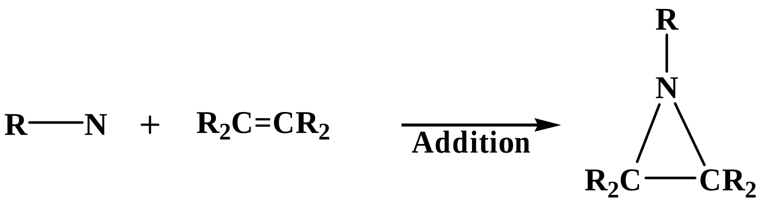
12.3.3. REACTIONS

In the chemical behavior, the nitrenes are similar to carbenes; nitrenes get inserted into some bonds e.g., C-H bond to give an amide. Aziridines are formed when nitrenes add to C=C bonds.

Insertion



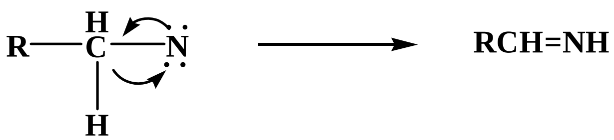
Addition



aziridine

Rearrangements:

Alkyl nitrenes do not generally give either of two proceeding reaction because the rearrangement is more rapid.



Abstraction: (eg)

$$R-N \; + \; R-H \longrightarrow R-\dot{N}-H \; + \; R\cdot$$

Dimerization: NH dimerizes to diimide N_2H_2

$$2Ar-N \longrightarrow Ar-N=N-Ar$$

The dimerization is more important for nitrines than carbenes.

12.4. LET US SUM UP

In this lesson, we:
Pointed out

- Structure
- Generation
- Reactions of carbenes and nitrenes

12.5. CHECK YOUR PROGRESS

1. How do you account for the formation of dichloro carbene in the alkaline hydrolysis of chloroform?
2. Why the triplet state of a carbene is more stable than the singlet state?

12.6. POINT FOR DISCUSSION

1. What are singlet and triplet carbenes? What is the state of their hybridization? Discuss various methods available for the generation of carbenes.
2. Discuss the chemical reactions of nitrenes.

12.7. REFERENCES

1. Jerry march, Advanced Organic Chemistry, Fourth edition, Wiley India edition.

2. P.S. Kalsi, Organic reactions and their mechanisms, Second edition, New age international publishers.

UNIT-V

LESSON: 13 – FREE RADICAL REACTIONS

CONTENTS

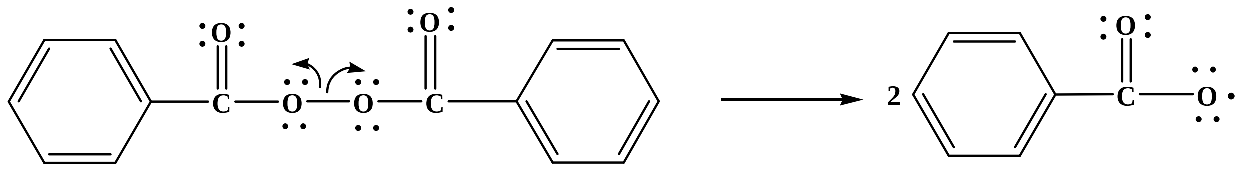
13.0. AIMS AND OBJECTIVES

The aim is to motivate and enable the student to comprehend the possible chemical route by which the free radical reactions may proceed.

On successful completion of this lesson the student should have learnt possible reaction pathways in free radical reactions.

13.1. INTRODUCTION

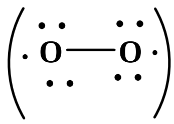
A covalent bond may get cleaved homolytically to form fragments carrying odd electrons which are called free radicals. Free radical intermediates are generally involved in reactions which are carried out either at high temperature or under the influence of light. Some reactions may proceed even at room temperature via free radical mechanism, particularly in the presence of non-polar solvents and in the presence of compounds like peroxides which produce free radicals.



benzoyl peroxide **benzoyloxy radical**

Free radicals may be electrically charged ions or noncharged species. The common characteristic of almost all free radicals is their high chemical reactivity which is due to the tendency of electrons to exist in pairs. Free radical is any atom or group that possesses one or more unpaired electrons. Elements such as halogen atom ($Cl^{\bullet}$) and alkali metal ($Na^{\bullet}$) are free radicals, since they have odd number of electrons.

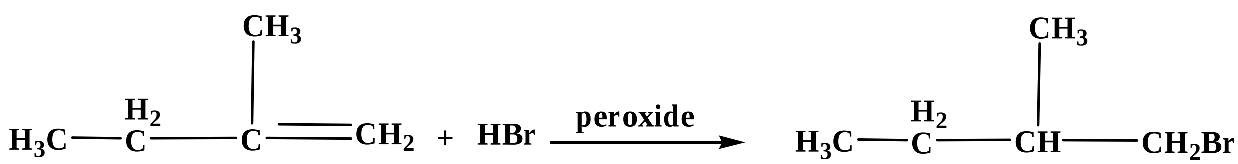
The oxygen molecule contains an even number of electrons (16) but all electrons are not paired. Ten of the valence electrons from five pairs, but the remaining two electrons possess identical spins. This unusual situation gives oxygen some interesting reactivity characteristic. Oxygen is commonly classed as a diradical.



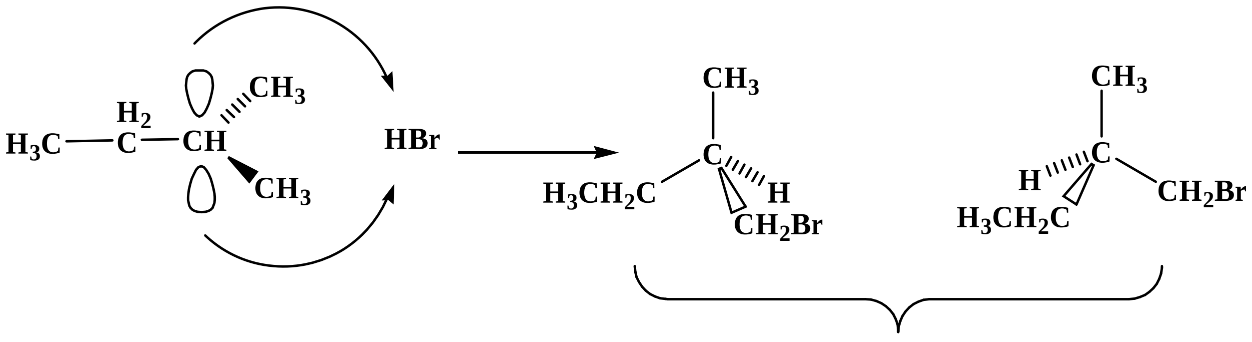
13.2. STRUCTURE AND GEOMETRY

A free radical is a species which has one or more odd electrons. In the species where all electrons are paired the total magnetic moment is zero. Since there are one or more unpaired electrons, there is a net magnetic movement and the radicals as a result are paramagnetic free radicals are usually detected by electron spin resonance.

Simple alkyl radicals have a planar structure (i.e.) these have SP^2 bonding with the odd electron in a p-orbital. The pyramidal structure is another possibility when the bonding may be SP^3 and the odd electron is in an SP^3 orbital. The planar structure is in keeping with loss of activity when a free radical is generated at a stereo centre. On adding HBr to 2-methyl-1-butane in the presence of peroxide, the product has a single stereo centre. However, equal amount of the R and S enantiomers are obtained. The product is a racemic mixture.



The carbon atom in the radical intermediate that bears the unpaired electron is planar and SP^2 hybridized. This means that the three substituents bonded to it are all in the same plane. R and S enantiomers are obtained in equal amounts because HBr has equal access to both sides of the achiral radical.



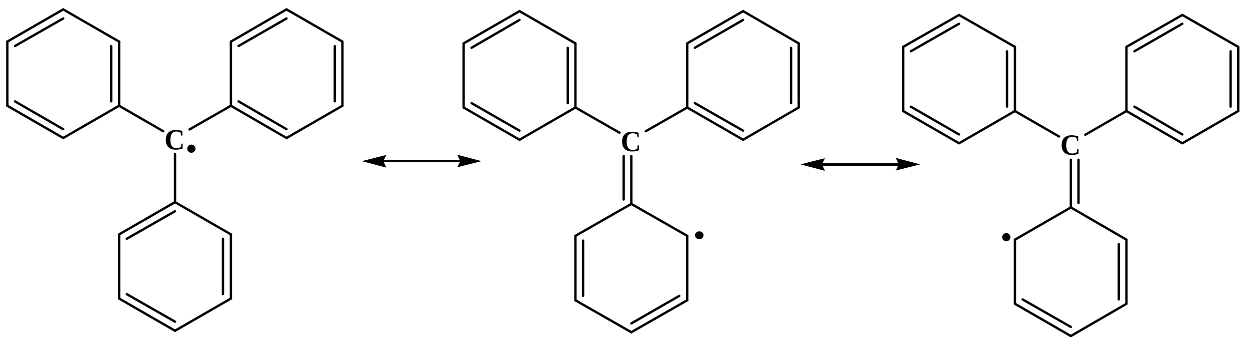
13.4. STABILITY

As in the case of carbocations, the stability of free radicals is tertiary > secondary > primary and primary and is explained on the basis of hyperconjugation. The stabilizing effects in allylic radicals and benzyl radical are due to resonance structures.

$$C_6H_5CH_3 \longrightarrow C_6H_5CH_2^{\bullet} + H^{\bullet}$$

Ease of formation of benzyl radical.

Bond dissociation energies show that 19 kcal/mol less energy is needed to form the benzyl radical from toluene than the formation of methyl radical from methane. The triphenyl methyl type radicals are no doubt stabilized by resonance the major cause of their stability is the steric hindrance to dimerization.

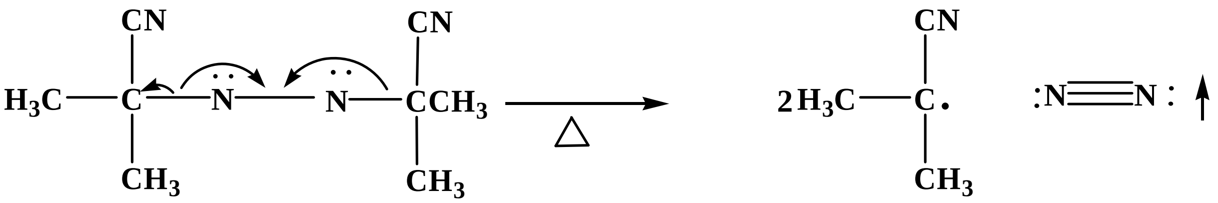


13.5. GENERATION OF FREE RADICALS

13.5.1. THERMAL GENERATION

Homolytic cleavage of sigma bond can be successful with any compound provided the temperature is successfully high. Thermal method is useful with selective bonds within a molecule which dissociates at temperature below about 200°C. Bonds of peroxy and azo compounds have bond dissociation energies below 40kcal /mol and are therefore sufficiently weak to be good sources of radicals under typical reaction conditions.

$$\text{Peroxide} \longrightarrow R(CO_2)_2 \xrightarrow{100\text{-}130^{\circ}} \underbrace{2RCO\dot{O} \longrightarrow 2R^{\bullet} + 2CO_2}_{\text{Free radicals}}$$



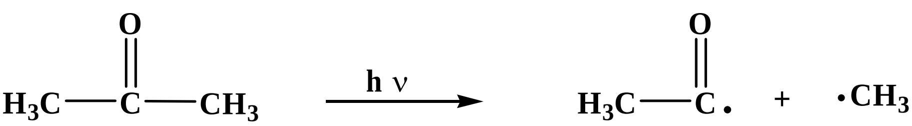
Stablized radicals

$$Me_2\dot{C}(CN) + SO_2Cl_2 \longrightarrow Me_2C(CN)Cl + {}^{\bullet}SO_2Cl$$

In the thermal decomposition of peroxide the reaction involves the fission of the oxygen-oxygen bond and the initially formed free radical then decarboxylates to give the fragmentation products. A fragmentation is thus a process where some initially formed radicals loses a small stable molecule.

13.5.2. PHOTOCHEMICAL GENERATION

By this method free radicals are formed by sigma bond cleavage



Acetyl radical **Methyl radical**

$$Cl_2 \xrightarrow{h\nu} 2Cl^{\bullet}$$

Chlorine radical

13.5.3. REDOX GENERATION

Free radicals may also be generated by various oxidation- reduction processes. Transfer of electron to or from metal atoms and ions is a common method for initiating radical reaction.

$$Fe^{2+} + H_2O_2 \longrightarrow Fe^{3+} + H\overset{\ominus}{O} + H\overset{\bullet}{O}$$

13.6. FREE RADICAL SUBSTITUTIONS

13.6.1. FREE RADICAL SUBSTITUTION MECHANISMS

In a free radical substitution reaction

$$R-X \longrightarrow R-Y$$

there must first be a cleavage of the substrate RX so that $R^{\bullet}$ radicals are produced. This may happen by a spontaneous cleavage.

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

It may be caused by light or heat or more often, there is actual cleavage, but $R^{\bullet}$ is produced by an abstraction.

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

$W^{\bullet}$ is produced by adding a compound such as peroxide which spontaneously forms free radicals. Such compound is called an initiator. Once $R^{\bullet}$ is formed, it may go to product in two ways by abstraction.

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

Coupling with another radical

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

13.6.2. SUBSTITUTION BY HALOGEN

Halogenation or Halo-de-hydrogenation

$$R-H+Cl_2 \xrightarrow{h\gamma} R-Cl$$

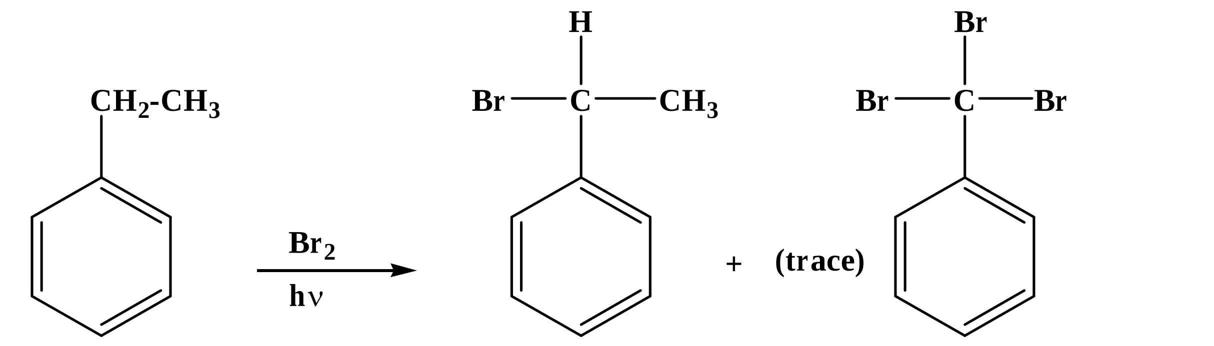
Initiation $\quad X_2 \xrightarrow{h\gamma} 2X^{\bullet}$

Propagation $\quad RH+X^{\bullet} \longrightarrow R^{\bullet}$

Propagation steps for chlorination by t-BuOCl

$$R-H+t-BuO^{\bullet} \longrightarrow R^{\bullet}+t-BuOH$$

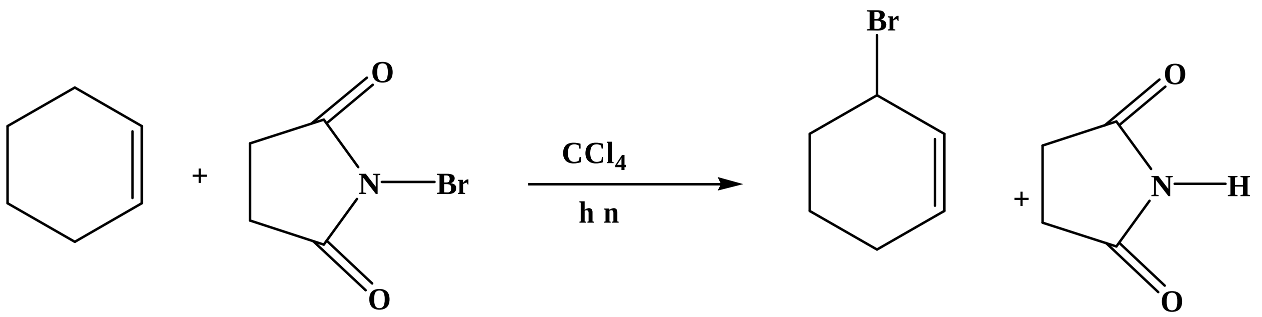
$$R^{\bullet}+t-BuOCl \longrightarrow RCl+t-BuO^{\bullet}$$



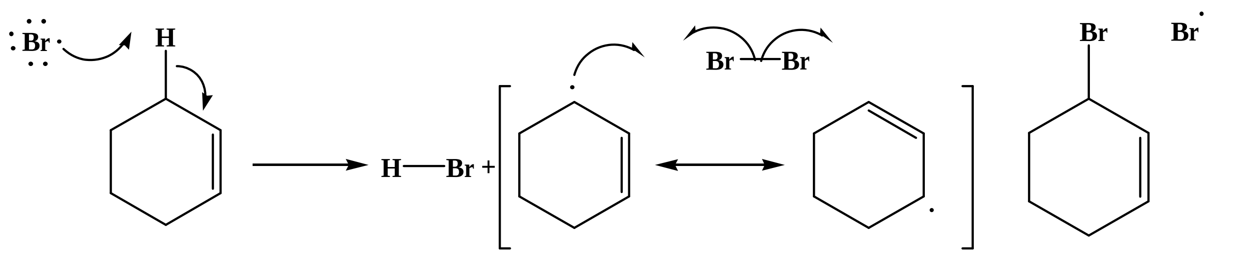
Ethylbenzene α-bromoethylbenzene α,α-dibromoethylbenzene

13.6.3. HALOGENATION WITH NBS

The low bond dissociation energy of allylic carbon-hydrogen bonds in free radical halogenation. Allylic bromination is carried out with N-Bromosuccinimide in CCl_4 in the presence of light to avoid addition to double bond.

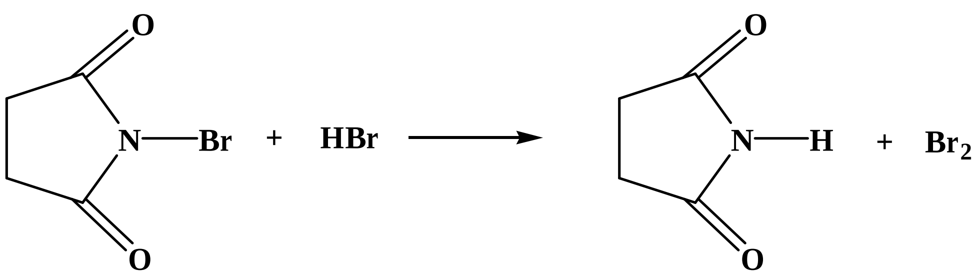


N-bromosuccinimide (NBS) Succinimide



A Resonance-stabilized radical

Recycles to continue the chain reaction



NBS Succinimide

13.6.4. SUBSTITUTION BY OXYGEN
13.6.4.1. HYDROXYLATION AT AN ALIPHATIC CARBON

$$R_3CH \xrightarrow[\text{Silica gel}]{O_3} R_3COOH$$

Compounds containing C-H bonds can be oxidized to alcohols. The C-H bond involved is tertiary so that the product is a tertiary alcohol.

13.6.4.2. HYDROXYLATION OF AN AROMATIC CARBON

$$ArH + H_2O_2 \xrightarrow{FeSO_4} ArOH$$

A mixture of hydrogen peroxide and ferrous sulfate called Fenton's reagent.

$$Fe^{2+} + H_2O_2 \longrightarrow Fe^{3+} + \overset{\ominus}{OH} + HO^{\bullet}$$

$$HO^{\bullet} + ArH \longrightarrow Ar^{\bullet} + H_2O$$

The rate determining step is formation of $HO^{\bullet}$ and not its reaction with the aromatic substrate.

13.6.5. SUBSTITUTION BY SULFUR
13.6.5.1. CHLOROSULFONATION

$$RH + SO_2 + Cl_2 \xrightarrow{h\nu} RSO_2Cl$$

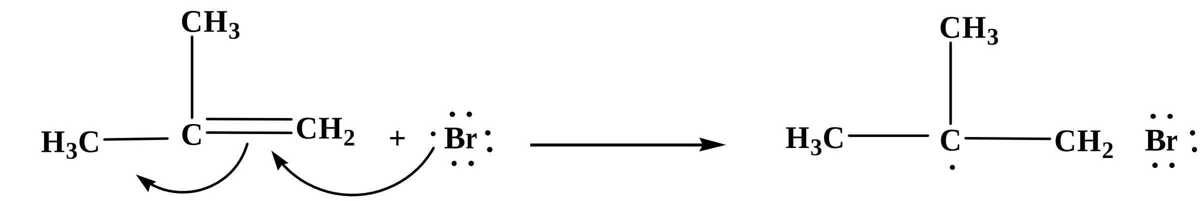
The chlorosulfonation of organic molecules with chlorine and sulphurdioxide is called the reed reaction. The mechanism is except that there two additional main propagation steps.

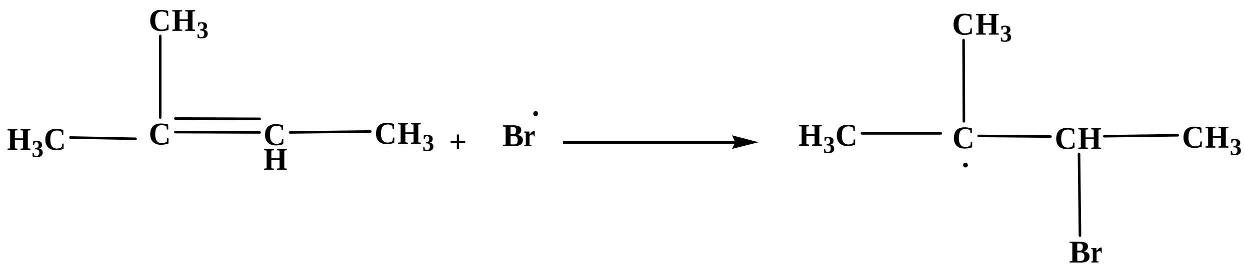
$$R^{\bullet} + SO_2 \longrightarrow R{-}SO_2^{\bullet}$$

$$R{-}SO_2^{\bullet} + Cl_2 \longrightarrow R{-}SO_2Cl + Cl^{\bullet}$$

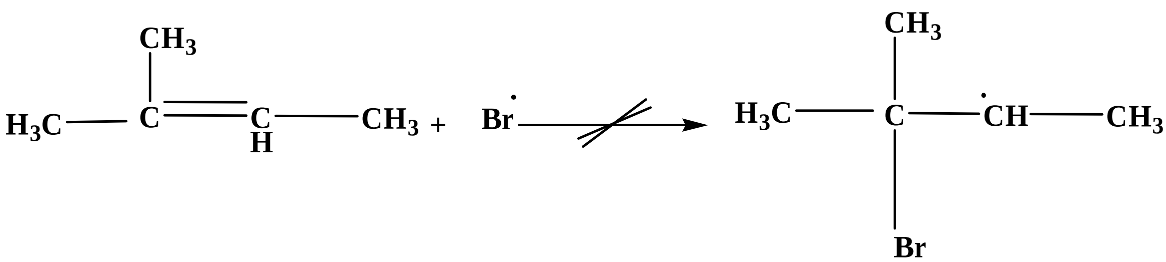
13.7. FREE RADICAL ADDITION

Free radicals add to the common unsaturated grouping to give new radicals. The most important of the unsaturated groups in free-radical synthesis is C=C bond, addition to which is markedly selective. In particular, addition to the olefins of the type CH_2=CHX occurs almost exclusively at the methylene group independently of the nature of X.





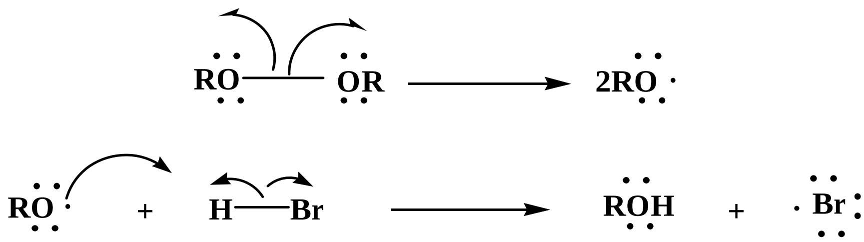
Tertiary radical

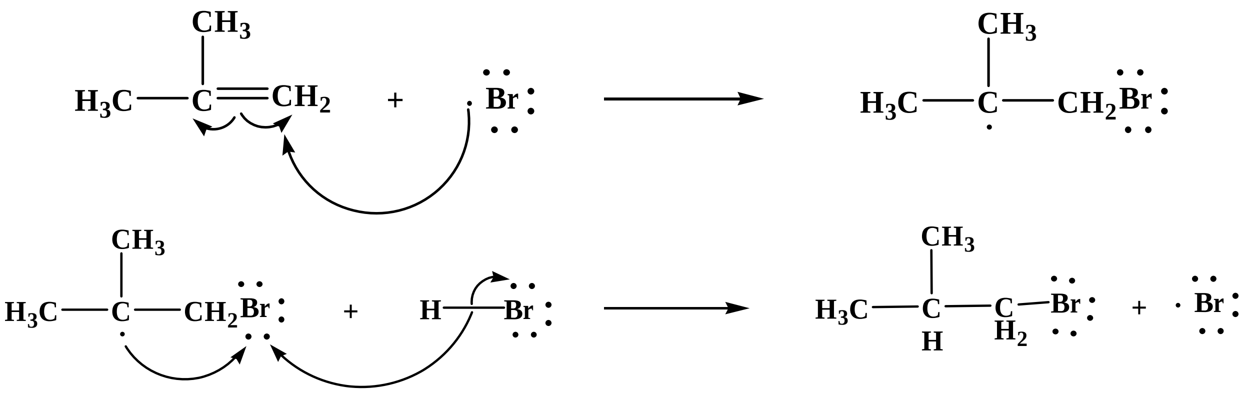


secondary radical (less stable)

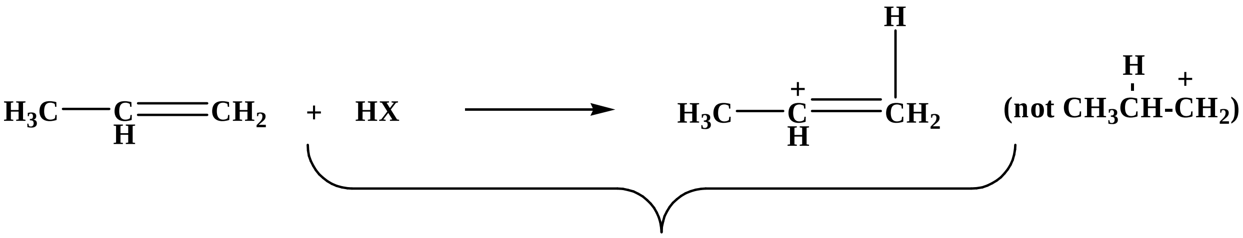
Three factors seem to control this selectivity. Firstly the steric hindrance between the radical and X avoids reaction at substituted carbon atom. Secondly, the grouping X stabilizes the radical. Moreover, if X is an alkyl group, the stabilization will result due to hyperconjugation. In case however X carries one or more pairs of *p*-electrons or is an unsaturated group, stabilization will be via usual delocalization.

Addition of HBr to an alkene involves radicals as intermediates; the more stable the radical the easier it is to form since the energy barrier is lower for its formation. Thus the bromine radical adds to that SP^2 carbon in the alkene that is bonded to most hydrogens to form stabler of the two possible free radical. In this reaction peroxide is a radical initiator.

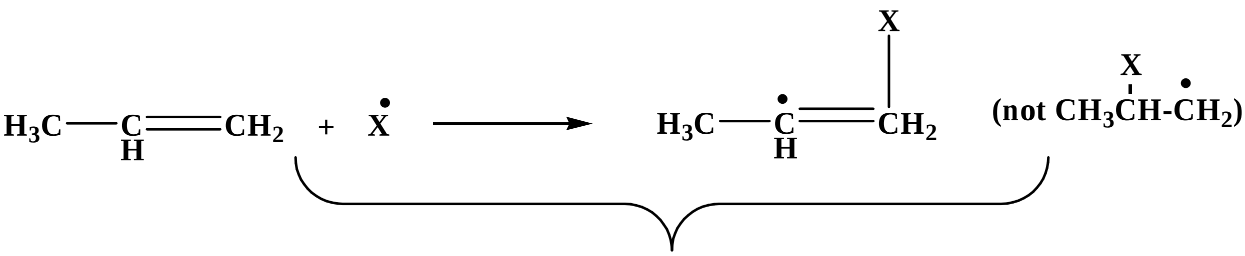




Thus in the reaction of HBr (absence of peroxide) to an alkene in the absence of peroxides the addition is ionic, initiated by the addition of H^+ to give the most stable carbocation (Markovnikov's addition).

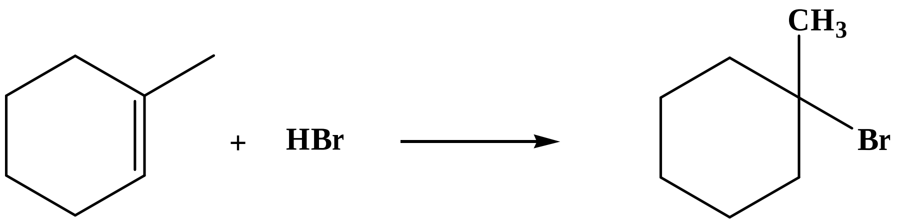


Free radical additions does not obey the Markovnikov's rule



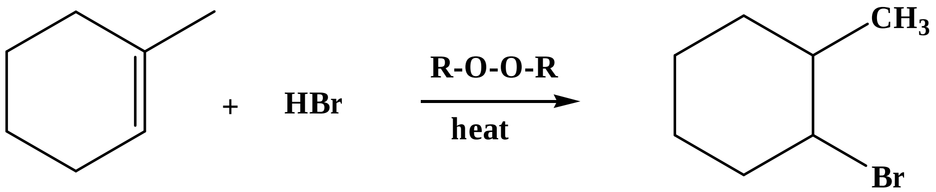
Free radical additions "disobey" the Markovnikov's rule

In the presence of peroxides the addition of HBr to an alkene is initiated by $Br^{\bullet}$ to produce the most stable free radical (anti Markovnikov's rule).Peroxide has no effect on the addition HCl or HI to an alkene, which, however, occurs according to Markovnikov rule only (heterolytic addition).



1-methylcyclohexene **1-bromo-1-methylcyclohexane**

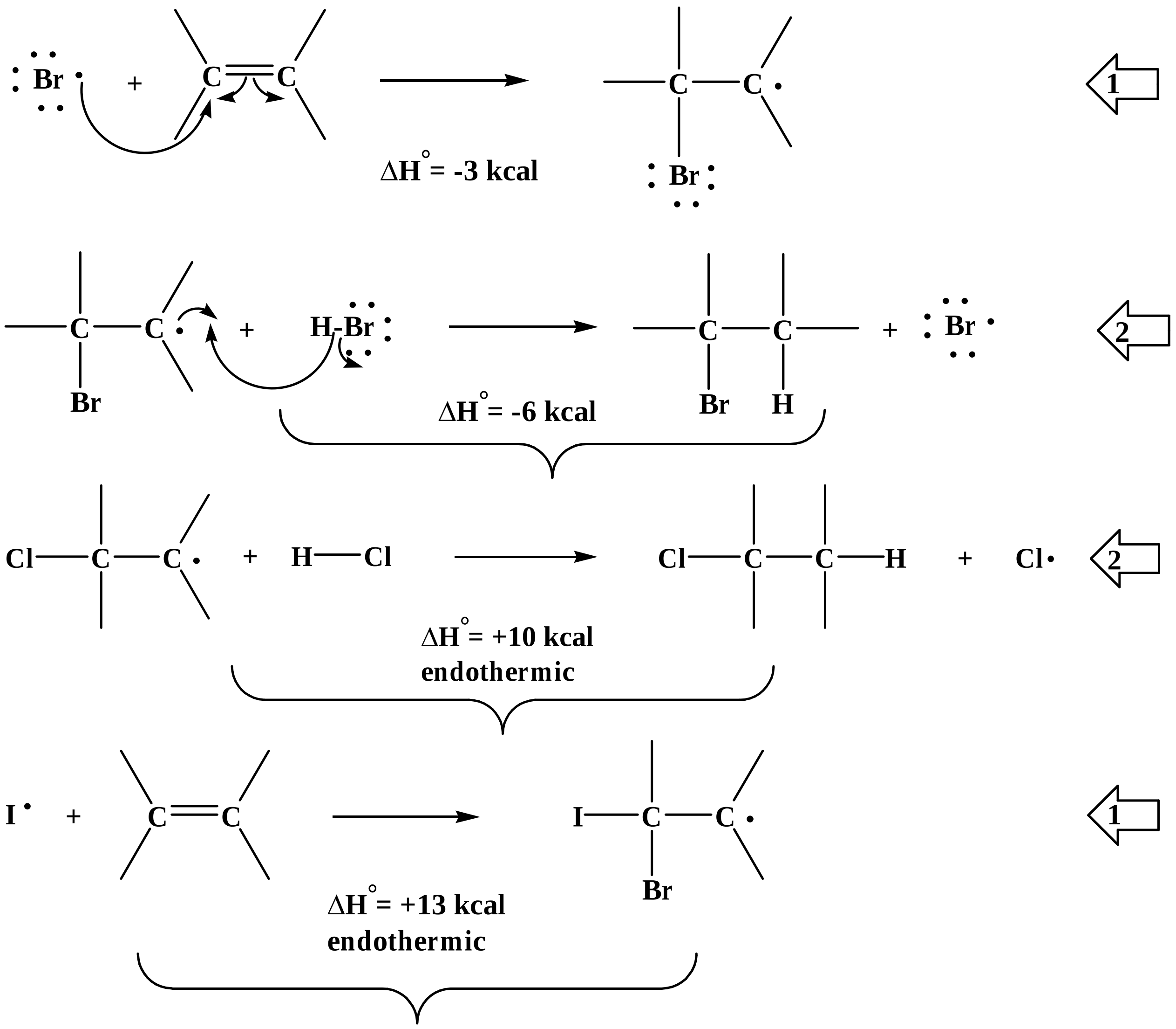
(Markovnikov's orientation)



1-methylcyclohexene **1-bromo-2-methylcyclohexane**

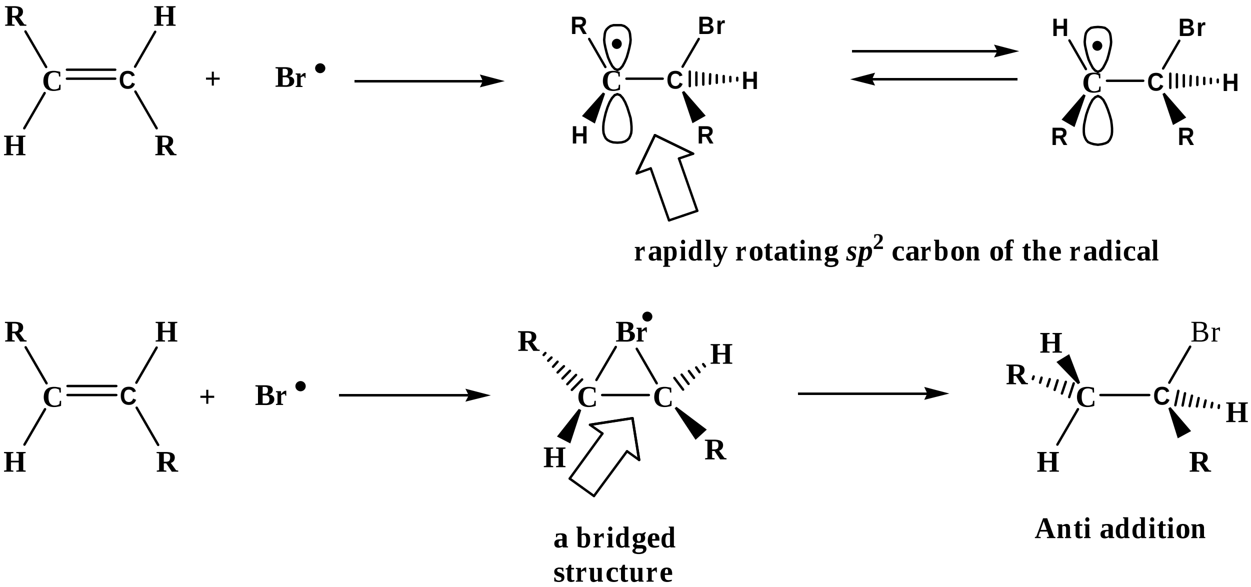
(anti - Markovnikov's orientation)

In a radical reaction, the steps which propagate the chain reaction compete with the steps which terminate it. Termination steps are always exothermic since only bond making occurs. Thus, only when both propagation steps are exothermic propagation compete with termination. When one considers the energetics of the two propagating steps (1 and 2) only for hydrogen bromide are both these steps exothermic. For HCl and HI one of these two steps is on the other hand endothermic.

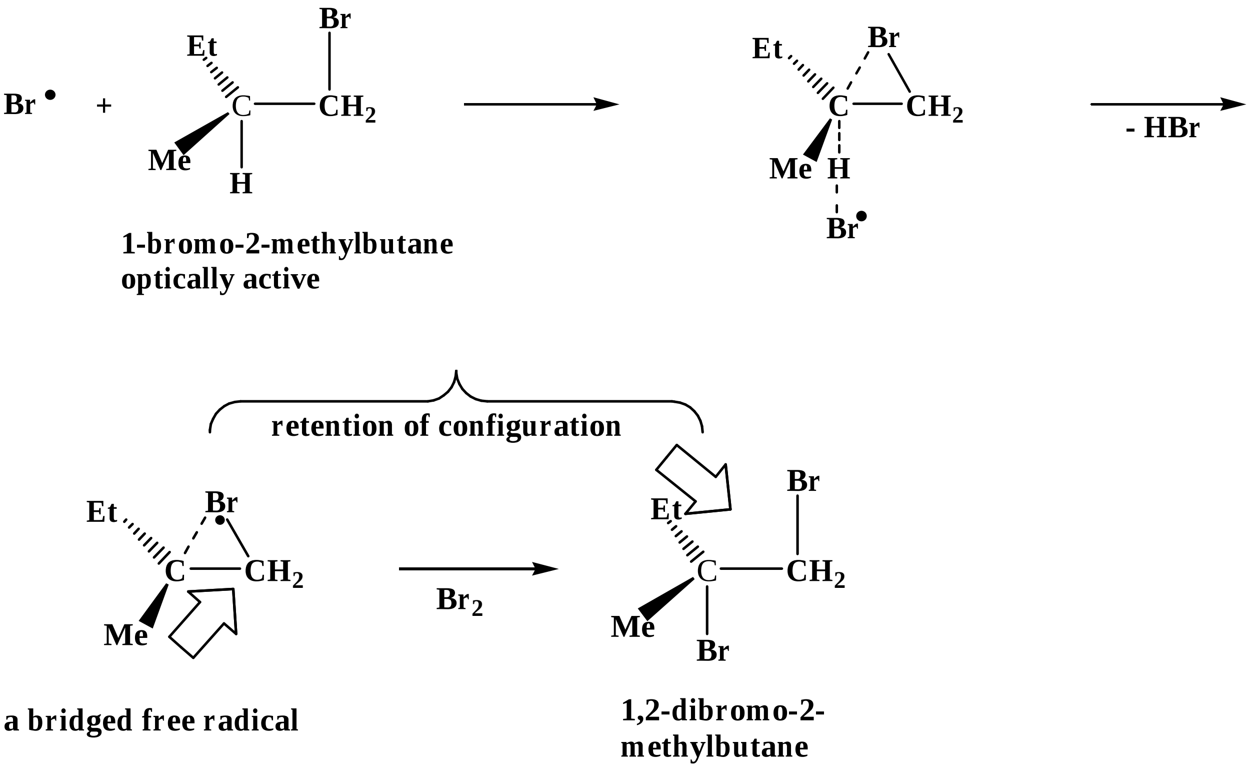


(ii) Stereochemistry of radical addition, of hydrogen bromide to alkenes-anti addition

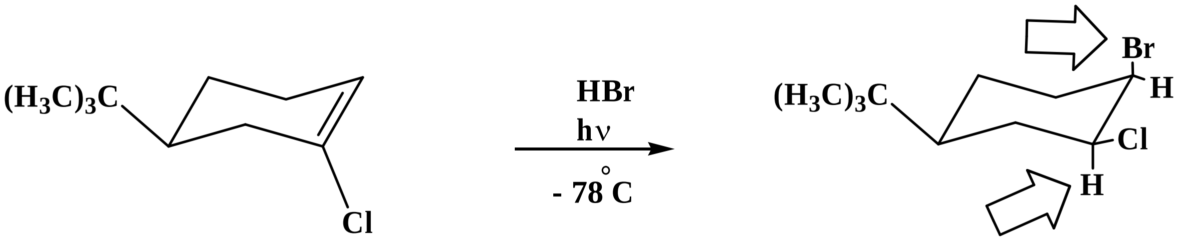
Radical addition of hydrogen bromide to alkenes is an anti addition. However, such stereospecificity, is in contradiction of the sp^2 carbon of the radical which would be rapidly rotating (Eq I) with respect to the remainder of the molecule. The observed stereospecificity



(anti – addition) of the radical addition is explained by invoking the intermediate formation of bridged species (Eq II). Evidence for a bromine-bridged radical i.e., a cyclic intermediate comes from the fact that the configuration at the chiral carbon (substituted carbon) of optically active 1-bromo-2-methylbutane was retained during radical substitution.



Other data showed that bromination of alkyl bromides gave substitution with high regioselectivity, i.e., about 85% at the carbon adjacent to the bromine already present in the molecule. This result is surprising, since the positions close to the polar group (e.g., bromine in this case) are actually deactivated by the operation of the polar effect. The unusual regioselectivity observed in scheme16.17 is the abstraction of hydrogen by $Br^{\bullet}$ which is now assisted by the bromine already present in the substrate. In fact this unusual abstraction is a result of neighboring group participation in a free radical reaction. Moreover, in the case of cyclohexenes and its derivatives the formation of trans diaxial addition products (anti addition) can be best explained on the basis of a bromine bridged intermediate.



***trans* - Diaxial addition**

(iii). Addition of Some Carbon Radicals to Alkenes-Formation of Carbon-Carbon Bonds

The addition of hydrogen bromide to C = C in radical catalysed reactions provides a good method of the formation of a carbon halogen bond. Several useful synthetic radical catalysed reactions are based on the addition of aliphatic carbon radicals to olefinic bonds. Thus a halomethane can be added to an alkene in the presence of peroxides e.g., the addition of bromoform to 1-butene.

$$\mathrm{PhCOO\text{-}OCOPh} \longrightarrow 2\,\mathrm{PhCO_2}^{\bullet}$$

$$\mathrm{PhCO_2}^{\bullet} + \underset{\text{bromoform}}{\mathrm{CHBr_3}} \longrightarrow \mathrm{PhCO_2H} + {}^{\bullet}\mathrm{CBr_3}$$

$$\underset{\text{1-butene}}{\mathrm{CH_3CH_2CH{=}CH_2}} + {}^{\bullet}\mathrm{CBr_3} \longrightarrow \mathrm{CH_3CH_2\dot{C}H\text{-}CH_2CBr_3}$$

$$\mathrm{CH_3CH_2\dot{C}H\text{-}CH_2CBr_3} + \mathrm{CHBr_3} \longrightarrow \underset{\text{1,1,1-tribromopentane}}{\mathrm{CH_3CH_2CH_2CH_2CBr_3}} + {}^{\bullet}\mathrm{CBr_3}$$

One may also use bromotrichloromethane and due to the preferential abstraction of bromine (C-Br bond is weaker than C-Cl bond), a trichloromethyl unit is added to the less substituted carbon atom of the alkene.

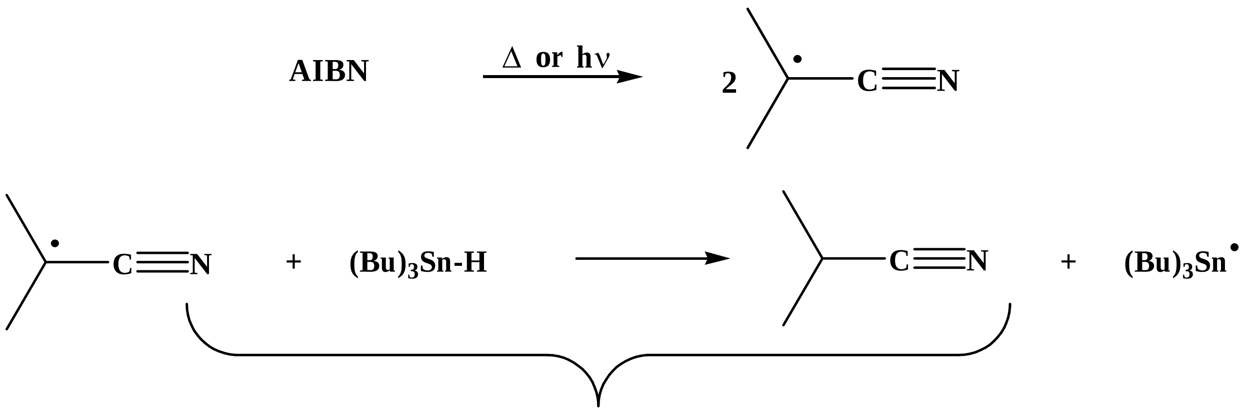
$$\mathrm{BrCCl_3} + \mathrm{CH_2{=}CHR} \xrightarrow[\Delta]{\text{peroxide}} \mathrm{Cl_3CCH_2\underset{\displaystyle Br}{C}HR}$$

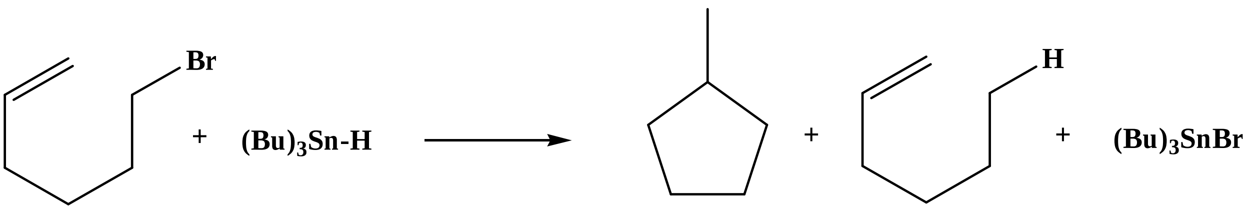
Other functional groups can also provide sufficient stabilization of radicals to permit successful chain additions to alkenes. Acyl readicals are formed by abstraction of the formyl hydrogen from aldehydes and the resulting acyl radicals (R*CO) are stabilized to some extent. The chain process results in formation of a ketone by addition of the aldehyde to an alkene.

$$CH_3CHO + C_6H_{13}\text{-}CH{=}CH_2 \xrightarrow{\text{peroxide}} C_6H_{13}\text{-}CH_2\text{-}CH_2\text{-}CO\text{-}CH_3$$

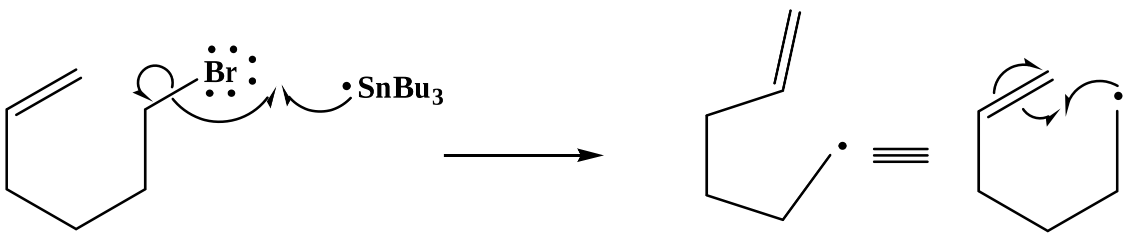
2-decanone

Intromolecular addition of a carbon radical to a C=C bone produces a ring. Five membered rings are greatly preferred kinetically, even when a five membered ring closure means generating a primary radical and a six membered ring closure a secondary radical (This situation may be compared with the order of ring formation in intramolecular S_N2 reactions : 5>6>3. Stability of the ring is not the only factor the probability that the ends can get together is also important). Thus five membered rings are readily formed by the tributylstannane method, i.e., on reaction of 6-brome-1-hexene with a tributyltin radical. AIBN initiates free radical formation from tributyl tin hydride.



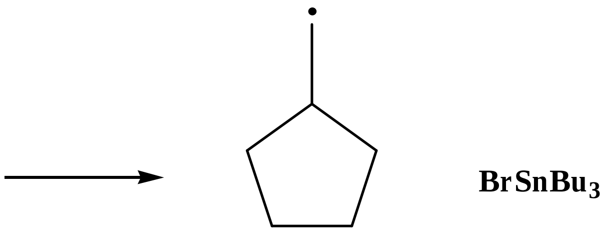


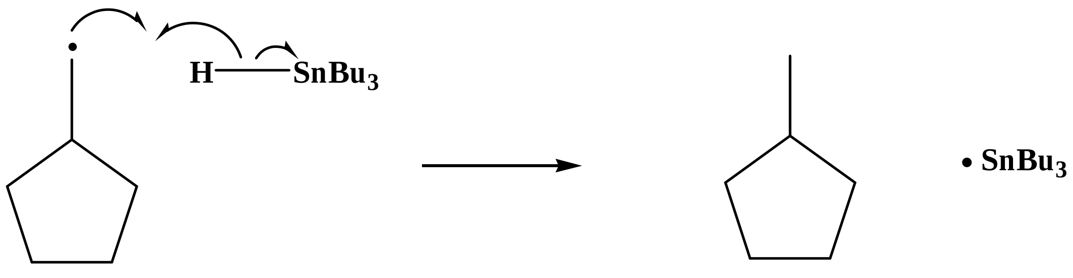
6-bromo-1-hexene **tributyl tin hydride** **methylcyclopentane 90%** **1-hexene 10%**



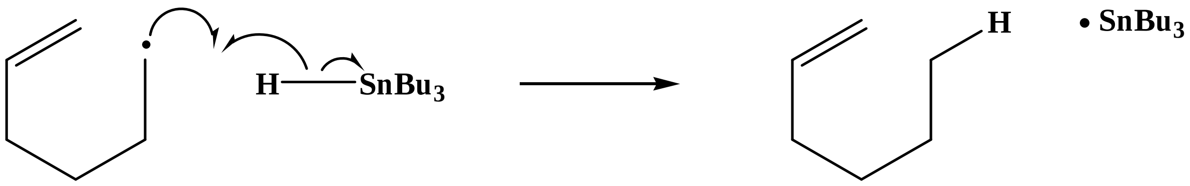
abstraction of a bromine atom

cyclization of the carbon radical





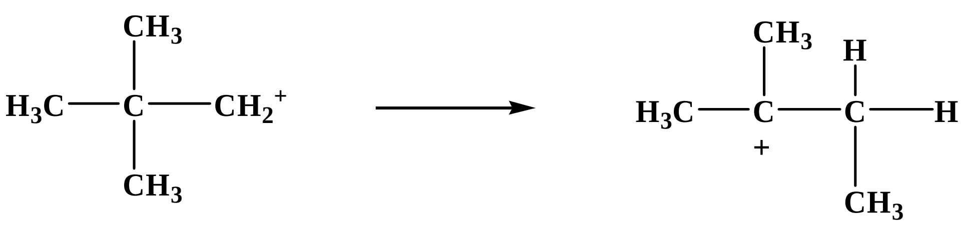
abstraction of a hydrogen **methylcyclopentane**



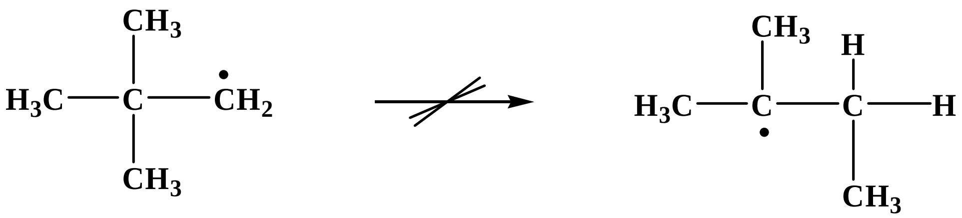
abstraction of a hydrogen **1-hexene**

13.8. MOLECULAR REARRANGEMENTS

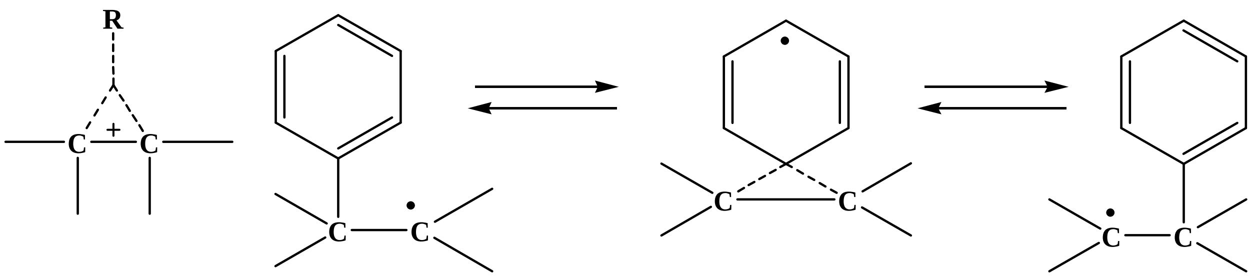
Rearrangements which are very common with carbocation intermediates are rare in the case of free radicals. In fact the migration of a saturated group is highly unlikely. In the case of cationic intermediates migration occurs through a bridged transition state (or intermediate) which involves a three center two electron bond. In the case of a free radical there is a third electron in the system. It however, cannot occupy the same orbital as the two other electrons. It shall then



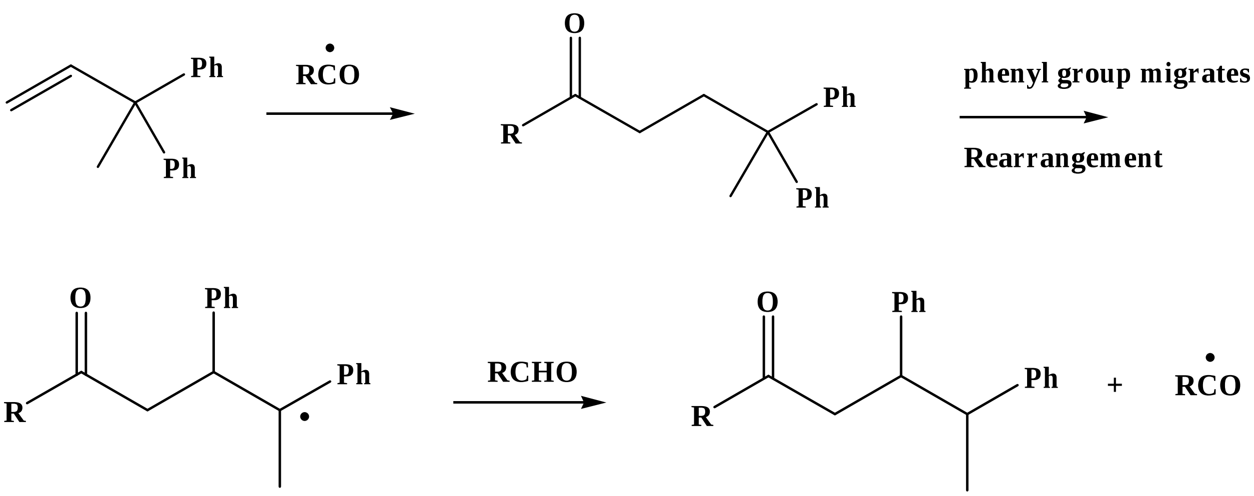
the migrationof a methyl group



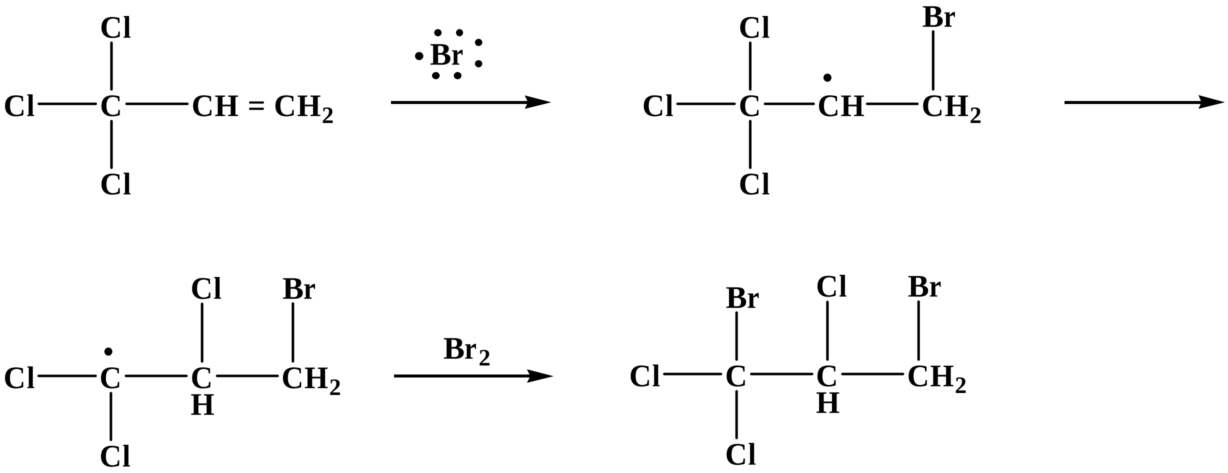
have to be in an antibonding level. Consequently the transition state for migration is less favorable compared to that in a carbocation. In the case of free radicals, migrations can occur with aryl, vinyl, acyl and other unsaturated groups. The migration of an aryl group e.g., involves the formation of bridged intermediate by an addition process and the intermediate is a cyclohexadienyl radical.



Thus the substrate (I) adds an acyl radical (acyl radicals are formed by the; abstraction of the formyl hydrogen from an aldehyde). The free radical (II) formed after phenyl group migration then abstracts a hydrogen atom from the aldehyde.



Migrations have also been observed for chloro groups. Thus in the reaction of (I) with bromine in the presence of peroxides a rearrangement to (II) was observed, which was formed along with the normal addition product $Cl_3CCHBrCH_2Br$. Migration of a halogen could occur via a transition state in which the odd electron is accommodated in a vacant d orbital of the halogen.



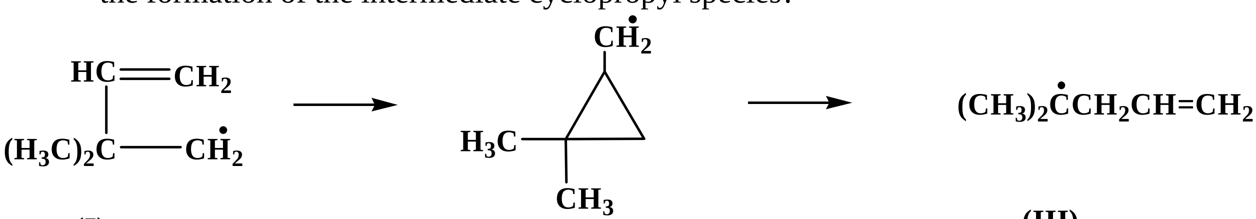
13.9. LET US SUM UP

In this lesson, we:
Pointed out

- Structure and geometry of free radicals
- Stability of free radicals
- Generation of free radicals
- Thermal generation
- Photochemical generation
- Redox generation
- Free radical substitutions
- Free radical addition
- Molecular rearrangements

13.10. CHECK YOUR PROGRESS

1. Among free radicals, tertiary is more stable. Explain.
2. How are free radicals generated?
3. Why in the free radical rearrangement of the vinyl group in (I) to give (III) one involves the formation of the intermediate cyclopropyl species?



(I) (II) (III)

4. Predict the radical catalyzed addition of carbon tetra chloride to β-pinene.

13.11. POINT FOR DISCUSSION

1. Explain the structure and geometry of free radicals.
2. Explain the factors affecting the stability of free radicals.
3. Explain the characteristics of free radical reactions.
4. Give the detailed account of free radical substitution reaction with mechanism.

13.12. REFERENCES

1. Jerry march, Advanced Organic Chemistry, Fourth edition, Wiley India edition.

2. P.S. Kalsi, Organic reactions and their mechanisms, Second edition, New age international publishers.

LESSON: 14 – TYPICAL FREE RADICAL REACTIONS

CONTENTS

14.0. AIMS AND OBJECTIVES

The aim is to motivate and enable the student to comprehend the possible chemical route by which the free radical reactions may proceed.

On successful completion of this lesson the student should have:

* learnt possible reaction pathways in typical free radical reactions.

14.1. SANDMEYER REACTION

Treatment of diazonium salts with cuprous chloride or bromide leads to aryl chlorides or bromides respectively. In either case the reaction is called the Sandmeyer reaction.

$$\mathrm{Ar\overset{+}{N}_2 + CuCl \longrightarrow ArCl}$$

MECHANISM

The mechanism of Sandmeyer reaction is not rigorously known however is believed to proceed in the following manner.

In the first two steps, the arenodiazonium ion species is reduced by Cu (II) salt to give an aryl radical species. But two alternative mechanisms are possible for the third step – either the resulting Cu (II) salt binds to the aryl radical forming the intermediate Ar–Cu (III) NuX followed by its dissociation into Cu (I)X and the substitution product Ar-Nu or the aryl radical reacts with the the Cu (III) salt giving the substitution product Ar-Nu through ligand transfer and Cu(I) through concomitant reduction.

$$\mathrm{Ar-\overset{\oplus}{N}\equiv N\overset{\ominus}{X} + \overset{+1}{CuNu} \longrightarrow Ar-N\equiv N^{\cdot} + \overset{+2}{CuNuX}}$$

$$Ar{-}N{\equiv}N^{\cdot} \longrightarrow Ar^{\cdot} + N_2$$

$$Ar^{\cdot} + \overset{+2}{Cu}NuX \longrightarrow Ar{-}\overset{+3}{Cu}NuX \longrightarrow Ar{-}Nu + \overset{+}{Cu}X$$

(intermediate)

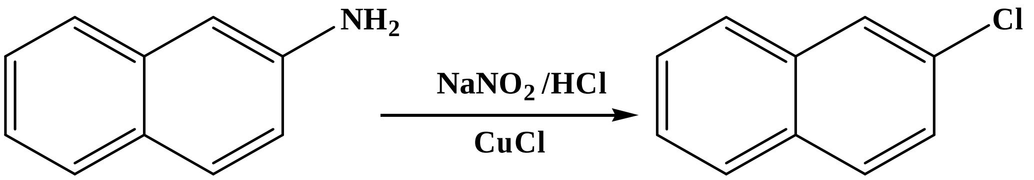
$$Ar^{\cdot} + \overset{+2}{Cu}NuX \longrightarrow Ar{-}Nu + \overset{+1}{Cu}X$$

APPLICATION

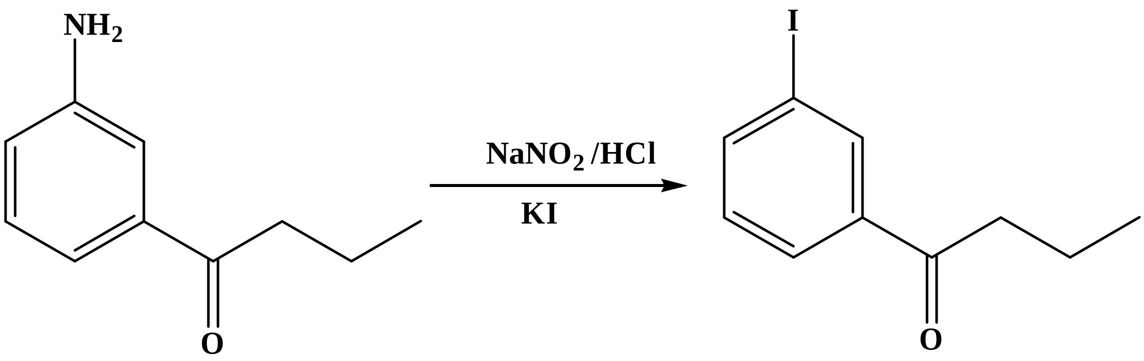
The Sandmeyer reaction is a very useful synthetic tool in organic synthesis.

Examples

(i)



(ii)



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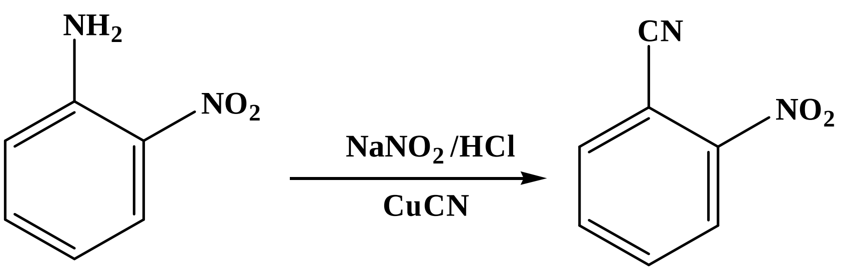
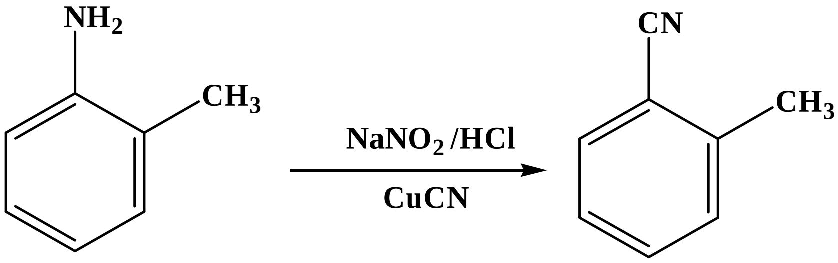
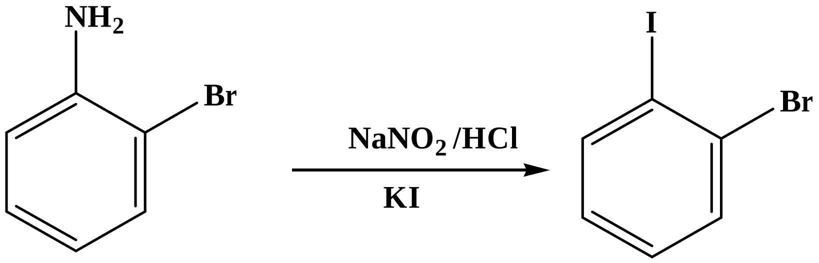


(iv) 

(v) 

14.2. GOMBERG REACTION

$$ArH + Ar'\overset{+}{N_2}\overset{-}{X} \xrightarrow{OH^{\ominus}} Ar\text{-}Ar'$$

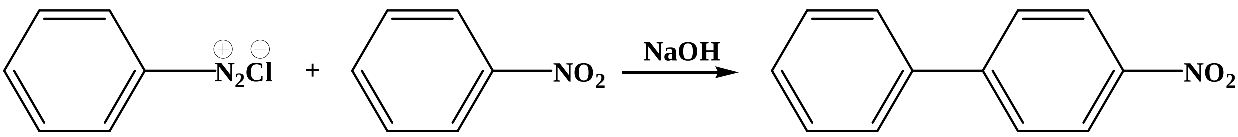
When the normally acidic solution of a diazonium salt is made alkaline, the aryl portion of the diazonium salt can couple with another aromatic ring known as Gomberg reaction.

$$C_6H_5\overset{+}{N_2}\overset{-}{Cl} \xrightarrow{OH^{\ominus}} C_6H_5N{=}N\text{-}OH \longrightarrow C_6\dot{H}_5 + N_2 + \dot{O}H$$

$$C_6\dot{H}_5 + C_6H_5NO_2 + \dot{O}H \longrightarrow p\text{-}C_6H_5\text{-}C_6H_4NO_2 + H_2O$$

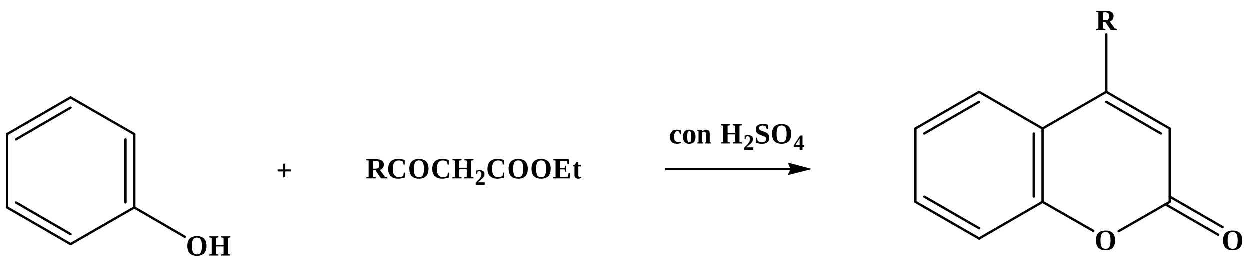
It has been performed on several types of aromatic rings and on quinines.

A FREE RADICAL MECHANISM



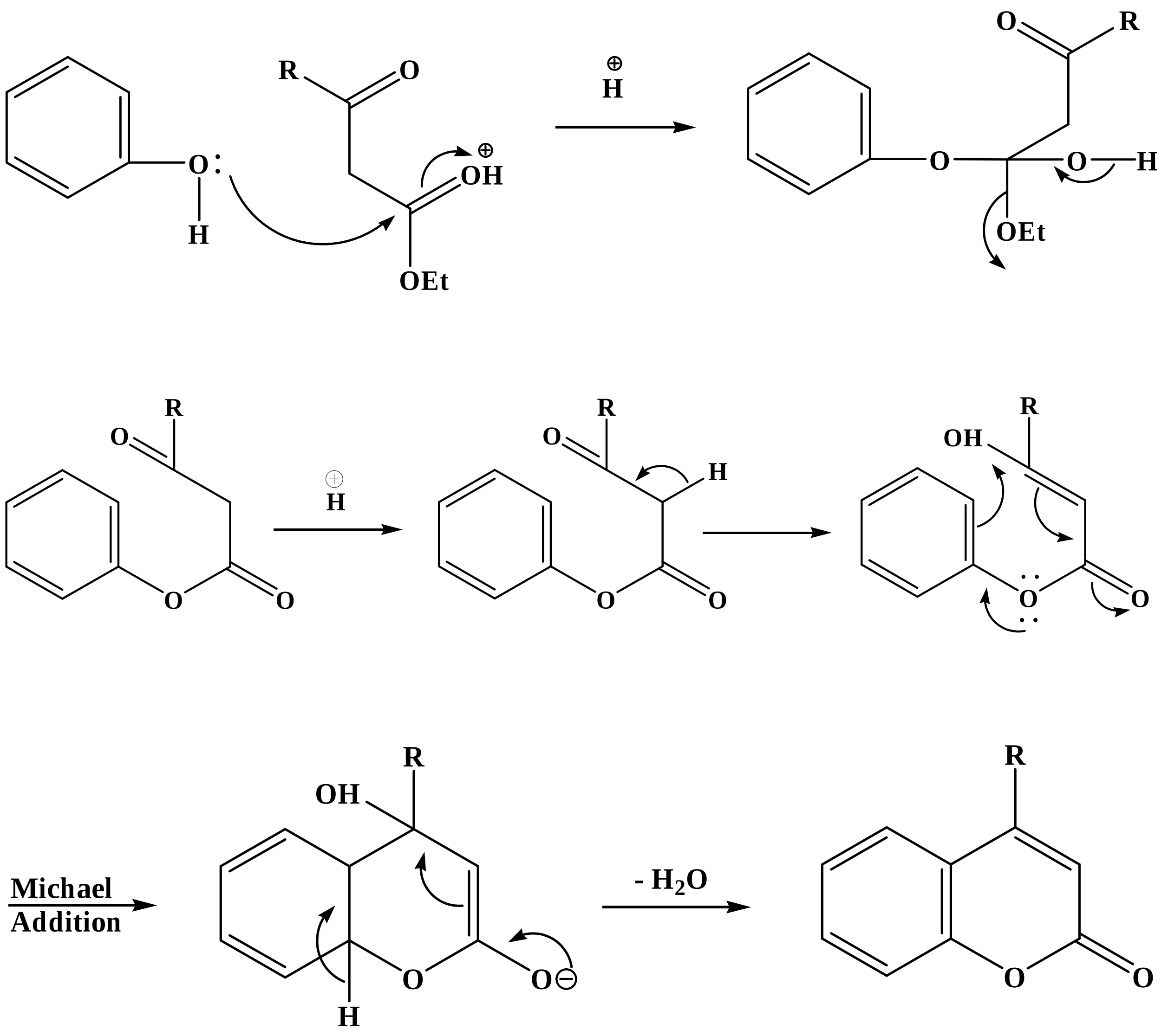
14.3. PECHMANN REACTION

The acid–catalyzed condensation of phenols with β - ketoesters to produce coumarins is called the Pechmann reaction. A variety of condensing reagents such as concentrated sulphuric acid, hydrogen fluoride, Lewis acids etc are used.



cumarin derivative

MECHANISM



14.4. ULLMANN REACTION

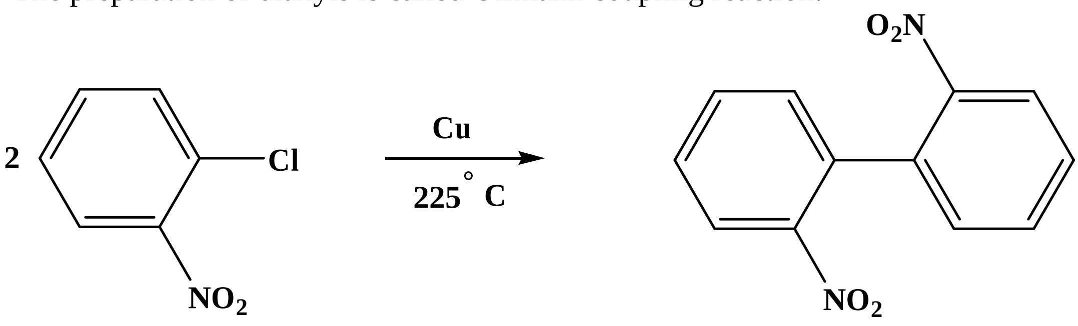
Ullmann reaction encompasses the synthesis of diphenyl amines, diphenyl ethers and diphenyls.

1. $C_6H_5NHCOCH_3 + C_6H_5Br + K_2CO_3 \xrightarrow[\text{Reflux}]{\text{Cu}} (C_6H_5)_2NH + CO_2 + CH_3COOK + KBr$

2. $C_6H_5OH + C_6H_5Br + KOH \xrightarrow[\text{Reflux}]{\text{Cu}} (C_6H_5)_2O + KBr + H_2O$

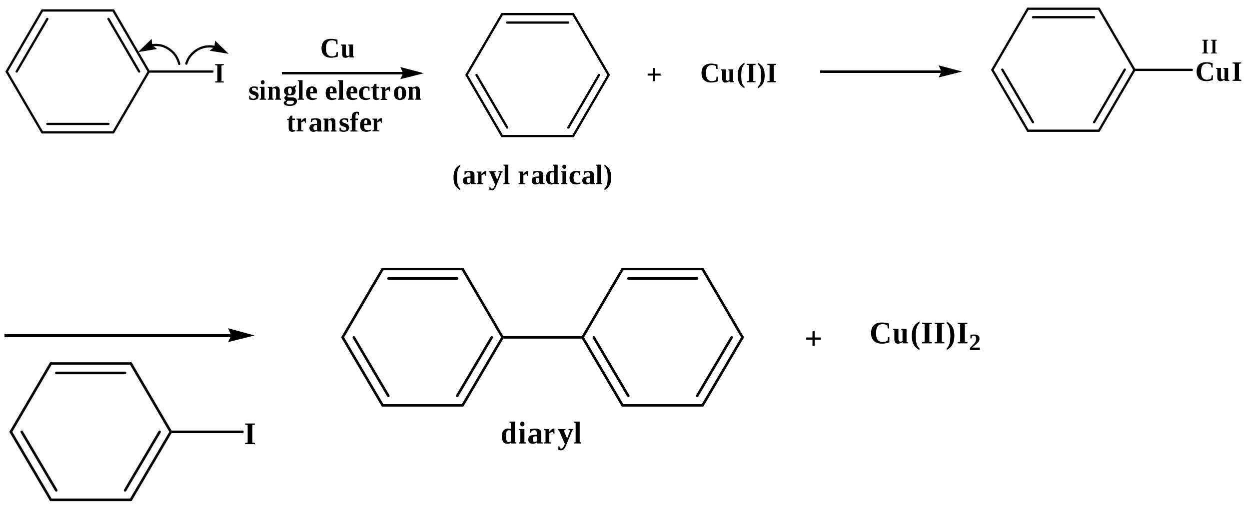
3. $2C_6H_5I + Cu \xrightarrow[\Delta]{C_6H_5NO_2} C_6H_5\text{-}C_6H_5 + CuI_2$

The preparation of diaxyls is called Ullmann coupling reaction.



***o*-nitrochlorobenzene** **2,2'-dinitrobiphenyl**

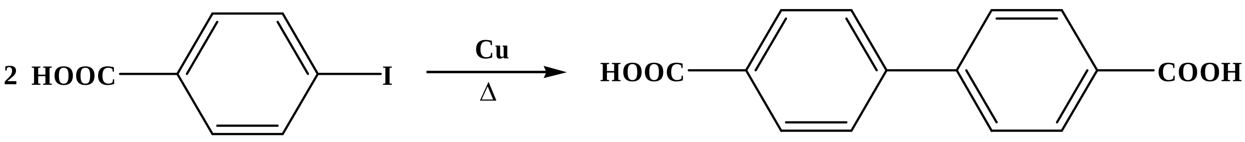
MECHANISM



APPLICATIONS

(a) A large number of diaryls and polyaryls have synthesized by the Ullmann coupling reaction.

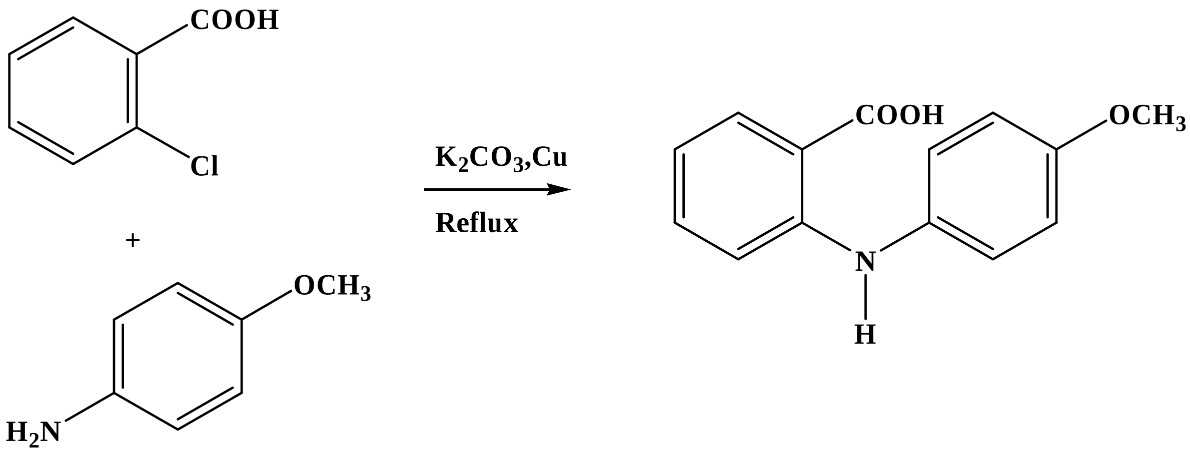
Symmetrical biaryls



4,4'-diphenicacid

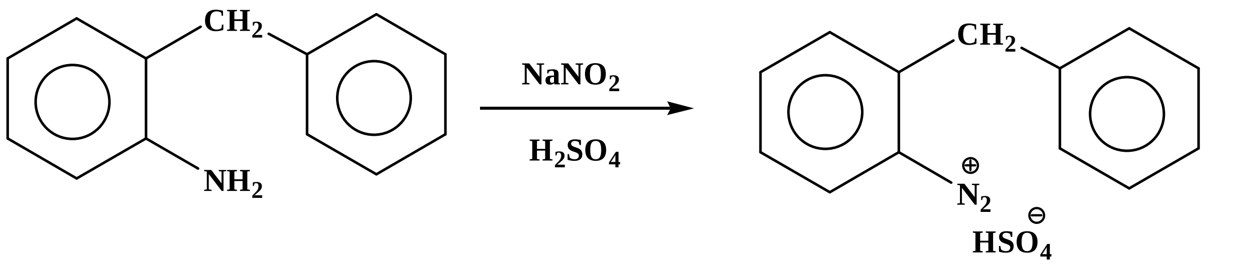
(b) Ullmann reaction also provides method for the preparation of diarylamines and diaryl ethers.

Diarylamines

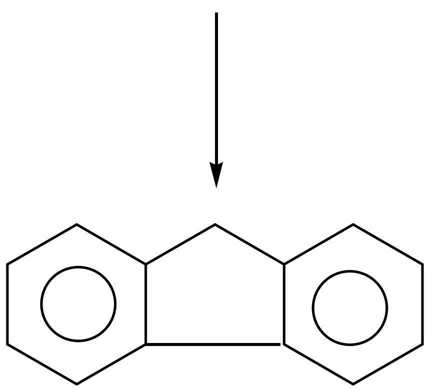


14.5. PSCHORR REACTION

When the Gomberg–Bachmann Reaction is performed intermolecularly either by alkaline solution or with copper powder the procedure is termed Pschorr ring closure. Fluorene is prepared starting with *o*-aminodiphenyl methane.



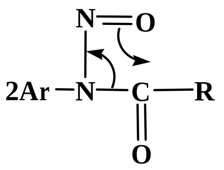
***o*-amino diphenyl methane**



Fluorene

The Pschorr synthesis

MECHANISM



N-nitrosoamide

$$\longrightarrow 2Ar\text{-}N{=}N\text{-}O\text{-}COR \longrightarrow Ar^{\bullet} + Ar\text{-}N{=}N\text{-}O^{\bullet} + N_2 + R(CO)_2O$$

14.6. HUNSDIECKER REACTION (DECARBOXYLATIVE BROMINE)

This is a free radical substitution reaction, where the reaction of a silver salt of carboxylic acid with bromine gives a bromo compound and is a method of decreasing the length of the carbon chain by one unit.

$$RCO_2Ag + Br_2 \xrightarrow[\text{reflux}]{CCl_4} RBr + CO_2 + AgBr$$

MECHANISM

Step - 1. $RCO_2Ag + Br_2 \longrightarrow R\text{-}C(=O)\text{-}O\text{-}Br + AgBr$

Step - 2. $R\text{-}C(=O)\text{-}O\text{-}Br \longrightarrow RCOO^{\bullet} + Br^{\bullet} \longrightarrow$ initiation

Step - 3. $RCOO^{\bullet} \longrightarrow R^{\bullet} + CO_2$

Step - 4. $R^{\bullet} + RCOOBr \longrightarrow RBr + RCOO^{\bullet}$

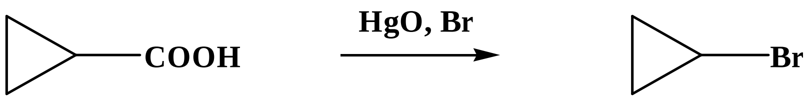
$\left.\begin{array}{l}\text{Step 3}\\ \text{Step 4}\end{array}\right\}$ propagation

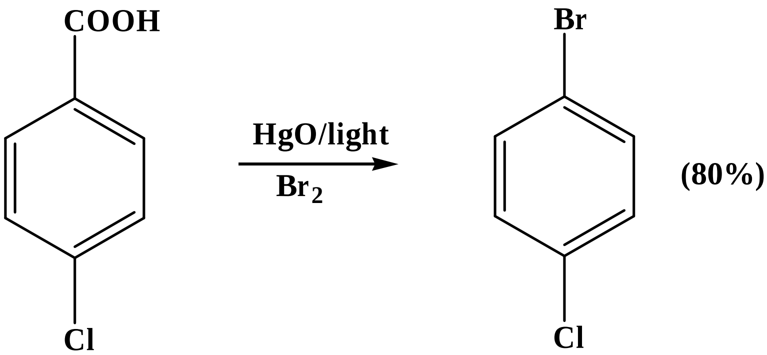
The reaction occurs by the formation an acyl hypobromite (Step 1) is not a free radical reaction. The acyl hypobromite then undergoes homolysis (Step 2). The acyloxy radical loses carbon dioxide (Step 3) and the resulting radical abstracts bromine from a second molecule of the hypobromite.

APPLICATION

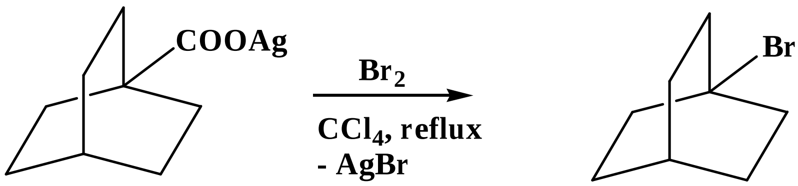
The reaction is of wide scope, producing alkyl and aryl halides.

(1). $$CH_3CO_2C(CH_2)_4COOAg \xrightarrow[\substack{CCl_4,\ \text{reflux}\\ -\ AgBr}]{Br_2} CH_3O_2C(CH_2)_3CH_2Br$$

(2). 

(3). 

(4). A free radical has been generated at bridge head position via the Hunsdiecker reaction to show that a free radical need not be planar



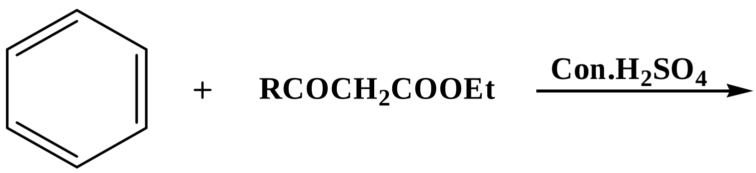
14.7. LET US SUM UP

In this lesson, we:
Pointed out

- Sandmeyer reaction
- Gomberg reaction
- Pechmann reaction
- Ullmann reaction
- Pschorr reaction
- Hunsdiecker reaction (decarboxylative bromine)

14.8. CHECK YOUR PROGRESS

1. Write the mechanism of Hunsdiecker reaction.
2. Identify the products formed in the following reaction.



14.9. POINT FOR DISCUSSION

1. Explain Sandmeyer's reaction with mechanism and application.
2. Give notes on
   (a) Pschorr reaction

(b) Ullmann reaction
(c) Gomberg reaction

14.10. REFERENCES

1. Jerry march, Advanced Organic Chemistry, Fourth edition, Wiley India edition.

2. P.S. Kalsi, Organic reactions and their mechanisms, Second edition, New age international publishers.

3. Goutam Brahmachari, Organic name reactions, Narosa publishing house, New Delhi.

UNIT-VI

LESSON: 15 – ADDITION REACTIONS

CONTENTS

15.0. AIMS AND OBJECTIVES

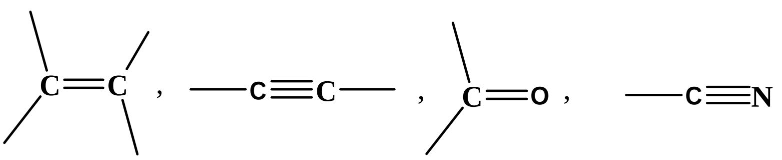
The aim is to motivate and enable the student to comprehend the possible chemical route by which the addition reactions may proceed.

On successful completion of this lesson the student should have:

* learnt possible reaction pathways in addition reactions.

15.1. INTRODUCTION

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

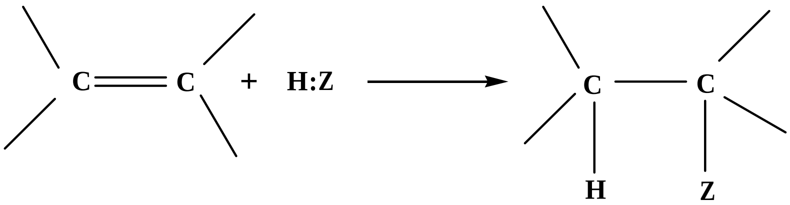


, etc.,

undergo addition reactions. The reactivity of these compounds is due to the more exposed and easily available π electrons to the electron-seeking (electrophilic) reagents.

15.1.1. ELECTROPHILIC ADDITION

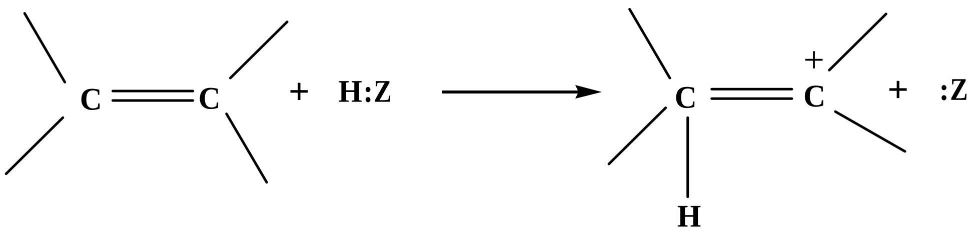
Let us take in general the addition of an acidic reagent, HZ, to an alkene



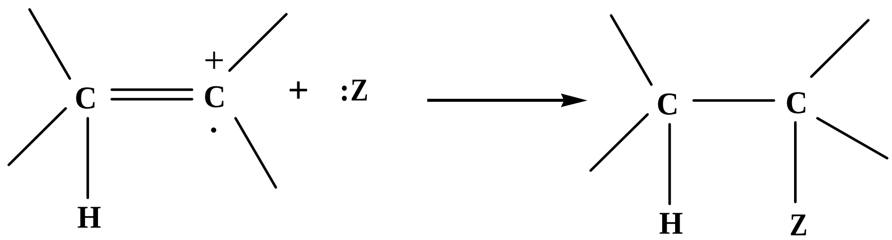
$[HZ = HCl, HBr, HI, H_2SO_4]$

MECHANISM

(1)



(2)

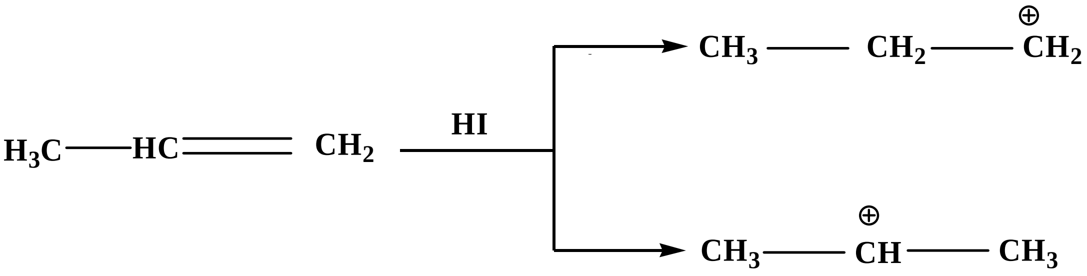


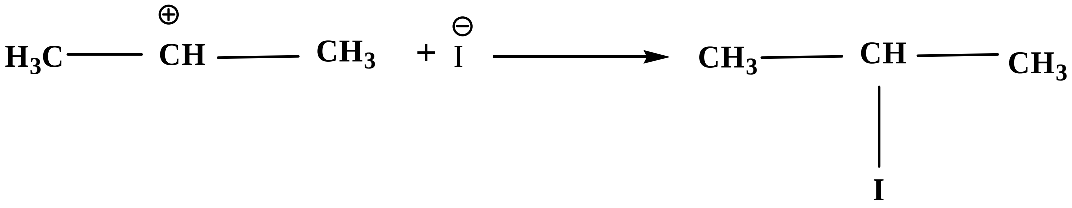
Step (1) involves transfer of hydrogen ion to the alkene to form a carbonium ion.
Step (2) is the union of the carbonium ion with base: z.

Step (1) is the difficult step and controls the rate of the reaction. This step involves attack by an acidic electron - seeking reagent that is an electrophillic reagent and hence is called electrophillic addition.

$$H_3C-HC=CH_2 \xrightarrow{HI} CH_3-\underset{\displaystyle I}{\underset{|}{CH}}-CH_3$$

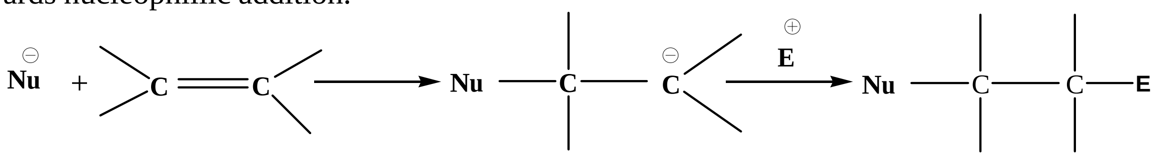
MECHANISM



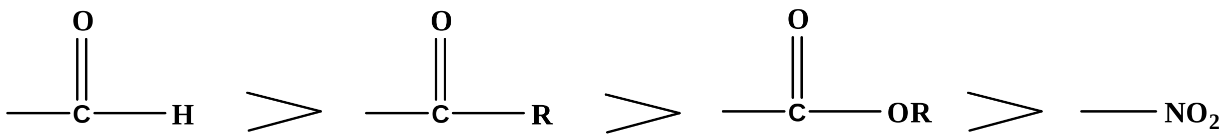


15.1.2. NUCLEOPHILIC ADDITION REACTION

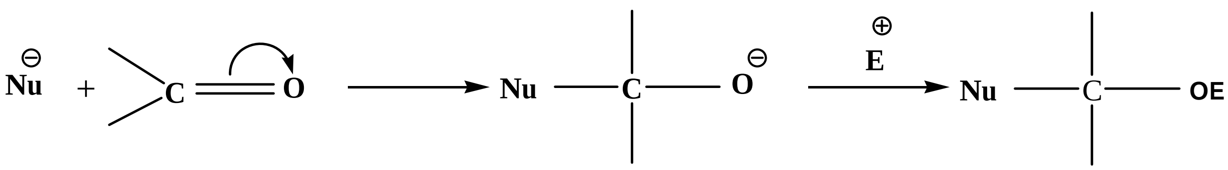
Conjugation of electron withdrawing groups activate the carbon-carbon multiple bonds towards nucleophillic addition.



The substituents reduce the π electron density, thereby aid the attack of the nucleophile and stabilize the carbanion formed on attack by delocalization of the negative charge.



Polar functional groups Eg >C = 0, $C \equiv N$ >C=N, >C=S etc., also undergo nucleophillic addition.

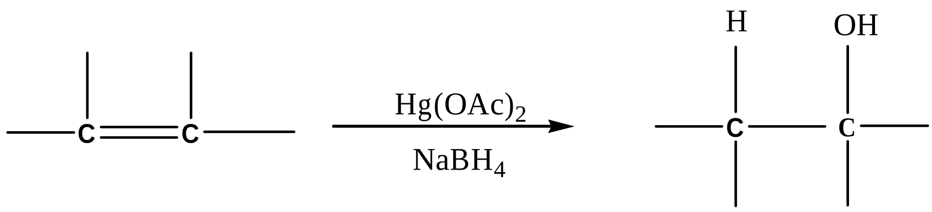


Nucleophilic addition to carbonyl group, therefore a characteristic reaction of aldehyde and ketones.Considering the steric and electronic factors (inductive effect) of the group attached to the carbonyl, carbon, the reactivity of the carbonyl groups decreases in the order:-

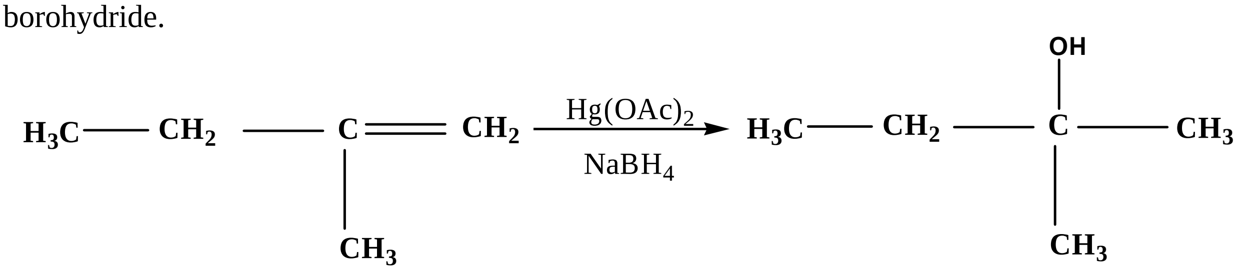
$$H_2C{=}O > RCHO > R_2CO > ArCHO > Ar_2CO$$

15.2. ADDITION TO DOUBLE AND TRIPLE BONDS

15.2.1. HYDRATION



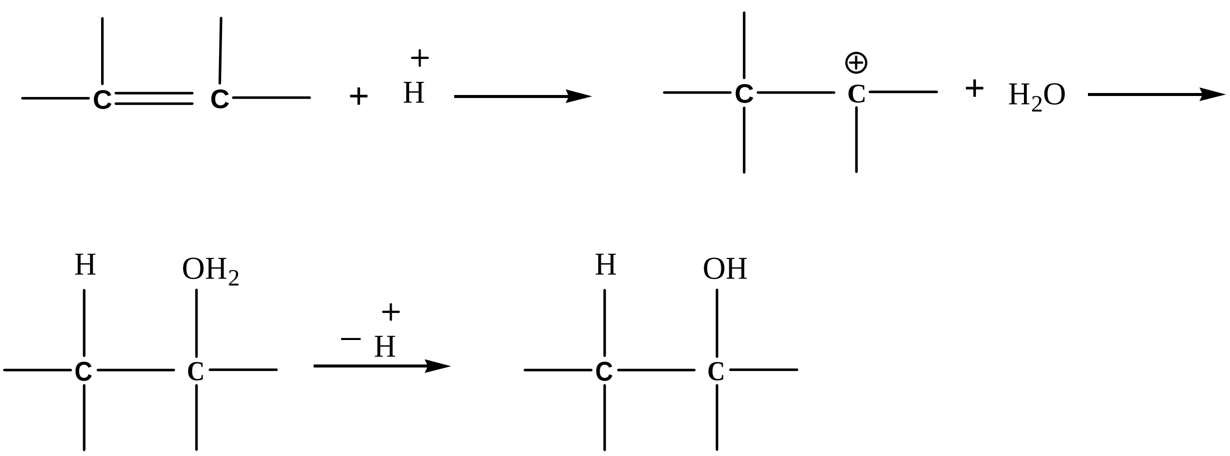
Olefins can be hydrated quickly under mild conditions in high yields without rearrangement product by the use of oxymer curation. Followed by in situ treatment with sodium borohydride.



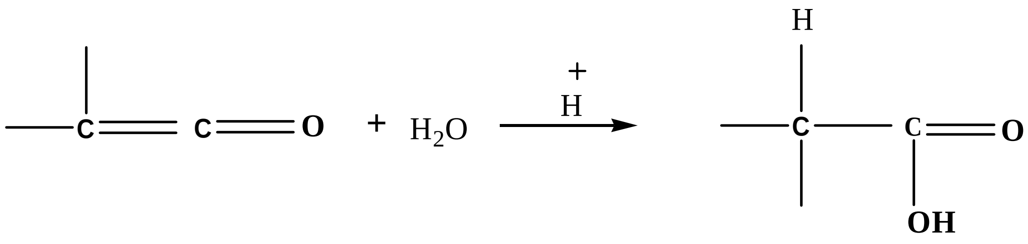
2-Methyl-1-Butane **2-Methyl-2-Butananol**

Double bond can be hydrated by treatment with water and acid catalyst. The most common catalyst is sulphuric acid.
The mechanism is electrophilic and begins with attack of proton. The negative attacking species may be HSO_4^-.

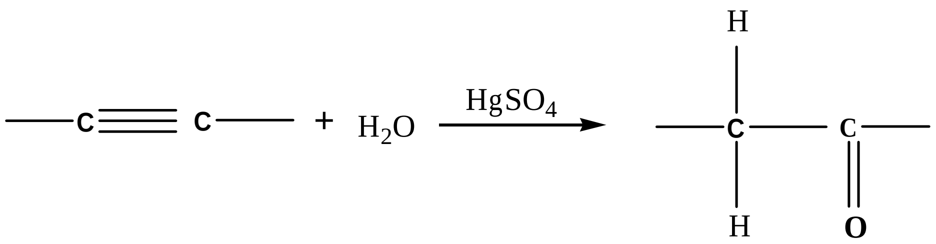
MECHANISM



The addition of water to vinyl ethers causes hydrolysis to aldehydes or ketones.

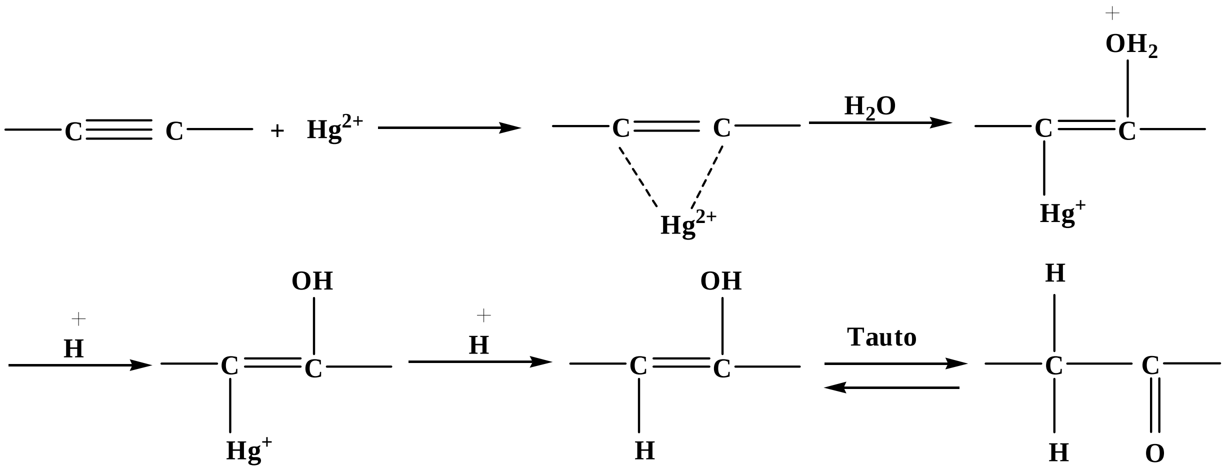


15.2.2. HYDRATION OF TRIPLE BONDS

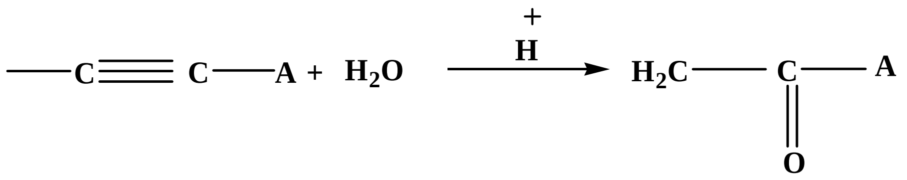


Mercuric ion salts used as catalyst. The addition follows markovnikov's rule, only acetylene gives an aldehyde.

MECHANISM



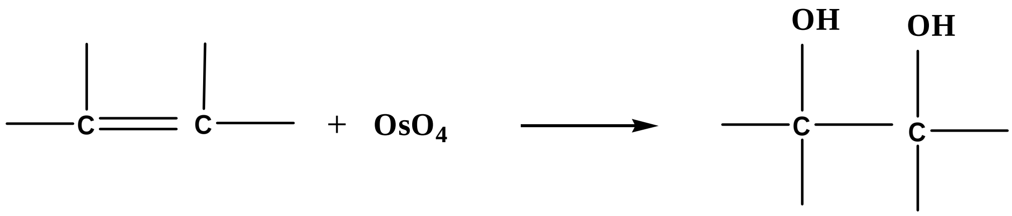
Carboxylic esters, thiol esters and amides can be made respectively by acid – catalyzed hydration of acetylenic ethers, thioethers without a mercuric catalyst.



A=OR,SN,NR$_2$

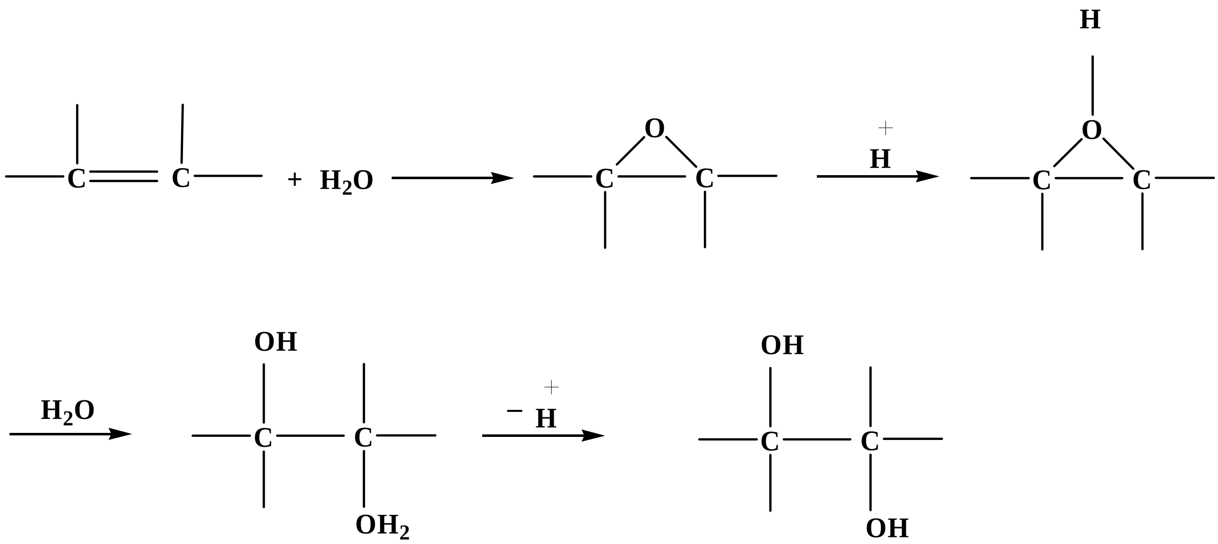
Ordinary electrophilic addition, with the rate determining propitiation as the first step.

15.2.3. HYDROXYLATION



There are many reagents that add two OH group to a double bond. OsO_4 and alkaline $KMnO_4$ give syn addition, from the less hindered side of the double bond.

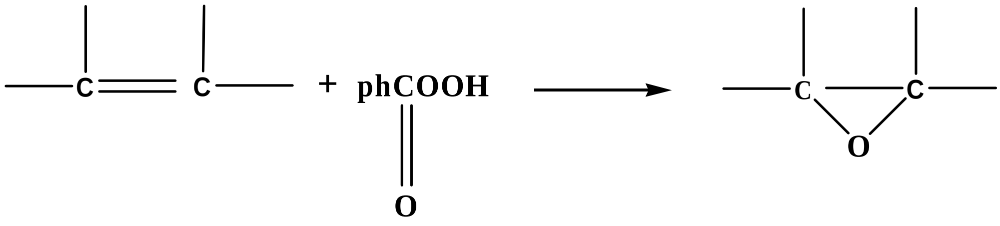
Antihydroxylation can be achieved by treatment with H_2O and fumic acid. In this case epoxidation occurs first, followed by an S_N2 reaction which results in overall antiaddition.



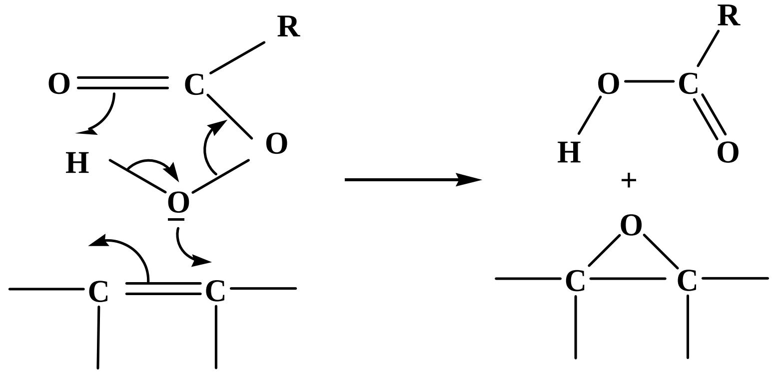
15.2.4. EPOXIDATION

Peroxycarboxylic acids Eg. Per benzoic acid or m-chloro peroxy benzoic acid are used to convert alkenes to epoxides.

Epoxidation is however a stereo specific syn addition. Eg. Cis 2-butene gives only the product. Thus it is a concerted process in which the two bonds are formed at the same, formation of two bonds at the same time cannot change the stereo chemical relationship of the group in the starting alkene.



MECHANISM

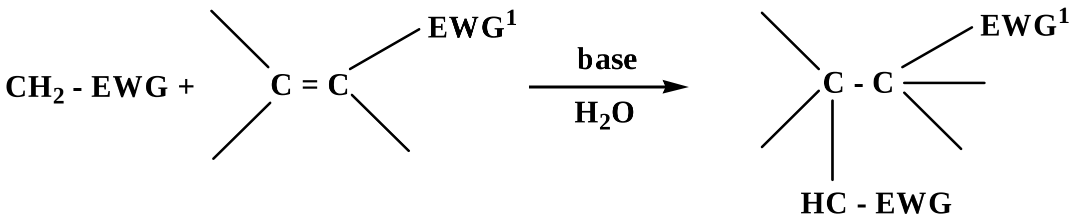


Evidence for this mechanism is as follows:-

1. The reaction is second order. If ionization were the rate – determining step, it would be first order in per acid.
2. The reaction readily takes place in non-polar solvents.
3. No carbocation character in the transition state.
4. The addition is stereo specific.

15.2.5. MICHAEL REACTION

The base-catalyzed addition of a 'donar' compound possessing at least one active α–hydrogen atom to an acceptor compound containing an active bond is known as Michael reaction.

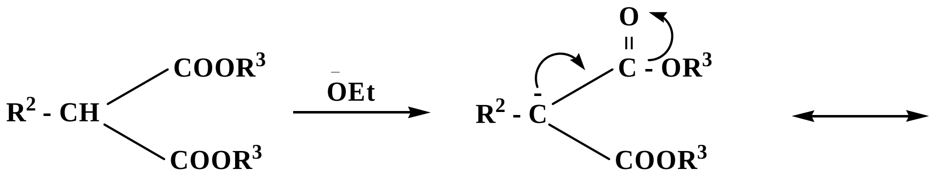


(EWG – electron withdrawing group)

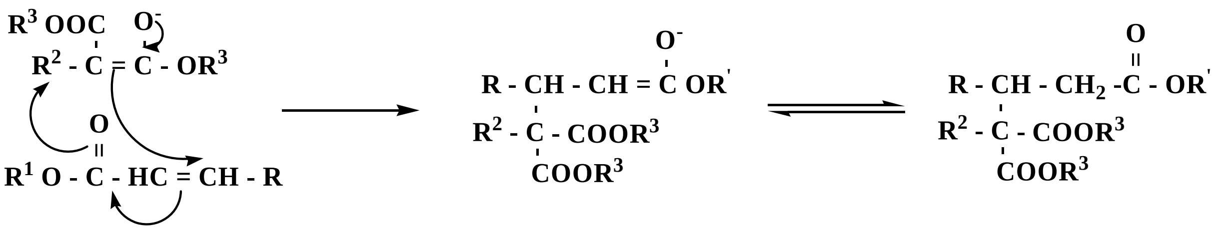
$$\mathrm{PhCH=CHCOOEt} \;+\; \mathrm{CH_2(COOEt)_2} \xrightarrow[\text{(ii) } H_2O]{\text{(i) } \overline{O}Et} \underset{\substack{|\\ \mathrm{CH(COOEt)_2}}}{\mathrm{Ph\text{-}CH\text{-}CH_2COOEt}}$$

The Michael reaction is carried out in a protic solvent (eg: Alcohol) by the use a base.

MECHANISM



(Resonance stabilized
carbanion)



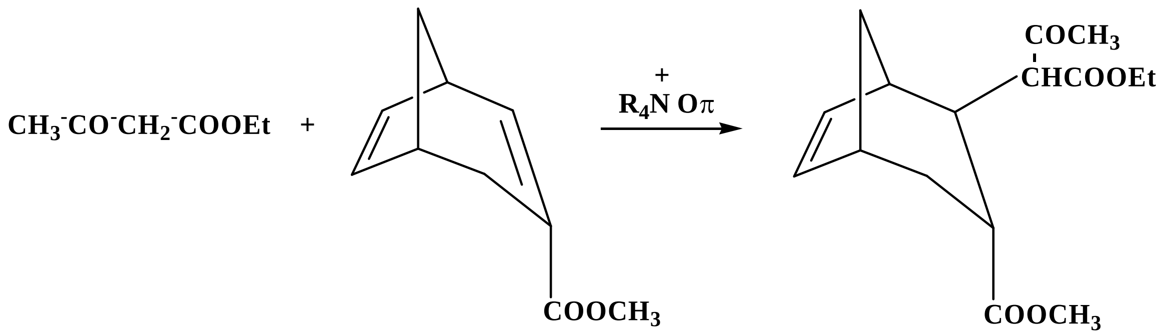
(nucleophilic attack
at the b-carbon)

enolate

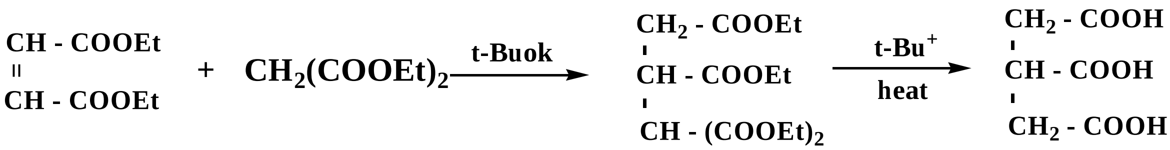
APPLICATION

The Michael reaction is of great importance in organic synthesis.

(i).

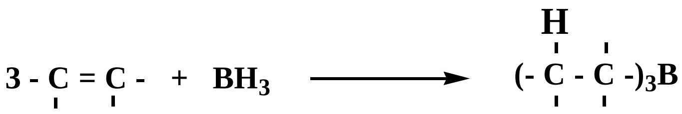


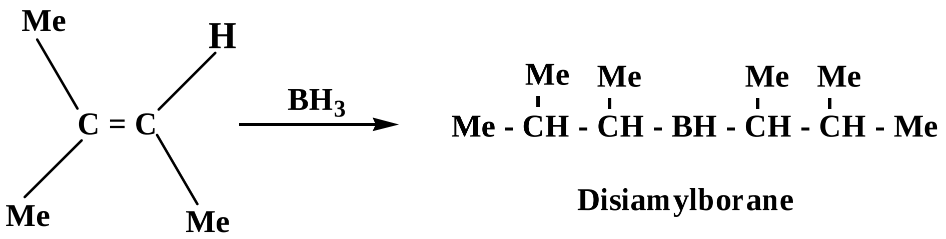
(ii).



15.2.6. HYDROBORATION

When olefins are treated with borane in ether solvent BH_3 adds across the double bond.





Disiamylborane

15.3. LET US SUM UP

In this lesson, we:

Pointed out

- Electrophilic addition
- Nucleophilic addition reaction
- Addition to double and triple bonds
- Hydration
- Hydration of triple bonds
- Hydroxylation
- Epoxidation
- Michael reaction
- Hydroboration

15.4. CHECK YOUR PROGRESS

1. What is addition reaction? Give examples.
2. How HBr will added to CH_2=CH_2?
3. Differentiate hydroxylation and Hydroboration reaction.
4. What is epoxidation reaction?

15.5. POINT FOR DISCUSSION

1. Give mechanism for electrophilic addition reaction.
2. Give mechanism for nucleophilic addition reaction.
3. Explain the Michael addition reaction with mechanism and application.
4. Explain Hydration reactions of double and triple bonds.

15.6. REFERENCES

1. Jerry march, Advanced Organic Chemistry, Fourth edition, Wiley India edition.

2. P.S. Kalsi, Organic reactions and their mechanisms, Second edition, New age international publishers**.**

3. Goutam Brahmachari, Organic name reactions, Narosa publishing house, New Delhi.

LESSON: 16 – ADDITION TO CARBONYL COMPOUNDS

CONTENTS

16.0. AIMS AND OBJECTIVES

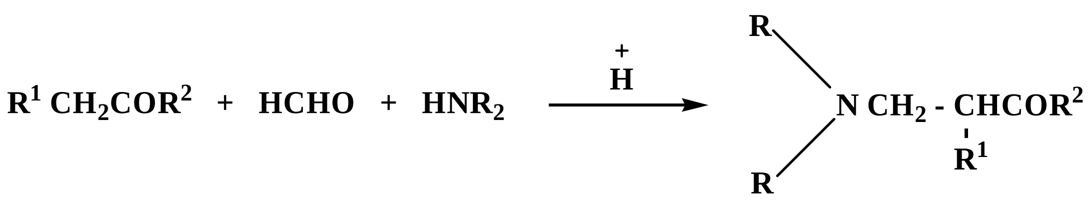
The aim is to motivate and enable the student to comprehend the possible chemical route by which the addition reactions of carbonyl compounds may proceed.

On successful completion of this lesson the student should have:

* learnt possible reaction pathways in addition reactions of carbonyl compounds.

16.1. MANNICH REACTION

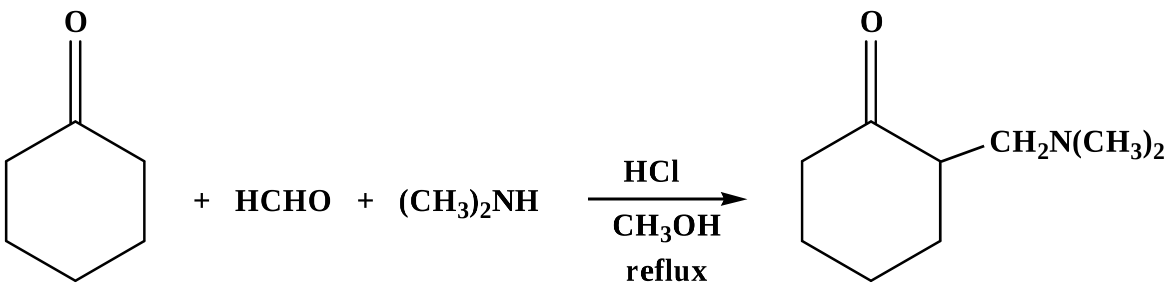
The three component condensation reaction between an active methylene compound, formaldehyde and an amine to form a β-amino carbonyl compound (called Mannich base) is known as Mannich reaction.



Mannich base

This is one of the most widely used reactions for the formation of carbon – carbon bonds. It is carried out in water, methanol, ethanol or acetic acid.

Example



$$PhCOCH_3 + HCHO + (CH_3)_2NH \xrightarrow[\text{CH}_3\text{OH, reflux}]{\text{HCl}} PhCOCH_2N(CH_3)_2$$

MECHANISM

It is suggested that in the first step, the amine and HCHO in the presence of H^+ condense to imminium Cation.

$$\text{(i).}\quad R_2\ddot{N}H + H_2C{=}O \rightleftharpoons R_2\ddot{N}-CH_2-OH \xrightarrow{H^{\oplus}} R_2\overset{+}{N}{=}CH_2 + H_2O$$

It is then attached by the enolate anion of the active hydrogen compound in the second step from the Mannich base.

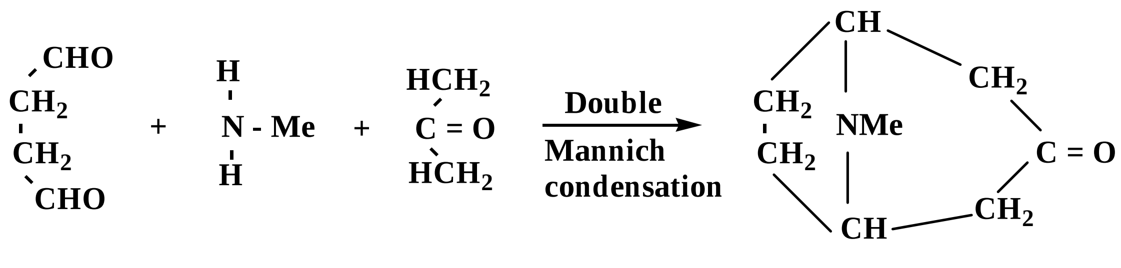
$$\text{(ii).}\quad R'-\overset{O}{\overset{\|}{C}}-CH_3 \underset{}{\overset{H^{\oplus}}{\rightleftharpoons}} R'-\overset{OH}{\overset{|}{C}}{=}CH_2$$

$$R'-\overset{OH}{\overset{|}{C}}{=}CH_2 + CH_2{=}\overset{+}{N}R_2 \xrightarrow{-H^{\oplus}} R-\overset{O}{\overset{\|}{C}}-CH_2-CH_2-\ddot{N}R_2$$

APPLICATIONS

Many important natural products, especially alkaloids have been synthesized by this reaction.

(1) A classical example is Robinson's synthesis of tropinone by a double Mannich condensation and subsequent synthesis of atropine.



Tropinone

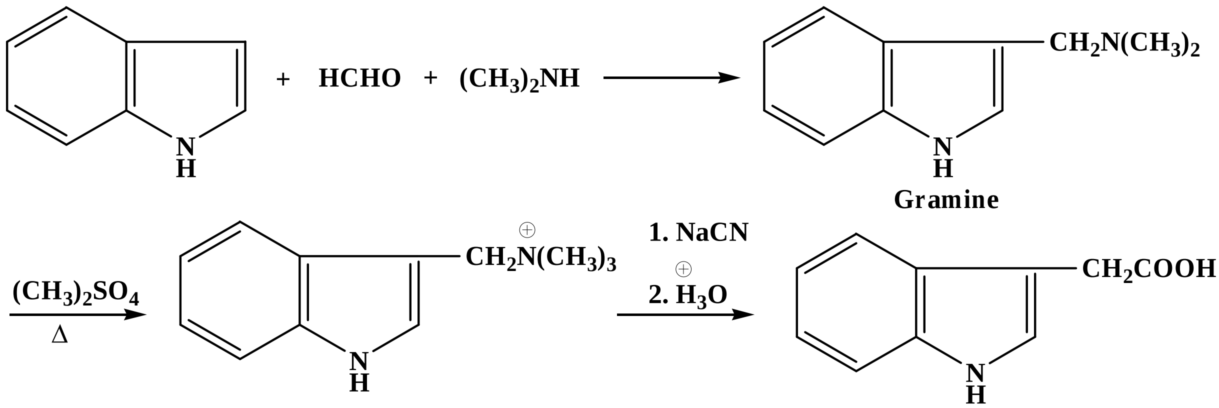
(2) Building up of ring system:

The easy elimination of R_2NH from Mannich base has synthetic application.

$$CH_3COCH_3 \; + \; HCHO \; + \; (CH_3)_2NH \longrightarrow CH_3COCH_2CH_2N(CH_3)_2 \xrightarrow[\Delta]{CH_3I}$$

$$CH_3COCH_2CH_2\overset{\oplus}{N}(CH_3)_3\overset{\ominus}{I} \xrightarrow[\Delta]{CH_3I} CH_3COCH{=}CH_2 \; + \; (CH_3)_3NHI$$

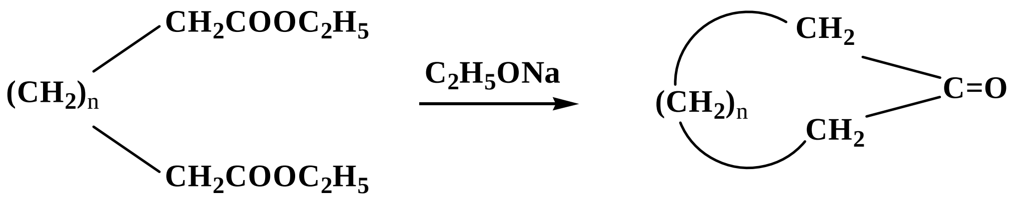
(3) The imminium salt, being a strong electrophile, replaces the active hydrogen of indole, phenol, nitroalkane etc., eg.



β - indole acetic acid

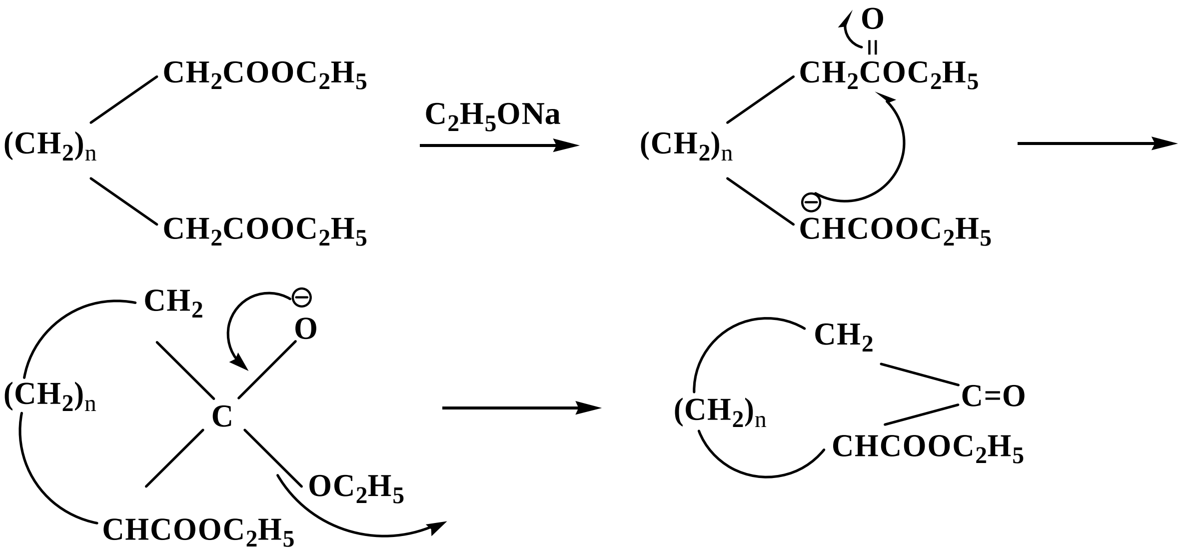
16.2. DIECKMANN REACTION

Intramolecular Claisen condensation in dibasic–acid esters is called Dieckmann reaction. The product is cyclic β–ketone derivatives. The condensing bases may be sodium, sodium ethoxide, sodium hydride, potassium tertiary butoxide etc.



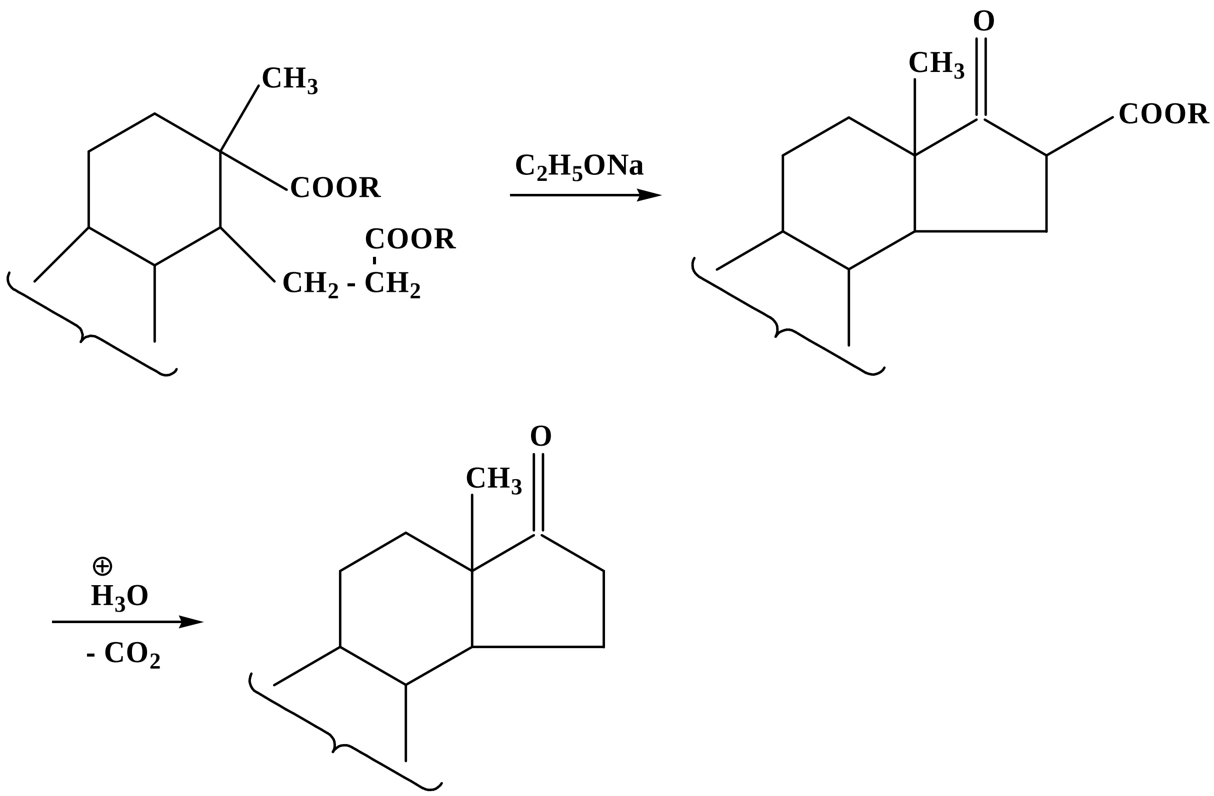
MECHANISM

The base abstracts a proton from one of the α–carbons. The resulting carbanion then attacks the carbonyl carbon of the ester group. Subsequent of the alkoxide ion gives the cyclic ketone derivative.



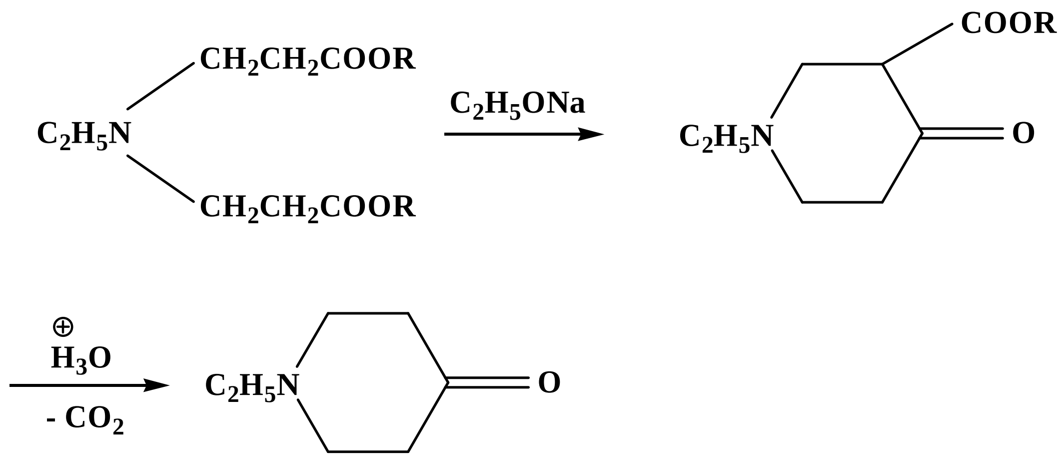
APPLICATION AND EXTENSION

1. Synthesis of various natural products.
   Synthesis of steroid.



2. Preparation of heterocyclic ketoesters:

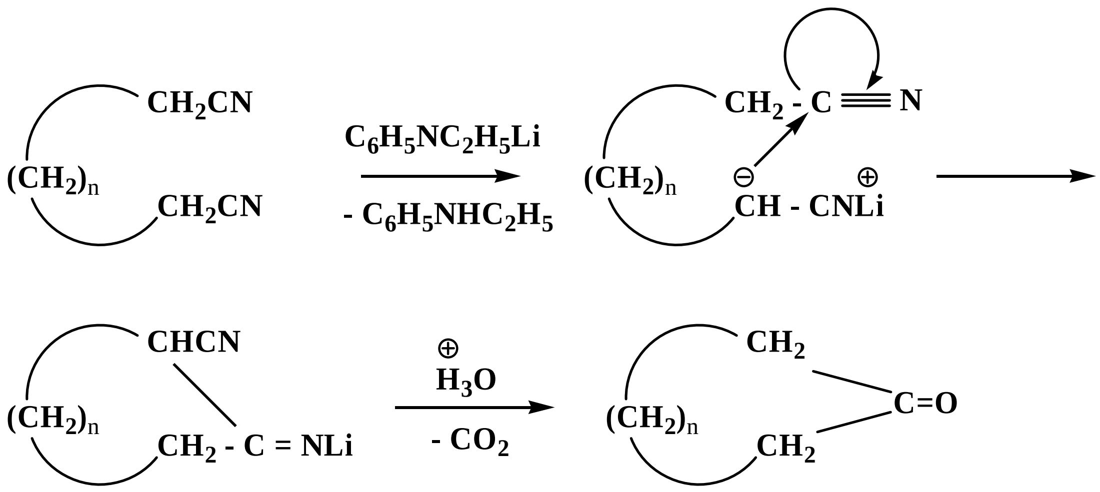
Piperidone derivative:-



1-ethyl-4-piperidone

3. Extension of the reaction:

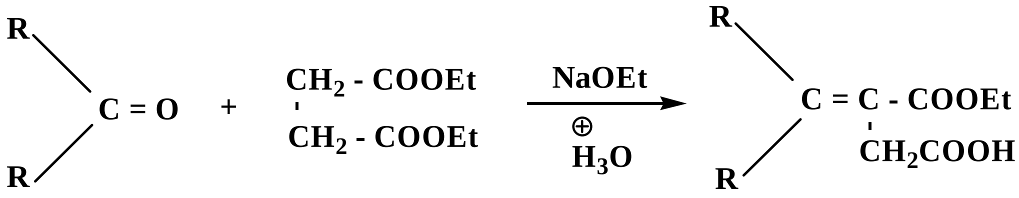
Ziegler applied Dieckmann reaction on dinitriles to obtain large high dilution technique.



16.3. STOBBE CONDENSATION

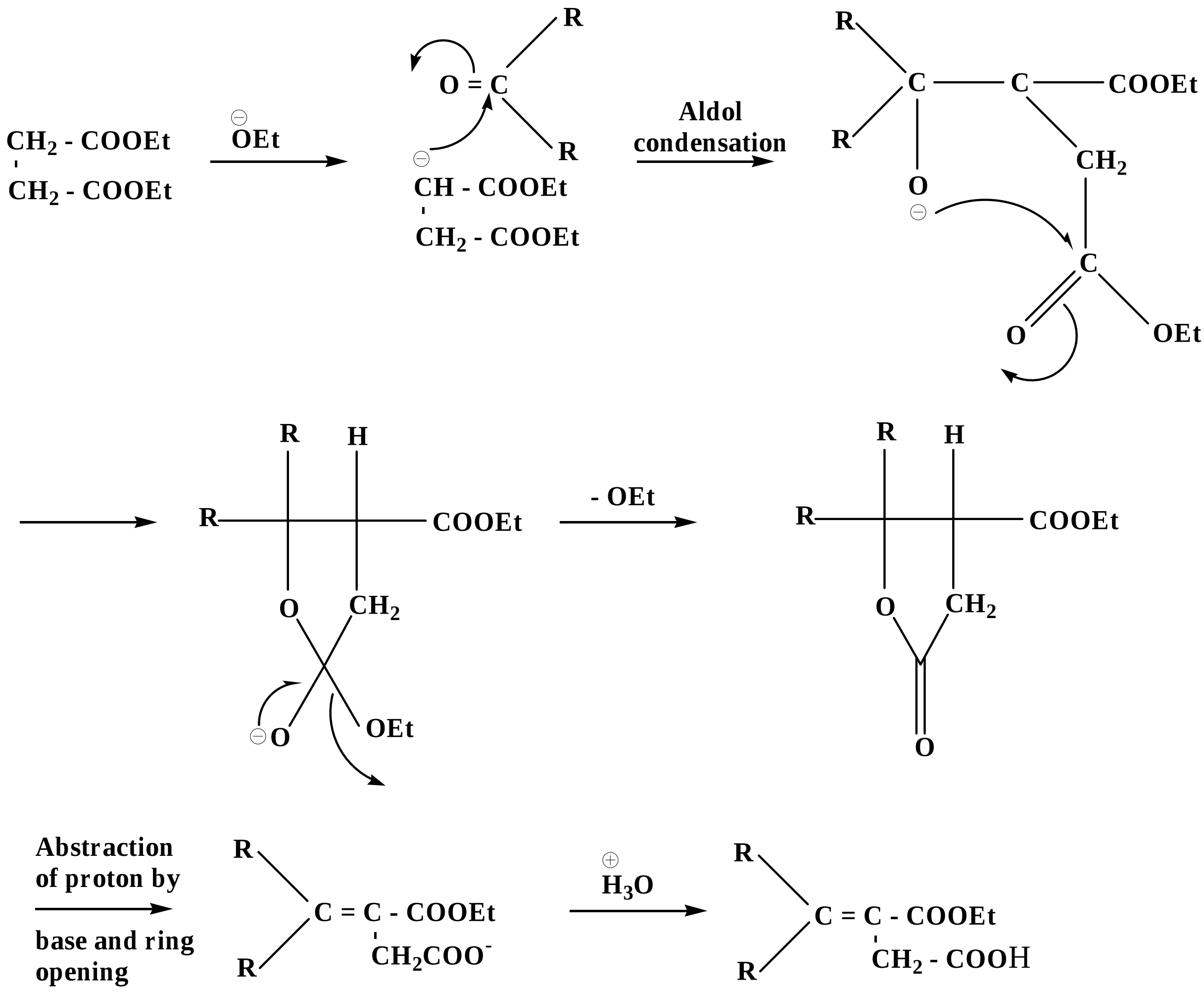
The base catalyzed condensation of aldehydes and ketones with diethyl succinate and its derivatives to from monoesters of an α–alkylidene succinic acid is called the Stobbe condensation.

The bases generally used are NaOEt, NaH, KOBu, etc.; one of the ester groups becomes hydrolyzed in the course of the reaction.



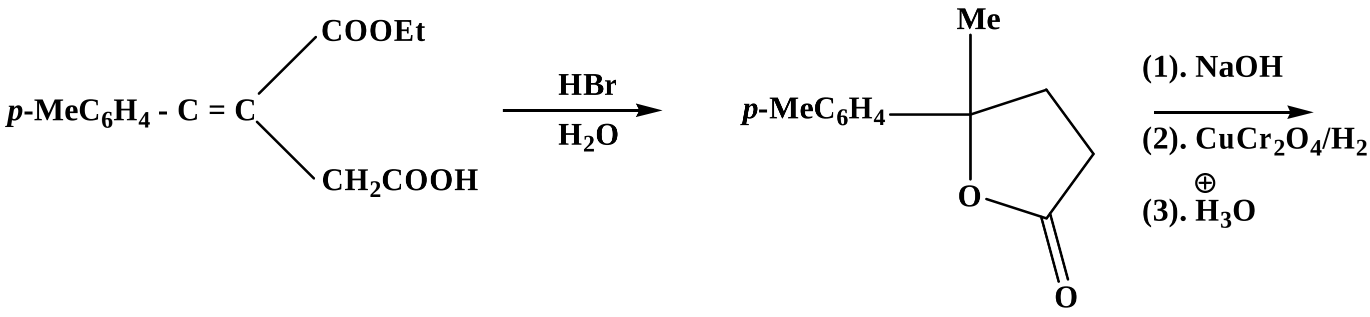
MECHANISM

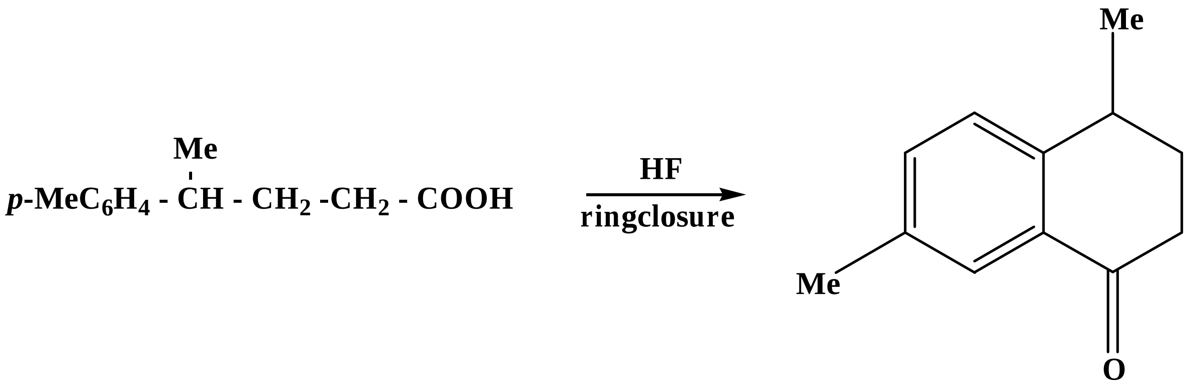
The reaction is believed to proceed by initial aldol condensation and subsequent intramolecular formation of a lactone intermediate, which then undergoes base – catalyzed elimination (E1 or E2) to yield the product.

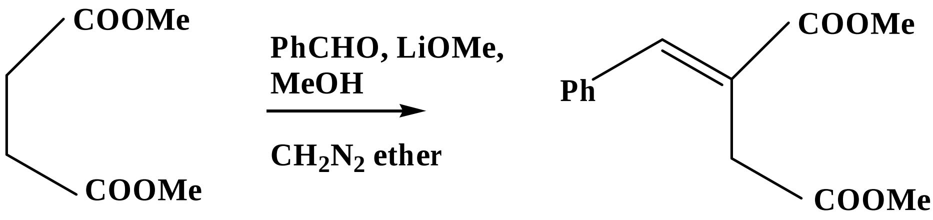


APPLICATION

Synthetically important cycle ketones can be prepared starting from Stobbe condensation product.





(ii) 

16.4. KNOEVENAGEL REACTION

Condensation of aldehyde and ketone with compound having active methylene groups in the presence of base catalyst to from α,β–unsaturated compounds is called knoevenagel reaction.

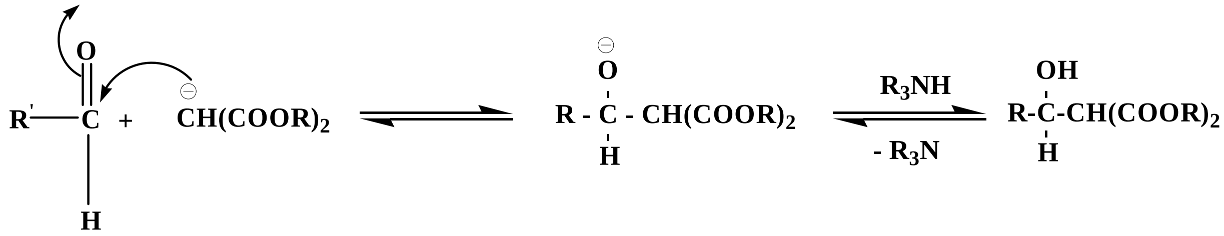
$$C_6H_5CHO + H_2C(COOR)_2 \xrightarrow[\text{Piperidine}]{\text{Pyridine}} C_6H_5CH{=}C(COOR)_2 \xrightarrow[\text{2. }\Delta\ -CO_2]{\text{1. }H_2O} \underset{\text{Cinnamic acid}}{C_6H_5CH{=}CHCOOH}$$

$$R_3\ddot{N} + H_2C(COOR)_2 \rightleftharpoons R_3\overset{\oplus}{N}H + H\overset{\ominus}{C}(COOR)_2$$

MECHANISM

The initial stage of the reaction is base catalyzed aldol condensation with dehydration.

$$R_3\ddot{N} + H_2C(COOR)_2 \rightleftharpoons R_3\overset{\oplus}{N}H + \overset{\ominus}{H}C(COOR)_2$$



$$\xrightarrow{-H_2O} R'\text{-}CH{=}C(COOR)_2 \xrightarrow[\text{2. } \Delta\ -CO_2]{\text{1. } H_2O/H^+} R'\text{-}CH{=}CHCOOH$$

APPLICATION

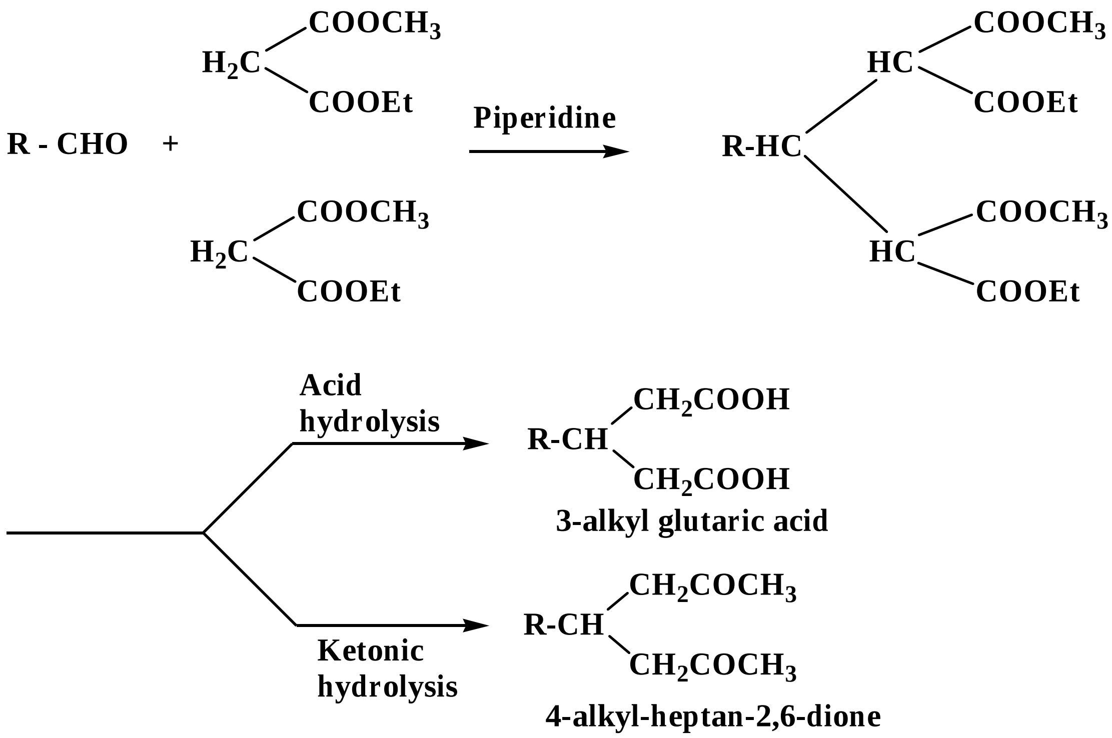
1. Various α,β–unsaturated acids such as crotonic, cinnamic and maleic acid can be prepared.

$$CH_3CHO + H_2C(COOR)_2 \xrightarrow{\text{Piperidine}} CH_3CH{=}C(COOR)_2 \xrightarrow[\text{2. } \Delta\ -CO_2]{\text{1. } H_2O/H^+} \underset{\text{Crotonic acid}}{CH_3CH{=}CHCOOH}$$

$$C_6H_5CHO + H_2C(COOR)_2 \xrightarrow{\text{Piperidine}} C_6H_5CH{=}C(COOR)_2 \xrightarrow[\text{2. } \Delta\ -CO_2]{\text{1. } H_2O/H^+} \underset{\text{Cinnamic acid}}{C_6H_5CH{=}CHCOOH}$$

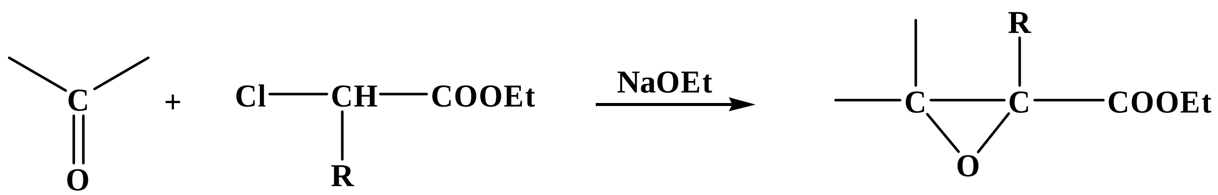
$$HOOC\text{-}CHO + H_2C(COOR)_2 \xrightarrow{\text{Piperidine}} HOOH\text{-}CH{=}C(COOR)_2 \xrightarrow[\text{2. } \Delta\ -CO_2]{\text{1. } H_2O/H^+} \underset{\text{Maleic acid}}{HOOCCH{=}CHCOOH}$$

2. By reacting aldehyde with active methylene compound in 1:2 molar proportions, various dibasic acids and diketones can be prepared.



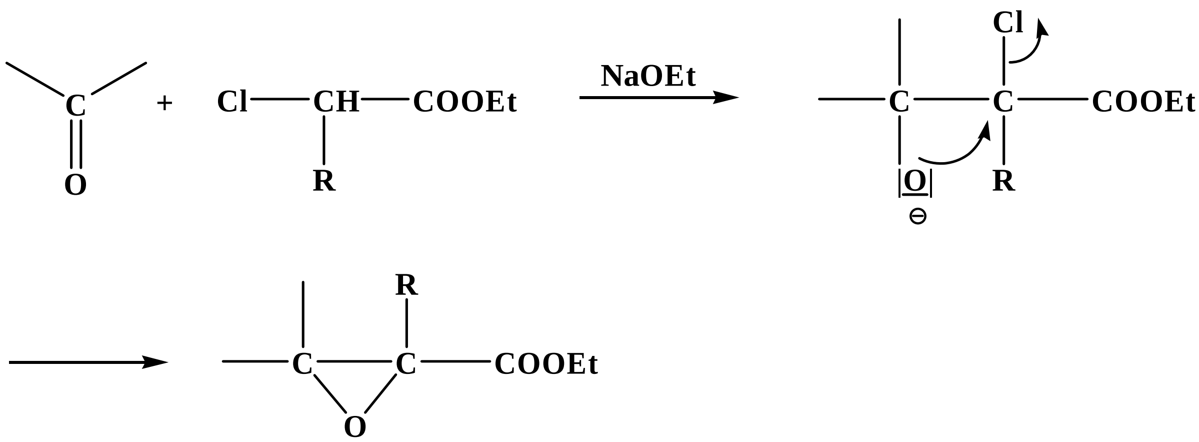
16.5. DARZEN REACTION

Aldehydes and ketones condense with α–halo esters in the presence of bases to given α,β–epoxy esters called glycidic esters. This is called Darzen's condensation.



MECHANISM

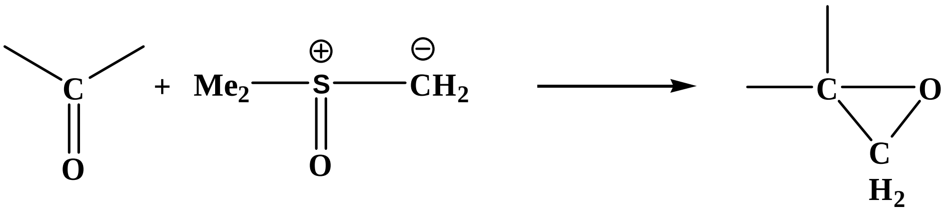
The reaction consists of an initial knoevenagel type condensation followed by an SN2 reaction.



Sodium ethoxide is often used as the base, although other bases, including sodium amide one sometimes used.

APPLICATION

The formation of epoxides from aldehydes and ketones.



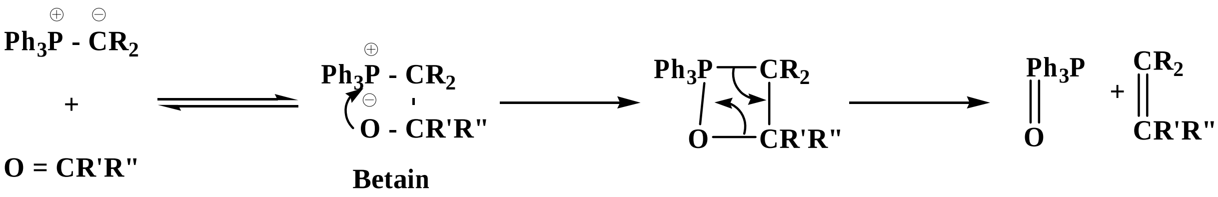
16.6. WITTIG REACTIONS

Witting reaction affords an important and useful method for the synthesis of alkenes by the treatment of aldhydes or ketones with alkylidenetriphenyl phosphorane ($Ph_3P{=}CR_2$).

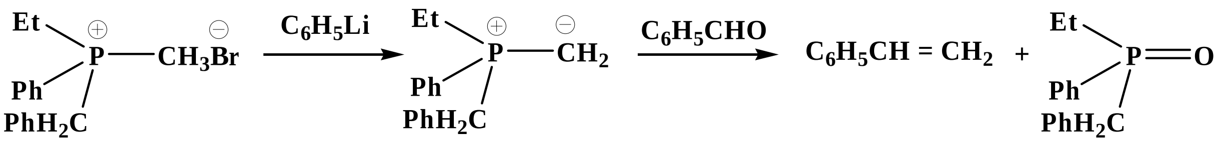
$$Ph_3P = CH_2 \quad + \quad Ph_2C = O \quad \longrightarrow \quad Ph_2C = CH_2 \quad + \quad Ph_3P = O$$

MECHANISM

The reaction probably proceeds by the nucleophillic attack of the yield on the carbonyl carbon. The dipolar complex so formed decomposes to keyton and triphenylphosphin oxide via a four centered transition state.

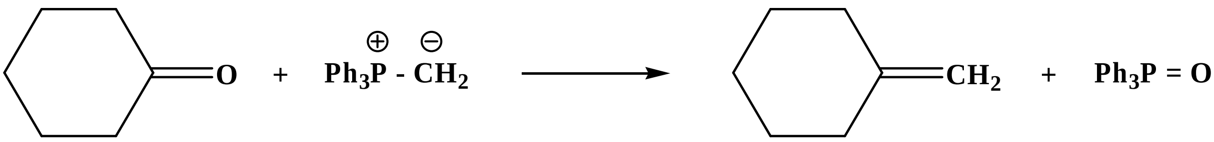


The mechanism is supported by the fact then an optically active phosphonium salt reacts to produce a phosphonium oxide with retention of configuration.



APPLICATION

1. Formation of exocyclic methylene group.



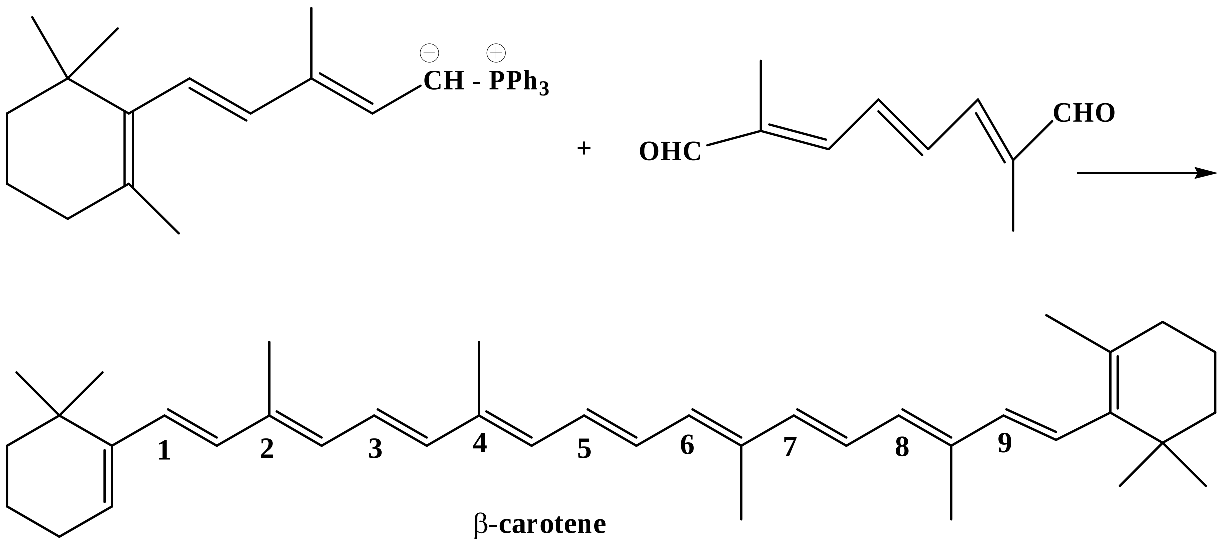
Cyclohexanone

Methylene cyclohexane

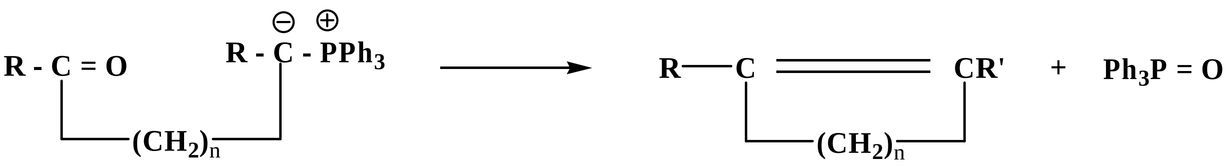
2. Preparation of β, γ unsaturated acids.

$$R_2C = O \quad + \quad Ph_3\overset{\oplus}{P} - \overset{\ominus}{C}H - CH_2CO\overset{\ominus}{O} \longrightarrow R_2C = CHCH_2COO \quad + \quad Ph_3P = O$$

3. Preparation of natural products.

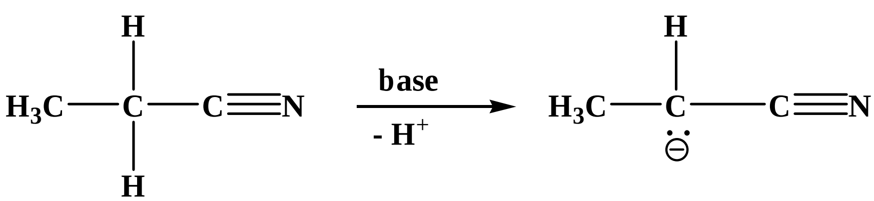


4. Formation of large rings containing 5 to 16 rings.

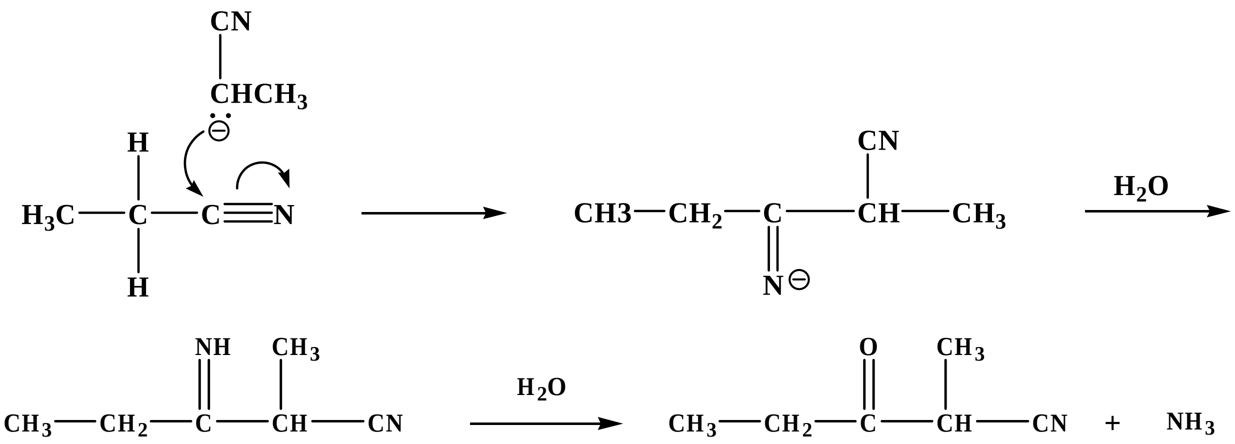


16.7. THORPE REACTION

In the Thorpe reaction, the α–carbon of one nitrile molecule adds to the CN carbon of another molecule. The C=NH bond that result can be hydrolyzed to get β–keto nitriles.



MECHANISM



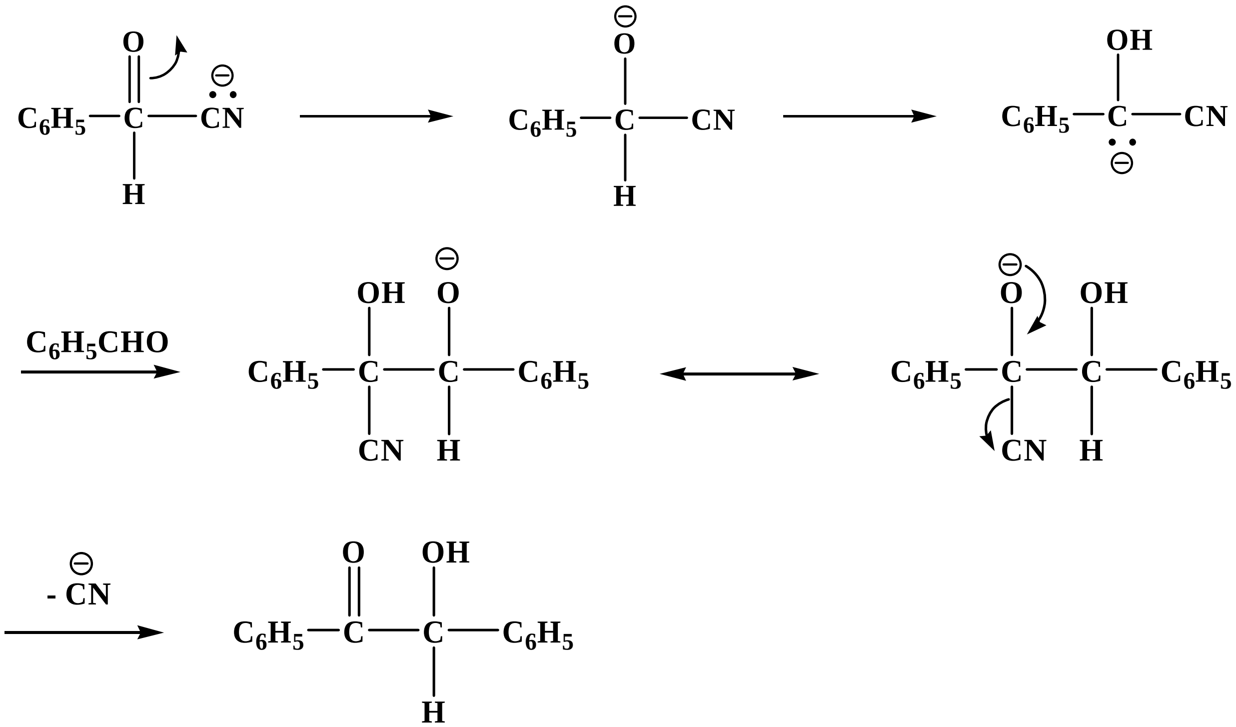
imino-nitrile

16.8. BENZOIN REACTION

This reaction id the cyanide ion catalyzed intermolecular condensation of an aromatic aldehyde to give an alyloin. The condensation of benzaldhyde gives benzoin.

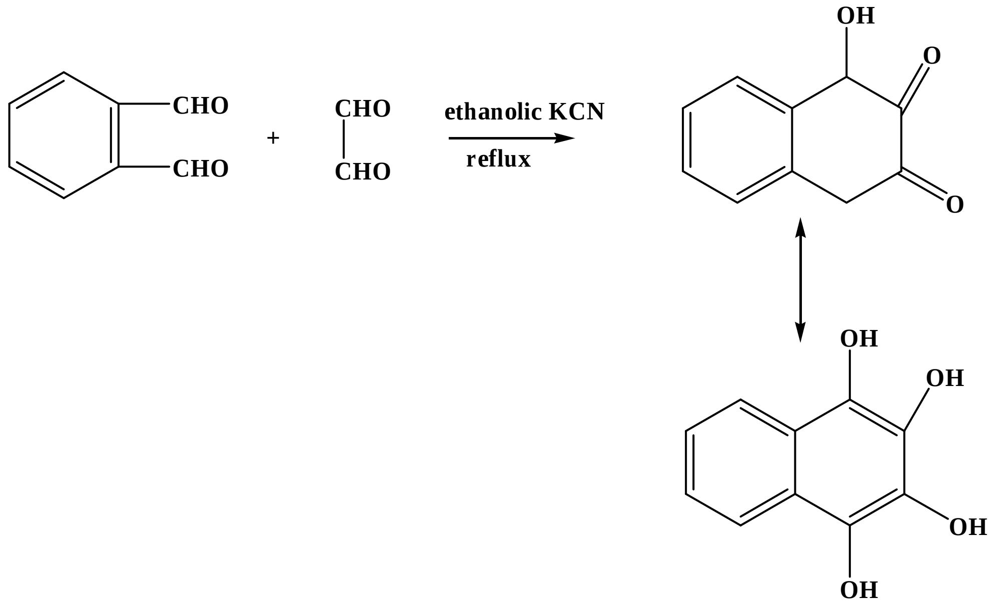
$$\underset{\text{benzaldehyde}}{2C_6H_5CHO} \xrightarrow{KCN} \underset{\text{benzoin}}{C_6H_5CHOHCOC_6H_5}$$

MECHANISM



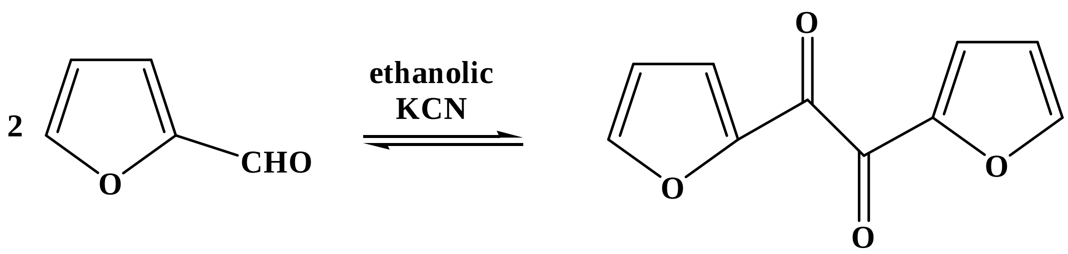
APPLICATIONS

Benzoin condensation can be accomplished for glyoxals also



The crossed benzoin condensation using glyoxals may be applied for synthesis of polynuclear hydrocarbons.

2. Heterocyclic aldehydes also undergo benzoin condensation reaction.



16.9. LET US SUM UP

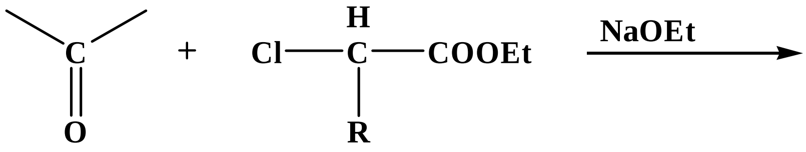
In this lesson, we:
Pointed out

- Mannich reaction
- Dieckmann reaction
- Stobbe condensation
- Knoevenagel reaction
- Darzen reaction
- Wittig reactions
- Thorpe reaction
- Benzoin reaction

16.10. CHECK YOUR PROGRESS

1. Give the products formed and mechanisms of the reactions.

(a)



(b) $2C_6H_5CHO \xrightarrow{KCN}$

2. Differentiate Thorpe and Wittig reactions.

16.11. POINT FOR DISCUSSION

1. Describe Mannich reaction with mechanism.
2. Explain with mechanism and applications of
   (a) Stobbe condensation
   (b) Knoevenagel reaction

16.12. REFERENCES

1. Jerry march, Advanced Organic Chemistry, Fourth edition, Wiley India edition.

2. P.S. Kalsi, Organic reactions and their mechanisms, Second edition, New age international publishers.

3. Goutam Brahmachari, Organic name reactions, Narosa publishing house, New Delhi.

UNIT-VII

LESSON: 17 – CONCERTED REACTIONS: PERICYCLIC REACTIONS

CONTENTS

17.0. AIMS AND OBJECTIVES

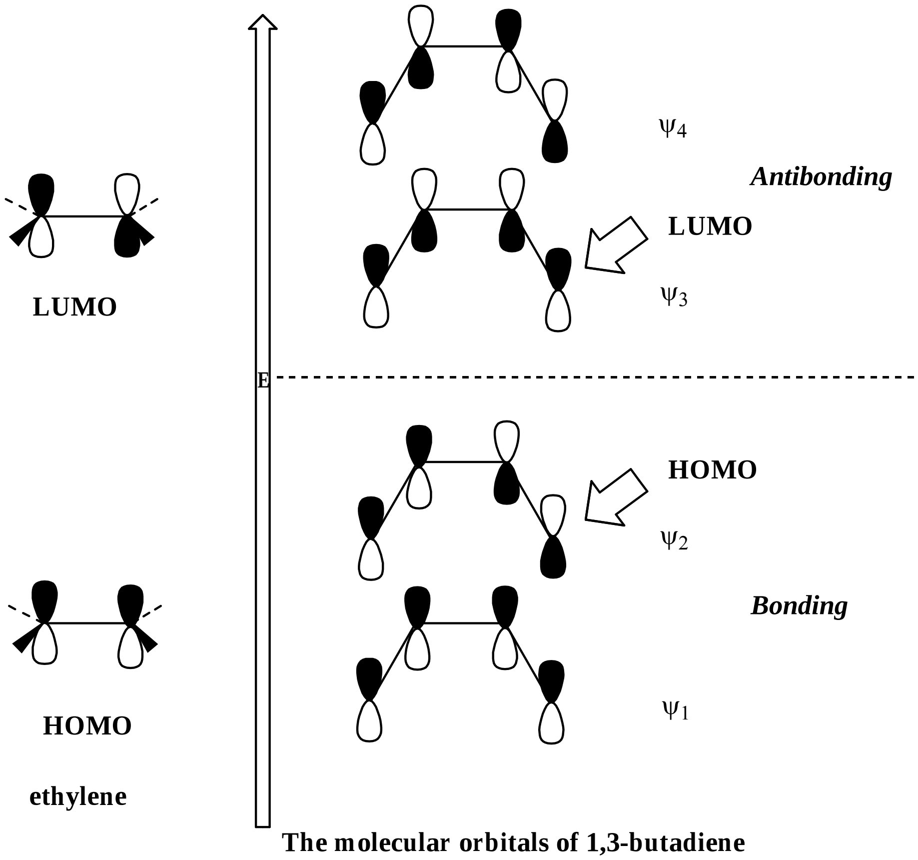
The aim is to motivate and enable the student to comprehend the possible chemical route by which the pericyclic reactions may proceed.

On successful completion of this lesson the student should have:

* learnt possible reaction pathways concerted reactions Woodward-Hofmann rules and organic photochemistry.

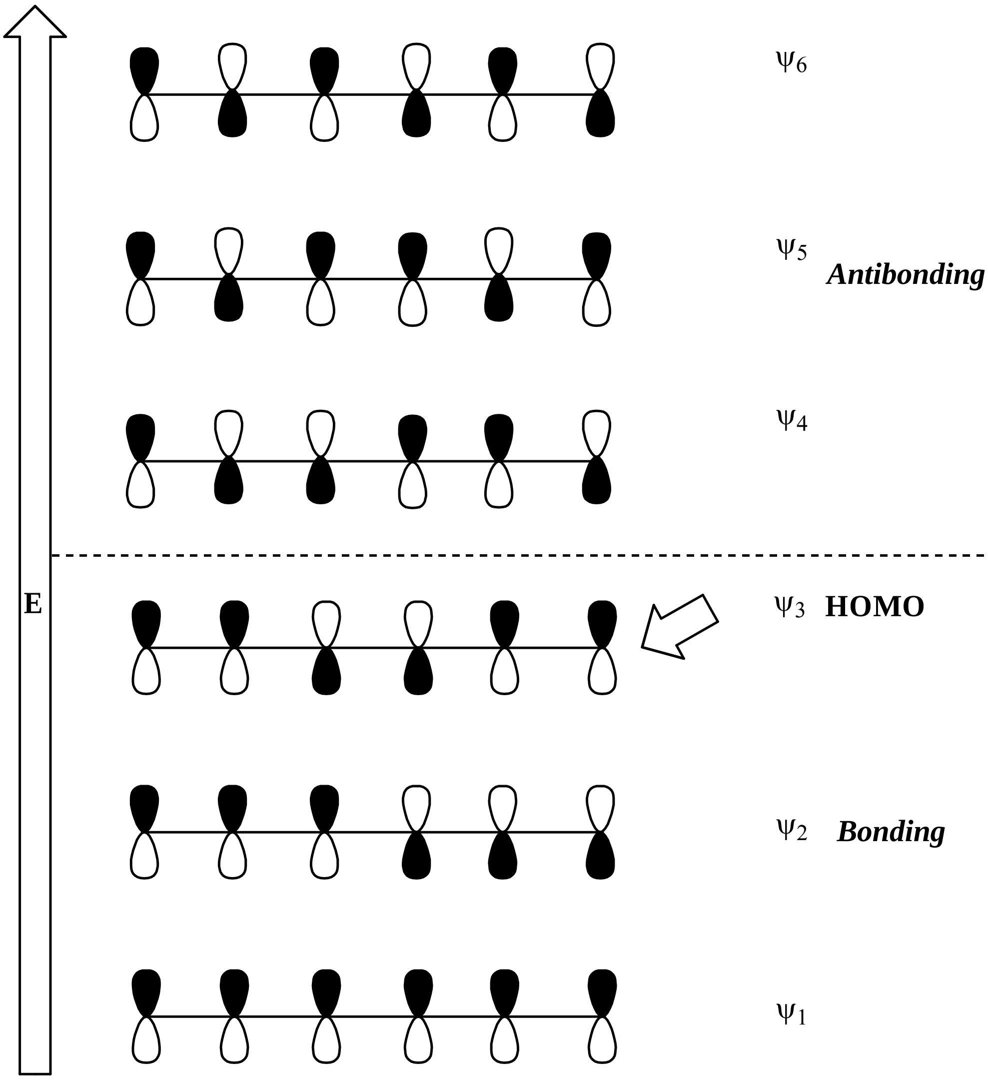
17.1. INTRODUCTION

In a pericyclic reaction, there is concerted bond reorganization and the essential bonding changes occur within a cyclic array of the participating atomic centers. These reactions do not involve the intermediate formation of either ions or radicals. Pericyclic reactions are also largely unaffected by polar reagents, solvent changes, radical initiators etc. These can however, be influenced only thermally or photochemically.



(Scheme 17.1)

A consideration of the phase of orbitals (Schemes 17.1.1 and 17.1.2) has significance, since only orbitals of the same phase will overlap to result in bonding. The orbitals of the different phase lead to a repulsive anti-bonding situation.



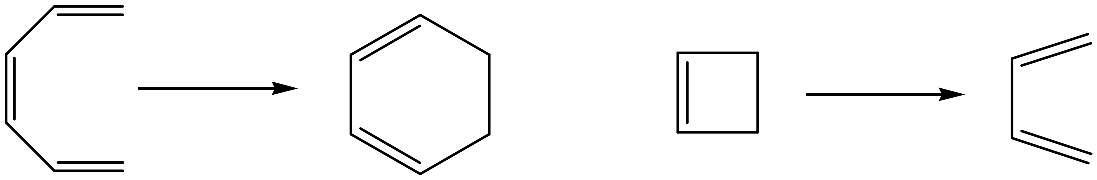
A 1,3,5-hexatriene. Configuration of π electrons in the ground state and the first excited state

(Scheme 17.1.2)

A reasonable way to understand the outcome of pericyclic reactions is by the use of frontier orbital approach. Here the electrons in the highest occupied molecular orbital (HOMO) of one reactant are taken as being similar to the outer valance electrons of an atom. The reaction then involves the overlap between the HOMO orbital (a potential electron donor) with LUMO, (the lowest unoccupied molecular orbital – a potential electron acceptor of the other reactant).

17.2. ELECTROCYCLIC REACTIONS

These are pericyclic reactions (intramolecular) which under the influence of heat or light involve either the formation of a ring, with the generation of one new sigma-bond and the consumption of one pi-bond or the reverse (Scheme 17.2.1).

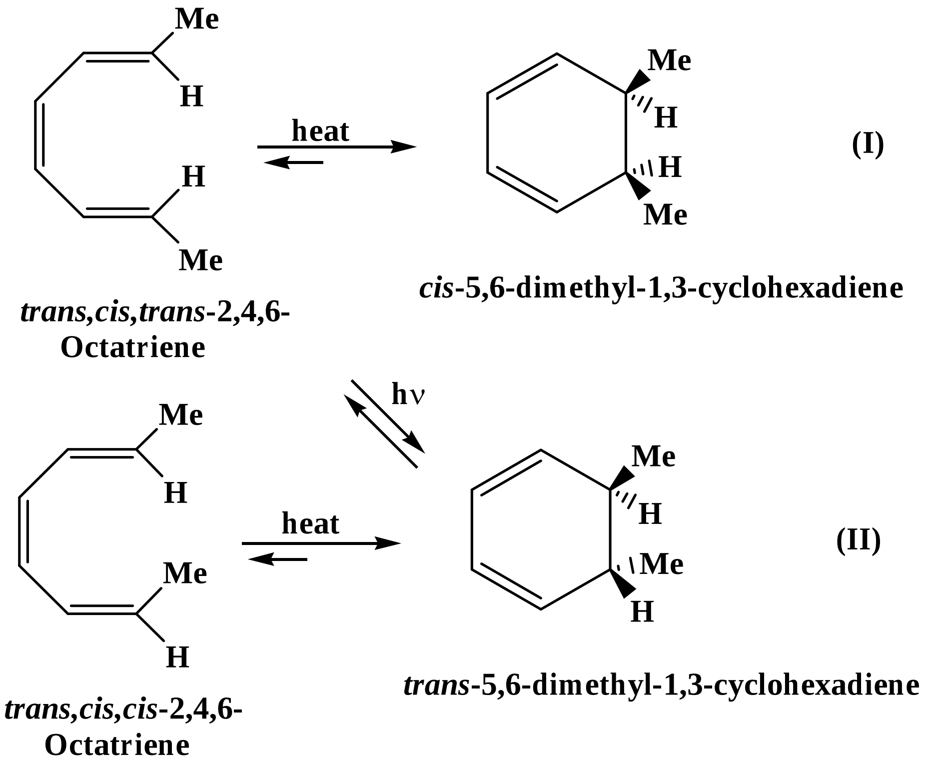


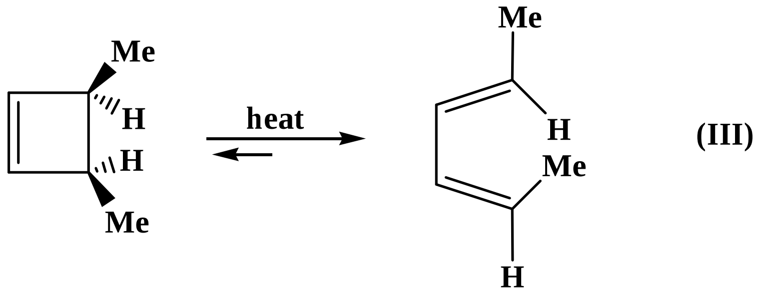
1,3,5-hexatriene **1,3-cyclohexadiene** **cyclobutene** **1,3-butadiene**

(Scheme 17.2.1)

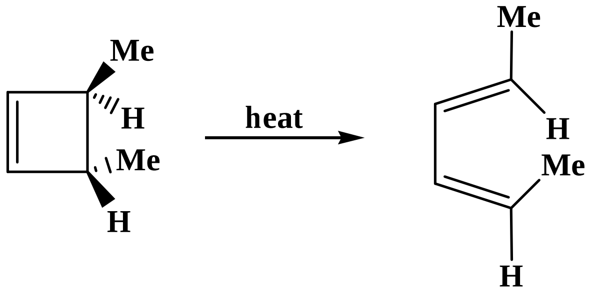
The stereochemistry of electrocyclic reactions can be studied by using suitably substituted molecules (Scheme 17.2.2). The reactions are thus:

1. Completely stereoselective. (A stereoselective reaction leads to the exclusive formation of one of the several possible stereoisomeric compounds. The reaction is solely concerned with the products).





***cis*-3,4-Dimethylcyclobutene** ***cis,trans*-2,4-Hexadiene**



(IV)

trans-3,4-Dimethylcyclobutene *trans,trans*-2,4-Hexadiene

(Scheme 17.2.2)

2. Electrocyclic reactions are also completely stereospecific (in a stereospecific reaction a given isomer gives one product (or d, l pair) while another stereoisomer gives the opposite product).

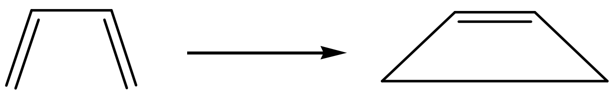
3. The stereochemical outcome of an electrocyclic reaction depends on the number of double bonds in a polyene and on whether the reaction is thermal or photochemical. A thermal electrocyclic reaction involving 4 n pi electrons (n=1, 2, 3 ...) proceeds with conrotatory motion (i.e., a motion in which the bonds rotate in the same direction) while the photochemical reaction involves disrotatory motion (a motion, in which the bonds rotate in opposite directions).

A thermal reaction involving (4n+2) pi electrons (where n=0, 1, 2...) proceeds with disrotatory motion while the photochemical reaction proceeds with conrotatory motion.

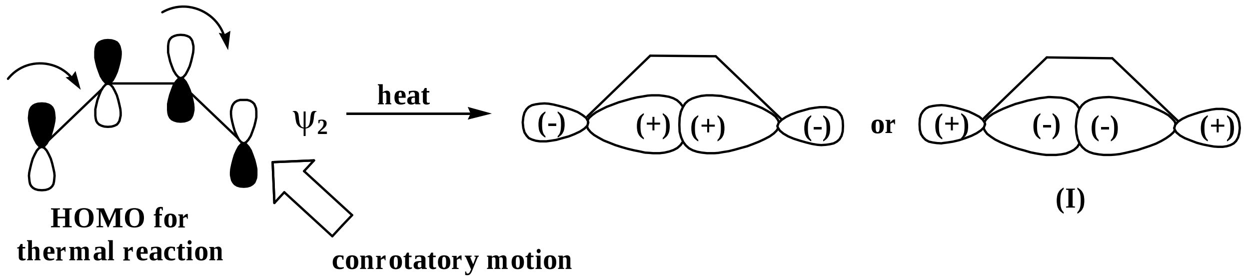
4. The direction taken by an electrocyclic reaction is dependent on the relative stabilities of the ring and open-chain reactants. In the case of cyclobutanes e.g., (Scheme 17.2,2, eq III) the open chain structure is favored because of the strain in the ring, during the thermal reaction.

17.2.1. THERMAL CYCLIZATION OF BUTADIENES

The HOMO of a conjugated diene is ψ_2 (see, Scheme 17.1.1). For the bond formation the overlap of lobes on C-1 and C-4 of the diene is required. It is only the conrotatory motion (Scheme 17.2.1.1, shown in a clockwise way) which brings the lobes of the same phase together for bond formation (In case the conrotatory motion occurs in the opposite, counter clockwise direction, even then the lobes of the same phase sign will still overlap as shown in I Scheme17.2.1.1). However, the disrotatory motion will bring the lobes of opposite phase together and this will be

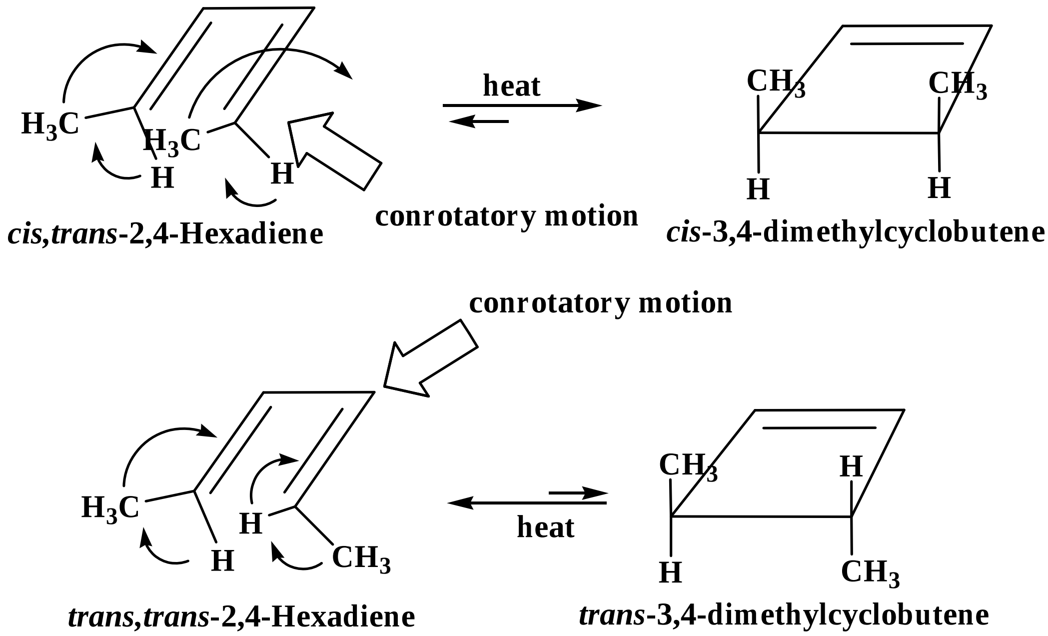


Thermal cyclization of a 1,3-butadiene to a cyclobutene



(Scheme 17.2.1.1)

Conrotatory motion allows p-orbital lobes of the same sign to overlap conrotatory motion leads to bonding. Disrotatory motion leads to antibonding repulsive and anti bonding. Conrotatory motion therefore, explains the observed stereochemistry of the product on thermal cyclization of a disubstituted butadiene (eqs III and IV, Scheme 17.2.2) as shown in (Scheme 17.2.1.2).



Thermal cyclization of substituted butadienes stereochemistry indicates conrotatory motion

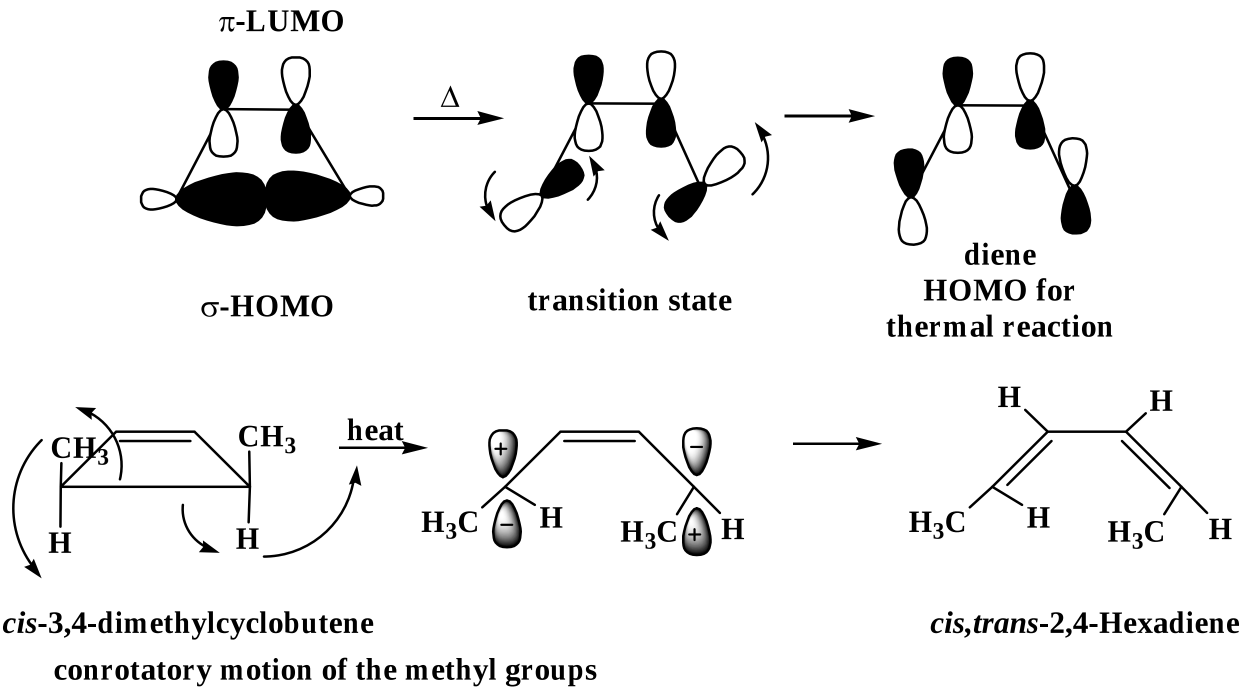
(Scheme 17.2.1.2)

17.2.2. THERMAL RING OPENING OF CYCLOBUTENES

In keeping with the principle microscopic reversibility the reverse process (Scheme 17.2.2, eqs III and IV) of thermal ring opening takes exactly the same path.

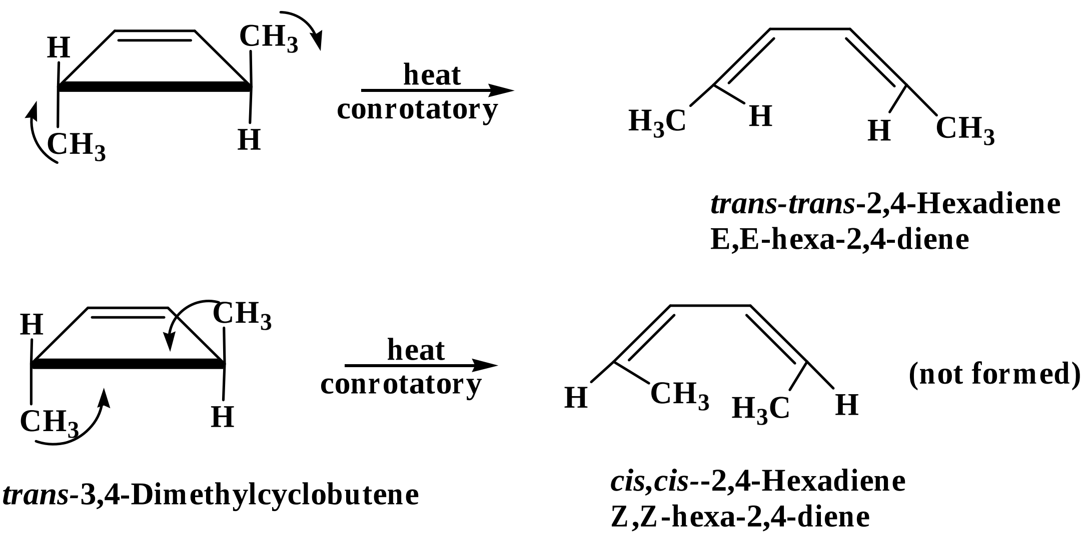
Due to conrotatory motion (Scheme 17.2.2.1). A σ bond will open so as to give the resulting *p* orbitals which will have the symmetry of the highest occupied π orbital of the product. Since in the case of cyclobutenes the HOMO of the product (i.e., a butadiene) in the thermal reaction is

ψ_2 therefore, the cyclobutene must open so that on one side the positive lobe lies above the plane, while on the other side it is below it. This process also forces the stereochemistry in the product from a substituted cyclobutene (Scheme 17.2.2.1).



(Scheme 17.2.2.1)

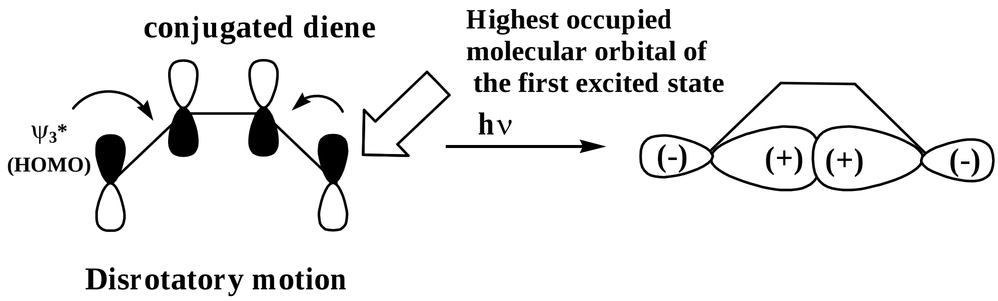
Trans-3, 4-dimethylcyclobutene can undergo conrotatory ring opening which could in principle give two products (Scheme 17.2.2.2) depending on the sense of conrotation. When however, both methyl groups turn inwords a severe steric crowding would result in the formation of cis-cis-dimethyldiene. This process will raise the activation energy compared with the process of formation of trans, trans-isomer. As a result only the trans, trans-isomer is formed.



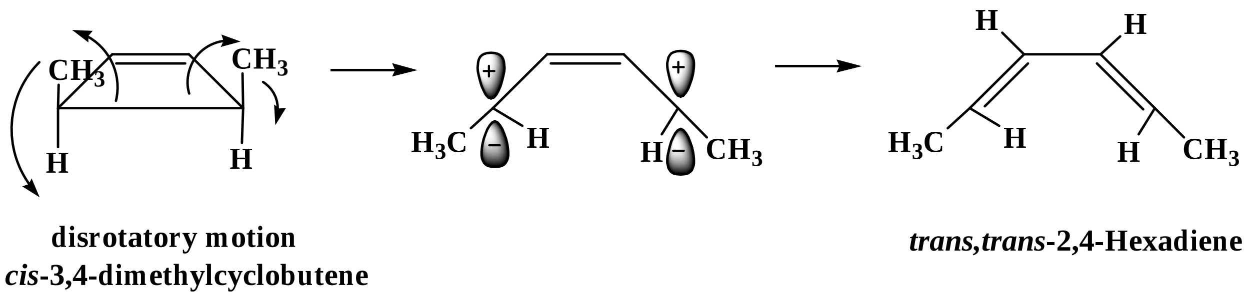
(Scheme 17.2.2.2)

17.2.3. PHOTOCHEMICAL INTERCONVERSION OF 3,4-DIMETHYLCYCLO- -BUTENE AND 2,4-HEXADIENE

This photochemical interconversion tends to lie over in favor of the cyclobutene. The irradiation of the diene will lead to the promotion of an electron into the orbital of next higher energy level i.e., ψ_3 and consequently the HOMO to be considered now is ψ_3 (see, Scheme 17.1.1). It is now the disrotatory motion, which results in bonding situation (Scheme 17.2.3.1). Similarly, the reverse reaction also involves a disrotatory motion, which establishes the stereochemistry on suitably substituted substrates (Scheme 17.2.3.2).



(Scheme 17.2.3.1)

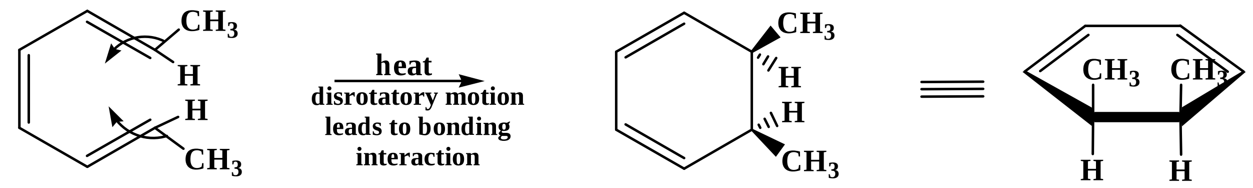


(Scheme 17.2.3.2)

The stereochemical outcome of these reactions thus depends on the relative phase of the lobes at the terminal carbon atoms of the molecular orbitals of these systems (see, Scheme 17.1.1). Two such terminal lobes with the same phase (in the HOMO after irradiation, ψ_3 of the diene with 4π electrons) require disrotatory movement for bond making/bond-breaking process. On the other hand two terminal lobes with opposite phases (as in the HOMO ψ_2 of the diene with 4π electrons) have to undergo conrotatory movement for bond-making / bond-breaking process.

17.2.4. OPENING OF A 1,3-CYCLOHEXADIENE AND RING CLOSURE

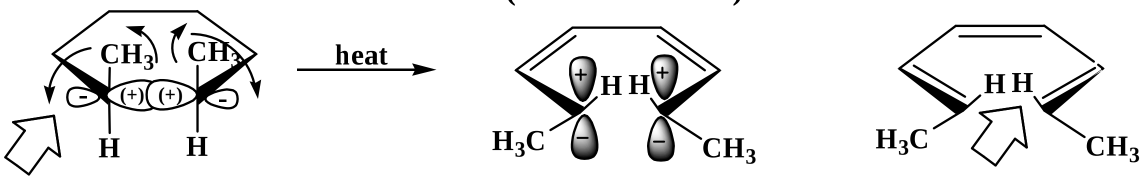
The HOMO for the ground state of a hexatriene is ψ_3 and when compared with the HOMO of the ground state of butadiene i.e., ψ_2 one finds that the relative symmetry about the terminal carbons is opposite (see, (Scheme 17.2.4.1 and 17.2.4.2). Thus unlike the thermal opening of a 1, 3-cyclo-hexadiene and likewise the ring closure requires a disrotatory motion. Based on these arguments trans, cis, trans -2, 4, 3-octatriene gives specifically cis-5, 6-dimethyl-cyclohexadiene (Scheme 17.2.4.1). Similarly, for the reverse reaction, since the positive lobes must lie on the same side of the plane (consider ψ_3 i.e., HOMO of a triene) a disrotatory motion has to occur (Scheme 17.2).



trans,cis,trans-**2,4,6-Octatriene**

cis-**5,6-dimethyl 1,3-cyclohexadiene**

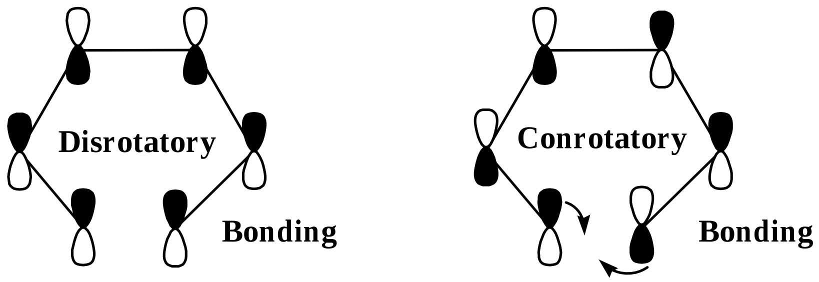
(Scheme 17.2.4.1)



cis-**5,6-dimethyl 1,3-cyclohexadiene** ***disrotatory motion*** ***trans,cis,trans***-**2,4,6-Octatriene**

(Scheme 17.2.4.2)

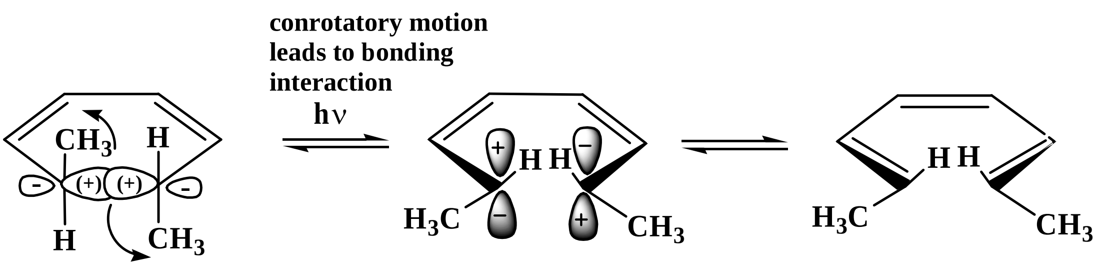
In the excited state of hexatriene ψ_4 is the HOMO (irradiation results in the promotion of an electron into the orbital of the next higher energy level). Therefore, the photochemical opening of a 1,3-cyclohexadiene, and likewise, the ring closure require conrotatory motion (Scheme 17.2.4.3). Thus e.g., the ring cleavage of trans-5, 6-dimethyl-1,3-cyclohexadiene proceeds as shown (Scheme 17.2.4.4)



The HOMO for the ground state of the hexatriene is ψ_3

In the excited state of the hexatriene, ψ_4 is the HOMO

(Scheme 17.2.4.3)



trans-**5,6-dimethyl 1,3-cyclohexadiene** ***trans,cis,trans***-**2,4,6-Octatriene**

(Scheme 17.2.4.4)

17.3. GENERALISED WOODWARD-HOFFMANN RULE

The above observations lead to the prediction that the reacting π-systems with a total number of 4q + 2 electrons (2, 6.10 etc) undergo thermal (s,s) cycloaddition while those with 4q electrons (4.8 etc.) undergo thermal (s,a) and photochemical (s,s) cycloaddition. They conform to the generalized Woodward-Hoffmann rule which states that a ground state pericyclic change is symmetry allowed (and so facile) when the total number of $(4n+3)_s$ and $(4n)_a$ components (say, X and Y respectively) is odd. Thus in the cycloaddition of butadiene and ethylene, ethylene serves as the $(4n+2)_s$ component and butadiene as the $(4n)_s$ component, i.e., X=1 and Y=0 making the total odd and the thermal ground state addition is symmetry allowed. A few relevant points emerge from the above discussion:

(i) For a two component cycloaddition, the maximum number of modes of addition is 2^2 (for n components, it is 2^n): (s,s),(s,a),(a,s), and (a,a).

(ii) Only in the (s,s) mode of addition, the two π-systems approach in parallel planes. In all other modes of addition, the components approach orthogonally.

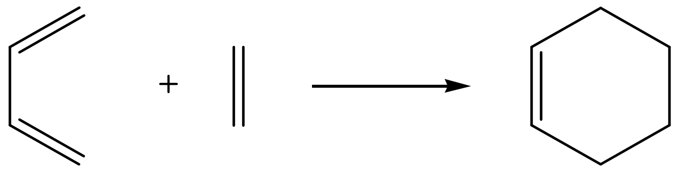
(iii) Configuration of groups at the two termini of a suprafacial component is retained while that on an antarafacial component is inverted.

(iv) For either m or n greater than 2, there are two modes of (s,s)-additions, the substitution pattern permitting, one giving endo product and the other giving exo product (to be illustrated later).

(v) The $[\pi 4_s+\pi 2_s]$ addition is most facile closely followed by $[\pi 4_a+\pi 2_a]$ addition.

17.4. CYCLOADDITION REACTIONS: CORRELATION DIAGRAM AND FRONTIER MOLECULAR ORBITAL METHOD

The most familiar example of a cycloaddition reaction is the Diels-Alder reaction which involves the formation of a cyclic compound from an alkene and a diene.

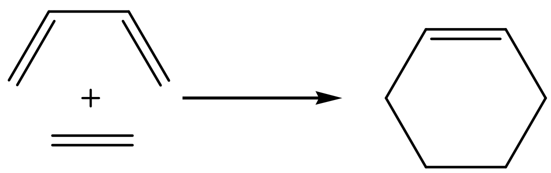


These reactions consist in the addition of a system of m π electrons to a system of n π electrons thereby forming a cyclic product. They offer a versatile route to the synthesis of cyclic compounds with a high degree of stereo-selectivity under thermal and photochemical conditions. Depending upon the number of π electrons participating in the process, these reactions are termed (m+n) or (m+n+.....) cycloaddition reactions.

1.

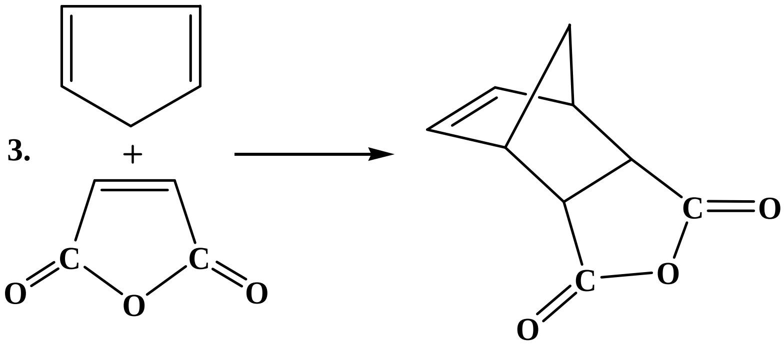
2+2 Cycloaddition

2.



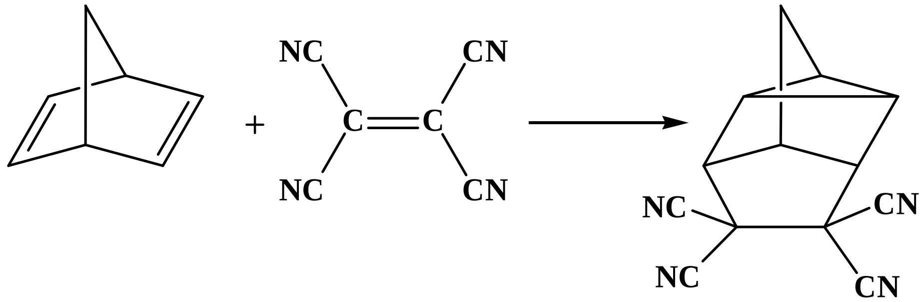
2+4 Cycloaddition

3.



2+4 Cycloaddition

4.



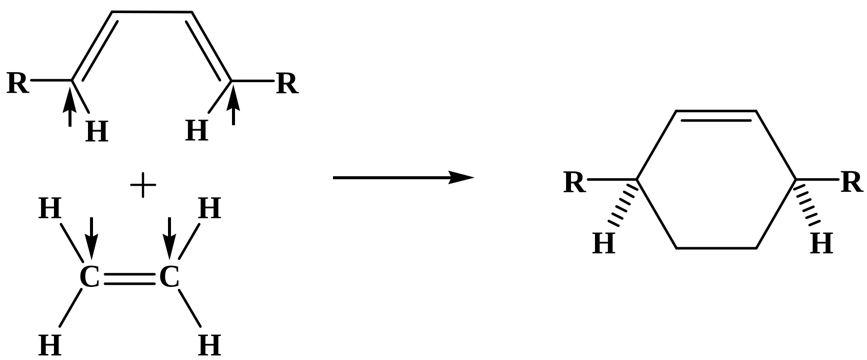
2+2+2
Cycloaddition

17.5. STEREOCHEMICAL MODES OF CYCLOADDITION: SUPRAFACIAL AND ANTARAFACIAL PROCESSES

Since in a typical cycloaddition reaction, there is addition of two systems containing double bonds, it is logical to expect the addition to occur on the same or the opposite side of the system. Furthermore, as both the π systems are undergoing addition, it is necessary to specify these modes of addition on each of them. These different modes have been termed *suprafacial* (on the same side) and *antarafacial* (on the opposite side).

suprafacial **antarafacial**

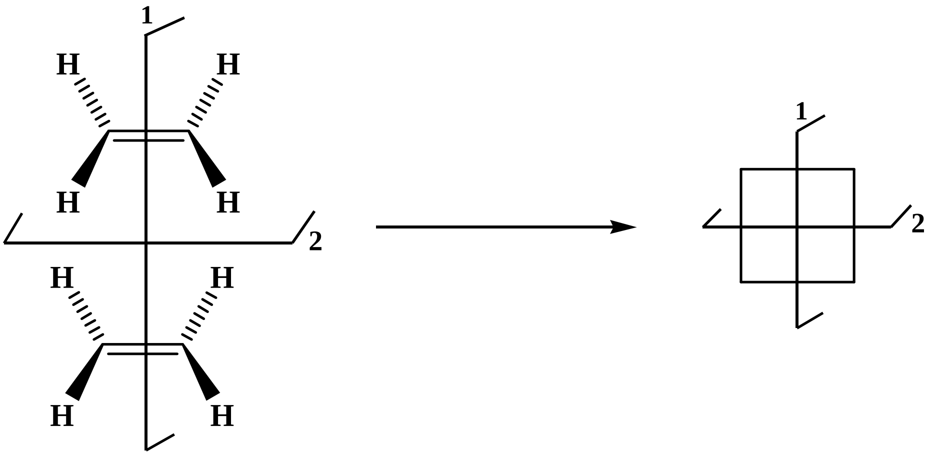
This specification is usually made by placing a suitable subscript (s or a) after the number referring to the pi component. The Diels-Alder reaction may be considered as a process involving 2s+4s cycloaddition.



(2s + 4s)

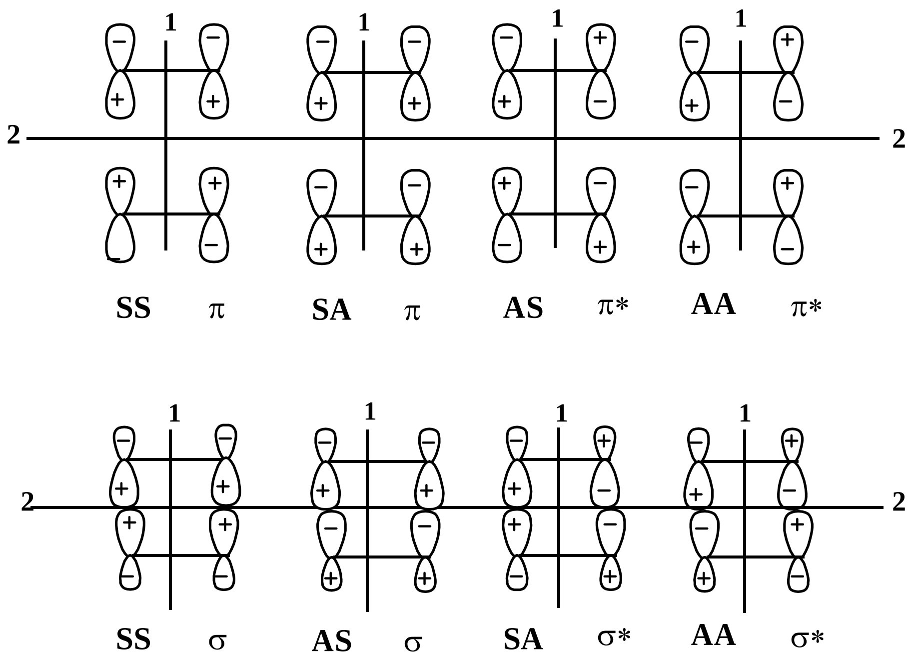
17.6. ORBITAL SYMMETRY IN CYCLOADDITION REACTION: CORRELATION DIAGRAMS

To illustrate the control of orbital symmetry on cycloaddition reactions, we choose the simplest example in which the two ethylene molecules approach each other vertically (2s+2s) to



form a molecule of cyclobutane. Such a system has vertical and horizontal planes of symmetry which shall be referred to as 1 and 2, respectively.

In the above transformation we are mainly concerned with the four π orbitals of the two ethylene molecules and the four σ orbitals of cyclobutane.

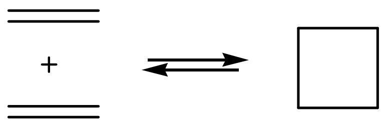


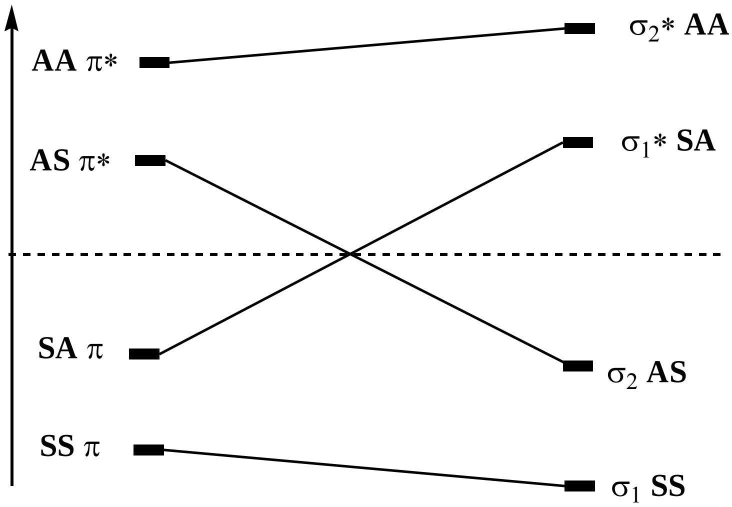
Symmetry properties of interacting ethylene π orbitals and cyclobutane σ orbitals

Fig. 1

The symmetry properties of the remaining orbitals remain unchanged during the reaction and need not be considered further. The shapes and symmetry properties of these four π orbitals (π,π bonding; π*,π* antibonding) and four σ orbitals (σ,σ bonding; σ*,σ* antibonding) are listed in Fig. 1. The symmetry classifications (SS, SA, AS and AA) are with respect firstly to plane of symmetry 1 and then to 2.

On the basis of the above information, a correlation diagram (Fig. 2) may be drawn in which the levels of like symmetry are connected by lines.





Correlation diagram for cycloaddition and cycloreversion of ethylene-cyclobutane system

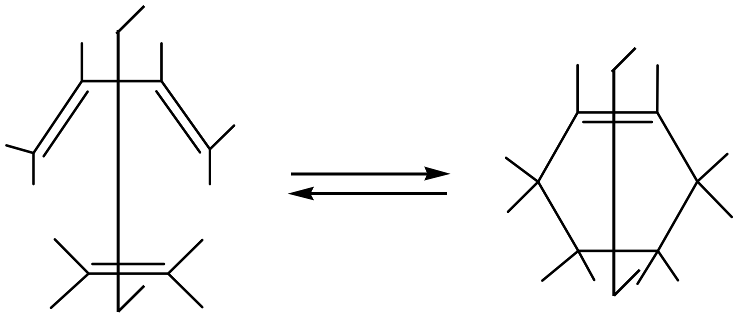
Fig. 2

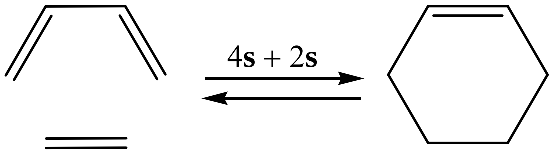
A close examination of the diagram leads us to the following two conclusions:

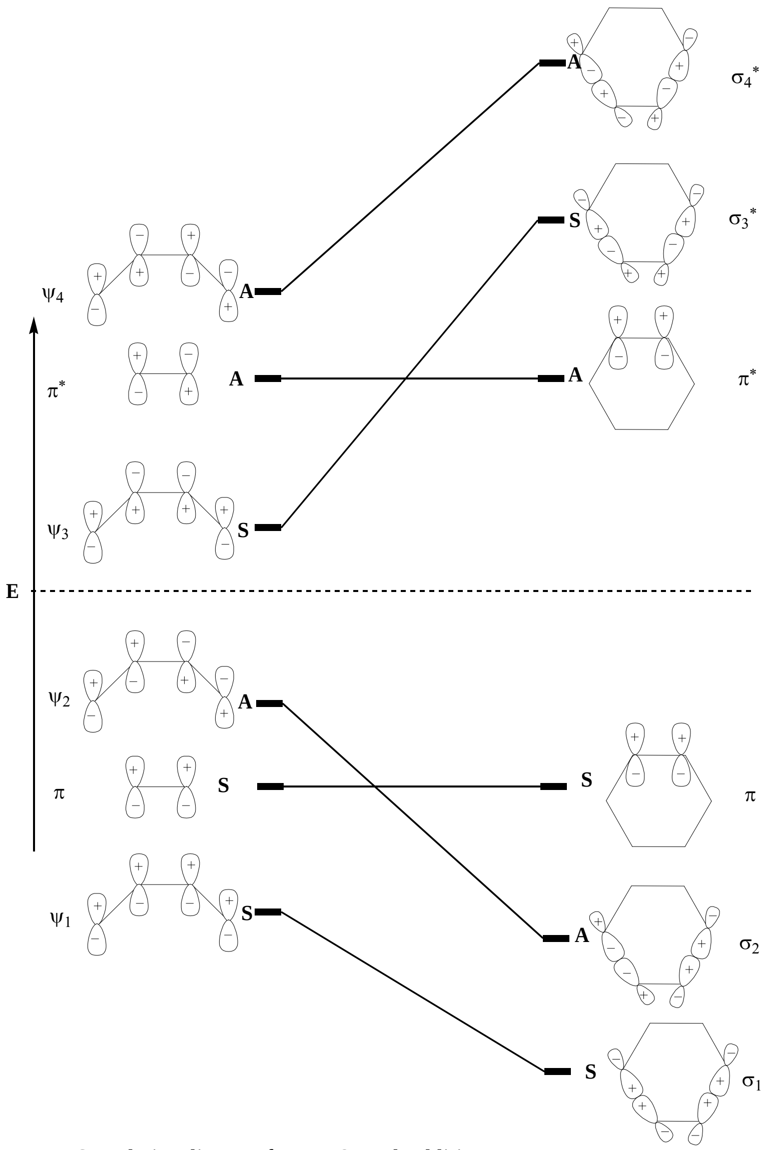
A. The ground state orbitals of ethylene correlate with an excited state of cyclobutane, $\pi^2\pi^2 \rightleftharpoons \sigma_1{}^2\sigma_1{}^{*2}$. Consequently, the combination of two ground state ethylene molecules cannot result in the formation of ground state cyclobutane while conserving the orbital symmetry. Hence the thermal process is *symmetry-forbidden*.

B. As there is correlation between the first excited state of the ethylene system and cyclobutane, $\pi^2\pi\pi^* \rightleftharpoons \sigma_1{}^2\sigma_2\sigma_1{}^*$, the photochemical process is *symmetry-allowed*.

A similar correlation diagram may be constructed for the Diels-Alder reaction which is a 4s+2s cycloaddition reaction. In this case there is only a single vertical plane of symmetry bisecting the carbon framework of two reactants and the product.







Correlation diagram for 4s + 2s cycloaddition (Diels-Alder reaction) and the reverse process

Fig. 3

In this transformation, we have to consider six orbitals each of the reactants and the product. The ground state orbitals of the reactants are $\psi_1\psi_2$ (of butadiene) and π (of ethylene) while ψ_3, π^* and ψ_4 are the corresponding antibonding orbitals. Similarly, the ground state orbitals of cyclohexene are represented by σ_1, σ_2 and π; the remaining three orbitals are antibonding. All these orbitals along with their symmetry properties are shown in the correlation diagram (Fig. 3).

It becomes immediately clear from an inspection of the above diagram that there is a smooth transformation of the reactant orbitals into the product orbitals.

$$\psi_1{}^2\pi^2\psi_2{}^2 \longrightarrow \sigma_1{}^2\sigma_2{}^2\pi^2$$

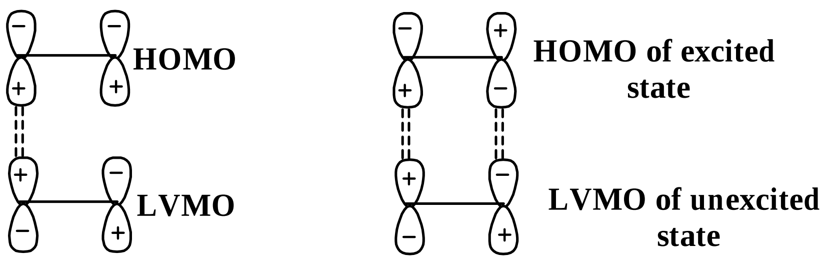
The Diels-alder reaction (4s+2s cycloaddition) is, therefore, a thermally allowed process. On the other hand, photochemical transformation is not possible as the first excited state of the reactant does not correlate with the first excited state of the product. Rather it correlates with the upper excited state of the product.

$$\psi_1{}^2\pi^2\psi_2\psi_3 \not\longrightarrow \sigma_1{}^2\sigma_2{}^2\pi\sigma_3{}^*$$

Hence there is a symmetry-imposed barrier to photochemical reaction of (4s+2s) type.

17.7. FRONTIER MOLECULAR ORBITAL (FMO) METHOD

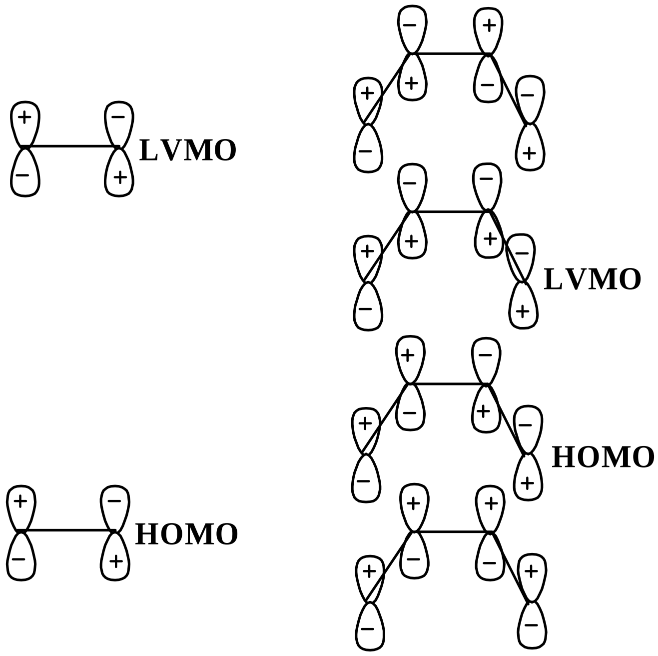
An alternative approach to determine whether or not a cycloaddition reaction is allowed depends upon the symmetry properties of the highest occupied molecular orbital (HOMO) of one reactant and the lowest vacant molecular orbital (LVMO) of the other. A favorable interaction is possible only when the signs of the coefficients of HOMO and LVMO are the same. In the 2s+2s cycloaddition of ethylene to form cyclobutane, lobes of HOMO in one molecule and that of LVMO in the other do not have corresponding signs and hence the reaction is thermally forbidden. Irradiation of ethylene, however, promotes an electron to the antibonding orbital which now becomes HOMO and corresponds with the LVMO of the second unexcited ethylene molecule. As expected, the combination now proceeds smoothly.



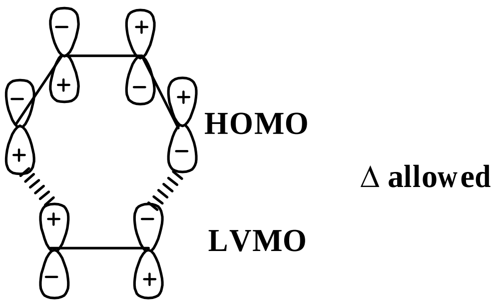
Ground state **(Δ forbidden)**

Excited state **(hν allowed)**

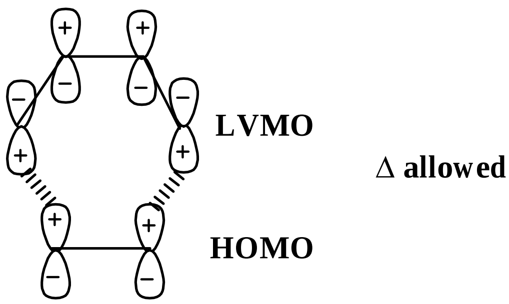
The Diels-Alder reaction may also be analyzed by a similar consideration of the molecular orbitals of ethylene and butadiene.



Since signs of the 1.4-lobes of butadiene HOMO match those in the LVMO of ethylene, the addition is thermally allowed.

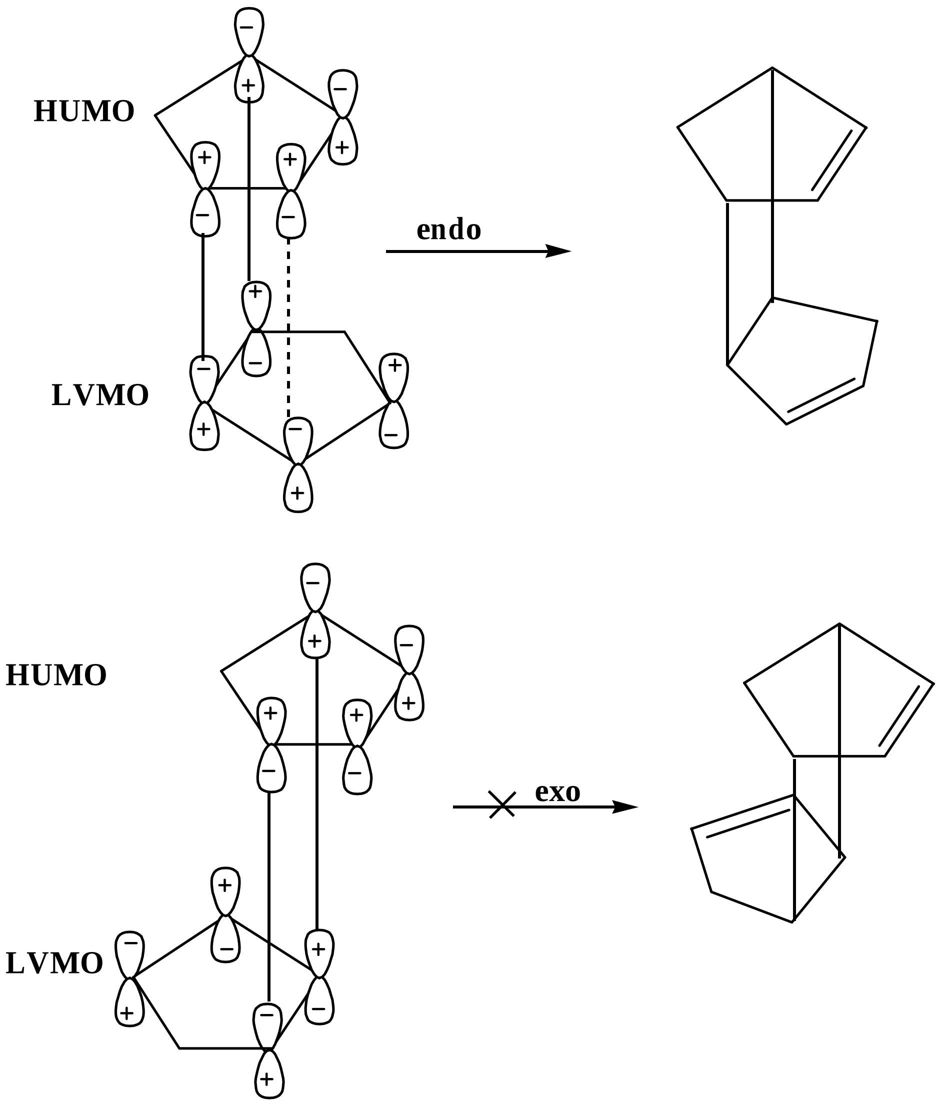


We reach a similar conclusion by considering the signs of butadiene LVMO and HOMO of ethylene.



No such correspondence is obtained by the irradiation of the reactants and consequently the Diels-Alder reaction is a photochemically forbidden process.

An interesting example of the role of frontier orbitals in determining the product is the Diels-Alder reaction of Cyclopentadiene forming dicyclopentadiene. Invariably, the endo dimer is formed rather that the exo. This is due to the favorable secondary forces as a result of interaction of frontier orbitals of diene and dienophile components which lower the energy of the transition state. In the following figure (Fig.4) orbitals involved in actual bonding are connected by broken lines. An inspection of the transition states reveals that these interactions are present in the endo transition state while they are absent in the exo. Thus, the endo transition state for this reaction is stabilized vis-a-vis the exo and, therefore, the endo attack should be favored. However, in some cases steric factors may be of a greater magnitude than this effect.

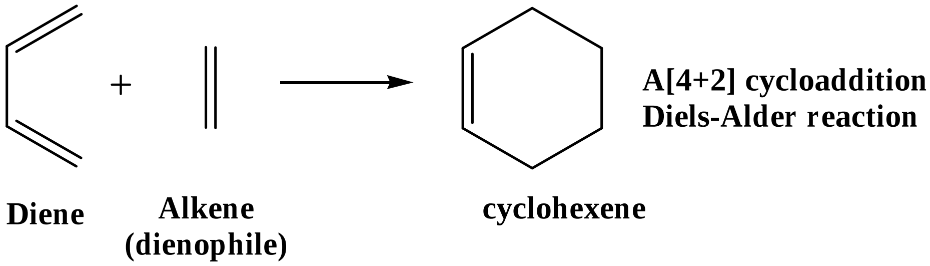


Orbital interaction in Diels-Alder reaction of Cyclopentadiene

Fig.4

17.8. CYCLOADDITIONS

The reactions of alkenes (the dienophiles) and polyenes (conjugated dienes) in which two molecules react to form a cyclic product, with π electrons being used to form two new σ bonds are called cycloaddition reactions. These reactions are classified on the basis of π electrons involves, in each component, the [4+2] cycloaddition being the well known Diels-Alder reaction (Scheme 17.8.1).

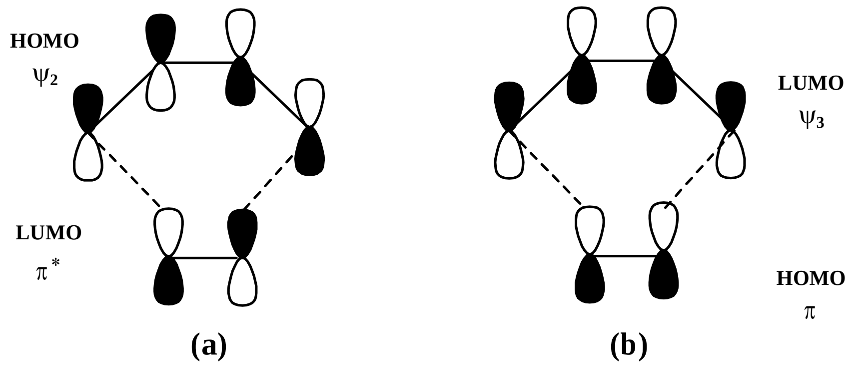


(Scheme 17.8.1)

17.8.1. DIELS-ALDER REACTIONS

These are concerted, thermal [4+2] cycloadditions. A cycloaddition reaction requires only heat or light for initiation, radical and ionic intermediates are not involved. A consideration of orbital interactions (two combinations) accounts for this (Scheme 17.8.1.1), i.e., the overlap can take place between the HOMO of one component and the LUMO of the other and vice versa. In either case, the overlap brings together lobes of the same phase. When in the dienophile there is conjugation to a group of –M type e.g., carbonyl, nitro etc.,. The reaction occurs under milder conditions and gives good yields. The substituent lowers the energy of the LUMO of the dienophile so as to bring it closer in energy to the HOMO of the diene. Consequently the bonding interactions in the transition in the transition state increases. As expected, the reactivity is also increased by an electron releasing group in the diene (Scheme 17.8.1.2). Conversely, when the diene contains an electron-withdrawing substituent the dienophile requires an electron-releasing substituent for ready reaction. In this situation the interaction is between diene's LUMO and thedienophile's HOMO.

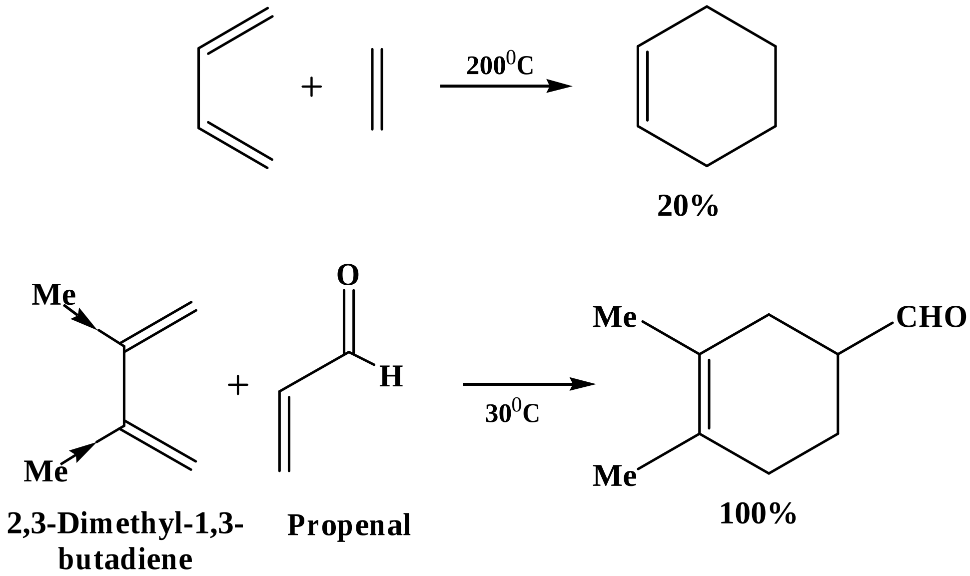
[π 4s+ π 2s] cycloaddition



Symmetry-allowed thermal [4+2] cycloaddition: 1,3-butadiene and ethylene Overlap of (a) the HOMO of 1,3-butadiene and the LUMO of ethylene, and (b) the HOMO of ethylene and the LUMO of 1,3-butadiene.

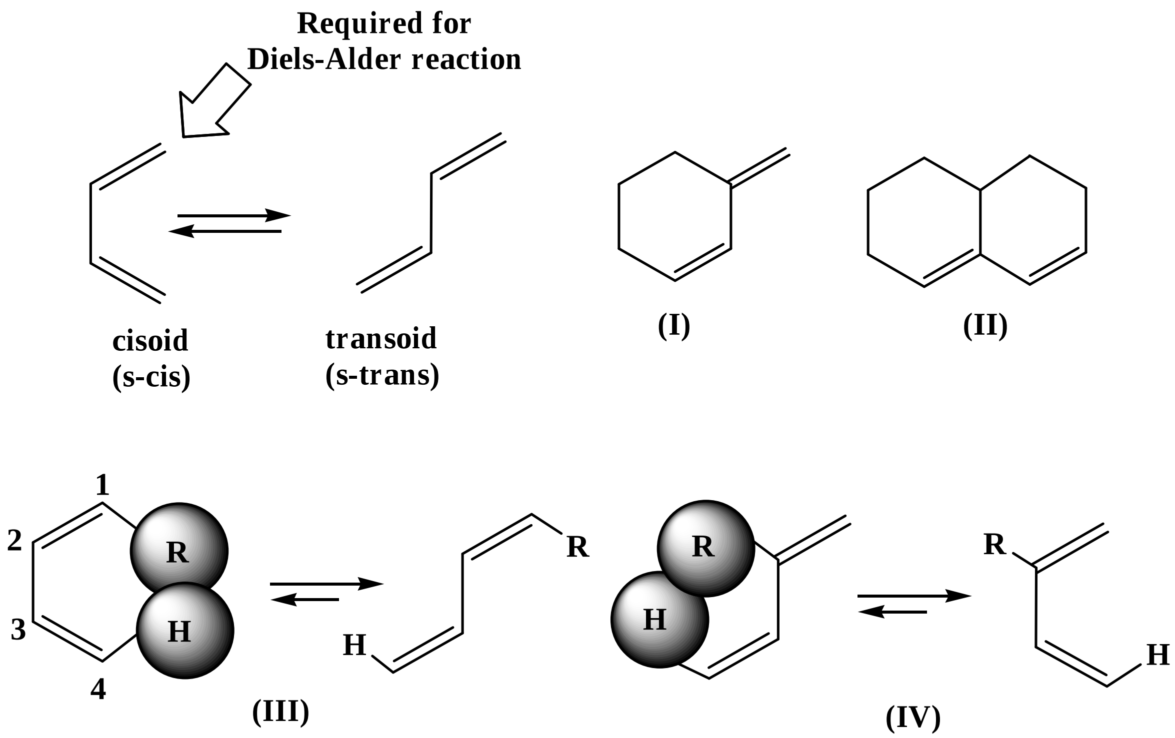
(Scheme 17.8.1.1)

Thus, the bonding at the transition state is more effective when the HOMO of one reactant and the LUMO of other are more closely matched in energy.



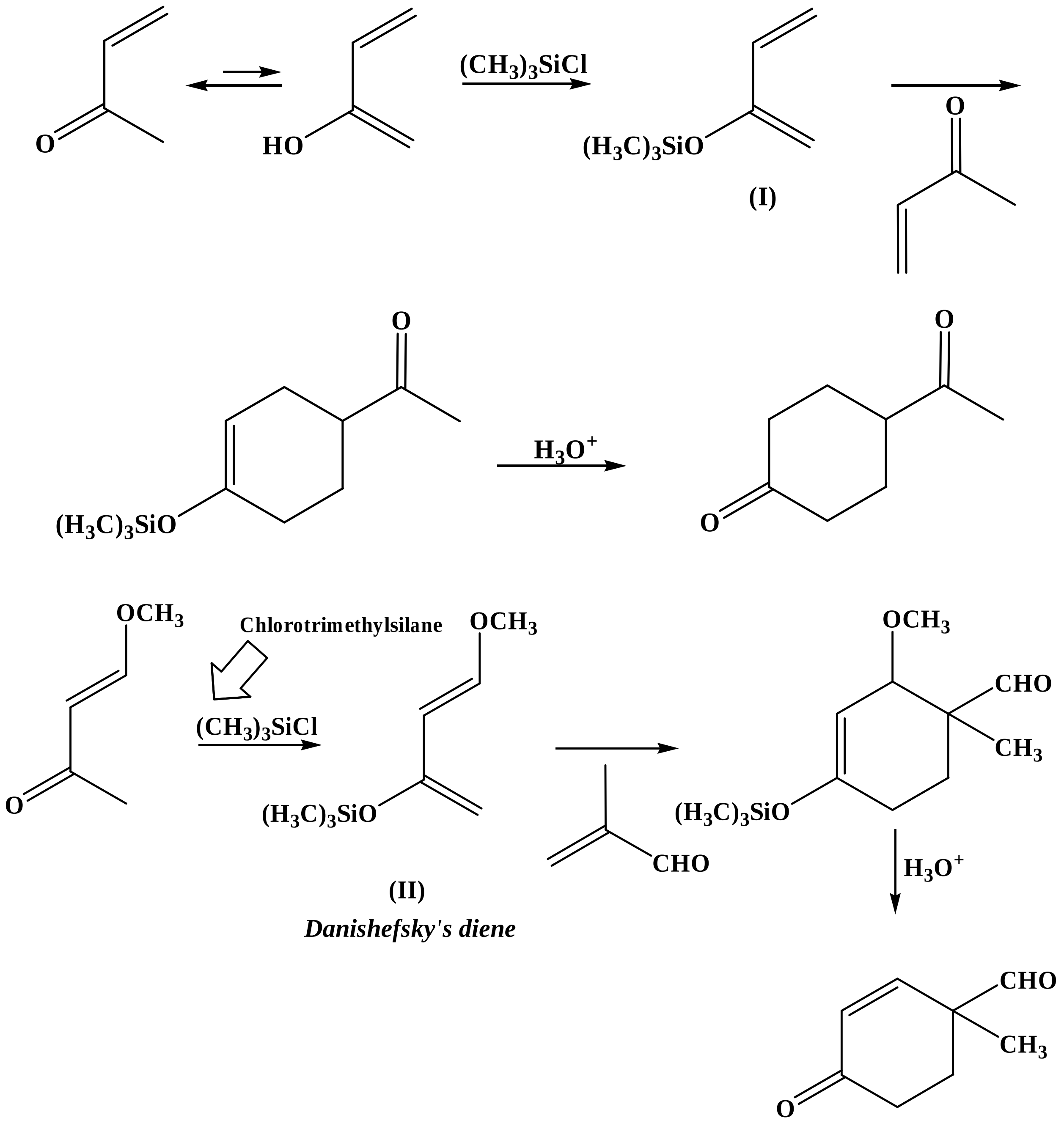
(Scheme 17.8.1.2)

As correctly shown (Scheme 17.8.1) the diene reacts in the s-cis conformation, which allows the ends of the conjugated system to reach the doubly bonded carbons of the dienophile. That the s-cis –geometry of the diene is essential is shown by the unreactive nature of the fixed transoid dienes (I and II, Scheme 17.8.1.3). Moreover, as expected the substituents in the dienes may also affect the cycloaddition sterically. The substituents affect the equilibrium proportion of the diene in the required cisoid form (Scheme 17.8.1.3).Consequently Z alkyl or aryl substituents in the 1-position (III, Scheme 17.8.1.3) of the diene slow down the reaction by sterically hindering formation of the hindering formation of the cisoid conformation, while bulky 2-substituents (IV, Scheme 17.8.1.3) make it fast.

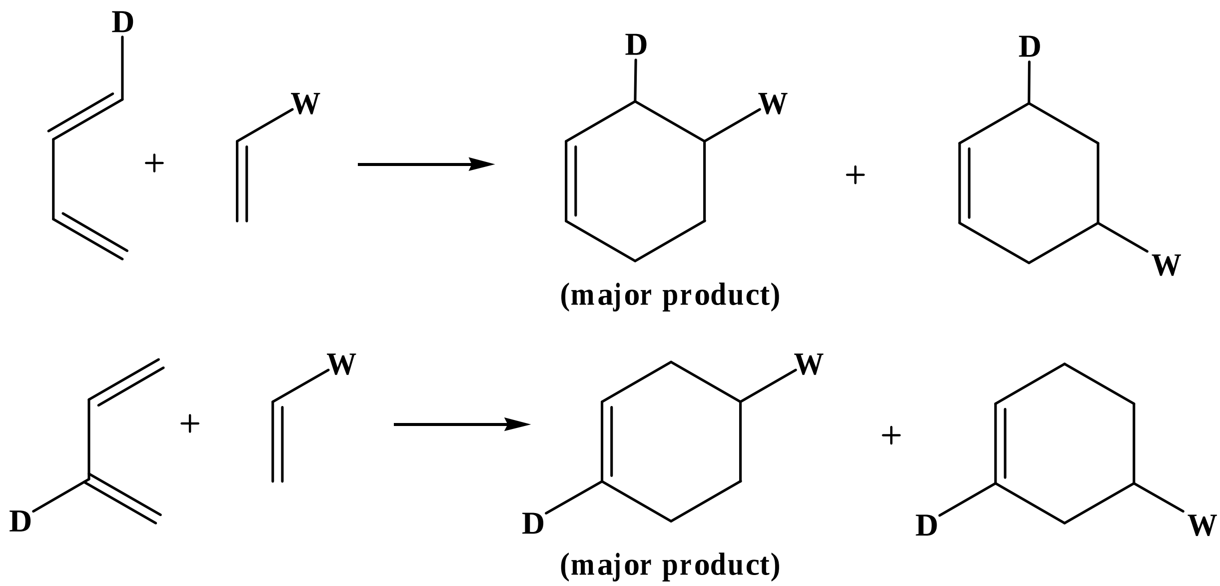


(Scheme 17.8.1.3)

Among the useful dienes used in Diels-Alder reaction mention may be made of derivatives of hydroxybutadienes. 2-Trimethylsilyloxy-butadiene (I, Scheme 17.8.1.4) react easily with dienophiles to give adducts which are enol ethers and these are readily hydrolysed to cyclohexanone derivatives. In a modification Danishefsky's diene (II, Scheme 17.8.1.4) is used to enable the formation of σ,β-unsaturated compounds. In these examples both the diene and the dienophile are unsymmetrical and one expects (see, Scheme 17.8.1.5) regioisomers, however, here the regioselectivity is marked.

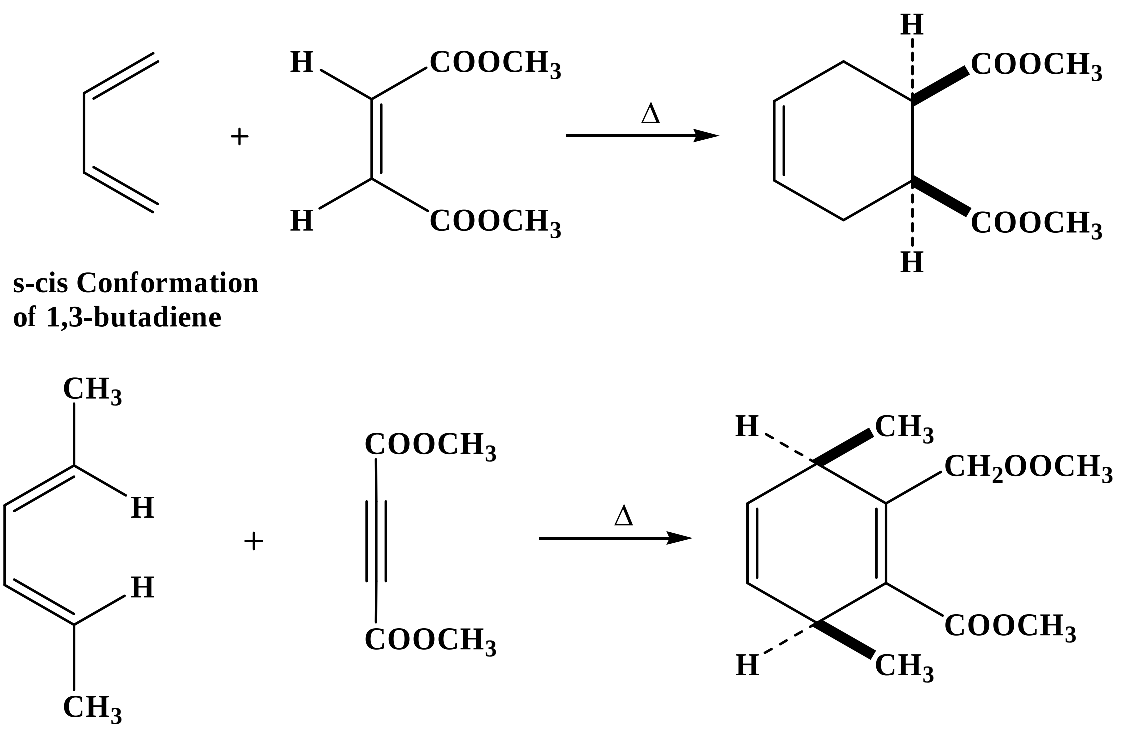


(Scheme 17.8.1.4)



(Scheme 17.8.1.5)

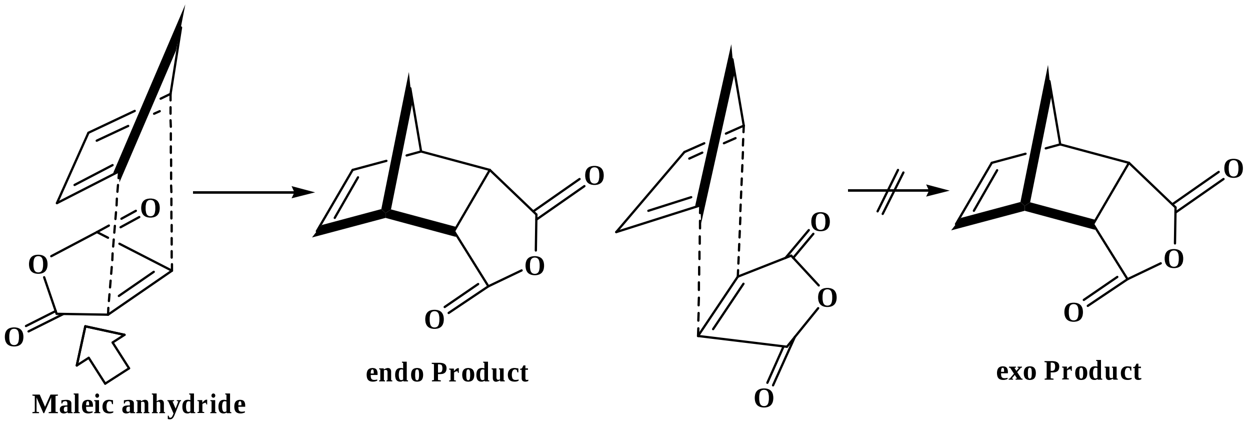
That the Diels-Alder reaction is concerted (both the new bonds are formed in the same transition state is shown by the fact, that it proceeds with retention of configuration of both the diene and the dienophile (Scheme 17.8.1.6) i.e., it proceeds stereoselectively *syn* with respect to both the diene and the dienophile as expected of a concerted (supra, supra) mode of addition.



Diels-Alder reaction is a syn addition with respect to both the diene and the dienophile

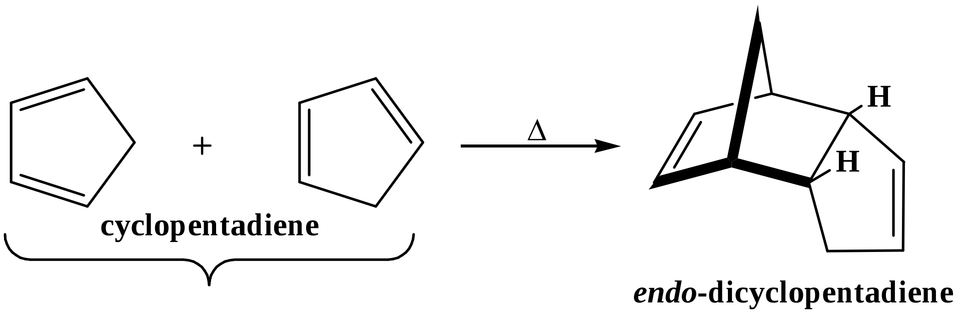
(Scheme 17.8.1.6)

The Diels-Alder reaction takes place generally to give the stable *endo* adduct as the major product. For the *endo* addition e.g., with Cyclopentadiene and maleic anhydride (Scheme 17.8.7), the transition state can be stabilized (speeding up the reaction) through secondary interactions.



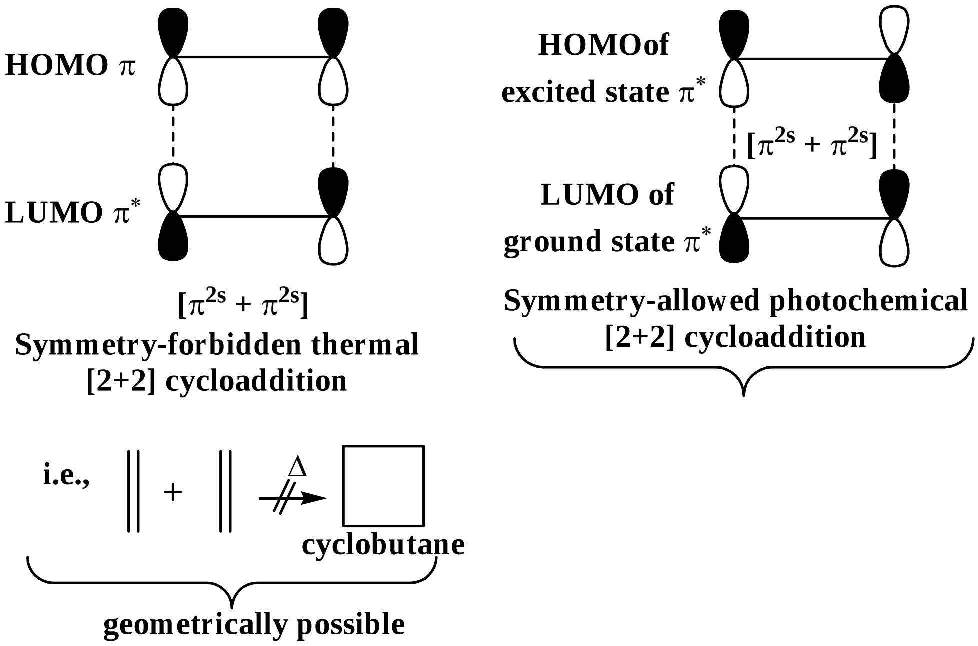
(Scheme 17.8.1.7)

These interactions involve the lobes of HOMO and LUMO of the same phase which themselves are not involved directly in the formation of bonds. One sees that for the endo addition the π system lies more completely over the other. These secondary interactions are not possible in the transition state for *exo* addition since the relevant set of centers in the diene and the dienophile are not too far apart, from each other. Attempted preparation of 1,3-cyclopentadiene by base catalysed loss of HBr from 3-bromocyclopentene (E2 elimination) instead gives the endo-Diels-Alder dimer (Scheme 17.8.1.8), by self condensation of the initially formed 1,3-cyclopentadiene as the major product. At high temperature, the Diels-Alder reaction reverse and the low boiling Cyclopentadiene can be collected and kept at low temperature.



(Scheme 17.8.1.8)

An interesting compound triptycene can be prepared by a Diels-Alder reaction between benzyne and anthracene (see, Scheme 17.8.1.9). From among pyrrole, furan and thiophene only furan undergoes a Diels-Alder reaction. The more stabilized aromatic thiophene, is inert. Pyrrole does react with maleic anhydride, but not in Diels-Alder manner.

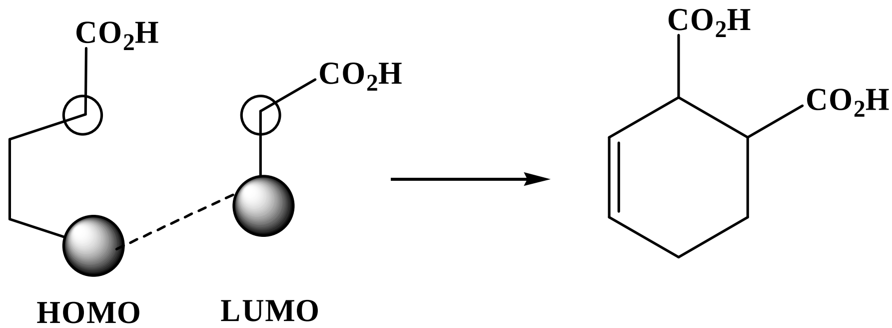


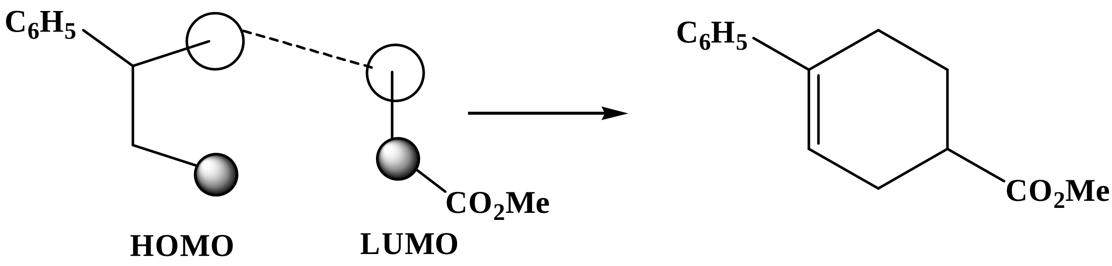
(Scheme 17.8.1.9)

Cycloaddition of an unsymmetrically substituted diene and an unsymmetrically substituted dienophile can lead to regioisomers (Scheme 17.8.1.5).

One has already seen that in a normal Diels-Alder reaction i.e., between an electron rich diene and electron-deficient dienophile, the main interaction is between the HOMO of the diene and LUMO of the dienophile (In this situation these orbitals are more closely matched in energy, the better is the overlap and thus the reaction occurs more readily). However, the orientation of the product from an unsymmetrical diene and an unsymmetrical dienophile depends mostly on the atomic orbital coefficients at the reacting termini. The atoms with the larger terminal coefficients on each reactant, bond preferentially in the transition state, because of better orbital overlap. Consequently with 1-substituted butadienes the major product is 1,2 ("*ortho*") adduct while with 2-substituted butadienes, the major adduct is 1,4 ("*para*").

In the case of butadiene-1 carboxylic acid and acrylic acid the frontier orbitals are polarized as shown (Scheme 17.8.1.10). The size of the circles as shown is roughly proportional to the size of the coefficients and an allowed reaction leads to 1, 2-adduct. Similarly, now with 2-phenyl-butadiene and methyl acrylate the major product formed would be 1,4.



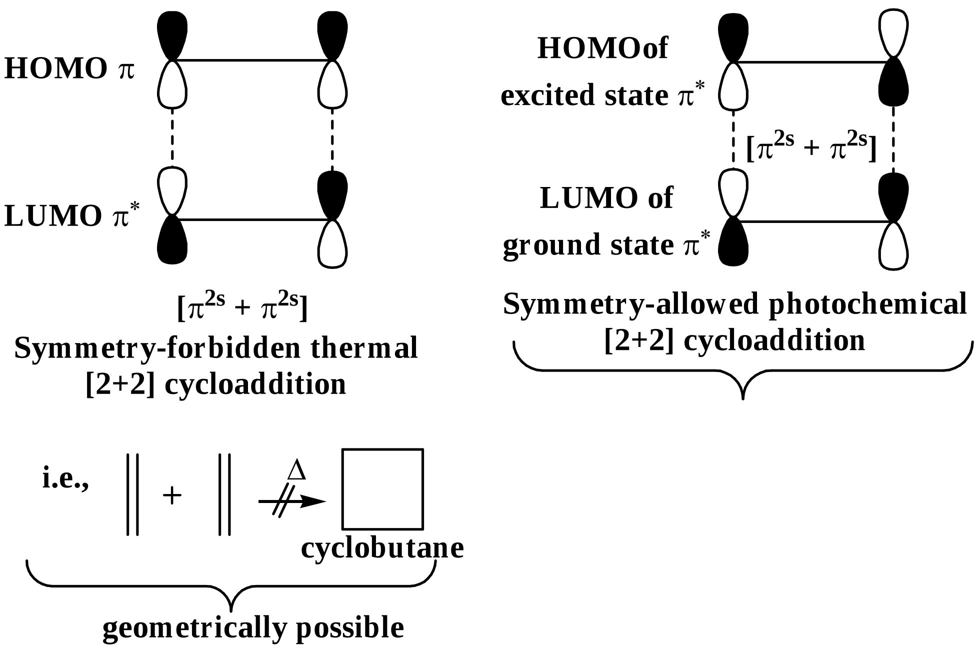


(Scheme 17.8.1.10)

Some Diels-Alder reactions are catalysed by Lewis acid catalysts. These catalysts form complexes with the polar groups on the dienophile which lower the energies of the frontier orbitals of the dienophile. Consequently, the energy difference between the HOMO of the diene and the LUMO of dienophile is reduced and the reaction becomes faster.

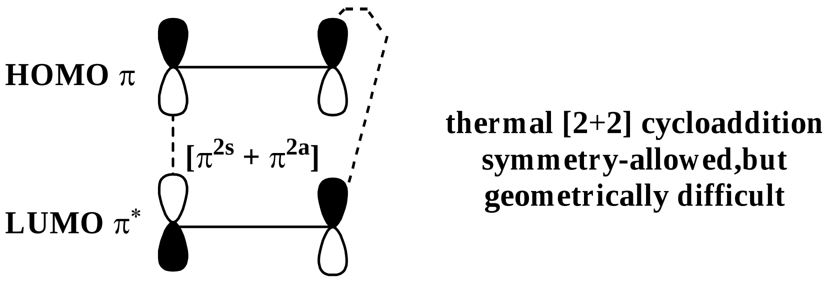
17.8.2. [2+2] CYCLOADDITIONS

In the dimerization of ethylene, a thermal [2+2] cyclization would involve overlap of HOMO, π of one molecule with the LUMO, π^* of the other (see Scheme 17.1). Now π and π^* are of opposite symmetry. If in this concerted reaction both bonds to a component are formed on the same face i.e., the process is suprafacial, the lobes of opposite phase would approach each other (Scheme 17.8.2.1). This interaction which is suprafacial with respect to both components (π^{2s} + π^{2s}) is therefore, antibonding and repulsive and the concerted reaction, does not take place (symmetry forbidden process).



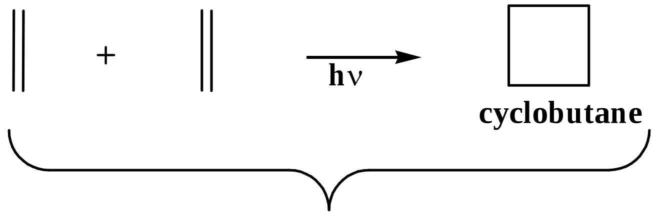
(Scheme 17.8.2.1)

The photochemical [2+2] cycloadditions which are suprafacial with respect to both the components (π^{2s} + π^{2s}) will, however, permit a previously forbidden reaction to become a symmetry allowed process. This is so, since here, one has the overlap of the HOMO π^* of an excited molecule with the LUMO (also π^*) of a ground state molecule (Scheme 17.8.2.1). The stereochemistry of the Diels-Alder reaction reveals that these are also π^{4s} + π^{2s} processes. However, a thermal [2+2] cycloaddition could occur provided it is suprafacial with respect to one component and antarafacial with respect to the other i.e., it is $\pi^{2s} + \pi^{2a}$ (Scheme 17.8.2.2). This process, though symmetry allowed is geometrically very difficult.



(Scheme 17.8.2.2)

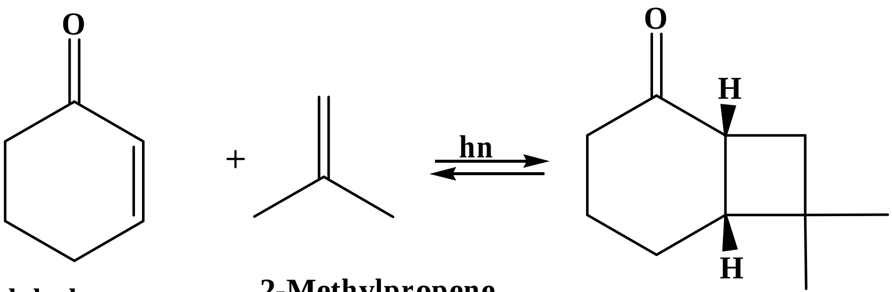
Thus the photochemical [2+2] cycloaddition reaction occurs smoothly and represents one of the best techniques to synthezise cyclobutane rings and cage compounds (Scheme 17.8.2.3).



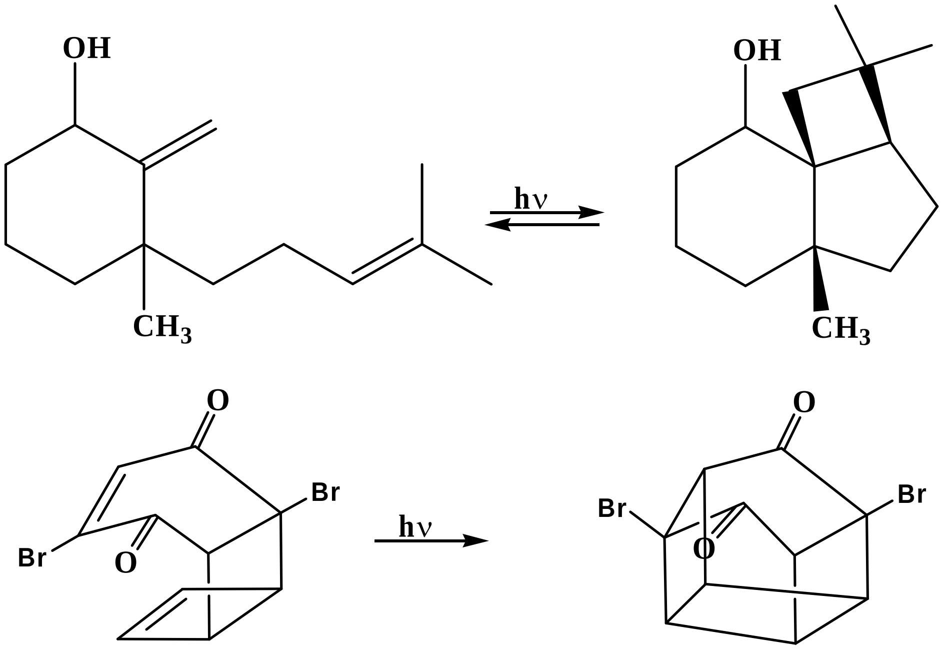
photochemical [2+2] cycloadditions

Cycloaddition Reactions Stereochemical Rules

Electron pairs (double bonds)	***Thermal reaction***	***Photochemical reaction***
Even number	**Antarafacial**	**Suprafacial**
Odd number	**Suprafacial**	**Antarafacial**

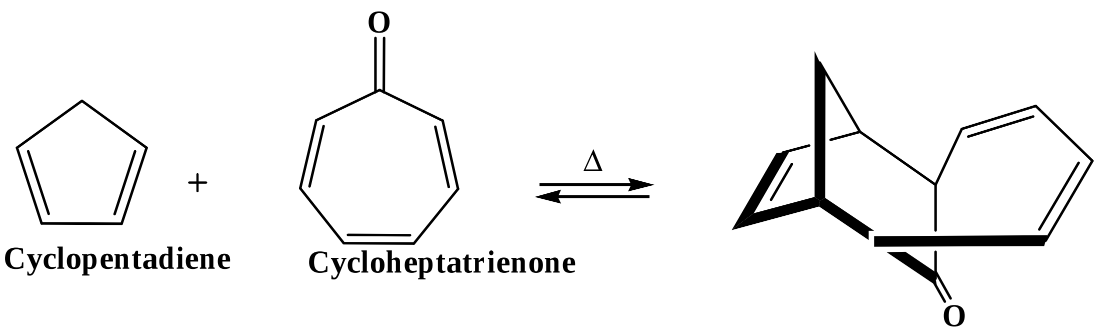


2-Cyclobuhexenone **2-Methylpropene**



(Scheme 17.8.2.3)

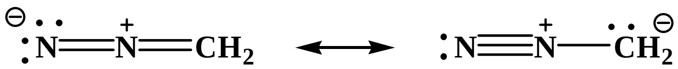
The reaction can occur inter-or intramolecularly (Scheme 17.8.2.3). Both thermal as well as photochemical cycloaddition reactions take place by opposite stereochemical pathways. As with electrocyclic reactions one can categorize cycloadditions according to the total number of electron pairs (double bonds) taking part in the rearrangement. Thus, a Diels-Alder [4+2] reaction between a diene and a dienophile involves an odd number (three) of electron pairs and takes place by a ground state suprafacial pathway. A [2+2] reaction between two alkenes involves an even number (two) of electron pairs and takes place by a ground-state suprafacial pathway. However, it may be impressed that both suprafacial and antarafacial cycloaddition pathways are symmetry allowed. Only the geometric constraints inherent in twisting a conjugated *pi* electron system out of planarity make antarafacial reaction geometrically difficult in most of the cases. As a last example of cycloaddition, Cyclopentadiene reacts with cycloheptatriene system to give a product-which is [6+4] suprafacial process (Scheme 17.8.2.4).



(Scheme 17.8.2.4)

17.9. 1, 3-DIPOLAR CYCLOADDITIONS

These cycloadditions are analogous to the Diels –Alder reaction in that they are concerted [$\pi^{4s} + \pi^{2s}$] reactions. The 1, 3- dipolar components are compounds whose representation requires ionic structures which include ones with charges on atoms bearing 1, 3-relationship, as in diazomethane (Scheme 17.9.1). These type of molecules which are called 1, 3-dipoles are isoelectronic with allyl anion. These have four π electrons and each has at least one charge separated resonance structure with opposite charges in a 1, 3 relationship. The other reactant (dipolarophile) in a dipolar cycloaddition has unsaturated bonds like, C = C, C ≡ C, C = O, C ≡N. The 1,3-dipolar cycloadditions form useful reactions for the synthesis of five membered heterocyclic rings.

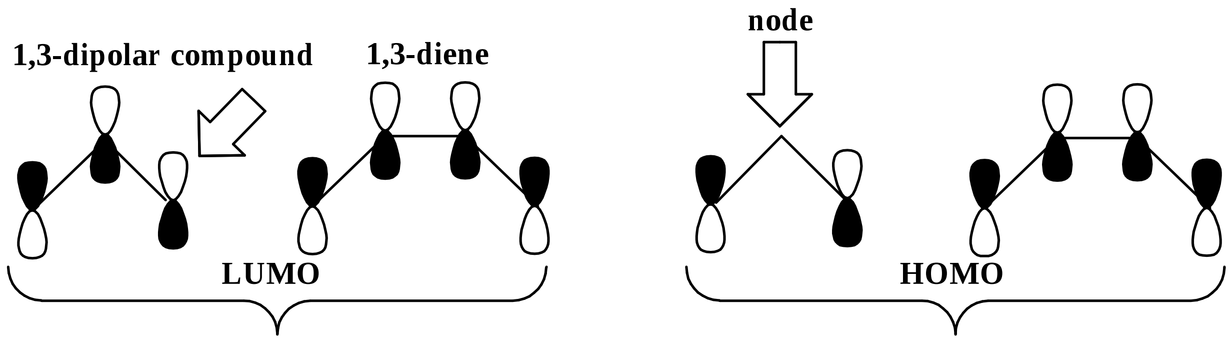


'1,3-dipolar' compound
diazomethane

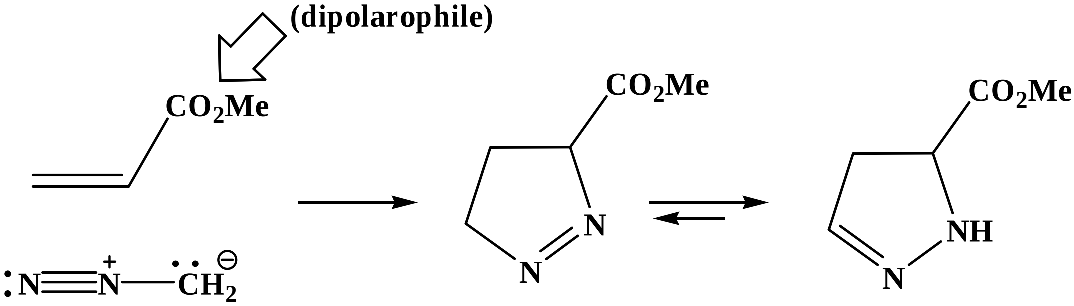
(Scheme 17.9.1)

Mechanistically the transition state for 1,3-dipolar cycloaddition is not high polar and the reaction rate is not strongly sensitive to solvent polarity. The loss of charge separation which is implied, is more apparent rather than real, since most 1,3-dipolar compounds are not highly polar. The polarity associated with a singly structure is balanced by other contributing structures.

A 1,3 –dipole represents a structural variant of the diene component in the Diels – Alder reaction; in the dipolar compound, four π-electrons are distributed over three atoms instead of the four in a diene. Moreover, the HOMO and LUMO of a 1, 3-dipole are similar in symmetry to that in a diene with respect to the two-fold axis and to the mirror plane which bisects the molecule (Scheme 17.9.2), a concerted cycloaddition e.g., to an alkene is a symmetry allowed process. The reaction of an alkene with diazomethane to give a pyrazoline (Scheme17.9.3 pyrazole derivative) belongs to this class.



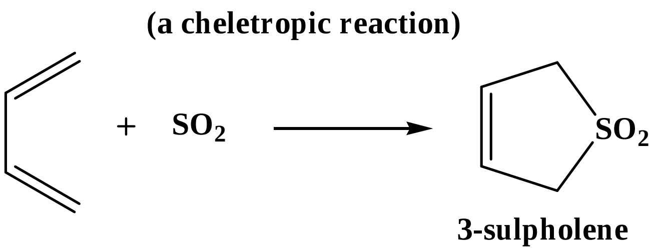
(Scheme 17.9.2)



(Scheme 17.9.3)

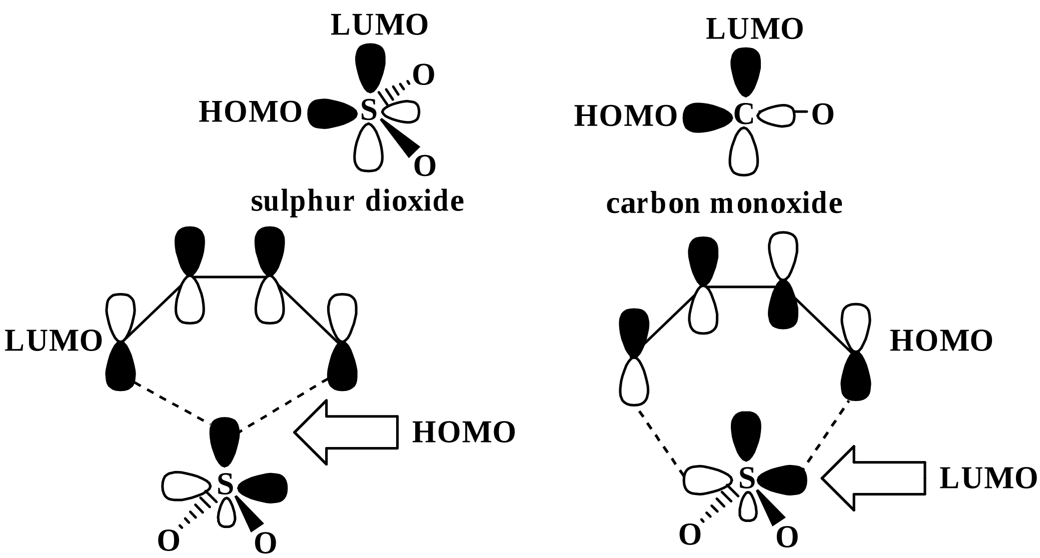
17.10. CHELETROPIC REACTIONS

In a cheletropic reaction two σ bonds that terminate at a single atom are made or broken during a concerted reaction (Scheme 17.10.1). In the case of molecules, sulfur dioxide or carbon monoxide the HOMO is that which has a lone pair of electrons in the plane having the atoms, while the LUMO represents the p orbital perpendicular to this plane (Scheme 17.10.2).



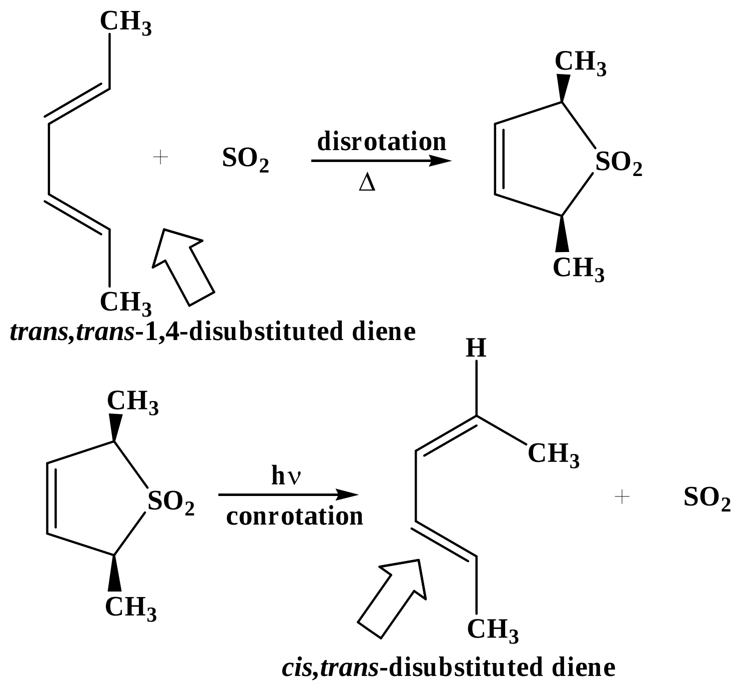
(Scheme 17.10.1)

For a symmetry allowed cycloaddition of e.g., SO_2 to a diene, the molecule of SO_2 must lie in a plane which bisects the *s-cis* conformation of the diene (Scheme 17.10.2). The interaction is suprafacial for diene and SO_2. In the transition state, the terminal carbon atoms of the diene must move in the disrotatory manner in order that the HOMO of SO_2 can interact with the LUMO of the diene, or the LUMO of SO_2 with the HOMO of the diene.



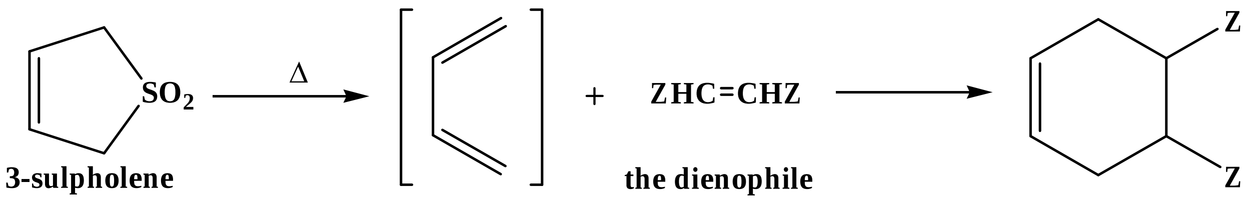
(Scheme 17.10.2)

In keeping with these arguments the *trans,trans*-1, 4-disubstituteed dienes give specifically more crowded cis-substituted 3-sulphones (Scheme 17.10.3). From similar arguments *cis*, *trans*-disubstituted dienes, on the other hand afford trans-substituted-3-sulphones. As with electrocyclic reactions, the opposite stereochemistry is observed when the reaction is photochemical rather than thermochemical (Scheme 17.10.3).



(Scheme 17.10.3)

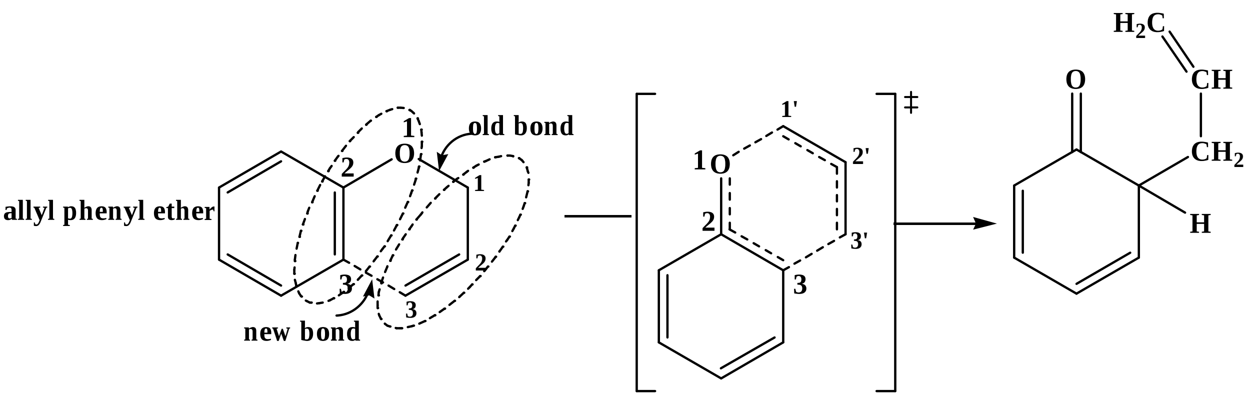
3-Sulpholene, a solid, is a convenient substitute for gaseous butadiene. Butadiene is generated at high temperatures from 3-sulpholene in a reverse reaction (Scheme 17.10.4) and when a dienophile is present it is trapped in a Diels-Alder reaction. The Diels-Alder reaction in itself is usually reversible and has been used to protect double bonds.



(Scheme 17.10.4)

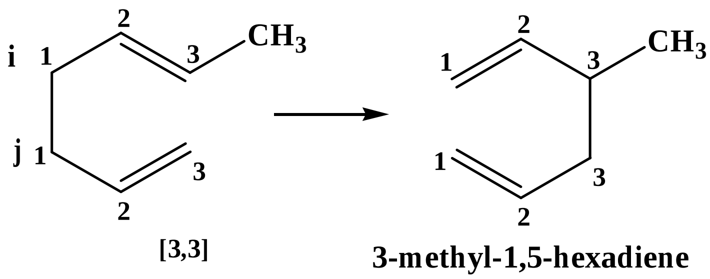
17.11. SIGMATROPIC REARRANGEMENTS

Sigmatropic rearrangements are pericyclic reactions which involve a concerted reorganization of electrons during which a group attached by a σ bond migrates to a more distant terminus of an adjacent π electron system. There is a simultaneous shift of p-electrons and overall, the number of π- and σ-electrons remain separately unchanged. These rearrangements are described by stating the relationship between the reacting centers in the migrating fragment and the π system. The order [i, j] of a sigmatropic rearrangement specifies the number of atoms in the migrating fragment and the number of atoms in π-system which are directly involved in the bonding changes. Thus the Claisen rearrangement of allyl phenyl ether is a [3,3] sigmatropic rearrangement (Scheme 17.11.1) as there is one oxygen atom and two aromatic ring carbons between the old and new bond on one side, and three carbons between the old and new bond on other. Thus in other words, the numbers set in brackets [I, j] are determined by counting the atoms over which each end of the σ bond has moved. Each of the original termini is given the number 1.



(Scheme 17.11.1)

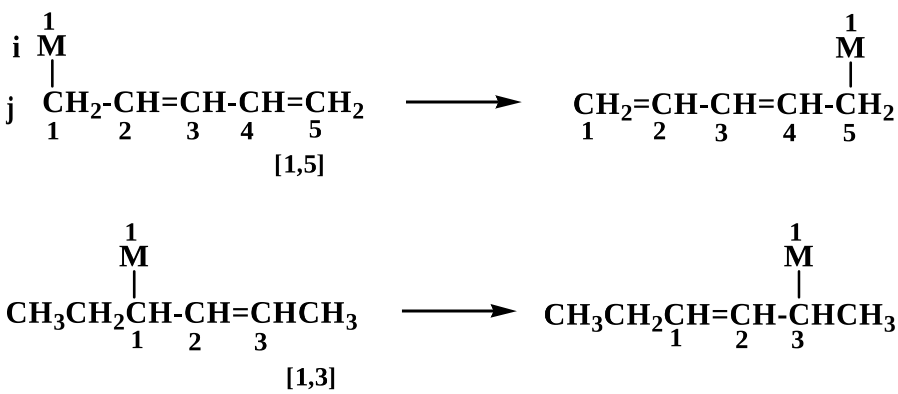
Similarly in the Cope rearrangement (in the 1, 5-heptadienyl system Scheme 17.11.2) 1,5-dienes isomerizes in a [3,3] sigmatropic rearrangement. In this case a sigma bond moves across two parts of a polyene system.



Cope rearrangement

(Scheme 17.11.2)

In the two examples below (Scheme 17.11.3) in the first the number 1 in the brackets indicates that the same atom which was attached to the migration origin now becomes bonded to the migration terminus. The number 5 designates migration along the five atoms of the polyene system. Similarly in the second case, the migrating group has moved across three atoms of an allylic system.

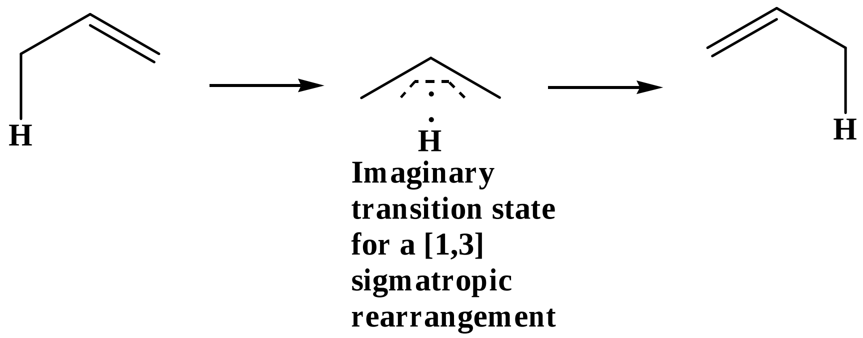


(Scheme 17.11.3)

17.11.1. SIGMATROPIC MIGRATION OF HYDROGEN

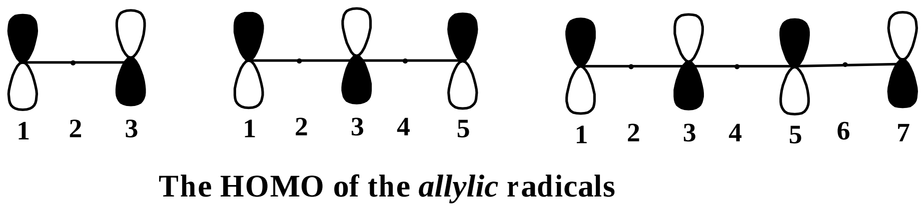
A hydrogen atom is reported to migrate from one end of a system of π bonds to the other, under thermal or photochemical rearrangements. In the transition state the hydrogen must be in contact with both ends of the chain at the same time. There are two distinct processes by which a sigmatropic migration can occur. If the hydrogen moves along the top or bottom face of the π-system i.e., migrating group remains associated with the same face of the conjugated system throughout the process, the migration is termed *suprafacial*. When the hydrogen moves across the π–system either from top to bottom or vice-versa i.e., the migrating group moves to the opposite face of the π-system during the course of migration then it is called *antarafacial*.

Ina given sigmatropic rearrangement, the migrating group is bonded to both the migration source and the migration termini in the transition state. It is imagined that the migrating H atom breaks away from the rest of the system which is treated as a free radical. Thus in a simplest case involving a [1,3] shift of hydrogen (Scheme 17.11.1.1). The frontier orbital analysis treats this system as a hydrogen atom interacting with an allyl radical. The electron of the hydrogen atom is in a 1s orbital which has only one lobe. The HOMO of an allylic free radical depends on the number of carbons in the π-framework (Scheme 17.11.1.2).



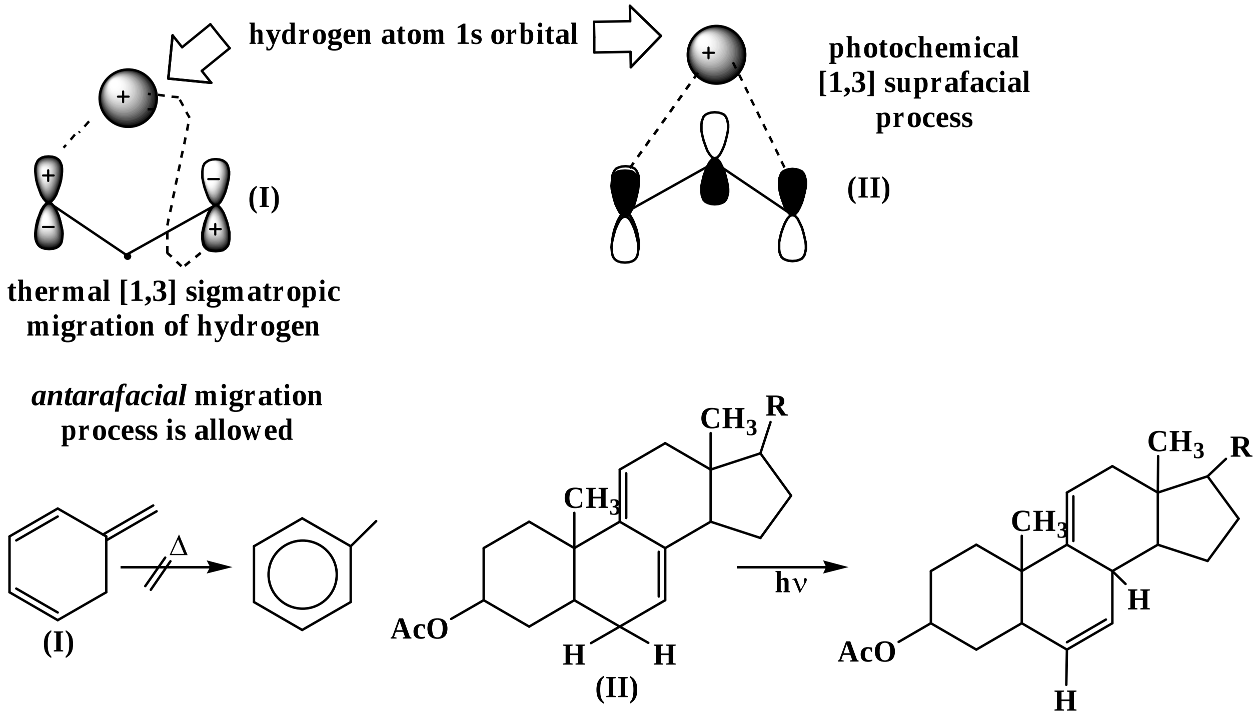
(Scheme 17.11.1.1)

In the migration of hydrogen the H must move from a plus to plus or from minus to a minus lobe of the HOMO, it cannot move to a lobe of opposite sign. Thus the rule predicts that antarafacial thermal [1, 3] sigmatropic rearrangements are symmetry allowed (and suprafacial pathway is forbidden).



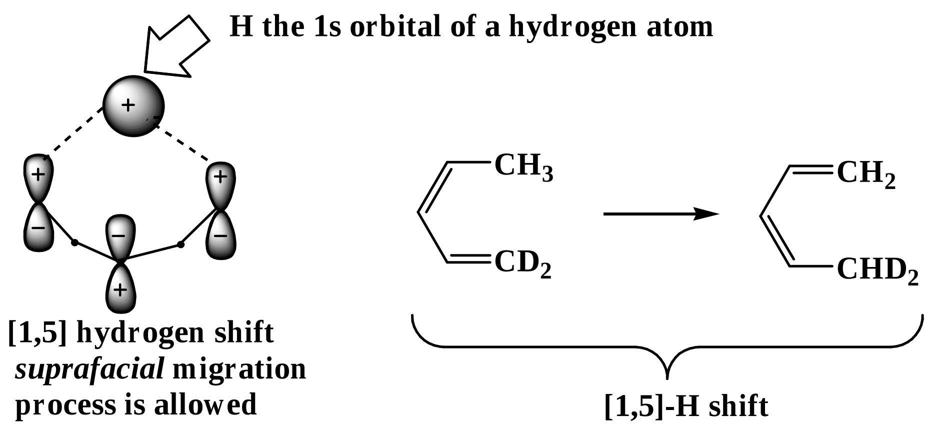
(Scheme 17.11.1.2)

However, such a transition state (I, Scheme 17.11.1.3) would be highly strainged, thus antarafacial [1, 3] thermal sigmatropic migrations of hydrogen are unknown. In a photochemical reaction promotion of an electron means that now (II, Scheme 17.11.1.3) becomes the HOMO. Superfacial pathway for [1,3] shift now becomes an allowed process and antarafacial pathway forbidden. Thus, the triene (I, Scheme 17.11.1.3) is stable and is not converted by a thermal [1,3] sigmatropic rearrangement to toluene a far more stable compound due to an aromatic sextet, while the steroid (II, Scheme 17.11.1.3) displays a [1,3] hydrogen shift under photochemical conditions.

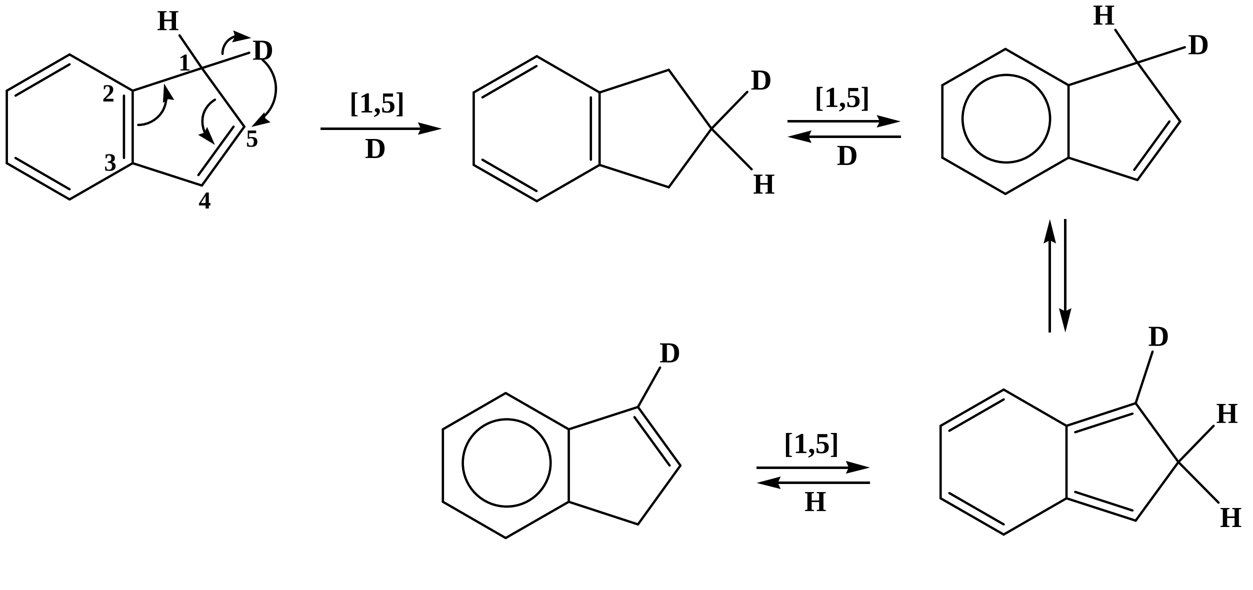


(Scheme 17.11.1.3)

On the other hand a [1,5] hydrogen shift in a thermal rearrangement being suprafacial (Scheme 17.11.1.4), is very common. Heating of indene (Scheme 17.11.1.5) causes the scrambling of the label to all the three non-aromatic positions.



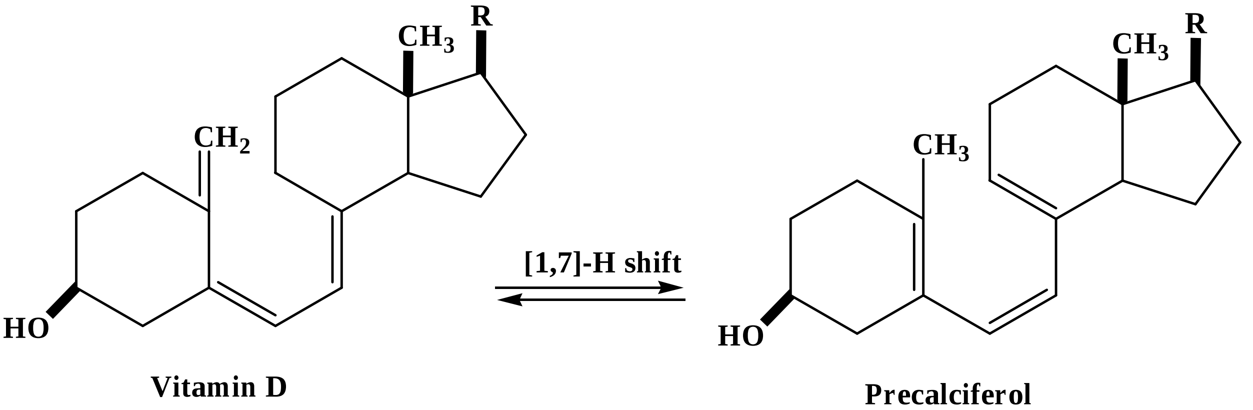
(Scheme 17.11.1.4)



(Scheme 17.11.1.5)

It is only via [1,5] shift of H or D (by including the p-orbitals of the benzene ring) that one can account for the results.

In the case of [1,7] hydrogen shifts, in a triene, the orbital symmetry rules predict that the transfer of hydrogen must be antarafacial compared to [1,3] shifts, the transition state is not much strained and the shift is sterically feasible. This is seen in the thermal Interconversion of vitamin D and precalciferol (Scheme 17.11.1.6).

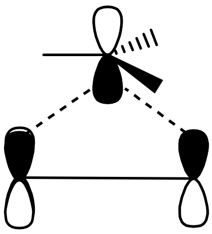


(Scheme 17.11.1.6)

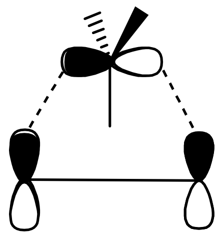
17.11.2. SIGMATROPIC MIGRATIONS OF CARBON

As compared to a hydrogen atom which has its electrons in a 1s orbital that has only one lobe, a carbon free radical (for imaginary transition state) has its odd electron in a p orbital which has two lobes of opposite sign. A consideration of the imaginary transition state, shows that if in place of hydrogen one has carbon, then during a thermal suprafacial [1,5] process, symmetry can be conserved only provided the migrating carbon moves in a manner that the lobe which was originally attached to the π system remains attached to it (Scheme 17.11.2.1). The only way for this to happen is the retention of configuration within the migrating group. However, a related

[1,3] thermal suprafacial migration would involve opposite lobes. Thus, if the migrating carbon was originally bonded via its positive lobe, it must now use its negative lobe to form the new C-C bond. The stereochemical outcome of such a process is the inversion of configuration in the migrating group.



a thermal suprafacial [1,5] migration configuration is retained within the migrating group

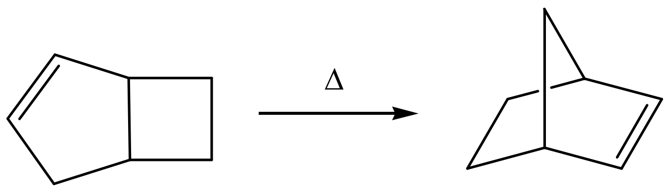


a thermal suprafacial [1,3] migration configuration in the migrating group will be inverted

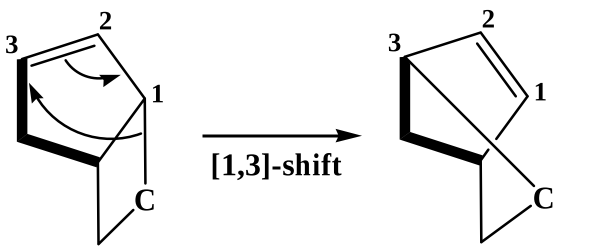
(Scheme 17.11.2.1)

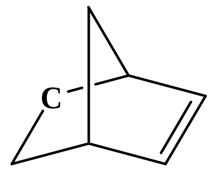
In summary, a suprafacial [1,5] thermal rearrangement proceeds with retention of configuration at the migrating carbon, while the related [1,3] suprafacial process proceeds with inversion.

In the thermal conversion of (I, Scheme 17.11.2.2) to (II) a carbon atom migrates across an allyl system, leaving C-1 and ending up at C-3 via a [1, 3] shift.



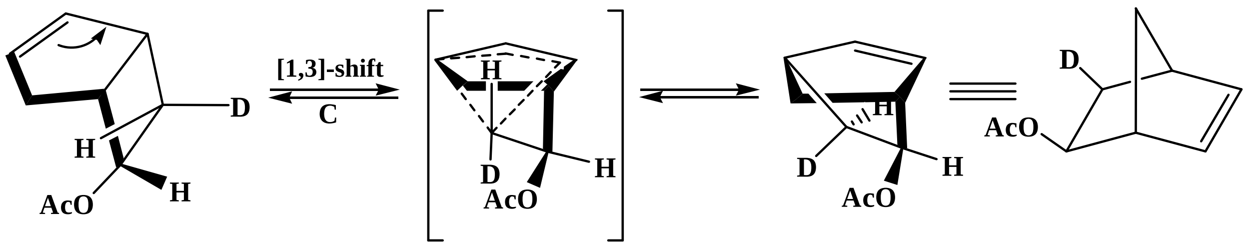
bicyclo [3.2.0]-hept-2-ene (I) **bicyclo [2.2.1]-hept-2-ene (II)**





(Scheme 17.11.2.2)

The results of pyrolysis on (III, (Scheme 17.11.2.3), a trans labeled compound) are in keeping with the predicted thermal [1, 3] sigmatropic reaction with inversion at C-7.

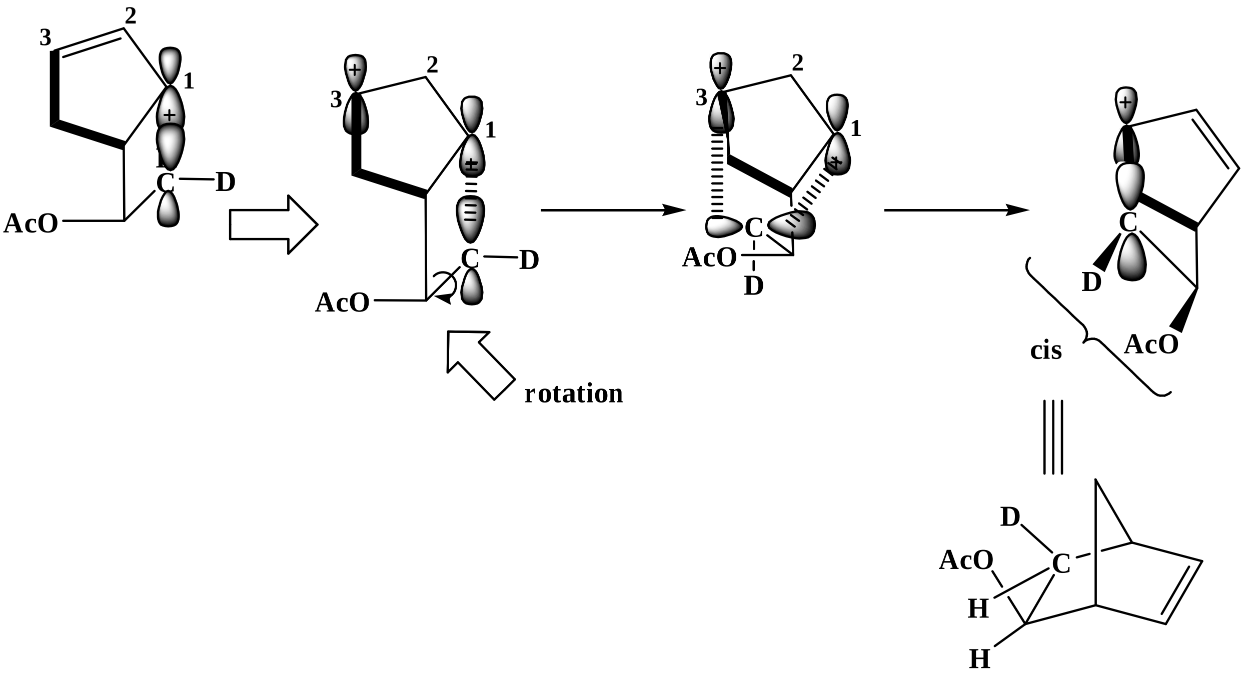


(III) the transition state

(Scheme 17.11.2.3)

Maintenance of bonding overlaps between C-1 and C-3 during the migration (Scheme 17.11.2.4) involves the following:

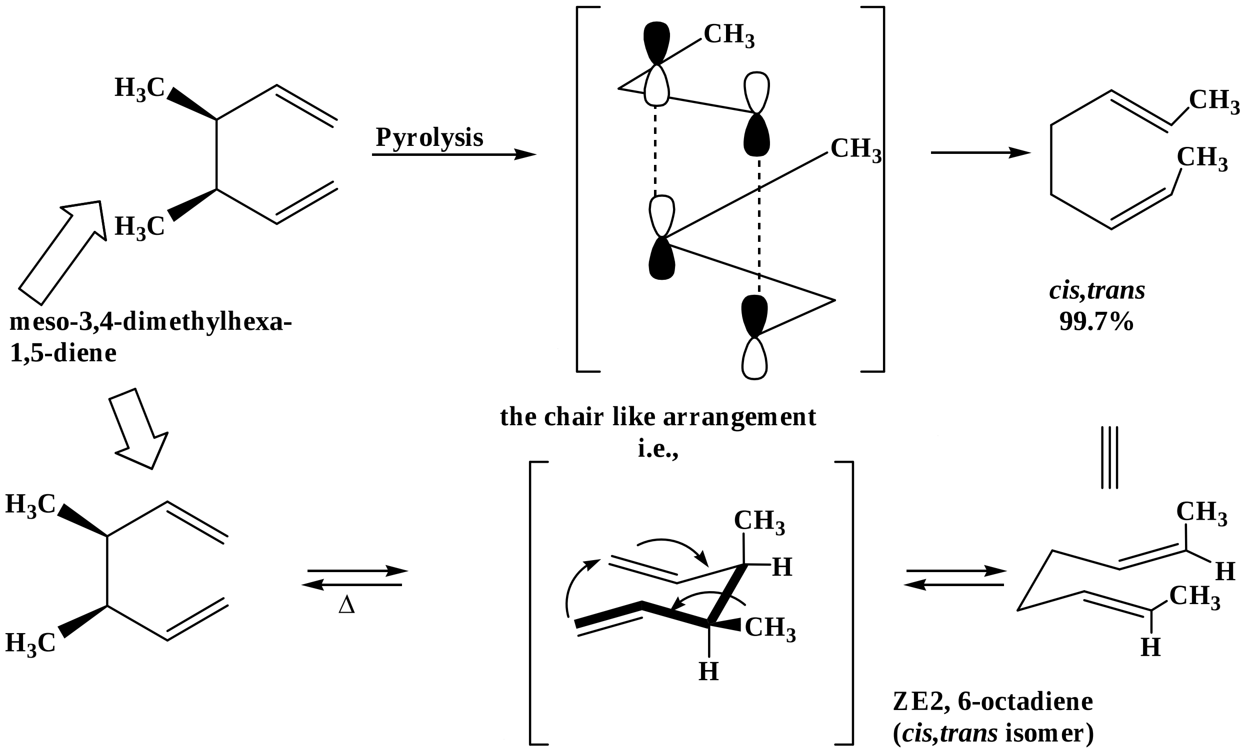
(1) Migration takes place by using the back lobe of the migrating carbon.
(2) The migrating carbon suffers inversion on reattachment at C-3 of the allyl framework.
(3) To preserve bonding overlaps with C-1 and C-3 rotation must occur and consequently the *trans*-starting material is converted into *cis*.



(Scheme 17.11.2.4)

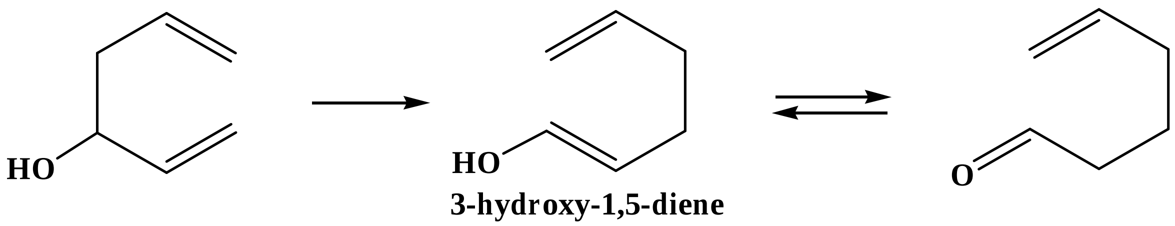
17.11.3. THE COPE REARRANGEMENT

1,5-Dienes on heating isomerizes in a [3, 3] sigmatropic rearrangement known as Cope rearrangement (see, Scheme 17.11.2). The stereochemical outcome of this rearrangement is in keeping with their occurrence through chair-shaped transition states (Scheme 17.11.3.1). *Meso* 3, 4-dimethyl-1,5-hexadiene gives cis,trans-2,6-octadiene (in the starting compound the two methyl groups are having cis relationship, in the chair form of a cyclohexane only 1, 2-axial, equatorial relationship is cis) while a boat shaped transition state would give trans, trans-or cis, cis-product.



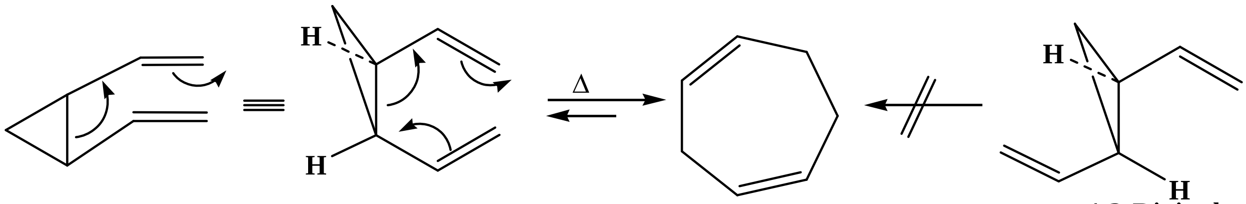
(Scheme 17.11.3.1)

The reaction is reversible and gives an equilibrium mixture of the two 1, 5-dienes which is richer in the thermodynamically more stable isomer. In the case of 3-hydroxy-1, 5-dienes, however, the reaction cannot be reversed, since the 3-hydroxy-1, 5-dienes tautomerize to the carbonyl compound ((Scheme 17.11.3.2), oxy-Cope rearrangement).



(Scheme 17.11.3.2)

Cis-Divinylcyclopropane rapidly undergoes Cope rearrangement to 1, 4-cycloheptadiene. Due to unfavorable molecular geometry, the corresponding rearrangement of trans-isomer to cycloheptadiene cannot be concerted (Scheme 17.11.3.3) since the ends of the molecule where bonding must occur are too far apart. This cis orientation not only provides a favorable geometry for interaction of the diene termini so that the loss in entropy in going to the transition state is smaller than for an acyclic diene, but the bond being broken is strained and this reduces the enthalpy of activation.



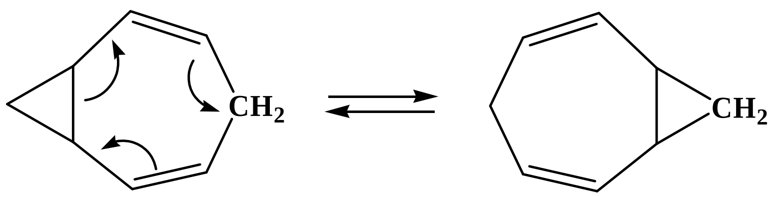
cis-1,2-Divinyl-cyclopropane

1,2-cycloheptadiene

trans-1,2-Divinyl-cyclopropane

(Scheme 17.11.3.3)

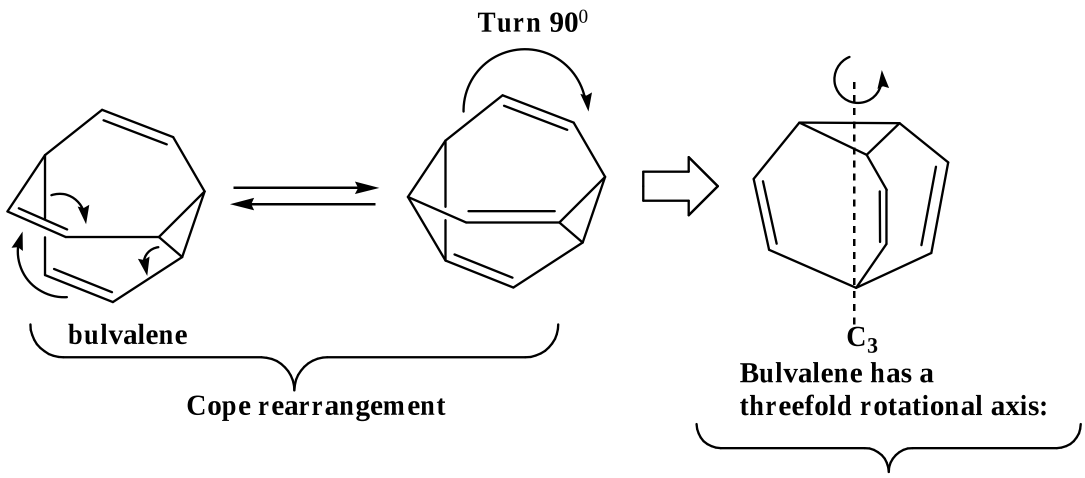
Divinylcyclopropane rearrangements can proceed even with more ease in case the entropy of activation is made still negative by incorporating both vinyl groups into a ring. The system then becomes homotropilidene (Scheme 17.11.3.4) which undergoes a degenerat4e cope arrangement. A degenerate rearrangement leads to a product which is indistinguishable from the reactant. By bridging the two methylene groups in homotropilidene one gets a molecule of bullvalene (Scheme 17.11.3.5). This is converted into itself at 25^{0}C. At 100^{0}C the ^{1}HNMR spectrum of bullvalene shows a singly peak at 4.22 ppm. Bullvalene has a three fold rotational axis; thus all the three double bonds are equivalent. The Cope rearrangement is degenerate which can occur in each of the three faces of the molecule and is degenerate in every case. Bullvalene has a three fold rotational axis; consequently all its three double bonds are equivalent. The cope rearrangement can occur in each of the three faces of the molecule and is degenerate in every case (Bullvalene is a fluxional molecule- a molecule which undergoes rapid degenerate rearrangement).



Homotropilidene **Still Homotropilidene**

The degenerate Cope rearrangement of homotropilidene

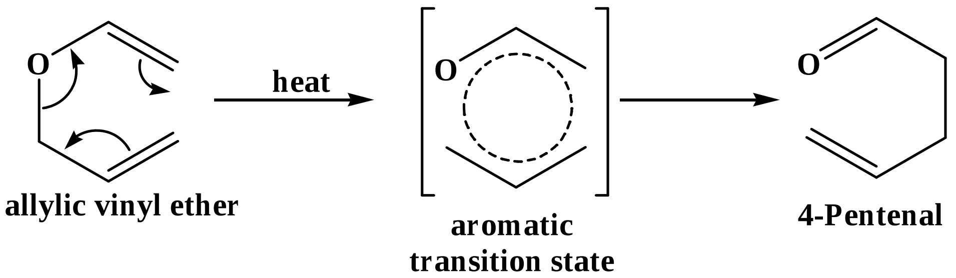
(Scheme 17.11.3.4)



(Scheme 17.11.3.5)

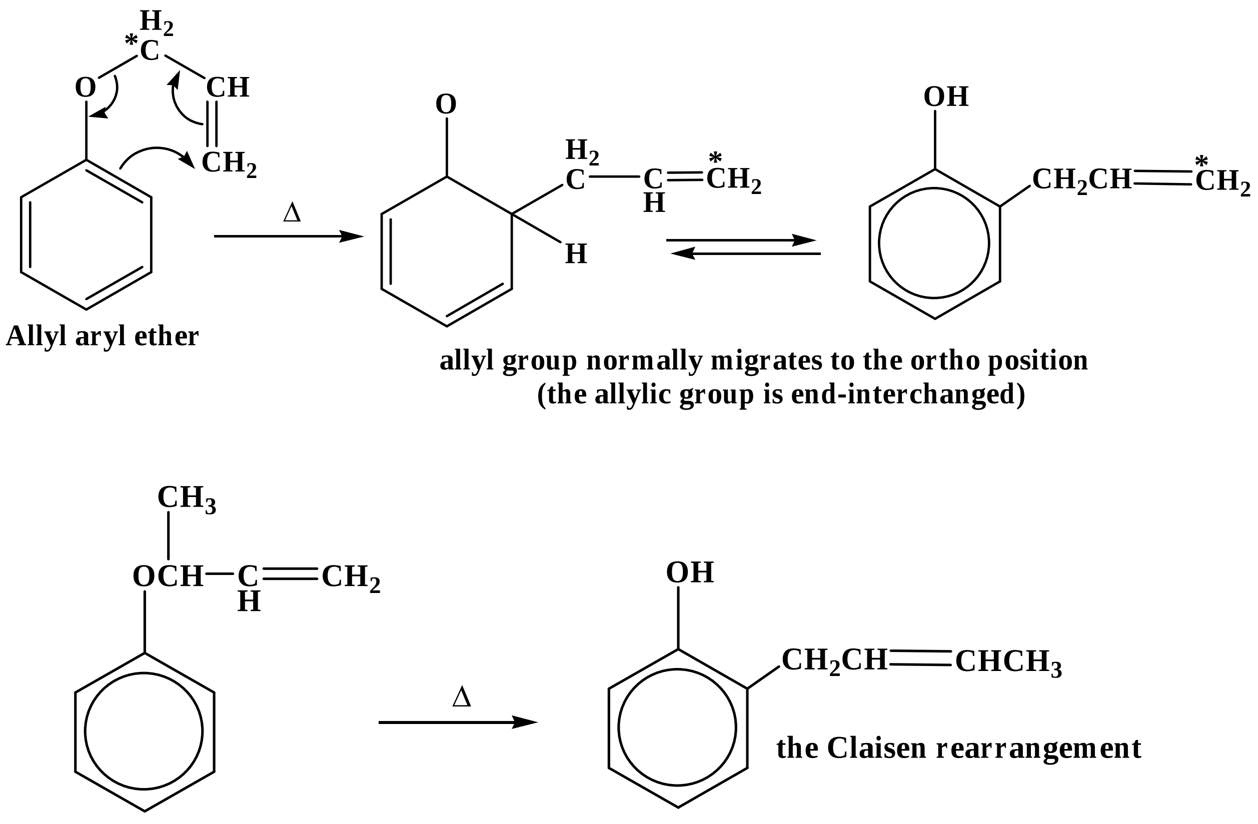
17.11.4. THE CLAISEN REARRANGEMENT

This rearrangement also involves a [3,3] sigmatropic pathway like cope rearrangement, however, in Claisen rearrangement the substrates incorporate one or more heteroatoms in place of carbon in the 1,5-hexadiene system. The simplest example of Claisen rearrangement is the thermal conversion of allyl vinyl ether to 4-pentenal (Scheme 17.11.4.1). The transition state involves a cycle of six orbitals and six electrons. With six electrons the transition state has aromatic character. Similarly allyl aryl ethers on heating rearrange to o-allyl phenols.

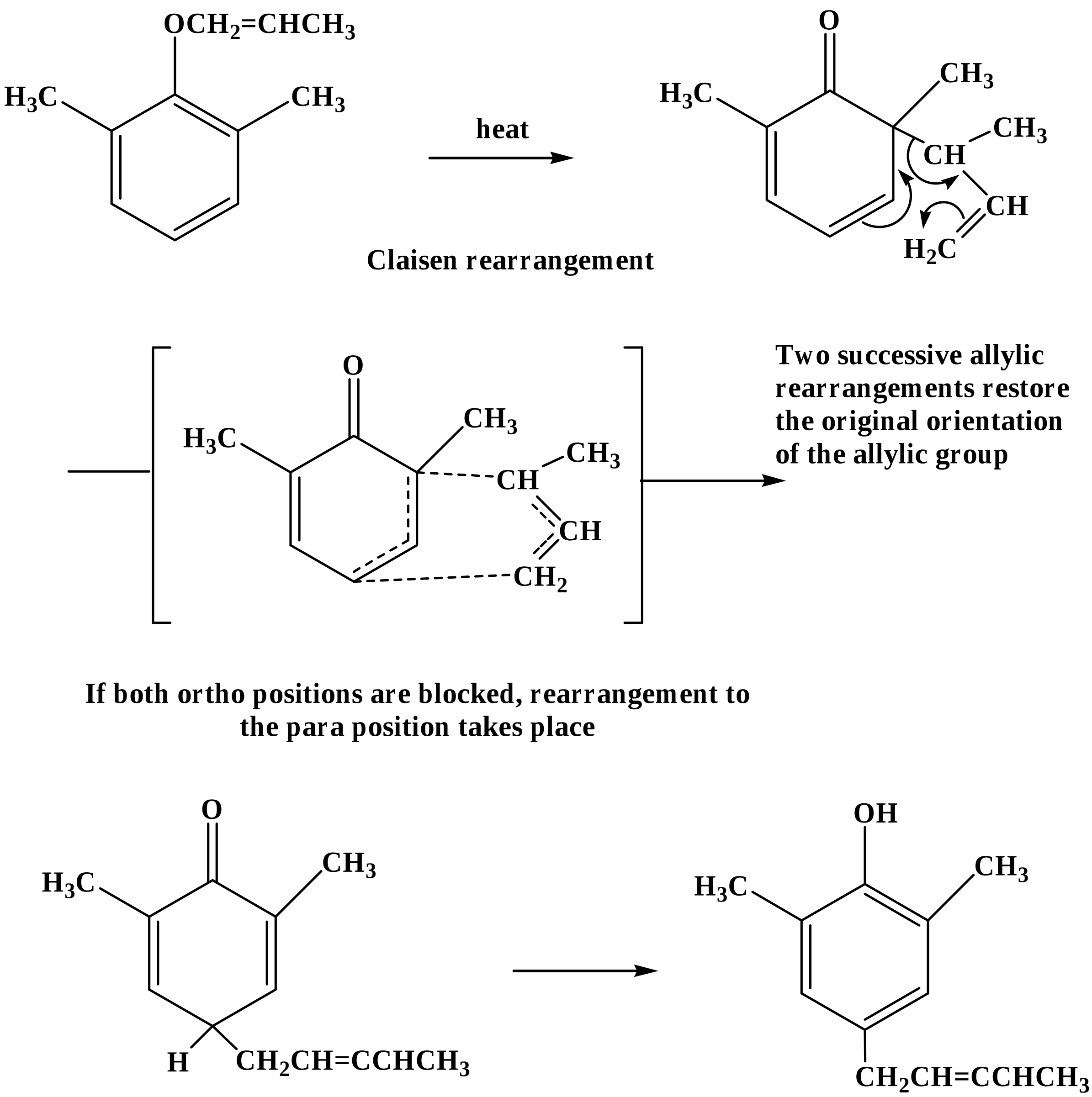


(Scheme 17.11.4.1)

Studies using migrating groups labeled with ^{14}C or with substituents show that the allylic group is end-interchanged during the ortho rearrangement (Scheme 17.11.4.2). These and other results which show that the Claisen rearrangement is intramolecular provide strong support for a concerted mechanism. When both o-positions are filled the allyl group migrates to the p-position (Scheme 17.11.4.3).



(Scheme 17.11.4.2)

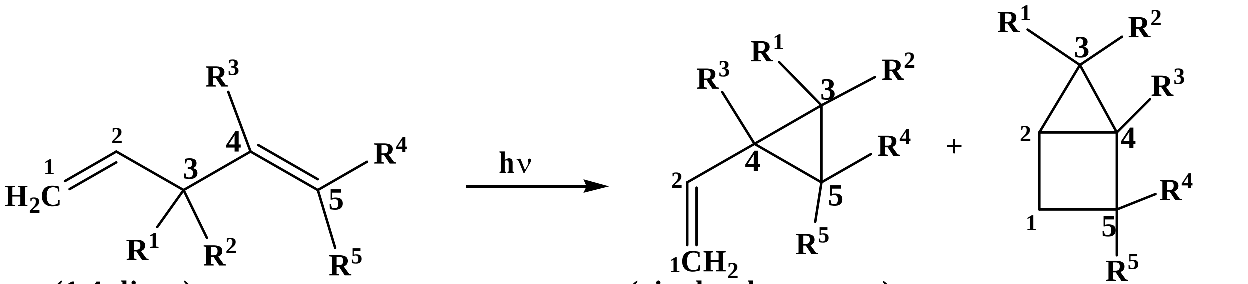


(Scheme 17.11.4.3)

In a [3, 2]-sigmatropic rearrangement, the reactants have a two-atom migrating unit where one atom has a negative charge; this is equivalent to the two π-electrons of an unsaturated bond in a three-atom moiety. The rearrangements of allylic sulfoxides, selenoxides and amine oxides are examples. Thus in the Sommelet rearrangement the two-atom unit is a nitrogen ylide-$\overset{+}{N}R_2$-$\overset{-}{C}H_2$.

17.11.5. DI-PI-METHANE REARRANGEMENT

Photochemical rearrangement reaction of 1,4-dienes leading to the formation of vinylcyclopropanes is widely known as *di-π-methane rearrangement.*



(1,4-diene)
di-π-methane unit

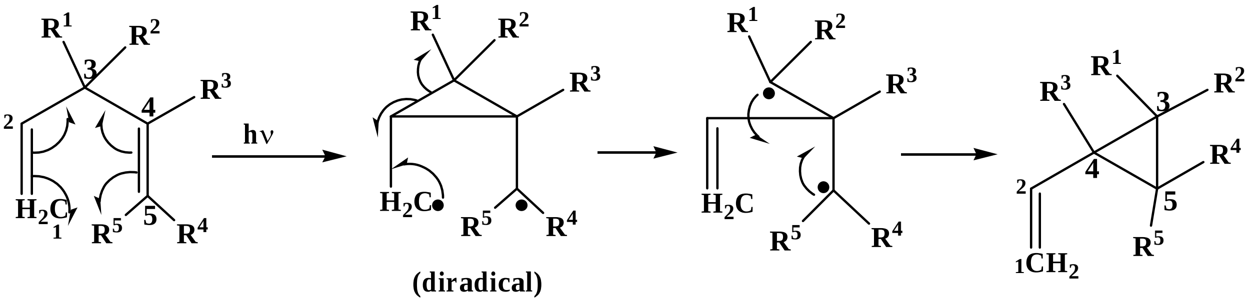
(vinylcyclopropane)
rearranged product

(bicyclic product)
side product

This is the most general photochemical reaction applicable to acyclic, cyclic, bi and tricyclic 1,4-dienes. Zimmermann and his collaborations had extensively studied the reaction, and that is why, now-a-days, this rearrangement reaction is also called as *Zimmermann reaction*.

Mechanism and Discussion

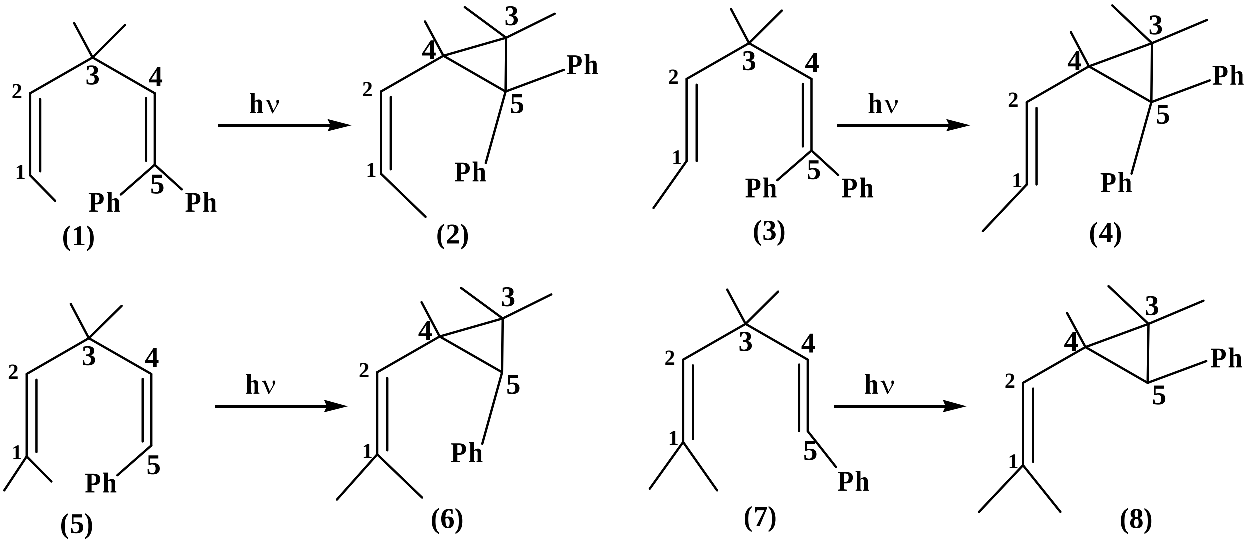
The reaction is believed to proceed through diradical pathway, though the species is not necessarily intermediate, but may be the transition state.



(diradical)

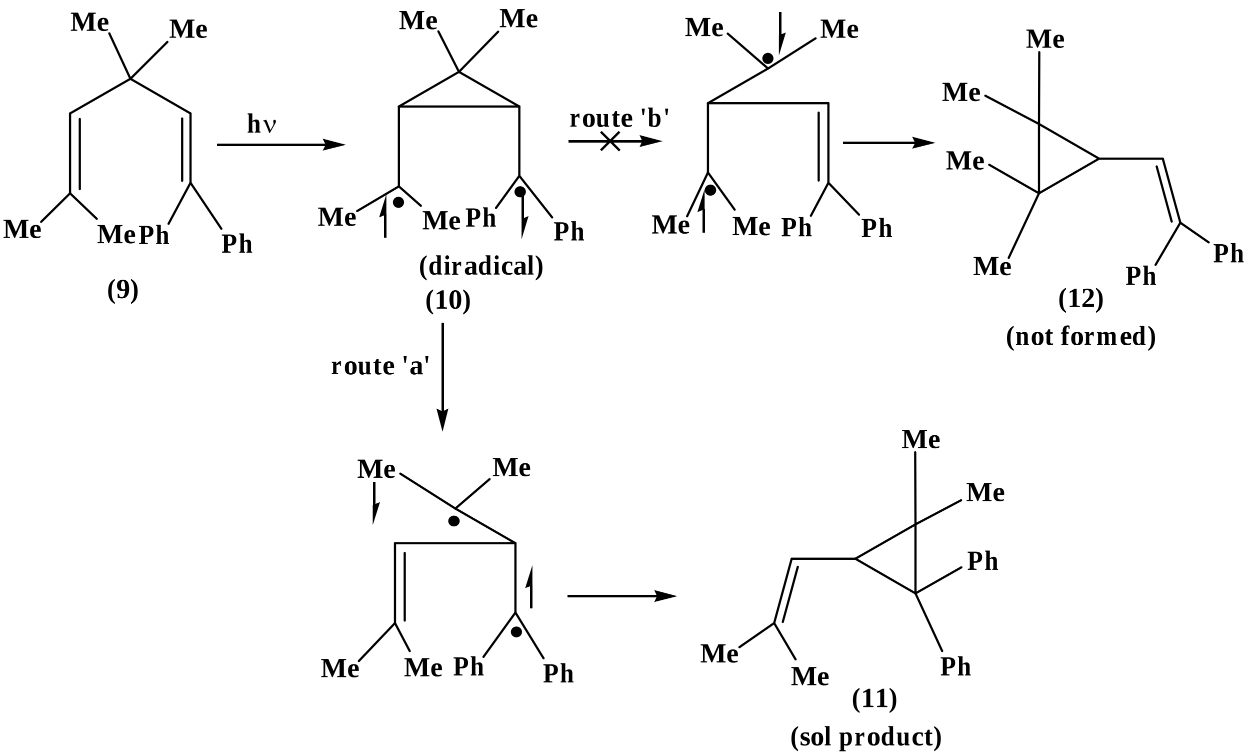
It has been established that for acyclic and monocyclic systems, the rearrangement proceeds through a singlet mechanism (viz. photochemical rearrangement of 3,3-dimethyl-1,1,5,5-tetraphenylpenta-1,4-diene to 1,1-dimethyl-2,2-diphenyl-3-(2,2-diphenyl)vinyl cyclopropanes), whereas for bicyclic or tricyclic systems the reaction follows triplet mechanism (viz. acetone-sensitized photochemical rearrangement of barrelene to semibulvalene).

The singlet state reaction is supposed to be concerted and to involve inversion of configuration only at C-3; configurations at C-1 and C-5 remain intact. For example, cis-1,1-diphenyl-3,3-dimethyl-1,4-hexadiene (1) rearranges to (2), in which the side chain is cis, but trans-1,1-diphenyl-3,3-dimethyl-1,4-hexadiene (3) rearranges to (4), in which the side chain is trans. Similarly, (5) and (6) yield predominantly (7) and (8) respectively.



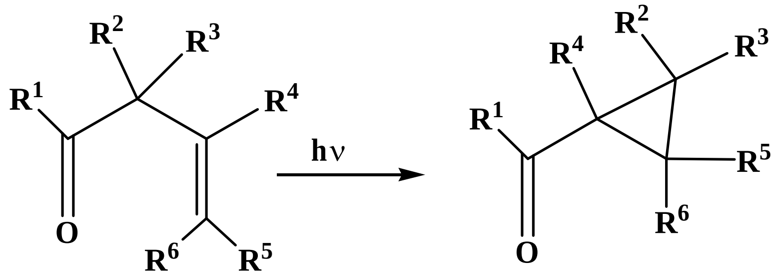
CRITICAL VIEWS

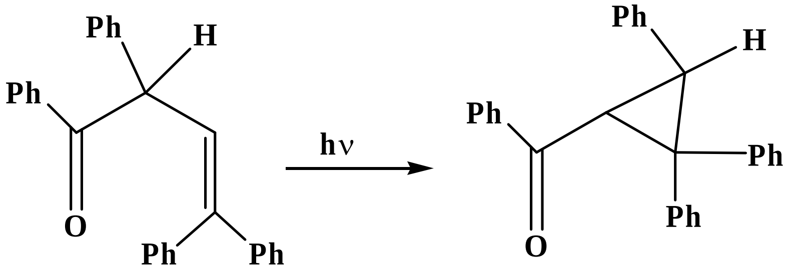
(a) The direction of rearrangement is controlled by the ease of electron availability for π-bond formation in the diradical formed; conversely, is directed by the extent of electron delocalization in the diradical formed during the reaction that may be exemplified by the following transformation (**Scheme I**). The substrate (9) gives exclusively (11), not the (12). This can be rationalized from the fact that the benzylic radical of (10) can be stabilized by delocalization into the aromatic rings and is not readily available for π-bond formation as required by route 'b'; route 'a' is therefore followed leading to the formation of (11) as a sole product.



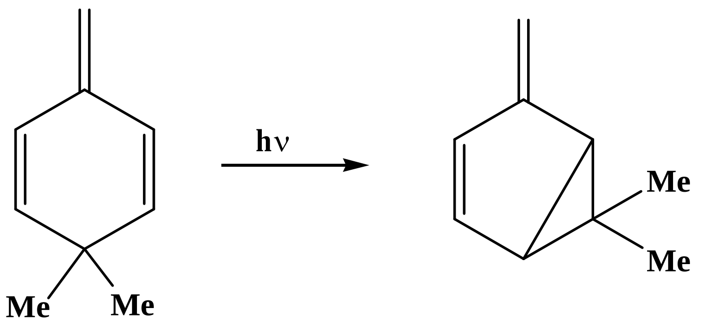
(b) The reaction has been extended to allylic benzenes, β,γ-unsaturated imines and to triple-bond systems. Asymmetrically sensitized *di-π-methane rearrangements* has also been observed, which leads to the synthesis of optically active products.

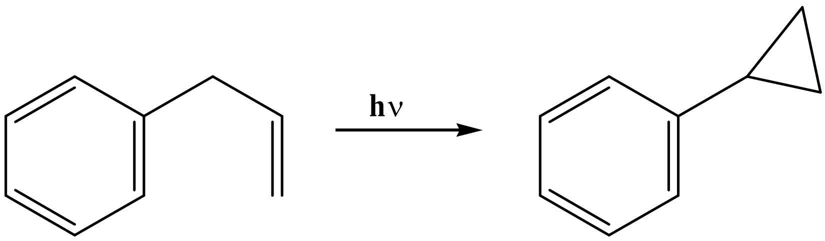
(c) It has been observed that β,γ-unsaturated ketones undergo photochemical reaction similar to *di-π-methane rearrangement* involving 1,2-acyl migration and formation of a three-membered ring; this particular reaction is known as *oxa-di-π-methane rearrangement*. Here the carbonyl group acts as one of the π-component.

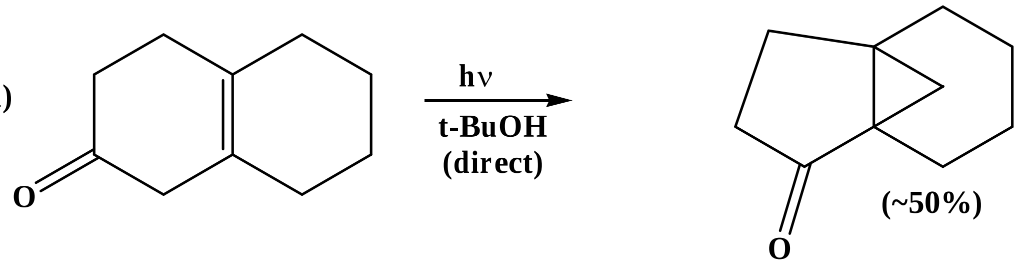


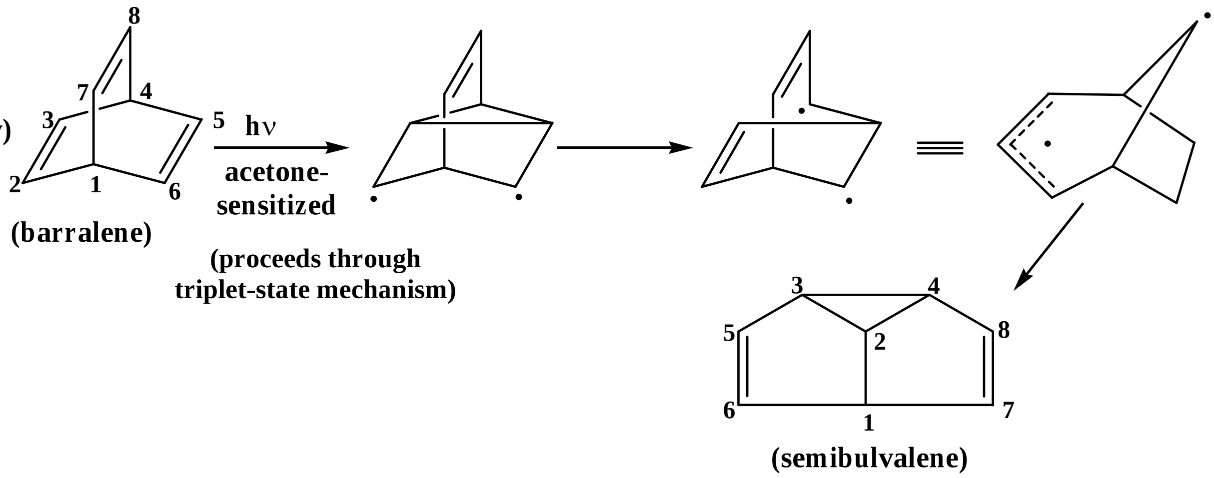


APPLICATIONS

i) 

ii) 

iii) 

iv) 

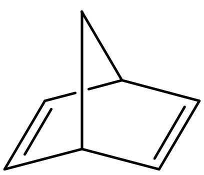
17.12. LET US SUM UP

In this lesson, we:
Pointed out

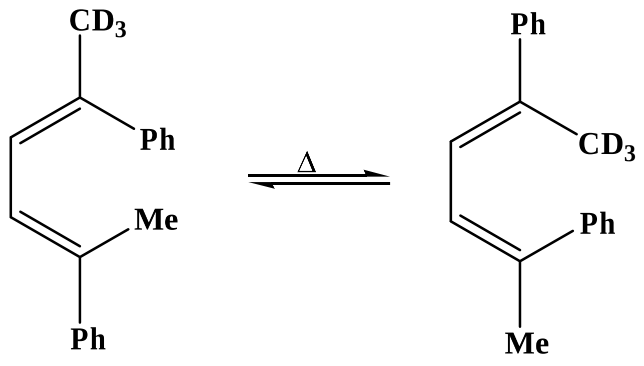
- Electrocyclic reactions
- Generalized Woodward-Hoffmann rule
- Cycloaddition reactions: correlation diagram and frontier molecular orbital method
- Stereochemical modes of cycloaddition: suprafacial and antarafacial processes
- Orbital symmetry in cycloaddition reaction: correlation diagrams
- Frontier molecular orbital (FMO) method
- Cycloadditions
- 1,3-dipolar cycloadditions
- Cheletropic reactions
- Sigmatropic rearrangements
- The Cope rearrangement
- The Claisen rearrangement
- The Di-pi-methane rearrangement

17.13. CHECK YOUR PROGRESS

1. How does a diene enter cyclo addition? Explain.
2. Which diene and dienophile one would employ to synthesize Norbornadiene?



3. The butadienes A and B are easily interconverted under thermal conditions. Suggest a mechanism.



(A) (B)

4. Explain the following.
   (a) Ring opening and ring closure of butadiene
   (b) Opening of a 1,3-cyclohexadiene and it's ring closure.
5. Illustrate cheleotropic reaction with a suitable example.
6. Why concerted 1, 3 sigmatropic shift of hydrogen is thermally forbidden?

17.14. POINT FOR DISCUSSION

1. Explain Frontier Molecular Approach for cycloaddition reaction with suitable examples.
2. Explain Woodward Hoffmann rule for electrocyclic reactions.
3. Write the stereo structure of the compound obtained by the Diels Alder reaction of dimethyl maleate with butadiene.
4. Explain di-pi methane rearrangement.
5. The transition state of the Diels Alder reaction is aromatic and compares with Cope rearrangement. Explain.
6. How is Claisen rearrangement related to Cope rearrangement? Give examples for both.

17.15. REFERENCES

1. P.S. Kalsi, Organic reactions and their mechanisms, Second edition, New age international publishers.

2. D. Nasipuri, Stereochemistry of Organic compounds, second edition, New age international (P) limited, Publisher, New Delhi.

UNIT-VIII

LESSON: 18 – STEREOISOMERISM: OPTICAL ACTIVITY AND CHIRALITY

CONTENTS

18.0. AIMS AND OBJECTIVES

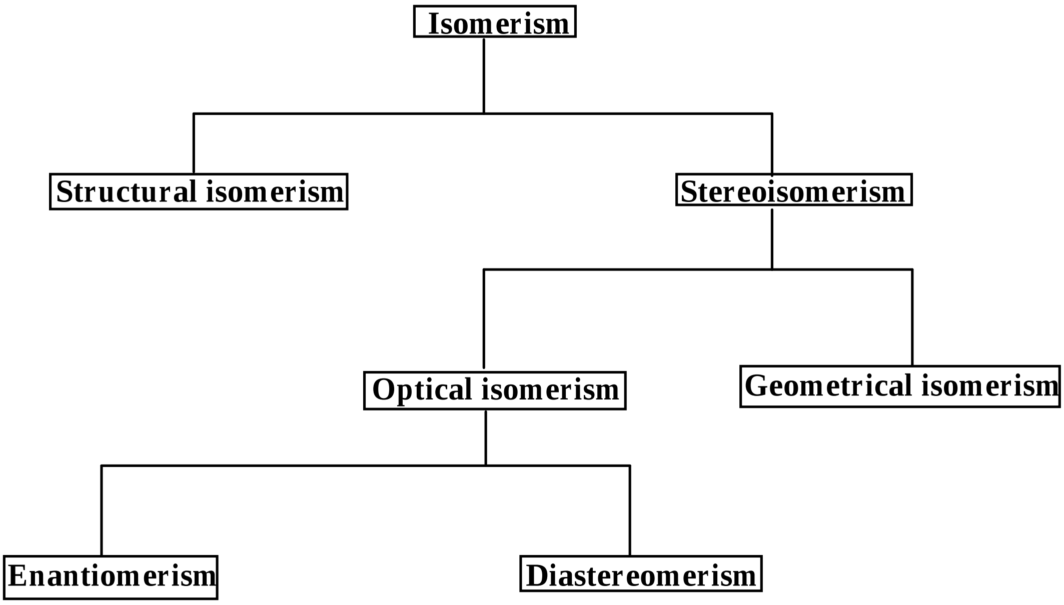
The aim is to motivate and enable the student to comprehensive knowledge on optical activity and Chirality of organic compounds.

On successful completion of this lesson the student should have:

* learnt the optical activity and Chirality of organic compounds.

18.1. INTRODUCTION

Stereochemistry is the branch of chemistry that deals with the study of the special structure of molecules and of influence of their structure on physical and chemical properties of compounds. In other words, stereochemistry deals with the study of physical and chemical properties of stereoisomers.



Isomers are different compounds with different properties that have the same molecular formula. This phenomenon is known as isomerism. Isomers that differ in the order in which their atoms are bonded are known as structural isomers or constitutional isomers. The order of atomic connections that defines a molecule is termed its constitution and two compounds are said to be constitutionally isomeric if they have same molecular formula but differ in the order in which their atoms are connected. Stereoisomerism is exhibited by isomers having the same structure but different configurations. That is, stereoisomers have the same constitution but differ only in the spatial orientation of their atoms.

Optical isomerism is characterized by the compounds having the same structure but different configurations and because of their molecular asymmetry (Chirality) they are optically active.

Geometrical isomerism or ***cis*-*trans*-**isomerism is characterized by compounds having the same structure but different configurations and because of their non-chiral (non-dissymmetric) nature they are not optically active, unless they happen to carry groups that contain asymmetric carbon atoms. This type of isomerism is exhibited by compounds that contain double bonds and certain ring compounds in which at least two ring atoms contain unequal substituents. Geometrical isomerism is a special case of diastereoisomerism.

18.1.1. OPTICAL ACTIVITY

Any discussion on stereochemistry starts with the phenomenon of optical activity. The ability of a substance to rotate the plane of polarized light is known as optical activity. If a substance rotates the plane of polarized light, it is called optically active. On the other hand if a substance does not rotate the plane of polarized light, it is said to be optically inactive. Optical activity is detected and measured by an instrument called polarimeter. If a substance rotates the plane of polarized light in clockwise direction (right), it is called **dextrorotatory** and is designated as (+)-isomer. If the substance rotates the plane of polarized light in anticlockwise direction (left), it is known as **laevorotatory** and is designated as (-)-isomer.

18.1.2. SPECIFIC ROTATION

The magnitude of optical rotation is directly proportional to the nature of the substance, its concentration, cell length, wavelength of light used and temperature. For a given substance under a given set of conditions, the magnitude of optical rotation (θ) can be expressed as:

Optical rotation (θ) $\propto$ cell length (l) $\times$ concentration (c).

i.e., $\theta \propto$ l (dm) $\times$ c (g/ml)

$\therefore \theta = [\alpha] \times$ l (dm) $\times$ c (g/ml), where $[\alpha]$ is called specific rotation.

$$[\alpha]_D^t = \frac{\theta}{\mathrm{l\,(dm)} \times \mathrm{c\,(g/ml)}}$$

$$\text{Specific rotation} = \frac{\text{Observed rotation(degrees)}}{\text{Cell length (dm)} \times \text{Concentration (g/ml)}}$$

18.1.3. ENANTIOMERS

The optical activity was discovered by the French Physicist Jean Baptiste Biot in 1815 at the College de France. In 1848, Louis Pasteur made an interesting observation that optically inactive sodium ammonium tartrate existed as a mixture of two different kinds of crystals which were mirror images of each other. With the help of a hand lens and a pair of tweezers, he carefully and laboriously separated them into right and left handed crystals. Although, the original mixture was optically inactive, each set of crystals when dissolved in water was found to be optically active. Further more, the specific rotations of two solutions were exactly equal in magnitude but opposite in sign. The two sets of solutions were exactly equal in magnitude but opposite in sign. The two sets of crystals are indeed enantiomers. Enantiomers are optical isomers which are related as **non-superimposable** object and its mirror image.

18. 2. OPTICAL ACTIVITY AND CHIRALITY

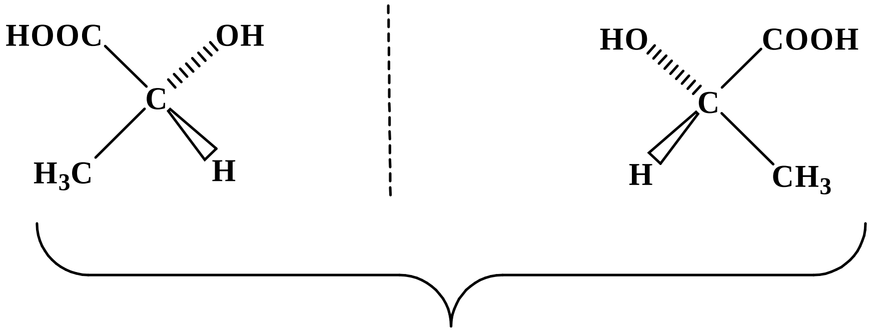
It is found that if a pure compound is optically active, the molecule is non-superimposable on its mirror image. **The property of non-superimposability of a molecule on its mirror image is known as Chirality. If a molecule is not superimposable on its mirror image, it is chiral. If it is superimposable on its mirror image then it is achiral. Thus Chirality is a necessary and sufficient condition for optical activity**. Thus if a molecule is **chiral**, it is non-superimposable on its mirror image and exhibits optical activity. On the other hand, if the molecule is **achiral**, it is superimposable on its mirror image and is optically inactive.

18.2.1. ASYMMETRIC CARBON (Chiral carbon atom or Stereogenic centre)

When a molecule contains just one asymmetric carbon atom, it is always chiral and hence optically active. Asymmetric carbon atom also called chiral carbon (or stereogenic carbon atom) is defined as a carbon atom attached to four different groups, no matter how slight the differences among the four groups. For example, optical activity is present in the following compound and optical activity has been detected even in such cases as 1-butanol-1-d, where one group is hydrogen and another is deuterium.

$$\begin{array}{c} \quad\quad\quad\quad\quad\quad\quad\quad\quad\quad H \\ CH_3\text{-}CH_2\text{-}CH_2\text{-}C\text{-}OH \\ \quad\quad\quad\quad\quad\quad\quad\quad\quad\quad D \end{array}$$

Molecules that contain just **one** asymmetric carbon atom always exist as a pair of isomers, which are related as non-superimposable object and its mirror image, called **enantiomers** or **enantiomorphs.**



Enantiomers of lactic acid

Enantiomers have identical physical and chemical properties except in two important respects.

(a) They rotate the plane of polarized light in opposite direction though in equal amounts. That is, they exhibit same magnitude of optical rotation but in opposite direction. The isomer which rotates the plane of polarized light to the right (clockwise) is called **dextro** isomer and designated as (+)-isomer, while the one that rotates the plane of polarized light to the left (anticlockwise) is called **leavo** isomer and is designated as (-)-isomer.

(b) They react at different rates with other chiral compounds. Enantiomers react at the same rate with achiral compounds.

In general enantiomers have identical properties in a symmetric environment but in an asymmetric environment their properties may differ. They react at different rates with achiral molecules in the presence of an optically active catalyst. They have different solubilities in an optically active solvent; they may have different indeces of refraction or absorption spectra when examined in circularly polarized light.

Although pure chiral molecules are always optically active, a mixture consisting of equimolar amounts of enantiomers [(+) and (-) forms] is always optically inactive, since their rotations cancel each other. Such a mixture is called racemic mixture or racemic modification. The properties of racemic modification are not always the same as those of individual enantiomers. Usually the properties of racemic modification tend to be same in gaseous or liquid state or in solution, since such mixture is nearly ideal. But the properties involving in solid state, such as melting points and solubilities are often different. Thus, racemic tartaric acid [($\pm$)-tartaric acid] has a melting point of 204-206^{0}C and solubility in water at 20^{0}C of 206g/litre, while for (+) or (-) enantiomers the corresponding figures are 170^{0}C and 139^0. The separation of racemic mixture into its optically active components or enantiomers is known as **resolution.**

Although, molecules with one asymmetric carbon atom are always optically active, the presence of an asymmetric carbon is neither a necessary nor a sufficient condition for optical activity, since optical activity is present in molecules with no asymmetric carbon atoms (eg:

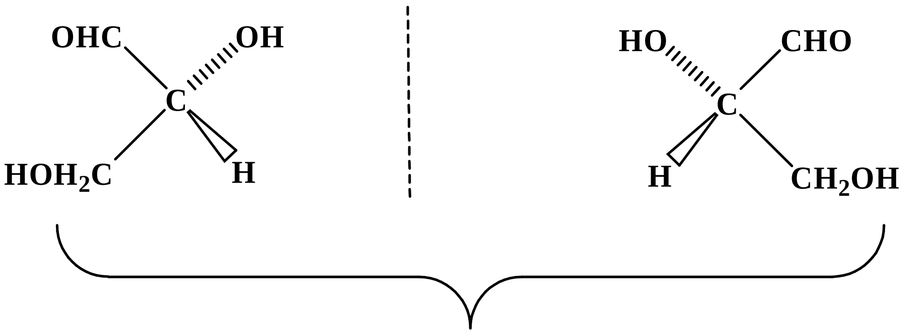
biphenyls, allenes, ansa compounds etc.) and some molecules with two or more asymmetric carbon atoms are superimposable on their mirror images and hence optically inactive (eg. meso-tartaric acid).

18.3. PROJECTION FORMULAE

Our media, the paper and the black-board for drawing chemical structures is two dimensional. Hence, it is difficult to represent the three dimensional molecules on a two dimensional paper in their three dimensional reality. For this reason, a number of two dimensional projections have been introduced. One such projection is wedge projection.

18.3.1. WEDGE PROJECTION

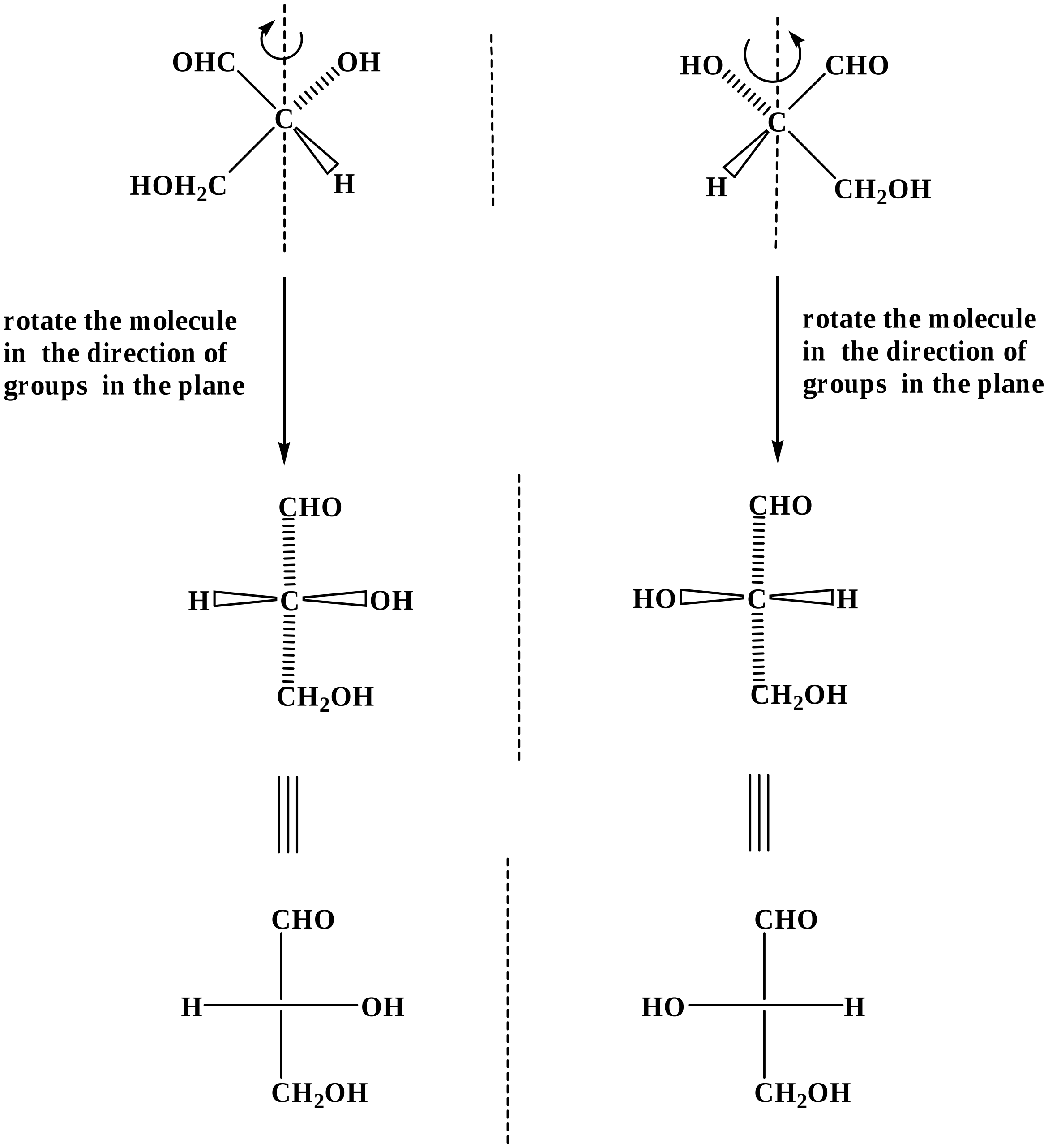
This projection is convenient to represent molecules with one and two asymmetric carbon atoms. This projection is constructed as follows: of the four groups attached to the tetrahedral carbon atom, two groups and the central carbon atom are placed in the plane of the paper such that, of the two remaining groups one lies above the plane and the other below the plane of the paper. The group which is above the plane of the paper is drawn with a bold or thick wedge and the one below the plane of the paper is drawn with a dotted wedge. The enantiomers of glyceraldehydes are represented below by the wedge projection. It is often convenient to place the longest carbon chain in the plane of the paper.



Enantiomers of glyceraldehyde

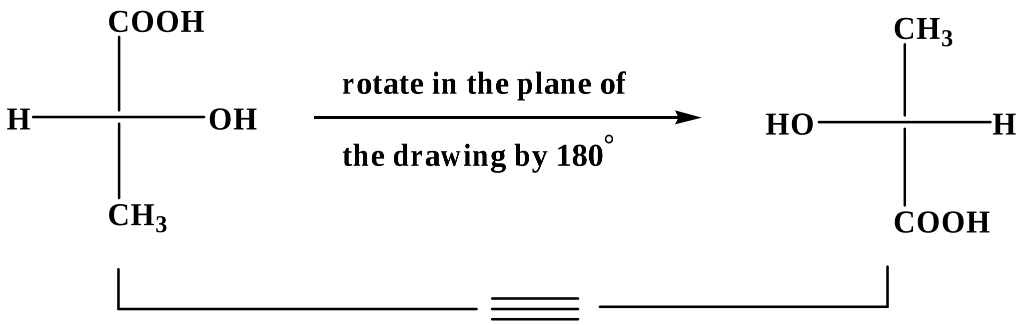
18.3.2. FISCHER PROJECTION

Although the wedge projection is convenient to represent three dimensional molecules with one and two asymmetric carbon atoms, wedge projections become increasingly complicated with increasing number of carbon atoms. For this reason, Emil Fischer introduced a projection in 1891 which is still in use. This projection is constructed as follows. The wedge projection or the three dimensional model of the molecule, is so rotated that two groups attached to the asymmetric carbon atom are above the plane of the paper and the two groups are below the plane of the paper. The molecule is then represented by two lines intersecting at right angles to each other. The asymmetric carbon atom is at the point of intersection which is usually not shown. Then, the groups which are above the plane of the paper are attached to the horizontal line and those groups which are below the plane are attached to the vertical line. It is convenient to place the longest carbon chain vertically. The construction of Fischer projection is illustrated with glyceraldehydes as an example.

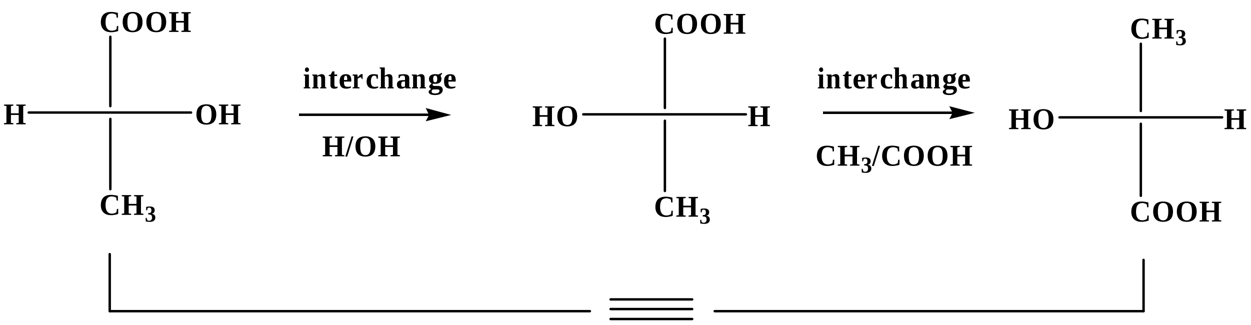


In order to standardize the Fischer projection formulae, the following rules must be observed.

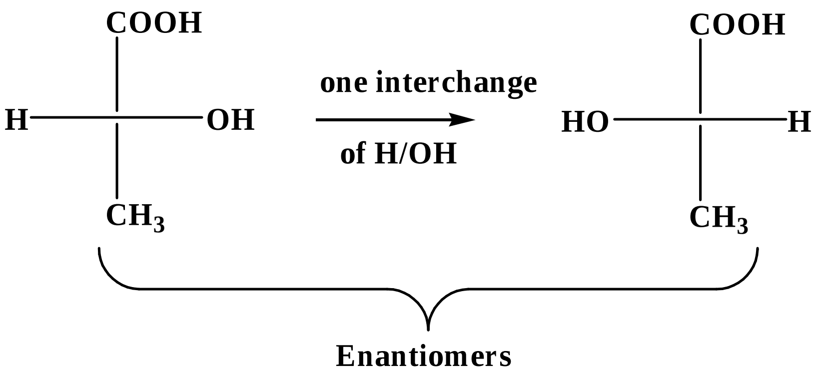
1. Projection formulas may be rotated in the plane of the paper by 180^0 with out their stereochemical meaning being changed; the two projections given below refer to the same molecule.



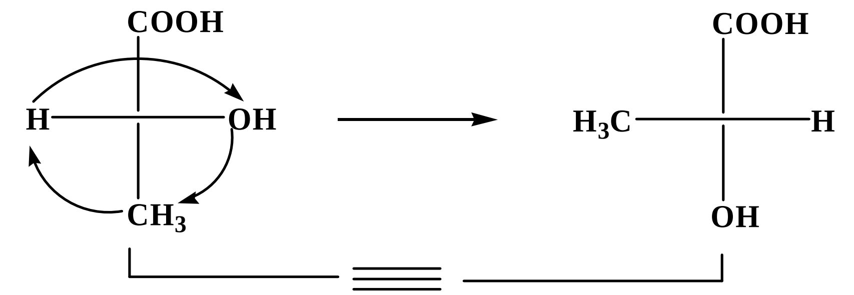
2. Two or any even number of interchanges (or transpositions) of substituents at an asymmetric carbon atom, do not alter the stereochemical of the projection formula.

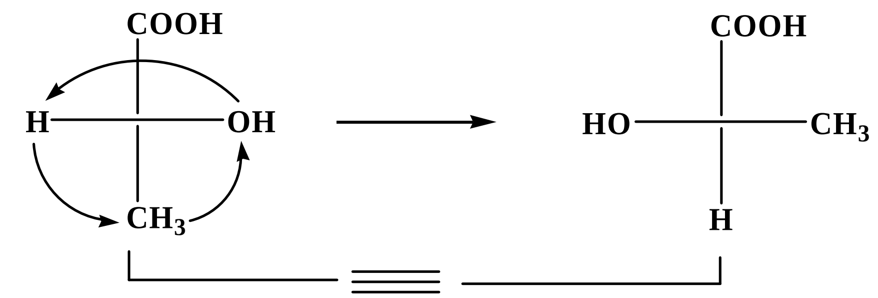


3. One such interchange or any other odd number of interchanges of substituents at the asymmetric carbon atom will lead to the projection formula of the optical antipode (enantiomers) of the original molecule.



4. It is not permissible to rotate the projection formulas in the plane of the paper by either 90^0 or 270^0.
5. Apart from transpositions, projection formulae can be transformed by rotating a group of three substituents either in clockwise or in anticlockwise direction, while keeping the fourth substituent stationary. Such a transformation is equivalent to two interchanges of substituents and does not alter the stereochemical meaning of the projection formula.





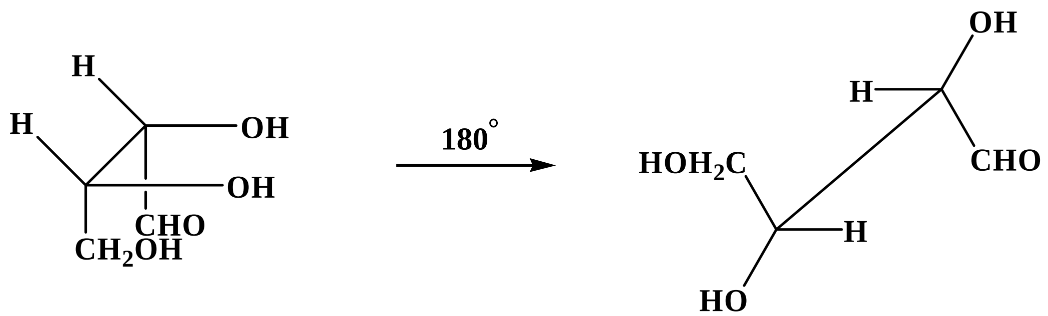
6. Projection formulas may not be lifted out of the paper that is, one must not for example, view them from opposite side of the paper; the stereochemical meaning of the formula will be changed.

Although widely used, Fischer projection has certain disadvantages. For compounds containing two or more asymmetric carbon atoms, Fischer projection represents the molecule as its high energy eclipsed conformation, whereas the staggered conformation is more stable. For example, the projection for **(-)-threose** implies an eclipsing relationship of groups attached to the two chiral centres.

In order to overcome the shortcomings of Fischer projection, two more projections have been introduced.

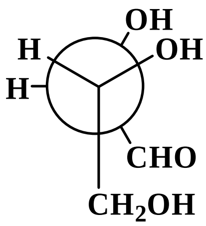
18.3.3. SAWHORSE REPRESENTATION

In sawhorse representation, the bond between the chiral carbon atoms is drawn diagonally, implying that it runs downwards through the plane of the paper and is slightly elongated for clarity. The substituents on each of the carbon atoms and is slightly elongated for clarity. The substituents on each of the carbon atoms are then projected on the plane of the paper and can be represented in staggered or eclipsed conformations. Eclipsed and staggered conformations of (-)-erythrose are shown below.

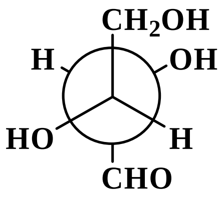


eclipsed **staggered**

In Newmann projection (introduced of Melvin S.Newman of Ohio State University), the molecules is viewed along the bond joining the chiral carbon atoms, and these are represented as superimposed circles, any one circle being drawn.



eclipsed



staggered

The remaining bonds and the substituents are then projected on to the plane of the paper. The bonds to the nearer carbon atom are drawn from the centre of the circle and those to the further carbon atom are attached to the perimeter.

18.4. LET US SUM UP

In this lesson, we:
Pointed out

- Optical activity
- Specific rotation
- Enantiomers
- Optical activity and chirality
- Asymmetric carbon (chiral carbon atom or stereogenic centre)
- 18.3. Projection formulae
- Wedge projection
- Fischer projection

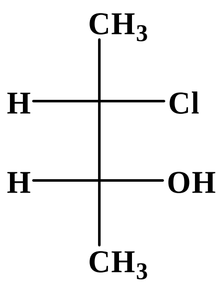
18.5. CHECK YOUR PROGRESS

1. How will you tell whether a molecule is chiral or not?
2. State the condition for optical inactivity of conformationally mobile molecule.

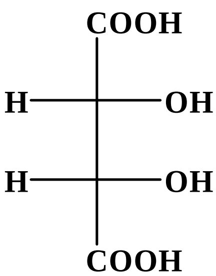
18.6. POINT FOR DISCUSSION

1. Translate the following Fischer projections into staggered forms of Sawhorse and Newmann projections.

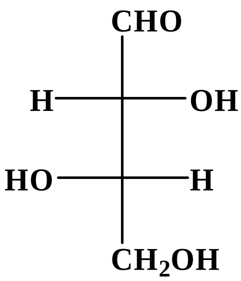
(a)



(b)



(c)



2. Secondary and tertiary amines with different alkyl groups are expected to be chiral. However such molecules have never been resolved. Explain.
3. Sketch the Sawhorse and Newmann projections of erythro- and threo- forms of 1-bromo-1,2-diphenylpropane both in eclipsed and staggered conformations.

18.7. REFERENCES

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2. I.L. Finar, Organic Chemistry, Vol. 2., 5th edition, ELBS & Longman group Ltd., 1974.

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LESSON: 19 – STEREOISOMERISM: CONFIGURATIONAL NOMENCLATURE

CONTENTS

19.0. AIMS AND OBJECTIVES

The aim is to motivate and enable the student to comprehensive knowledge on configurational nomenclature of organic compounds.

On successful completion of this lesson the student should have:

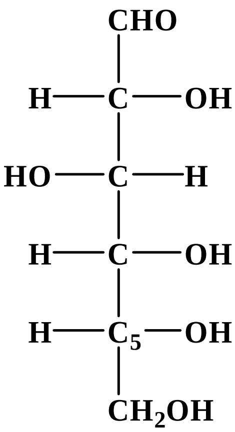
* learnt the configurational nomenclature of organic compounds.

19.1. INTRODUCTION

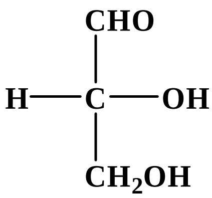
The different modes of representation of three-dimensional chiral molecules on two-dimensional paper, have already been discussed which include Fischer projection formula, sawhorse and Newman projection formulae. These formulae show the spatial structures of the molecules in their relative and absolute configuration which might be or might not be known but no nomenclatures were given to the formulae. For example, lactic acid has been represented by two Fischer projection formulae, one for dextrorotatory and the other for the levorotatory enantiomers.The problem now resolves itself into two: (i)Appropriate configurational 'descriptors' have to be given to the structures in the way one say's 'right' and ' left' to distinguish one's two hands (ii) Next, one must know which structure belongs to which enantiomers (assignment of configuration).It is necessary first to settle on some system of configurational nomenclature so that each structure may be identified by a specific name.

19.2 FISHER'S D AND L NOMENCLATURE

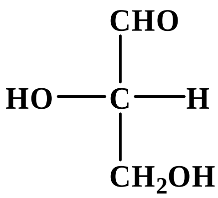
As early as 1890, Fisher while working in the sugar and amino acid chemistry felt the need for establishing relationship among members of a family of compounds (e.g., carbohydrates). He established the relative configuration of (+)-glucose and arbitrarily represented it by the structure (xvi, Figure 4.5) (he could have very well chosen its mirror image)*. He called it D-(+)-glucose, the descriptor 'D' referring to the configuration implied in the formula (I). Any sugar which could be genetically related to (+)-glucose through chemical transformations such as (+)-mannose and (-)-fructose was placed in the D family irrespective of their sign of rotation (Fisher originally used lower case d and l). the enantiomers were put in the L family. Since D-glucose (I) can be degraded into or synthesized from (+)-glyceraldehyde, the latter was arbitrarily given the D-configuration represented by II and (-)- glyceraldehydes the L-configuration represented by III (they retain the C-5 chiral centre of D and L-glucose respectively). Most of the sugars (and analogous compounds) may, in principle, be genetically related either to D- or to L-glyceraldehyde and their configurations were accordingly defined by D or L. This genetic nomenclature, however, did not work since in many cases, both the enantiomers of a compound may be chemically correlated to the same glyceraldehydes, e.g., (+)- and (-)- lactic acid to D-glyceraldehyde; the former is obtained by reduction of CHO to Me and oxidation of CH_2OH to CO_2H and the latter by oxidation of CHO to CO_2H and reduction of CH_2OH to CH_3.



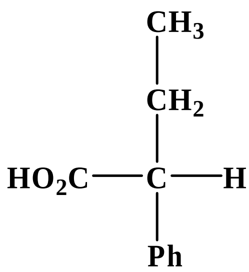
(I)



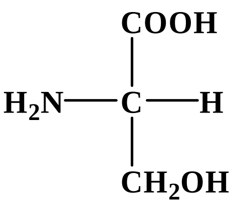
(II)



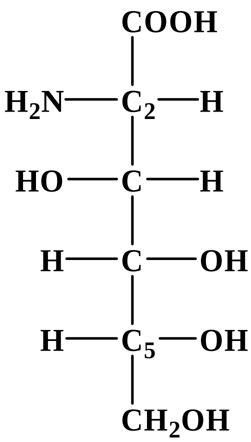
(III)



(IV)



(V)



(VI)

To circumvent the difficulty, Rosanoff (1906) modified the system and suggested a projection nomenclature according to the following conventions:

(i) As in Fischer's system, the molecule is written with the longest carbon chain placed vertically.

(ii) The most highly oxidized end of the chain is placed at the top (as CHO in glucose), again following Fischer's convention.

(iii) If in the projected structure, the OH group (or any negative group,X) at the bottom-most (highest-numbered) chiral centre (C-5 in glucose) is on the right hand side, the molecule is given D configuration and if it is on the left, the molecule is given L configuration (as in D- and L-glyceraldehyde respectively). The Fischer- Rosanoff system does not refer to the origin of the compound (non-generic) and is commonly used in all textbooks.

However, only molecules which can be projected in a manner similar to sugars can fit into this scheme of nomenclature. For example, 1-phenylbutyric acid (IV) cannot be written in Fischer projection following both the specifications (i) and (ii) simultaneously : either the longest carbon chain can be placed vertically as in IV or the highest oxidized end, carboxylic group be placed at the top.

For amino acids, L-(-)-serine with the configuration (V) is used as reference which introduces a further complication in defining the configuration of molecule containing both hydroxyl and amino groups. Thus 2-amino-2-deoxymannonic acid (VI) may be given D label with reference to glyceraldehyde (see C-5) but L label with reference to serine (see C-2). The problem can be solved by using subscripts 'g' for glyceraldehyde and 's' for serine so that the amino- mannonic acid may be designated either as D_g or as L_s (Slocum, Sugarman, and Tucker 1971).

19.3. R AND S NOMENCLATURE

A self-consistent and unambiguous system of configurational nomenclature based on the three-dimensional structures of molecules was first introduced by Cahn and Ingold (1951) and subsequently elaborated by Cahn, Ingold, and Prelog (1955,1966).The system is known as CIP nomenclature after the names of the authors. According to this system, the configuration of a molecule is specified uniquely either as R (from rectus, Latin for right) or as S (from sinister, Latin for left) which is independent of nomenclature and numbering. Like D and L,R and S are also topographical descriptors, used as prefixes* and have nothing to do with the signs of rotation.

Assignment of configuration is done by the application of two rules: the sequence rule (consisting of several standard subrules) and the Chirality rule. The sequence rule arranges the four ligands of a chiral centre (Cabcd) in a priority sequence, e.g., a>b>c>d ('a' having the highest priority and'd' the lowest), or the ligands may be numbered : 1>2>3>4. The chiral centre is then viewed from the side remote from the lowest ranking group ('d' or 4) (Figure 19.3.1). If from this point of view, the arrangement $a \rightarrow b \rightarrow c$ $(\text{or}\, 1 \rightarrow 2 \rightarrow 3)$ appears in the clockwise (right-handed) direction, the configuration is R and if the arrangement appears in the anticlockwise (left-handed) direction, the configuration is S. This is known as the Chirality rule.

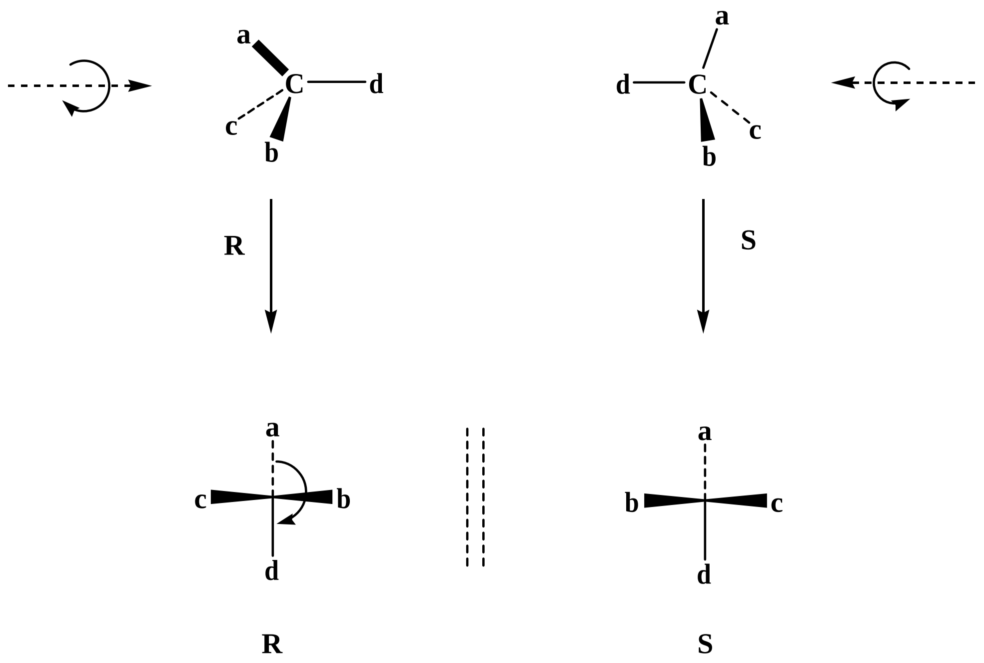


Fig. 19.3.1 Chirality rule: R and S nomenclature

The standard subrules which determine the priority order are six in number (actually, they themselves may be called the sequence rules) and have been stated under the headings (0)-(5) (Cahn, Ingold, and Prelog 1966)*.They must be applied in succession, i.e., one after the other in the order stated.

Sequence rules or standard subrules

(0) Nearer end of an axis or a plane precedes the farther end (proximity rule).
(1) Higher atomic number precedes lower, e.g., S>F>O>N>C>H.
(2) Higher atomic mass number precedes lower, e.g., T>D>H.
(3) Cis precedes trans; and Z precedes E.
(4) Like pair R,R or S,S precedes unlike pair R,S or S,R; M,M or P,P precedes M,P or P,M; R,M or S,P precedes R,P or S,M M,R or P,S precedes M,S or P,R; and r precedes s.
(5) R precedes S; and M precedes P.

For the majority of compounds, only subrules (1) and (2) are important; the other subrules apply only to special cases. Subrule (0) is applicable to axial and planar Chirality. Subrule (1) needs further elaboration which is done in the following paragraphs:

1. Atoms directly attached to the central chiral atom must be sequenced first according to subrule (1). If the priority still remains undecided for some of the ligands, one passes over to the Next atom in the ligands and the exploration continues until a decision is reached on the basis of subrules. The following examples illustrate the point:

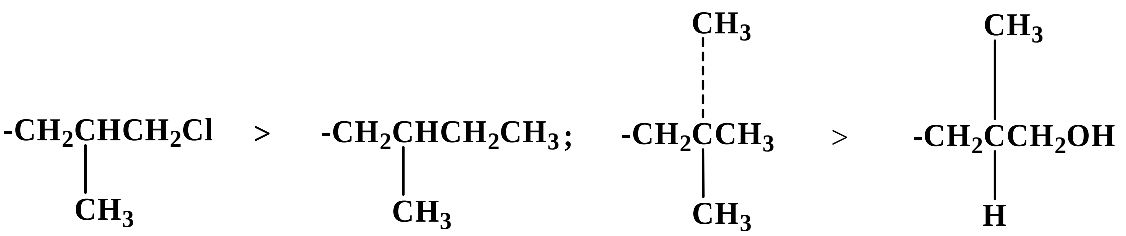
$-CH_2\mathit{CH_3}$ > $-CH_2\mathit{H}$;$-CH_2\mathit{OH}$ > $-CH_2\mathit{N}H_2$; $-CH_2CHF\,\mathit{Br}$ > $-\ CH_2CHF\mathit{Cl}$

(Decision is reached at the italicized atoms)

It may be noted that subrule (2) must not be used until subrule (1) is completely exhausted; thus

$-CH_2CH_2CH_3$ > - CD_2CH_3 because propyl > ethyl (subrule 1); but $-CH_2CD_2CH_3$ > $-CH_2CH_2\,CH_3$ (subrule 2).

2. In case a ligand bifurcates, one must proceed along the branch providing the highest precedence until a difference is encountered. The decision must be made at the earliest opportunity and once made, cannot be changed from consideration of substituents farther along the chain. These points are illustrated below:



3. When the central atom is a part of ring system, each branch is followed until a decision is reached as shown in Figure 19.3.2a below (see Prelog and Helmchen 1982 for complicated cases):

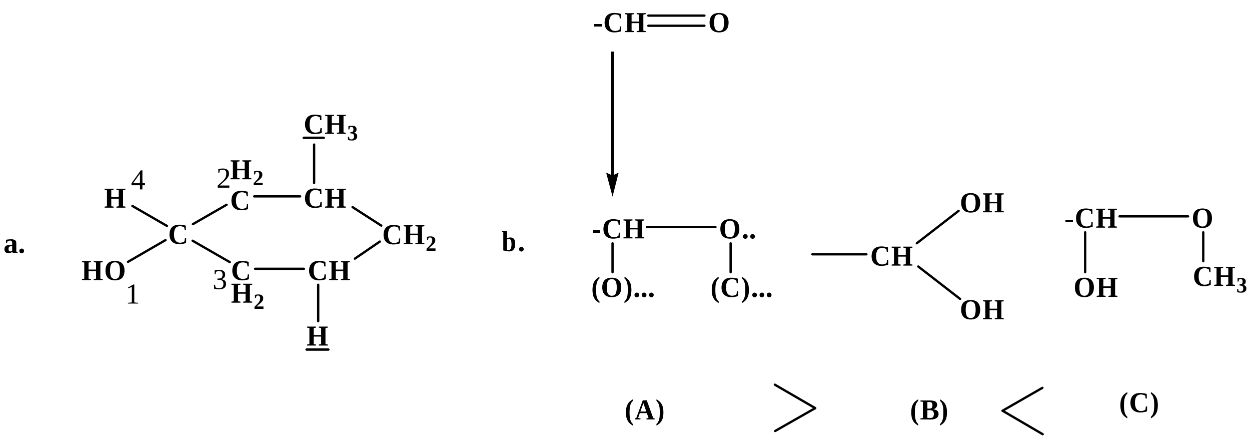


Fig. 19.3.2. (a) Priority sequence in ring system; (b) aldehyde versus hydrated aldehyde versus hemiacetal.

4. In the case of atoms with multiple linkages, the atom to which they are multiply bonded must be duplicated or triplicated as the case may be at both ends of the multiple bond. The duplicate atoms are put into parenthesis and except for hydrogen are made up (complemented) to ligancy four with phantom atoms of atomic number zero. Thus the representation of the aldehyde group, -CHO is shown (Figure 19.3.2b) along with its hydrated form and hemiacetal for comparison. From the structures (A),(B), and (C), it is clear that –CHO has preference over the hydrated form (B) but the hemiacetal (C) has preference over the aldehyde (A). The last point illustrates the utility of the phantom atom which has lower priority than hydrogen. In the following illustrations, (Figure 19.3.3) the phantom atoms are omitted.

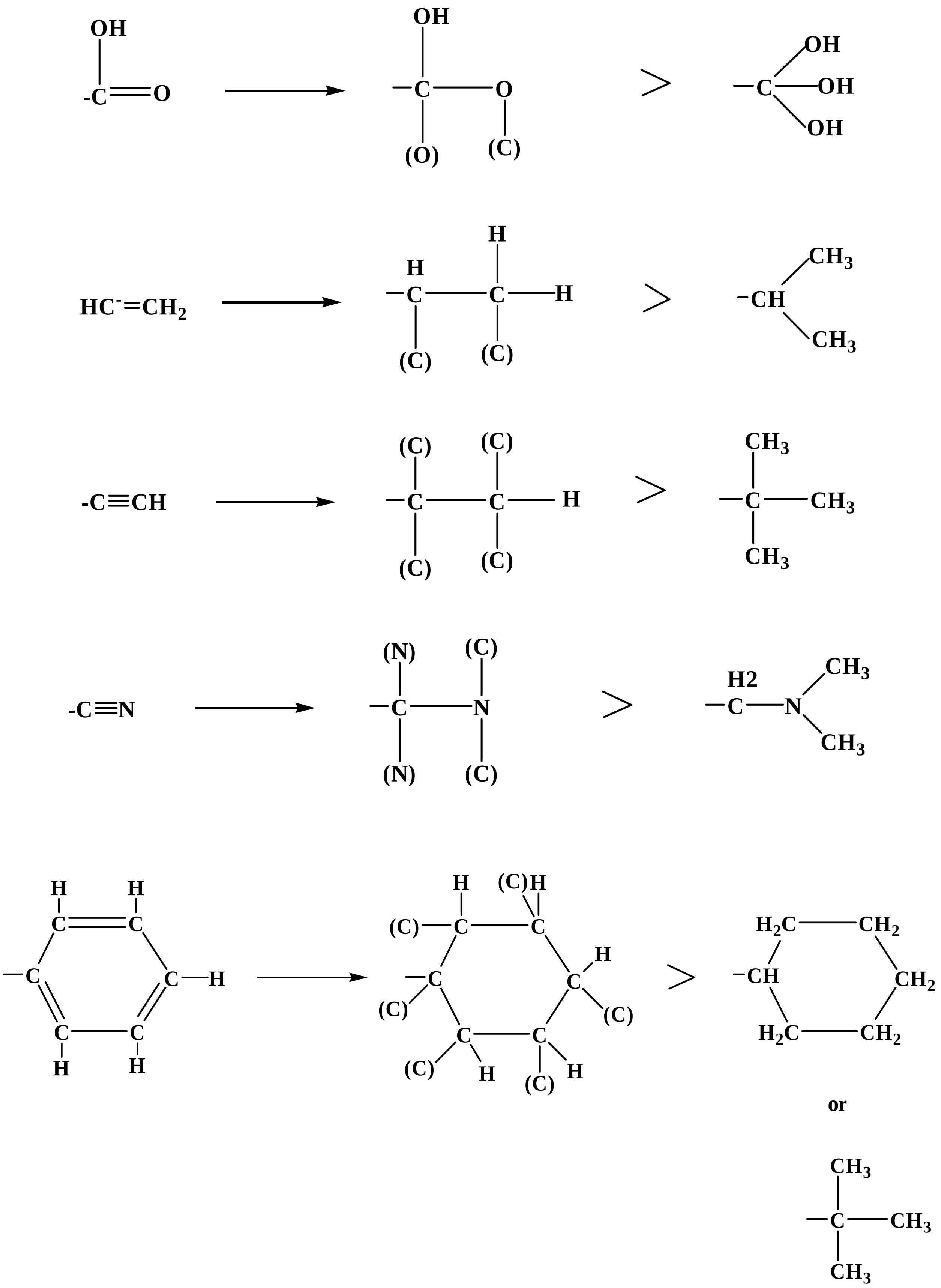


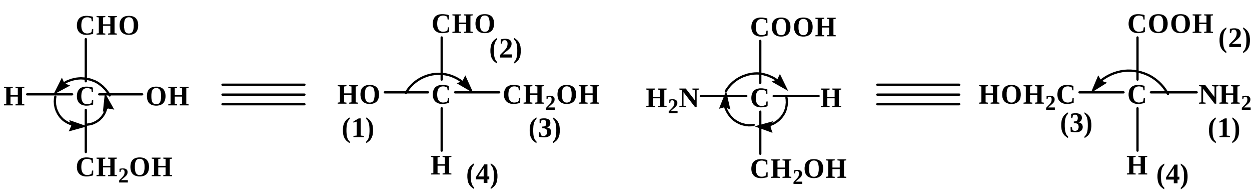
Fig. 19.3.3 Priority sequence of some common groups

In Table 19.3.1, a few atoms and groups are listed in order of increasing priority. In the absence of a lone pair of electrons (in the case of tricoordinate atoms), H has the lowest priority. Actually, a lone pair (as on N) is equated to a phantom atom of atomic number zero.

Table 19.3.1 Atoms and groups with increasing priority

1. H	10. $CH=CH_2$	19. CO_2R	28. OCOR
2. D	11. $C(CH_3)_3$	20. NH_2	29. F
3. CH_3	12. $C\equiv CH$	21. $NHCH_3$	30. SH
4. CH_2CH_3	13. C_6H_5	22. $N(CH_3)_2$	31. SR
5. $CH_2(CH_2)nCH_3$	14. CH_2OH	23. NO	32. SOR
6. CH_2-$CH=CH_2$	15. CH=O	24. NO_2	33. SO_2R
7. CH_2-$C\equiv CH$	16. COR	25. OH	34. Cl
8. $CH_2C_6H_5$	17. $CONH_2$	26. OCH_3	35. Br
9.$CH(CH_3)_2$	18. CO_2H	27. OC_6H_5	36. I

Once the priority order of the ligands is settled, the configurational assignment is made by applying the Chirality rule. If one deals with a three-dimensional model, the task is very simple one only has to look at the molecule from the side opposite to'd' and determine the order of $a \rightarrow b \rightarrow c$. Difficulty arises since most of the molecules are represented by Fischer projection. The method recommended earlier by Eliel (1962) was to draw the projection always with 'd' at the bottom as shown in Figure 19.3.1 (bottom row) and then describe a semicircle joining $a \rightarrow b \rightarrow c$ the direction of which indicates the configuration. Any Fischer projection can be manipulated either by exchanging two pairs of ligands or rotating a group of three either clockwise or anticlockwise to conform to this requirement. This is demonstrated in assigning the configurational descriptors to D-(=)-glyceraldehyde and L-(-)-serine respectively (Figure 19.3.4). In both the instances, R and S correspond to D and L respectively but this does not mean that the two pairs of descriptors are necessarily synonymous (e.g., L-cysteine≡R-cysteine)*

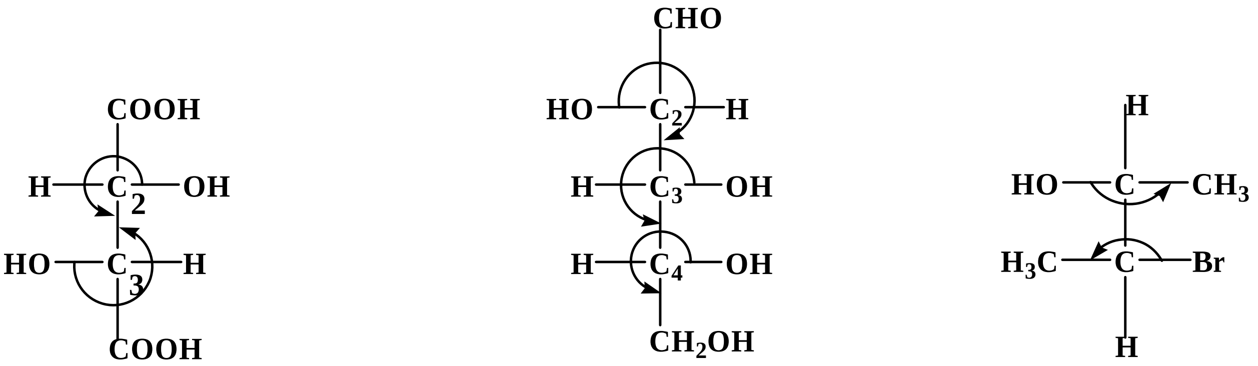


D (I) R L (II) S

Fig. 19.3.4. Assignment of R and S descriptors

A number of alternative procedures for assigning R and S on the basis of Fischer projection have been suggested from time to time. The simplest and most widely accepted one is due to Epling (1982). The procedure, named as "very good" (a mnemonic device for "vertical = good") consists of two operations : fixing up the priority order of the ligands and tracing a semicircle joining $a \rightarrow b \rightarrow c$ ignoring 'd', the lowest priority group. If 'd' is on the vertical line in Fischer projection (it does not matter whether it is at the top or at the bottom), the sequence gives the correct descriptor* ; if on the other hand, 'd' is on the horizontal line, the sequence gives the wrong answer and the descriptor assigned on this basis should be reversed. The procedure is illustrated with (+) –tartaric acid (I), D-(-)-arabinose (II), and 3-bromobutan-2-

ol (III) (Figure 19.3.5). In the descriptors arrived at from the sequence $a \rightarrow b \rightarrow c$ have to be reversed. In the third case, H is on the vertical line in both the chiral cerntres and the sequence $a \rightarrow b \rightarrow c$ gives the correct descriptor.

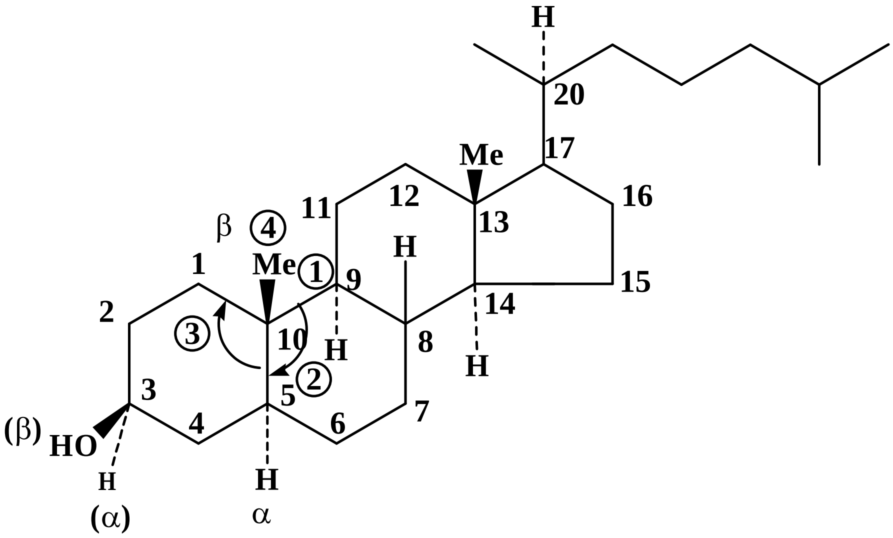


(I) **(II)** **(III)**

2(R), 3(R) **2(S), 3(R), 4(R)** **2(S), 3(S)**

Fig. 19.3.5. Example of the 'very good' mnemonic

Cyclic molecules such as steroids and terpenes are usually projected on the plane of the paper and hydrogens (or substituents) located below and above the plane are assigned α and β descriptors respectively (α represented by dotted and β by thick lines as shown in 3-cholestanol I in Figure 19.3.6) – a system recommended by the Chemical Abstract Service (Pure and Applied Chem., 1972,**31**,283). These descriptors relate to relative configuration and are meaningful if the cyclic system is drawn in an accepted way as in steroids and terpenes. For absolute configuration, each of the chiral centre in the cyclic molecule must be defined by RS descriptors following CIP nomenclature. A convenient method has been suggested by Eliel (1985) which is as follows. At any particular chiral centre, one ligand must be clearly in the front (F) or clearly in the back (B). This would be regarded as the reference ligand. The order (clockwise or anticlockwise) of the remaining three can be very easily determined, all three being in the plane of the paper. If this reference ligand is 4/B (lowest locant and in the back), the sequence of the remaining three ligands would give the correct descriptor. So 4/B(+) may be used as a mnemonic [(+) stands for correct]. For other combinations, the numbers will alternate with signs, e.g.,4/B(+),3/B(-),2/B(+),1/B(-) and 4/f(-),3/F(+),2/F(-),1/F(+). For example, the C-10 chiral centre of cholestanol (**XXIV**) corresponds to 4/F and so although the order $1 \rightarrow 2 \rightarrow 3$ is



(XXIV)

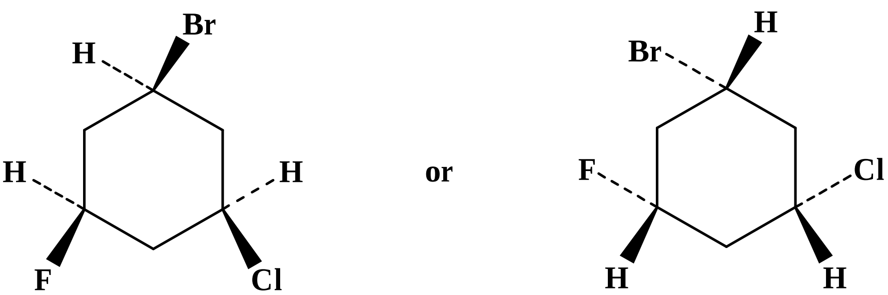
Fig. 19.3.6. 3(S), 5(S), 8R, 9(S), 10(S), 13R, 14(S), 17R, 20(S), -cholestan-3-ol (Numericals in circle represent priority order of substituents at C-10).

clockwise, the configuration is S. The configurational labels at the other chiral centres may be worked out likewise.

An algorithmic rule for assigning R and S descriptors to a chiral centre in cyclic molecules has recently been worked out (Kotera 1986). However, the procedure is difficult to remember and it may be of academic interest only.

19.4. R* AND S* NOMENCLATURE

The R, S nomenclature when applied to a molecule with multiple chiral centres, fixes both the relative and the absolute configuration. Thus 1R-bromo-3S-chloro-5R-flurocyclohexane refers only to the enantiomers (I) (Figure 19.4.1). It often happens that pure enantiomers are available with known relative but unknown absolute configuration. In such cases, the R, S system of nomenclature is modified as follows (IUPAC Commission 1976). The atoms are numbered such that the chiral centre having the highest priority ligand, e.g., C-Br in I is given the lowest number (lowest lovant). The molecule is so written that the lowest chiral lovant gets the R configuration. Assignment to the other chiral centres is made by the usual method and



(I) (II)

Fig. 19.4.1. R* and S* nomenclature: 1(R*)-bromo-3(S*)-chloro-5(R*)-fluorocyclohexene

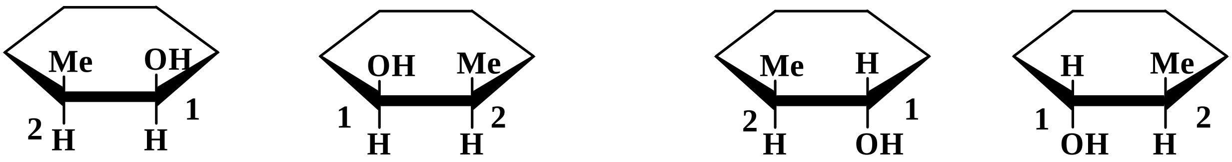
each of the descriptors is put under asterisk (pronounced as R-star and S-star) to indicate that they represent relative configuration. Thus 1R*-bromo-3S*-chloro-5R*-fluorocyclohexane represents either of the enantiomeric structures (I) and (II).

19.5. CIP NOMENCLATURE OF RACEMATES

For the configurational assignment to racemates, IUPAC Commission recommends the joint use of R,S for labeling, a chiral centre, Thus (±)-tartaric acid is designated 2RS,3RS-dihydroxysuccinic acid.

19.6. NOMENCLATURE OF POLYSUBSTITUTED CYCLANES

Polysubstituted cyclanes, e.g., cyclopentanes, cyclohexanes etc. exit in a number of stereoisomers (diastereomers and enantiomers) depending on the number and nature of the substituents. The disubstituted cyclanes give two diastereomers which can be conveniently and unambiguously described as cis and trans isomers, e.g., cis-and trans-2-methylcyclohexanols (I) and (II) (Figure 19.6.1). Each of the diastereomers in turn gives two enantiomers which can be named, following the R,S nomenclature, as R,S and S,R for the cis and S,S and R,R for the trans isomer (use 4/B rule) as shown in the Figure.

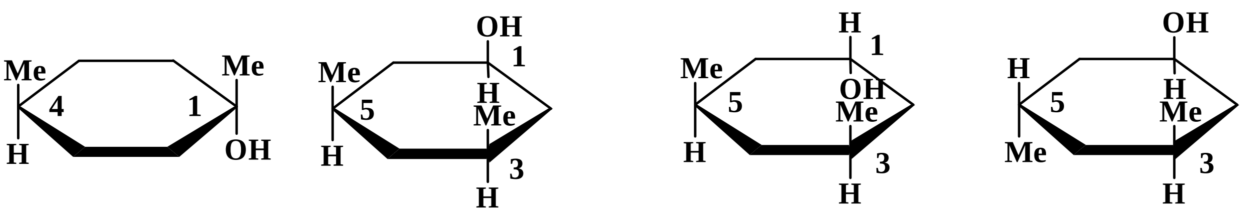


1R, 2S **1S, 2R** **1S, 2S** **1R, 2R**

(I), cis **(II), trans**

Fig. 19.6.1. Disubstituted cyclohexanes

Difficulty arises when the number of substituents increases, e.g., dimethylcyclohexanols (I)-(IV) (Figure 19.6.2). The prefixes, cis and trans are no longer unambiguous and, if applied without any reference, lead to confusion; thus compound (I) may be called cis with respect to the two methyl groups but trans with respect to the 4-methyl and 1-hydroxyl group. Since many of these compounds are achiral (meso) (I-IV), the R, S nomenclature also becomes inapplicable. Moreover, the steric relationship does not become immediately apparent from such



(I) **(II)** **(III)** **(IV)**

Fig. 19.6.2. Polysubtituted cyclohexanes

nomenclature. To obviate this difficulty, a method of nomenclature known as Beilstein system (see Eliel 1971) has been adopted which is as follows:

(i) A reference group denoted by symbol ‘r’ is specified with respect to which the other substituents are described as cis or trans.

(ii) The r-group is so chosen that it is attached to the lowest lovant (the lowest numbered ring member) according to IUPAC rules (vide supra).

(iii) If two ligands are attached to the lowest locant, that one is selected as r-group which has preference in the IUPAC nomenclature.

(iv) When there are two constitutionally equivalent pathways of going around the ring starting from the lowest lovant, that giving the cis attachment to the second substituent (the first being the r-group) is chosen.

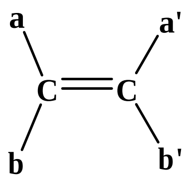
Following the rules, the compounds (I), (II), (III), and (IV) are named respectively as 1, trans-4-dimethylcyclohexan-r-1-ol, (4-Me is trans to OH), cis-3,cis-5-dimethylcyclohexan-r-1-ol, trans-3,trans-5-dimethylcyclohexan-r-1-ol, and cis-3-trans-5-dimethylcyclohexan-r-1-ol [according to rule(iv), the carbon bearing cis methyl is counted as 3]. The common practice is to abbreviate the names, by replacing cis and trans by c and t respectively.

The structure (IV), although chiral, has S-configuration both at C-3 and at C-5 which makes it impossible to give a configurational descriptor to C-1. In fact, C-1 is chirotopic (as judged by local symmetry) but non-stereogenic (exchange of H and OH does not give any new stereoisomer). On the other hand, C-1 in I-IV is achirotopic but stereogenic.

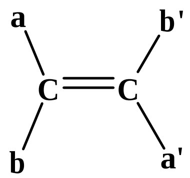
19.7. E AND Z NOMENCLATURE

It has been shown that olefinic compounds like 2-butene can exist in two diastereomeric forms which are called cis and trans isomers. The necessary and sufficient condition for this type of isomerism is that ‘a’ and ‘b’ in Cab = Cab must be non-equivalent. In the case of Cab = Nx, (Nx = Nx), the missing substituent is the lone pair of electrons on nitrogen. Since this isomerism owes its existence to the presence of a π - bond, it has been called π -diastereomerism (Pierre 1971) to distinguish it from σ -diastereomerism exhibited by cyclic compounds*. The π -diastereomers are two-dimensional molecules (if one ignores the geometry of the ‘a’ and ‘b’ groups), possess a plane of symmetry, and therefore are achiral. On the other hand, the σ -diastereomers are three dimensional and may be chiral. For molecules of the type, Cab = Cab or Cab = Cac, the terms ‘cis’ and ‘trans’ are adequate and unambiguous. But if three or four of the substituents are different, this nomenclature leads to ambiguity and sometimes to total confusion.

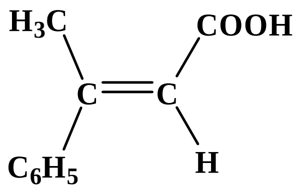
An easy solution to the problem is provided by arranging the pair of ligands at each trigonal carbon in CIP sequence. Then if the groups of higher priority are on the same side, the configuration is seq-cis; if they are on the opposite sides, the configuration is seq –trans (CIP 1966). Thus if a precedes b and a’ precedes b’, the configuration of the compounds (I) and (VIII) (Figure 19.7.1) are seq-cis and seq-trans respectively. Later, the system has been modified (Blackwood et al 7968), the two terms being replaced by two shorter symbols, X (from the German zusammen meaning ‘together’) and E (from the German entgegen meaning ‘across’) which are used as prefixes to the olefins. According to this system, β - methylcinnamic acid (III) is called E-3-phenylbut-2-enoic acid (here Ph and CO_2H groups are fiducial*). The previously called cis-1,2-dichlorobromoethene (**c**) is now known as E-1-bromo-1,2-dichloroethene which goes to prove that E and Z do not always correspond to trans and cis.



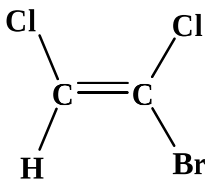
(I)



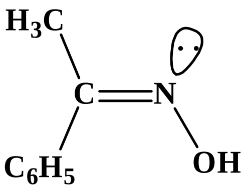
(II)



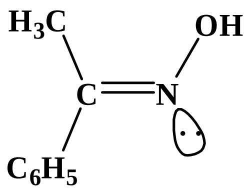
(III)



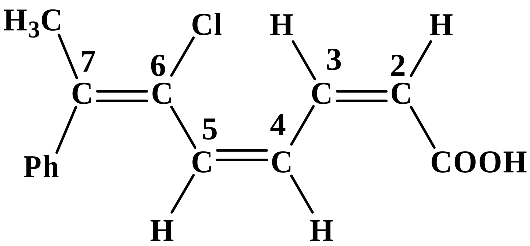
(IV)



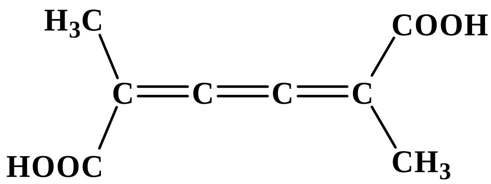
(V)



(VI)



(VII)



(VIII)

Fig. 19.7.1. Examples of *E* and *Z* nomenclature

This system leads to a great simplification in the nomenclature of the diastereomeric oximes for which the (often ambiguous) terms ‘syn’ and ‘anti’ were previously coined. Thus the syn (V) and the anti (VI) oximes of acetophenone are now called Z- and E-isomers respectively.

In the case of compounds, containing more than one non-cumulated (belonging to different carbon atoms) double bonds, the number of π -diastereomers (2^n where n is the number of non-equivalent double bonds) increases. The descriptors Z and E can be applied to each diastereogenic unit. Thus the triene (VII) is 6-chloro-7-phenylocta-2Z, 4Z, 6E-trienoic acid.Cumulenes with an odd number of cumulated (consecutive) double bonds with two = Cab as terminal groups display π -diastereomerism and E,Z nomenclature is applicable to them also. Thus the cumulene (VIII) is E-isomer.

19.8. LET US SUM UP

In this lesson, we:
Pointed out

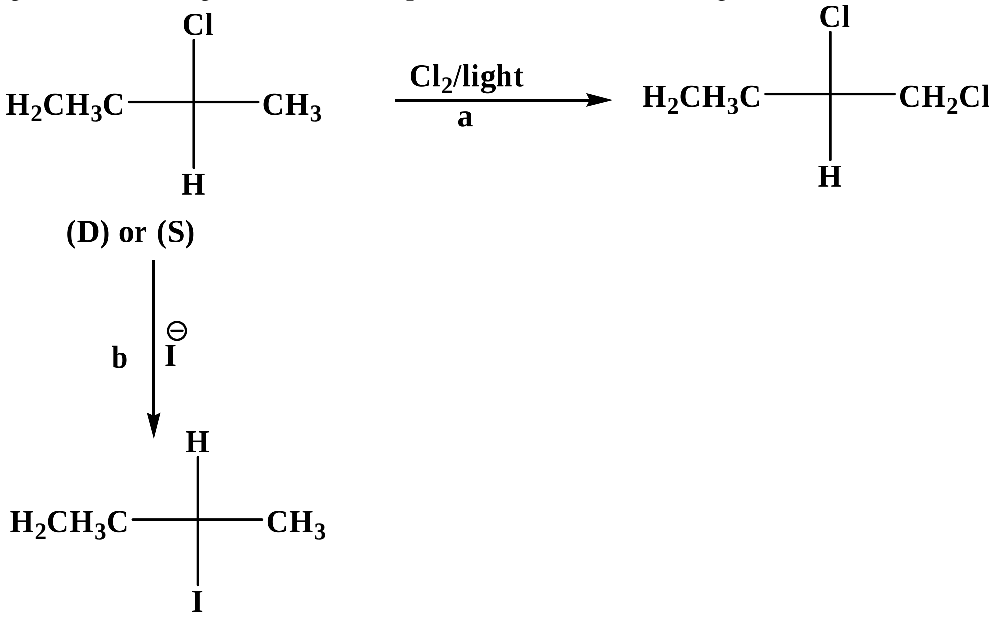
- Fisher’s D and L nomenclature
- R and S nomenclature

- R* and S* nomenclature
- Cip nomenclature of racemates
- Nomenclature of polysubstituted cyclanes
- E and Z nomenclature

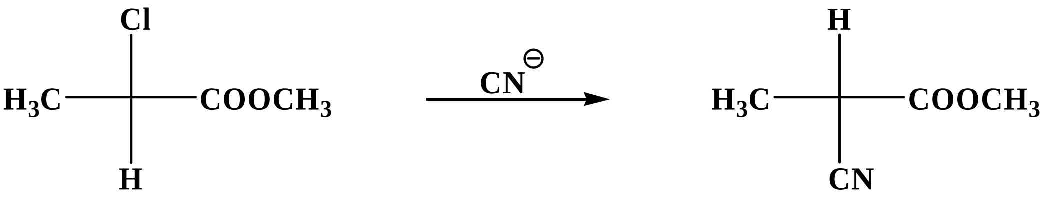
19.9. POINTS FOR DISCUSSION

1. Designate the configurations of the products of the following reaction as D/L and R/S.

(i)



(ii)



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LESSON: 20 – STEREOISOMERISM: CONFORMATION OF ACYCLIC AND CYCLIC COMPOUNDS

CONTENTS

20.0. AIMS AND OBJECTIVES

The aim is to motivate and enable the student to comprehensive knowledge on conformation of acyclic and cyclic organic compounds.

On successful completion of this lesson the student should have:

* learnt the conformation of acyclic and cyclic organic compounds.

20.1. INTRODUCTION

The total energy possessed by a molecule is directly related to its geometry. A molecule will adopt that geometry that minimizes its total energy. Many molecules exhibit strain caused by non-ideal geometry and the decreased stability of a molecule is called strain energy. The sources of strain in alkanes and cycloalkanes are :

a) **Bond length distortion :** It is the destabilization of a molecule that results when one or more of its bond distances are different from normal values.

b) **Angle strain :** It is the destabilization that results from the distortion of bond angles from the normal values.

c) **Torsional strain :** It is destabilization that results from eclipsing of bonds on adjacent atoms.

d) **Van der Waals strain :** It is the destabilization that results when atoms or groups on non-adjacent atoms approach too close to each other.

The various momentary spatial arrangements of atoms of a molecule that result from rotation about single bonds are known as conformations. That is, a molecule of a given structure and configuration can have different conformations. Conformational analysis of physical and chemical properties of a compound in relation to its geometry and population of its conformers.

20. 2. CONFORMATIONS OF ETHANE

Consider the ethane molecule, CH_3-CH_3 and imagine that one methyl group is rotated about C-C bond as axis with other methyl group at rest. Figure 20.2.1 represents the change in

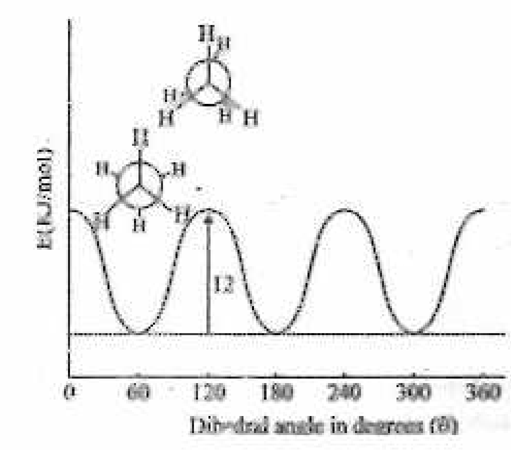
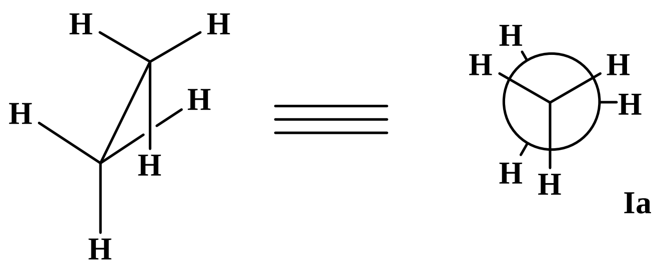


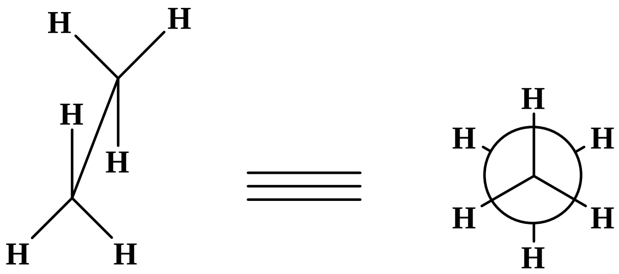
Fig. 20.2.1. Potential energy of ethane as a function of angle of torsion (dihedral angle).

potential energy of thane in the course of one complete rotation about C-C bond. Potential energy is plotted on Y-axis and the angle of torsion (or dihedral angle) (θ) is plotted on X–axis. In the case of ethane, there are six conformations of interest, the so called eclipsed conformations (Ia, Ib and Ic) corresponding to energy maxima for which $\theta = 0°$, 120° or 240° and the so called staggered conformations (IIa,IIb and IIc) which correspond to energy minima for which $\theta = 60°$, 180° and 300°. These conformations are represented in saw-horse and Newman projections (Figure 20.2.1)



Ia

Eclipsed conformations of ethane ($\theta =$ 0°, 120°, 240° and 360°).



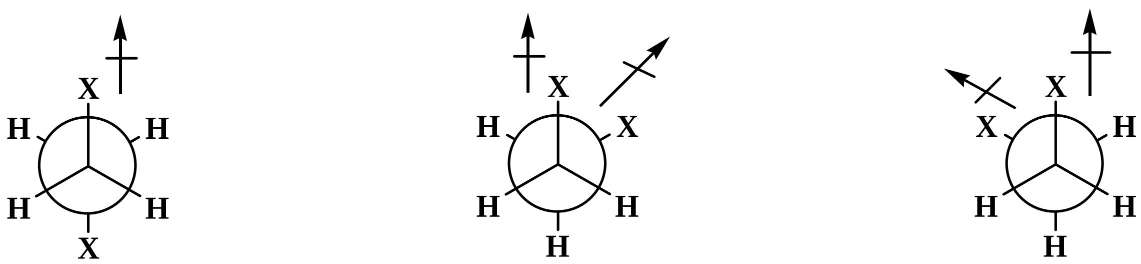
IIa

Staggered conformations of ethane (θ = 60°, 180° and 300°).

Figure 20.2.1shows that the staggered conformations (IIa, IIb and IIc) of ethane are 12 KJ/mol (2.9 Kcal/mol) lower in energy than the eclipsed conformations (Ia,Ib and Ic) and all energy minimia (stable conformers) are identical. A number of factors contribute to the stability of the staggered conformations. The staggered conformations allow for the maximum separation of bonded electron pairs. Electron pair repulsions are greatest when the bonds are eclipsed and least when the bonds are staggered. The destabilization associated with the eclipsing of bonds on adjacent atoms is called **torsional strain**. Since three pairs of eclipsed bonds produce 12.0 KJ/mol (2.9 Kcal/mol) of **torsional strain,** it is reasonable to assume that each pair of eclipsed bonds contribute 4 KJ/mol (1 KJ/mol) for an alkane. The 12 KJ/mol of rotational barrier in ethane is quite small and even at room temperature the fraction of collisions with sufficient energy is large enough that rapid interconversion between staggered conformations occurs. In other words, internal rotation in ethane is not completely free but is in an exceedingly rapid process and conformational equilibrium is reached readily.

20. 3. CONFORMATIONS OF 1,2–DIHALOGENOETHANES

In gaseous state at 22° C,1,2-dichloro and 1,2-dibromoethane exist predominantly in anti conformation (Ia) (73% and 83%) like n-butane (67%). However, the greater stability of anti form (Ia) in case of 1, 2–dihalogenoethanes compared with n-butane is due to the combined electronic (dipole-dipole) and steric effects. In polar solvents and in liquid state the dipole-dipole repulsion decreases due to high dielectric constant of the solvent and the proportion of the **gauche** conformations (Ib & Ic) increases.



anti (Ia) more stable **gauche (Ib)** **gauche (Ic)**

Fig. 20.3.1. Conformation of 1,2-dihalogenoethanes

As the number of halogen substituents increases as in 1,1,2,2- tetrahalogenoethenes (Figure 20.3.2), the **gauche** conformations (IIIb & IIIc) become forms (IIIb & IIIc) over **anti** (IIIa) is attributed to the widening of X-C-X bond **which** stablies the **gauche** over **anti**.

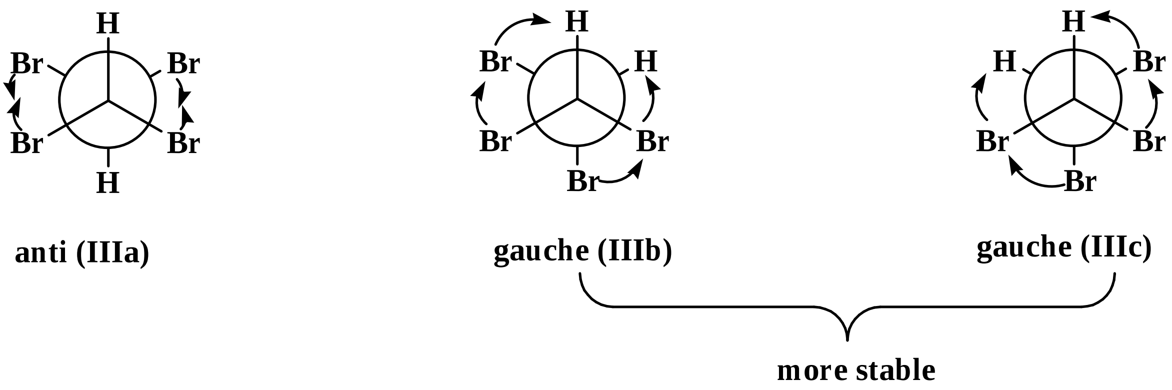


Fig. 20.3.2. Conformation of polyhalogenoalkanes

20. 4. CONFORMATIONS OF CYCLOHEXANE

The cyclohexane ring system is by far the most commonly occurring of cycloalkanes in natural products doubtless because of its stability and ease of its formation. In 1890, Sachse proposed that cyclohexane ring can exist in two non-planar (puckered) forms (chair and boat) which are free from bond angle strain. Since Sachse's theory of strainless rings required the existence of two isomeric forms of cyclohexane and all attempts to isolate them failed at that time, Sachse's theory was unrecognized for a long time. In 1918, Mohr revived Sachse's theory and explained the absence of isomeric forms of cyclohexane due to rapid interconversion of two forms. Mohr later pointed out that the union of two cyclohexane rings may result in the formation of two stereoisomeric forms – the **cis** and the **trans** decalins which can no longer be interconverted without bond rupture. Later, the two isomeric forms of declaims were realized.

According to the original assumption, the boat and chair conformations were considered to be equally probable for cyclohexane. However, the 1947, Hassel established by means of electron diffraction studies that cyclohexane exists predominantly in two chair conformations.

20. 4. 1. GEOMETRY OF THE CYCLOHEXANE RING SYSTEM

The chair form of cyclohexane ring system (I) is represented in the Figure 20.4.1.1, with the vertical C_3 axis. The Newman projections of chair forms of cyclohexane reveal that there are six gauche-butane interactions of chair forms of cyclohexane reveal that there are six gauche-butane interactions and consequently the enthalpy of cyclohexane chair form is estimated as $3.3 \times 6 = 19.8$ KJ/mol.

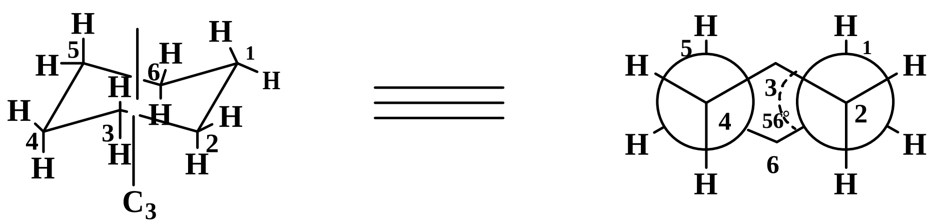
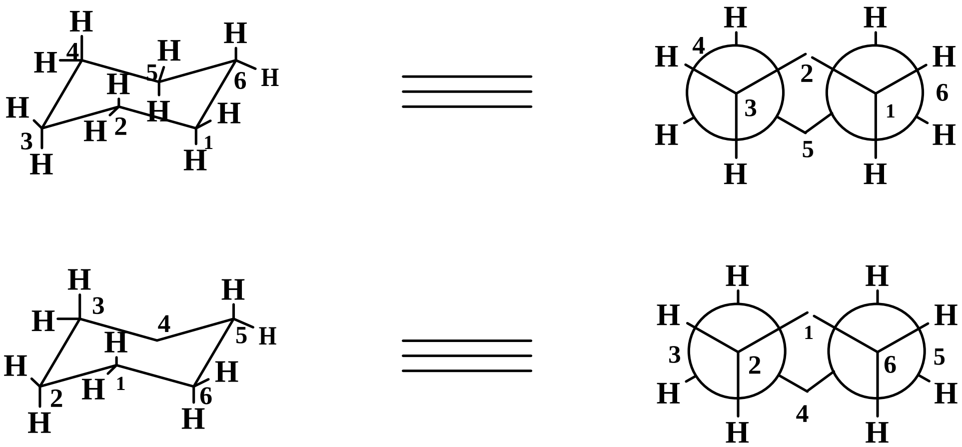


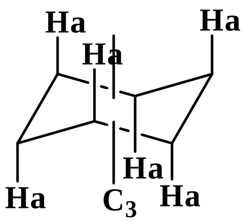
Fig. 20.4.1.1

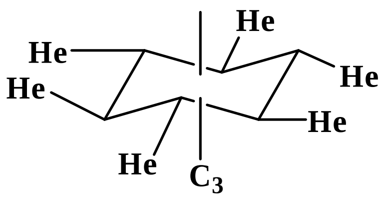


The chair form of cyclohexane belongs to D_3 point group. The principal axis is C_3 and there are three binary axes passing through the three opposite sides three diagonal planes (σ_v) pass through the opposite corners. Its symmetry number (σ) is 6.

20. 4. 2. EQUATORIAL AND AXIAL BONDS

The twelve C-H bonds in the chair form of cyclohexane (I) are of two types. Six of the C-H bonds called **axial** are parallel to the C_3 axis and are represented by vertical lines in the plane of the paper. These **axial** bonds are (three above and three below the plane of the molecule) alternately directed up and down on adjacent carbon atoms. The remaining six C-H bonds are inclined at an angle of 109^0 28' to the axis and are described as **equatorial** bonds. The **axial** hydrogens are **homotopic** relative to each other, since they can be interchanged by rotation around C_3 and C_2 axes. The same is true of **equatorial** hydrogens relative to each other. However, the **axial** set of hydrogens is **diastereotopic** with **equatorial** set of hydrogen atoms.





(I)

20. 4. 3. RING INVERSION

The cyclohexane ring is conformationally mobile. Through a process known as ring inversion or ring flipping, one chair conformation (Ia) is converted into another chair (Ib). Since the activation energy for the cyclohexane ring inversion is only 42KJ/mol, ring inversion occurs rapidly at room temperature. In between the chair forms, there are two other notable conformations, the skew boat (III) which is less stable than the chair and the boat (II) which is 30KJ/mol less stable than the chair (Figure 20.4.1).

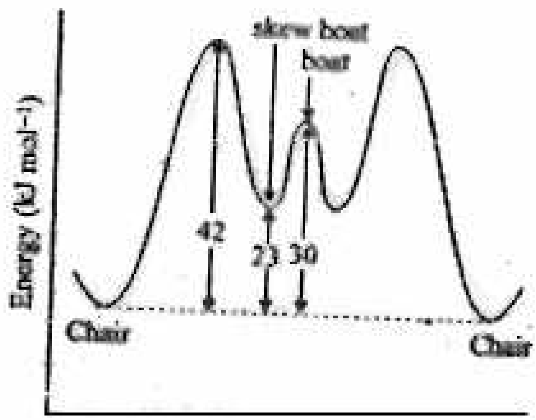
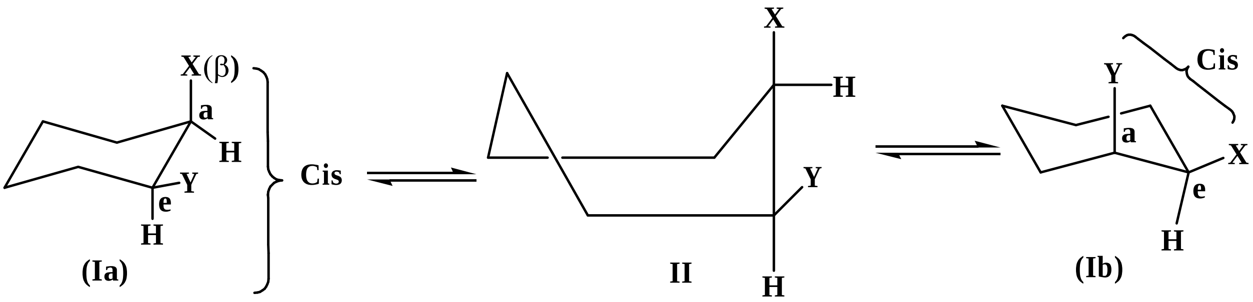


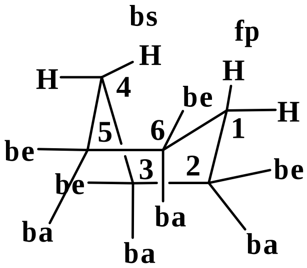
Fig. 20.4.1. Energy profile and conformations of cyclohexane.

The most important consequence of ring inversion is that any substituent that is **axial** in the original chair conformation (Ia) becomes **equatorial** in the ring flipped form (Ib) and vice-versa. It should be noted that during ring inversion no change in the relative configuration ever occurs, that is, α-substituent remains α and β-substituent remains β; likewise, **cis**-remains **cis** and **trans** remains **trans**; (R) remains (R) and (S) remains (S).

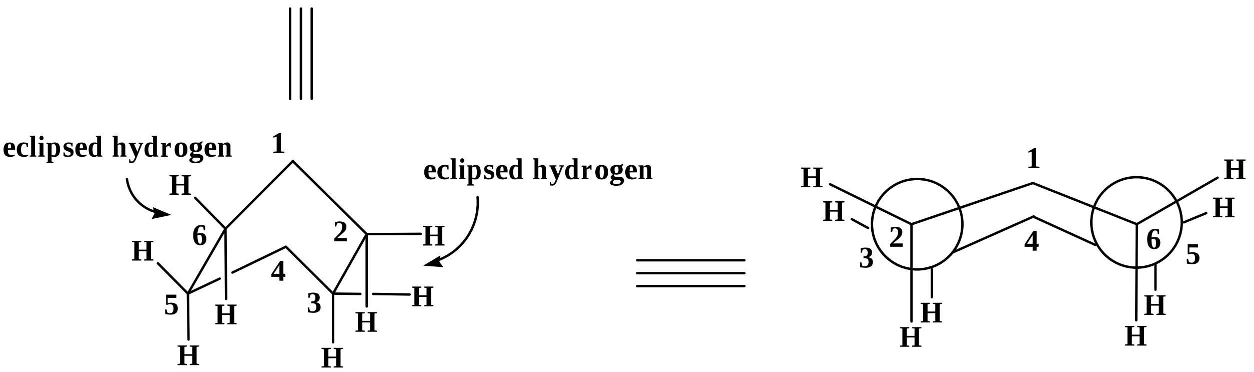


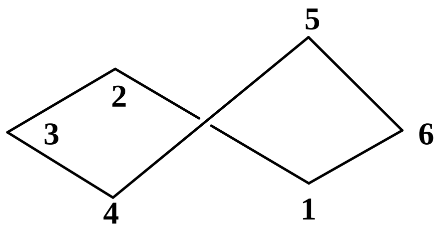
20.4.4. FLEXIBLE CONFORMATIONS

The boat (II) and the twist boat (III) constitute two significant conformations of the cyclohexane. The conventional boat (II) belongs to C_{2v} point group and is free from bond angle strain but suffers from significant torsional strain due to eclipsing of four **boat equatorial** and **boat axial** hydrogens on C-2, C-3 and C-5, C-6. In addition, the hydrogens at C-1 and C-4 approach so close to each other that the distance between them (183pm) is less than the sum of the van der Waals radii (241 pm) of hydrogen atoms. This leads to a non-bonded interaction between C-1 and C-4 hydrogen atoms, often called bowsprit-flagpole interaction.



(II)





(III)

Fig. 20.4.4.1. Extreme boat form of cyclohexane showing interfering and eclipsed hydrogens.

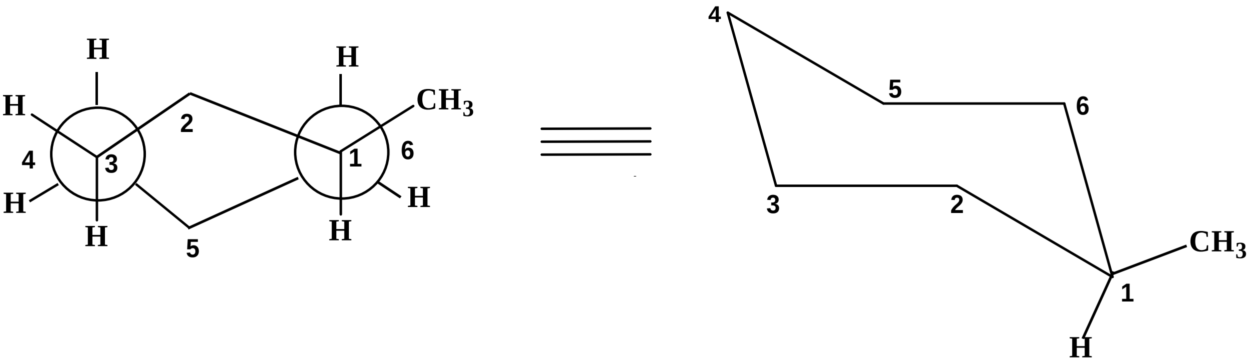
The boat form (II) consists of **four** gauche-butane interactions (1:2, 3:4, 4:5 and 6:1) and **two** eclipsed butane interactions (2:3 and 5:6) and the total strain may be computed as $4 \times 3.3 + 2 \times 18 = 49.2$ KJ/mol. The difference in enthalpy between the chair and boat forms is thus 29.4 KJ/mol, the enthalpy of the chair being 19.8 KJ/mol.

A modified boat conformation known as twist boat (or skew boat) (III) results when the boat (II) form is so twisted that the flagpole bowsprit hydrogens move away from each other and torsional interactions are also reduced. As a result the conformation becomes more stable. Twist boat conformation (III) belongs to D_2 point group and hence chiral. Although, the boat and twist boat conformations are of high energy they have favorable entropy due to more degrees of freedom than chair and the population of flexible form is approximately one in 10,000 at ambient temperature.

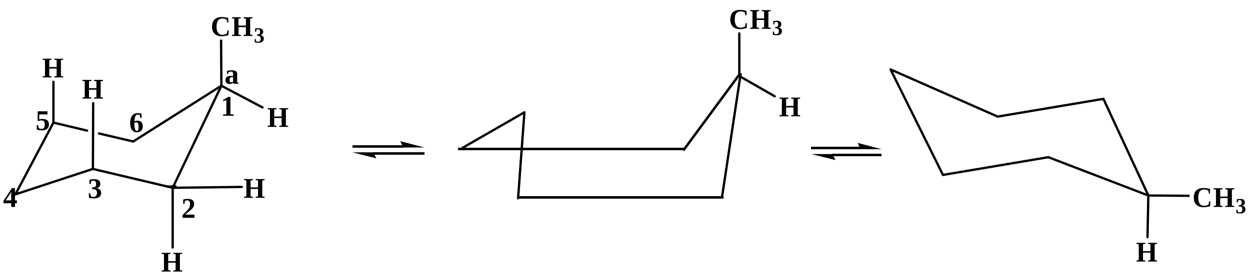
20. 5. CONFORMATIONS OF MONO AND DI-SUBSTITUTED CYCLOHEXANES

20.5.1. MONOSUBSTITUTED CYCLOHEXANE

Introduction of a substituent does not significantly affect the rate of conformational inversion, but does affect the equilibrium distribution between alternative chair forms. All substituents that are **axial** in one chair conformation become **equatorial** on ring inversion and vice-versa. Monosubstituted cyclohexane (e.g. methylcyclohexane) exists in two non-equivalent diastereomeric chair conformations, one with **equatorial** substituent (IVa) and the other having the substituent in **axial** position (IVb), the former predominates at the equilibrium. For methylcyclohexane, ΔG^0 for the equilibrium is 7.50 KJ/mol, corresponding to a composition of 95% equatorial methylcyclohexane.

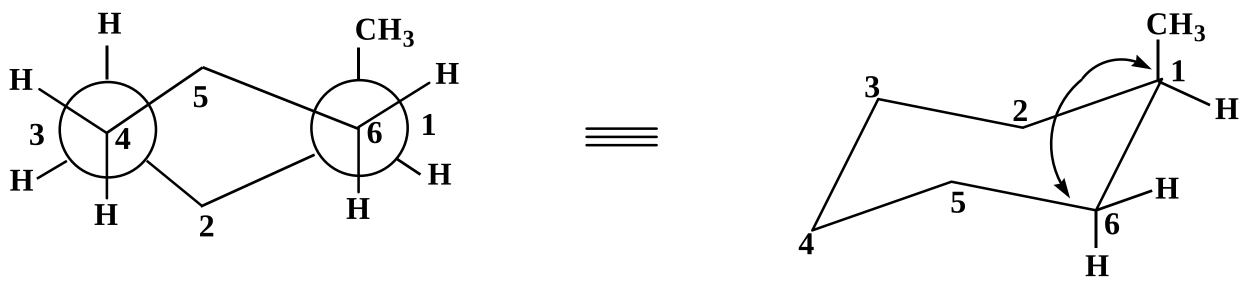


The equatorial preference of the methyl group may be related conceptually to the greater stability of the **anti** conformation of η -butane compared to **gauche** conformation. The axial methyl group of methylcyclohexane forms a part of two gauche-butane fragments (Me-C_1-C_2-C_3 and Me-C_1-C_6-C_5) while an equatorial methyl group is stereochemically similar to **anti** butane conformation. These are shown in heavy lines in the figure 9. 4 and one of them can be seen



(IVb) **(IVa)**

and



clearly in Newman projection. No such interaction is present in equatorial methylcyclohexane. Since the **gauche** conformer of η -butane is 3.3 KJ/mol higher in energy than the **anti** conformer, interactions is less stable than the equatorial methylcyclohexane (IVa) by 6.6 KJ/mol (2×3.3 KJ/mol). The potential energy diagram of methylcyclohexane as a function of conformation is given in Figure 20.5.1.1.

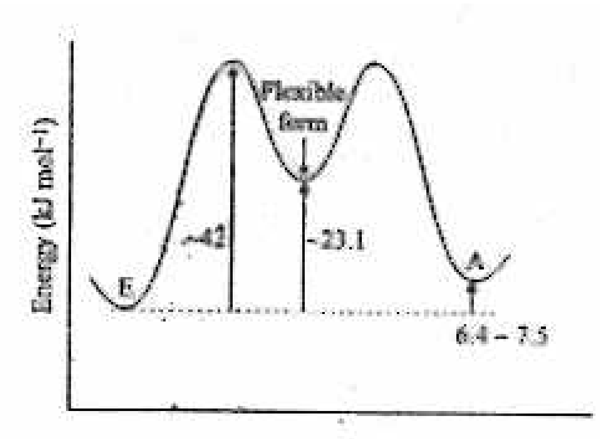


Fig. 20.5.1.1. Potential energy methylcyclohexane as a function of conformation.

The **axial methyl** group of methylcyclohexane (IV b) experiences VanderWaals repulsion with axial hydrogens at C-3 and C-5. Interactions of this type are called **1,3-diaxial** interactions and substituents in **1,3-diaxial** orientation with respect to each other are said to be **syn** axial. The result of repulsion between **axial** methyl group and **syn** axial hydrogen leads to a slight flattening of the ring.

The free energy difference between conformers is referred as conformational free energy or sometimes A value. For substituted cyclohexanes, the equilibrium is written as

$$\textbf{axial} \rightleftharpoons \textbf{equatorial}$$

$$\Delta G^0 = -RT\ln K \qquad \text{where } K = \frac{[\text{equatorial}]}{[\text{axial}]}$$

Since the ΔG^0 will be negative when equatorial conformation is more stable than the axial, the value of $-\Delta G^0$ is positive for substituents that favour equatorial position. The $-\Delta G^0$ value is larger, the greater the preference for the equatorial position.

Conformational free energy values (- ΔG^0) for many substituents have been determined by NMR method at low temperature. At -80° C, the NMR spectrum of cyclohexyl iodide is well resolved and clearly indicates the presence of two conformations. In general **equatorial hydrogens** resonate at lower field than the constitutionally similar **axial hydrogens.** The multiplet at higher field (δ 3.80) is a triplet of triplet with vicinal coupling constant of 3.5 and 12Hz. This multiplet is assigned to the axial methane proton of equatorial cyclohexyl iodide, since it is coupled to the adjacent **axial** proton (C-2) by a large **trans** coupling and to the adjacent **equatorial** proton (C– 2) by a small **gauche** coupling constant. The multiplet at the lower field (δ 4.50) appears as a broad peak because the **equatorial** methane proton of the axial cyclohexyl iodide is coupled approximately equally to **vicinal equatorial** and **axial** protons by small **gauche** coupling. F the coupling constants were equal, the signal would appear as a quintet. The relative area of axial methane proton to equatorial methane proton is 3.4 and corresponds to a - ΔG^0 value of 1.88 KJ/mol.

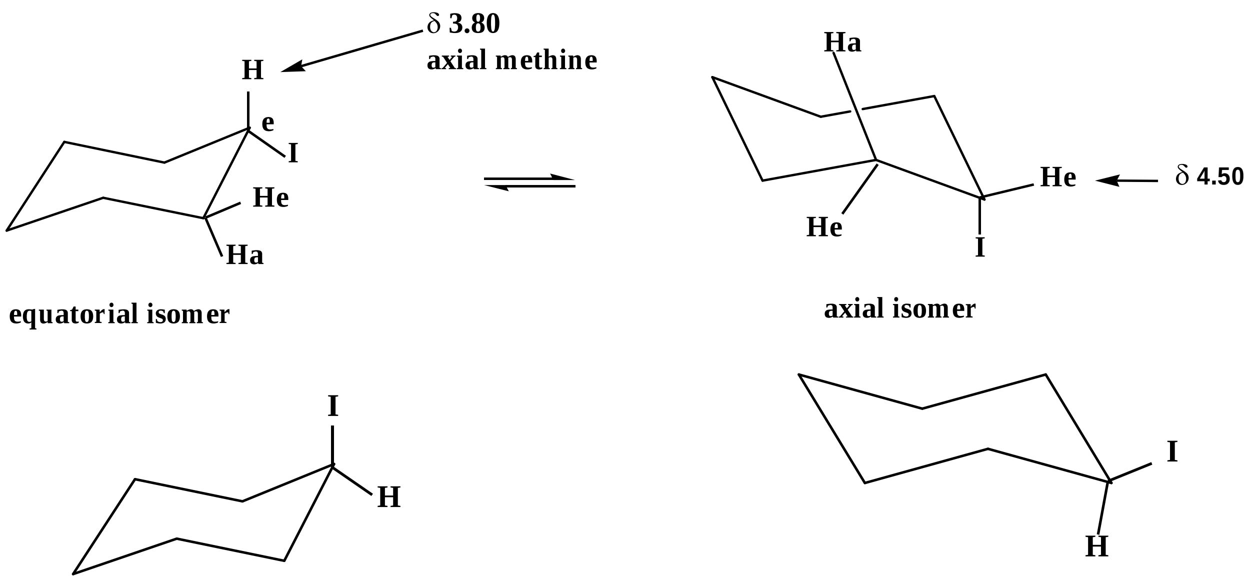
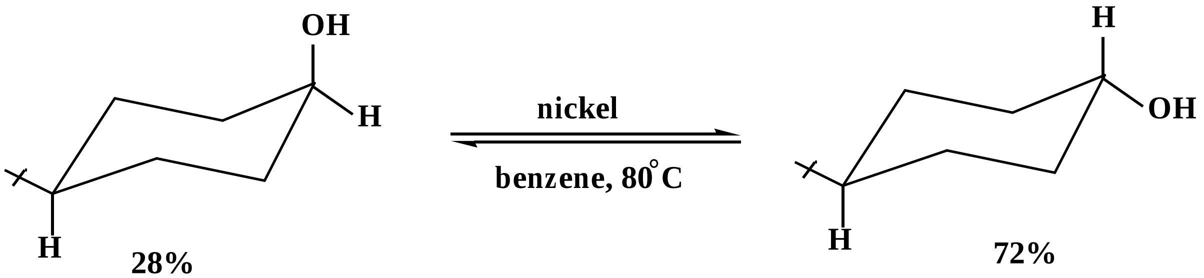


Fig. 20.5.1.2. NMR spectrum of cyclohexyl iodide at -80° C

A second important method for determining the conformational free energies involves establishing an equilibrium between diastereoisomers differing only in the orientation of the designated substituent. The equilibrium constant can then be determined and used to calculate the free energy difference between the diastereoisomers. For example, **cis**- and **trans**-4-t-butylcyclohexanols can be equilibrated using a nickel catalyst in refluxing benzene to give a mixture containing 28% **cis**-4-t-butylcyclohexanol (diaxial-OH) and 72% **trans**-4-butylcyclohexanol (equatorial-OH) (Figure).

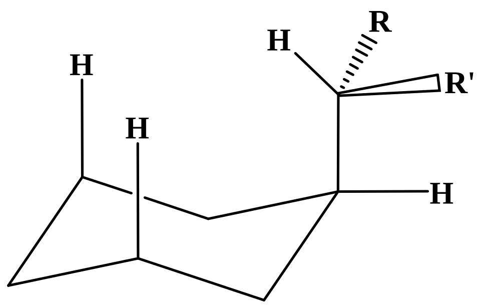


***cis*-4-t-butylcyclohexanol** **_trans_-4-t-butylcyclohexanol**

The equilibrium constant for the above reaction leads to a value of 2.9 KJ/mol for $-\Delta G^0$ for the hydroxyl substituent.

Among the halogen substituents, fluorine is the least conformationally demanding and the preference for the equatorial orientation is nearly same for chlorine, bromine and iodine. The larger van der Waals radii of iodine and bromine relative to chlorine are compensated by the greater C-I and C –Br bond lengths, which decrease the repulsion between halogen and **syn**-axial hydrogens. The electrons of C-I and C-Br bonds are also more polarisable and lead to increased attractive interaction between halogen and other atoms.

The alkyl groups' methyl, ethyl and isopropyl have similar conformational energies with isopropyl being slightly larger than methyl and ethyl. The similarity of the conformational energies of these three substituents is due to the rotation of the alkyl groups around the bond between the substituent and the ring so that the ring adopts a conformation that minimizes the effect of additional methyl substituents in ethyl and isopropyl groups.



methyl : **R = R^1 = H**
ethyl : **R = H$_1$ R^1 = CH$_3$**
isopropyl : **R = R^1 = CH$_3$**

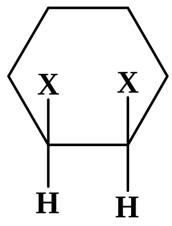
A tertiary butyl substituent experiences strong van der Waals repulsion with **syn** axial hydrogens and this strain is not relieved by rotation of tertiary butyl substituent about the bond to the ring. The conformational free energy of t-butyl group has been estimated as 22.5KJ/mol. The strong preference for t-butyl group to occupy the equatorial orientation has made it a highly useful group for the study of conformationally biased systems.

20. 5. 2. DISUBSTITUTED CYCLOHEXANES

Non-gemninally disubstituted cyclohexanes exist as a set of three positional isomers, 1,2-, 1,3 and 1,4. Each set can exist as a pair of geometrical isomers, **cis** and **trans,** each of which in turn can exist in two interconvertible chair conformations. Depending upon symmetry, each positional isomer may exhibit enantiomerism. (Each positional isomer has 2 chiral centers, so the number of stereoisomers is 4 (2^2). They are a **cis** – pair of enantiomers and **trans** pair of enantiomers. Further the **cis and trans** isomers exist in two interconvertible chair conformations). The stereochemical aspects of disubstituted cyclohexanes are illustrated with dimethylcyclohexanes.

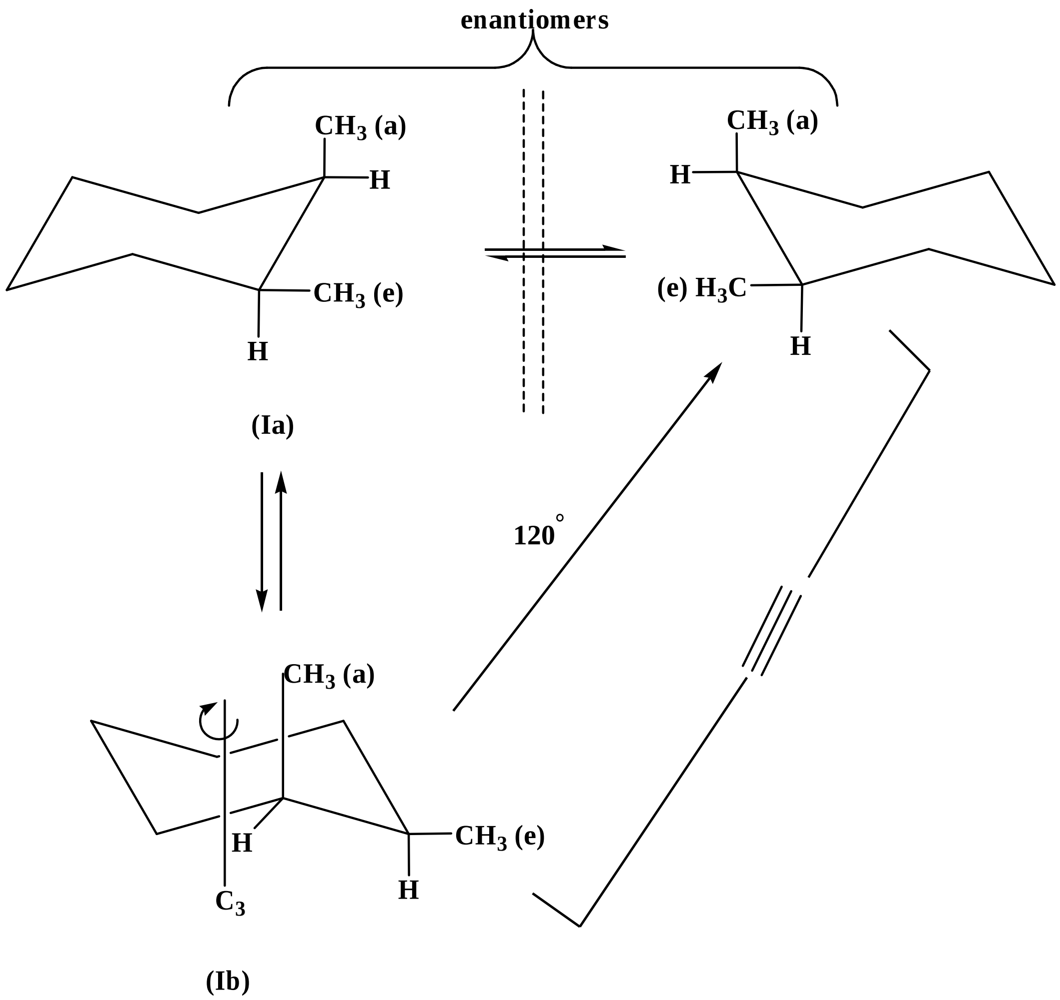
20.5.2.1. 1,2–DISUBSTITUTED CYCLOHEXANE

1. *cis*-1, 2-Disubstitutedcyclohexane (eg. *cis*-1,2-dimethylcyclohexane)



X = Y = Me

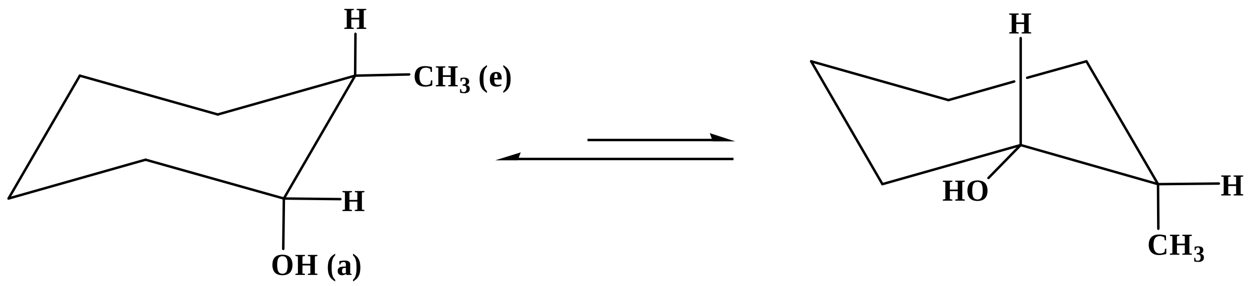
1,2-Substituents of a cyclohexane are said to be **cis,** if they occupy axial and equatorial orientation. **Cis-**1,2-dimethylcyclohexane exists as two **energetically equivalent** axial-equatorial (a,e) (Ia) and equatorial–axial (e,a) (Ib) chair conformations which are not superimposable on **their mirror images.** However, the classical (planar) formula of BcisB-1,2-dimethylcyclohexane has a plane of symmetry and therefore, represents a **meso** form. If the conformational representations of **cis**-1, 2-dimethylcyclohexane are examined, each chair form is devoid of mirror symmetry and hence expected to be chiral. However, the two conformational



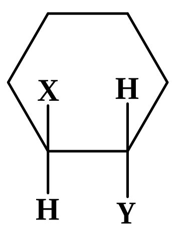
isomers resulting from ring inversion are also mirror images of each other. This can readily be seen by rotating the chair form Ib by 120^0 around the C_3-axis. Since the two conformational isomers are equienergetic and are present in equal amounts, **cis**-1, 2 –dimethylcyclohexane exists as a racemate ($\pm$); since the potential energy barrier between the two conformers is too low to allow separation, the racemate is inseparable. Thus, **cis**-1,2-dimethylcyclohexane is a non-separable racemate.

Either of the chair conformations contain three gauche-butane interactions (two for **one** axial methyl and one for a-e dimethyl) corresponding to a potential energy difference of 11.2KJ/mol (with respect to hypothetical structure with no extra interaction). The entropy of such compounds originates from three sources (i) entropy due to symmetry number (-RTlnσ) ii) entropy due to mixing of conformers iii) entropy due to ($\pm$)-mixture. For **cis**-1,2-dimethylcyclohexane (C_1 symmetry) σ is 1 and so its contribution to the entropy is nil; the second and third factors happen to be the same. The two conformers being enantiomeric contribute an entropy of mixing, Rln2.

If the substituents are different and differ in size ($X \neq Y$), the conformer with lower energy (the preferred conformer) is the one in which the larger group is equatorial. In **cis**-2-methyl-1-cyclohexanol (X= OH and Y= Me), the methyl group is larger than the hydroxyl and the preferred conformation is the one in which the methyl group is equatorial.

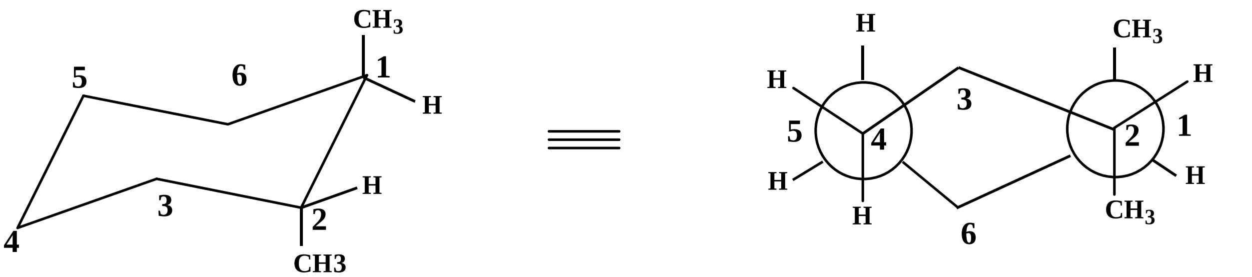


2. *trans*-1,2-dimethylcyclohexane

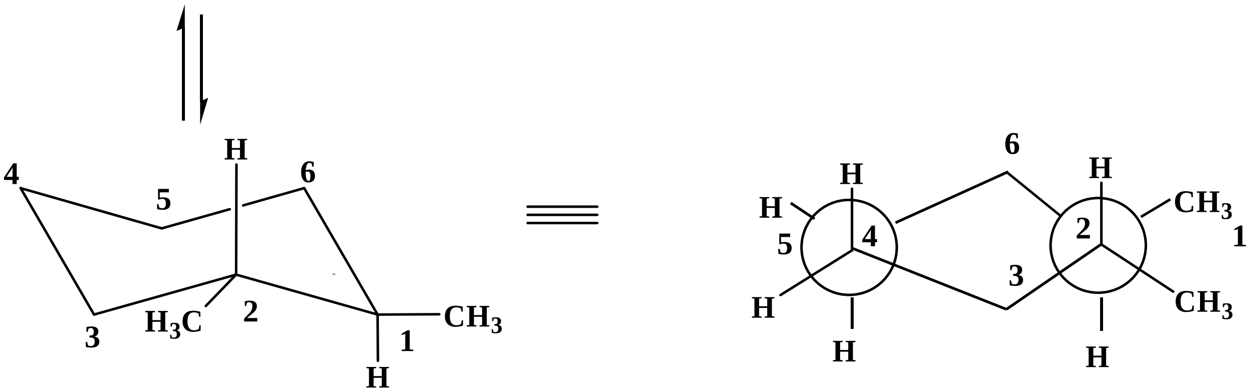


(X = Y = Me)

Two substituents on 1, 2-positions of a cyclohexane are said to be **trans,** if they occupy diequatorial (e,e) or diaxial (a,a) orientation, *trans*-1,2-dimethylcyclohexane exists in **two** energetically **non-equivalent** conformations- diaxial (a,a) (IIa) and diequatorial (e,e) (IIb) which are chiral (C_2 symmetry). Unlike 1,2-***cis***, the ***trans***-1,2-dimethylcyclohexane exists as a resolvable pair of enantiomers (racemte). The diequatorial conformation contains one gauche-butane interaction (e,e-Me), while the diaxial conformer contains four gauche-butane interactions (two for each axial methyl). As a result, the diequatorial form is preferred over diaxial form by three gauche-butane interactions (11.2 KJ/mol) corresponding to 99% of equatorial isomer.



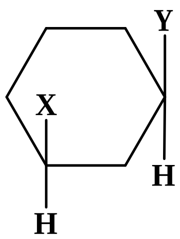
(IIa)



(IIb) trans

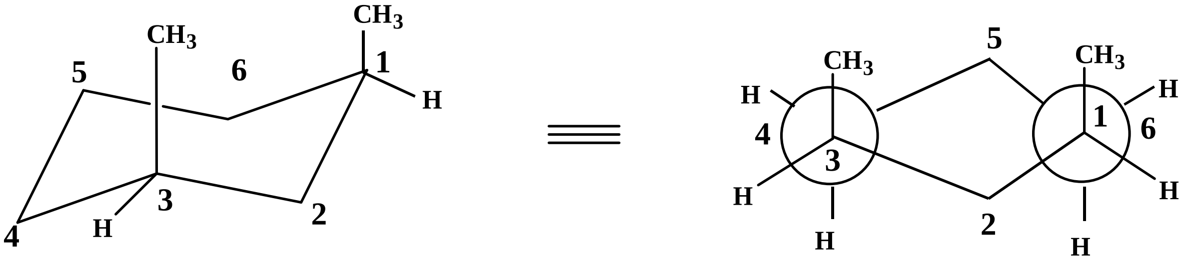
3. 1,3-DISUBSTITUTED CYCLOHEXANE

3. 1. *cis*-1,3-dimethylcyclohexane

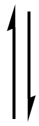


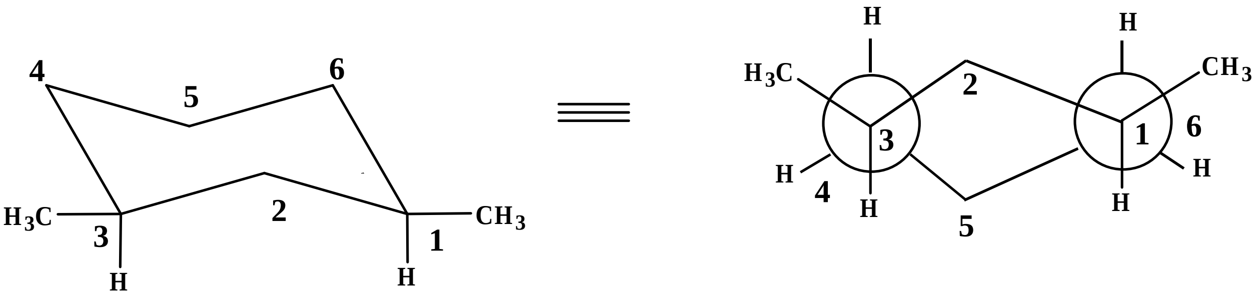
(X = Y = Me)

Two substituents occupying 1, 3-positions of a cyclohexane are said to be **cis,** if they occupy diaxial (a, a) or diequatorial (e, e) orientation. **Cis**-1, 3-dimethylcyclohexane exists as two energetically **non-equivalent chair conformations** (a, a and e, e) (III a & III b) which are **achiral** due to the presence of a σ-plane ($\equiv S_1$) (passing through C-2 and C-5) and so they constitute **meso** forms. The diequatorial conformer (III b) has no gauche-butane interactions while the diaxial form (III a) has two (one for each methyl) corresponding to an enthalpy of 7.5KJ/mol and in addition a 1, 3-diaxial Me/Me interaction which contributes an additional energy of 15.5KJ/mol. The total enthalpy of diaxial isomer is thus 23.0KJ/mol higher than that of the diequatorial one. Hence the contribution of diaxial form is almost negligible to the equilibrium.



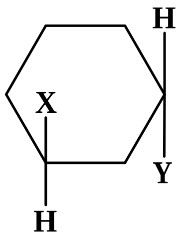
(IIIa)





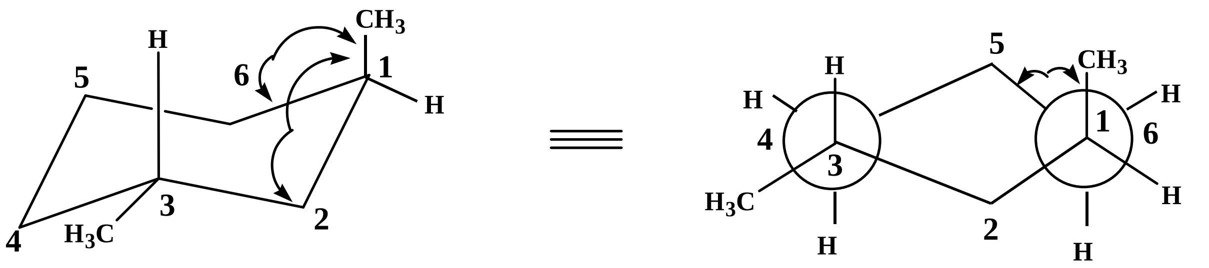
(IIIb)

3. 2. *trans*-1,3-dimethylcyclohexane

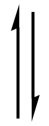


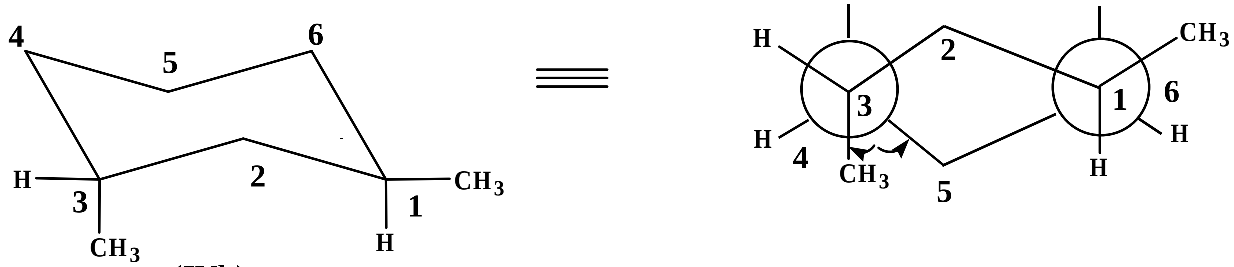
(X = Y = Me)

Two substituents of cyclohexane ring occupying 1, 3-positions are said to be ***trans,*** if they bear axial-equatorial orientation. ***trans***-1,3-dimethylcyclohexane exists as two non-superimposable chair conformations (a,e) (IVa & IV b) each with two gauche-butane interactions corresponding to an enthalpy of 7.5 KJ/mol and is less stable than 1,3-***cis***-isomer (e,e) by the same amount.



(IVa)



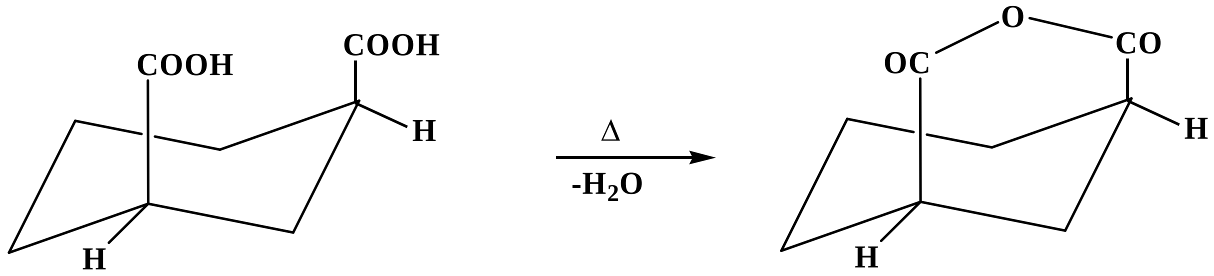


(IVb)

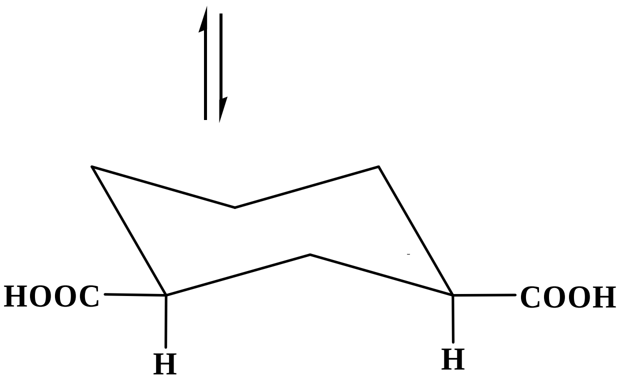
Thus, unlike the 1,2 (also 1,4-) series, 1,3-**cis** is more stable than 1,3-**trans**-isomer. It is to be noted that ***trans***-1,3-dimethylcyclohexane exists as a resolvable racemate [(±)], since the chair inversion converts the molecule into an identical structure (unlike ***cis***-1,2-dimethylcyclohexane where chair inversion converts the molecule into its mirror image).

When the two substituents are different (X ≠ Y) both ***cis*** and ***trans*** isomers are resolvable, the former (**cis**) exists in the predominantly diequatorial form and the latter (**trans**) in the equatorial –axial conformation with bulkier group occupying equatorial position.

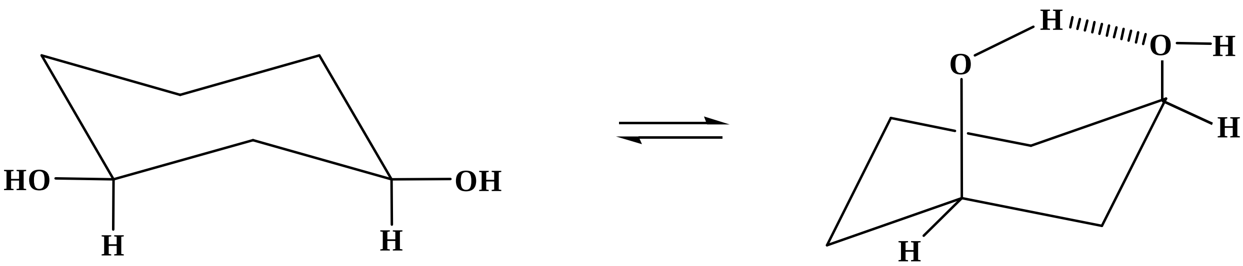
The preferred diequatorial conformation of **cis**-1,3-isomer is not suitable for certain reactions (eg. anhydride formation, hydrogen bond formation between 1,3-groups etc.) as the 1,3-groups are far apart in this conformation. However, ring inversion of the diequatorial form converts it into a diaxial conformation in which 1,3-groups are close to each other, The formation of anhydride from **cis** -1,3–cyclohexanedicarboxylic acid (V) and the intramolecular hydrogen bond formation in **cis**-1,3-cyclohexane diol (VI) takes place through the diaxial conformations (V b & VI b) of 1,3-**cis**-isomer.



(Vb)



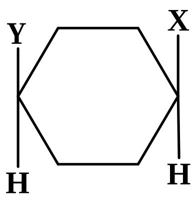
(Va)



(VIa) (VIb)

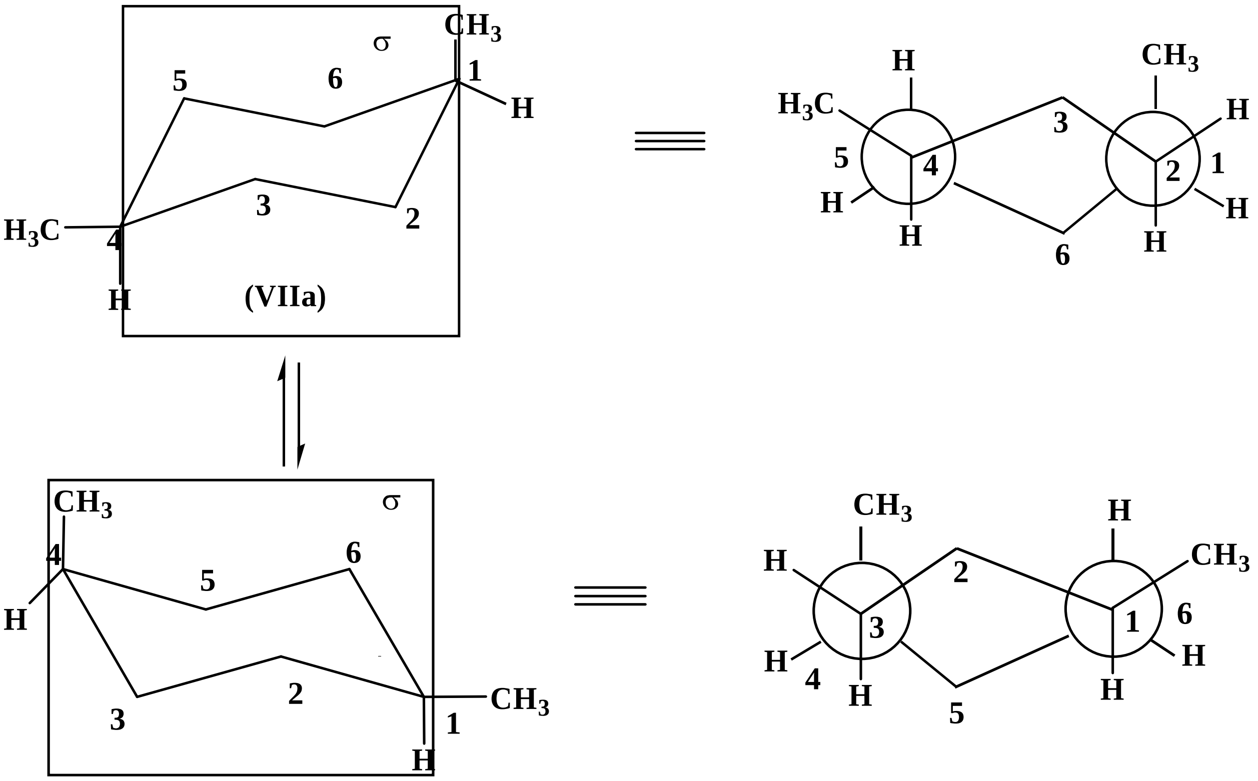
1, 4-Disubstituted cyclohexanes

i) Cis-1, 4-dimethylcyclohexane



(X = Y = Me)

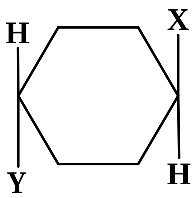
Two substituents on 1, 4-position of a cyclohexane ring are said to be **cis,** if they bear axial-equatorial orientation. **Cis**- 1, 4 –dimethylcyclohexane exists in **two identical** (a, e) and (e , a) conformations (VII a & VII b). A vertical σ-plane passes through 1,4–positions and so all conformations are achiral even when the two substituents are different. When both substituents are different (X ≠ Y), the **cis**–isomer exists in two unequally populated conformers, the preferred conformer is the one with bulkier group in equatorial position.



(VIIa)

(VIIb)

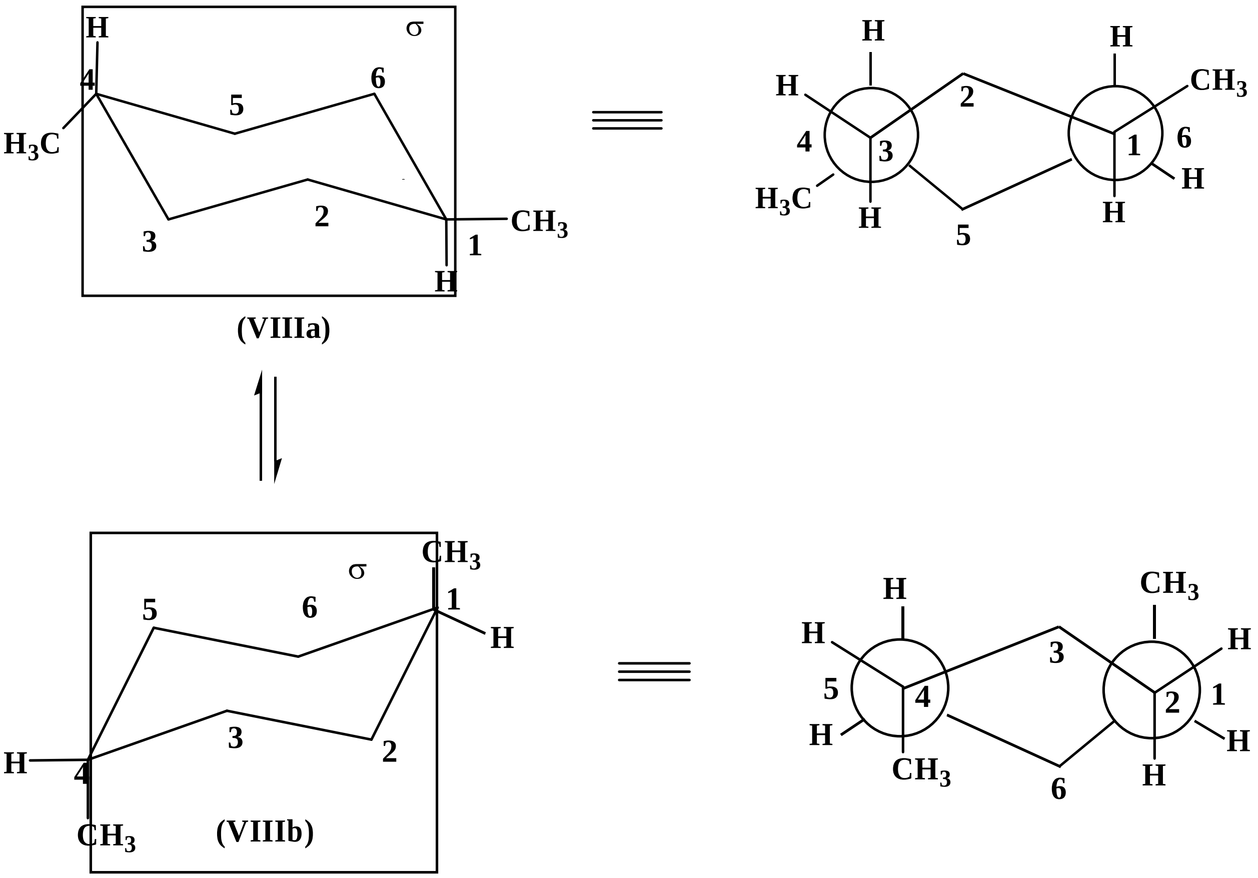
ii) *trans* – 1, 4 – dimethylcyclohexane



(X = Y = Me)

Two substituents occupying 1, 4 – positions of a cyclohexane ring are said to be **trans**, if they bear diaxial or diequatorial orientation. **Trans** -1, 4 – dimethylcyclohexane exists in two **non – equivalent** diequatorial (VIII a) and diaxial (VIII b) conformers, of which the latter (a, a) (VIII b) is destabilized by **four** gauche – butane interactions (15.0 KJ/mol). Both conformers are **achiral** as a plane of symmetry passes through 1, 4 – positions.

The **trans** -1,4–isomer is preferred over the **cis** – 1, 4 by **two** gauche – butane interactions while **trans** – 1,4– has none. When both substituents are different (X ≠ Y), the ***trans***– 1,4 isomer exists predominantly in diequatorial conformation.



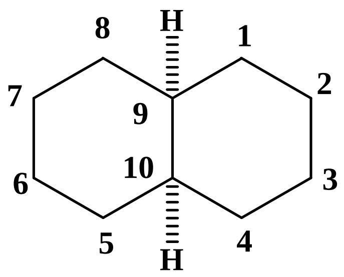
(VIIIa) (VIIIb)

20.6. DECALINS: Bicyclo [4.4.0] decane

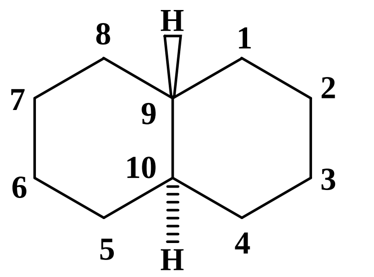
A fused ring system is one in which adjacent rings have two atoms in common. By for the most important fused ring system is the decalin which exists in two diastereoisomeric forms, the **cis** and the **trans**. If cyclohexane ring system were to be planar as suggested by Baeyer, only one form of decalin with ring system junction hydrogens projecting on the same side of the molecule should exist. On the other hand, Sachse –Mohr concept of puckered rings permits the existence of two isomeric forms of decalin. In fact, Mohr predicted that two isomeric forms of decalin molecule should exist before W.Huckel succeeded in preparing them. Both isomeric forms of decalin occur in petroleum ether.

20.6.1. GEOMETRY

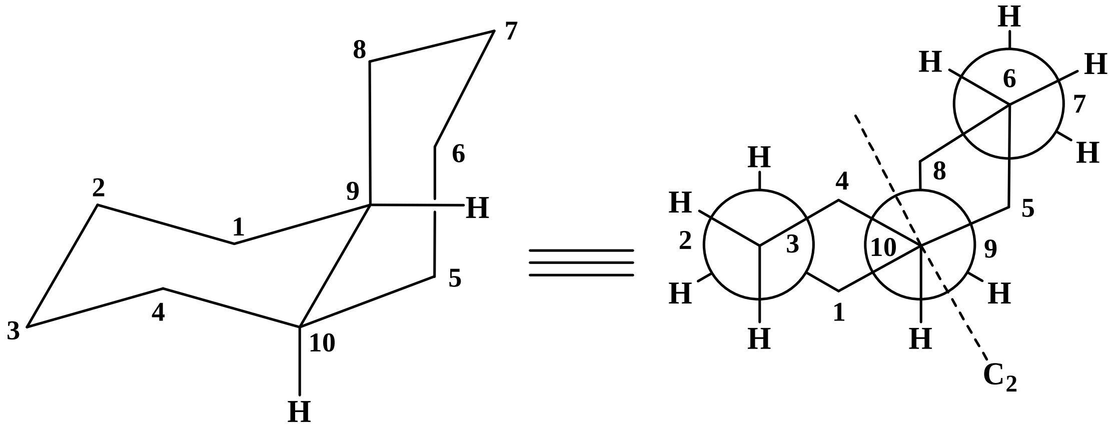
The cyclohexane rings in both **cis** and **trans**-decalins exist in chair conformation. **Cis**-decalin (I) is formed when both cyclohexane rings are joined through **axial-equatorial** bonds, whereas, the **trans**-decalin (II) is produced by joining the two cyclohexane rings through **equatorial** bonds only. **Trans**-decalin (II) has rigid geometry and cannot undergo ring inversion which would lead to a highly strained ring system with diaxial fusion. In contrast, cis decalin in which two cyclohexane rings are fused through **axial-equatorial** bonds can readily undergo ring inversion by exchanging **a,e** bonds at ring junction. The two interconvertible chair conformations (Ia & Ib), similar to cis-1,2-dimethylcyclohexane are equienergetic and so equally populated at room temperature. as in the case of **cis**-1,2- dimethylcyclohexane, the ring inversion converts one conformer into its mirror image; **cis**-decalin (I) is therefore, a non-resolvable racemate(±).



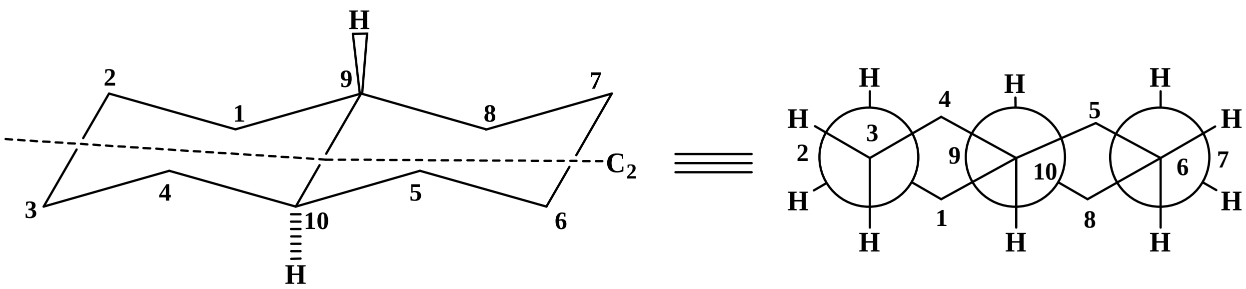
(I)



(II)



(Ia)

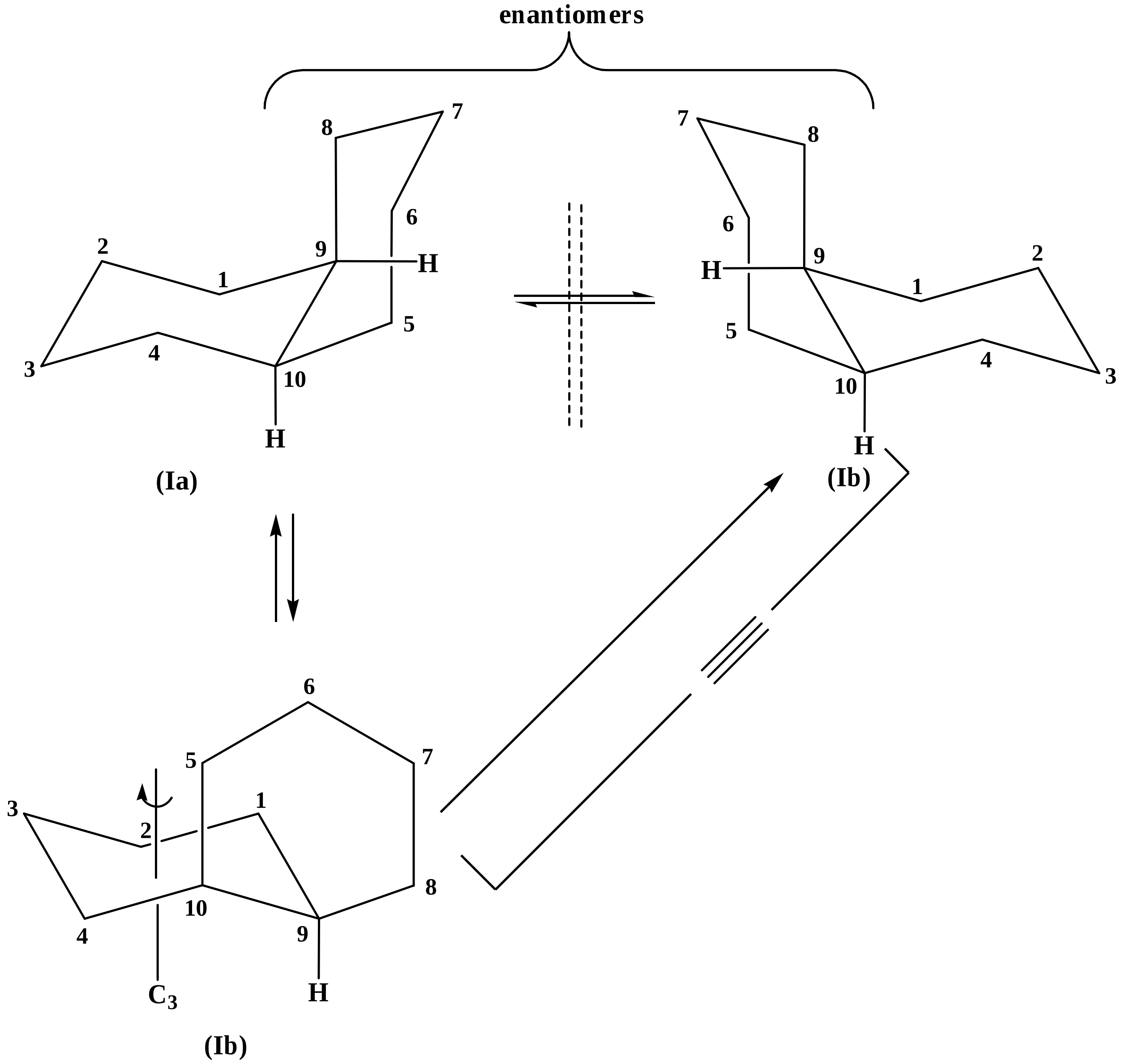


(II)

20.6.2. SYMMETRY

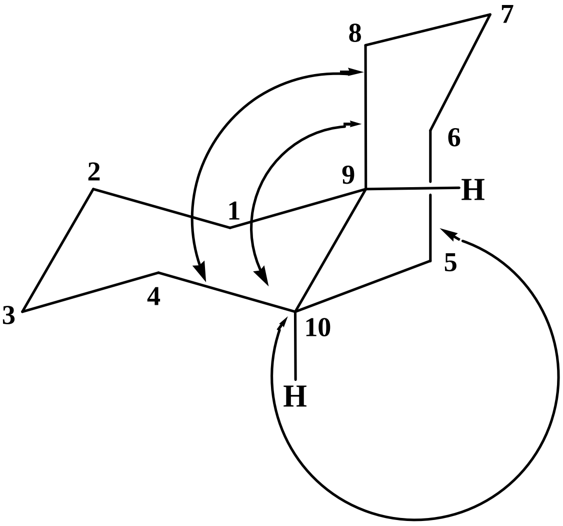
The conformation of **trans**-decalin (II) has a centre of symmetry (mid point of 9-10 bond) and is **achiral**. In addition, it possesses a C_2 axis passing through C_2-C_3 ,C_9-C_{10} and C_6-C_7 bonds and a σ-plane perpendicular to C_2 axis and passing through the ring junction .It belongs to C_{2h} point group and its symmetry number is 2. On the other hand, the individual conformations of **cis**-decalin molecule are **chiral** as they are devoid of mirror symmetry. They have a C_2 axis passing through the mid point of C_9-C_{10} bond and bisecting the dihedral angle between 9-H and 10-H. Their symmetry number is also 2 and belongs to C_2 point group.

Since the two individual conformations of **cis**-decalin are enantiomeric and equienergetic they are readily interconvertible at a rate too fast to separate them. So cis –decalin molecule is a non-separable racemate.



20.6.3. ENTHALPY AND FREE ENERGY

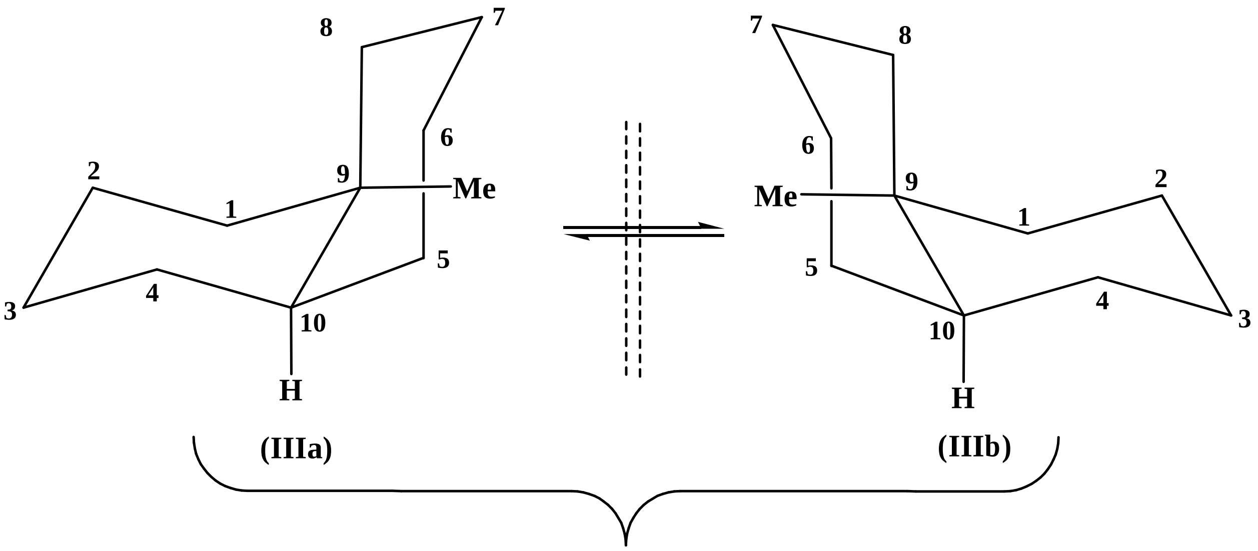
The difference in enthalpy between **cis**- and **trans**-decalins can be determined by counting the number of gauche-butane interactions. In **trans**-decalin, since each ring is fused through the equatorial bonds, no gauche- butane interactions exist. In **cis-**decalin, there are **three** such interactions and the difference in enthalpy is therefore amounts to 10.5 KJ/mol ($3\times$ 3.3 KJ/mol).Therefore, **trans-**decalin is more stable than **cis**.



Gauche units
1-2/9-8
4-10/5-6
4-10/9-8

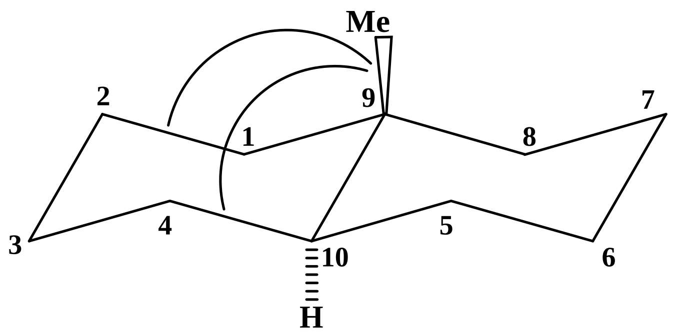
20.6.4. EFFECT OF ANGULAR METHYL GROUP

Introduction of a methyl group at one of the fused carbon atoms as in steroids (C-9 or C-10) gives rise to additional gauche-butane interactions and consequently the potential energy difference between **cis**- and **trans**-9-methyldecalin system (III &IV) is less than that of **cis**- and **trans**- decalin (I &II). The angular methyl group in **trans**-9-methyldecalin (IV) is axial and gives rise to four butane-gauche interactions (two with respect to each ring). In **cis**-9-methyldecalin (III), the 9- methyl group is axial with respect to one ring only and equatorial with respect to the other, giving rise to two gauche-butane interactions in addition to three already present in **cis**-decalin.Thus, the total number of gauche butane interactions in the **cis**-compound is therefore five that is one more than the **trans**-isomer. Thus, the original difference between **cis** and **trans**-decalins is reduced to one in 9-methyldecalin in favor of the **trans**-isomer which is more stable than the **cis**-isomer by 3.35 KJ/mol.



(IIIa) **(IIIb)**

enantiomers



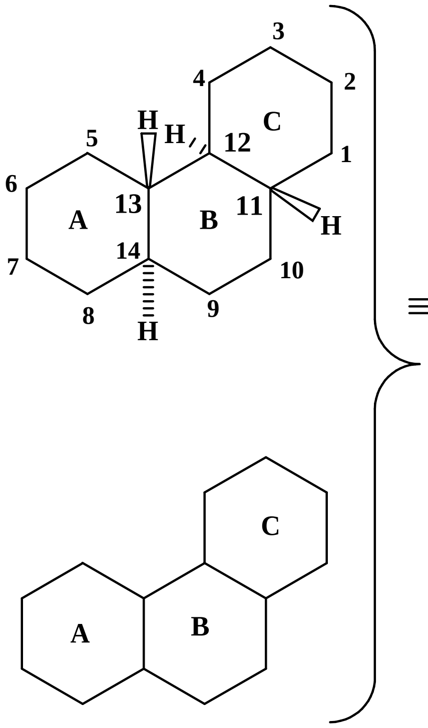
***cis* (IV)**

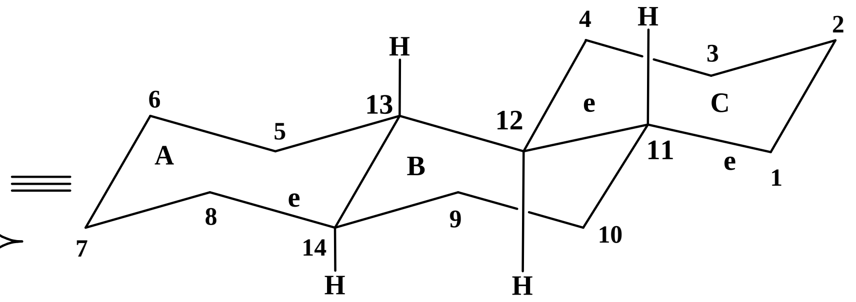
Trans-9-methyldecalin (IV) does not have any C_2-axis but possesses a plane of symmetry (σ) passing vertically along 9-10 bond and hence **achiral** (C_s point group).The individual conformations of cis-9-methyldecalin (IIIa &III.b) are **chiral** as they are devoid of mirror symmetry (C_1 point group) and constitute a pair of equienergetic enantiomers.However, the two enantiomers are readily interco0nvertible by ring inversion and cis- isomer is thus a non-separable racemate (±).

20.7. CONFORMATIONS OF PERHYDROPHENANTHRENE

Among the fused tricyclic system, the perhydrophenanthrene molecule is interacting in that it illustrates many stereochemical aspects of polycyclic natural products such as steroids and triterpenoids. Perhydropherianthrene molecule contains four like chiral (ABAB) and so exists as **two meso** and **four racemates** (the number of chiral centers is even and so the number of **meso** forms is $2^{(4-2)/2} = 2$ and the number of optical active forms is $2^{(4-1)} = 2^3 = 8$ which forms four racemates). The six diastereoisomeric forms are shown along with their conformational representations (for chiral forms, only one enantiomers of each (±) -form is drawn).

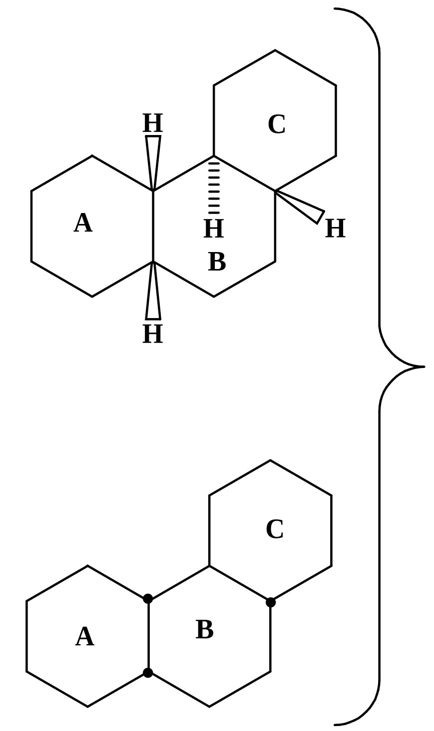
The prefixes **cis** and **trans** are used to denote the stereochemistry of fusion of terminal rings (A and C) to the central ring (B) , whereas **syn** and **anti** are used to indicate the orientation of terminal rings (A and C) with respect to each other (that is by considering the relative position of hydrogens at C – 12 and C – 13 . The prefixes **syn** and **anti** are used when these hydrogens are on the **same** or **opposite side** respectively). A heavy dot indicates that the hydrogen atom is above the plane of the ring system whereas the absence of a dot indicates that the hydrogen is below the plane of the ring system. The relative stabilities of the six diastereoisomers have been assessed by counting butane – gauche interactions.

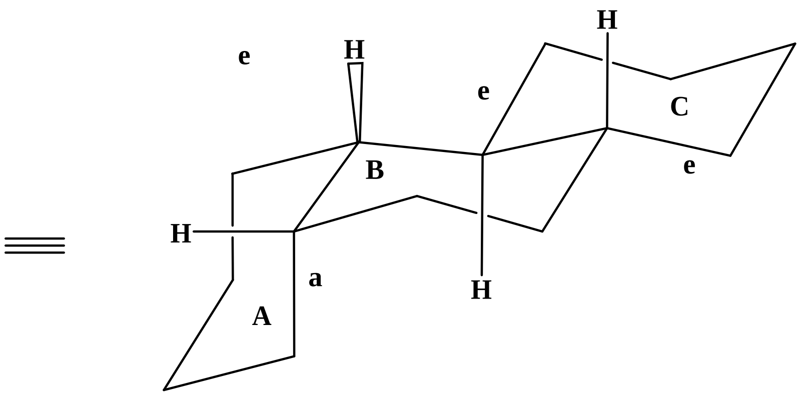




number of gauche interactions =
(1+0) = 3.35 KJ/mole

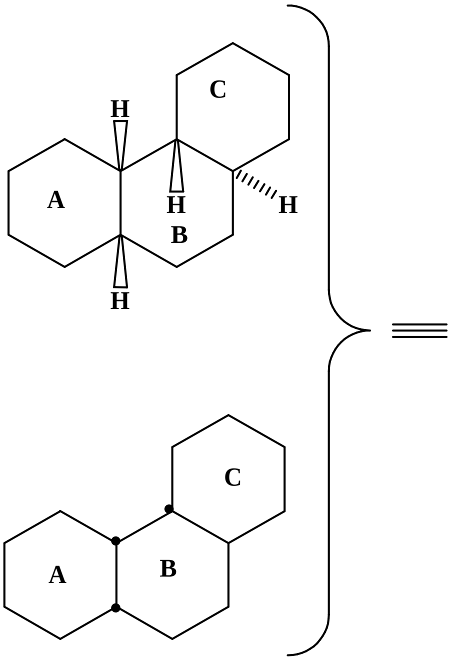
***trans-anti-trans*(±)-(4e) (I)**

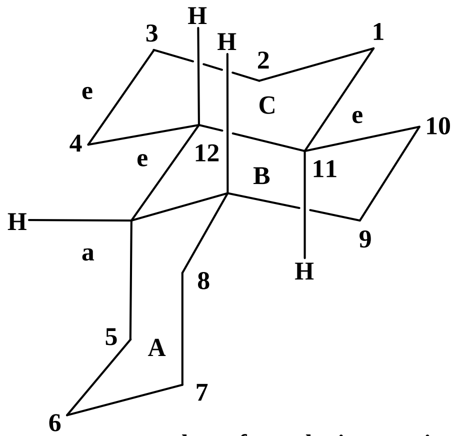




number of gauche interactions =
(1+3) = 13.4 KJ/mole

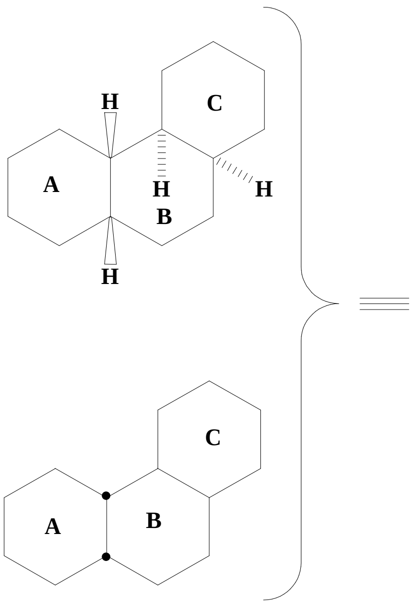
(±)-*cis-anti-trans*(3e + 1a) (II)

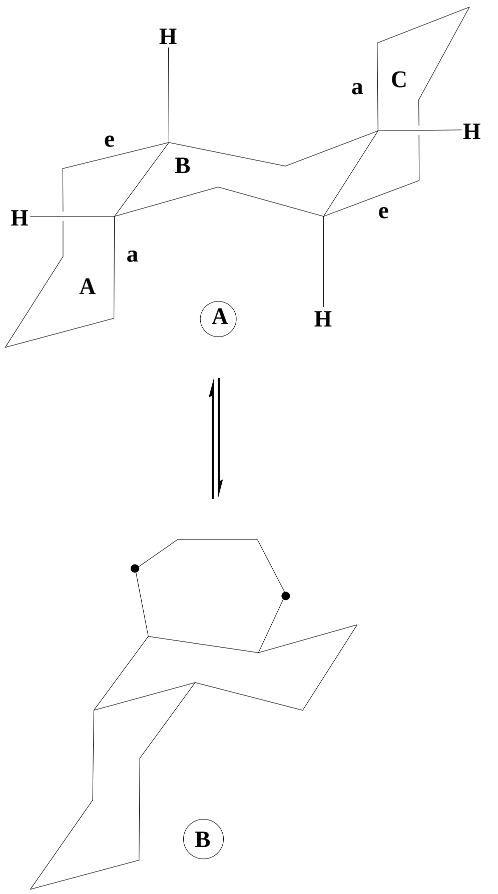




number of gauche interactions =
(1+3) = 13.4 KJ/mole

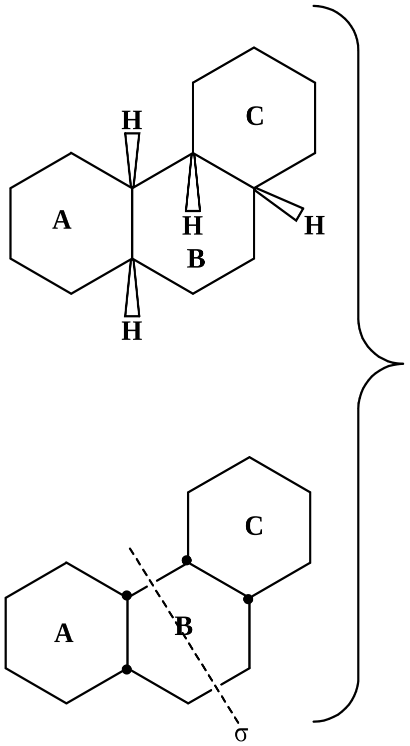
(±)-*cis-syn-trans*(3e + 1a) (III)



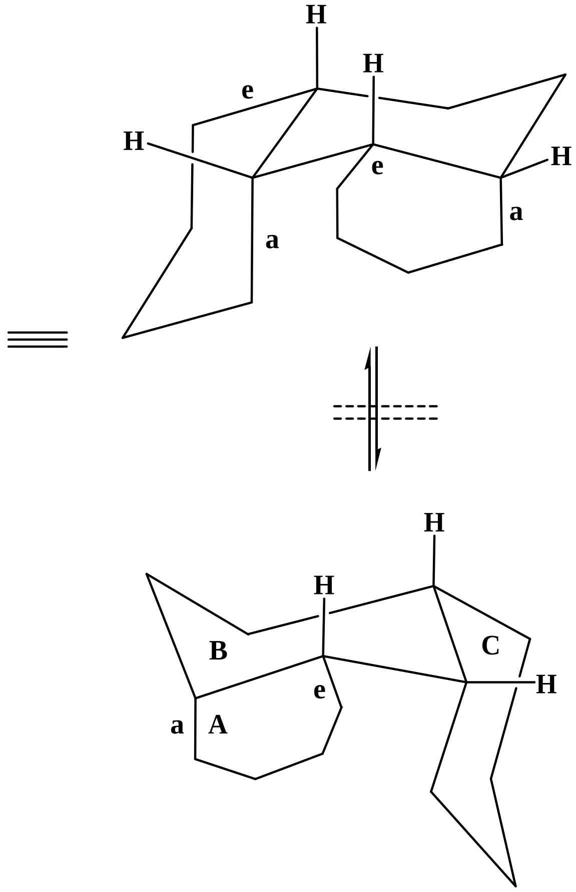


(±)-*cis-anti-cis*(2e + 2a) (IV)

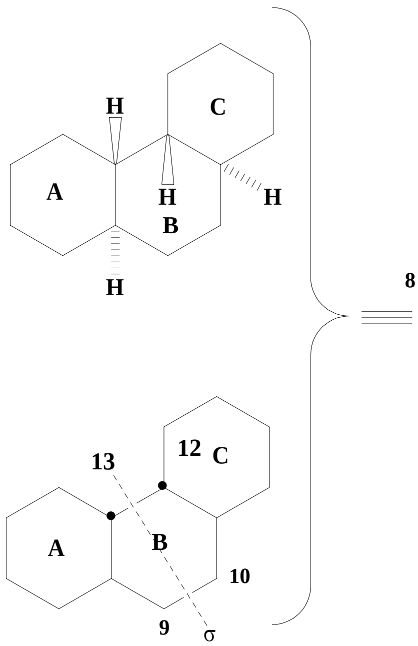
number of gauche interactions =
(0+6) = 20.1 KJ/mole



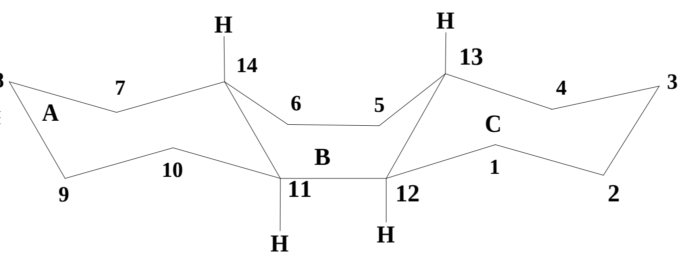
cis-syn-cis **(2e + 2a)(meso) (V)**



enantiomers
(30.1 KJ/mole)



trans-syn-trans (meso)
(4be)
(VI)



23.4 KJ/mole

Johnson predicated the relative stabilities of the six diastereoisomers on the basis of the following assumptions:

i) The system in which the central ring (B) is fused to other rings by **larger number of equatorial bonds** is more stable**.**

ii) In case when **axial bonds** of the central ring (B) are used in ring fusion , 1,2– and 1,4–diaxial arrangements are preferred over 1,3–diaxial which h suffers from a severe 1,3–diaxial methylene interaction.

iii) Regardless of the assumption 1 and 2, if the central ring junction involves two **axial** bonds either way the system is labeled, the central erring cannot exist in chair form but adopts a boat or twist – boat conformation.

Based on these assumptions, the stabilities of the six diastereoisomers are assessed.

a) The **trans–anti–trans** isomer (I) is the most stable in which the central ring (B) is fused to the other rings (A and C) by **four equatorial** bonds. However, unlike the **trans**–decalin, this system has **one gauche–butane** interaction resulting from hydrogen on C–4 and C–5 (4,5- interaction) (Although two adjacent e,e or a,e bonds of cyclohexane ring form a gauche – butane interaction, this interaction is present in all isomers).

b) The **cis–anti–trans** isomer (II) has a cis–decalin unit involving three gauche–butane interactions, in addition to the 4,5–interaction. So its estimated energy is 13.4 KJ/mol (4×3.5 KJ/mol).

c) The situation is same in case of **cis–syn-trans** isomer (III), the 4,5–interaction is due to a,e – substitution.

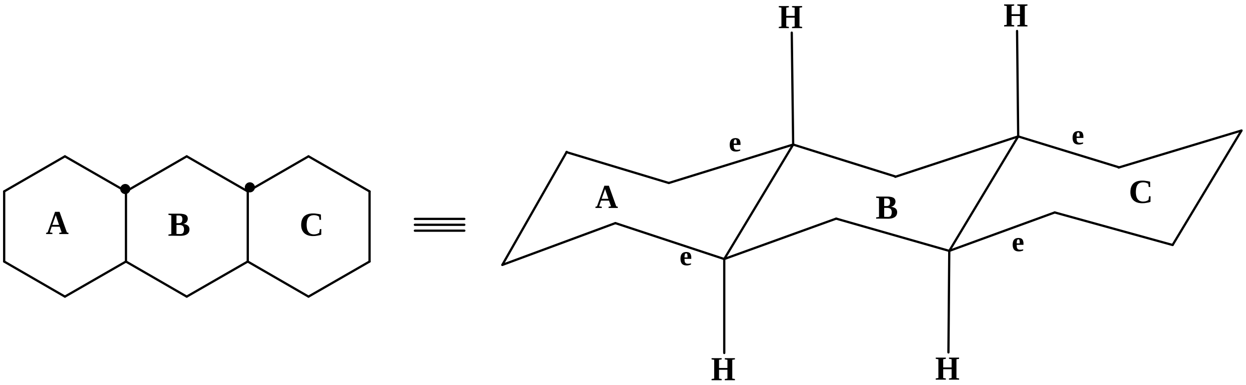
d) The **cis–anti–cis** isomer (IV) is flexible can undergo ring inversion to give energetically non–equivalent conformers A and B.

e) The **cis-syn-cis** isomer (V) also exists as a mixture of two equienergetic conformations and like cis-decalin is an inseparable racemate. The planar structure contains a σ –plane and hence it is designated as **meso**. In addition to the usual 4,5 – interaction, this isomer has two **cis**-decalin units and a **1,3-syn diaxial** interaction (22.6KJ/mol), so the total energy of this isomer is 29.3 KJ/mol.

f) The **trans-syn-trans** isomer (VI) cannot have both ring junctions **trans**-fused with **cis**-orientation of 12-13 and 11-14. In order to achieve this geometrical requirement, the central ring (B) adopts a boat conformation with terminal rings fused through four boat equatorial (be) bonds. The estimated energy of this isomer is 23.4 KJ/mol and is **achiral**. The planar structure shows a plane of symmetry passing through 9–10 and 12–13 bonds.

20.8. CONFORMATIONS OF PERHYDROANTHRACENE

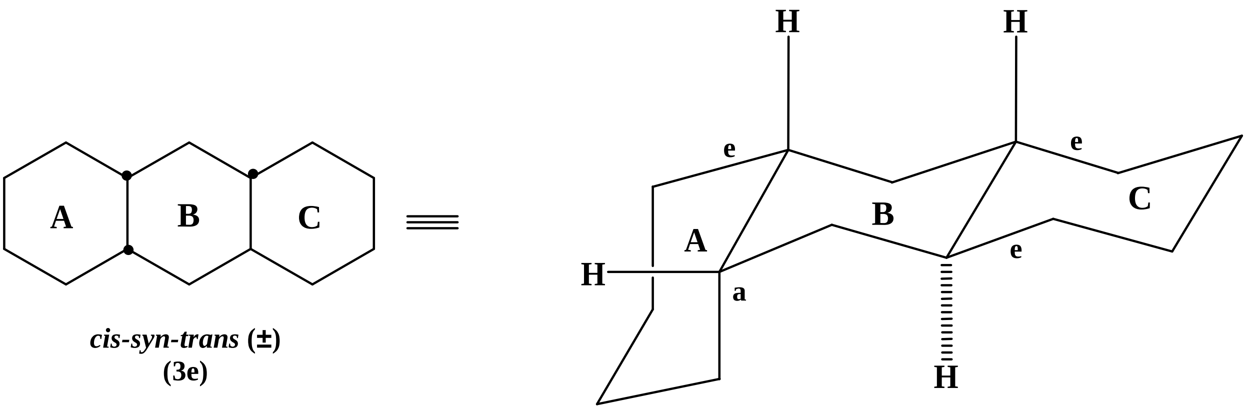
In perhydroanthracene molecule, the three rings are fused in a linear manner. The four chiral centres are equivalent and correspond to AAAA type so that the number of isomers is less than predicated. Perhydroanthracene exists as **five** diastereoisomers: **trans-syn-trans (meso)** (I), **cis-syn-trans** (II), **cis-anti-cis (meso)** (III), **trans-anti-trans** (IV) and **cis-syn-cis**(meso) (V). It must be noted that the **cis-syn-trans** (II) may well be called **cis-anti-trans** depending on whether one looks at the bridgehead atoms in clockwise or anticlockwise direction.



trans-syn-trans **(meso)**
(4e)

(I)

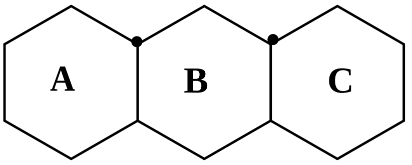
no of gauche interactions = 0



cis-syn-trans **(±)**
(3e)

(II)

no of gauche interactions = 3
(10.05 KJ/mole)



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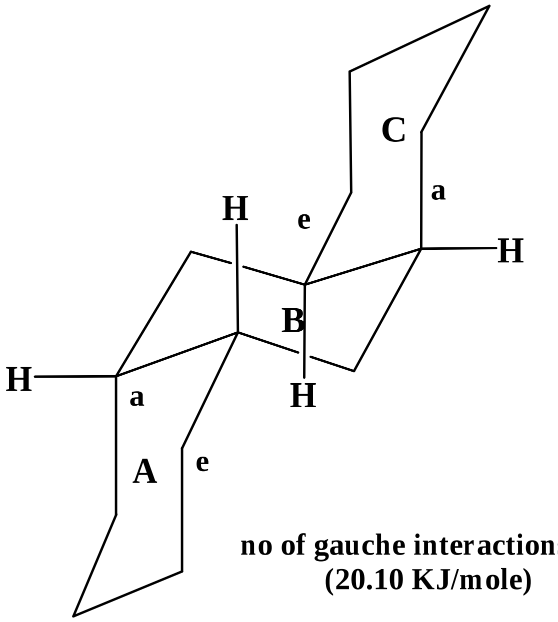
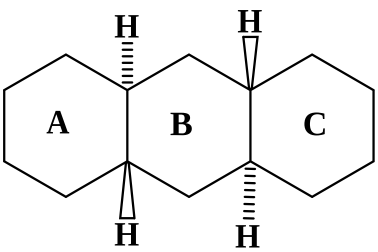


cis-anti-cis **(meso)**
(2e)

(III)

no of gauche interactions = 6
(20.10 KJ/mole)



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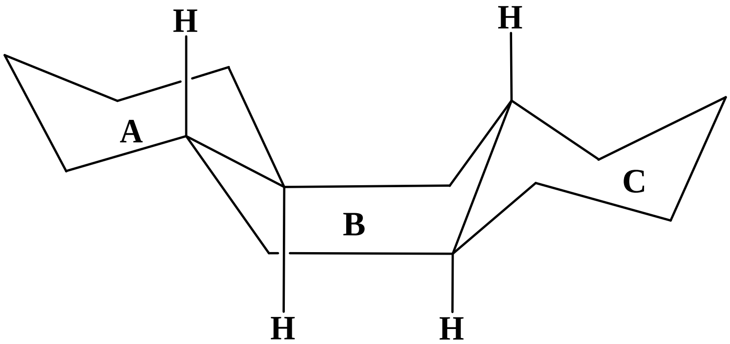
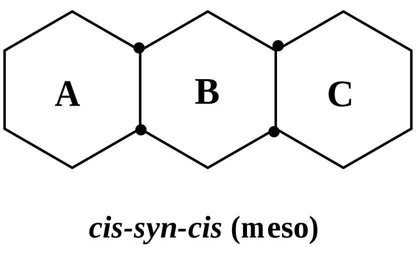


trans-anti-trans **(±)**
(4be)

(IV)

> 23.4 KJ/mole



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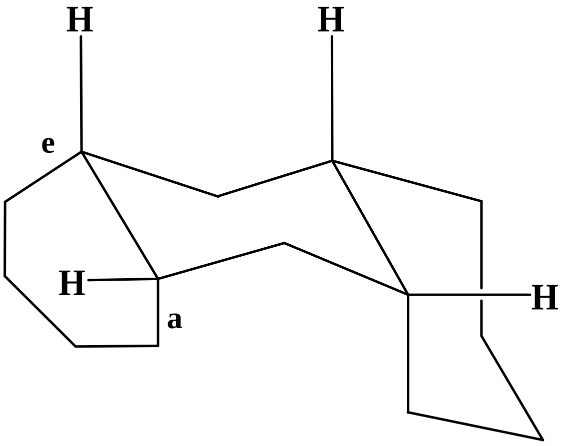

cis-syn-cis **(meso)**

(V)

> 35.0 KJ/mole

20.9. LET US SUM UP

In this lesson, we:
Pointed out

- Conformations of ethane
- Conformations of 1,2–dihalogenoethanes
- Conformations of cyclohexane
- Geometry of the cyclohexane ring system
- Equatorial and axial bonds
- Ring inversion
- Flexible conformations
- Conformations of mono and di-substituted cyclohexanes
- Monosubstituted cyclohexane
- Disubstituted cyclohexanes
- 1,2–disubstituted cyclohexane
- Decalins: bicyclo [4.4.0] decane
- Conformations of perhydrophenanthrene
- Conformations of perhydroanthracene

20.10. CHECK YOUR PROGRESS

1. Although, the anti conformation of n-butane is more stable than the gauche, in case of 2, 3-dimethylbutane, the population of gauche forms is twice that of anti. Explain.
2. Explain the greater population of the anti-conformation of 1, 2-dibromoethane (83%) relative to the anti-conformation of n-butane (67%).

20.11. POINT FOR DISCUSSION

1. Discuss the conformations of acyclic and cyclic molecules.
2. Of cis- and trans- decalin which is more stable and why?
3. Of cis- and trans- 1,3-dimethyl cyclohexanes, which is more stable and why?
4. Draw the conformations of perhydrophenanthrene.
5. Draw the conformations of perhydroanthracene.

20.12. REFERENCES

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