KARPAGAM ACADEMY OF HIGHER EDUCATION
(*Deemed to be University Established Under Section 3 of UGC Act 1956*)
Pollachi Main Road, Eachanari Post, Coimbatore–641021.

DEPARTMENT OF CHEMISTRY

M.Sc-Chemistry Syllabus (2017-18 Batch)

Semester-I

17CHP101	**ORGANIC CHEMISTRY- I (REACTION MECHANISMS)**	**4H 4C**

Instruction Hours/week:L: 4 T:0 P:0 Marks: Internal:40 External: 60 Total:100

Scope:
The course presents the knowledge about the basics of organic chemistry, involving aromaticity, principles of various organic reactions and their mechanisms and also describes the application of reactions.

Programme Outcome:
1. To understand aromaticity.
2. To provide a versatile knowledge of different name reactions and their application in synthesis.
3. To understand the principles and reaction mechanisms involving various electrophilic and nucleophilic, addition and elimination reactions.

Programme Learning Outcome:
After the completion of the course the students knows about aromaticity, a versatile knowledge about name reactions and their applications. In addition to that he knows about the reaction mechanisms involving various electrophilic and nucleophilic, addition and elimination reactions

UNIT – I
Aromaticity and chemical methods in mechanisms: Aromaticity - introduction - aromaticity of benzenoid and heterocyclic compounds. Non-benzenoid aromatics – annulenes, azulenes, ferrocenes and fulvenes.

Kinetic and non-kinetic methods of study of reaction mechanisms - kinetic methods- Primary and secondary kinetic isotopic effects. Non-kinetic methods - study of intermediates, isotopic labeling, stereochemical studies, energy profile diagrams and cross over experiments. Hammond's postulate. Kinetic and thermodynamic control.

Linear free energy relationship - Hammett equation and Taft equation.

UNIT–II

Addition reactions: Electrophilic, nucleophilic and free radical addition to double and triple bonds - hydration, hydroxylation, Michael addition, hydroboration and epoxidation.

Addition reactions to carbonyl compounds – Mannich reaction, Meerwein Pondroff-Verley reduction, Grignard, Claisen, Dieckmann, Stobbe, Knovenagel, Darzen, Wittig, Thorpe and Benzoin reactions.

UNIT–III

Electrophilic substitution reactions: Aromatic electrophilic substitution reactions-formylations–Gattermann, Gattermann Koch, Riemer Tiemann and Vilsmeier-Haack reactions. Kolbes, Bischler-Napieralski and Hofmann-Martius reactions. Friedel crafts alkylation and acylations.

Aliphatic electrophilic substitution reactions - mechanisms- SE1, SE2 and SEi - structure reactivity relationship, typical electrophilic substitution reactions - Friedel crafts acylation at olefinic carbon, Stork enamine reaction and decarboxylation of aliphatic acids.

UNIT–IV

Nucleophilic substitution reactions: Aliphatic nucleophilic substitution reactions-mechanisms - SN1, SN2, ion pair and SNi- substitution at vinyl carbon. Stereochemistry of nucleophilic substitution reaction - effect of substrate structure - solvent effects - leaving group effect – nucleophilicity, ambident nucleophiles and ambident substrates-neighbouring group participation.

Aromatic nucleophilic substitution reactions - benzyne mechanism, intermediate complex mechanism and SN1 mechanism, structure reactivity relationship.

Ziegler alkylation and Chichibabin reaction.

UNIT–V

Elimination reactions: Mechanisms - E1, E2, Ei and E1cB mechanisms- stereochemistry of eliminations. Hofmann rule-Saytzeff rule-Bredts rule – Substitution versus Elimination. Typical elimination reaction - Chugaev reaction, Hofmann degradation and Cope elimination.

Carbenes and nitrenes - structure, generation and reactions.

SUGGESTED READINGS:

Text Books:

1. Smith, M. B. (2015). *March's Advanced Organic Chemistry: Reactions, Mechanisms, and Structure* (VII Edition). New Jersey: John Wiley & Sons, Inc., Hoboken.

2. Finar, I. L. (2013). *Organic Chemistry Vol. II: Stereochemistry and the Chemistry of Natural Products* (V Edition). New Delhi: Pearson Education, Ltd.
3. Peter Sykes, (1995). *A guide book to Mechanism in Organic Chemistry* (VI Edition): John Wiley & Sons Inc., New York.

Reference Books:

1. Sanyal, S. N. (2014). *Reactions, Rearrangements and Reagents* (IV Edition). New Delhi: Bharathi Bhawan (Publishers and Distributors).
2. Tewari, N. (2011). *Advanced Organic Reaction Mechanism* (III Edition). Kolkata: Books and Allied (P) Ltd.

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DEPARTMENT OF CHEMISTRY

LECTURE PLAN

Name of the Staff	:	**Dr. A. THANGAMANI**
Department	:	Chemistry
Title of the Paper	:	**ORGANIC CHEMISTRY-I (REACTION MECHANISMS)**
Paper Code	:	**17CHP101**
Class	:	I-M.Sc-Chemistry
Year and Semester	:	I Year and I-Semester
Batch	:	2017-18
Total Hours	:	60 Hours

UNIT-I

HOURS REQUIRED-12

S.No.	Lecture Hour	Topics to be Covered	Support Materials
1.	1	**Aromaticity and chemical methods in mechanisms:** Aromaticity-introduction-conditions-Huckel (4n+2) rule. Aromaticity of benzenoids and heterocyclic compounds.	T1:50-60 R1:79-81
2.	1	Non-benzenoid aromatics-annulenes and azulenes.	T1:62-63, 65-66, 72-80 R1:86-87, 92-93
3.	1	Non-benzenoid aromatics-ferrocenes and fulvenes.	T1:61, 63, 67 R1:89
4.	1	Kinetic methods of study of reaction mechanisms-primary and secondary kinetic isotopic effects.	T1:285-288 R1: 124-125
5.	1	Non-kinetic methods of study of reaction mechanisms- study of intermediates and isotopic labeling.	T1:275-278, R1:120-121
6.	1	Stereochemical studies and energy profile diagrams.	T1:264-270, 278 R1:121
7.	1	Cross over experiments. Hammond's postulate.	T1:272-273 R1:118-119, 122-123

8.	1	Kinetic and thermodynamic control.	T1:271-272
9.	1	Linear free energy relationship-introduction-Hammett equation.	T1:352-354
10.	1	Hammett equation-uses.	T1:354-355
11.	1	Taft equation-polar substituent constants-steric substituent constants.	T1:356-361
12.	1	Recapitulation and discussion of important questions.	

Text Book:

T1. Smith, M. B. (2015). *March's Advanced Organic Chemistry: Reactions, Mechanisms, and Structure* (VII Edition). New Jersey: John Wiley & Sons, Inc., Hoboken.

Reference Book:

R1. Tewari, N. (2011). *Advanced Organic Reaction Mechanism* (III Edition). Kolkata: Books and Allied (P) Ltd.

UNIT-II

HOURS REQUIRED-12

S.No.	Lecture Hour	Topics to be Covered	Support Materials
1.	1	**Addition reactions:** Introduction-electrophilic, nucleophilic and free radical additions.	T1:859-869 R1:355-360
2.	1	Addition to double and triple bonds- hydration - mechanisms.	T1:885-885 R1:445-449, 453-456
3.	1	Addition to double and triple bonds- hydroxylation-mechanisms.	T1:992-998 R1:445-449, 453-456
4.	1	Michael addition.	T1:943-948 R1:467-472 R2:148-152
5.	1	Hydroboration- introduction-mechanism-applications. Epoxidation- introduction-sharpless asymmetric epoxidation.	T1:920-926, 998-1006 R1:402-409, 456-459
6.	1	Addition reactions to carbonyl compounds-Mannich reaction.	T1:1100-1103 R1: 589-591 R2:143-148
7.	1	Meerwein Pondroff-Verley reduction.	T1:1507-1508 R1: 549-550
8.	1	Grignard and Claisen reactions.	R1: 602-606, 641-648

			R2:101-104
9.	1	Dieckmann and Stobbe reactions.	T1:1154, 1234-1235 R1:577-581, R2: 114-116, 174-177
10.	1	Knovenagel and Darzen reactions.	T1:1157-1162 R1:586-588 R2: 141-143,
11.	1	Wittig, Thorpe and Benzoin reactions.	T1: 1165-1173, 1179-1180, 1187-1188 R1:581-584, 592-601 R2:182-184
12.	1	Recapitulation and discussion of important questions.	

Text Book:

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R2. Sanyal, S. N. (2014). *Reactions, Rearrangements and Reagents* (IV Edition). New Delhi: Bharathi Bhawan (Publishers and Distributors).

UNIT-III

HOURS REQUIRED-12

S.No.	Lecture Hour	Topics to be Covered	Support Materials
1.	1	**Electrophilic substitution reactions:** Aromatic electrophilic substitution reactions-introduction.	T1:570-575 R1:735-738
2.	1	Formylations-Gattermann and Gattermann Koch reactions.	T1:626-627 R1:797-799
3.	1	Reimer-Tiemann reaction.	T1:627-628 R1: 803-808 R2:164-167
4.	1	Vilsmeier-Haack and Kolbes reactions	T1:625-626, 853-854

			R1: 799-800
5.	1	Bischler-Napieralski and Hofmann-Martius reactions.	T1: 617-618, 640-641
6.	1	Friedel crafts alkylation reactions.	T1:609-615 R1:778-781
7.	1	Friedel crafts acylation reactions.	T1:621-625 R1:787-791
8.	1	Aliphatic electrophilic substitution reactions-the SE_2 and SE_i mechanisms.	T1:650-653
9.	1	The SE_1 mechanism. Structure reactivity relationship-effect of substrate- effect of leaving group- effect of solvent.	T1: 654-660
10.	1	Typical electrophilic substitution reactions-Friedel crafts acylation at olefinic carbon.	T1: 619-620
11.	1	Stork enamine reaction and decarboxylation of aliphatic acids.	T1:550-552, 718-721 R1:540-548, 623-624
12.	1	Recapitulation and discussion of important questions.	

Text Book:

T1. Smith, M. B. (2015). *March's Advanced Organic Chemistry: Reactions, Mechanisms, and Structure* (VII Edition). New Jersey: John Wiley & Sons, Inc., Hoboken.

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R1. Tewari, N. (2011). *Advanced Organic Reaction Mechanism* (III Edition). Kolkata: Books and Allied (P) Ltd.

R2. Sanyal, S. N. (2014). *Reactions, Rearrangements and Reagents* (IV Edition). New Delhi: Bharathi Bhawan (Publishers and Distributors).

UNIT-IV

HOURS REQUIRED-12

S.No.	Lecture Hour	Topics to be Covered	Support Materials
1.	1	**Nucleophilic substitution reactions:** Aliphatic nucleophilic substitution reactions-introduction-S_N2 reaction.	T1:373-379 R1:183-185
2.	1	S_N1 reaction.	T1:379-383 R1:185-187
3.	1	Ion pair and S_Ni reactions.	T1:383-387, 408-409

			R1:244-247
4.	1	Nucleophilic substitution at vinyl carbon	T1:413-416
5.	1	Stereochemistry of nucleophilic substitution reaction-effect of substrate structure, solvent effect and leaving group effect.	T1:417-424, 432-440 R1:189-192
6.	1	Nucleophilicity, ambident nucleophiles and ambident substrates.	T1:427-431, 446-451 R1:191-192
7.	1	Neighbouring group participation by π and σ bonds	T1:391-407 R1:230-244
8.	1	Aromatic nucleophilic substitution reactions- S_N1 mechanism, intermediate complex mechanism or S_NAr mechanism.	T1:732-736 R1:841-842
9.	1	Benzyne mechanism.	T1: 737-739 R1:843, 862-867
10.	1	Structure reactivity relationship-the effect of substrate-leaving group-attacking nucleophile.	T1: 741-745
11.	1	Ziegler alkylation and Chichibabin reaction.	T1: 785-788 R1:852-853
12.	1	Recapitulation and discussion of important questions.	

Text Book:

T1. Smith, M. B. (2015). *March's Advanced Organic Chemistry: Reactions, Mechanisms, and Structure* (VII Edition). New Jersey: John Wiley & Sons, Inc., Hoboken.

Reference Book:

R1. Tewari, N. (2011). *Advanced Organic Reaction Mechanism* (III Edition). Kolkata: Books and Allied (P) Ltd.

UNIT-V

HOURS REQUIRED-12

S.No.	Lecture Hour	Topics to be Covered	Support Materials
1.	1	**Elimination reactions:** Introduction.	T1:1253-1254 R1:289-292, 303-305, 311-313, 329-330
2.	1	E_1 and E_2 elimination reactions.	T1:1254-1262 R1:289-292, 303-305
3.	1	E_i and E_{1CB} elimination reactions.	T1:1262-1267, 1278-1280 R1: 311-313,

			329-330
4.	1	Stereochemistry of eliminations. Hofmann rule and Saytzeff rule.	T1:1269-1274 R1: 313-315
5.	1	Bredts rule. Substitution versus elimination-effect of substrate structure, attacking base, medium and temperature.	T1:203-204, 1269-1270, 1274-1278 R1:64-65, 325-327
6.	1	Typical elimination reaction- Chugaev reaction, Hofmann degradation and Cope elimination reaction.	T1:1288-1293 R1:321-322, 330-333
7.	1	Carbenes- structure, generation and reactions.	T1:249-257 R1: 459-467
8.	1	Nitrenes- structure, generation and reactions.	T1:257-260
9.	1	Recapitulation and discussion of important questions.	
10.	1	Discussion of previous ESE question papers.	
11.	1	Discussion of previous ESE question papers.	
12.	1	Discussion of previous ESE question papers.	

Text Book:

T1. Smith, M. B. (2015). *March's Advanced Organic Chemistry: Reactions, Mechanisms, and Structure* (VII Edition). New Jersey: John Wiley & Sons, Inc., Hoboken.

Reference Book:

R1. Tewari, N. (2011). *Advanced Organic Reaction Mechanism* (III Edition). Kolkata: Books and Allied (P) Ltd.

UNIT-I

Aromaticity and chemical methods in mechanisms: Aromaticity–introduction -aromaticity of benzenoid and heterocyclic compounds. Non-benzenoid aromatics–annulenes, azulenes, ferrocenes and fulvenes.

Kinetic and non-kinetic methods of study of reaction mechanisms - kinetic methods-Primary and secondary kinetic isotopic effects. Non-kinetic methods - study of intermediates, isotopic labeling, stereochemical studies, energy profile diagrams and cross over experiments. Hammond's postulate. Kinetic and thermodynamic control.

Linear free energy relationship - Hammett equation and Taft equation.

AROMATICITY AND CHEMICAL METHODS IN MECHANISMS

Aromaticity

Benzene and compounds that resemble benzene in chemical behaviour possess unusual stability. This quality which renders these compounds especially stable is referred to as aromaticity.

Conditions for aromaticity

The necessary conditions for a compound to possess aromatic character (aromaticity) are as follows:

(i) The structure must be cyclic.

(ii) Each atom in the ring must have an unhybridized p orbital.

(iii)These p orbitals must be parallel, so that they can overlap to form a continuous ring of parallel orbitals. In most cases the structure must be planer (or nearly planer) for effective overlap to occur.

(iv)The overlapping π system must have $(4n + 2)\pi$ electrons, where n = 0,1,2, etc.(Huckel's rule) and therefore all the bonding orbitals must be completely filled.

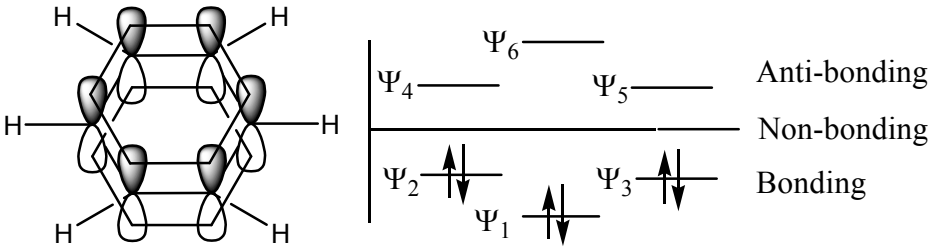
(v) Delocalization of the π electrons over the ring must lower the electronic energy, i.e., the species must be stabilized by delocalization.

Conditions for antiaromaticity

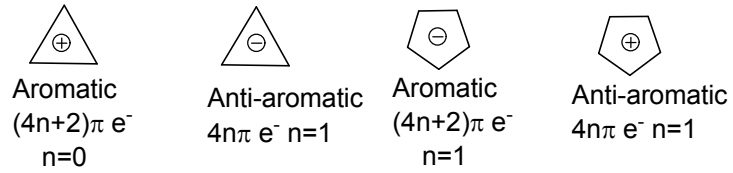
An antiaromatic compound is one that meets the first three criteria, but the overlapping π system must have $4n\pi$ electrons, where, n=1, 2, 3 etc., and delocalization of the π electrons over the ring must increases the electronic energy, i.e., the species must be destabilized by delocalization.

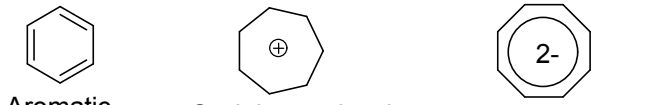
Benzene is the best known example of compounds possessing aromatic character, since this molecule is planer (effective overlap of p orbitals occurs) and it has a closed shell

of six π electrons [(4n + 2)π electrons, when n=1], i.e., all the occupied bonding orbitals are completely filled.

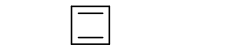


Planar benzene molecule Molecular orbitals of benzene





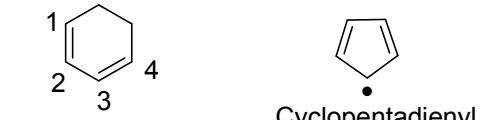
Cyclobutadiene is an example of antiaromatic compound, since this molecule is planer (effective overlap of p orbitals occurs) and it has a closed shell of four π electrons i.e., 4nπ electrons, where n=1.



Cyclobutadiene
4π electrons system:
antiaromatic

Conditions for nonaromaticity

A cyclic compound that does not have a continuous, overlapping ring of p orbitals is said to be nonaromatic (or aliphatic). 1,3-Cyclohexadiene is an example of nonaromatic compound.



1,3-Cyclohexadiene Cyclopentadienyl radical

[A (4n + 2)π electron system that have a continuous ring of p orbitals is also nonaromatic if overlapping of orbitals is inhibited due to nonplanarity.]

Modern definition of aromaticity

The modern definition of aromaticity is the ability to sustain an induced ring current by a planer or nearly planer cyclic system with (4n+2) delocalized π electrons, where n = 0, 1, 2, 3.....etc.

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 an NMR spectrum depends on the electron density of its bond; the greater the electron density of the electron cloud surrounding or partially surrounding a proton, the more upfield is its chemical shift (a lower value of δ).

However, this rule has several exceptions; one is for protons in the vicinity of an aromatic ring. When an external magnetic field is imposed upon an aromatic ring (as in an NMR instrument), 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 **Fig. 1**, this induced field curves around and in the area of the proton is parallel to the external field, so the field 'seen' by the aromatic proton is greater than it would have been in the absence of diamagnetic ring current. The protons are moved downfield (to higher δ) compared to where they would be if electron density were the only factor. Thus ordinary alkene hydrogens are found at ~5-6 δ, which the hydrogens of benzene rings are located at about ~7-8 δ.

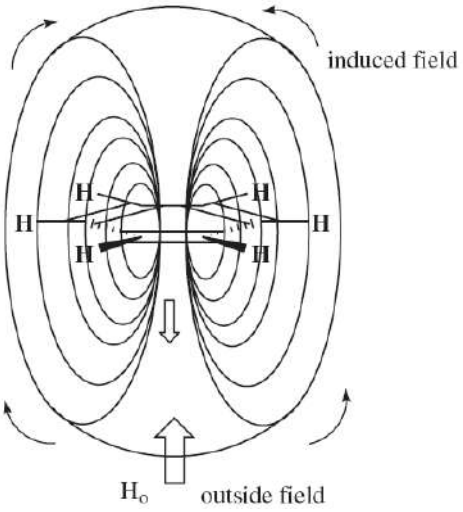


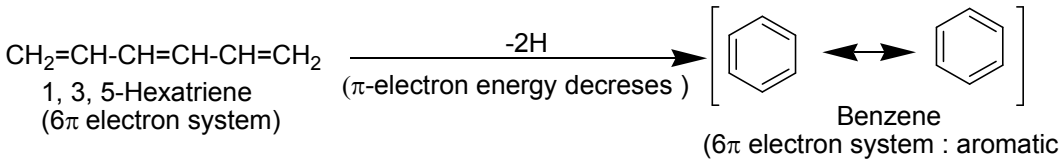
Fig. 1. Ring current in benzene.

It follows that aromaticity can be determined from an NMR spectrum. If the protons attached to the ring are shifted downfield from the normal alkene region, we can conclude that the molecule is diatropic, and hence aromatic. In addition, if the compound has protons above or within the ring, then if the compound is diatropic, these will be shifted upfield. One drawback to this method is that it cannot be applied to compounds that have no protons in either category, for example, the dianion of squaric acid.

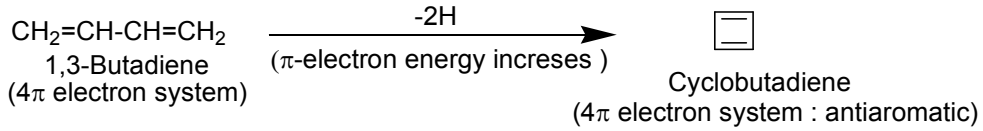
1. How are aromatic, antiaromatic and nonaromatic compounds classified by comparing the π-electron energy of the cyclic system with that of the corresponding open chain compound? Illustrate with examples.

Solution:

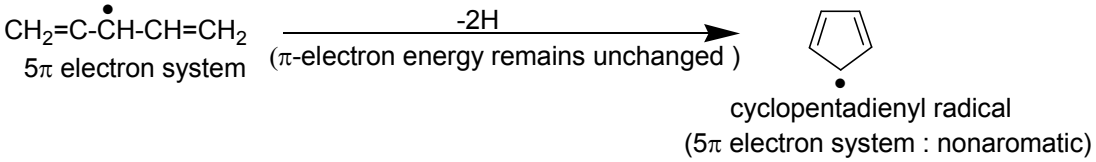
If the ring has lower π-electron energy than the open-chain counterpart, i.e., if on ring closure the π-electron energy decreases, the compound is classified as being aromatic. For example, when 1, 3, 5-hexatriene is hypothetically converted to benzene by abstraction of two H atoms from two end carbons, the π-electron energy decreases and hence benzene is classified as being aromatic.



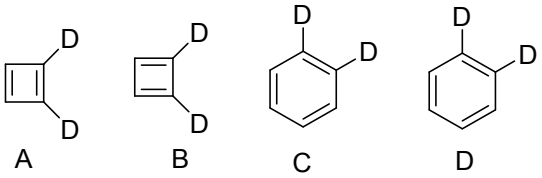
If the ring has higher π-electrons energy than the acyclic analog, i.e., if on ring closure the π-electron energy increases, the compound is classified as being antiaromatic. For example, when 1, 3-butadiene is hypothetically converted to cyclobutadiene by abstraction of two H atoms from two end carbons, the π-electron energy increases (destabilized by delocalization) and so, Cyclobutadiene is classified as being antiaromatic.



If the ring and its open-chain analog have the same π-electron energy, i.e., if on ring closure the π-electron energy remains unchanged the compound is classified as being nonaromatic. For example, cyclopentadienyl radical is nonaromatic.



2. Using the theory of aromaticity, explain the finding that A and B are different compounds, but C and D are identical.



Solution:

Since Cyclobutadiene being an antiaromatic system (destabilized by resonance) contains localized double bonds, A and B are different compounds (in fact, these are two isomers of dideuterocyclobutadiene). However, since benzene, being an aromatic system (stabilized by resonance) contains delocalized double bonds, compound C and D are identical (in fact, these are two resonance structures of 1,2-dideuterobenzene).

Huckel rule

Erich Huckel, a German chemical physicist, proposed this rule in early 1930s. Based on certain quantum mechanical calculations. This rule enables us to predict whether a given system is aromatic or antiaromatic. Huckel's rule is applicable only if the system meets the following pre-requisite:

1. A cyclic structure.

2. An unhybridized p orbital on each atom of the ring.

3. A planar or nearly planar structure so that there is a continuous or nearly continuous overlap of all p orbitals of the ring.

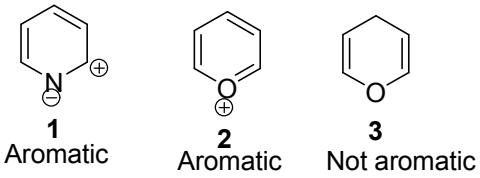
Once the compound/system fulfills these pre requisites, Huckel's rule applies. **Huckel's Rule** states that if the number of π electrons in the system is (4n + 2), the system is **aromatic**, and if it is (4n), the system is **antiaromatic** or **nonaromatic**, where **n is a positive integer** (0, 1, 2, 3, 4, - - -). Thus, common aromatic system have 2, 6, 10 - - - - π electrons and antiaromatic and nonaromatic systems have 4, 8, 12, - - - - π electrons. Benzene and cyclobutadiene, for example, fulfill all the three pre-requisites cited above. Whereas benzene with six π electrons is a (4n + 2) system, cyclobutadiene with four π electrons is a (4n) system. Therefore, benzene should be **aromatic** and cyclobutadiene should be **antiaromatic,** according to Huckel's rule. This is actually so.

Aromaticity of benzenoid and heterocyclic compounds

Benzenoid compounds

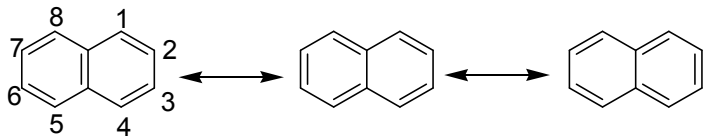
Six-membered rings

Not only is the benzene ring aromatic, but so are 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 the unshared pair of the nitrogen does not participate in the aromaticity. Therefore, derivatives such as *N*-oxides or pyridinium ions are still aromatic. However, for nitrogen heterocycles there are more significant canonical forms (e.g.,**1**) than for benzene. Where oxygen or sulfur 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 pyrylium ion (**1**) is.



1 Aromatic **2** Aromatic **3** Not aromatic

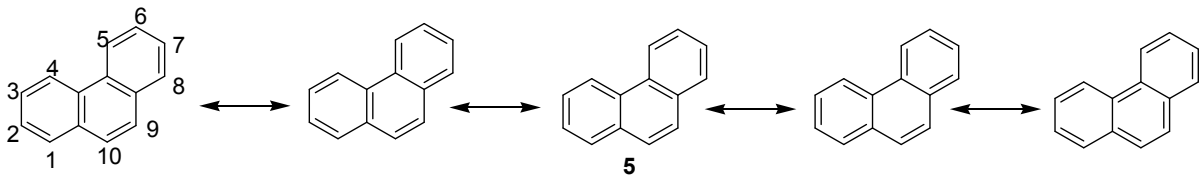
In systems of fused six-membered aromatic rings, the principal canonical forms are usually not all equivalent. Compound **4** has a central double bond and is thus different from the other two canonical forms of naphthalene, which are equivalent to each other. For naphthalene, these are the only forms that can be drawn without consideration of Dewar forms or those with charge separation. If we assume that the three forms contribute equally, the 1,2-bond has more double bond character than the 2,3-bond. Molecular orbital calculations show bond orders 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 1.415 Å, 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.



4

Phenanthrene and anthracene

In phenanthrene, where the 9, 10 bond is a single bond in only one of 5 forms (**5**), bond fixation becomes extreme and this bond is readily attacked by many reagents: It has been observed that increased steric crowding leads to an increase in Dewar-benzene type structures.

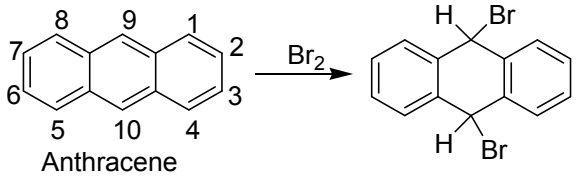


5

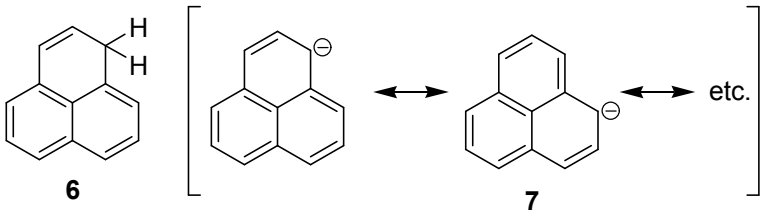
In general, there is a good correlation between bond distances in fused aromatic compounds and bond orders. Another experimental quantity that correlates well with the bond order of a given bond in an aromatic system is the NMR coupling constant for coupling between the hydrogens on the two carbons of the bond.

The resonance energies of fused systems increase as the number of principal canonical forms increases. Thus, for benzene, naphthalene, anthracene and phenanthrene, for which we can draw, respectively 2, 3, 4 and 5 principal canonical forms the resonance energies are, respectively, 36, 61, 84 and 92 kcal/mol calculated from heat of combustion data. Note that when phenanthrene, which has a total resonance energy of 92 kcal/mol loses the 9, 10 bond by attack of a reagent, such as ozone or bromine, two complete benzene rings remain, each with 36 kcal/mol that would be lost if benzene was similarly attacked. The fact

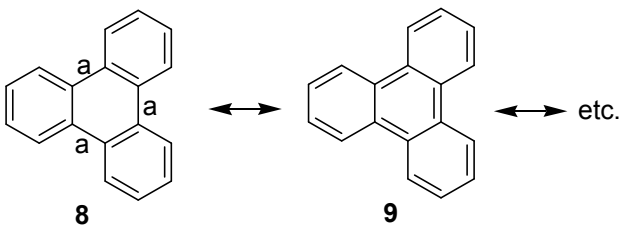
that anthracene undergoes many reactions across the 9,10 positions can be explained in a similar manner. Resonance energies for fused systems can be estimated by counting canonical forms.



Not all fused systems can be fully aromatic. Thus for phenalene (**6**) there is no way double bonds can be distributed so that each carbon has one single and one double bond. However, phenalene is acidic and reacts with potassium methoxide to give the corresponding anion (**7**), which is completely aromatic. So are the corresponding radical and cation, in which the resonance energies are the same.



Molecules that contain fused rings, such as phenanthrene or anthracene, are generally referred to as linear or angular polyacenes. In a fused system, there are not six electrons for each ring. In naphthalene, if one ring is to have six, the other must have only four. One way to explain the greater reactivity of the ring system of naphthalene compared with benzene is to regard one of the naphthalene rings as aromatic and the other as a butadiene system. This effect can become extreme, as in the case of triphenylene. For this compound, there are eight canonical forms like **8**, in which none of the three bonds marked a is a double bond and only one form (**9**) in which at least one of them is double. Thus the molecule behaves as if the 18 electrons were distributed so as to give each of the outer rings a sextet, while the middle ring is ‘‘empty.’’ Since none of the outer rings need share any electrons with an adjacent ring, they are as stable as benzene; triphenylene, unlike most fused aromatic hydrocarbons, does not dissolve in concentrated sulfuric acid and has a low reactivity. This phenomenon, whereby some rings in fused systems give up part of their aromaticity to adjacent rings, is called *annellation* and can be demonstrated by UV spectra as well as reactivities. In general, an increase of size of both linear and angular polyacenes is associated with a substantial decrease in their aromaticity, with a greater decrease for the linear polyacenes.

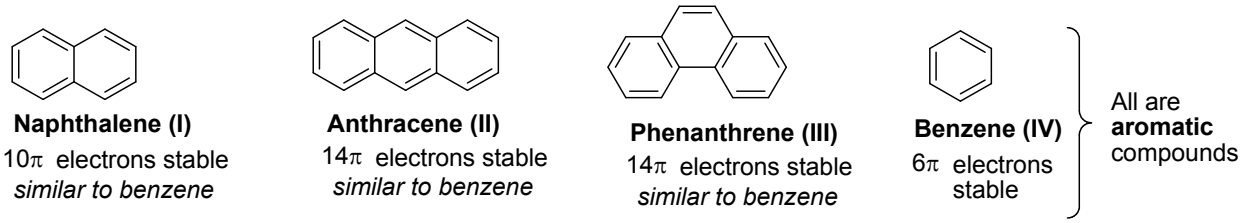


Polycyclic compounds

Strictly speaking, **Huckel's rule for aromaticity** and **antiaromaticity** is applicable to **monocyclic** systems only. However, certain polycyclic systems also respond positively to this rule for **aromaticity** and **antiaromaticity**, though the rule has to be **modified slightly** sometimes.

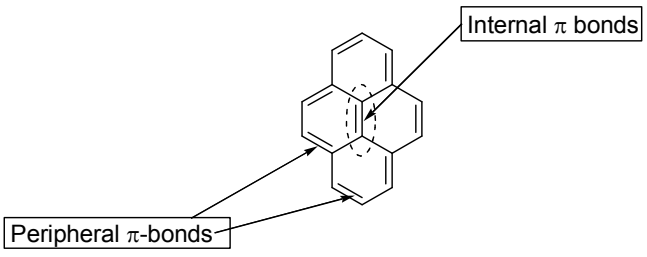
(a) Polynuclear hydrocarbons

Naphthalene (**I**), anthracene (**II**) and phenanthrene (**III**) have 10, 14 and 14π electrons respectively (the typical Huckel numbers for aromaticity). They also show chemistry typical to benzene. These polynuclear hydrocarbons are **aromatic** even on the basis of Huckel's rule. This conclusion is supported by the resonance energy data of these ring systems. Compared with benzene (150.5 kJ/mol); Naphthalene, anthracene and phenanthrene have shown resonance energies **per benzene ring** of 127 kJ, 117 kJ and 128 kJ/mol respectively.

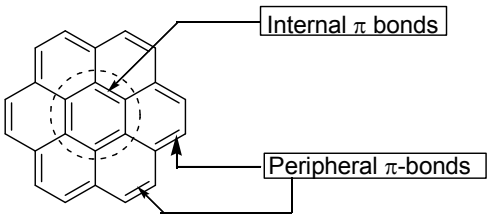


(b) Pyrene and related hydrocarbons

Since pyrene with 16-pi electrons is a 4n system, it is expected to be an **anti-aromatic** compound under the Huckel's rule (where, n = 4). Experimentally, it behaves like a typical **aromatic** compound. To account for this anomaly, **Huckel's rule** was **modified slightly**. The **modified Huckel's rule** states that "**in polycyclic systems, Huckel's rule is applicable only to the peripheral π electrons of the compound**". Pyrene has only 14 *peripheral π electrons* (a typical Huckel number for aromaticity, where, n = 3). With the **modified Huckel's rule**, pyrene also falls in line with **aromatic**, rather than anti-aromatic, compounds. This prediction was confirmed when **V. Boekelheide** (University of Oregon) synthesized ***trans***-15,16-dimethyldihydropyrene and showed that it is aromatic.



Pyrene 16 π electron (**14**-Peripheral) with one Kekule' structure behave like **aromatic** compounds satisfies Modified Huckel Rule, the internal double bond enclosed in a dotted circle.



Coronene
24 π electrons(**18**-Peripheral) with one Kekule' structure behave like **aromatic** compounds satisfies Modified Huckel Rule, the internal double bond enclosed in a dotted circle.

Similarly, **coronene**, with 24 π electrons but only **18 peripheral π electrons**, should be expected to show **aromaticity** according to the **modified Huckel's rule** and it is actually so.

Thus, we see that **Huckel's rule** gives a fairly reliable guideline to determine if a given cyclic compound is **aromatic or anti-aromatic**. Strictly speaking, Huckel's rule is applicable only to **mono-cyclic compounds**. However, the **modified Huckel rule** accounts for aromaticity of **complex polycyclic compounds** such as **pyrene** and **coronene** also. In conclusion, it must be stressed that an *aromatic compound does not have to have at least a benzene ring always*. **Non-benzenoide aromatic compounds/ions** *are also known today*.

Non-benzenoid-aromatic compounds

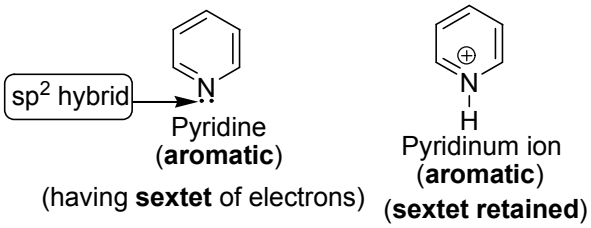
The compounds which contain no benzene ring and yet they show aromatic character or aromaticity. Such compounds are called **nonbenzenoid aromatic compounds.**

Heterocyclic compounds

Hitherto, we have applied Huckel's rule to only hydrocarbons. Let us now apply Huckel's rule to **heterocyclic compounds** with rings containing **sp^2 hybridized** atoms other than carbon (say, **N**, **O** and **S**). These are known as **non-benzenoid** aromatic compounds.

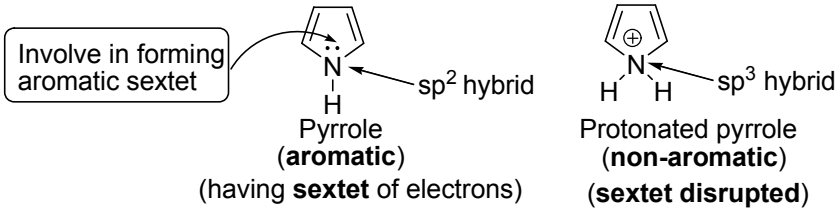
Pyridine

It is a nitrogen analogue of benzene in which one of the (C-H) units of benzene has been replaced by nitrogen with a **nonbonding pair** of electron. These nonbonding electrons on nitrogen are in an sp^2 hybrid orbital in the plane of the ring. They are perpendicular to the π system and do not overlap with it. Pyridine is thus, a planar molecule with **six delocalized electrons** (sextet) in its π system and the **nonbonding electrons on N are not interacting** with the π electrons of the ring. Pyridine, therefore, should be and actually is, **aromatic** (resonance energy ≈ 125 kJ/mol) in character. Since pyridine is basic, it can be protonated to give a **pyridinium ion** $\left(C_5H_5\overset{\oplus}{N}H\right)$. Since the additional proton on **N** has no effect on the electrons of the aromatic sextet, **pyridinium ion** is also **aromatic**. It may be noted that both **pyridine** and **pyridinium ion** fulfil **Huckel's** criteria of aromaticity (*monocyclic, planar, a 2p orbital on each atom of the ring and the **sextet** of electron in the π-system*). Thus, **the aromaticity of pyridine and pyridinium ion is in accord with Huckel's rule**.



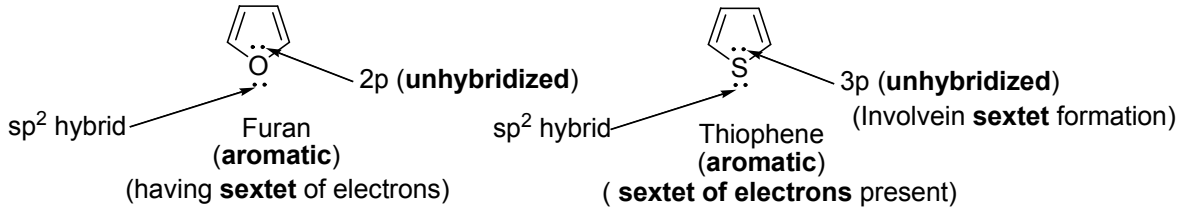
Pyrrole

In pyrrole, N atom is **sp^2 hybridized** and its unhybridized p orbital overlaps the p orbitals of carbons to form a continuous ring. Unlike the lone pair of electrons on pyridine N, the **lone pair of pyrrole N occupies the p orbital** and these **electrons take part in the π bonding system**. These two electrons, together with the four π electrons of the two double bonds, complete the **aromatic sextet**. Thus, **pyrrole** is **aromatic** (resonance energy ≈ 88 kJ/mol) as per *Huckel's rule*. Pyrrole is a much **weaker base than pyridine** because of the structure of the **protonated pyrrole** (pyrrole N has to become **sp^3 hybridized** to abstract a proton and this eliminates the unhybridized p orbital needed for aromaticiy). Therefore, **protonated pyrrole**, unlike protonated pyridine, should be, and is, **non-aromatic**.

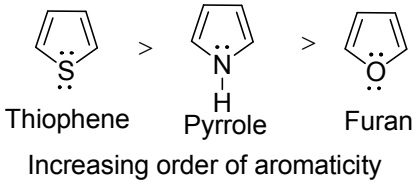


Furan and Thiophene

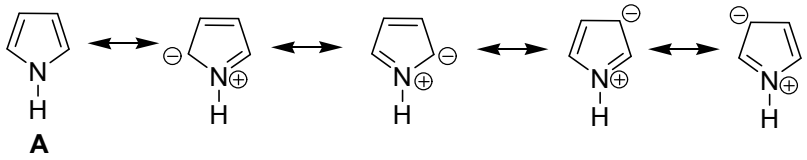
In furan one lone pair of electrons of the hetero atom (O) lies in the **unhybridized 2p orbital** and is a part of the π system whereas the other lone pair lies in an sp^2 hybrid perpendicular to the p orbitals and is not a part of the π system. Thiophene with S having two lone pairs of electrons is similar, expect that S uses an unhybridized 3p orbital to overlap with the 2p orbitals on carbons. Thus, furan and thiophene, with their **aromatic sextets** are **aromatic** (resonance energies of 67 kJ/mol and 117 kJ/mol respectively). This is in accord with **Huckel's rule** too.



The heterocyclic compounds pyrrole, thiophene and furan are the most important examples of this kind of aromaticity, although furan has a lower degree of aromaticity than the other two. Resonance energies for these three compounds are, respectively, 21, 29 and 16 kcal/mol.



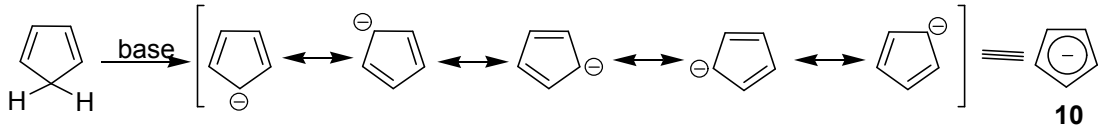
The aromaticity can also be shown by canonical forms, for example, for pyrrole.



A

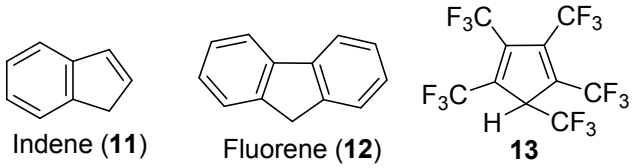
In contrast to pyridine, the unshared pair in canonical structure **A** in pyrrole is needed for the aromatic sextet. This is why pyrrole is a much weaker base than pyridine.

The fifth atom may be carbon if it has an unshared pair. Cyclopentadiene has unexpected acidic properties (p*K*a ≈16) since on loss of a proton, the resulting carbanion is greatly stabilized by resonance although it is quite reactive. The cyclopentadienide ion is usually represented as in **10**. Resonance in this ion is greater than in pyrrole, thiophene, and furan, since all five forms are equivalent. The resonance energy for **10** has been estimated to be 24–27 kcal mol^{-1} (100–113 kJ mol^{-1}).



10

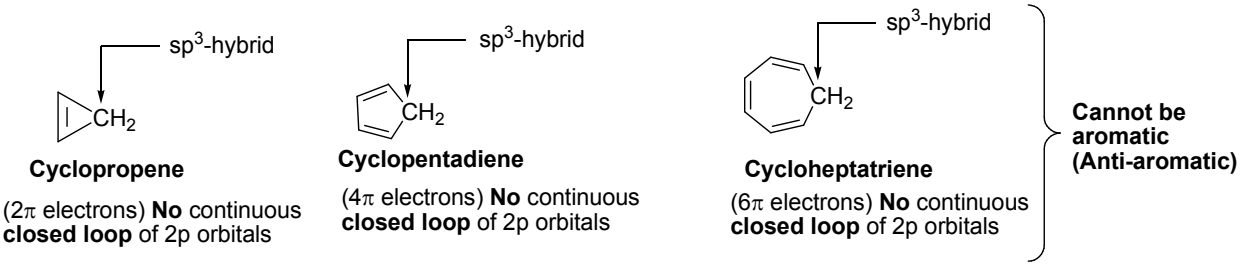
Indene (**11**) and fluorine (**12**) are also acidic (p*K*a ≈ 20 and 23, respectively), but less so than cyclopentadiene, since annellation causes the electrons to be less available to the five-membered ring. On the other hand, the acidity of 1,2,3,4,5-pentakis(trifluoromethyl)cyclopentadiene (**13**) is greater than that of nitric acid, because of the electron-withdrawing effects of the trifluoromethyl groups.



Indene (**11**) Fluorene (**12**) **13**

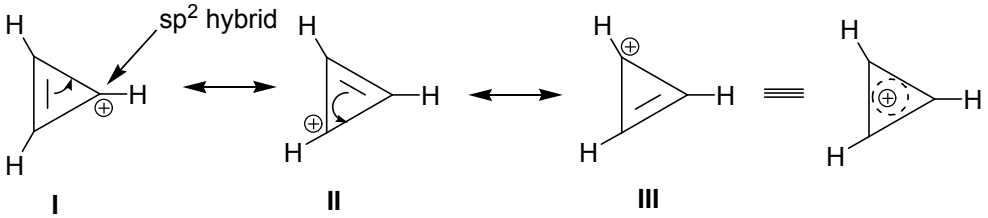
Cyclic hydrocarbons and their ions

If we recall the hydrocarbons to which **Huckel's rule** has been applied so far, we find that all those hydrocarbons (aromatic as well as antiaromatic) were mono-cyclic unsaturated hydrocarbons having an *even* number of carbon atoms. A neutral **mono-cyclic** unsaturated hydrocarbon with an *odd* number of carbon atoms in the ring must necessarily have atleast one methylene (-CH_2-) group in the ring, but such molecules **cannot be aromatic** because they cannot have a continuous **closed loop of 2p orbitals**. For example,



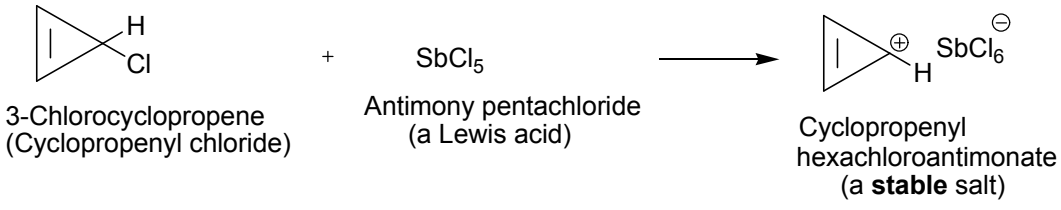
(a) Cyclopropene versus Cyclopropenyl cation

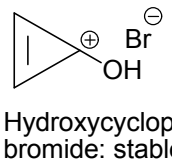
Cyclopropene has two π electrons [a typical Huckel number under Huckel's (4n + 2) rule for aromaticity, where n = 0, i.e., 4(0) + 2 = 2. Apparently, cyclopropene can be aromatic, but it lacks a continuous closed ring of 2p oritals and this makes **Huckel's rule untenable** in the case of cyclopropene. However, if we convert cyclopropene into cyclopropenyl cation, we create an **sp^2 hybridized** carbon with an empty 2p orbital. In that case, the *overlap of p orbitals becomes continuous*. Therefore, **cyclopropenyl cation**, unlike cyclopropene, is **aromatic** in accordance with Huckel's rule. Further, cyclopropenyl cation is a resonance hybrid of **three equivalent** contributing structures, as shown below:



Resonance hydrid of cyclopropenyl cation continuous closed loop of 2p orbitals is aromatic.

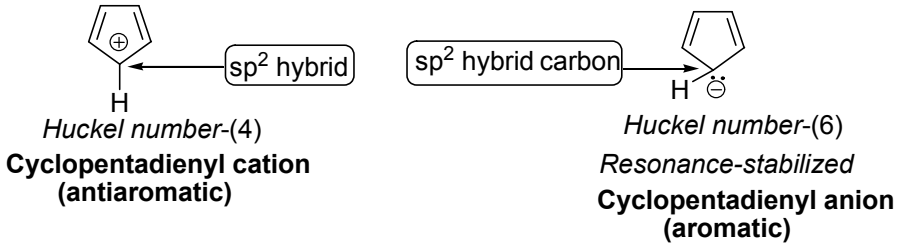
The following experimental fact also furnished proof for the aromatic stabilization of cyclopropenyl cation. *Stable* **cyclopropenium salts** such as *cyclopropenyl hexachloroantimonate* and *hydroxy-cyclopropenyl bromide* have been prepared by **R. Breslow** (1967). Presence of **three** equivalent *protons* in cyclopropenyl cation also confirms the structure of this **non-benzenoid aromatic** ring system.



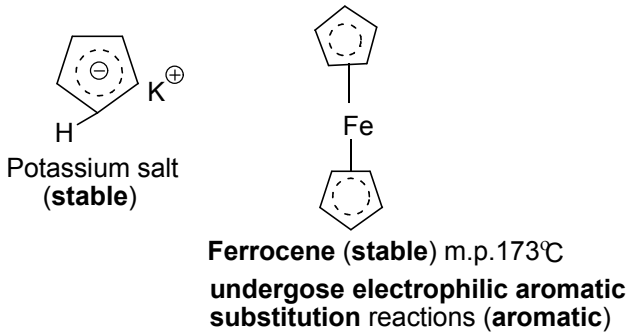


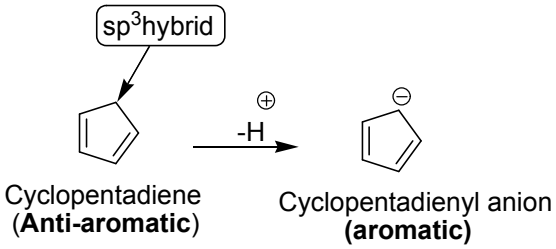
Thus, cyclopropenyl cation fulfils all the requirements of **Huckel's rule** for aromaticity. In addition, its aromaticity is supported by experimental evidence cited above. Therefore, **cyclopropenyl cation, unlike cyclopropene, is aromatic**.

(b) Cyclopentadienyl cation versus Cyclopentadienyl anion: The *cyclic, planar and conjugated* cyclopentadienyl cation with four π electrons is a (4n) system under Huckel's rule. Therefore, **cyclopentadienyl cation** should be expected to be **anti-aromatic**. This is confirmed by the fact that cyclopentadienyl cation, unlike cyclopropenyl cation, **fails to form a stable salt** regardless of the fact that it can be shown as a resonance hybrid of five equivalent contributing structures.



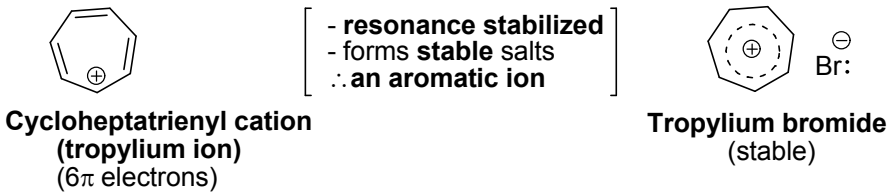
Cyclopentadienyl anion (also called cyclopentadienide ion) has **sp^2 carbon** and has two electrons in its unhybridised 2p orbital. This anion, with a **sextet of electrons** (n = 1), is a (4n+2) system and fulfils all the criteria of **Huckel rule** for aromaticity. Therefore, cyclopentadienyl anion is **aromatic**. The aromaticity of this anion is further confirmed by the experimental observations that cyclopentadienide ion (i) forms a **stable potassium cyclopentadienide salt** and (ii) **ferrocene** (a stable orange solid, m.p. 173ºC) is dicyclopentadienyl iron.





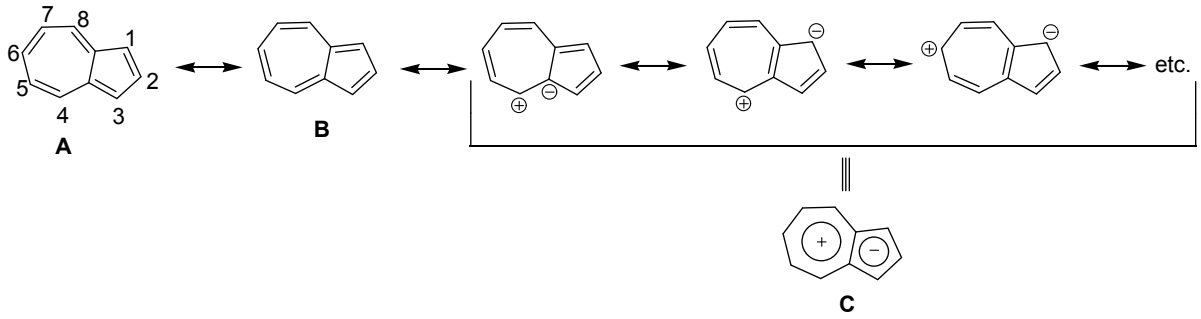
(c) Cycloheptatrienyl cation (tropylium ion)

It contains an **sp^2 hybridized carbon** with an empty 2p orbital. Thus, cycloheptatrienyl cation is *planar, has a sextet of π electrons, forms a continuous ring of p orbitals*, *and is a resonance hybrid of* **seven** *equivalent* **contributing structures**. In other words, cycloheptatrienyl cation fulfils the Huckel rule of aromaticity. Therefore, cycloheptatrienyl cation is **aromatic**. Its aromaticity is further supported by existence of **stable tropylium salts** such as **tropylium bromide** and **hydroxy tropylium chloride**.



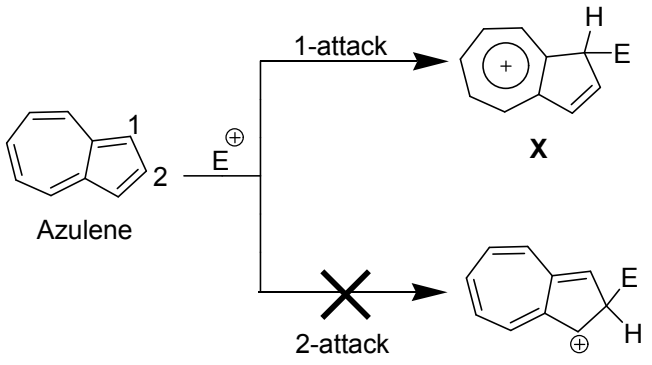
(d) Azulene

Azulene, a ten-π electron system, can be represented as a hybrid of two Kekule structures (A and B) plus a dipolar structure (C) which, infact, is a hybrid of several charge-separated structures.



In structure C, both the rings possess a closed shell of six π electrons; this structure is considerably stable because it may be regarded as a combination of the aromatic cycloheptatrienyl cation (tropylium ion) and the aromatic cyclopentadienyl anion. Since this stable dipolar structure has significant contribution to the hybrid, azulene possesses dipole moment.

The five-membered ring is more susceptible to electrophilic attack, since this is more electron rich than the seven-membered ring. Substitution occurs at 1-position because 1-attack leads to a stable intermediate (X) in which the seven-membered ring is an aromatic system (tropylium ion).



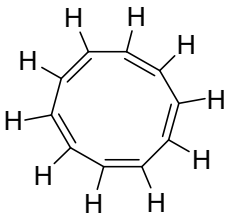
(e) Annulenes

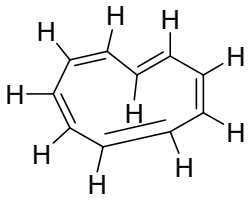
Conjugated monocyclic polyenes, C_nH_n in which n≥10 are usually called annulenes, and were prepared by Sondheimer *et al.* (1962) to test the Huckel's rule. The annulenes prepared have n=12, 14, 16, 18, 20, 24 and 30. Out of these only [14], [18] and [30]

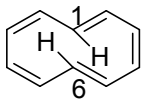
annulenes are (4n+2)π electrons molecules, whereas the rest are 4nπ electrons molecules, some examples are

[10]Annulene

There are three geometrically possible isomers of [10]annulene: the all-cis (**14**), the mono-trans (**15**), and the cis–trans–cis–cis–trans (**16**). If Huckel's rule applies, they should be planar. But it is far from obvious that the molecules would adopt a planar shape, since they must overcome considerable strain to do so. For a regular decagon (**14**) the angles would have to be 144°, considerably larger than the 120° required for sp^2 angles. Some of this strain would also be present in **15**, but this kind of strain is eliminated in **16** since all the angles are 120°. However, it was pointed out by Mislow that the hydrogens in the 1 and 6 positions should interfere with each other and force the molecule out of planarity.


all cis **14**


mono-trans **15**

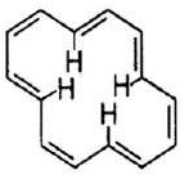


cis-trans-cis-cis-trans **16**

Compounds **14** and **15** have been prepared as crystalline solids at -80°C. The NMR spectra show that all the hydrogens lie in the alkene region and it was concluded that neither compound is aromatic. Calculations on **15** suggest that it may indeed be aromatic, although the other isomers are not.

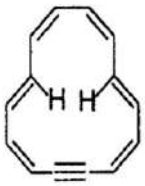
[14]Annulene

Mislow predicted that [14]annulene would possess the steric strains. This is borne out by experiment. [14]-annulene, is aromatic (it is diatropic; inner protons at 0.00 δ, outer protons at 7.6 δ), but is completely destroyed by light and air in 1 day. X-ray analysis shows that although there are no alternating single and double bonds, the molecule is not planar. Hence it is non-aromatic system.


[14]Annulene

Dehydro[14]annulene

Another way of eliminating the hydrogen interferences of [14]annulene is to introduce one or more triple bonds into the system, as in dehydro[14]annulene. All five known dehydro[14]annulenes are diatropic. The extra electrons of the triple bond do not form part of the aromatic system, but simply exist as a localized bond.

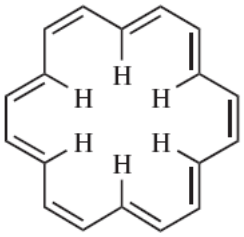


Dehydro[14]annulene

Dehydro[14]annulene-obey Huckel's (4n+2) π electron rule where, n=3. The molecule is aromatic.

[18]Annulene

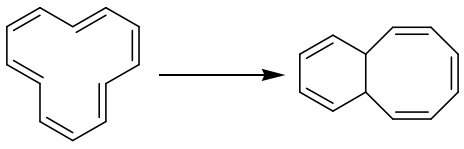
[18]Annulene is diatropic: the 12 outer protons are found at ~ δ = 9 and the 6 inner protons at ~ δ = -3. X-ray crystallography shows that it is nearly planar, so that interference of the inner hydrogens is not important in annulenes this large. [18]Annulene is reasonably stable, being distillable at reduced pressures, and undergoes aromatic substitutions. The C-C bond distances are not equal, but they do not alternate. There are 12 inner bonds of ~1.38Å and 6 outer bonds of ~1.42Å. [18]Annulene has been estimated to have a resonance energy of ~37 kcal mol^{-1} (155 kJ mol^{-1}), similar to that of benzene.



[18] Annulenes is aromatic. The obey Huckel's (4n+2) π electron rule, where n=4.

[12]Annulene

The [12]annulene **17** has been prepared. In solution, **17** undergoes rapid conformational mobility (as do many other annulenes), and above -150°C in this particular case, all protons are magnetically equivalent. However, at -170°C the mobility is greatly slowed and the three inner protons are found at ~ 8 δ while the nine outer protons are at ~6 δ. Interaction of the ''internal'' hydrogens in annulene **17** leads to nonplanarity. Above -50°C, **17** is unstable and rearranges to **18**.

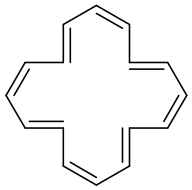


17 **18**

[12] Annulene
non-planar **(Non aromatic)**

[16]Annulene

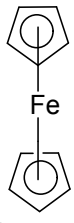
[16] Annulene is (4nπ) electron systems. They cannot be aromatic as per **Huckel's rule**. They may be expected to be **antiaromatic**, but contrary to the requirement of Huckel's rule, they cannot adopt planarity. Rather, they adopt nonplanar conformations thereby ruling out antiaromatic for them. They react like polyalkenes. Thus, they are also classified as nonaromatic systems.



[16] annulene
non-planar **(Non aromatic)**

Ferrocene

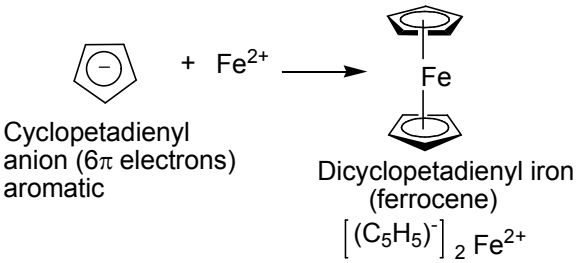
Another type of five-membered aromatic compound is the *metallocenes* (also called *sandwich compounds*), in which two cyclopentadienide rings form a sandwich around a metallic ion. The best known of these is ferrocene, where the η^5-coordination of the two cyclopentadienyl rings to iron. Other sandwich compounds have been prepared with Co, Ni, Cr, Ti, V, and many other metals.As a reminder (see p. 43), the η terminology refers to π-donation of electrons to the metal (η^3 for π-allyl systems, η^6 for coordination to a benzene ring, etc.), and η^5 refers to donation of five π-electrons to the iron. Ferrocene is quite stable, subliming >100°C and unchanged at 400°C. The two rings rotate freely. Many aromatic substitutions have been carried out on metallocenes. Metallocenes containing two metal atoms and three cyclopentadienyl rings have also been prepared and are known as *triple-decker sandwiches*. Even tetradecker, pentadecker, and hexadecker sandwiches have been reported.



Ferrocene

The bonding in ferrocene may be looked upon in simplified molecular-orbital terms as follows. Each of the cyclopentadienide rings has five molecular orbitals: three filled bonding and two empty antibonding orbitals. The outer shell of the Fe atom possesses nine atomic orbitals, that is, one 4*s*, three 4*p*, and five 3*d* orbitals. The six filled orbitals of the two cyclopentadienide rings overlap with the *s*, three *p*, and two of the *d* orbitals of the Fe to form twelve new orbitals, six of which are bonding. These six orbitals make up two ring-to-metal triple bonds. In addition, further bonding results from the overlap of the empty antibonding

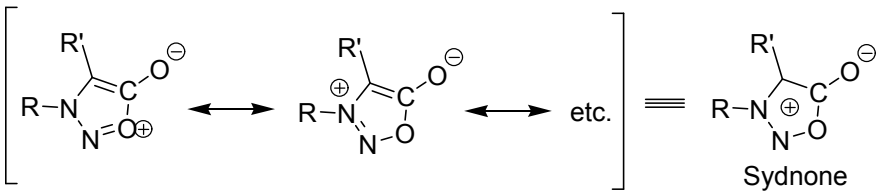
orbitals of the rings with additional filled *d* orbitals of the iron. All told, there are 18 electrons (10 of which may be considered to come from the rings and 8 from iron in the zero oxidation state) in nine orbitals; six of these are strongly bonding and three weakly bonding or nonbonding.



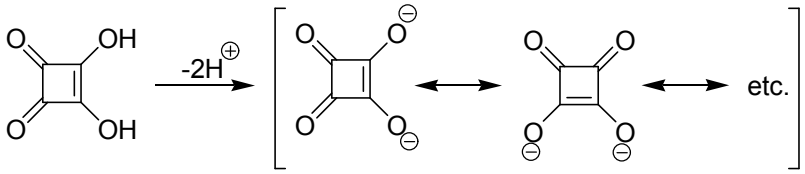
Other aromatic compounds

We will briefly mention three other types of aromatic compounds.

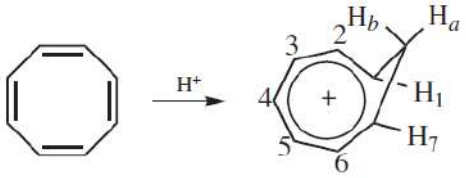
1. *Mesoionic Compounds*. These compounds cannot be satisfactorily represented by Lewis structures not involving charge separation. Most of them contain five-membered rings. The most common are the sydnones, stable aromatic compounds that undergo aromatic substitution when R´ is hydrogen.



2. *The Dianion of Squaric Acid*. The stability of this system is illustrated by the fact that the pK_1 of squaric acid is ~1.5 and the pK_2 is ~ 3.5, which means that even the second proton is given up much more readily than the proton of acetic acid, for example. The analogous three-, five-, and six-membered ring compounds are also known.



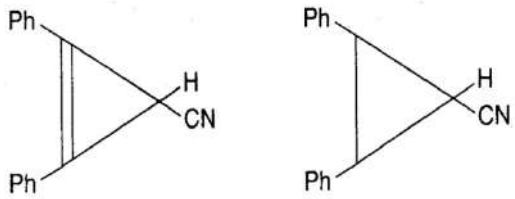
3. *Homoaromatic Compounds*. When cyclooctatetraene is dissolved in concentrated H_2SO_4, a proton adds to one of the double bonds to form the homotropylium ion. In this species, an aromatic sextet is spread over seven carbons, as in the tropylium ion. The eighth carbon is an sp^3 carbon and so cannot take part in the aromaticity. The NMR spectra show the presence of a diatropic ring current: H_b is found at δ = -0:3; H_a at 5.1 δ; H_1 and H_7 at 6.4 δ; H_2–H_6 at 8.5 δ. This ion is an example of a homoaromatic compound, which may be defined as a compound that contains one or more sp^3-hybridized carbon atoms in an otherwise conjugated cycle.



In order for the orbitals to overlap most effectively so as to close a loop, the sp^3 atoms are forced to lie almost vertically above the plane of the aromatic atoms. In homotropylium ion, H_b is directly above the aromatic sextet, and so is shifted far upfield in the nmr. All homoaromatic compounds so far discovered are ions, and it is questionable as to whether homoaromatic character can exist in uncharged systems. Homoaromatic ions of 2 and 10 electrons are also known.

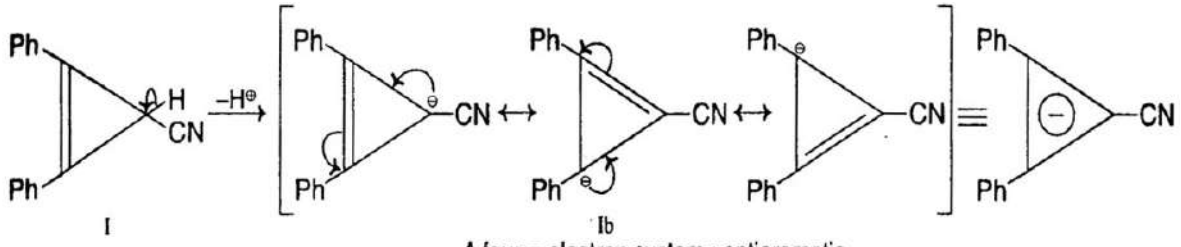
Provide an explanation for each of the following observations:

3. In hydrogen-exchange reactions, the nitrile **I** loses its proton at a very slower rate (1000 times slower) than the nitrile **II**.



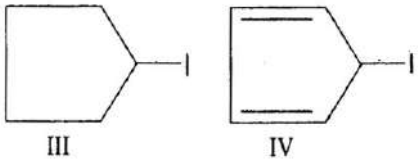
Solution:

The compound **I** on proton loss gives a cyclopropenyl anion (**Ib**), whereas the compound II on proton loss yields an ordinary carbanion (**IIb**).



The carbanion **Ib** has 4n π electrons, where n=1. So it is antiaromatic and less stable than the ordinary carbanion **IIb**. Because of this, **I** loses its proton at a very slower rate than **II** in hydrogen exchange reactions.

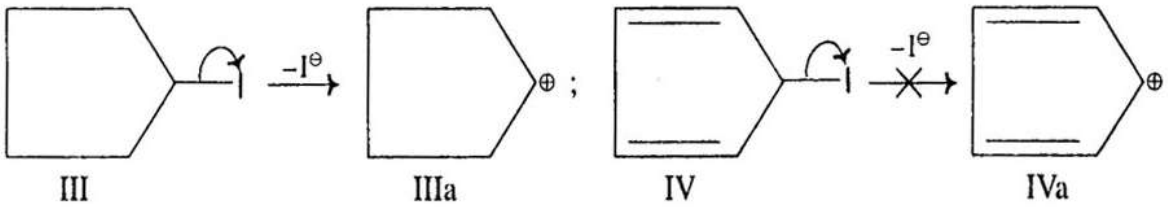
4. When treated with silver perchlorate in propionic acid, iodocyclopentane (**III**) undergoes solvolysis, whereas 1-iodocyclopenta-2, 4-diene (**IV**) does not.



III IV

Solution:

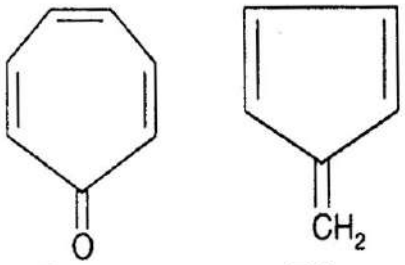
When treated with silver perchlorate in propionic acid, the compound **III** undergoes S_N1 solvolysis. The reaction proceeds through rate-limiting formation of an intermediate carbocation (**IIIa**). The intermediate expected to be involved in the solvolysis of compound **IV** is cyclopentadienyl cation (**IVa**).



III IIIa IV IVa

The carbocation **IVa** having 4n π electrons, where n=1, is antiaromatic and so it is much less stable than the corresponding ordinary carbocation **IIIa**. For this reason, the compound **III** undergoes solvolysis, whereas solvolysis of **IV** does not occur at all.

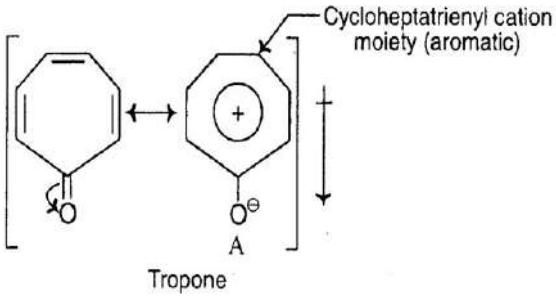
5. Compounds like tropone and fulvene possess significant dipole moments.



Tropone (μ = 4.17 D) Fulvene (μ = 1.5 D)

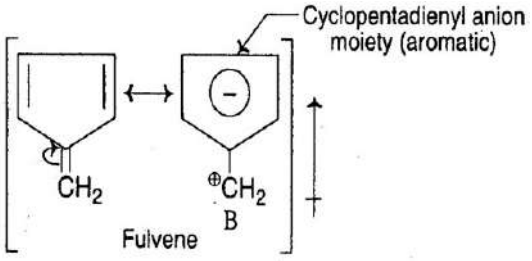
Solution:

In tropone, the seven-membered ring releases electrons to the electronegative oxygen atom and this is because in the betaine structure (**A**) the ring has an aromatic sextet spread over seven carbon atoms.



Tropone

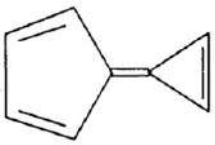
Due to large contribution of the betaine structure **A**, tropone is found to possess significant dipole moment. In fulvene, polarization of the exocyclic double bond occurs in the direction of the ring because in the charge separated structure **B** the five-membered ring with a sextet possesses considerable aromatic properties.

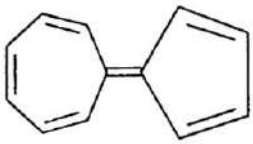


Fulvene

Due to significant contribution of the stable dipolar structure **B**, fulvene possesses considerable dipole moment.

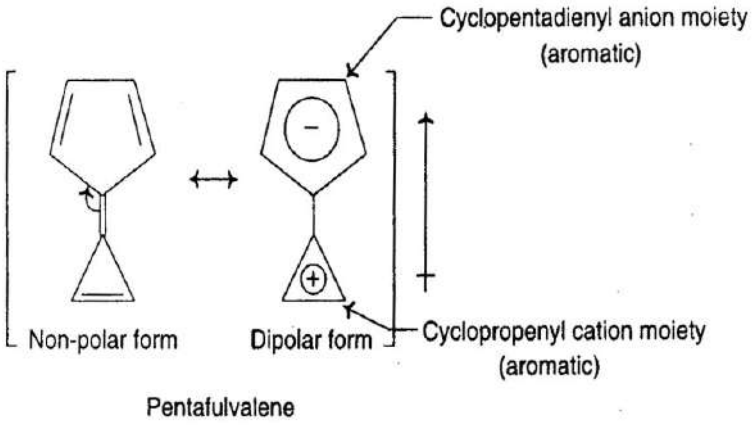
6. The following fulvalenes are significantly polar:


Pentafulvalene


Sesquifulvalene

Solution:

Pentafulvalene, an eight-л-electron system, can be represented as a hybrid of a non-polar form and a dipolar form which, in fact, is a hybrid of several charge-separated structures. The dipolar form which consists of two aromatic ions (a cyclopentadienyl anion and a cyclopropenyl cation) is considerably stable and has significant contribution to the hybrid. Because of this, pentafulvalene is significantly polar.

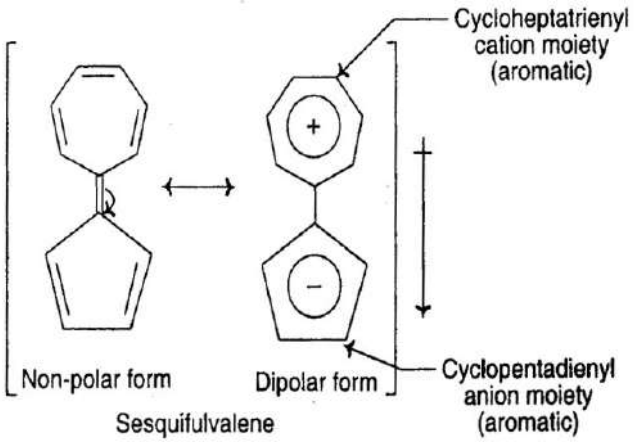


Pentafulvalene

Non-polar form-eight π electrons

Polar form- several charge-separated structures

The dipolar form of sesquifulvalene which also consists of two aromatic parts (a cyclopentadienyl anion and a cycloheptatrienyl cation) is considerably stable. So also this compound is significantly polar.



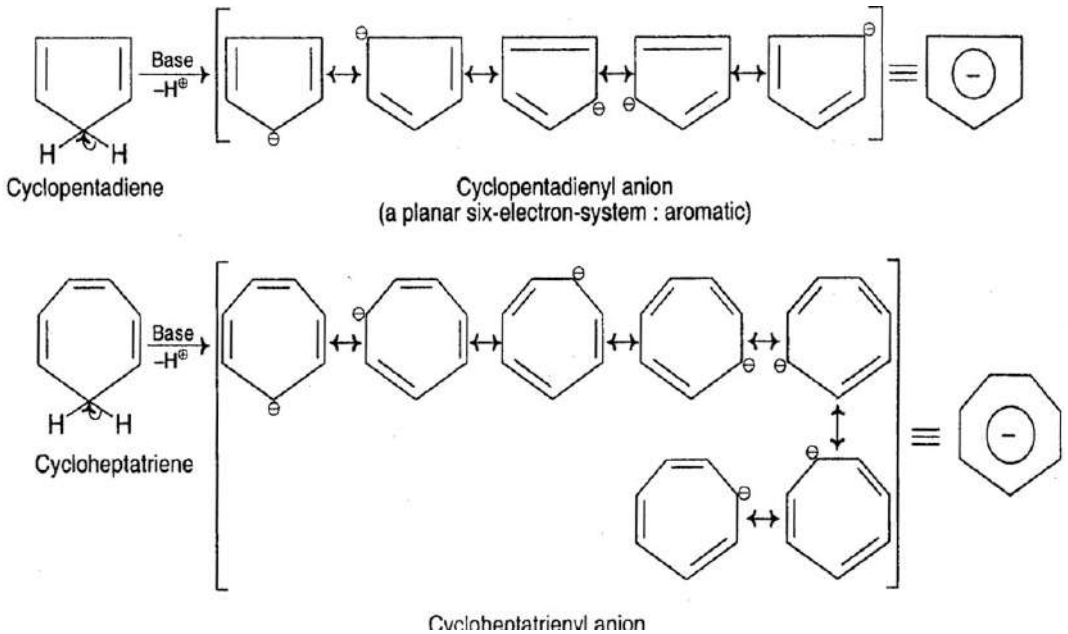
Sesquifulvalene

[In both the compounds, the π bond connecting the two rings does not break in opposite direction (toward the small ring in pentafulvalene and toward the large ring is sesquifulvalene) to give another dipolar form because in that case both the rings will be antiaromatic.]

7. Cyclopentadiene ($K_a = 10^{-15}$) is much more acidic than cycloheptatriene ($K_a = 10^{-45}$), even though greater number of contributing structures can be drawn for the anion of the latter compound.

Solution:

The cyclopentadienyl anion, the conjugate base of cyclopentadiene, can be represented as a hybrid of five resonance structures, while the cycloheptatrienyl anion, the conjugate base of cycloheptatriene, can be represented as a hybrid of seven resonance structures.

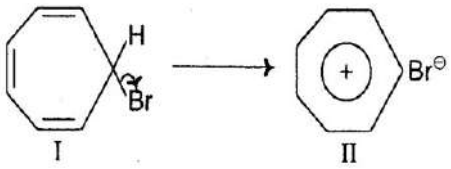


Although greater number of contributing structures can be drawn for the cycloheptatrienyl anion, it is less stable than the cyclopentadienyl anion, and that is due to fact that the former anion with 4n π electrons, where n=2 is antiaromatic (destabilized by delocalization), whereas the latter anion with (4n+2)π electrons, where n=1, is aromatic (highly stabilized by resonance). Due to the formation of a relatively stable conjugate base, cyclopentadiene is a much stronger acid than cycloheptatriene.

8. Tropylium bromide behaves as an ionic compound.

Solution:

Tropylium bromide having a covalent structure (**I**) is not a planer closed shell of six (a Huckel number) π electrons and so it is not aromatic i.e., unusually stable. On the other hand, the ionic tropylium bromide is a very stable compound because the cyclic carbocation, known as tropylium ion (**II**) has an aromatic sextet [(4n + 2) π electrons, where n = 1] spread over seven carbon atoms.



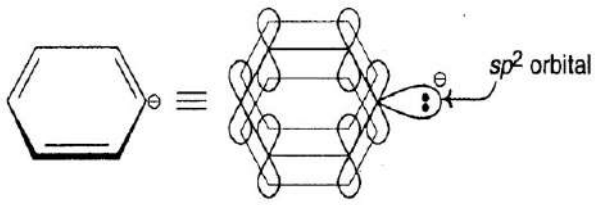
It is, therefore, energetically favourable for tropylium bromide to exist as an ion pair. So the compound is found to behave as an ionic compound.

9. Although there are eight free electrons, phenyl anion, $C_6H_5^-$ is aromatic.

Solution:

The unshared electron pair of the phenyl anion is located in an sp^2 orbital which is coplanar with the ring and perpendicular to the π electron cloud. The negative charge,

therefore, cannot be delocalized through resonance interaction with π electron cloud of the aromatic nucleus. Thus this species (planer) is a closed loop of six [(4n+2) π, n=1] π electrons and it is aromatic.

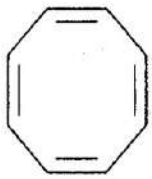


Phenyl anion : a [(4n + 2), n = 1]π electron system and aromatic.

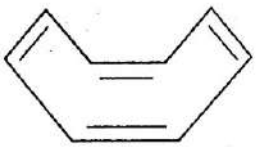
10. Cyclooctatetraene is nonplaner (a tub-shaped structure), whereas its dianion is planer.

Solution:

Cyclooctatetraene is not planer but tub-shaped. The reason for the lack or planarity is that it suffers from angle strain (a regular octagon has angle of 135˚, while sp^2 angle are most stable at 120˚). Also, this 4n π (n=2) electron antiaromatic system is destabilized by delocalization. To avoid the unfavourable delocalization and strain, the molecule assumes a non-planer shape (tub-shaped) which is now nonaromatic.

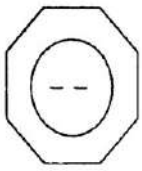


Planar antiaromatic cyclooctatetraene (less stable)



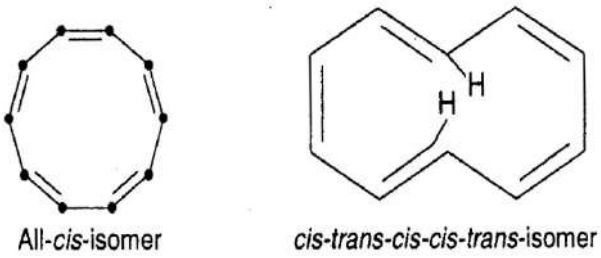
Tub-shaped nonaromatic cyclooctatetraene (more stable)

Cyclooctatetraene dianion, on the other hand, is a ten π [(4n+2) π, n=2) electron system and is aromatic. So the delocalization energy of this system is large enough to overcome the angle strain in it and so the molecule exists in the stable planar state.



Cyclooctatetraene dianion
(a ten-π-electron system : aromatic)

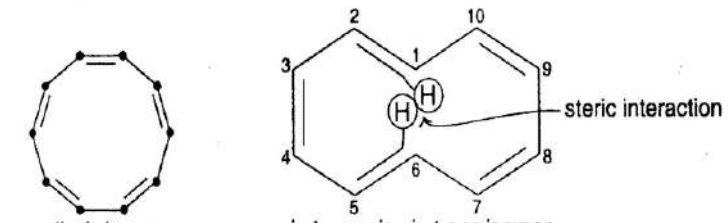
11. The following stereoisomeric cyclodecapentenes are not aromatic, even though these are ten- π- electron systems.



All-*cis*-isomer *cis-trans-cis-cis-trans*-isomer

Solution:

Huckel's rule is applicable to a system which is planar. There is considerable angle strain in the planar all-cis-isomer of cyclodecapentene (required angle is 120˚; actual angle is 144˚). Although there is no angle strain in the planar cis-trans-cis-cis-trans-isomer, the source of strain here is the steric repulsion between the hydrogen at 1-position and the hydrogen at 6-position. To overcome these steric strains, both the isomeric molecules assume nonplanar conformation. As a result, conjugation in them becomes very poor and neither of them is found to display aromaticity.



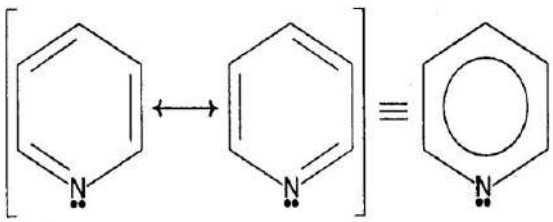
all-*cis*-isomer of cyclodecapentene (angle strain in the planar conformation)

cis-trans-cis-cis-trans-isomer of cyclodecapentene (Transannular strain in the planar conformation)

12. Pyrrole is a much weaker base than pyridine.

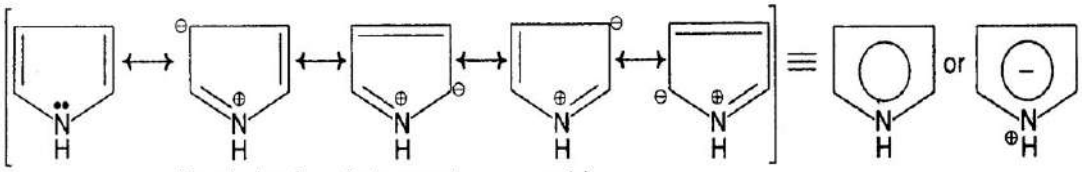
Solution:

Pyridine and pyrrole are aromatic heterocyclic bases. The nonbonding electrons on nitrogen in pyridine are not used to complete the aromatic sextet and so these are readily available for co-coordinating with a proton.



Pyridine
(a six π electron system : aromatic)

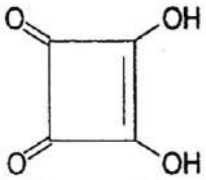
In pyrrole, on the other hand, the unshared electron pair on nitrogen is used to complete the aromatic sextet.



Pyrrole (a six π electron system : aromatic)

Because of this, the availability of the unshared electron pair on nitrogen is very poor and pyrrole behaves as a much weaker base than pyridine.

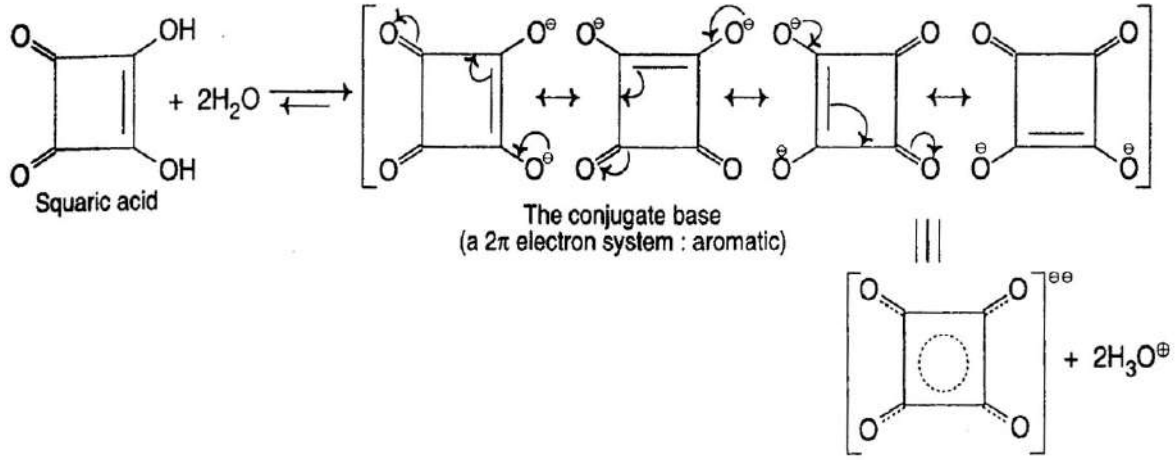
13. The following cyclic diol (squaric acid) is almost strong an acid as H_2SO_4.



Squaric acid

Solution:

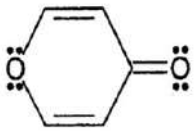
The dianionic conjugate base of this cyclic diol is very much stable because it is a cyclic resonance system of (4n +2) π (n=0) electrons (aromatic) and for this reason, the compound is almost as strong an acid as H_2SO_4.



Squaric acid

The conjugate base
(a 2π electron system : aromatic)

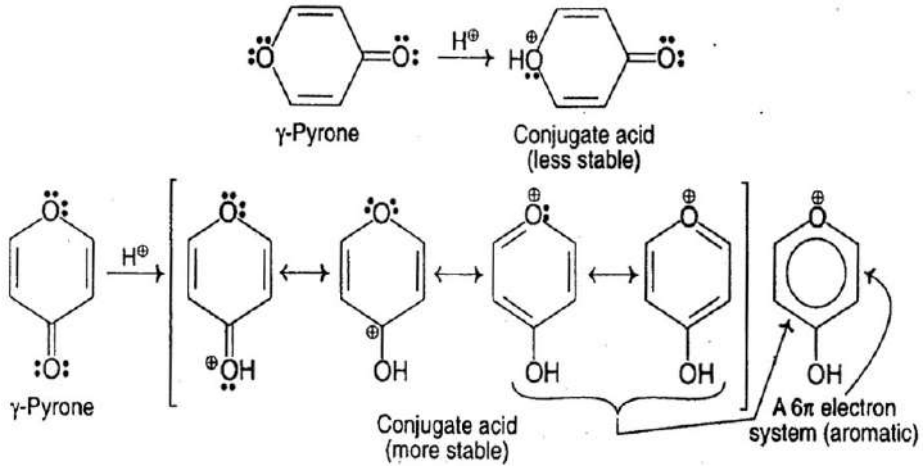
14. Carbonyl oxygen of γ-pyrone is more basic than the ring oxygen.



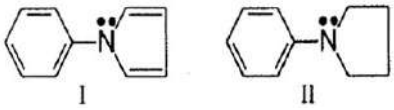
γ-Pyrone

Solution:

Protonation of the carbonyl oxygen of γ-pyrone leads to the formation of a stable aromatic system whereas protonation of the ring oxygen does not. It is for this reason the carbonyl oxygen is more basic than the ring oxygen.

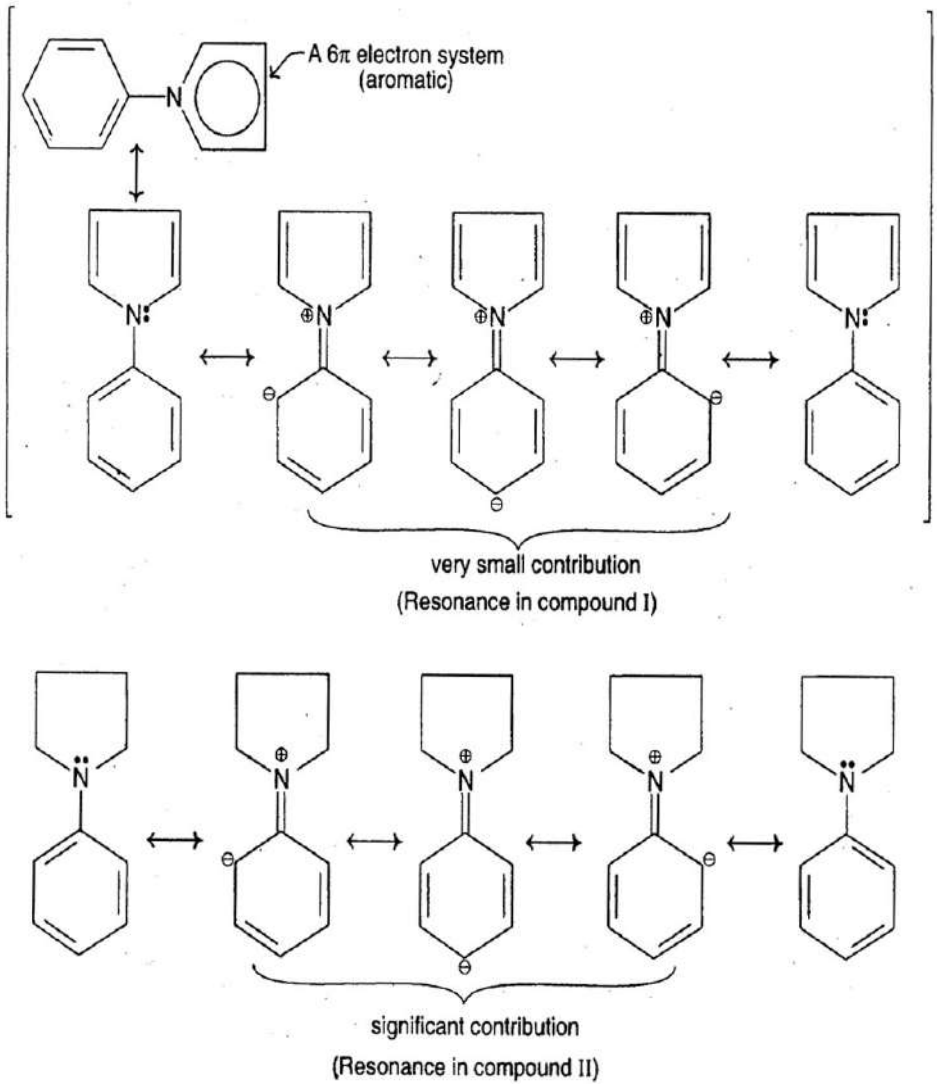


15. The rotational energy barrier around the C-N bond of compound **II** is higher than compound **I**.

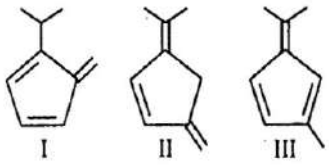


Solution:

In compound **I**, the unshared electron pair on nitrogen is involved in maintaining an aromatic system of 6π electrons in the pyrrole ring and its resonance interaction with the benzene ring is actually very small. Because of this, the C-N bond has a very small amount of double bond character (negligible contribution of structures with carbon-nitrogen double bond). Since the unshared electron pair on nitrogen in compound **II** is not used to complete an aromatic sextet, it is highly delocalized with the benzene ring. As a consequence, the C-N bond possesses considerable double bond character (significant contribution of structures with carbon-nitrogen double bond). Because of much better double bond character of the C-N bond, the rotational energy barrier of compound **II** is higher than compound **I**.

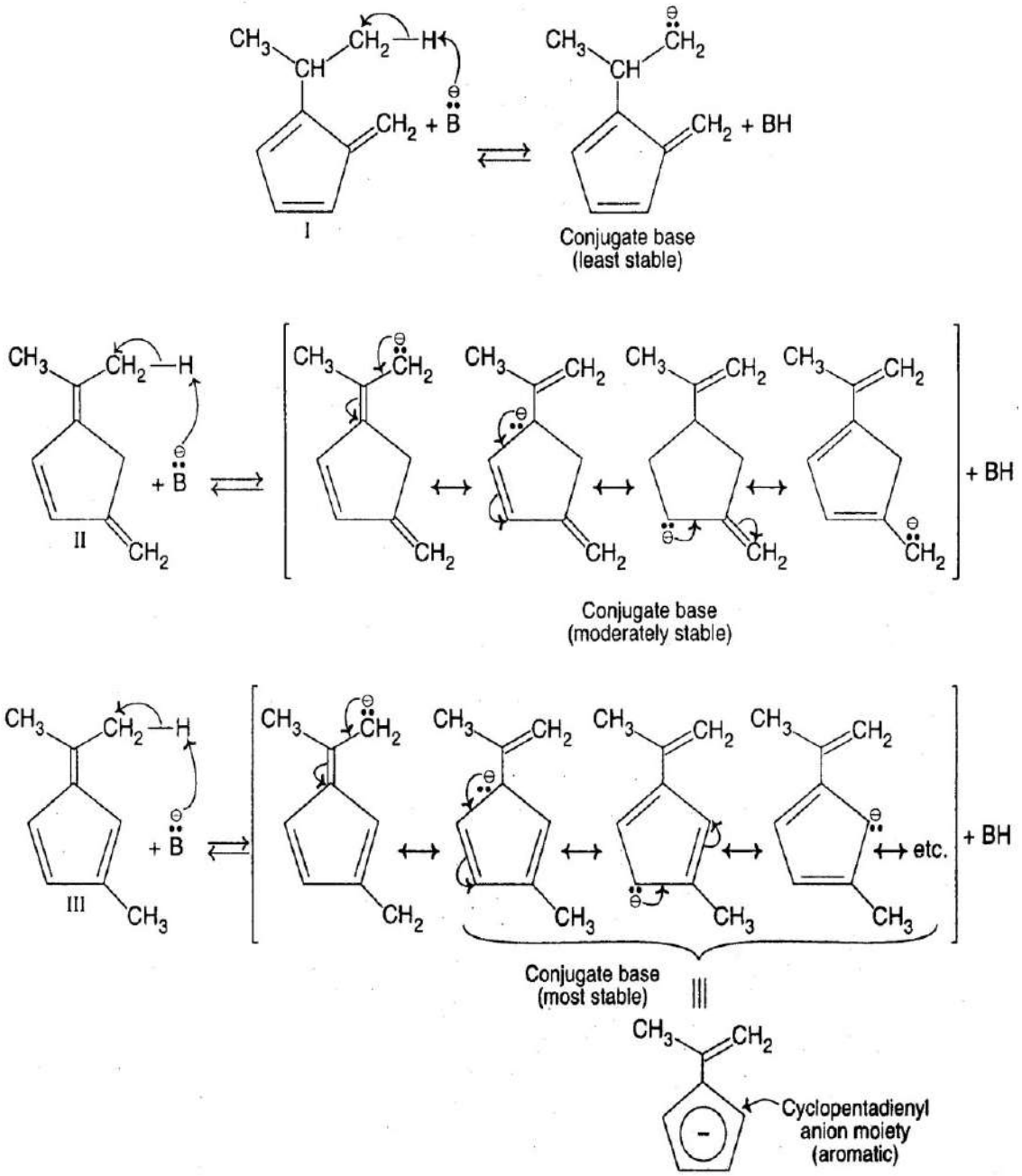


16. One of the following hydrocarbons is much more acidic than the others:

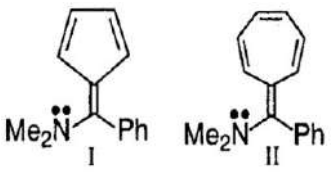


Solution:

Due to lack of conjugation the conjugate base of the compound **I** is not resonance stabilized. The conjugate base of **II** is resonance-stabilized because the negative charge on carbon is in proper conjugation with the double bonds. The conjugate base of **III** is also resonance-stabilized. However, because of constituting an aromatic system [(4n+2) π, n =1], it is much more stable than either the conjugate base of **I** or the conjugate base of **II**. For this reason, the hydrocarbon **III** is much more acidic than the others.



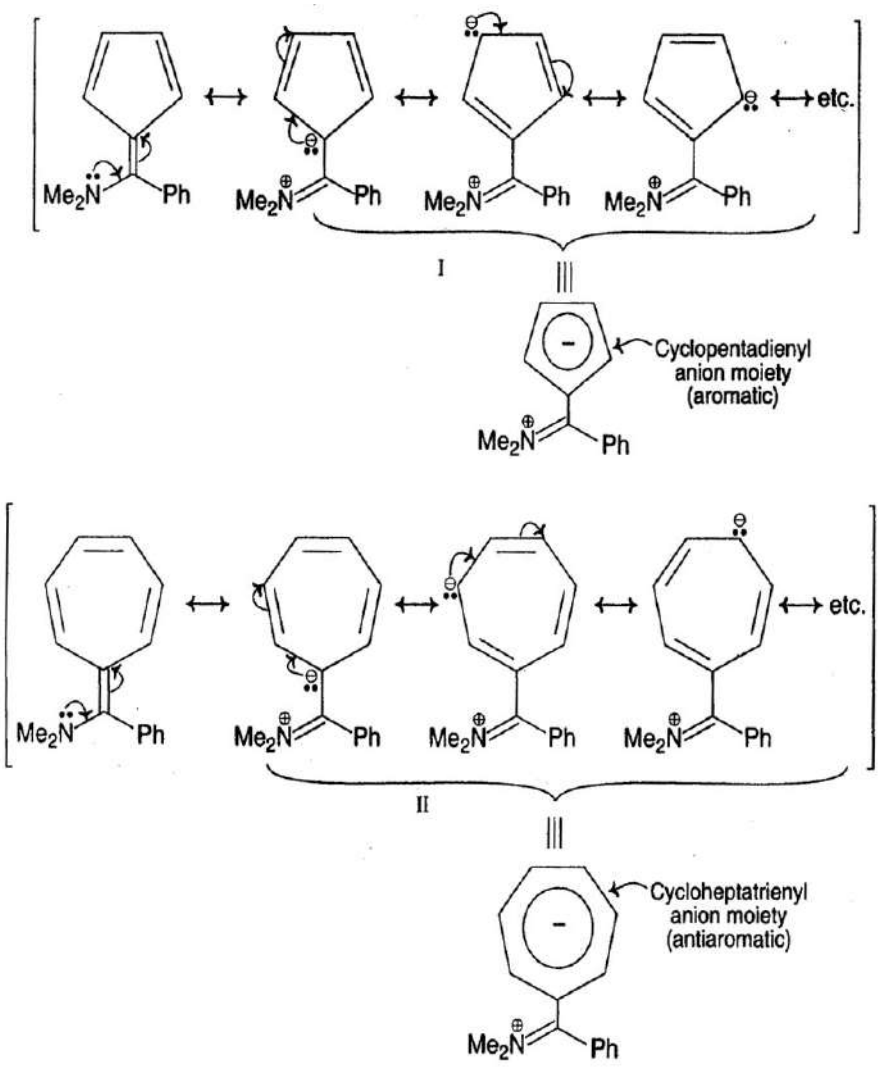
17. The amine **II** is more basic than the amine **I**.



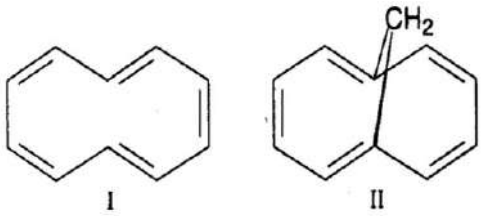
Solution:

The unshared electron pair on nitrogen in the amine **I** is well delocalized because the charge separated structure constitute a stable aromatic system [cyclopentadienyl anion with (4n+2) π electron where n=1]. On the other hand, the unshared electron pair on nitrogen in the amine **II** is not at all delocalized because the charge separated structure constitute an

unstable antiaromatic system (cycloheptatrienyl anion with 4nπ electron, where n=2). Therefore, the availability of the lane pair of electrons on nitrogen in **II** is greater than in **I**. Consequently, **II** is more basic than **I**.



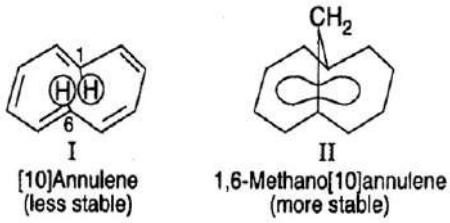
18. The compound **II** is more stable than the compound **I**.



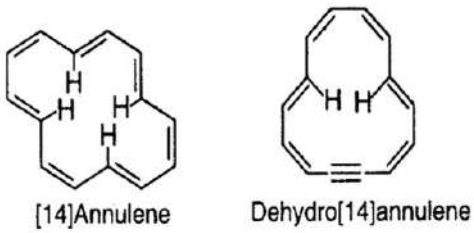
Solution:

In [10]annulene (**I**), the hydrogens in the 1 and 6 positions interfere sterically with each other and force the molecule out of planarity and because of this, being a 10π [(4n +2) π, n=2] electrons system it is not aromatic. On the other hand, in 1,6-methano[10]annulene (**II**), the internal H's in [10]annulene are replaced by a methylene bridge above the molecule, permitting it to be flat. So, there occurs extensive electron delocalization in a 10π electron

system and therefore, the compound is aromatic. Hence, the compound **II** is more stable than the compound **I**.



19. Dehydro[14]annulene is aromatic whereas [14]annulene behaves like a nonaromatic compound.



Solution:

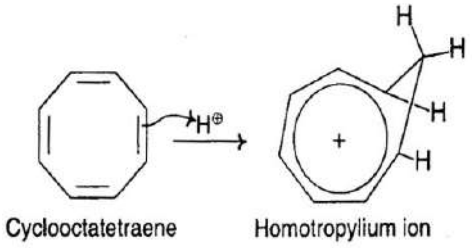
On the basis of its Huckel number [(4n+2) π, n =3], [14] annulene is expected to be aromatic. However, the H's that point to the interior of the ring interfere with each other and force the molecule out of planarity. For this reason, it behaves like a nonaromatic compound. On the other hand, in dehydro[14]annulene two of the interfering H's are removed to form the triple bond, and the compound is planar. Two electrons of one of the π bonds of the C≡C are delocalized into the π system. The other pair of electrons do not interact (simply exists as a localized bond) because they are in a π orbital at right angles to the extended π system. Therefore, it is a planer 14 π [(4n+2) π, n=3] electron system, i.e., aromatic.

20. What is called a homoaromatic compound? Give an example and discuss its structure.

Solution:

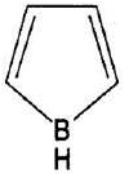
A homoaromatic compound is a compound that contain one or more sp^3– hybridized carbon atoms in an otherwise conjugated cycle [a (4n+2) system].

When cyclooctatetraene is dissolved in concentrated sulphuric acid, a proton adds to one of the double bonds to form the homotropylium ion. In this species aromatic sextet is spread over seven carbons, as in the tropylium ion. The eighth carbon is an sp^3 carbon and cannot take part in the aromaticity. This ion is an example of a homoaromatic compound. In order for the orbitals to overlap most effectively so as to close a loop, the sp^3 atom is forced to lie almost vertically above the plane of the aromatic atoms.



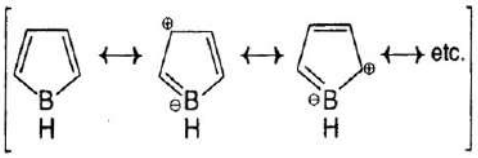
21. Classify each of the following molecules and ions as aromatic, antiaromatic and non-aromatic and gives reasons:

(i)

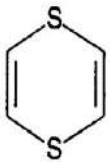


Solution:

Antiaromatic: There is a vacant p orbital in boron. So, the compound has a continuous ring of overlapping p orbitals, but it has 4n π (n=1) electrons.

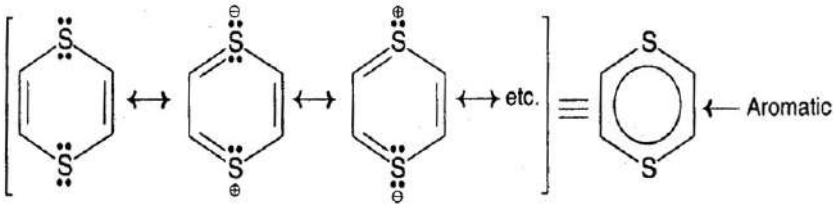


(ii)

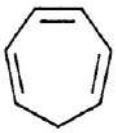


Solution:

Aromatic: One sulphur atom uses its unshared electron pair and the other uses its vacant d orbital to make the system aromatic [(4n+2) π, n =1].



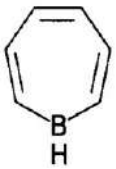
(iii)



Solution:

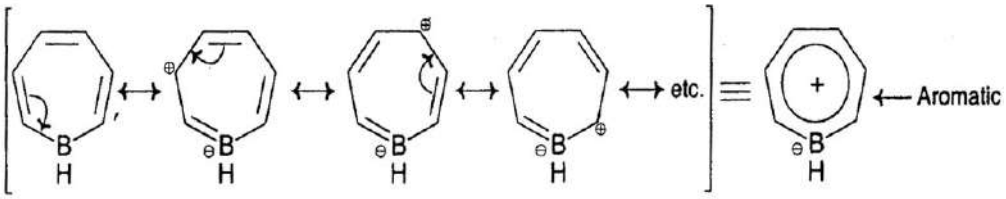
Nonaromatic: Although it contains 6 π electrons, it does not have a continuous ring of overlapping p orbitals.

(iv)

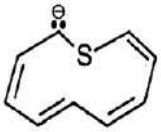


Solution:

Aromatic: The compound has a continuous ring of overlapping p orbitals and it is a (4n +2) π electron system, with n=1.

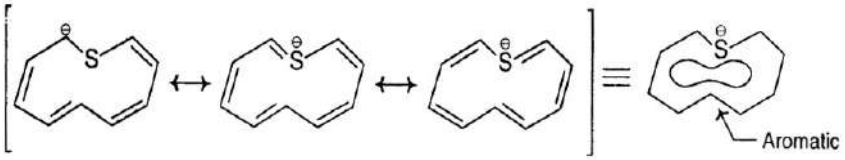


(v)

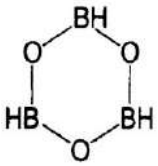


Solution:

Aromatic: Sulphur uses its vacant d orbital to make a cyclic conjugated system having (4n+2) π electrons, where n = 2.

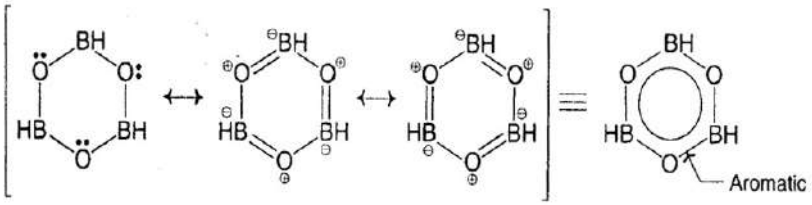


(vi)

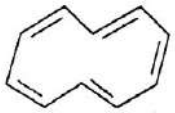


Solution:

Aromatic: Due to formation of dative π bond between boron and oxygen, the system is aromatic [(4n+2) π, n =1].

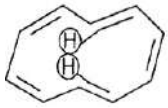


(vii)

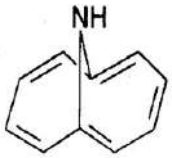


Solution:

Nonaromatic: A nonplanar 10π [(4n+2) π, n = 2] electron system. Two hydrogen atoms pointing to the interior of the ring interfere with each other and to avoid this strain the system becomes nonplanar.

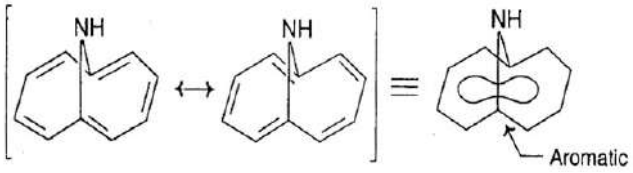


(viii)

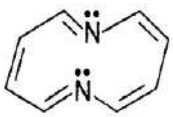


Solution:

Aromatic: A planar 10π [(4n+2) π, n = 2] electron system. (Two interfering H's are removed to form a bridge).



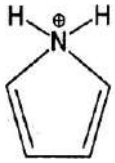
(ix)



Solution:

Aromatic: A planer 10 π [(4n+2) π, n = 2) electron system. The unshared electron pairs on N's do not interfere to make the system nonplanar.

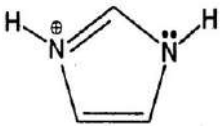
(x)



Solution:

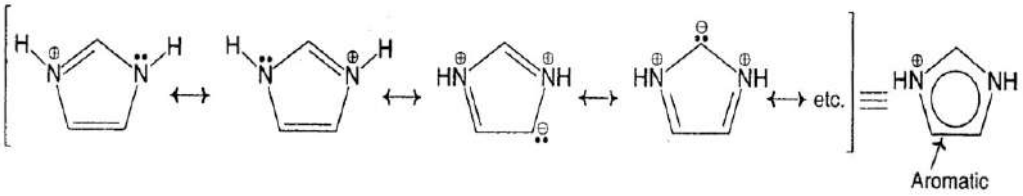
Nonaromatic: The nitrogen atom is bonded to four different atoms (two carbon atom and two hydrogen atoms), requiring sp^3 hybridization and leaving no unhybridized p orbital. Therefore, it does not have a continuous ring of overlapping p orbitals.

(xi)

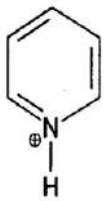


Solution:

Aromatic: A 6π [(4n+2) π, n=1] electron system. The uncharged nitrogen atom is sp^2 hybridized, with a lone pair of electrons in the p orbital. This p orbital overlaps with the p orbitals of the carbon and nitrogen atoms to form a continuous ring.



(xii)



Solution:

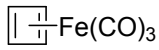
Aromatic: A 6π [(4n+2) π, n=1) electron system. Pyridine takes up a proton to give the pyridinium ion ($C_6H_5NH^+$). The additional proton has no effect on the electrons of the aromatic sextet. If simply bonds to pyridine nonbonding pair of electrons.

22. $Fe(CO)_3$ reacts with the very unstable cyclobutadiene to form a very stable complex. Explain this observation.

Solution:

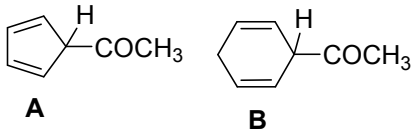
The cyclobutadiene system can be stabilized as a η^4-complex with metals, as with the iron complex **I**, but in these cases electron density is withdrawn from the ring by the metal and there is no aromatic quartet. In fact, these cyclobutadiene–metal complexes can be

looked upon as systems containing an aromatic duet. The ring is square planar, the compounds undergo aromatic substitution, and NMR spectra of monosubstituted derivatives show that the C-2 and C-4 protons are equivalent.



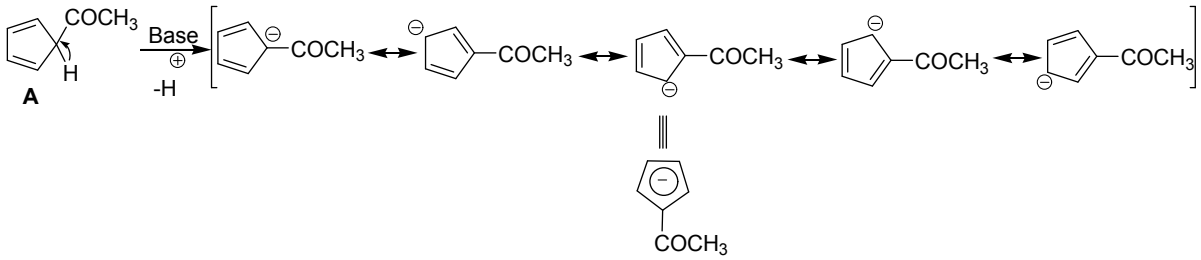
(I)

23. The compound **A** is more acidic than the compound **B**:

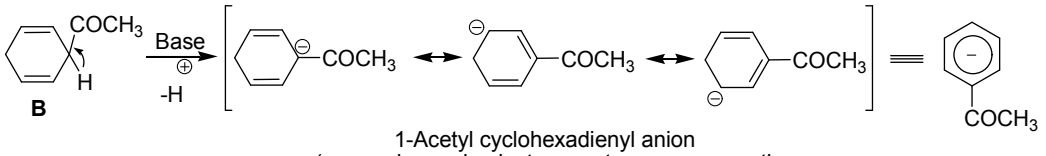


Solution:

The 1-acetyl cyclopentadienyl anion, the conjugate base of 1-acetyl cyclopentadiene, can be represented as a hybrid of five resonance structures, while the 1-acetyl cyclohexadienyl anion, the conjugate base of 1-acetyl cyclohexadiene, can be represented as a hybrid of three resonance structures.



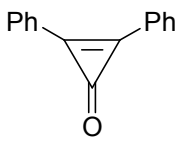
1-Acetyl cyclopentadienyl anion
(a planar six-electron-system: aromatic



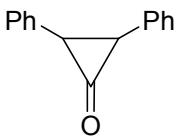
1-Acetyl cyclohexadienyl anion
(a non-planar six-electron-system: non-aromatic

Although less number of contributing structures can be drawn for the 1-acetyl cyclohexadienyl anion, it is less stable than the 1-acetyl cyclopentadienyl anion, and that is due to fact that the former anion with 6π electrons, where n=1 is non-aromatic (does not have a continuous ring of overlapping p orbitals), whereas the latter anion with (4n+2)π electrons, where n=1, is aromatic (highly stabilized by resonance). Due to the formation of a relatively stable conjugate base, 1-acetyl cyclopentadiene is a much stronger acid than 1-acetyl cyclohexadiene.

24. Which of the following two compounds has higher dipole moment? Give reasons.



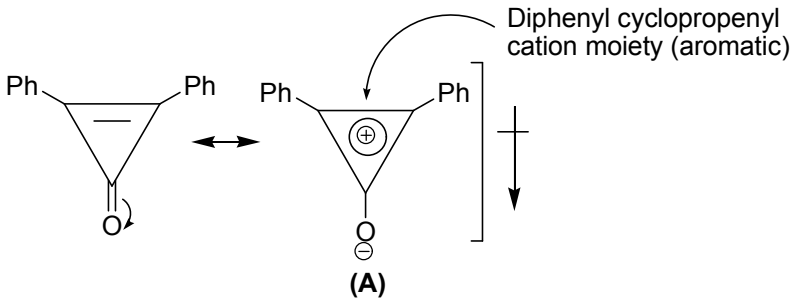
2,3-Diphenylcycloprop-2-en-1-one



2,3-Diphenylcyclopropanone

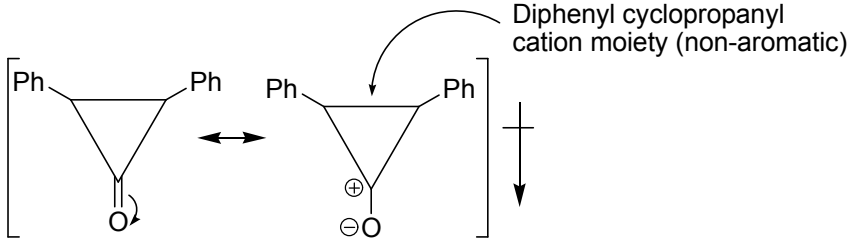
Solution:

In 2,3-diphenylcycloprop-2-en-1-one, the three-membered ring releases electrons to the electronegative oxygen atom and this is because in the betaine structure (**A**) the ring has an aromatic sextet spread over three carbon atoms.



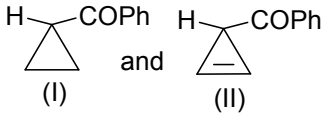
(A)

Due to large contribution of the betaine structure **A**, 2,3-diphenylcycloprop-2-en-1-one is found to possess significant dipole moment. In 2,3-diphenylcyclopropanone, strong polarization of the carbonyl group, which gives a partial positive charge on the cyclopropanone ring and a partial negative charge on the oxygen (charge separated structure **B)** with considerable dipole moment.



(B)

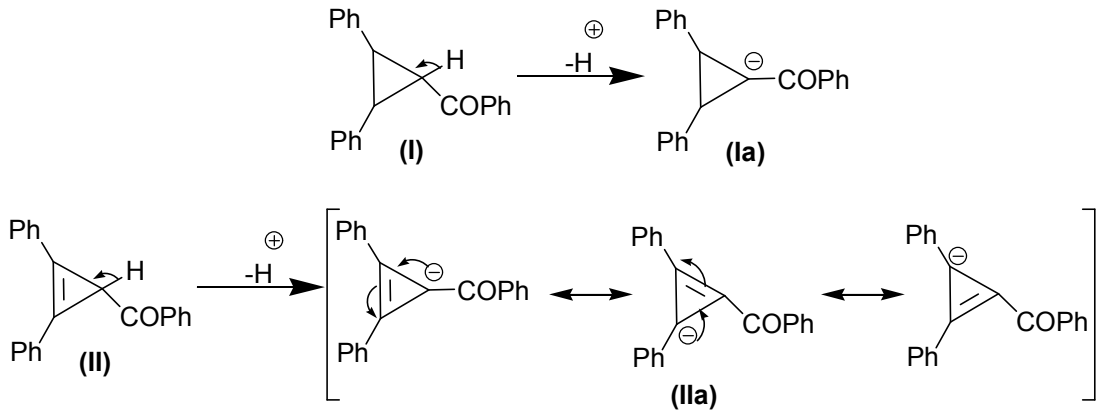
25. Compare the acidities of



(I) (II) and justify.

Solution:

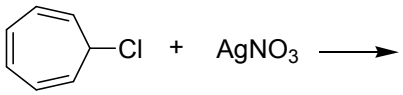
The compound **I** on proton loss gives a ordinary carbanion (**Ia**), whereas the compound **II** on proton loss yields an cyclopropenyl anion (**IIa**).



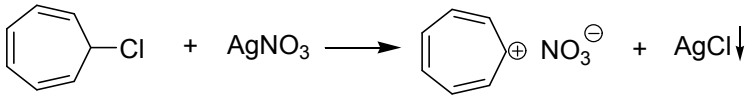
A four-π-electron system: antiaromatic

The carbanion **IIa** has 4n π electrons, where n=1. So it is antiaromatic and less stable than the ordinary carbanion **Ia**. Because of this, **II** loses its proton at a very slower rate than **I** in hydrogen exchange reactions.

26. Predict the products, if any and explain.

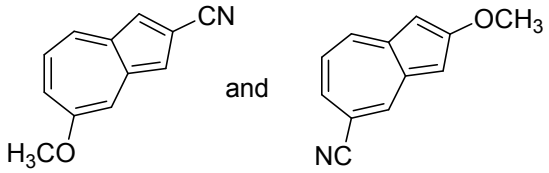


Solution:



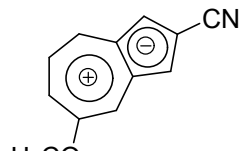
The reaction occurs because this leads to the formation of cycloheptatrienyl cation, a stable aromatic system.

27. Compare the dipole moments of the following compounds with reasons.

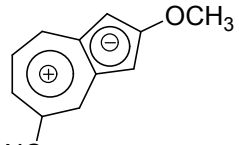


Solution:

Azulene can be represented as a combination of two aromatic systems such as cycloheptatrienyl cation and cyclopentadienyl anion. Therefore, the first compound in which the electron-withdrawing –CN group is attached to the negatively polarized five-memberd ring and the electron-donating –OCH_3 group is attached to the positively polarized seven-membered ring is relatively more polar, i.e., possesses higher dipole moment than the second compound.



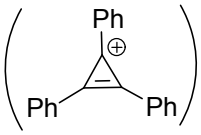
more polar



less polar

28. Which species is the smallest aromatic substance? Give its structure. Can it be stored in a bottle?

Solution:

Cycloproenyl cation  . It triphenyl derivative, i.e., triphenylcyclopenyl cation 

is so stable that many of its salts can be isolated and stored in bottles.

Kinetic methods of study of reaction mechanism

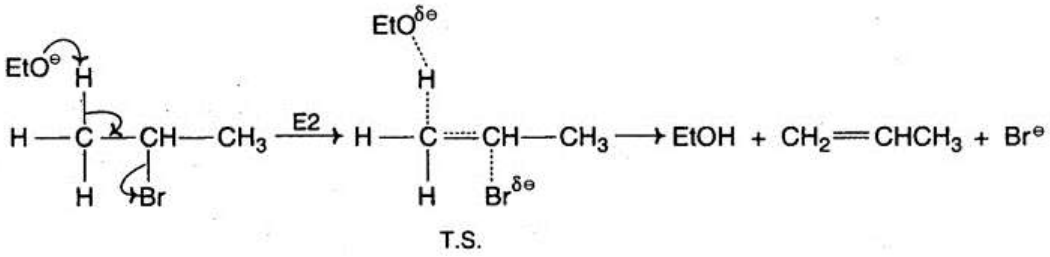
29. What do you understand by kinetic isotope effect? What are primary and secondary isotope effects? Illustrate these techniques of elucidation of reaction mechanisms with suitable examples.

Solution:

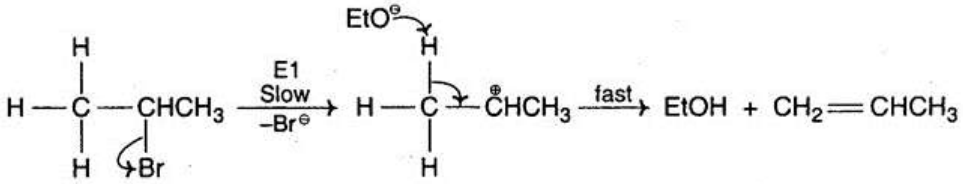
The change in the rate of a reaction observed due to replacement of one isotope of an element for another is called kinetic isotope effect.

A large difference in the rate of a reaction is observed when one of the atoms of a bond that breaks in the rate determining step is replaced by its isotope. This is called primary isotope effect. If a C-H bond breaks in the rate-determining step of a reaction, substitution of D for H results in decrease in reaction rate and that is because a C-D bond is stronger than a C-H bond. For example, the rate of elimination of HBr from 2-bromopropane on treatment with sodium ethoxide has been found to be slowed down when the hydrogens in the methyl group of the alkyl halide are replaced by deuteriums. A large kinetic isotope effect (k_H/k_D = 6.7) is observed. This observation strongly suggests that the rate-determining step of the reaction involves the cleavage of the C-H (or C-D) bond, i.e., the reaction proceeds through the mechanistic pathway **I** and not through the pathway **II**.

Pathway I:



Pathway II:



Deuterium isotope effects have also been observed in reactions in which the C-H bond does not break at all. Such effects are known as secondary isotope effects, secondary because it is a bond other than that carrying the isotope label that is being broken. For example, the rate of solvolysis of tert-butylchloride in 60% aqueous ethanol is found to be faster than the rate of solvolysis of its nonadeuterio analog. The k_H/k_D ratio was found to be 2.32.

$$(CH_3)_3CCl \xrightarrow[k_H]{EtOH/H_2O} (CH_3)_3COEt + (CH_3)_3COH$$

$$(CD_3)_3CCl \xrightarrow[k_D]{EtOH/H_2O} (CD_3)_3COEt + (CD_3)_3COH$$

This secondary isotope effect indicates that the $–CH_3$ (or $–CD_3$) groups by hyperconjugative electron-release stabilize the transition state (of the rate-determining step) which has considerable carbenium ion character. The reaction is thus expected to proceed through the rate-determining formation of tert-butyl cation.

$$(CH_3)_3C—Cl \xrightarrow[-Cl^{\ominus}]{Slow} (CH_3)_3C^{\oplus} \xrightarrow{EtOH/H_2O} (CH_3)_3C—OEt + (CH_3)_3COH$$

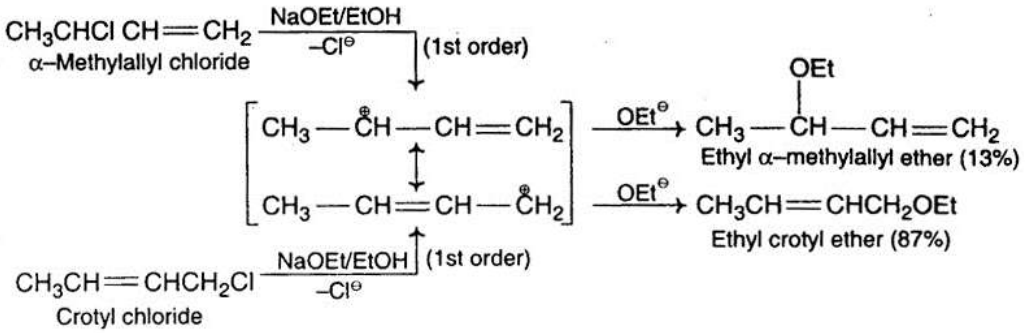
S_N1

Non-kinetic methods of study of reaction mechanism

1. Identification of products

The fundamental information about the mechanism of a reaction is obtained from a knowledge of the structures of all the products and their relative proportions. For example,

each of α-methylallyl and crotyl chloride yields a mixture of 13% ethyl α-methylallyl and 87% ethyl crotyl ether when treated with ethanolic sodium ethoxide under S_N1 conditions.



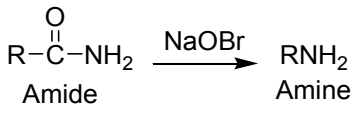
Since each of the isomeric allylic chlorides gives the same mixture of isomeric ethers, the substitution reactions proceed through a common intermediate carbocation which is a resonance hybrid of two canonical forms.

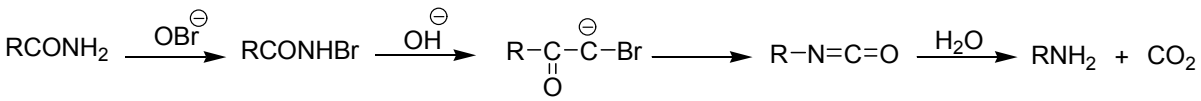
2. Identification of Intermediates

Many organic reactions proceed through the formation of one or more intermediates. Useful informations about the mechanistic course of a reaction can be obtained from knowledge of the structure of that intermediates which can be isolated, detected by spectroscopic methods, or trapped.

(i) Isolation of an intermediate

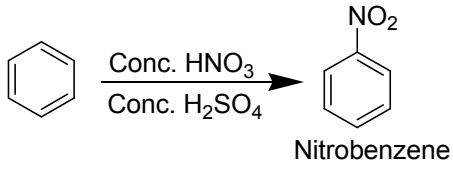
An intermediate can be isolated from a reaction mixture by arresting the reaction after a short period or using very mild conditions. For example, in Hofmann rearrangement in which amides are converted into amines by Br_2 and alkali ($RCONH_2 + Br_2 \rightarrow RNH_2$), three intermediates, e.g., an N-bromoamide (RCONHBr), its anion ($RCON^{\ominus}Br$) and an isocyanate (RNCO), have been isolated. When subjected to normal reaction conditions, these intermediates result in the formation of usual reaction products at a rate not slower than the rate of the overall reaction. Hence the mechanistic pathway to be suggested for this reaction is that which accounts for the formation of these intermediates.



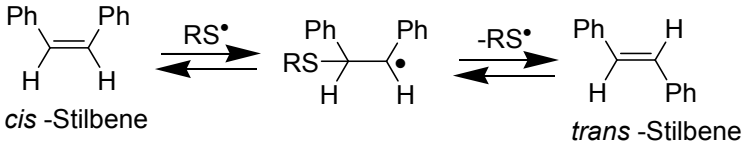


(ii) Detection of an intermediate

A non-isolable intermediate can often be detected by spectroscopic studies (e.g., IR, NMR, ESR, etc.). For example, the nitronium ion ($^{+}NO_2$) involved in nitration of benzene has been detected by Raman spectra.



Free radical and triplet intermediates can often be detected by ESR and by CIDNP. Free radicals (as well as radical ions and EDA complexes) can also be detected by a method that does not rely on spectra. In this method, a double bond compound is added to the reaction mixture, and its fate traced. One possible result is *cis–trans* conversion. For example, *cis*-stilbene is isomerized to the *trans* isomer in the presence of RS• radicals, by this mechanism:



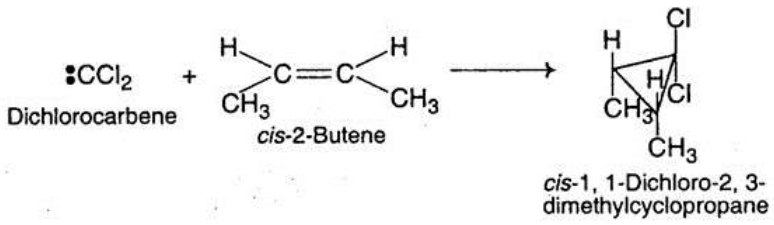
Since the *trans* isomer is more stable than the *cis*, the reaction does not go the other way, and the detection of the isomerized product is evidence for the presence of the RS• radicals.

(iii) Trapping of intermediate

An intermediate can also be detected by trapping. The reaction is carried out in the presence of a compound with which the intermediate reacts; the resultant compound is isolated and form knowledge of its structure the structure of the intermediate is predicted. For example, dichlorocarbene, $:CCl_2$, the intermediate believed to be involved in the alkaline hydrolysis of chloroform can be detected by trapping.

$$CHCl_3 + OH^{\ominus} \xrightarrow{H_2O} CO + HCO_2^{\ominus} + Cl^{\ominus}$$

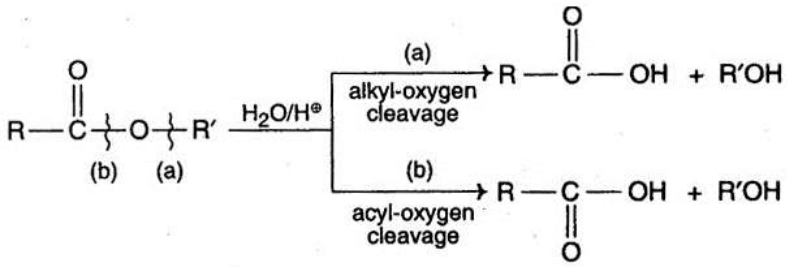
A cyclopropane derivative is isolated when cis-2-butene is added into the reaction mixture; this suggests that the reaction proceeds through the formation of dichlorocarbene.



3. Isotopic labeling

The mechanistic pathway of a reaction can be ascertained by carrying out the reaction with isotopically labelled compound and then identifying the location of the isotope in the

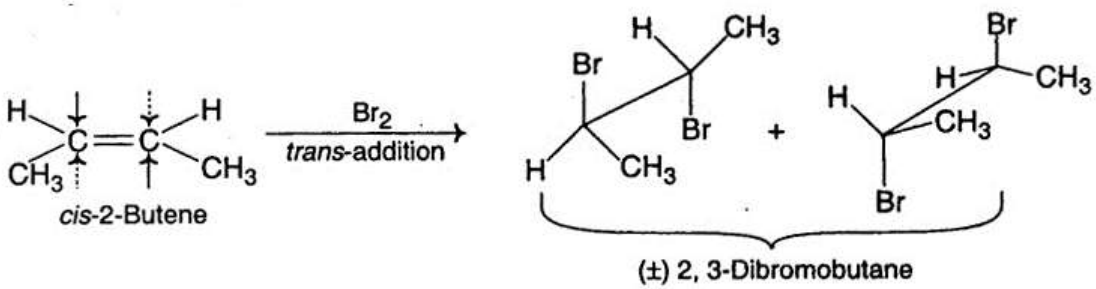
products. For example, the hydrolysis of an ester to yield a carboxylic acid and an alcohol could theoretically take place in two ways: (a) alkyl-oxygen bond cleavage, and (b) acyl-oxygen bond cleavage.



To ascertain the pathway the reaction is carried out in $H_2{}^{18}O$. If alkyl-oxygen bond breaks, a mixture of R-^{18}OH and RCOOH will be obtained and if acyl-oxygen bonds break, a mixture of RCO^{18}OH and ROH will be obtained. Actually, a labelled acid and an unlabelled alcohol are obtained. This indicates that the reaction proceeds through acyl-oxygen bond cleavage (b).

4. Stereochemical evidence

The stereochemical course of a reaction, which can be obtained from a knowledge of the stereochemistry of the products, is often helpful in determining the mechanism. For example, bromination of cis-2-butne yields (±)-2,3-dibromobutane and not meso-2,3-dibromobutane.

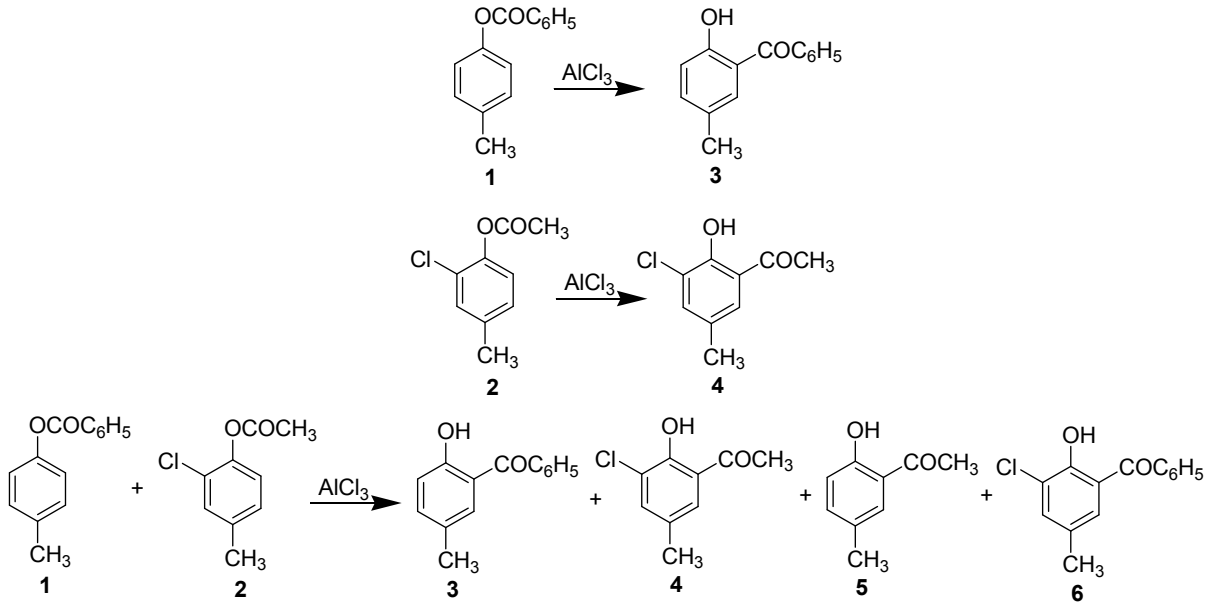


The formation of optically inactive racemic product indicates that the two bromine atoms add to the double bond from opposite sides, i.e., it is a case of *trans*-addition. This *trans*-mode of addition rules out the possibility of one-step (concerted) mechanism because the atoms in a bromine molecule are very close and unable to add simultaneously in an *anti*-fashion. Hence, the addition is a two-step process.

Crossover experiments

Whether a rearrangement is a one step or a two-step process can be decided by carringout the reaction with a mixture of two similarly constituted but not-identical reactants

and then analyzing the products. Since the migrating group must become free in a two-step process, we should get a product containing fragments of both the reactants which involves migration of an acyl group of a phenyl ester to the benzene ring, provides such an example. The two esters, **1** and **2** rearrange under identical conditions and at approximately the same rate to give the products **3** and **4** respectively. Rearrangement of a mixture of **1** and **2**, however, not only gives **3** and **4** but also the cross products **5** and **6**. Isolation of cross products unequivocally demonstrates that the Fries rearrangement is a two step-process.



Kinetic and thermodynamic control

There are many cases in which a compound under a given set of reaction conditions can undergo competing reactions to give different products.

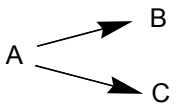


Figure 1 shows a free energy profile for a reaction in which B is thermodynamically more stable than **C** (lower ΔG) but C is formed faster (lower $\Delta G^{\#}$). It neither reaction is reversible, **C** will be formed in large amount because it is formed faster. The product is said to be kinetically controlled. However, if the reactions are reversible, this will not necessarily be the case. If such a process is stopped well before the equilibrium has been established, the reaction will be kinetically controlled since more of the faster-formed product will be present. However, if the reaction is permitted to approach equilibrium, the predominant or even

exclusive product will be **B**. under these conditions the **C** that is first formed reverts to **A**, while the more stable **B** does so much less. We say the product is thermodynamically controlled. Of course, Figure 1 does not describe all reactions in which a compound **A** can give two different products. In many cases the more stable product is also the one that is formed faster. In such cases, the product of kinetic control is also the product of thermodynamic control.

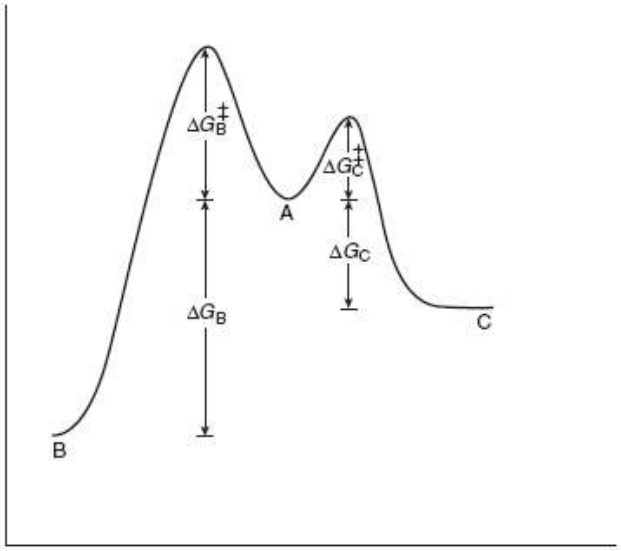


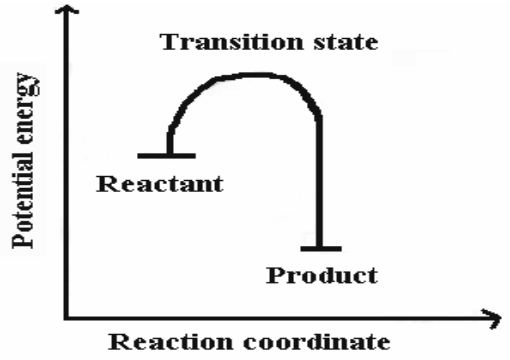
Figure 1. Free-energy profile illustrating kinetic versus thermodynamic control of products. The starting compound (**A**) can react to give either **B** or **C**.

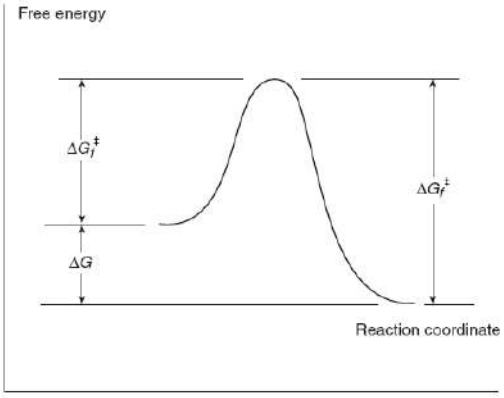
Hammond's postulate

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

Example (i):

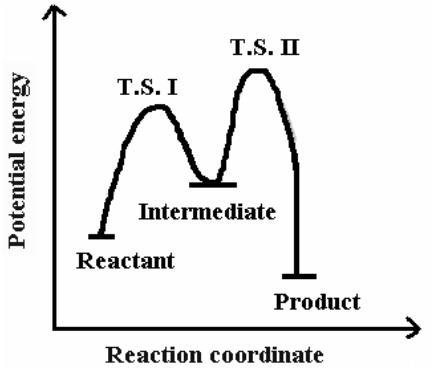
In the exothermic reaction the energy of transition state is closer to reactants. So the geometry of transition state resembles as reactant.

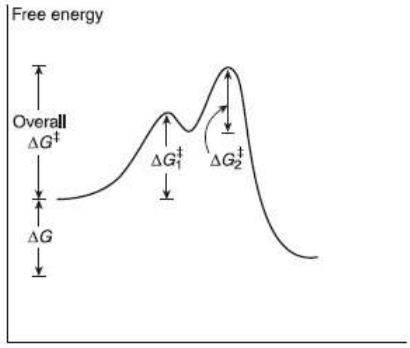




Example (ii):

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.



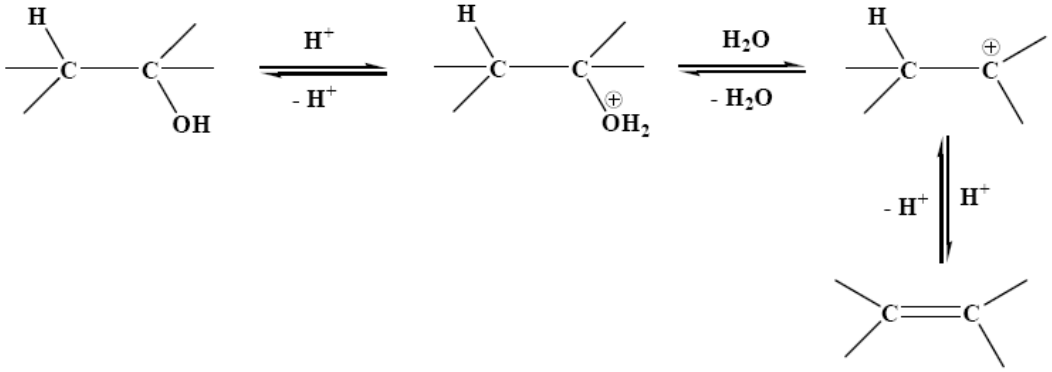


Microscopic Reversibility

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.



Hammett equation

The first and most important linear free energy relationship is the Hammett σρ 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.

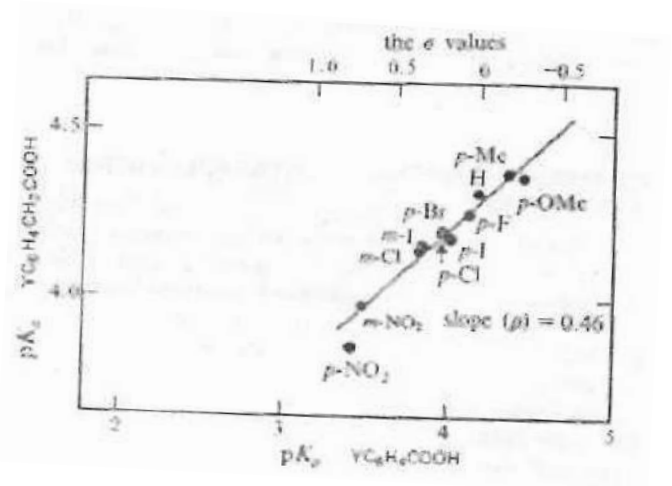


Fig. I. Hammett plot.

[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 (withdrawal 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 *pKa* values for phenylacetic and benzoic acids

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

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 represents the equilibrium constants for substituted and un-substituted compounds.

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

$$\log K_{PA}/K_{OPA} = \rho \log K_B/K_{OB} \ldots \text{(III)}$$

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 ($\sigma > 0$), the hydrogen atom having a sigma value of zero.

$$\sigma = \log K_B/K_{OB} \ldots\ldots\ldots\ldots \text{(IV)}\ \ (\sigma\text{-substituent constant})$$

$$\log K_{PA}/K_{OPA} = \sigma\rho \ldots\ldots \text{(V)}$$

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 σ 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 σ values of the substituent.

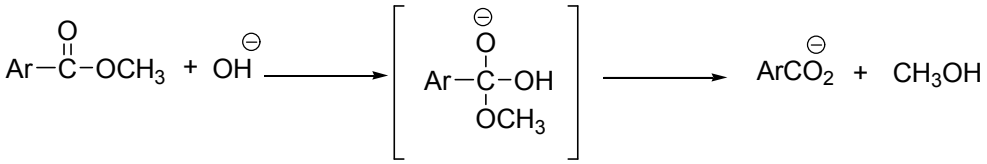
Substituent	σ_m	σ_p
NH_2	-0.16	-0.66
CH_3	-0.07	-0.17
OH	0.12	-0.37
C_6H_5	0.06	-0.01
OCH_3	0.12	-0.27
SCH_3	0.15	-0.0
F	0.34	0.06
I	0.35	0.18
Cl	0.37	0.23
Br	0.39	0.23
CF_3	0.43	0.54
CN	0.56	0.66
NO_2	0.71	0.78

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.



Scheme 1

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.

Taft equation

The **Taft equation** is a linear free energy relationship (LFER) used in physical organic chemistry in the study of reaction mechanisms and in the development of quantitative structure activity relationships for organic compounds. It was developed by Robert W. Taft in 1952 as a modification to the Hammett equation. While the Hammett equation accounts for how field, inductive, and resonance effects influence reaction rates, the Taft equation also describes the steric effects of a substituent. The Taft equation is written as:

$$\log\left(\frac{k_s}{k_{\mathrm{CH3}}}\right) = \rho^*\sigma^* + \delta E_s$$

where $\log(k_s/k_{CH3})$ is the ratio of the rate of the substituted reaction compared to the reference reaction, σ* is the polar substituent constant that describes the field and inductive effects of the substituent, E_s is the steric substituent constant, ρ* is the sensitivity factor for the reaction to polar effects, and δ is the sensitivity factor for the reaction to steric effects.

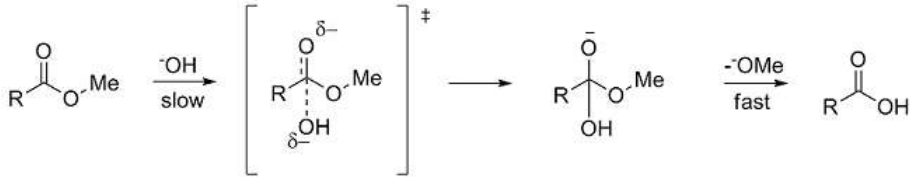
Constants used in the Taft equation

Substituent	E_s	σ*
–H	1.24	0.49
$–CH_3$	0	0
$–CH_2CH_3$	–0.07	–0.1
$–CH(CH_3)_2$	–0.47	–0.19
$–C(CH_3)_3$	–1.54	–0.3
$–CH_2Ph$	–0.38	0.22
–Ph	–2.55	0.6

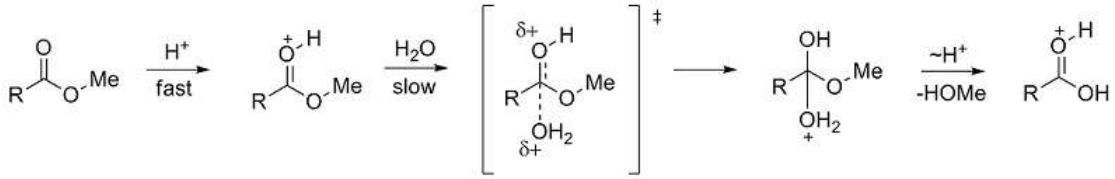
1. Polar Substituent Constants, σ*

Polar substituent constants describe the way a substituent will influence a reaction through polar (inductive, field, and resonance) effects. To determine σ^* Taft studied the hydrolysis of methyl esters (RCOOMe). The use of ester hydrolysis rates to study polar effects was first suggested by Ingold in 1930.The hydrolysis of esters can occur through either acid and base catalyzed mechanisms, both of which proceed through a tetrahedral intermediate. In the base catalyzed mechanism the reactant goes from a neutral species to negatively charged intermediate in the rate determining (slow) step, while in the acid catalyzed mechanism a positively charged reactant goes to a positively charged intermediate.

Base Catalyzed Ester Hydrolysis:



Acid Catalyzed Ester Hydrolysis:



Due to the similar tetrahedral intermediates, Taft proposed that under identical conditions any steric factors should be nearly the same for the two mechanisms and therefore would not influence the ratio of the rates. However, because of the difference in charge buildup in the rate determining steps it was proposed that polar effects would only influence the reaction rate of the base catalyzed reaction since a new charge was formed. He defined the polar substituent constant σ* as:

$$\sigma^* = \left(\frac{1}{2.48\rho^*}\right)\left[\log\left(\frac{k_s}{k_{CH3}}\right)_B - \log\left(\frac{k_s}{k_{CH3}}\right)_A\right]$$

where $\log(k_s/k_{CH3})_B$ is the ratio of the rate of the base catalyzed reaction compared to the reference reaction, $\log(k_s/k_{CH3})_A$ is ratio of a rate of the acid catalyzed reaction compared to the reference reaction, and ρ* is a reaction constant that describes the sensitivity of the reaction series. For the definition reaction series, ρ* was set to 1 and R = methyl was defined as the reference reaction (σ* = zero). The factor of 1/2.48 is included to make σ* similar in magnitude to the Hammett σ values.

2. **Steric substituent constants, E_s**

Although the acid catalyzed and base catalyzed hydrolysis of esters gives transition states for the rate determining steps that have differing charge densities, their structures differ only by two hydrogen atoms. Taft thus assumed that steric effects would influence both reaction mechanisms equally. Due to this, the steric substituent constant E_s was determined from solely the acid catalyzed reaction, as this would not include polar effects. E_s was defined as:

$$E_s = \frac{1}{\delta} \log \left(\frac{k_s}{k_{CH3}} \right)$$

where k_s is the rate of the studied reaction and k_{CH3} is the rate of the reference reaction (R = methyl). δ is a reaction constant that describes the susceptibility of a reaction series to steric effects. For the definition reaction series δ was set to 1 and E_s for the reference reaction was set to zero. This equation is combined with the equation for σ* to give the full Taft equation.

From comparing the E_s values for methyl, ethyl, isopropyl, and tert-butyl, it is seen that the value increases with increasing steric bulk. However, because context will have an effect on steric interactions some E_s values can be larger or smaller than expected. For example, the value for phenyl is much larger than that for *tert*-butyl. When comparing these groups using another measure of steric bulk, axial strain values, the *tert*-butyl group is larger.

Other Steric Parameters for LFERs

In addition to Taft's steric parameter E_s, other steric parameters that are independent of kinetic data have been defined. Charton has defined values *v* that is derived from van der Waals radii. Using molecular mechanics, Meyers has defined *V* values that are derived from the volume of the portion of the substituent that is within 0.3 nm of the reaction center.

Sensitivity Factors

Polar Sensitivity Factor, ρ*

Similar to ρ values for Hammett plots, the polar sensitivity factor ρ* for Taft plots will describe the susceptibility of a reaction series to polar effects. When the steric effects of substituents do not significantly influence the reaction rate the Taft equation simplifies to a form of the Hammett equation:

$$\log \left(\frac{k_s}{k_{CH3}} \right) = \rho^* \sigma^*$$

The polar sensitivity factor ρ* can be obtained by plotting the ratio of the measured reaction rates (k_s) compared to the reference reaction (k_{CH3}) versus the σ* values for the substituents. This plot will give a straight line with a slope equal to ρ*. Similar to the Hammett ρ value:

- If ρ*>1, the reaction accumulates negative charge in the transition state and is accelerated by electron withdrawing groups.
- If 1 >ρ* > 0, negative charge is built up and the reaction is mildly sensitive to polar effects.
- If ρ* = 0, the reaction is not influenced by polar effects.
- If 0 > ρ* > -1, positive charge is built up and the reaction is mildly sensitive to polar effects.
- If -1 > ρ*, the reaction accumulates positive charge and is accelerated by electron donating groups.

Steric Sensitivity Factor, δ

Similar to the polar sensitivity factor, the steric sensitivity factor δ for a new reaction series will describe to what magnitude the reaction rate is influenced by steric effects. When a reaction series is not significantly influenced by polar effects, the Taft equation reduces to:

$$\log\left(\frac{k_s}{k_{\mathrm{CH3}}}\right) = \delta E_s$$

A plot of the ratio of the rates versus the E_s value for the substituent will give a straight line with a slope equal to δ. Similarly to the Hammett ρ value, the magnitude of δ will reflect to what extent a reaction is influenced by steric effects:

- A very steep slope will correspond to high steric sensitivity, while a shallow slope will correspond to little to no sensitivity.
- If δ is negative, increasing steric bulk decreases the reaction rate and steric effects are greater in the transition state.
- If δ is positive, increasing steric bulk increases the reaction rate and sterics effects are lessened in the transition state.

Reactions Influenced by Polar and Steric Effects

When both steric and polar effects influence the reaction rate the Taft equation can be solved for both ρ* and δ through the use of standard least squares methods for determining a bivariant regression plane.

Text Book:

1. Smith, M. B. (2015). *March's Advanced Organic Chemistry: Reactions, Mechanisms, and Structure* (VII Edition). New Jersey: John Wiley & Sons, Inc., Hoboken.

Reference Book:

1. Tewari, N. (2011). *Advanced Organic Reaction Mechanism* (III Edition). Kolkata: Books and Allied (P) Ltd.

POSSIBLE QUESTIONS

PART- A – Multiple Choice Questions

(Each Question Carry One Mark)

1. Which of the following contains a 5-membered ring found with 7-membered ring?

A) **azulene** B) annulene C) ferrocene D) syndone

2. The Hammett equation can be used

A) to find out the order of the reaction

B) to correlate the structure and reactivity in ortho substituted compound

C) to correlate the structure and reactivity in aliphatic compounds

D) **to explain the influence of polar m- or p- substituent's on the side reactions of benzene derivatives**

3. In the following isomers of [10] annulene, pick out the aromatic

A) all-cis-isomer B) mono-trans C) cis–trans-cis-cis-trans D) **dehydro[14]annulene**

4. Cyclooctatetraene is

A) aromatic compound B) antiaromatic compound

C) **non aromatic compound** D) aliphatic compound

5. Which of the following is called a sandwich compound?

A) **Ferrocene** B) azulene C) annulene D) naphthalene

6. Which of the following is used to determine whether the reaction is inter/ intermolecular?

A) product analysis B) isotopic effect

C) isolation of intermediate D) **crossover experiment**

7. Huckel's rule is called as

A) 4nπ rule B) (4n+1)π rule C) **(4n+2)π rule** D) (2n+2)π rule

8. The number of outer and inner protons in [14] annulene is

A) **10 and 4** B) 4 and 10 C) 12 and 2 D) 2 and 12

9. Azulene is obtained by the fusion of

A) two 6-membered rings B) **one 5 and one 7 membered ring**

C) two 7-membered rings D) two 5-membered rings

10. Which is having greater resonance energy?

A) **heterocyclic compound** B) alicyclic compound

C) antiaromaric compound D) aliphatic compound

11. Cyclopropenylium salts dissolved in

A) non polar solvents B) **polar solvents**

C) benzene D) petroleum ether

12. Compounds having one or more sp^3 hybridized carbon atom in an conjugated cycle are called as

A) **homoaromatic compounds** B) homo cyclic compounds

C) antiaromatic compounds D) aromatic compounds

13. The main criteria for anti aromaticity in annulene is the presence of

A) **paramagnetic ring current** B) diamagnetic ring current

C) cyclic system D) conjugated system

14. Cyclopentadienyl anion is

A) **aromatic** B) non aromatic C) anti aromatic D) not aromatic

15. Cyclopropenyl anion is

A) aromatic B) non aromatic C) **anti aromatic** D) not aromatic

16. Pick out the compound which is anti-aromatic

A) **tropylium anion** B) tropylium cation

C) cyclopropenyl cation D) benzene

17. Hammet equation is not applicable to

A) **o-substituted aromatic system** B) p-substituted aromatic system

C) m-substituted aromatic system D) aliphatic system

18. Which is having lower degree of aromaticity?

A) pyridine B) **furan** C) thiophene D) pyrrole

19. Butadiene is

A) aromatic B) **non aromatic** C) anti aromatic D) homo aromatic

20. An example for heteroaromatic compound is

A) cyclopentadienyl anion B) **pyridine**

C) [14] annulene D) tropylium ion

21. Cyclopentadiene is

A) aromatic B) **non aromatic** C) anti aromatic D) homoaromatic

22. The ability to sustain induced ring current is known as

A) **aromaticity** B) anti-aromaticity C) non-aromaticity D) not aromatic

23. Ferrocene is an example for

A) benzenoid compound B) **non-benzenoid compound**

C) heterocyclic compound D) aliphatic compound

24. Ferrocene is an

A) cyclopentadienyl iron B) **dicyclopentadienyl iron**

C) tricyclopentadienyl iron D) cyclohexadienyl iron

25. In fused ring systems, some rings give up their part of their aromaticity to adjacent ring is known as

A) annelation B) **annulation** C) anisotropic D) conjugation

26. Azulene is a

A) aromatic compound B) aliphatic compound

C) heterocyclic compound D) **non-benzenoid aromatic compound**

27. A cyclic compound that does not have a continuous, overlapping ring of p orbital is said to be

A) anti-aromatic compound B) **non-aromatic compound**

C) aromatic compound D) heterocyclic compound

28. Cyclobutadiene is

A) aromatic compound B) **anti aromatic compound**

C) non aromatic compound D) heterocyclic compound

29. Compounds that sustain a paramagnetic ring current is called

A) diatropic B) **paratropic** C) anisotropic D) isotropic

30. Non-aromatic compound is also called as

A) heterocyclic compound B) **aliphatic compound**

C) benzenoid compound D) non-benzenoid compound

31. Which of the following is aromatic?

A) pyran B) **pyrlium ion** C) cyclobutadiene D) cyclopetadienyl cation

32. The corresponding anion of cyclopetadienyl is

A) **aromatic** B) non aromatic

C) antiaromatic D) straight chain compound

33. How many canonical forms are possible for phenanthrene?

A) 8 B) 10 C) **5** D) 3

34. The example for non-aromatic compound is

A) Benzene B) ferrocenes C) fulvenes D) **1,3-cyclohexadiene**

35. Ferrocene is readily under does

A) aliphatic electrophilic substitution reactions

B) **aromatic electrophilic substitution reactions**

C) aliphatic nucleophilic substitution reactions

D) aromatic nucleophilic substitution reactions

36. The Hammett equation the negative ρ value is indicate that

A) **carbocation intermediate** B) carbanoin intermediate

C) free radical intermediate D) no intermediate

37. The Hammett equation is a

A) non-linear free energy relationship

B) **linear free energy relationship**

C) linear entropy relationship

D) non-linear entropy relationship

38. The molecule is planer and it has a closed shell of four π electrons is known as

A) aromatic compound B) **non-aromatic compound**

C) heterocyclic compound D) anti-aromatic compound

39. Sydnones are

A) **5 membered ring compounds** B) 4 membered ring compounds

C) 3 membered ring compounds D) 6 membered ring compounds

40. Hammonds postulate deals with

A) energy B) **geometry of transition state**

C) geometry of reactants D) geometry of products

41. Carbonyl oxygen of γ-pyrone is more basic than the ring oxygen is due to

A) protonation of the carbonyl oxygen of γ-pyrone leads to anti-aromatic system

B) protonation of the carbonyl oxygen of γ-pyrone leads to non-aromatic

C) **protonation of the carbonyl oxygen of γ-pyrone leads to aromatic system**

D) protonation of the ring oxygen of γ-pyrone leads to aromatic system

42. Dipole moment of ferrocene is

A) one B) two C) **zero** D)three

43. Conjugated monocyclic polyenes are

A) azulenes B) fulvenes C) **annulenes** D) ferrocenes

44. Azulene is aromatic due to

A) **charge separated structures** B) both rings are aromatic

C) both rings having 6π electrons D) two Kekule structures

45. Cycloheptatrine loses a hydride ion to form a carbonium ion is called

A) tropylium anion B) cyclopentadienyl anion

C) **tropylium cation** D) tropylium radical

46. The number double bonds in tropylium cation is

A) two B) **three** C) four D) one

47. Although there are eight free electrons, phenyl anions, C6H5- is

A) anti-aromatic B) **aromatic** C) non-aromatic D) heterocyclic

48. The compounds like tropone and fulvene possess significant dipole moments is due to

A) **stable dipolar structure** B) unstable dipolar structure

C) stable non-polar structure D) unstable non-polar structure

49. Cyclopentadiene is much more acidic than cycloheptatriene is due to

A) the conjugate base of cycloheptatriene is aromatic

B) the conjugate base of cyclopentadiene is anti-aromatic

C) the conjugate base of cycloheptatriene is non-aromatic

D) **the conjugate base of cyclopentadiene is aromatic**

50. Metallocene is also known as

A) **sandwich compound** B) ionic compound

C) fused ring compound D) heterocyclic compound

51. The system contain 4n electrons are predicated to be

A) sandwich compound B) ionic compound

C) fused ring compound D) **anti-aromatic compound**

52.The change in the rate of a reaction observed due to replacement of one isotope of an element for another is called

A)non-kinetic isotopic effect B) **kinetic isotopic effect**

C) isotopic labeling D) cross over experiment

53. The nitronium ion involved in nitration of benzene has been detected by

A) NMR spectrum B) UV spectrum C) **Raman spectrum** D) ESR spectrum

54. In Hofmann rearrangement how many intermediates are possible?

A) 1 B) 2 C) 4 D) **3**

55. In the exothermic reaction the energy of transition state is closer to

A) product B) intermediate C) **reactant** D) transition state

56. The squaric acid is

A) aliphatic compound B) anti-aromatic compound

C) non-aromatic compound D) **aromatic compound**

57. In S_N1 reaction, there will be two transition state are closer to

A) product B) **intermediate** C) reactant D) transition state

58. In a reversible reaction the forward and reverse reactions must follow the same mechanism. This phenomenon is called the

A) isotopic labeling B) cross over experiment

C) identification of intermediate D) **microscopic reversibility**

59. A non-isolable intermediate can often be dected by spectroscopic studies is known as

A) cross over experiment B) Hammond's postulate

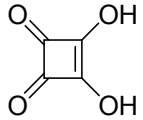
C) microscopic reversibility D) **detection of an intermediate**

60. Which one has highest energy in energy profile diagram?

A) Reactant B) **transition state** C) product D) intermediate

PART-B (Each Question Carry Two Mark)

61. Write a note on microscopic reversibility.
62. Explain the aromatic nature of ferrocene.
63. Explain why cyclooctatetraene is nonplanar (a tub-shaped structure), whereas its dianion is planer.
64. Pyrrole is a much weaker base than pyridine.
65. Tropylium bromide behaves as an ionic compound.
66. Write a note on cross over experiments.
67. Explain why although there are eight free electrons, phenyl anion is aromatic.
68. What is called a homoaromatic compound? Give an example and discuss its structure.
69. Explain why dehydro[14]annulene is aromatic whereas [14]annulene behaves like a nonaromatic compound.
70. The following cyclic diol (squaric acid) is almost strong an acid as H_2SO_4.

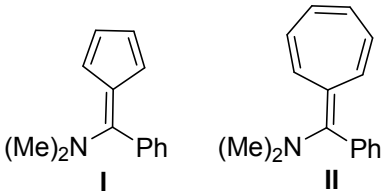


Squaric acid

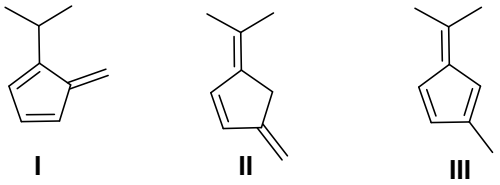
PART-C (Each Question Carry Six Mark)

71. Provide an explanation for each of the following observations:

(i) The amine **II** is more basic than the amine **I**.



(ii) One of the following hydrocarbons is much more acidic than the others.



72. (i) Write a note on isotopic labeling.

(ii) Write a note on microscopic reversibility.

(iii) Write a note on identification of products.

73. (i) Explain the Huckel's rule with example.

(ii) Write a note on fulvenes.

74. (i) Explain the following observation:

Azulene, an isomer of naphthalene, possesses dipole moment (1.0 D) and electrophilic substitution in it occurs at 1-position of the five-membered ring.

(ii) Explain the Hammonds postulate.

75. Explain the conditions for a compound to be aromatic, non-aromatic and anti aromatic with examples.

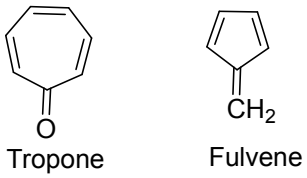
76. (i) Explain the aromaticity of non-benzenoid aromatic compounds.

(ii) Explain the resonance structure of cyclopropenyl cation and cyclopentadiene cation.

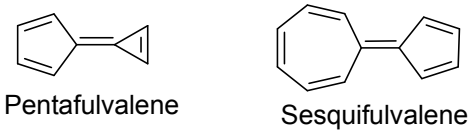
77. Explain the non-kinetic methods of study of reaction mechanisms.

78. Provide an explanation for the each of the following observations:

(i) Compound like tropone and fulvene possess significant dipole moments.



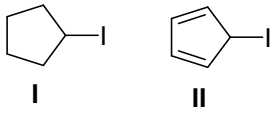
(ii) The following fulvalenes are significantly polar:



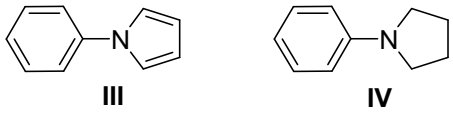
79. Explain the Hammett equation and its applications.

80. Provide an explanation for each of the following observations:

(i) When treated with silver perchlorate in propionic acid, iodocyclopentane (**I**) undergoes solvolysis whereas 1-iodocyclopenta-2,4-diene (**II**) does not.

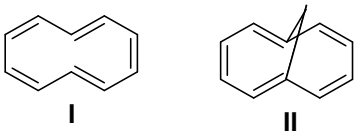


(ii) The rotational energy barrier around the C-N bond of compound **IV** is higher than compound **III**.

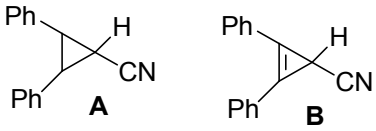


PART-D (Each Question Carry Ten Mark)

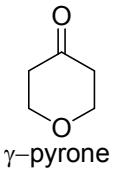
81. (i) Explain why the compound **II** is more stable than the compound **I**.



(ii) The cyclopropane (**A**) loses its proton in hydrogen-exchange reaction ≈10, 000 times faster than the cyclopropene (**B**). Explain.



(iii) Explain why carbonyl oxygen of γ-pyrone is more basic than the ring oxygen.



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DEPARTMENT OF CHEMISTRY

UNIT-I

AROMATICITY AND CHEMICAL METHODS IN MECHANISMS

PART-A–Multiple Choice Questions
(Each Question Carry One Mark) (Online Examinations)

1. Which of the following contains a 5-membered ring found with 7-membered ring?

A) **azulene** B) annulene C) ferrocene D) syndone

2. The Hammett equation can be used

A) to find out the order of the reaction

B) to correlate the structure and reactivity in ortho substituted compound

C) to correlate the structure and reactivity in aliphatic compounds

D) **to explain the influence of polar m- or p- substituent's on the side reactions of benzene derivatives**

3. In the following isomers of [10] annulene, pick out the aromatic

A) all-cis-isomer B) mono-trans C) cis–trans-cis-cis-trans D) **dehydro[14]annulene**

4. Cyclooctatetraene is

A) aromatic compound B) antiaromatic compound

C) **non aromatic compound** D) aliphatic compound

5. Which of the following is called a sandwich compound?

A) **Ferrocene** B) azulene C) annulene D) naphthalene

6. Which of the following is used to determine whether the reaction is inter/ intermolecular?

A) product analysis B) isotopic effect

C) isolation of intermediate D) **crossover experiment**

7. Huckel's rule is called as

A) 4nπ rule B) (4n+1)π rule C) **(4n+2)π rule** D) (2n+2)π rule

8. The number of outer and inner protons in [14] annulene is

A) **10 and 4** B) 4 and 10 C) 12 and 2 D) 2 and 12

9. Azulene is obtained by the fusion of

A) two 6-membered rings B) **one 5 and one 7 membered ring**

C) two 7-membered rings D) two 5-membered rings

10. Which is having greater resonance energy?

A) **heterocyclic compound** B) alicyclic compound

C) antiaromaric compound D) aliphatic compound

11. Cyclopropenylium salts dissolved in

A) non polar solvents B) **polar solvents**

C) benzene D) petroleum ether

12. Compounds having one or more sp^3 hybridized carbon atom in an conjugated cycle are called as

A) **homoaromatic compounds** B) homo cyclic compounds

C) antiaromatic compounds D) aromatic compounds

13. The main criteria for anti aromaticity in annulene is the presence of

A) **paramagnetic ring current** B) diamagnetic ring current

C) cyclic system D) conjugated system

14. Cyclopentadienyl anion is

A) **aromatic** B) non aromatic C) anti aromatic D) not aromatic

15. Cyclopropenyl anion is

A) aromatic B) non aromatic C) **anti aromatic** D) not aromatic

16. Pick out the compound which is anti-aromatic

A) **tropylium anion** B) tropylium cation

C) cyclopropenyl cation D) benzene

17. Hammet equation is not applicable to

A) **o-substituted aromatic system** B) p-substituted aromatic system

C) m-substituted aromatic system D) aliphatic system

18. Which is having lower degree of aromaticity?

A) pyridine B) **furan** C) thiophene D) pyrrole

19. Butadiene is

A) aromatic B) **non aromatic** C) anti aromatic D) homo aromatic

20. An example for heteroaromatic compound is

A) cyclopentadienyl anion B) **pyridine**

C) [14] annulene D) tropylium ion

21. Cyclopentadiene is

A) aromatic B) **non aromatic** C) anti aromatic D) homoaromatic

22. The ability to sustain induced ring current is known as

A) **aromaticity** B) anti-aromaticity C) non-aromaticity D) not aromatic

23. Ferrocene is an example for

A) benzenoid compound B) **non-benzenoid compound**

C) heterocyclic compound D) aliphatic compound

24. Ferrocene is an

A) cyclopentadienyl iron B) **dicyclopentadienyl iron**

C) tricyclopentadienyl iron D) cyclohexadienyl iron

25. In fused ring systems, some rings give up their part of their aromaticity to adjacent ring is known as

A) annelation B) **annulation** C) anisotropic D) conjugation

26. Azulene is a

A) aromatic compound B) aliphatic compound

C) heterocyclic compound D) **non-benzenoid aromatic compound**

27. A cyclic compound that does not have a continuous, overlapping ring of p orbital is said to be

A) anti-aromatic compound B) **non-aromatic compound**

C) aromatic compound D) heterocyclic compound

28. Cyclobutadiene is

A) aromatic compound B) **anti aromatic compound**

C) non aromatic compound D) heterocyclic compound

29. Compounds that sustain a paramagnetic ring current is called

A) diatropic B) **paratropic** C) anisotropic D) isotropic

30. Non-aromatic compound is also called as

A) heterocyclic compound B) **aliphatic compound**

C) benzenoid compound D) non-benzenoid compound

31. Which of the following is aromatic?

A) pyran B) **pyrlium ion** C) cyclobutadiene D) cyclopetadienyl cation

32. The corresponding anion of cyclopetadienyl is

A) **aromatic** B) non aromatic

C) antiaromatic D) straight chain compound

33. How many canonical forms are possible for phenanthrene?

A) 8 B) 10 C) **5** D) 3

34. The example for non-aromatic compound is

A) Benzene B) ferrocenes C) fulvenes D) **1,3-cyclohexadiene**

35. Ferrocene is readily under does

A) aliphatic electrophilic substitution reactions

B) **aromatic electrophilic substitution reactions**

C) aliphatic nucleophilic substitution reactions

D) aromatic nucleophilic substitution reactions

36. The Hammett equation the negative ρ value is indicate that

A) **carbocation intermediate** B) carbanoin intermediate

C) free radical intermediate D) no intermediate

37. The Hammett equation is a

A) non-linear free energy relationship

B) **linear free energy relationship**

C) linear entropy relationship

D) non-linear entropy relationship

38. The molecule is planer and it has a closed shell of four π electrons is known as

A) aromatic compound B) **non-aromatic compound**

C) heterocyclic compound D) anti-aromatic compound

39. Sydnones are

A) **5 membered ring compounds** B) 4 membered ring compounds

C) 3 membered ring compounds D) 6 membered ring compounds

40. Hammonds postulate deals with

A) energy B) **geometry of transition state**

C) geometry of reactants D) geometry of products

41. Carbonyl oxygen of γ-pyrone is more basic than the ring oxygen is due to

A) protonation of the carbonyl oxygen of γ-pyrone leads to anti-aromatic system

B) protonation of the carbonyl oxygen of γ-pyrone leads to non-aromatic

C) **protonation of the carbonyl oxygen of γ-pyrone leads to aromatic system**

D) protonation of the ring oxygen of γ-pyrone leads to aromatic system

42. Dipole moment of ferrocene is

A) one B) two C) **zero** D)three

43. Conjugated monocyclic polyenes are

A) azulenes B) fulvenes C) **annulenes** D) ferrocenes

44. Azulene is aromatic due to

A) **charge separated structures** B) both rings are aromatic

C) both rings having 6π electrons D) two Kekule structures

45. Cycloheptatrine loses a hydride ion to form a carbonium ion is called

A) tropylium anion B) cyclopentadienyl anion

C) **tropylium cation** D) tropylium radical

46. The number double bonds in tropylium cation is

A) two B) **three** C) four D) one

47. Although there are eight free electrons, phenyl anions, $C_6H_5^-$ is

A) anti-aromatic B) **aromatic** C) non-aromatic D) heterocyclic

48. The compounds like tropone and fulvene possess significant dipole moments is due to

A) **stable dipolar structure** B) unstable dipolar structure

C) stable non-polar structure D) unstable non-polar structure

49. Cyclopentadiene is much more acidic than cycloheptatriene is due to

A) the conjugate base of cycloheptatriene is aromatic

B) the conjugate base of cyclopentadiene is anti-aromatic

C) the conjugate base of cycloheptatriene is non-aromatic

D) **the conjugate base of cyclopentadiene is aromatic**

50. Metallocene is also known as

A) **sandwich compound** B) ionic compound

C) fused ring compound D) heterocyclic compound

51. The system contain 4nπ electrons are predicated to be

A) sandwich compound B) ionic compound

C) fused ring compound D) **anti-aromatic compound**

52.The change in the rate of a reaction observed due to replacement of one isotope of an element for another is called

A)non-kinetic isotopic effect B) **kinetic isotopic effect**

C) isotopic labeling D) cross over experiment

53. The nitronium ion involved in nitration of benzene has been detected by

A) NMR spectrum B) UV spectrum C) **Raman spectrum** D) ESR spectrum

54. In Hofmann rearrangement how many intermediates are possible?

A) 1 B) 2 C) 4 D) **3**

55. In the exothermic reaction the energy of transition state is closer to

A) product B) intermediate C) **reactant** D) transition state

56. The squaric acid is

A) aliphatic compound B) anti-aromatic compound

C) non-aromatic compound D) **aromatic compound**

57. In S_N1 reaction, there will be two transition state are closer to

A) product B) **intermediate** C) reactant D) transition state

58. In a reversible reaction the forward and reverse reactions must follow the same mechanism. This phenomenon is called the

A) isotopic labeling B) cross over experiment

C) identification of intermediate D) **microscopic reversibility**

59. A non-isolable intermediate can often be detected by spectroscopic studies is known as

A) cross over experiment B) Hammond's postulate

C) microscopic reversibility D) **detection of an intermediate**

60. Which one has highest energy in energy profile diagram?

A) Reactant B) **transition state** C) product D) intermediate

UNIT-II-Part-I

Addition reactions: Electrophilic, nucleophilic and free radical addition to double and triple bonds - hydration, hydroxylation, Michael addition, hydroboration and epoxidation.

Addition reactions to carbonyl compounds – Mannich reaction, Meerwein Pondroff-Verley reduction, Grignard, Claisen, Dieckmann, Stobbe, Knovenagel, Darzen, Wittig, Thorpe and Benzoin reactions.

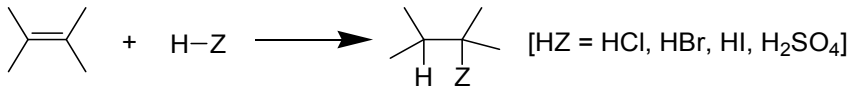
ADDITION REACTIONS

A reaction in which the substrate and the reagent add up to form a product is called addition reaction. The reaction occurs at the site of unsaturation in a molecule. Thus, compounds having multiple bonds such as >C═C<, ─C≡C─, >C═O, ─C≡N, etc. undergo addition reactions.

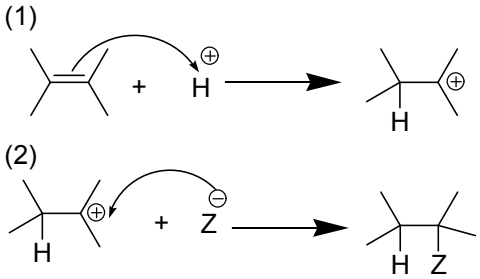
The reactivity of these compounds is due to the more exposed and easily available π electrons to the electron-seeking (electrophilic) reagent.

(i) **Electrophilic addition reaction**

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



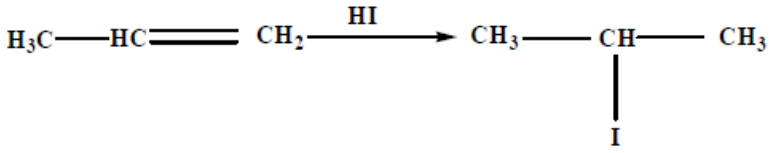
Mechanism



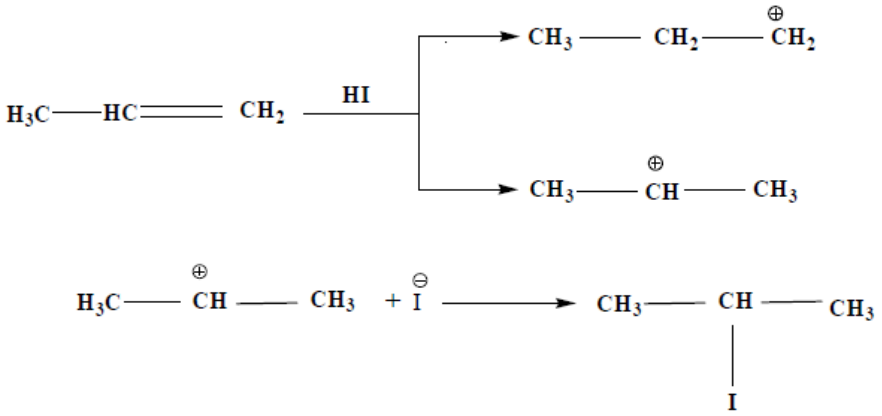
Step (1) involves transfer of hydrogen ion to the alkene to form a carbonium ion.

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 and hence is called electrophilic addition.



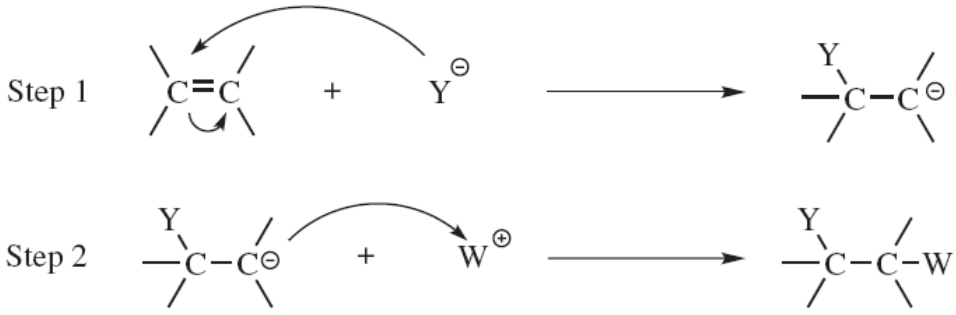
Mechanism



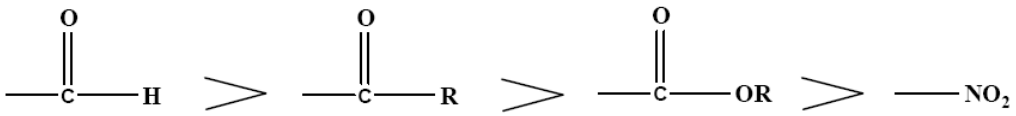
Nucleophilic addition reaction

We have seen that electron-releasing groups conjugated to carbon-carbon multiple bonds promote electrophlic addition. In the same way, conjugation of electron withdrawing groups activate the carbon-carbon multiple bonds towards nucleophilic addition.

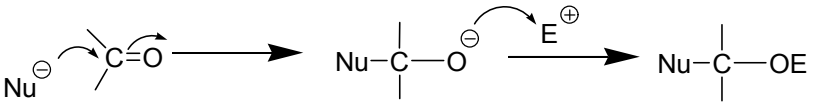
In the first step of nucleophilic addition, a nucleophile brings its pair of electrons to one carbon atom of the double bond or triple bond, creating a carbanion. The second step is combination of this carbanion with a positive species:



The substituents reduce the π-electron density, thereby aid the attack of the nucleophilic and stabilize the carbanion formed on attack by delocalization of the negative charge. Some common electron-withdrawing groups are:



Polar functional groups e.g., >C=O, -C≡N, >C=N, >C=S etc., also undergo nucleophilic addition. The hetero atoms, like the electron-withdrawing substituents, reduce the π-electron density on the carbonyl carbon and stabilize the anion, formed on attack of the nucleophile, by accommodating the –ve charge.

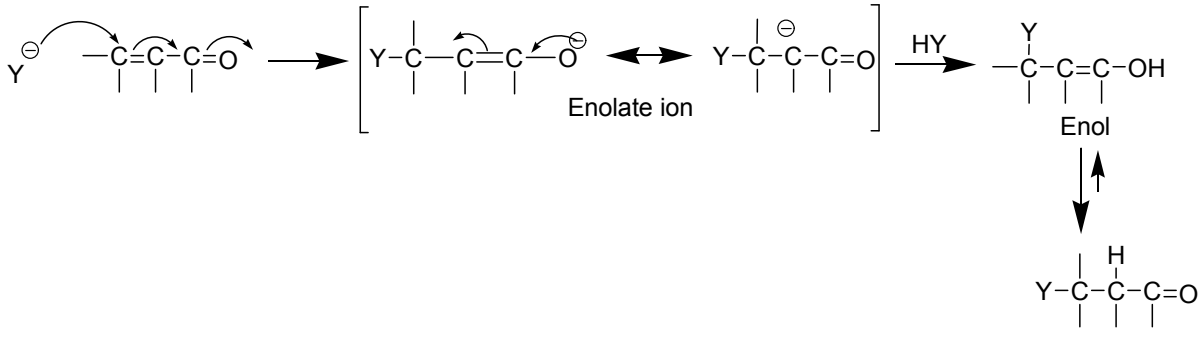


However, the addition product will be stable enough to be isolated provided the carbonyl group is not attached to a good leaving group such as, OH, OR, Cl, NH_2, etc. carboxylic acids and their derivatives, therefore, undergo substitution rather than addition on attack of nucleophiles.

Nucleophilic addition to carbonyl group is, therefore a characteristic reaction of aldehydes and ketones since $H^{\ominus}$, $R^{\ominus}$, and $Ar^{\ominus}$ are not good leaving groups. 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.

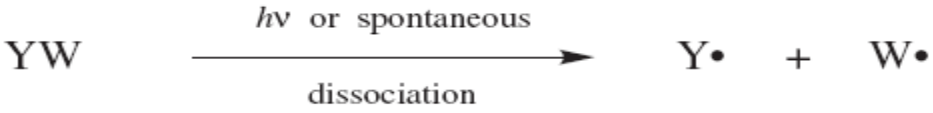
$$H_2C{=}O > RCHO > R_2CO > ArCHO > Ar_2CO$$

In the special case of addition of HY to a substrate of the form ─C═C─Z, where Z= CHO, COR (including quinones), COOR, $CONH_2$, CN, NO_2, SOR, SO_2R and so on, addition nearly always follows a nucleophilic mechanism with $Y^{\ominus}$ bonding with the carbon away from the Z group, for example,



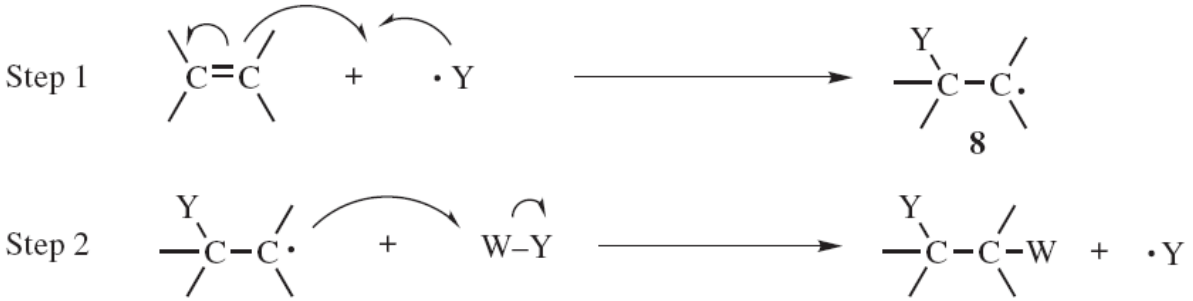
Free radical addition reaction

The method of principal component analysis has been used to analyze polar and enthalpic effect in radical addition reactions. A radical is generated by



(Or)

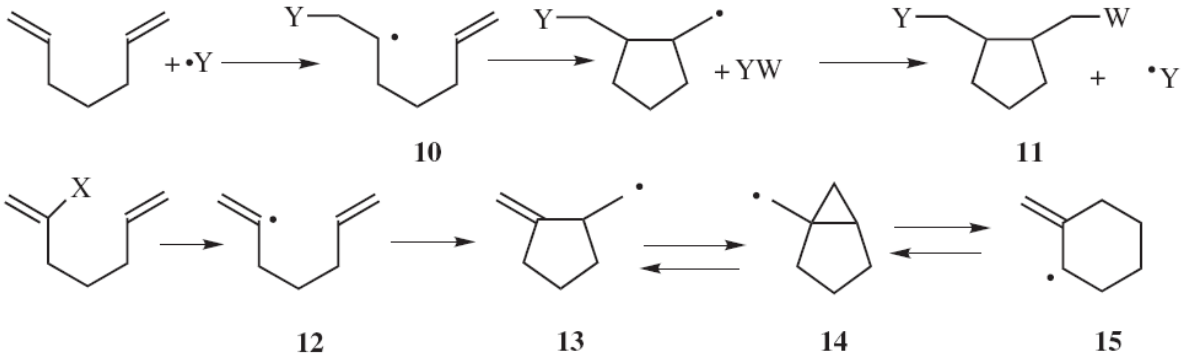
Propagation then occurs by



Step 2 is an abstraction (an atom transfer), so W is nearly always univalent, either hydrogen or hydrogen. Termination of the chain can occur in any of the ways. If **9** adds to another olefin molecule,

a dimer is formed. This can add to still another, and chains, long or short, may be built up. This is the mechanism of free-radical polymerization. Short polymeric molecules (called telomers), formed in this manner, are often troublesome side products in free-radical addition reactions.

When free radicals are added to 1,5- or 1,6-dienes, the initially formed radical (**10**) can add intramolecularly to the other bond, leading to a cyclic product (**11**). When the radical is generated from an precursor that gives vinyl radical **12**, however, cyclization leads to **13**, which is in equilibrium with cyclopropylcarbinyl radical (**14**) via a 5-exo-trig reaction. A 6-endo-trig reaction leads to **15**, but unless there are perturbing substituent effects, however, cyclopropanation should be the major process.

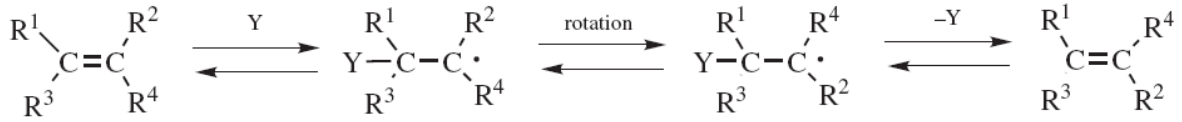


Radicals of the type **10**, generated in other ways, also undergo these cyclizations. Both five- and six-membered rings can be formed in these reactions.

The free-radical addition mechanism just outlined predicts that the addition should be non-stereospecific, at least if **9** has any, but an extremely short lifetime. Not all free-radical additions have been found to be selective, but many are. For example, addition of HBr to 1-bromocyclohexene is regioselective in that it gave only cis-1,2-dibromocyclohexane and none of the trans isomer (anti addition), and propyne (at -78 to -60°C) gave only cis-1-bromopropene (anti addition), making it stereoselective. However, stereospecificity has been found only in a few cases. Selectivity was observed in radical cyclization reactions of functionalized alkenes, which proceeded via a trans-ring closure. The most important case is probably addition of HBr to 2- bromo-2-butene under free-radical conditions at -80°C. Under these conditions, the cis isomer gave 92% of the meso product, while the trans isomer gave mostly the *dl* pair. This stereospecificity disappeared at room temperature, where both alkenes gave the same mixture of products (~78% of the *dl* pair and ~2% of the meso compound), so the addition was still stereoselective but no longer stereospecific. The stereospecificity at low temperatures is probably caused by a stabilization of the intermediate radical through the formation of a bridged bromine radical.

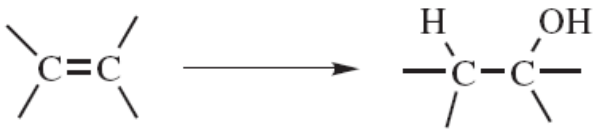
This species is similar to the bromonium ion that is responsible for stereospecific anti addition in the electrophilic mechanism. Further evidence for the existence of such bridged radicals was obtained by addition of Br• to alkenes at 77 K. The ESR spectra of the resulting species were consistent with bridged structures.

For many radicals, step 1 (C═C + Y• → •C─C─Y) is reversible. In such cases, free radicals can cause cis→trans isomerization of a double bond by the pathway.

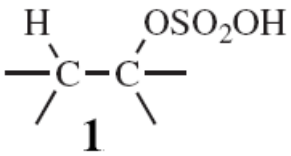


Addition to double and triple bonds

Hydration of Double bonds (Hydro-Hydroxy-addition)

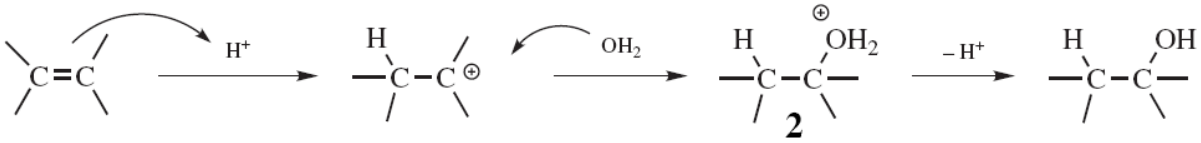


Double bonds can be hydrated by treatment with water and an acid catalyst. The most common catalyst is sulfuric acid, but other acids that have relatively non-nucleophilic counterions, such as nitric or perchloric can also be used. The mechanism is electrophilic and begins with attack of the π -bond on an acidic proton. The resulting carbocation is then attacked by negative species, such as HSO_4^- (or similar counterion in the case of other acids), to give the initial product **1**, which can be isolated in some cases, but under the conditions of the



1

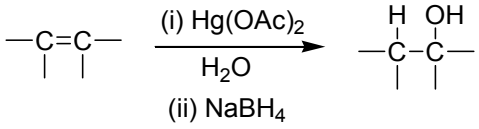
reaction, is usually hydrolyzed to the alcohol. However, the conjugate base of the acid is not the only possible species that attacks the initial carbocation. The attack can also be by water to form **2**.



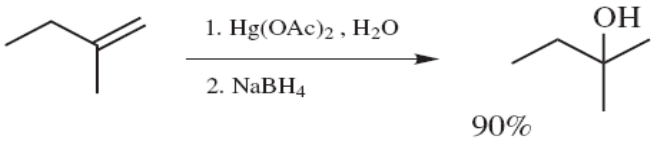
2

When the reaction proceeds by this pathway, **1** and similar intermediates are not involved and the mechanism is exactly (by the principle of microscopic reversibility) the reverse of El elimination of alcohols. It is likely that the mechanism involves both pathways. *The initial carbocation occasionally rearranges to a more stable one*. For example, hydration of CH_2=CHCH$(CH_3)_2$ gives $CH_3CH_2COH(CH_3)_2$. With ordinary alkenes the addition predominantly follows Markovnikov's rule. Another method for Markovnikov addition of water consists of simultaneously adding an oxidizing agent (O_2) and a reducing agent (either

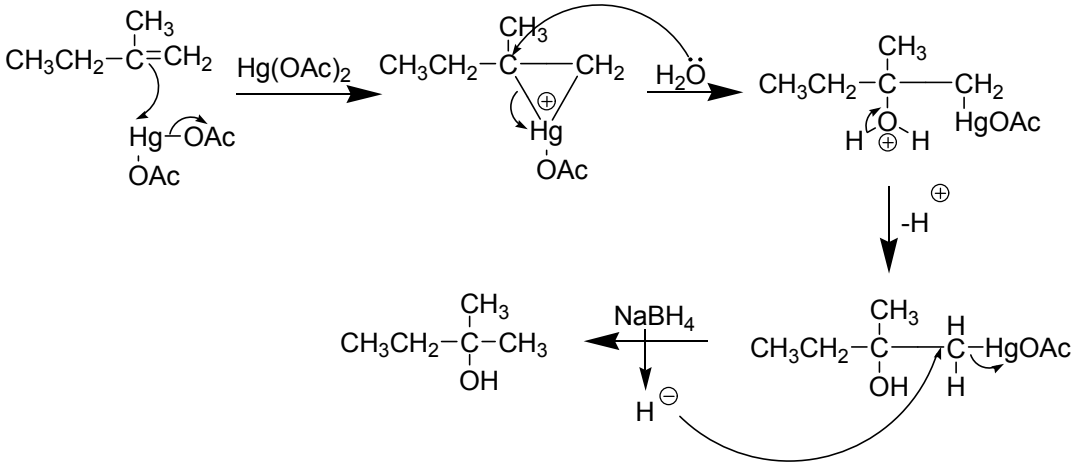
Et_3SiH or a secondary alcohol, e.g., 2-propanol) to the alkene in the presence of a cobalt-complex catalyst. No rearrangement is observed with this method. The corresponding alkane and ketone are usually side products.



Alkenes can be hydrated quickly under mild conditions in high yields without rearrangement products by the use of *oxymercuration* (addition of oxygen and mercury) followed by *in situ* treatment with sodium borohydride. For example, 2-methyl-1-butene treated with mercuric acetate, followed by $NaBH_4$, gave 2-methyl-2-butanol.

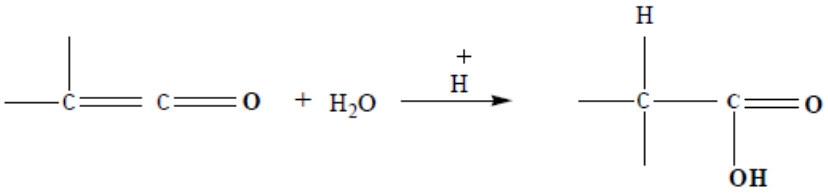


Mechanism

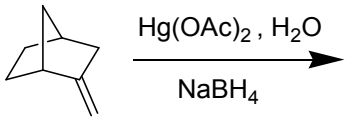


This method, which is applicable to mono-, di-, tri-, and tetraalkyl as well as phenyl-substituted alkenes, gives almost complete Markovnikov addition. Hydroxy, methoxy, acetoxy, halo, and other groups may be present in the substrate without, in general, causing difficulties. When two double bonds are present in the same molecule, the use of ultrasound allows oxymercuration of the less-substituted one without affecting the other. A related reaction treats an alkene with zinc borohydride on silica gel to give a 35:65 mixture of secondary: primary alcohols.

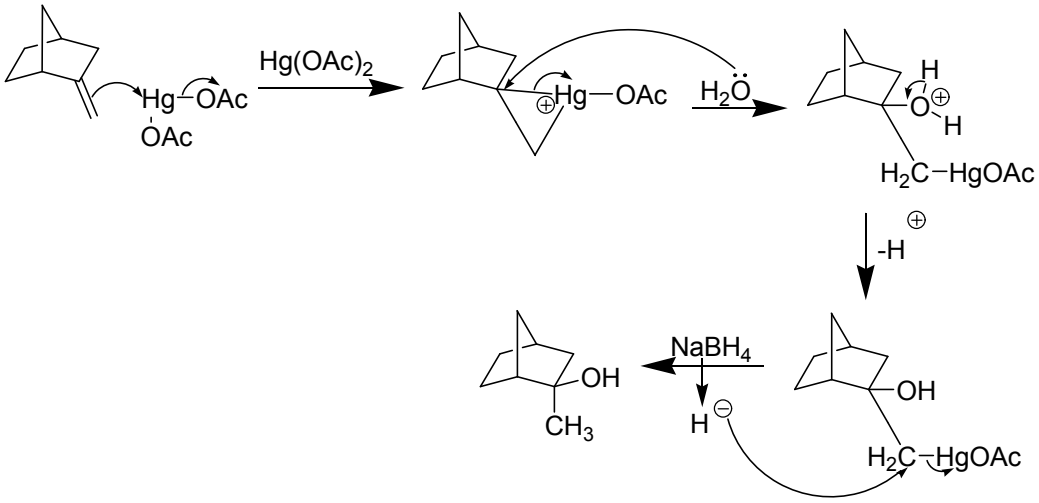
The addition of water to enol ethers causes hydrolysis to aldehydes or ketones. Ketenes add water to give carboxylic acids in a reaction catalyzed by acids.



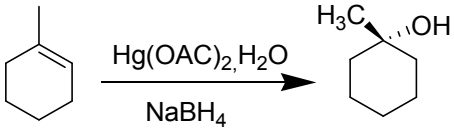
1. Complete the following reaction. Provide mechanism.



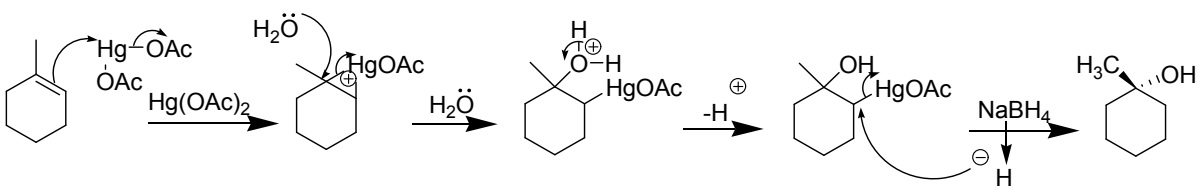
Solution:



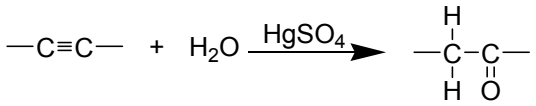
2. Explain the mechanism of the following conversion.



Solution:



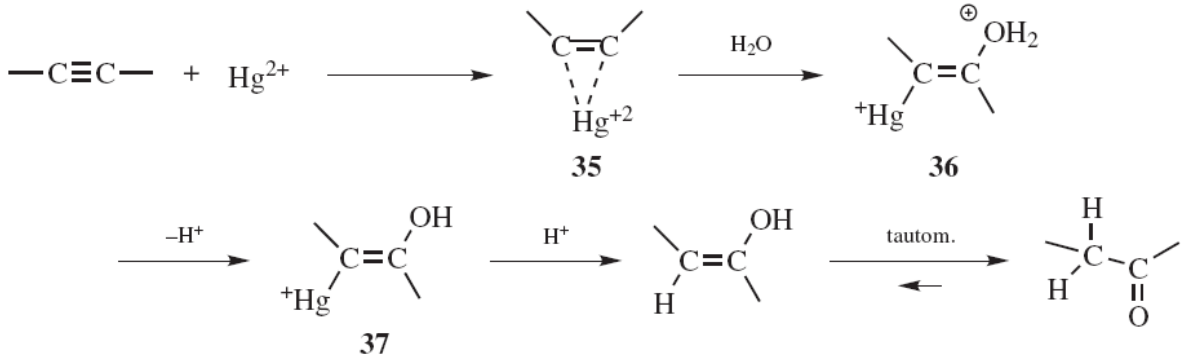
Hydration of Triple Bonds (Dihydro-oxo-biaddition)



The hydration of triple bonds is generally carried out with mercuric ion salts (often the sulfate or acetate) as catalysts. Mercuric oxide in the presence of an acid is also a common reagent. Since the addition follows Markovnikov's rule, only acetylene gives an aldehyde. All other triple-bond compounds give ketones (for a method of reversing the orientation for terminal alkynes). With alkynes of the form RC≡CH methyl ketones are formed almost exclusively, but with RC≡CR' both possible products are usually obtained. The reaction can be conveniently carried out with a catalyst prepared by impregnating mercuric oxide onto Nafion-H (a superacidic perfluorinated resinsulfonic acid). Terminal alkynes react with water at 200°C with microwave irradiation to give the corresponding methyl ketone. A gold catalyst was used in aqueous methanol with 50% sulfuric acid to convert terminal alkynes to the ketone. Conversion of phenyl acetylene to acetophenone was accomplished in water at 100°C with a catalytic amount of Tf_2NH (trifluoromethanesulfonimide). In a modified reaction, internal alkynes were treated with 2-aminophenol in refluxing dioxane using a palladium catalyst to produce the corresponding ketone.

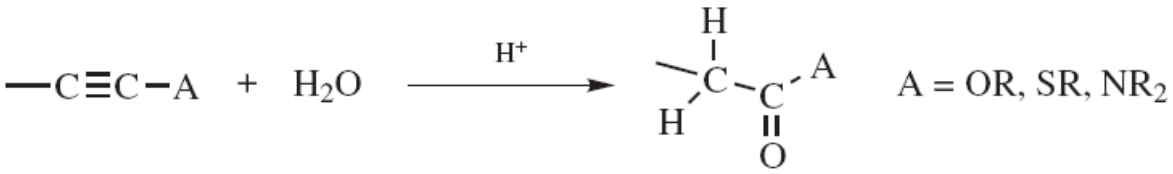
Hydration of terminal alkynes can proceed with anti-Markovnikov addition. When 1-octyne was heated with water, isopropanol and a ruthenium catalyst, for example, the product was octanal. A similar reaction was reported in aqueous acetone using a ruthenium catalyst. The presence of certain functionality can influence the regioselectivity of hydration. 1-Seleno alkynes, such as PhSe-C≡C-Ph, react with tosic acid in dichloromethane to give a seleno ester $PhSeC(=O)SH_2Ph$ after treatment with water.

The first step of the mechanism is formation of a complex (**35**) (ions like Hg^{2+} form complexes with alkynes). Water then attacks in an S_N2-type process to give the intermediate **36,**



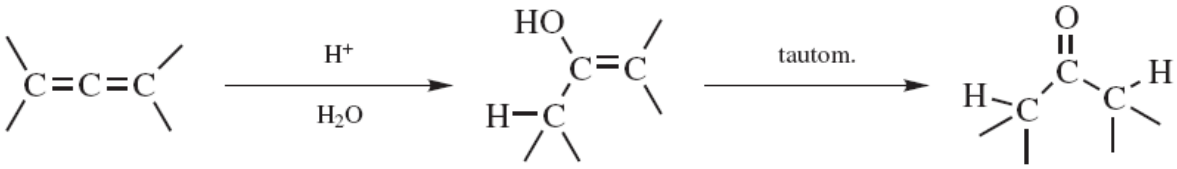
which loses a proton to give **37**. Hydrolysis of **37** gives the enol, which tautomerizes to the product. A spectrum of the enol was detected by flash photolysis when phenyl acetylene was hydrated photolytically.

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



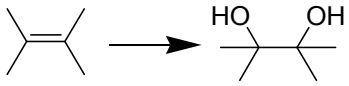
This is ordinary electrophilic addition, with rate-determining protonation as the first step. Certain other alkynes have also been hydrated to ketones with strong acids in the absence of mercuric salts. Simple alkynes can also be converted to ketones by heating with formic acid, without a catalyst. Lactones have been prepared from trimethylsilyl alkenes containing an hydroxyl unit elsewhere in the molecule, when reacted with molecular oxygen, $CuCl_2$, and a palladium catalyst.

Allenes can also be hydrolyzed to ketones with an acid catalyst.



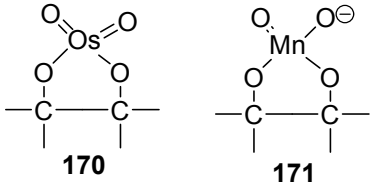
Hydroxylation (Addition of Oxygen, Oxygen)

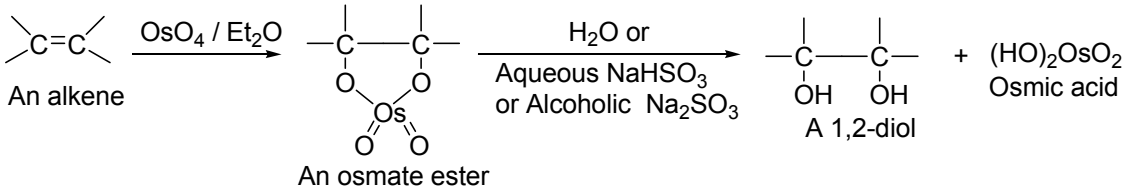
Dihydroxy-addition

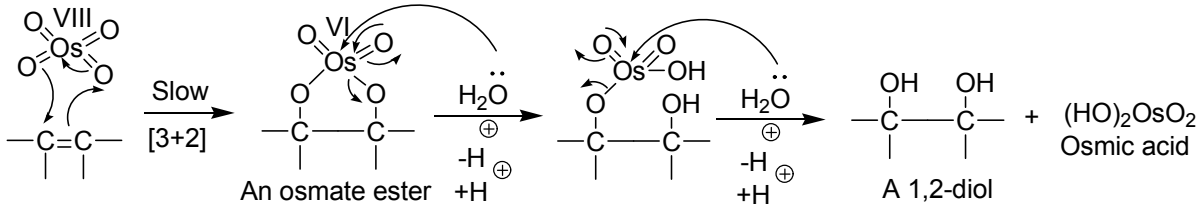


There are many reagents that add two OH groups to a double bond. The most common are OsO_4 and alkaline KMnO4, which give syn addition from the less-hindered side of the double bond. Less substituted double bonds are oxidized more rapidly than more substituted alkenes. Permanganate adds to alkenes to form an intermediate manganate ester (**171**), which is decomposed under alkaline conditions. Bases catalyze the decomposition of **171** by coordinating with the ester. Osmium tetroxide adds rather slowly but almost quantitatively to form a cyclic ester, such as **170**, as an intermediate, which can be isolated, but is usually decomposed solution, with sodium sulfite in ethanol or other reagents. The chief drawback to the use of OsO_4 is expensive and highly toxic, but the reaction is made catalytic in OsO_4 by using *N*-methylmorpholine-*N*-oxide (NMO), *tert*-butyl hydroperoxide in

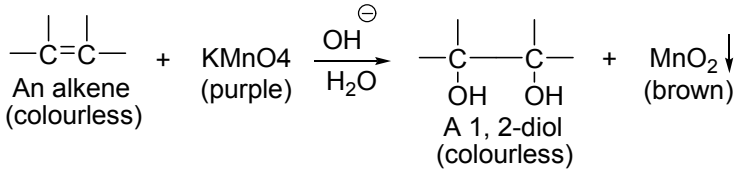
alkaline solution, H_2O_2, peroxyacid, flavin and TEAA, $K_3Fe(CN)_6$ and non-heme iron catalysts. Polymer-bound OsO_4, and encapsulated OsO_4 have been shown to give the diol in the presence of NMO, as well as OsO_4^{2-} on an ion exchange resin. Dihydroxylation has also been reported in ionic liquids, and with fluorous osmium tetroxide. A catalytic amount of K_2OsO_4 with a Cinchona alkaloid on a ordered inorganic support, in the presence of $K_3Fe(CN)_6$, gives the cis-diol. Oxidation of pent-4-en-1-ol to valerolactone was accomplished with Oxone and a catalytic amount of OsO_4 in DMF.

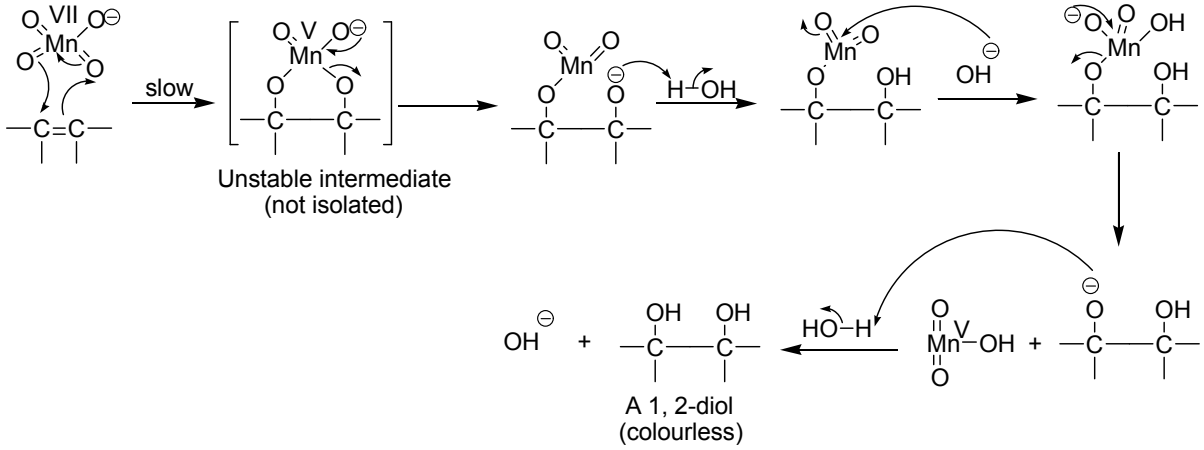




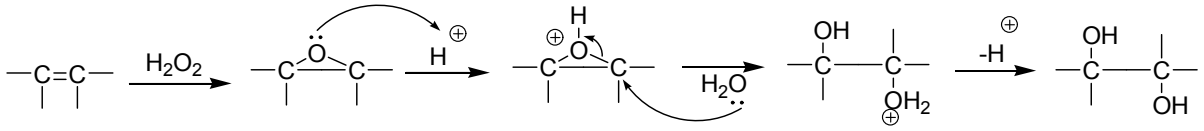


The end-product of the reaction of either potassium permanganate or osmium tetroxide under the conditions described above is a 1,2-diol. Potassium permanganate is a strong oxidizing agent and can oxidize the glycol product. In acid and neutral solution it always does so; hence glycols must be prepared with alkaline permanganate, but the conditions must be mild. Even so, yields are seldom >50%, although they can be improved with phase-transfer catalysis or increased stirring. The use of ultrasound with permanganate dihydroxylation has resulted in good yields of the diol. There is evidence that cyclic esters (**171**) are intermediates for OsO_4 dihydroxylation. This reaction is the basis of the *Baeyer test* for the presence of double bonds. The oxidation is compatible with a number of functional groups, including trichloroacetamides.

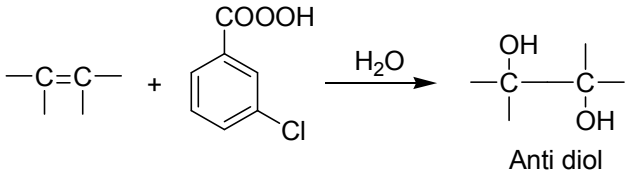




Anti hydroxylation can be achieved by treatment with H_2O_2 and formic acid. In this case, epoxidation occurs first, followed by an S_N2 reaction, which results in overall anti addition:



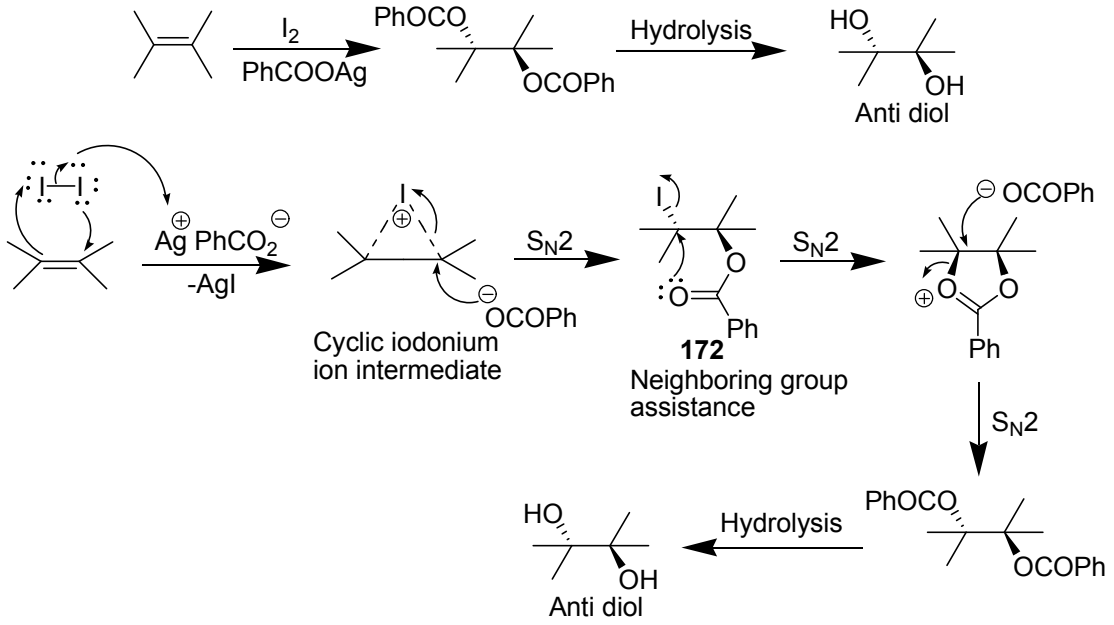
The same result can be achieved in one step with *m*-chloroperoxybenzoic acid and water.



Overall anti addition can also be achieved by the method of Prevost (the *Prevost reaction*).

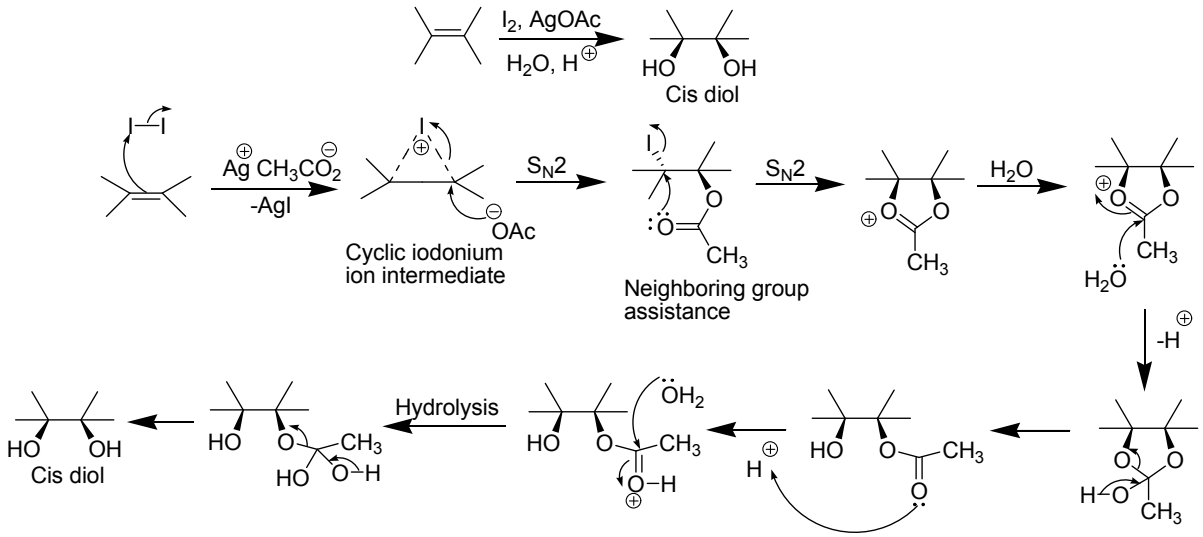
Prevost anti hydroxylation

In this method, the alkene is treated with iodine and silver benzoate in a 1:2 molar ratio. The initial addition is anti and results in a β-halo benzoate (**172**). These can be isolated, and this represents a method of addition of IOCOPh. However, under the normal reaction conditions, the iodine is replaced by a second PhCOO group. This is a nucleophilic substitution reaction, and it operates by the neighboring-group mechanism, so the groups are still anti:



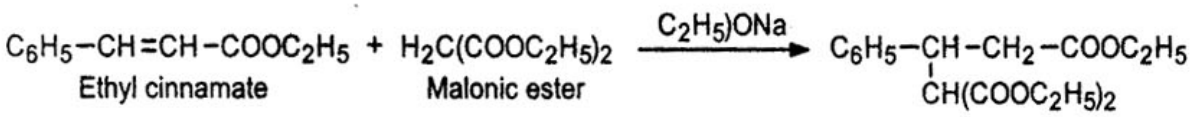
Woodward's cis (or) syn hydroxylation

The alkene is treated with iodine and silver acetate in a 1:1 molar ratio in acetic acid containing water. Here again, the initial product is a β-halo ester; the addition is anti and a nucleophilic replacement of the iodine occurs. However, in the presence of water, neighboring-group participation is prevented or greatly decreased by solvation of the ester function, and the mechanism is the normal S_N2 process, so the monoacetate is syn and hydrolysis gives the glycol that is the product of overall syn addition. Although the Woodward method results in overall syn addition, the product may be different from that with OsO_4 or $KMnO_4$, since the overall syn process is from the more-hindered side of the alkene. Both the Prevost and the Woodward methods have also been carried out in high yields with thallium (I) acetate and thallium (I) benzoate instead of the silver carboxylates. Note that cyclic sulfates can be prepared from alkenes by reaction with PhIO and SO_3.DMF.



Michael Reaction

The base-catalysed addition of compounds having active methylene group (or relatively acidic hydrogens) to an activated olefinic bond of the type –C=C–Z (Z = electron–withdrawing) is classified as Michael reaction.



The compounds having an active methylene group or having relatively acidic hydrogens are called *donors* and the compounds having an activated olefinic bond are called *acceptors*. A large variety of donors and acceptors are employed in Michael reaction.

The donors include malonic ester, cyanoacetic ester, acetoacetic ester, phenylacetic acid ester, cyanoacetamide, aliphatic nitro compounds, benzyl cyanide, sulphones, cyclopentadienes, indenes, fluorenes, etc.

The acceptors include (a) Aldehydes, e.g., acraldehyde, CH_2=CH–CHO; cinnamaldehyde, C_6H_5CH=CHCHO.

(b) Ketones, e.g., benzylideneacetone, C_6H_5CH=CHCOCH$_3$; mesityloxide, $(CH_3)_2$C = CHCOCH$_3$; quinones, etc.

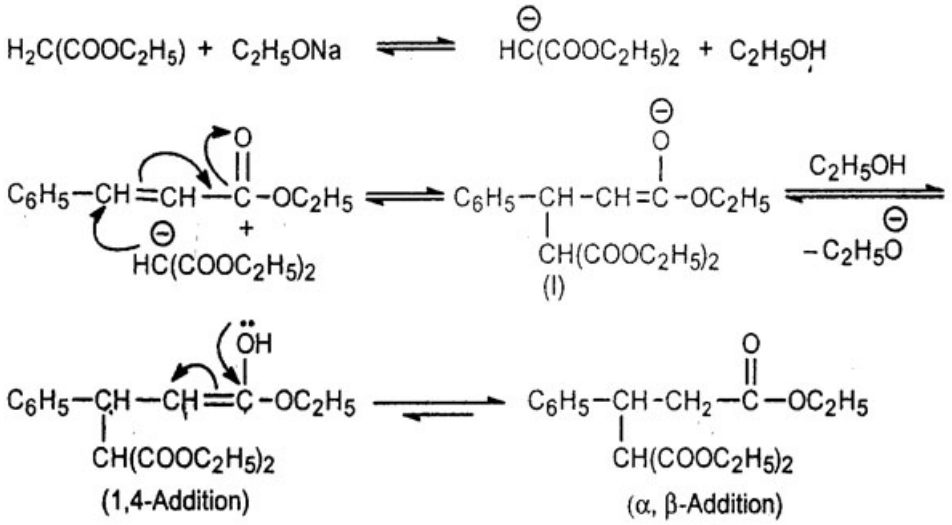
(c) Nitriles, e.g., acrylonitrile, CH_2=CH-CN.

(d) Esters of α, β-unsaturated acids, e.g., C_6H_5-CH=CH-COOC$_2$H$_5$.

Various types of basic catalysts are used. Most commonly used are alkali metal alkoxides, such as sodium or potassium ethoxides, potassium tertiary butoxide, potassium isopropoxide, etc. Mild basic catalysts such as 2° amines, 3° amines, piperidine and pyridine have been used with success.

Mechanism

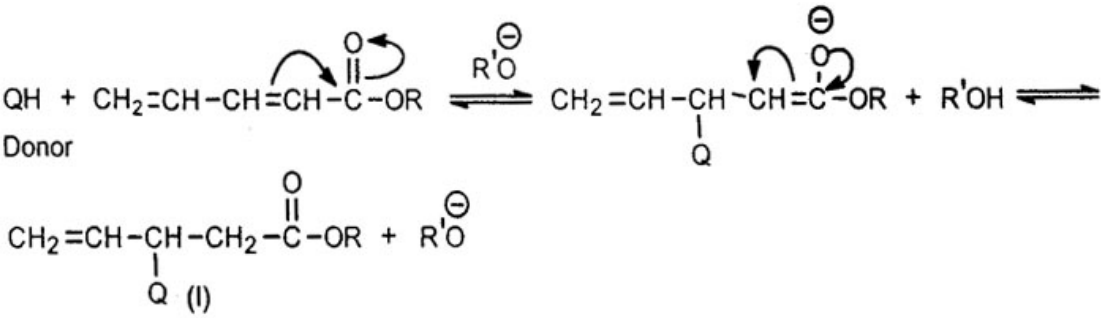
The base generates a carbanion from the donor, malonic ester. The carbanion then adds to the β-carbon of the α, β-unsaturated ester acceptor, ethyl cinnamate to yield the anion (I) which takes up a proton form alcohol to produce an enol. The enol then tautomerises to the more stable product, ketone.



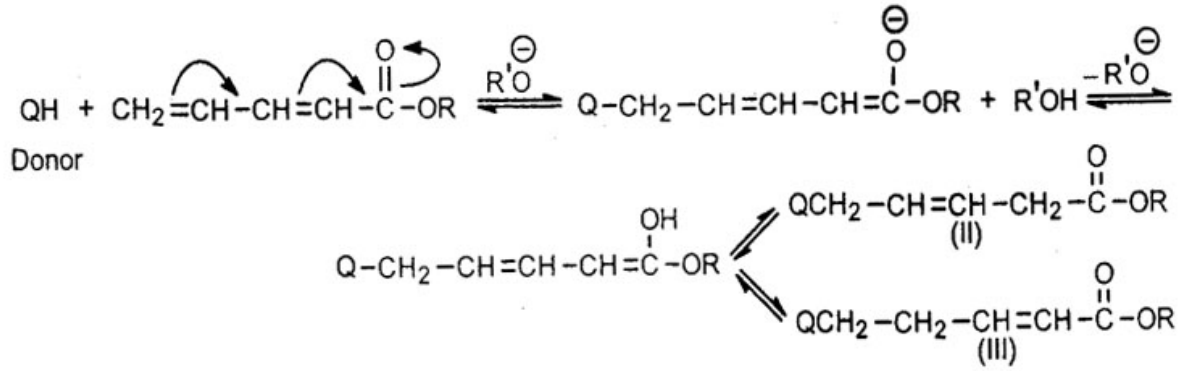
The electron-attracting group $-COOC_2H_5$ (Z) facilitates the attack by stabilizing the intermediate anion (I) by dispersal of the charge. It is seen that although 1,4-addition occurs initially, the final result is addition to the α, β-unsaturated carbons. This is because the enol reverts to the more stable ketone (recall that vinyl alcohol is unknown). In the presence of strong base, the product may undergo cyclisation. No cyclisation occurs with mild bases such as 2° or 3° amines and piperidine.

Compounds with two double bonds in conjugation with the electron-withdrawing group may undergo nucleophilic attack at β-carbon or δ-carbon to give three products. Thus:

(a) On attack at β-carbon



(b) On attack at δ-carbon



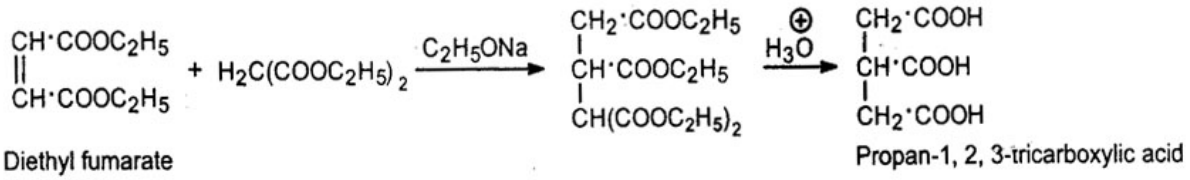
Since the double bond is conjugated in (III), it is the most stable of the three products. Hence it is the predominant product.

Applications

The reaction is of great synthetic importance since a variety of organic compounds can be synthesized with the help of this reaction.

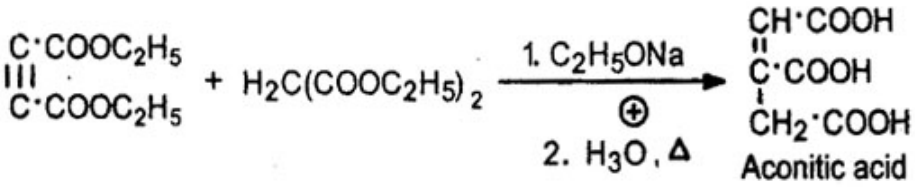
1. Synthesis of polybasic acids

(a) Tricarboxylic acids



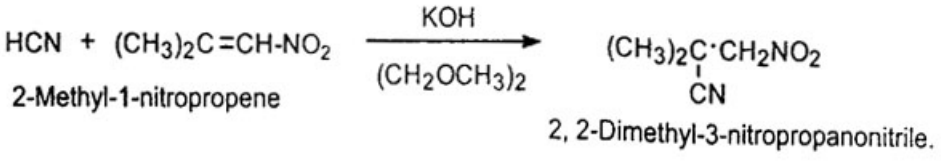
Esters of tricarboxylic acids are used as plasticisers.

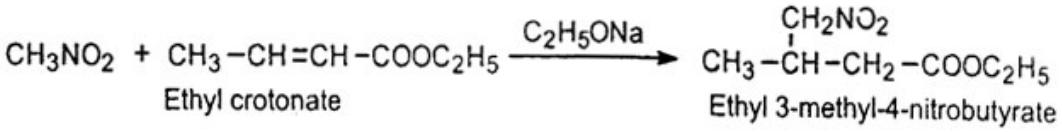
(b) Aconitic acid



Aconitic acid is used in the preparation of medicines for relieving pain (analgesic) and reducing fever (febrifuge). Its esters are used as plasticisers.

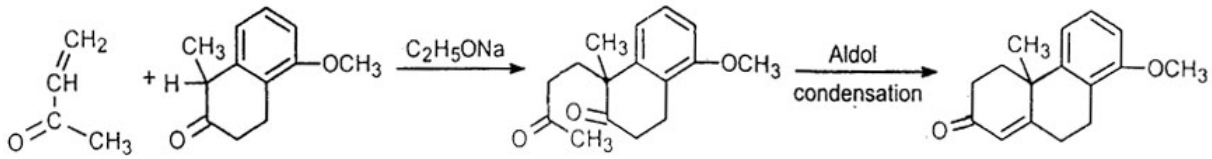
2. Preparation of cyano and nitro compounds





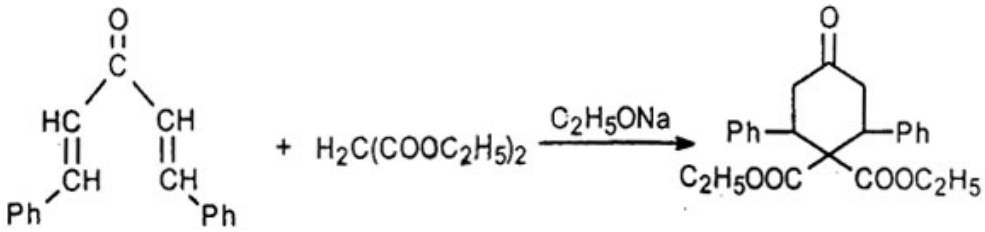
3. **Building of ring system**

(a) Condensed alicyclic ring

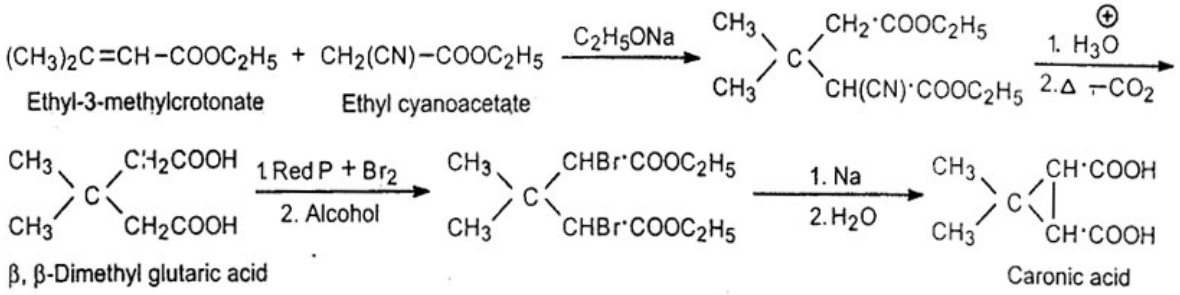


This method has been employed during the synthesis of cholesterol to build the ring system.

(b) Double Michael addition for ring formation

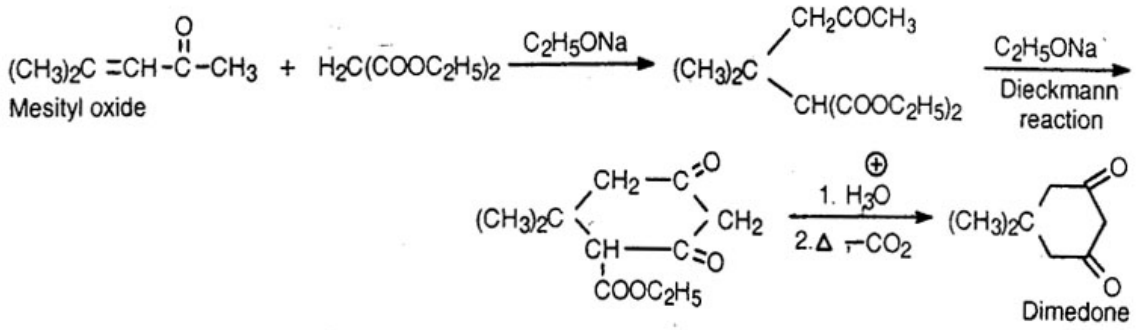


(c) Cyclopropane derivative-Caronic acid

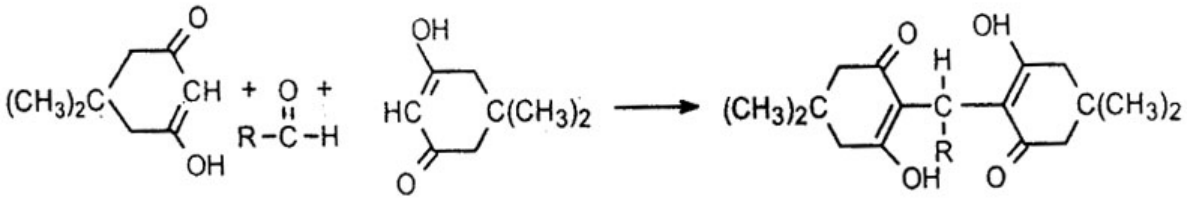


4. **Synthesis of dimedone**

Dimedone is a reagent for the identification of aldehydes in the presence of ketones.

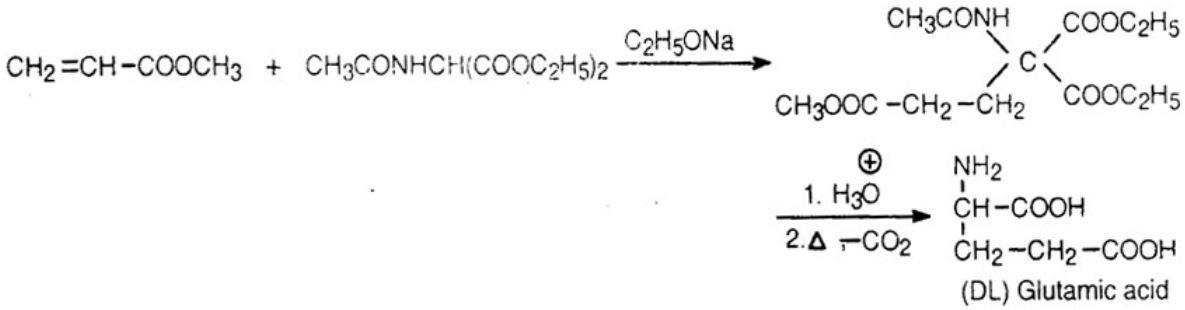


Dimedone is also employed for the separation of aldehydes from ketones because it reacts only with aldehydes.



Reaction with formaldehyde is quantitative and hence, the reagent is used for the quantitative estimation of formaldehyde.

5. Synthesis of amino acids

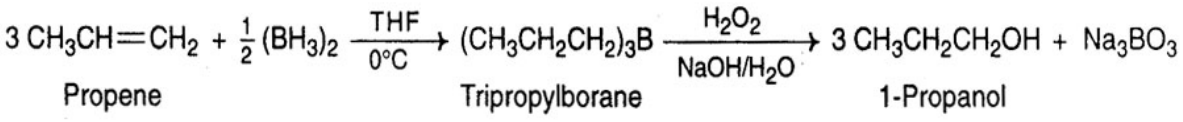


Michael reaction has been employed to synthesize anthracene from naphthalene.

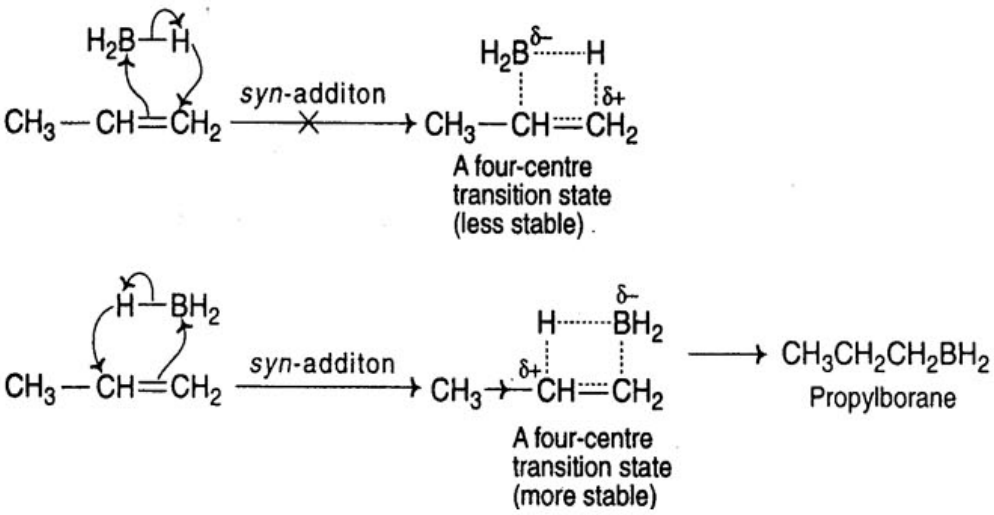
Hydroboration

Addition of water to carbon-carbon double bond in an Anti-Markownikoff fashion can be effected by an indirect, convenient and high yielding process known as hydroboration-oxidation. This two step sequence involves addition of hypothetical borane, BH_3

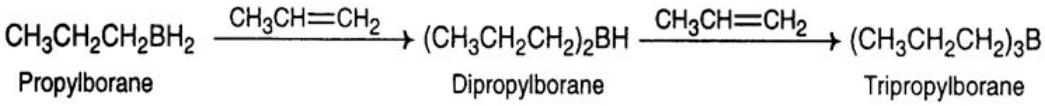
(form diborane, B_2H_6; $B_2H_6 \rightleftharpoons 2BH_3$) to the double bond followed by oxidation and hydrolysis of the resulting alkylborane with alkaline solution of hydrogen peroxide. For example:



Although borane, BH_3, is unknown, its dimer, diborane, B_2H_6, undergoes additions as if it were the monomer, borane. Because of the tendency of boron to combine with an electron pair to form an octet, borane may act as an electrophile. According to the electronegativity table, the boron-hydrogen bond is polarized in the sense that boron is the positive end and hydrogen is the negative end of the dipole. For this reason, the π-electrons of the carbon-carbon double bond attack the more electropositive boron atom; the boron atom becomes attached to the less substituted doubly-bonded carbon atom. Transfer of a hydrogen atom from boron to the other doubly-bonded carbon then completes the reaction. The addition occurs in a single-step (concerted) involving a four-centre transition state. A π-complex is formed initially by a donation of π electrons of the double bond to the vacant p orbital on boron. The π-complex then forms the transition state in which boron atom is partially bonded to the less substituted doubly-bonded carbon atom and one hydrogen atom is partially bonded to the other carbon atom. As the transition state is approached, shifting of electrons in the direction of boron atom and away from the more substituted carbon atom of the double bond occurs. Because of this, the more substituted carbon atom, which is better able to accommodate positive charge, acquires a partial positive charge. This results in a relatively stable transition state that leads to the formation of Markownikoff addition product predominantly. Also, because of steric reason boron becomes attached predominantly to the less substituted doubly–bonded carbon.

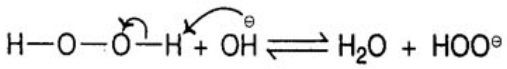


The resulting alkylborane reacts in a similar way with excess of propene to form di- and tripropylborane respectively.

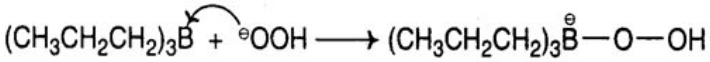


Mechanism of oxidation and hydrolysis:

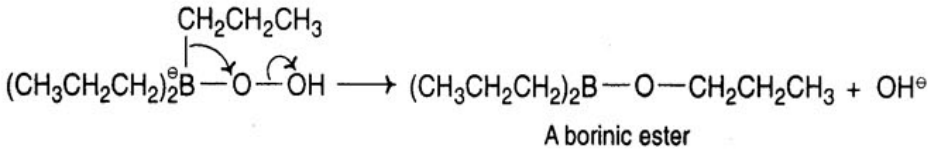
Hydrogen peroxide, in the presence of alkali, gives hydroperoxide anion $^{(-)}OOH$.



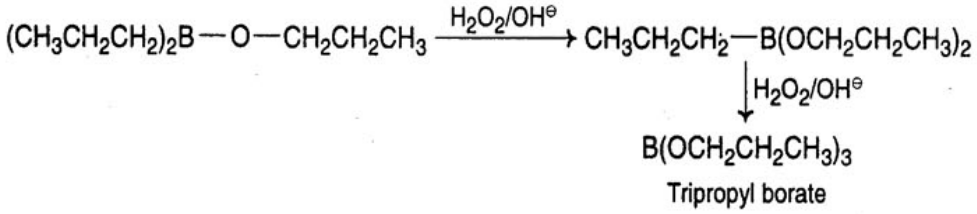
The first step of oxidation involves nucleophilic attack by the hydroperoxide anion on the electron-deficient boron atom to give tetra covalent boron intermediate.



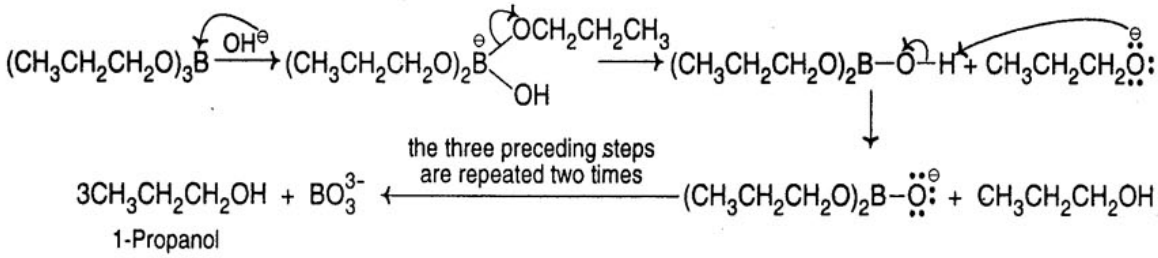
In the second step the resulting compound undergoes rearrangement. An alkyl group migrates with its bonding electrons from boron to oxygen (a 1, 2-anionic shift) and thereby displaces a hydroxide ion to form a borinic ester. The driving force for the rearrangement is the formation of the strong boron-oxygen bond.



The borinic ester reacts further by the same process to give a trialkyl borate ester.

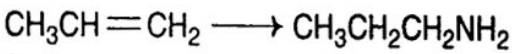


This borate ester then undergoes hydrolysis under the reaction conditions to produce three molecules of 1-propanol and borate ion.

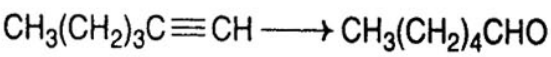


1. Give a scheme for carrying out each of the following transformations using hydroboration reaction. Give the plausible mechanistic courses of the reactions involved.

(a)

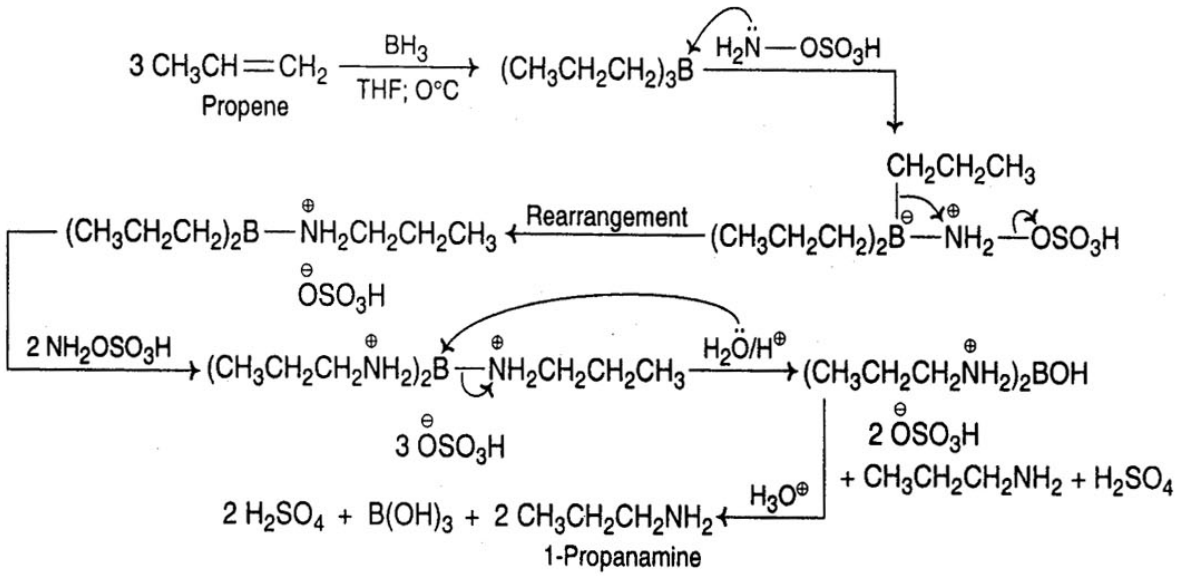


(b)

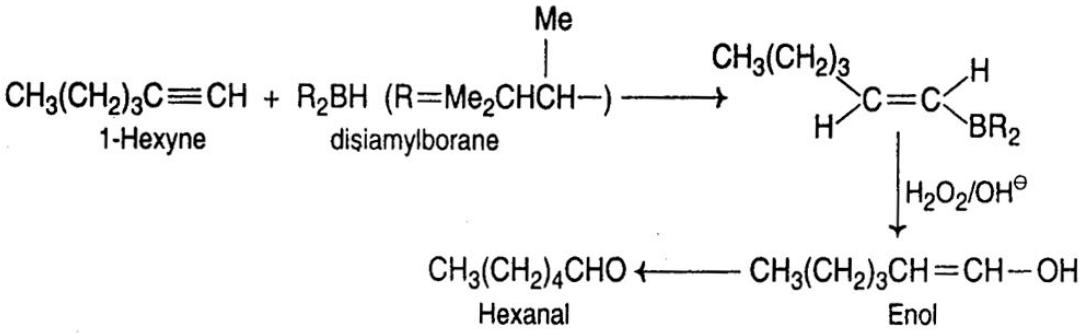


Solution:

(a) 1-Propanamine may be prepared from propene by the procedure which consists of: (1) hydroboration of propene by the usual manner, then (2) treatment of the trialkylborane with hydroxylamine-O-sulfonic acid, H_2NOSO_3H, to give an intermediate ammonium boride (which undergoes rearrangement), and finally, (3) acidic hydrolysis of the rearranged product to yield 1-propanamine.

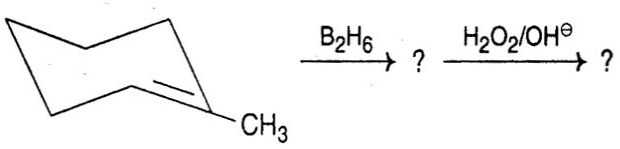


(b) 1-Hexyne may be converted to hexanal by hydroboration with di-(1,2-dimethylpropyl) borane or disiamylborane (Sia_2BH) followed by oxidative hydrolysis of the resulting vinylborane with alkaline hydrogen peroxide (the name 'disiamyl' comes from "di-secondary-iso-amyl"). This bulky borane is a very selective hydroborating agent. When it reacts with this terminal alkyne, boron becomes attached to the less crowded terminal carbon predominantly. Also, using Sia_2BH hydroboration can be stopped at the alkenylborane stage which is otherwise very difficult by using diborane.

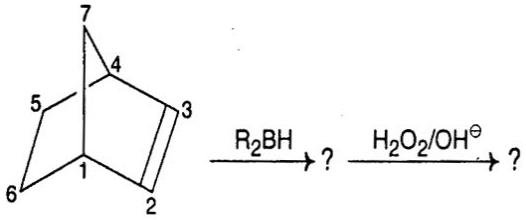


2. Predict the products in each step of the following reaction sequences. Give stereochemistry when it is appropriate.

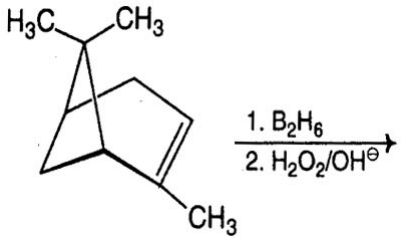
(a)



(b)

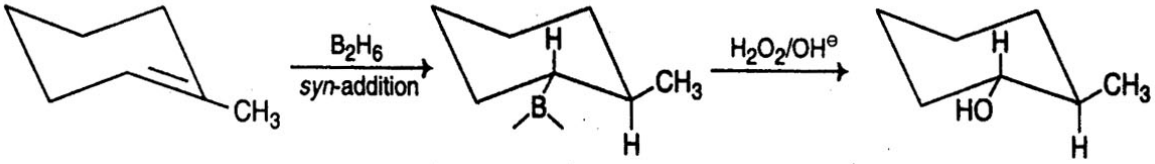


(c)

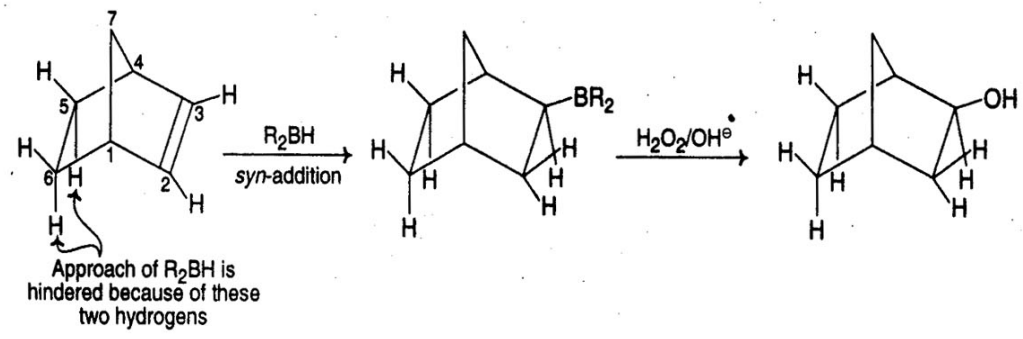


Solution:

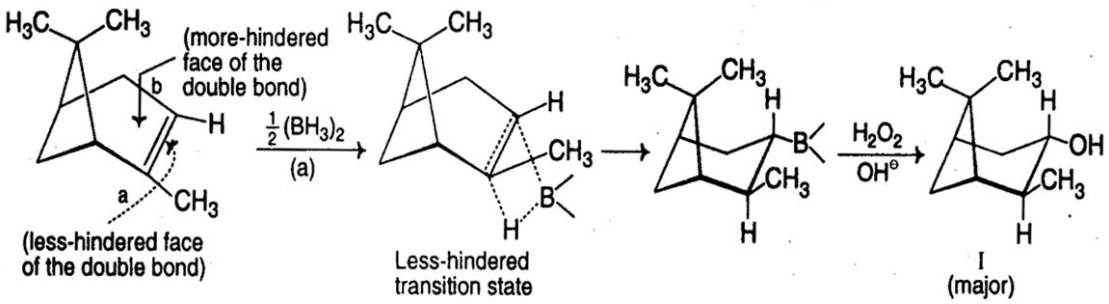
(a) The addition of BH_3 to the double bond is stereospecifically syn and the conversion of the C-B bond to the C-O bond by oxidative hydrolysis proceeds with retention of configuration. Hence the products of this reaction sequence are as follows:



(b) When there is a choice, hydroboration occurs preferentially from the less crowded side of the double bond. In this bicyclic compound the lower side of the double bond is more hindered than the upper side because of two hydrogens at C-5 and C-6 respectively.



(c)



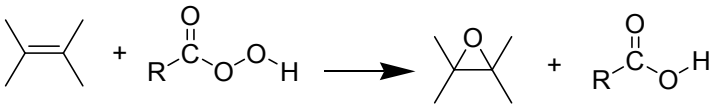
The addition of BH_3 occurs preferably from the less-hindered face of the double bond to give mainly the alcohol **I**.

UNIT-II-Part-II

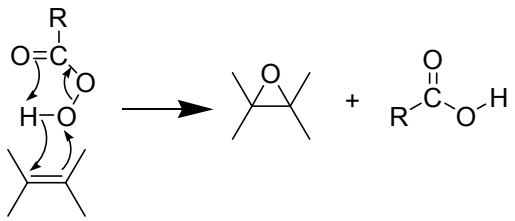
Addition reactions: Electrophilic, nucleophilic and free radical addition to double and triple bonds - hydration, hydroxylation, Michael addition, hydroboration and epoxidation.

Addition reactions to carbonyl compounds – Mannich reaction, Meerwein Pondroff-Verley reduction, Grignard, Claisen, Dieckmann, Stobbe, Knovenagel, Darzen, Wittig, Thorpe and Benzoin reactions.

Epoxidation



Alkenes can be epoxidized with many peroxyacids, of which *m*-chloroperoxybenzoic has been the most often used. The reaction, called the *Prilezhaev reaction*, has wide utility. Alkyl, aryl, hydroxyl, ester, and other groups may be present, although not amino groups, since these are affected by the reagent. Electron-donating groups increase the rate, and the reaction is particularly rapid with tetraalkyl alkenes. Conditions are mild and yields are high. Other peroxyacids, especially peroxyacetic and peroxybenzoic, are also used; trifluoroperoxyacetic acid and 3,5-dinitroperoxybenzoic acid are particularly reactive ones. Transition metal catalysts can facilitate epoxidation of alkenes at low temperatures or with alkenes that may otherwise react sluggishly. Magnesium monoperoxyphthalate (MMPP) is commercially available, and has been shown to be a good substitute for *m*-chloroperoxybenzoic acid in a number of reactions.



177

The one-step mechanism involving a transition state, such as **177**, was proposed by Bartlett:

Evidence for this concerted mechanism is as follows:

(1) The reaction is second order. If ionization were the rate-determining step, it would be first order in peroxyacid.

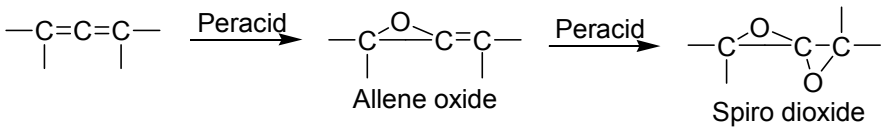
(2) The reaction readily takes place in nonpolar solvents, where formation of ions is inhibited.

(3) Measurements of the effect on the reaction rate of changes in the substrate structure show that there is no carbocation character in the transition state.

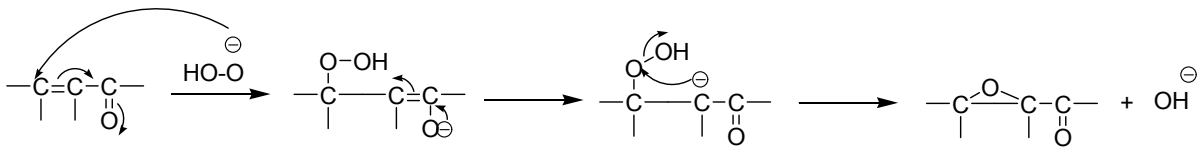
(4) The addition is stereospecific (i.e., a trans-alkene gives a trans-epoxide and a cis-alkene a cis epoxide) even in cases where electron-donating substituents would stabilize a hypothetical carbocation intermediate.

However, where there is an OH group in the allylic or homoallylic position, the stereospecificity diminishes or disappears, with both cis and trans isomers giving predominantly or exclusively the product where the incoming oxygen is syn to the OH group. This probably indicates a transition state in which there is hydrogen bonding between the OH group and the peroxy acid.

Conjugated dienes can be epoxidized (1,2-addition), though the reaction is slower than for corresponding alkenes, but α,β-unsaturated ketones do not generally give epoxides when treated with peracids. However, α,β-unsaturated esters react normally to give glycidic esters. When a carbonyl group is in the molecule but not conjugated with the double bond, the Baeyer-Villiger oxidation may compete. Allenes are converted by peracids to allene oxides or spiro dioxides both of which species can in certain cases be isolated but more often are unstable under the reaction conditions and react further to give other products.



The epoxidation of α,β-unsaturated ketones with hydrogen peroxide under basic conditions is known as the *Waits–Scheffer epoxidation*, discovered in 1921. This fundamental reaction has been extended to α,β -unsaturated ketones (including quinones), aldehydes, and sulfones. This is a nucleophilic addition by a Michael-type mechanism, involving attack by HO_2^-.



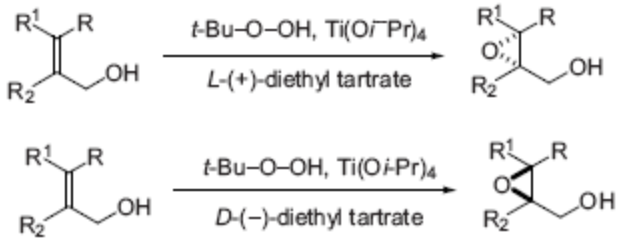
Sharpless asymmetric epoxidation

Allylic alcohols can be converted to epoxy-alcohols with *tert*-Butyl hydroperoxide on molecular sieves or with peroxy acids.The addition of an appropriate chiral ligand to the metal-catalyzed hydroperoxide epoxidation of allylic alcohols leads to high

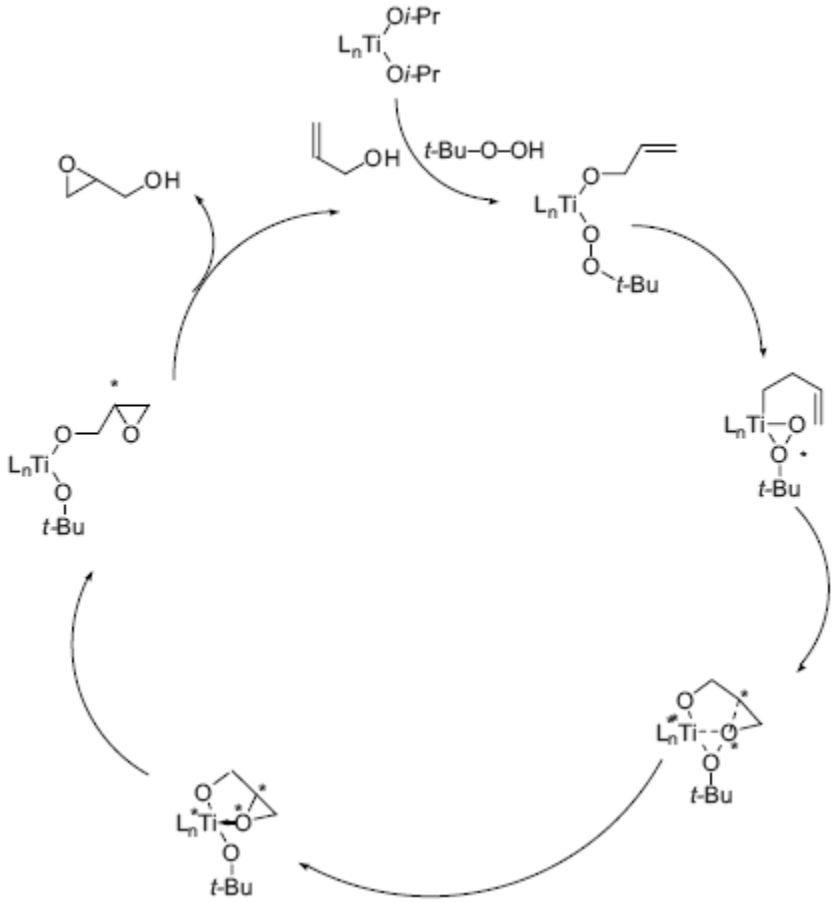
enantioselectivity. This important modification is known as the *Sharpless asymmetric epoxidation*, where allylic alcohols are converted to optically active epoxides with excellent enantioselectivity by treatment with *t*-BuOOH, titanium tetraisopropoxide and optically active diethyl tartrate. The $Ti(OCHMe_2)_4$ and diethyl tartrate can be present in catalytic amounts (15–10 mol%) if molecular sieves are present. Polymer-supported catalysts have also been reported.

Both (+) and (-) diethyl tartrate are readily available, so either enantiomer of the product can be prepared. The method has been successful for a wide range of primary allylic alcohols, including substrates where the double bond is mono-, di-, tri-, and tetrasubstituted, and is highly useful in natural product synthesis. The mechanism of the Sharpless epoxidation is believed to involve attack on the substrate by a compound formed from the titanium alkoxide and the diethyl tartrate to produce a complex that also contains the substrate and the *t*-BuOOH.

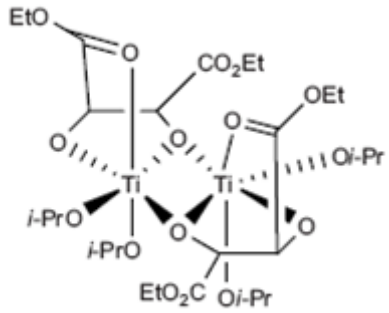
Enantioselective epoxidation of allylic alcohols using *t*-butyl peroxide, titanium tetra-*iso*-propoxide, and optically pure diethyl tartrate.



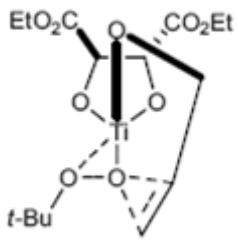
The catalytic cycle:



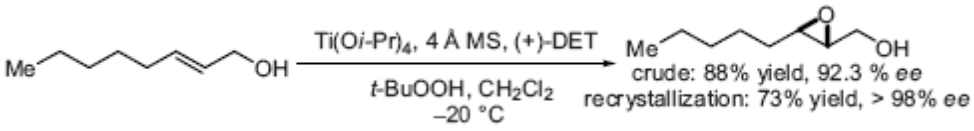
The putative active catalyst:



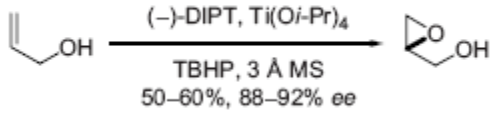
The transition state:



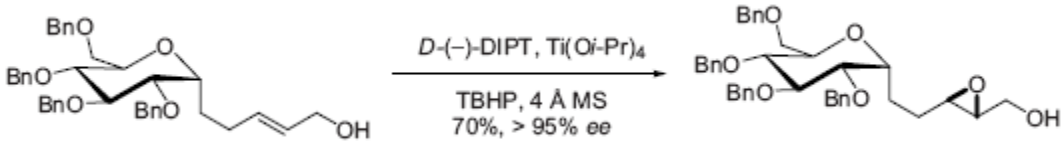
Example **1**



Example **2**

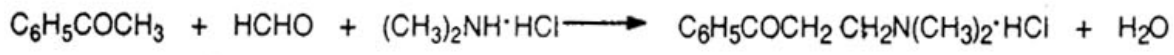


Example **3**

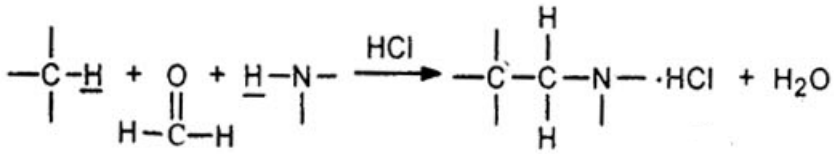


Mannich Reaction

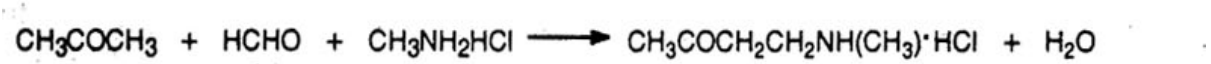
The condensation of a compound containing active hydrogen with formaldehyde and ammonia or 1° or 2° amines usually as their hydrochlorides (HCl being used as catalyst) to form aminomethyl or substituted aminomethyl derivatives is known as Mannich reaction. The base, called Mannich base, is usually isolated as its hydrochloride. Aryl amines do not normally respond to this reaction.

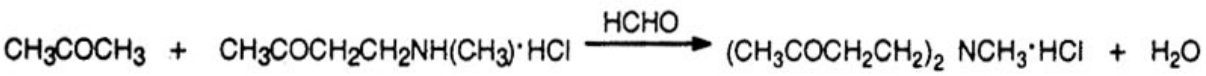


Thus, the overall reaction is (active hydrogens underlined):



With ammonia or primary amines, the reaction may proceed further since the first formed Mannich base still contains hydrogen on the nitrogen atom, i.e., active hydrogen.





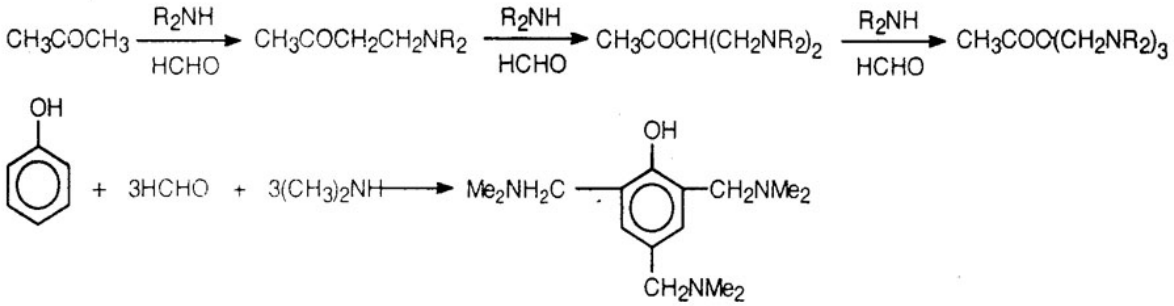
Hence, 2° amine is preferred for the reaction.

Similarly, three successive reactions with ammonia give a 3° amine.

Thus, with a 1° or 2° amine, the reaction may proceed further to give a 3° amine.

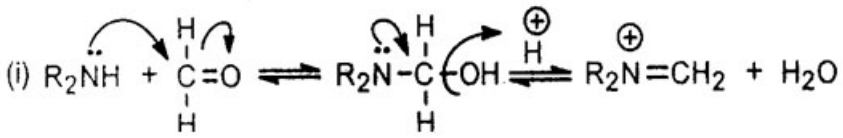
The compounds containing active hydrogens which react include aldehydes, ketones, esters, phenols, nitroalkanes, α-and γ-methyl pyridines, α-and γ-methyl quinolines, acetylenes, etc.

Ketones with active hydrogen are more commonly used. If the compound contains more than one active hydrogen, all of them may be substituted by amino methyl groups.

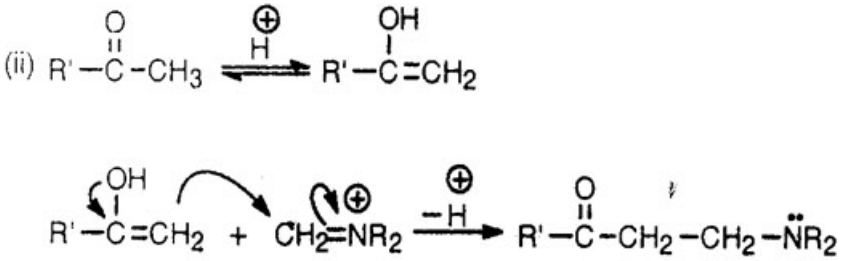


Mechanism

It is suggested that in the first step, the amine and HCHO in the presence of (H^+) condense to form imminiumcation.

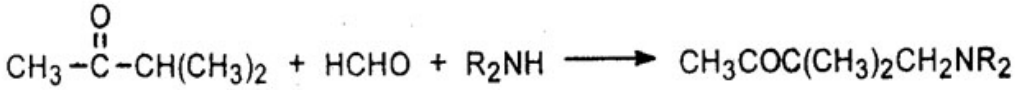


It is then attacked by the enolate anion of the active hydrogen compound in the second step to form the Mannich base.



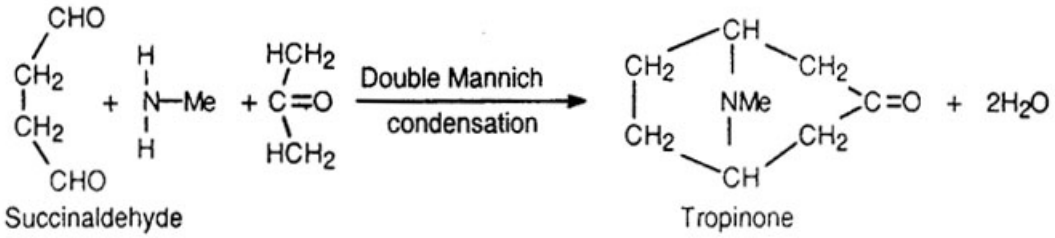
Base has also been used as catalyst.

With unsymmetrical ketones the more highly alkylated α-carbon is substituted by the aminomethyl group. This is due to the more acidic character of the hydrogen on the more highly alkylated carbon and for that matter due to more facile enolisation.

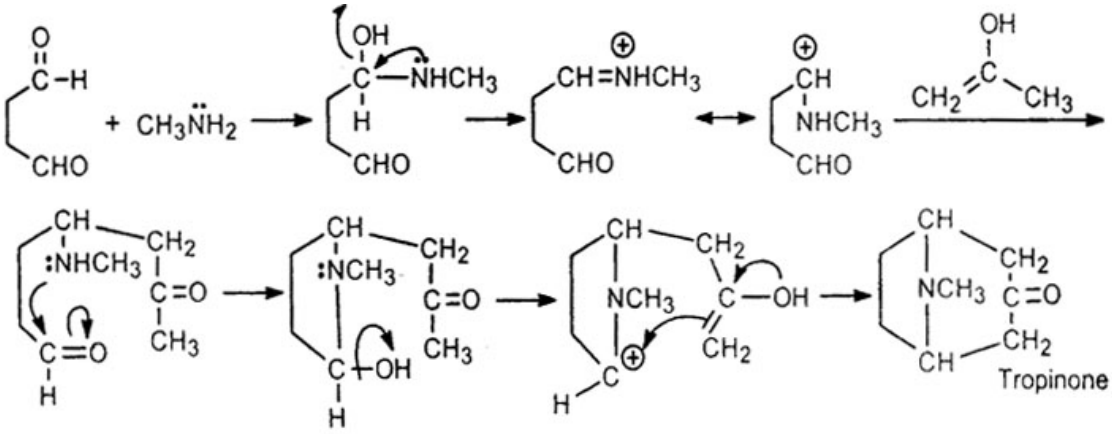


Applications

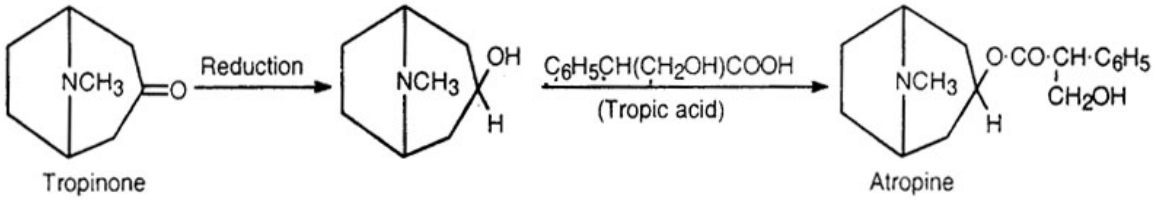
1. Many important natural products, especially alkaloids, have been synthesized by this reaction. A classical example is Robinson's synthesis of tropinone by a double Mannich condensation and subsequent synthesis of atropine.



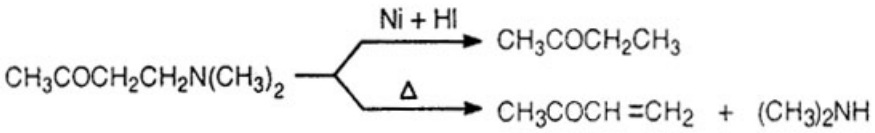
Mechanism



Better yield of tropinone is obtained by the use of calcium acetone dicarboxylate in place of acetone.

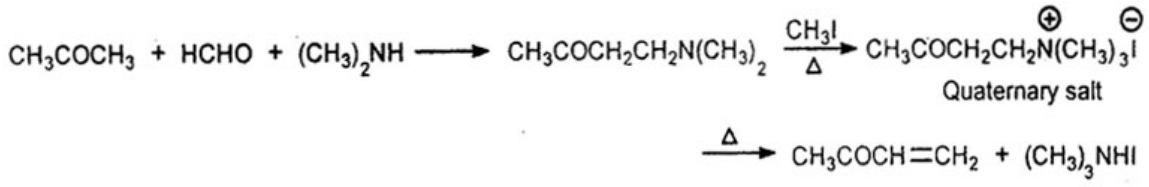


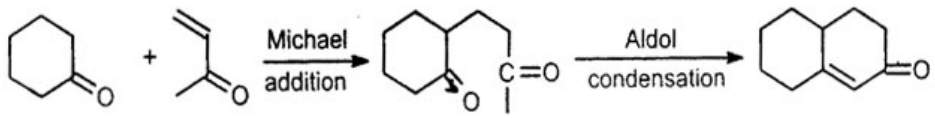
2. Decomposition to saturated and unsaturated ketones on reduction and on heating respectively.



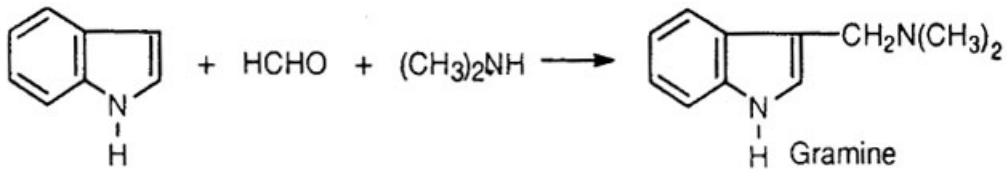
Quaternary salts give better yield of unsaturated ketones on heating. The reaction is useful for introducing vinyl group.

3. Building up of ring system–The easy elimination of R_2NH from Mannich base has synthetic applications. Thus, the unsaturated ketones obtained by heating the quaternary salts may be used for building ring systems.

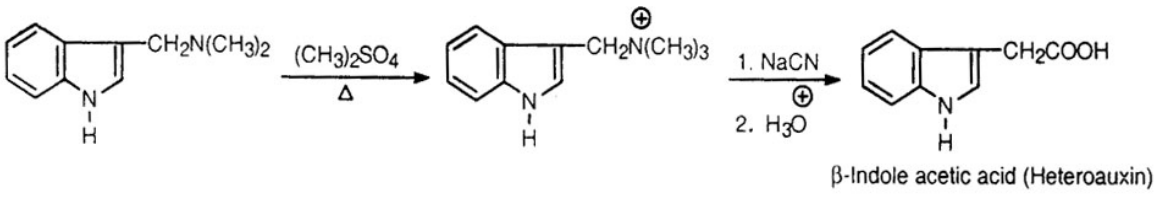




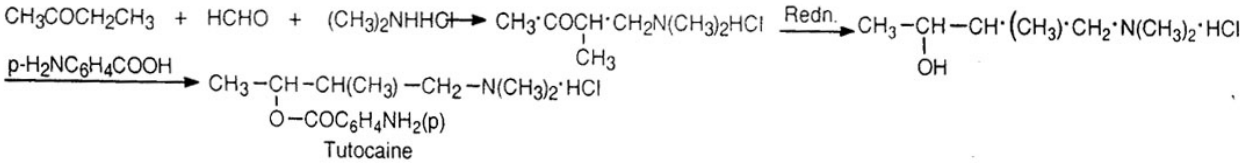
4. The imminium salt, being a strong electrophile, replaces the active hydrogens of indole, phenol, nitroalkane, etc., e.g.,



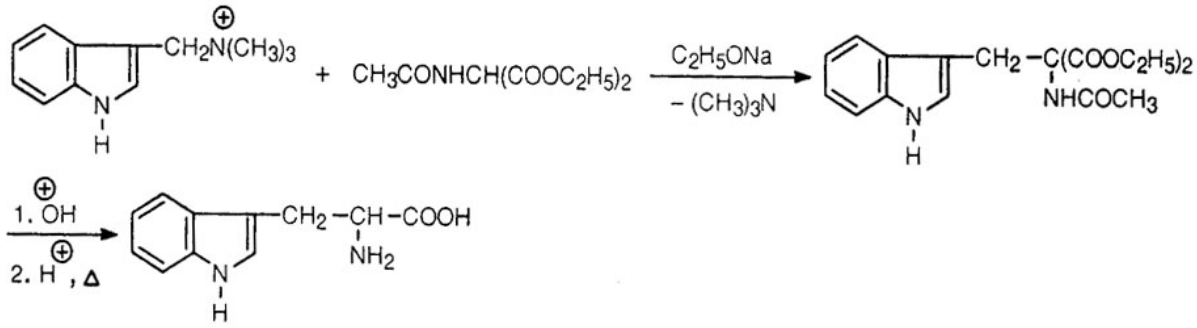
The product may be quaternised and the amino group may be substituted by other groups.



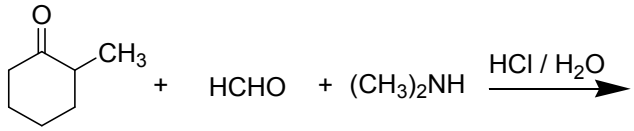
5. Tutocaine, a commercially useful anaesthetic, is prepared as below.



6. Synthesis of tryptophan–The amino acid, tryptophan is synthesized from the quaternary salt of gramine (see 4 above) and acetamidomalonic ester.

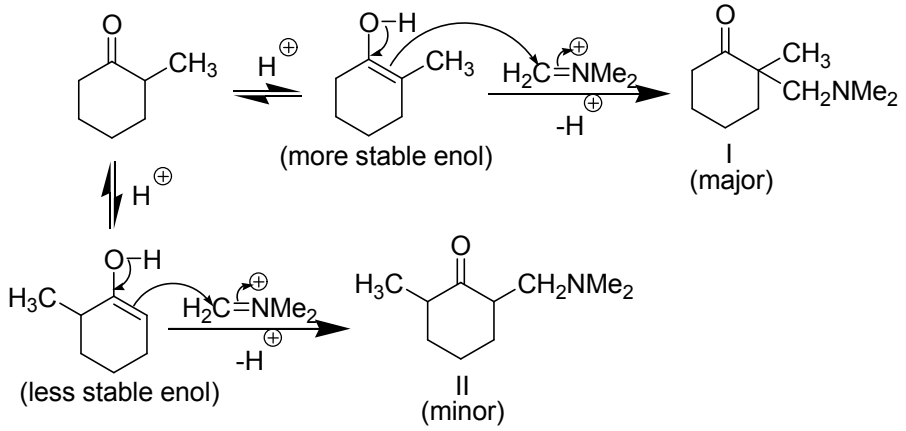


1. Predict the major product in the following reaction and give you reasoning:



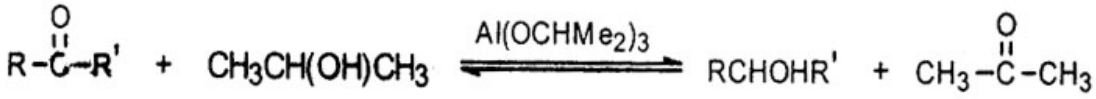
Solution:

The more substituted enol is thermodynamically more stable. It thus follows that this unsymmetrical ketone reacts with the iminium ion mainly through the more substituted enol to give the Mannich base I as the major product.



Meerwein-ponndorf-verley reduction

The reaction involves the reduction of aldehydes or ketones to alcohols by treatment with aluminium isopropoxide in excess of isopropyl alcohol.

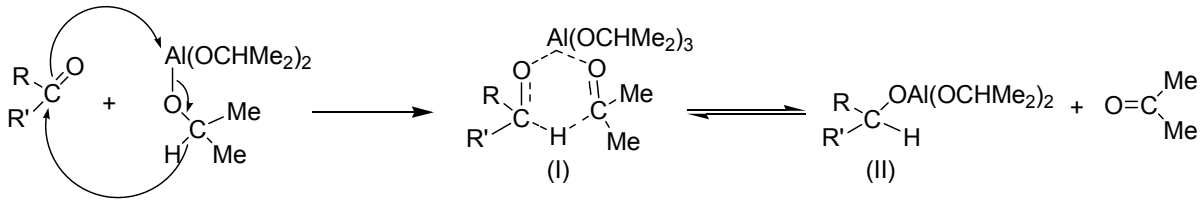


The reaction is reversible. The reverse reaction called, Oppenauer oxidation, is employed for the oxidation of alcohols, using aluminium t-butoxide as catalyst in the presence of excess acetone.

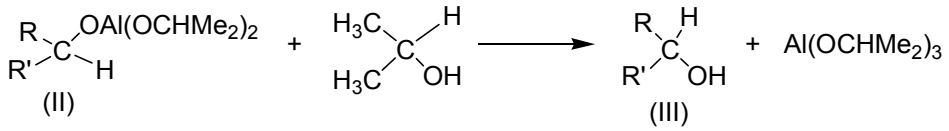
The reaction shifts in the forward direction by the removal of acetone by distillation. The reaction occurs under mild condition, is rapid, side reactions are negligible and the yield is high. The reaction is specific for carbonyl group, other reducible groups such as olefinic bonds, NO_2 etc., present in the substrate remain unaffected. If a compound contains two carbonyl groups, one may be protected by acetal formation and the other is then reduced. Ketones with high enol content, eg., β-ketoesters, β-diketones, etc., do not give this reaction.

Mechanisms

The reaction probably involves a cyclic transition state (I) in which a hydride ion from the α-CH bond of the alkoxide migrates to the carbonyl carbon of the ketone to yield the mixed alkoxide (II).



An excess of isopropyl alcohol is used so that it exchanges with the mixed alkoxide (II) to liberate the reduced ketone (III), i.e., the desired alcohol.



Thus, for the reduction one hydrogen is supplied by the catalyst and the other hydrogen by the solvent.

That a hydride ion is transferred from aluminium isopropoxide to the ketone is proved by the fact that when $Al(ODCMe_2)_3$ is used, the ketone is reduced to alcohol, R_2CDOH, which contains deuterium. This indicates that the reaction is proceeding via a cyclic transition state as shown above.

Specificity of aluminum isopropoxide

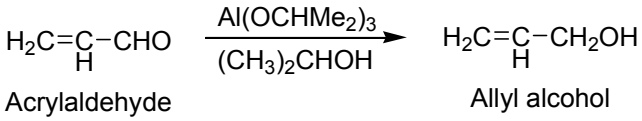
A number of metal alkoxide have been used but aluminum isopropoxide is found to be the best reagent.

Aluminium alkoxides are much less polar than alkali metal alkoxides since, aluminum-oxygen bond is nearly covalent in nature. Hence, this undergoes very little dissociation to give alkoxide ions which generally cause some polymerization of the carbonyl compounds, specially the sensitive aldehydes. Thus, the side reactions are negligible. Its boiling point is 140-150ºC (12 mm). This enables acetone to be distilled over so as to shift the equilibrium in the forward direction.

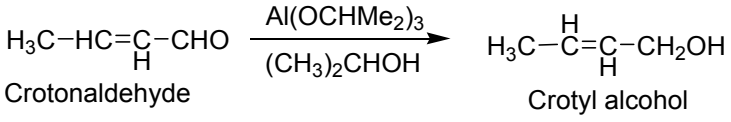
Applications

The reduction has many useful applications

1. The reduction has been employed to reduce α, β-unsaturated aldehydes to α, β-unsaturated alcohols.

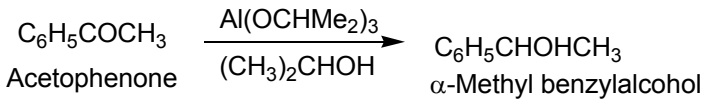


Acrylaldehyde — Allyl alcohol



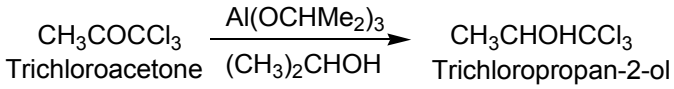
Crotonaldehyde — Crotyl alcohol

2. Reduction of aromatic ketones



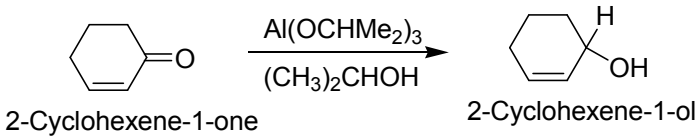
Acetophenone — α-Methyl benzylalcohol

3. Reduction of α-halogenated ketones



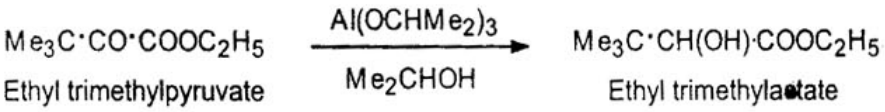
Trichloroacetone — Trichloropropan-2-ol

4. Reduction of alicyclic ketones



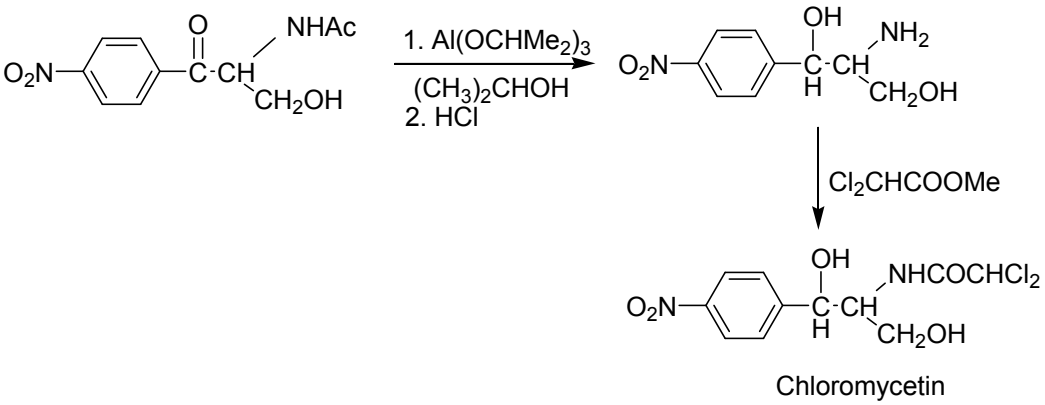
2-Cyclohexene-1-one — 2-Cyclohexene-1-ol

5. Reduction of ketoesters

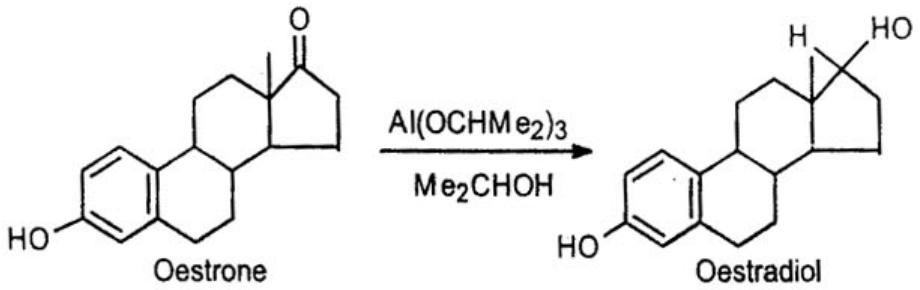


6. The reduction has been helpful during the course of synthesis of chloromycetin and oestradiol.

(a)



(b)



Grignard reaction

1. What are Grignard reagents? How are they prepared? Give the plausible mechanism by which the Grignard reagents are formed.

Solution:

Grignard reagents are organomagnesium halides having the general formula R-MgX, where R is a hydrocarbon group such as alkyl (1°, 2 ° or 3°), allylic, aralkyl or aryl and X is Cl, Br, or I.

Grignard reagents are usually prepared by the reaction of an organic halide and magnesium turnings in alcohol-free ether.

$$R{-}X + Mg \xrightarrow{\text{dry ether}} R{-}MgX$$

A Grignard reagent

Available evidence suggest that the formation of a Grignard reagent involves the following SET (single electron transfer) mechanism:

Step I : $R{:}\ddot{X}{:} + \dot{M}g\cdot \longrightarrow [R{:}\ddot{X}{:}]^{\cdot-} + \overset{\oplus}{M}g\cdot$

Alkyl halide; Anion radical

Step II : $[R{:}\ddot{X}{:}]^{\cdot-} \longrightarrow \dot{R} + {:}\ddot{X}{:}^{\ominus}$

Alkyl radical

Step III : ${:}\ddot{X}{:}^{\ominus} + \overset{\oplus}{M}g\cdot \longrightarrow XMg\cdot$

Step IV : $\dot{R} + XMg\cdot \longrightarrow RMgX$

2. Discuss the Grignard synthesis of (i) alcohols, (ii) carboxylic acids, (iii) aldehydes and (iv) ketones.

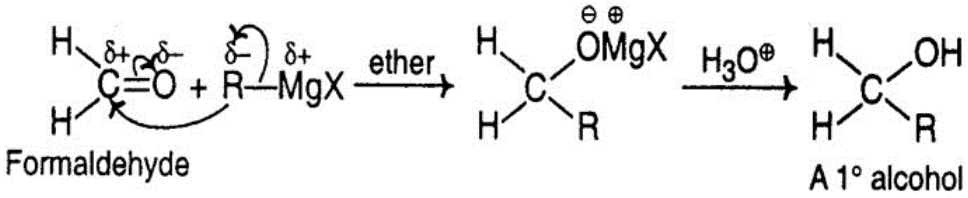
Solution:

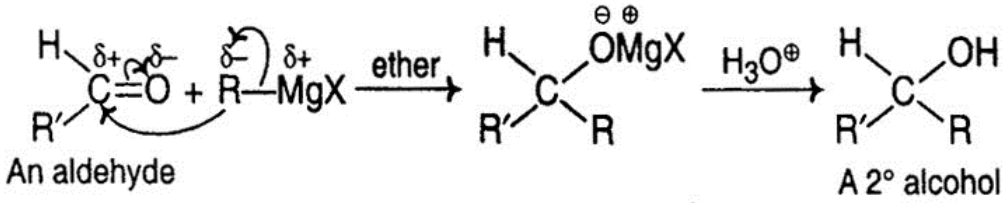
(i) The Grignard reagent behaves as if it contained a carbanion. The nucleophilic hydrocarbon group attacks the carbonyl carbon of an aldehyde or ketone to form a halomgnesium alkoxide which is subsequently converted to the corresponding alcohol simply by the addition of water or dilute mineral acid. The sequence may be shown as follows:

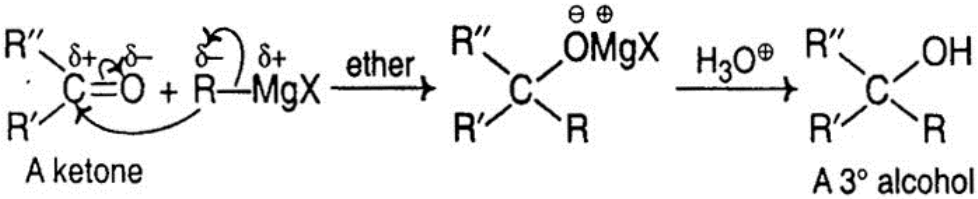
$$\underset{\text{A carbonyl compound}}{>C^{\delta+}=O^{\delta-}} + \underset{\text{A Grignard reagent}}{R^{\delta-}{-}Mg^{\delta+}X} \xrightarrow{\text{ether}} \underset{\text{A halomagnesium alkoxide}}{>C(R)(O^{\ominus}MgX^{\oplus})} \xrightarrow[\text{dil.HCl}]{[H{-}O^{\oplus}H_2]Cl^{\ominus}} \underset{\text{An alcohol}}{>C(R)(OH)} + H_2O + Mg^{2\oplus} + x^{\ominus} + Cl^{\ominus}$$

From the above general scheme, it is evident that the class of alcohol obtained from a Grignard reagent and a carbonyl compound depends on the number of hydrogen atoms attached to the carbonyl carbon atom, i.e., upon the type of the carbonyl compound used.

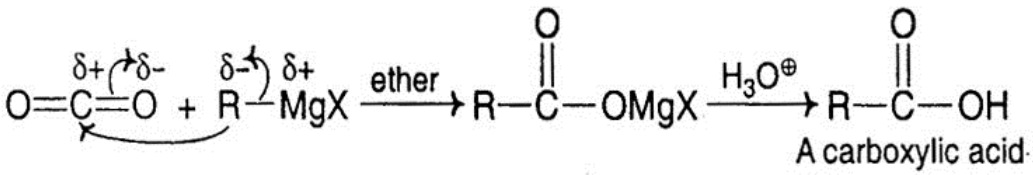
Formaldehyde, HCHO (the carbonyl carbon bears two hydrogens) yields primary alcohols; other aldehydes, RCHO (the carbonyl carbon bears one hydrogen) yields secondary alcohols; and ketones, R_2CO (the carbonyl carbon bears no hydrogen) yield tertiary alcohols.



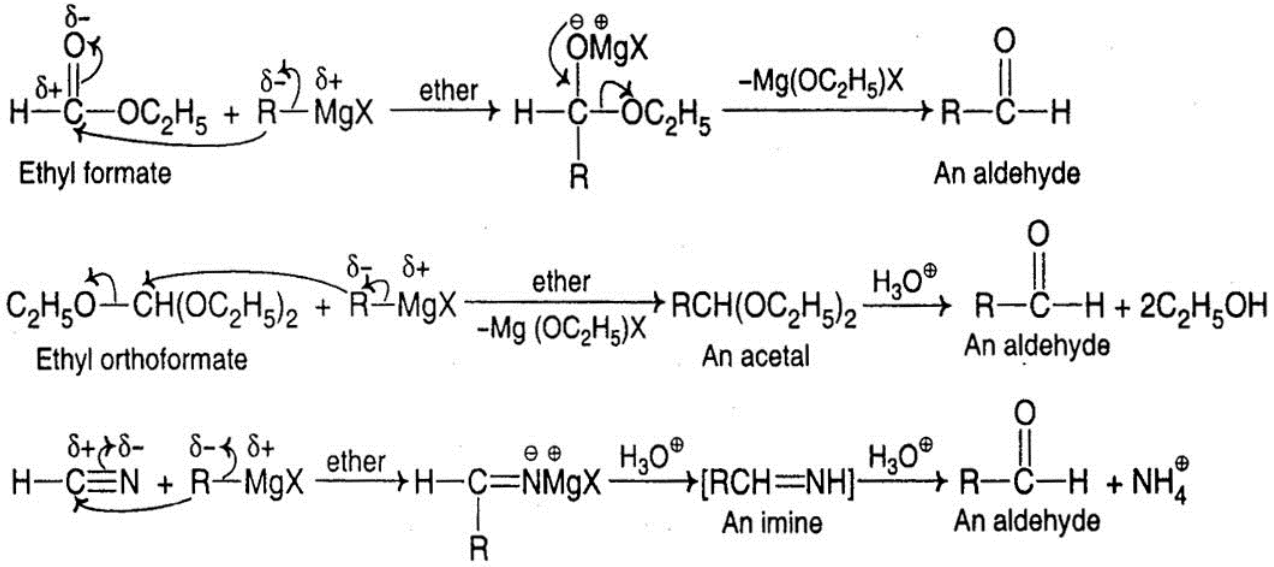




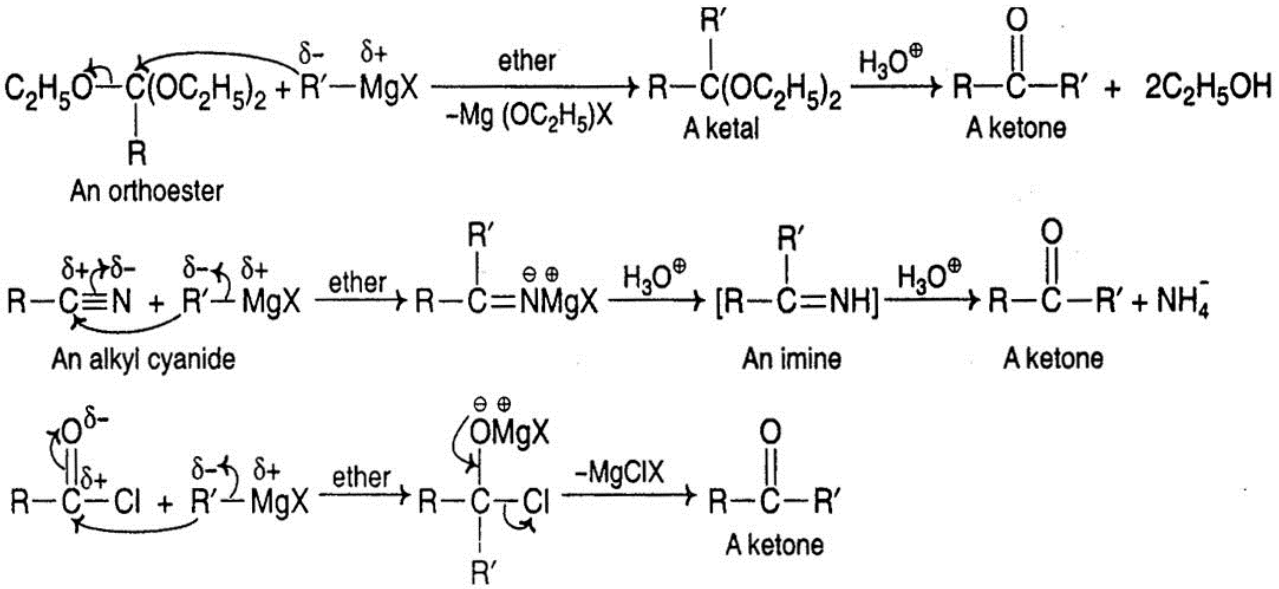
(ii) A Grignard reagent reacts with carbon dioxide to give a carboxylic acid.



(iii) A Grignard reagent (1 mole) reacts with ethyl formate (1 mole) or ethyl orthoformate (1 mole) or HCN (1 mole) to give an aldehyde.



(iv) A Grignard reagent (1 mole) reacts with an orthoester (1 mole) or an alkyl cyanide (1 mole) or an acyl chloride (1 mole) to give a ketone.



3. Discuss the limitations of the Grignard synthesis

Solution:

In planning a Grignard synthesis of an alcohol, it is to be noted that (a) the Grignard reagent must be stable, and (b) the substrate must contain only one function group capable of reacting with the Grignard reagent. Since the Grignard is a very strong base, it reacts rapidly with compounds containing hydrogen attached to an electronegative element such as oxygen, nitrogen, sulphur, or even triply bonded carbon. Thus, we cannot, for example, prepare a Grignard reagent from a compound containing –OH, -NH_2, -SH, -COOH, -SO_3H or, -C≡CH

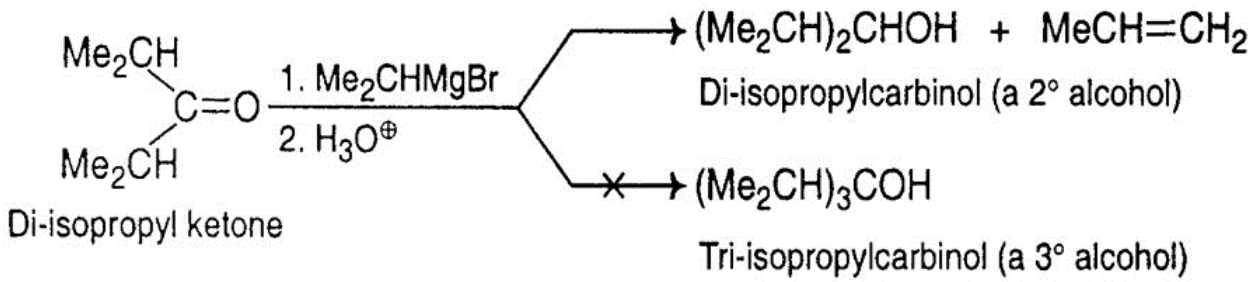
group. Since the Grignard reagent is a powerful nucleophile, it reacts rapidly with nearly every organic compound containing a carbon-oxygen or carbon-nitrogen multiple bond. Thus, we cannot prepare a Grignard reagent from any organic halide containing a >C=O, -COOR, -COX, -$CONH_2$, or -CN group. Since an epoxy group opens up by a Grignard reagent and a –NO_2 group is reduced by a Grignard reagent, these two groups also must not be present in the halide molecule. A Grignard reagent reacts rapidly with O_2, CO_2 and water vapour. So the reaction system is to be protected from O_2, CO_2 and moisture of the air. The alkyl halide, the carbonyl compound and the ether used as solvent must be scrupulously dry and alcohol free. The apparatus must also be completely dry.

The aldehydes or ketones with which a Grignard reagent is to react must be free of any other groups that might react with Grignard reagent. The acidic functional groups simply destroy the Grignard reagent by a process that does not alter the functional group in a significant way. The difficulty can be overcome by using an excess of the Grignard reagent. The other type of interfering functional group (such as –COOR, -COX, etc.,) also destroys the Grignard reagent, but, in doing so, the group itself is permanently destroyed. Use of an excess of the Grignard reagent does not solve this problem.

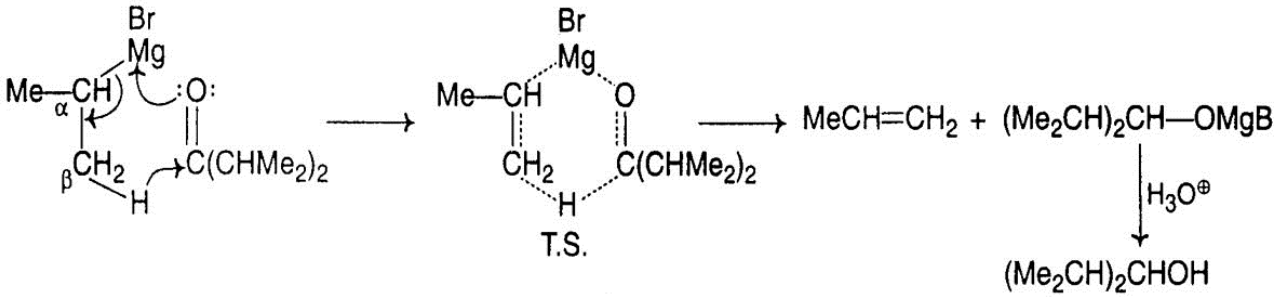
4. (a) How and when does a Grignard reagent show reducing property?

Solution:

When the R group of the Grignard regent and the groups attached to the carbonyl carbon of a ketone are highly branched, normal addition reaction does not take place due to steric reason. In that case, reduction takes place if the Grignard reagent contains a hydrogen on the carbon adjacent to the point of attachment of –MgX (i.e., a β hydrogen). For example, when isopropylmagnesium bromide is added to di-isopropyl ketone, no tri-isopropylcarbinol (a 3° alcohol) is obtained instead di-isopropylcarbinol (a 2° alcohol) is obtained through reduction.



This abnormal reaction may be explained by the transfer of a hydride ion ($H^{\ominus}$) from the Grignard reagent via a six-membered cyclic transition state.

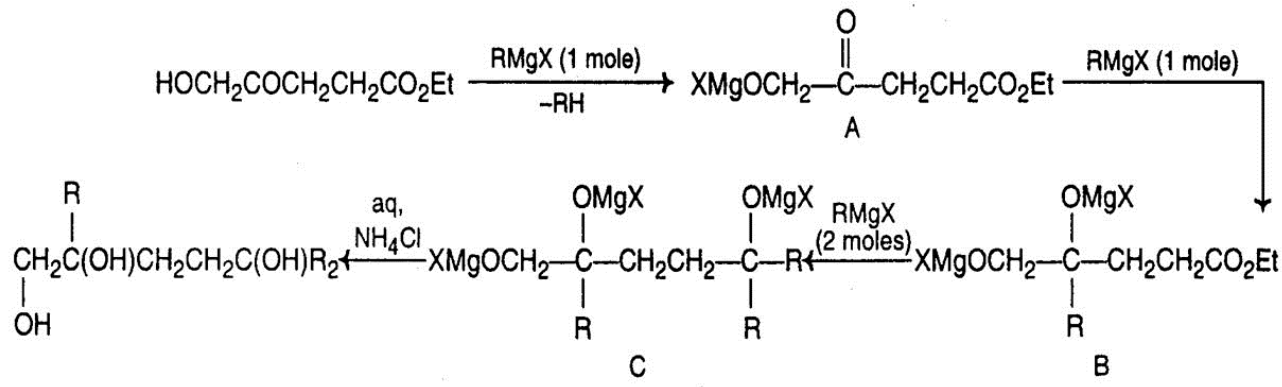


(RMgX's without a β-H, such as MeMgX or C_6H_5MgX cannot act as reducing agents.)

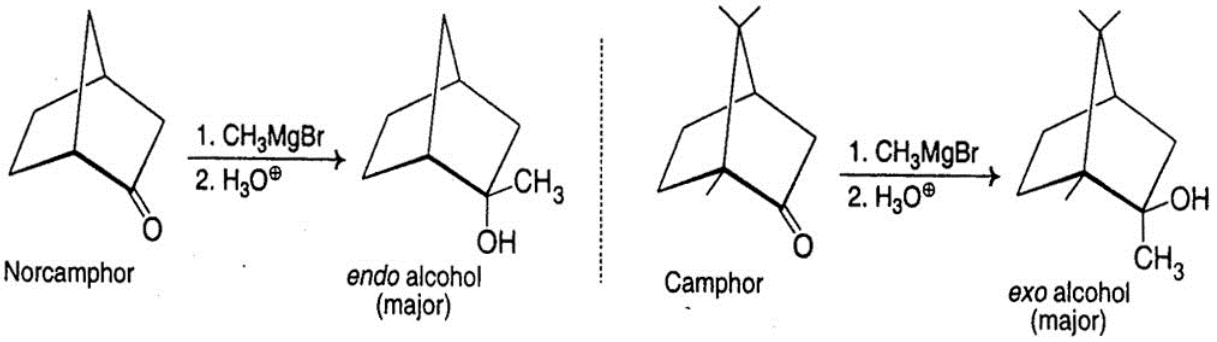
(b) Predict the intermediates **A**, **B** and **C** in the following reaction sequence:

Solution:

The order of reactivity of different groups towards Grignard reagent is as follows: active hydrogen > –CHO > >C=O > –COOR. So, in the first step, RMgX reacts with the alcoholic OH group to form A, in the second step, it reacts with the carbonyl group to form B and in the third step, two moles of it reacts with the ester group to form C.

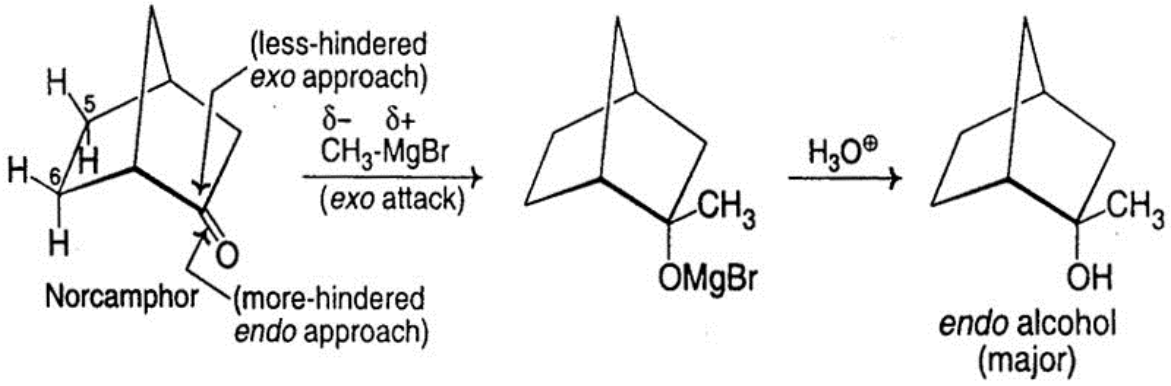


(c) Explain the following observations:

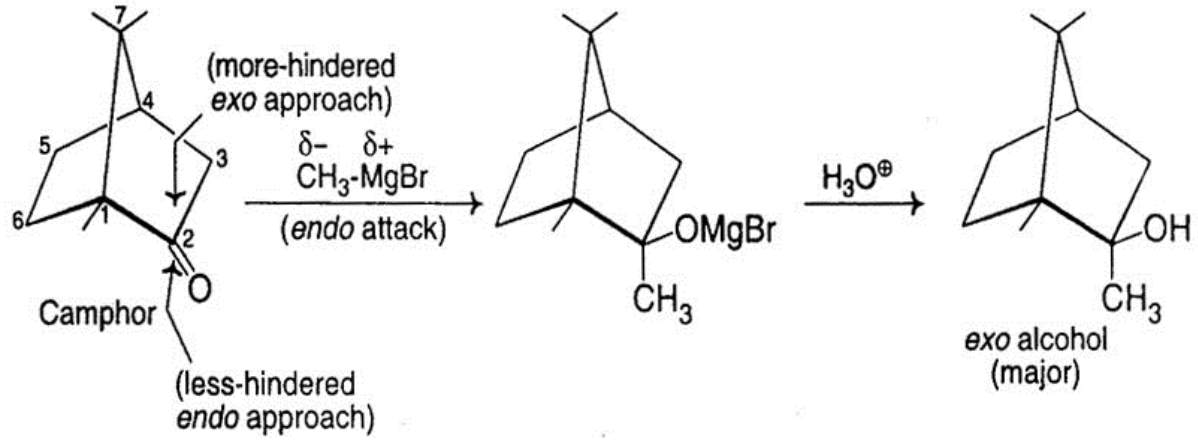


Solution:

The Grignard reagent CH_3MgBr approaches the carbonyl group of norcamphor from the less-hindered exo side (the endo approach is sterically more hindered due to boat-axial H's at C-5 and C-6) to give mainly the endo alcohol.



The Grignard reagent CH_3MgBr approaches the carbonyl group of camphor from the less-hindered endo side (the exo approach is sterically more hindered due to one $-CH_3$ group at C-7) to give mainly the exo alcohol.

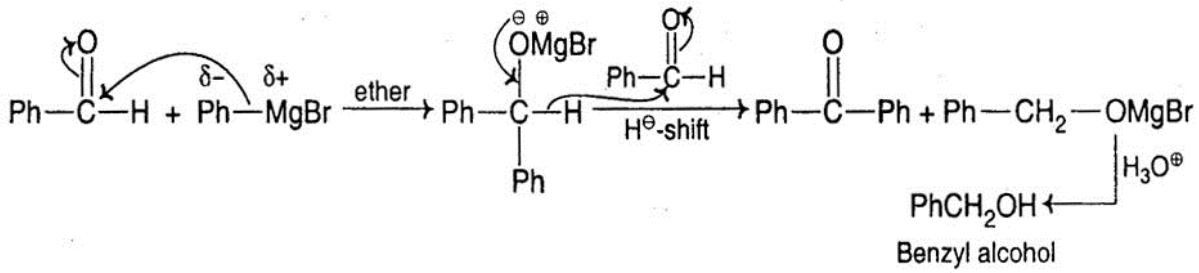


(d) Predict the products in the following reaction giving explanation:

$$PhCHO\ (2\ equiv)\ + PhMgBr \xrightarrow[2.\ H_3O^{\oplus}]{1.\ ether}$$

Solution:

Phenylmagnesium bromide reacts with two equivalents of benzaldehyde to give benzophenone (a ketone) and benzyl alcohol (a primary alcohol) by a hydride transfer (as in *Cannizzaro reaction*).



(e) Explain which of the following procedures appears to be most effective in order to get the best yield of an aldehyde, RCHO, when $HCO_2C_2H_5$ (I) is allowed to react with RMgBr (II) under usual conditions for Grignard reaction : (i) addition of I to II, (ii) addition of II to I.

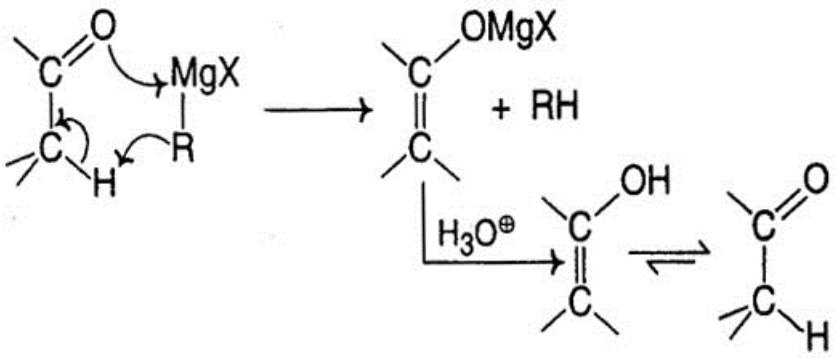
Solution:

If HCO_2Et (I) is added to RMgBr (II), there will always be present an excess of Grignard which will react with the resulting aldehyde to produce a primary alcohol. However, if II is added to I, the Grignard will not be available in excess to react further with the resulting aldehyde. Therefore, II is to be added to I to get the best yield of an aldehyde (RCHO).

5. Enolization of ketones is a dominant side reaction during addition reactions of Grignard reagent. Illustrate with an example.

Solution :

When a Grignard reagent with bulky R group is treated with a hindered ketone having an α-H atom, the normal addition reaction does not take place instead the Grignard reagent removes this hydrogen (behaves as a base) to form the corresponding enolate salt. This takes place particularly with a Grignard reagent which cannot undergo oxidation to olefin.


O
C
MgX
C
H
R
OMgX
C
C
+ RH
$H_3O^{\oplus}$
OH
C
C
O
C
C
H

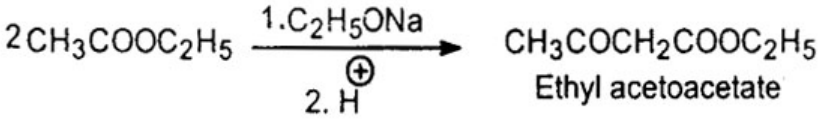
UNIT-II-Part-III

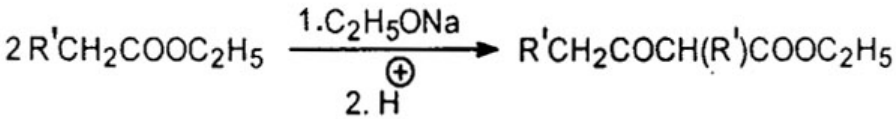
Addition reactions: Electrophilic, nucleophilic and free radical addition to double and triple bonds - hydration, hydroxylation, Michael addition, hydroboration and epoxidation.

Addition reactions to carbonyl compounds – Mannich reaction, Meerwein Pondroff-Verley reduction, Grignard, Claisen, Dieckmann, Stobbe, Knovenagel, Darzen, Wittig, Thorpe and Benzoin reactions.

Claisen Condensation

Esters having α-hydrogen on treatment with a strong base, e.g., C_2H_5ONa, undergo self-condensation to produce β-ketoesters.





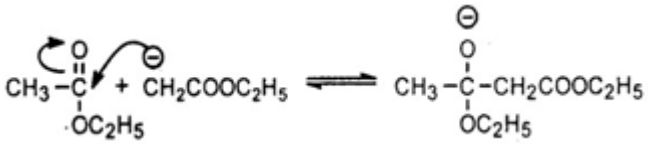
This reaction is called Claisen condensation although there are several closely related reactions which follow the same mechanistic pattern.

Mixed or crossed Claisen condensation also occurs between two different esters or between an ester and a ketone.

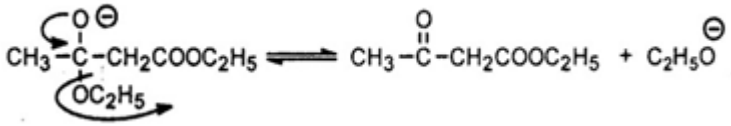
Mechanism

The ethoxide ion abstracts a proton from the α-carbon of the ester to produce the anion (of the ester) which is a powerful nucleophile (1st step). The nucleophilic attack of the anion on the carbonyl carbon of a second molecule of ester produces an oxonium ion (IInd step), which eliminates an ethoxide ion to give the β-ketoester (IIIrd step). The β-ketoester having an active methylene group is acidic and reacts with sodium ethoxide to form enolate salt (IVth step). Subsequent acidification with acetic acid (1:1) regenerates the β-ketoester.

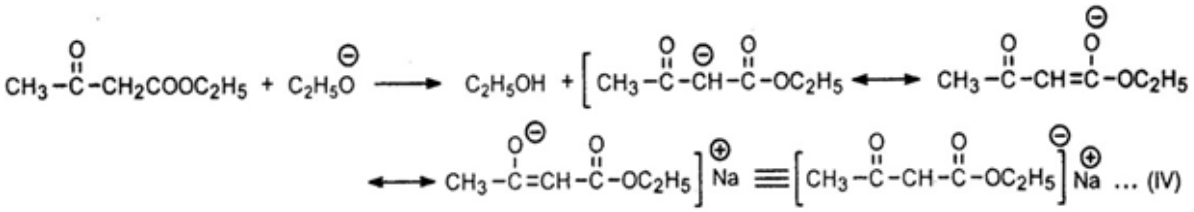
…….(I)

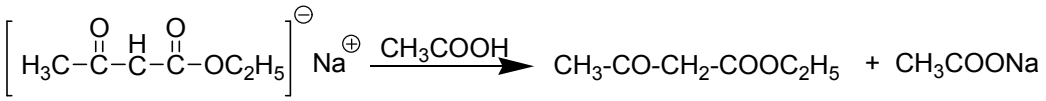


…….(II)



.....(III)

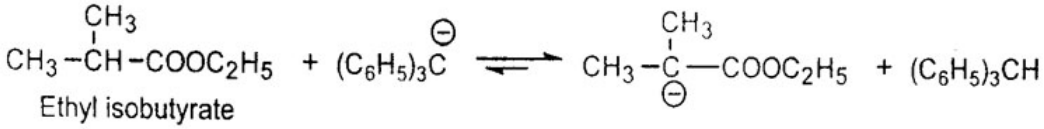




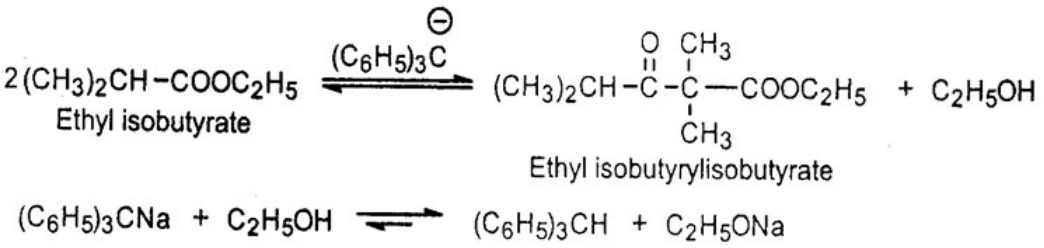
The first three steps are in unfavourable equilibrium state. Hence, excess sodium ethoxide is used to force the equilibrium to shift in the forward direction by the formation of a resonance–stabilized enolate anion (IVth step). This is substantiated by the fact that esters having only one α-hydrogen do not undergo Claisen condensation with C_2H_5ONa. This is because the ketoester formed (analogous to step III) cannot be converted to its enolate anion due to the absence of a second α-hydrogen, with the result that the equilibrium does not shift to the right.

However, in the presence of a very strong base such as triphenylmethyl sodium, such esters, e.g., ethyl isobutyrate, undergo Claisen condensation to give β-ketoesters. This is because the very strong base, $(C_6H_5)_3CNa$ acts in two ways.

(i) It withdraws the weakly acidic α-hydrogen irreversibly from the ester (analogous step 1 is highly reversible).



(ii) It completely removes one of the equilibrium products. i.e., ethyl alcohol, so that the equilibrium shifts to the right. (Compare step III).



Applications

Simple and crossed Claisen condensations have been extensively used in the synthesis of a wide variety of organic compounds, e.g., vitamins, sex hormones, alkaloids, terpenes, flavones, etc.

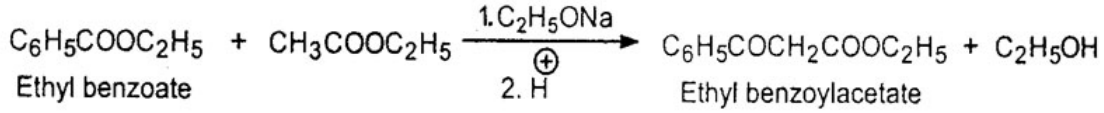
Crossed Claisen condensations between two different esters (both having α-hydrogens) have little synthetic value, for a mixture of four products are obtained. However, if one of the esters has no α-hydrogen, it acts as a carbanion acceptor and the self–condensation of the other ester is minimized. Commonly used esters with no α-hydrogen are ethylbenzoate, ethyl formate, ethyloxalate, ethyl carbonate, etc. These esters are good carbanion acceptors.

Ketones are generally more acidic than esters and the rate of their base-catalyzed condensation (aldol) is very slow. Hence, ketones serve as nucleophiles in mixed Claisen condensation to give a large variety of products.

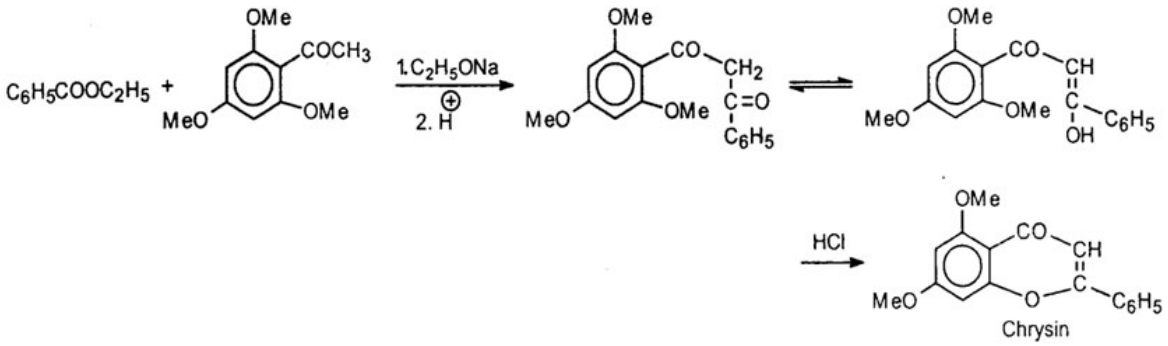
Some of the examples of crossed Claisen condensation and their applications are given below.

1. Condensation with ethyl benzoate

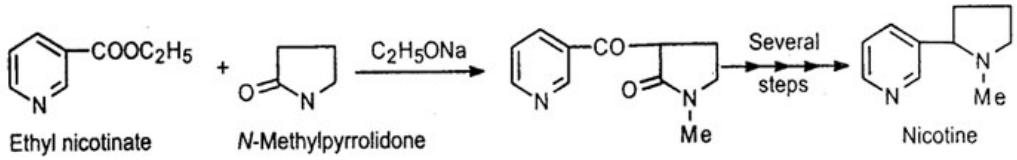
(a)



(b) Synthesis of flavones (chrysin)

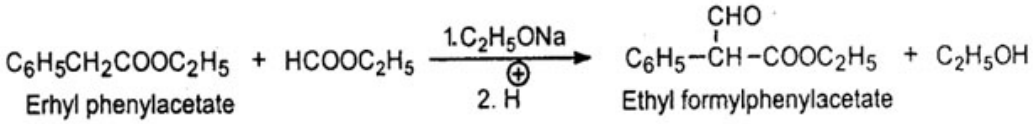


(c) Synthesis of nicotine from ethyl nicotinate.



2. Condensation with ethyl formate

(a) Formylation

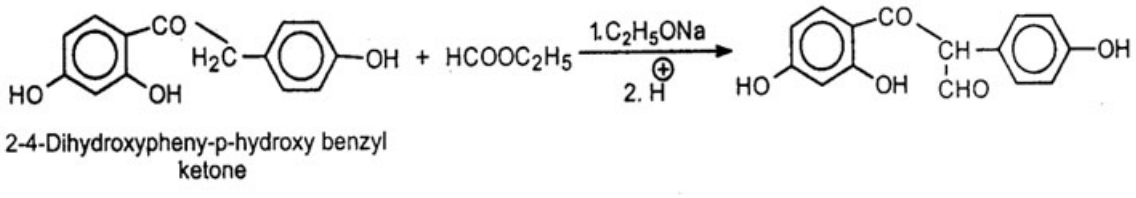


Erhyl phenylacetate

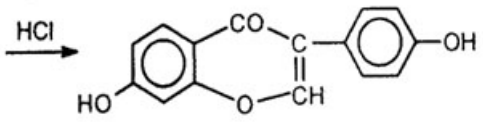
Ethyl formylphenylacetate

The reaction is utilized for formylation during the synthesis of various natural products, e.g., equilenine, thiamin (vitamin B_1), isoflavones, etc.

(b) Synthesis of daidzein (isoflavone)



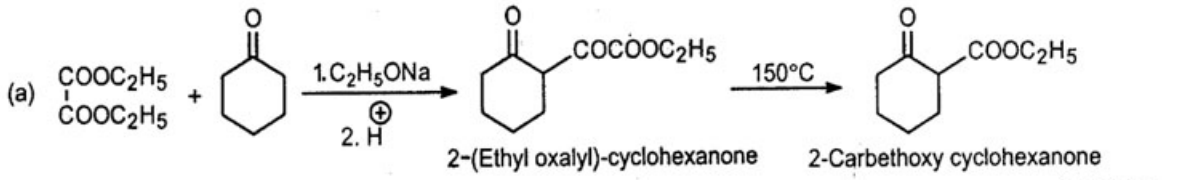
2-4-Dihydroxypheny-p-hydroxy benzyl ketone



Daidzein(isoflavone)

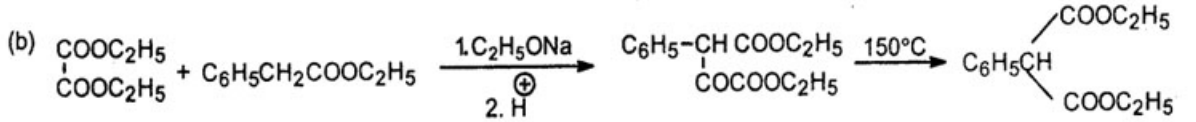
3. Condensation with diethyl oxalate

(a) Ketones and esters condense with diethyl oxalate to give oxalyl derivatives which have synthetic utility since they lose carbon monoxide on heating to give malonic ester derivatives which may be used for the preparation of aryl-substituted dibasic acid derivatives and α-keto acids.



2-(Ethyl oxalyl)-cyclohexanone

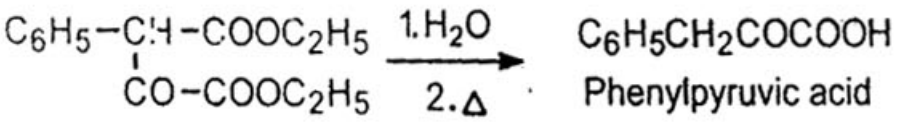
2-Carbethoxy cyclohexanone



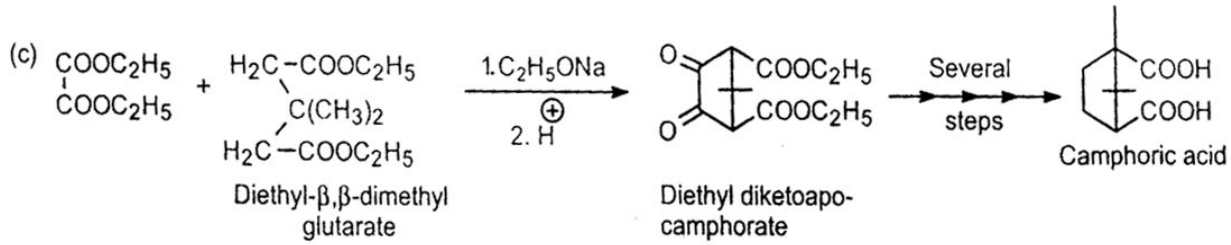
Diethyl-α-oxalylphenyl acetate

Diethyl phenylmalonate

Phenyl-substituted malonic ester has important synthetic applications, e.g., phenobarbitone may be prepared. Diethyl α-oxalylphenylacetate on hydrolysis and heating gives α-keto acid.

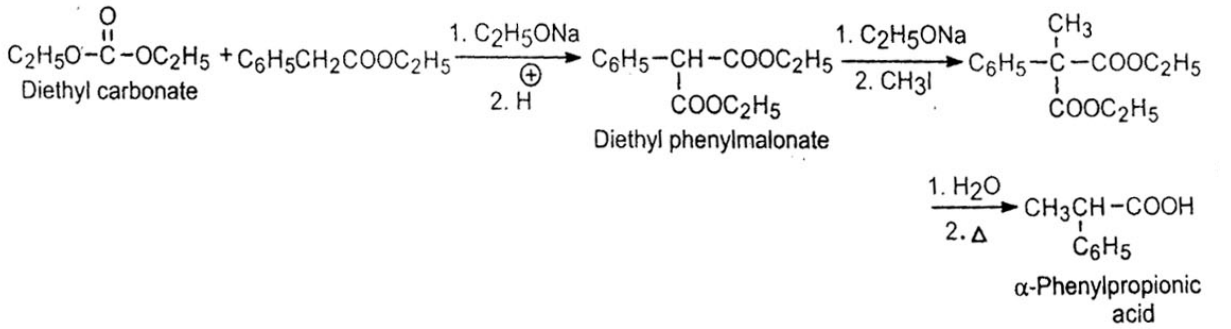


(b) Camphoric acid may be synthesized

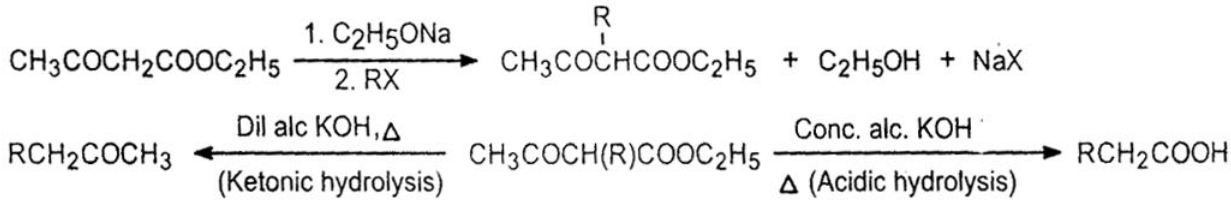


4. Condensation with diethyl carbonate

Esters condense with diethyl carbonate to form malonic ester derivatives which can be further transformed into various compounds.

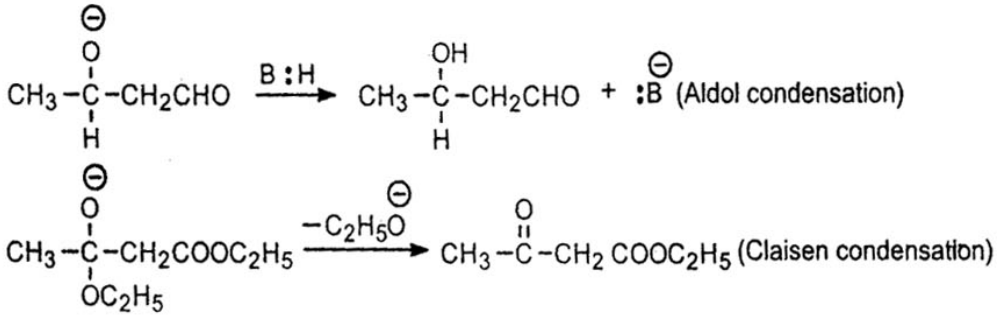


5. A very important product of Claisen condensation is the β-ketoester, ethyl acetoacetate (EAA). It can be easily alkylated. Ethyl acetoacetate and its alkyl derivatives under different conditions undergo ketonic and acidic hydrolysis to yield ketones and acids respectively.



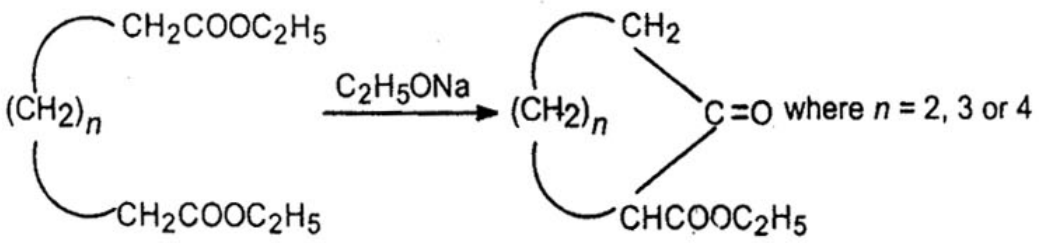
This reaction has been employed for the synthesis of a large variety of ketones, acids and many heterocyclic compounds. Intramolecular Claisen condensation in dibasic esters of six to eight carbons is called Dieckmann reactions. The product is a cyclic ketone derivative.

Claisen condensation is very similar to aldol condensation. They only difference is that, in aldol condensation no group is lost while in Claisen condensation the group $C_2H_5O^-$ is lost because it is a good leaving group.



Dieckmann Reaction

Intramolecular Claisen condensation in dibasic acid esters is called Dieckmann reaction. The resulting products are invariably cyclic β-ketone derivatives. The condensing bases may be sodium, sodium ethoxide, sodium hydride, potassium *t*-butoxide, etc.

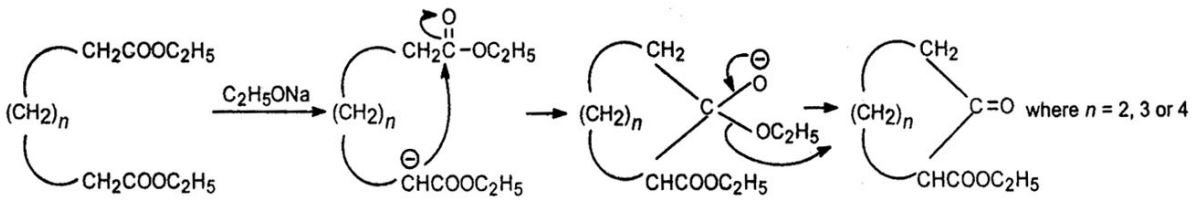


The reaction best proceeds with dibasic acid esters having 6, 7 or 8 carbon atoms which give stable rings with 5, 6 or 7 carbons. Yields for rings of 9 to 12 carbons are very low. High–dilution technique is used for the formation of large-size rings.

Mechanism

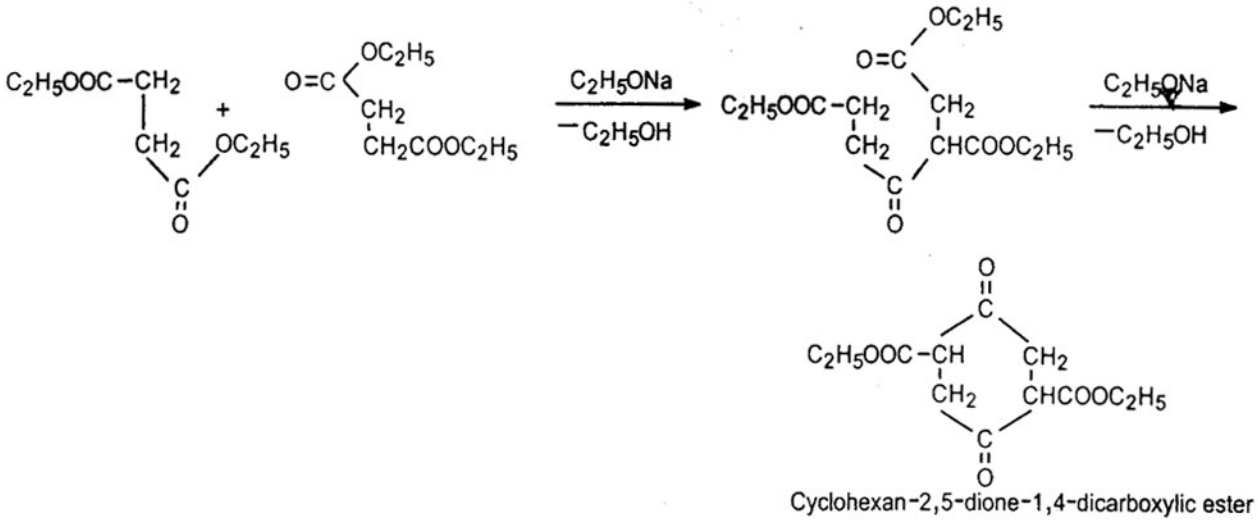
The mechanism of the reaction is similar to that of Claisen condensation.

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



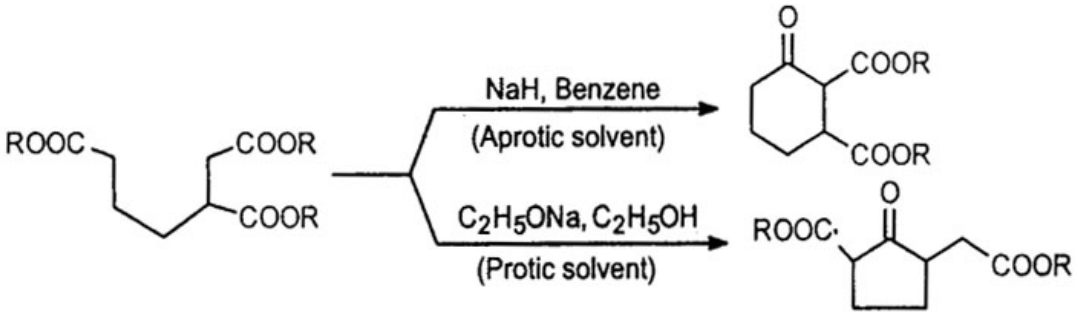
The compound on hydrolysis and decarboxylation gives cyclic ketone.

Esters of acids lower than adipic acid undergo more of intermolecular condensation with subsequent cyclisation. Thus, ethyl succinate gives cyclohexandione derivative. This may be due to reasons of stability of six-membered rings.



Cyclohexan-2,5-dione-1,4-dicarboxylic ester

Effect of experimental condition on the ring size has been observed in some compounds.

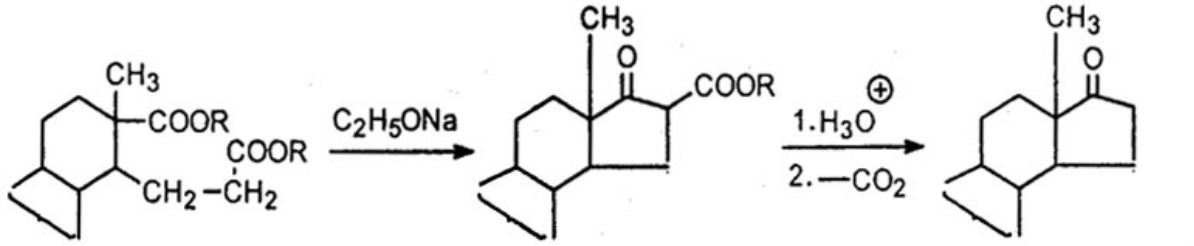


Applications and extension

The reaction affords a useful route for the synthesis of cyclopentanone and cyclohexanone derivatives. Some examples are given for illustration.

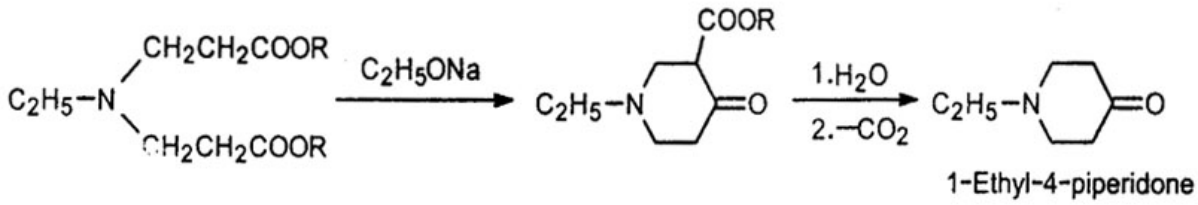
1. The reaction has been used to build up five–or six-membered rings in the synthesis of various natural products. The general process is given below.

Synthesis of steroid



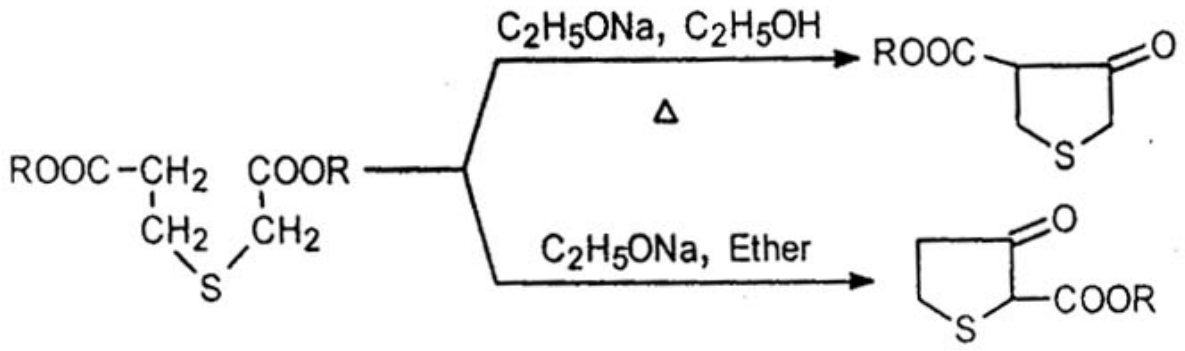
2. Preparation of heterocyclic ketoesters

(a) Piperidone derivative



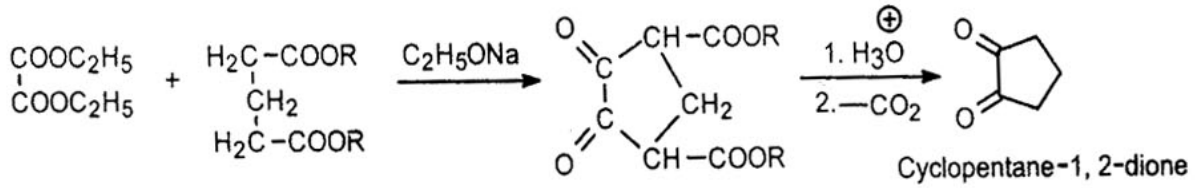
1-Ethyl-4-piperidone

(b) Thiophene derivatives – Depending on the conditions of the reaction, two isomers are obtained.



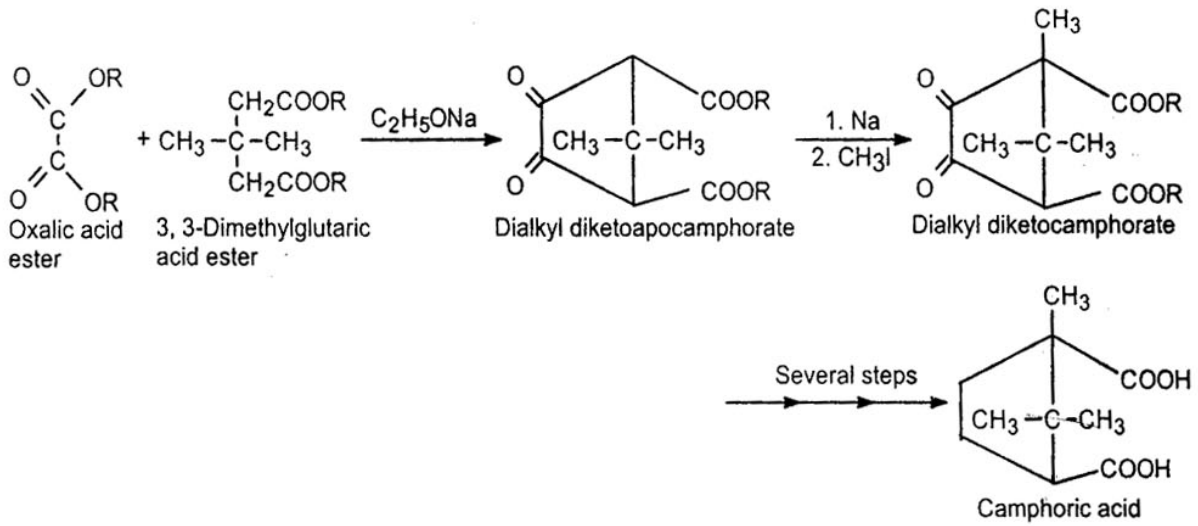
3. Extension of the reaction

(a) Intermolecular condensation between two lower acid esters has been effected to obtain different products.



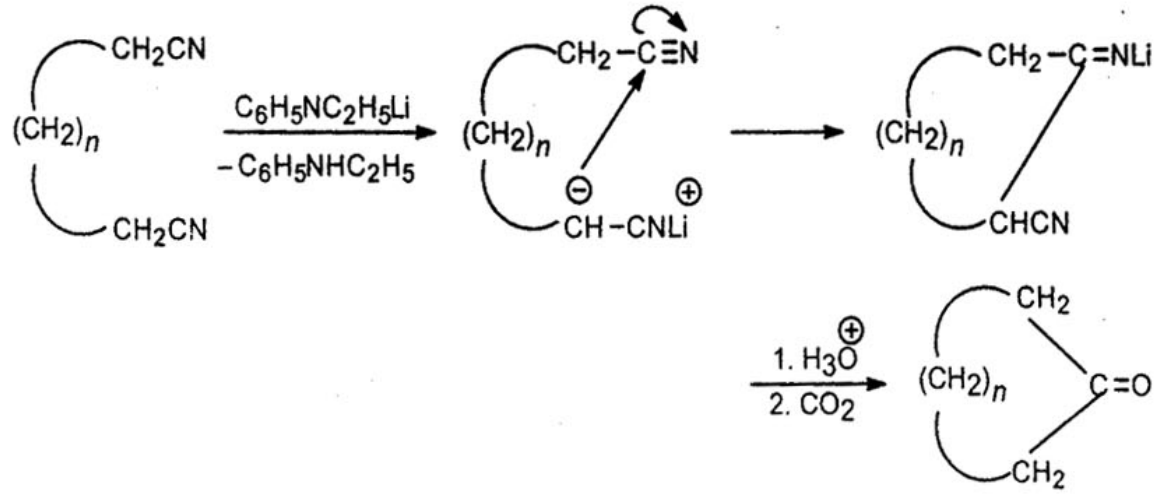
Cyclopentane-1, 2-dione

Above synthesis was utilized for the synthesis of camphoric acid.



This, incidentally, elucidates the structure of camphor.

(b) Ziegler applied Dieckmann reaction on dinitriles to obtain large–size rings using lithium ethyl anilide and high dilution technique.



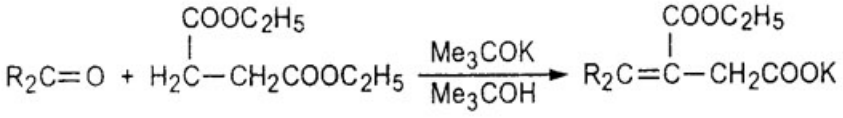
UNIT-II-Part-IV

Addition reactions: Electrophilic, nucleophilic and free radical addition to double and triple bonds - hydration, hydroxylation, Michael addition, hydroboration and epoxidation.

Addition reactions to carbonyl compounds – Mannich reaction, Meerwein Pondroff-Verley reduction, Grignard, Claisen, Dieckmann, Stobbe, Knovenagel, Darzen, Wittig, Thorpe and Benzoin reactions.

Stobbe Condensation

Aldehydes and ketones condense with the esters of succinic acid in the presence of bases such as C_2H_5ONa, Me_3COK or NaH to give the salts of α, β-unsaturated half esters but not the alcohol. This is known as Stobbe condensation



The reaction is specific for succinic esters although the carbonyl compound may be varied over a wide range. The carbonyl compounds which may be used are:

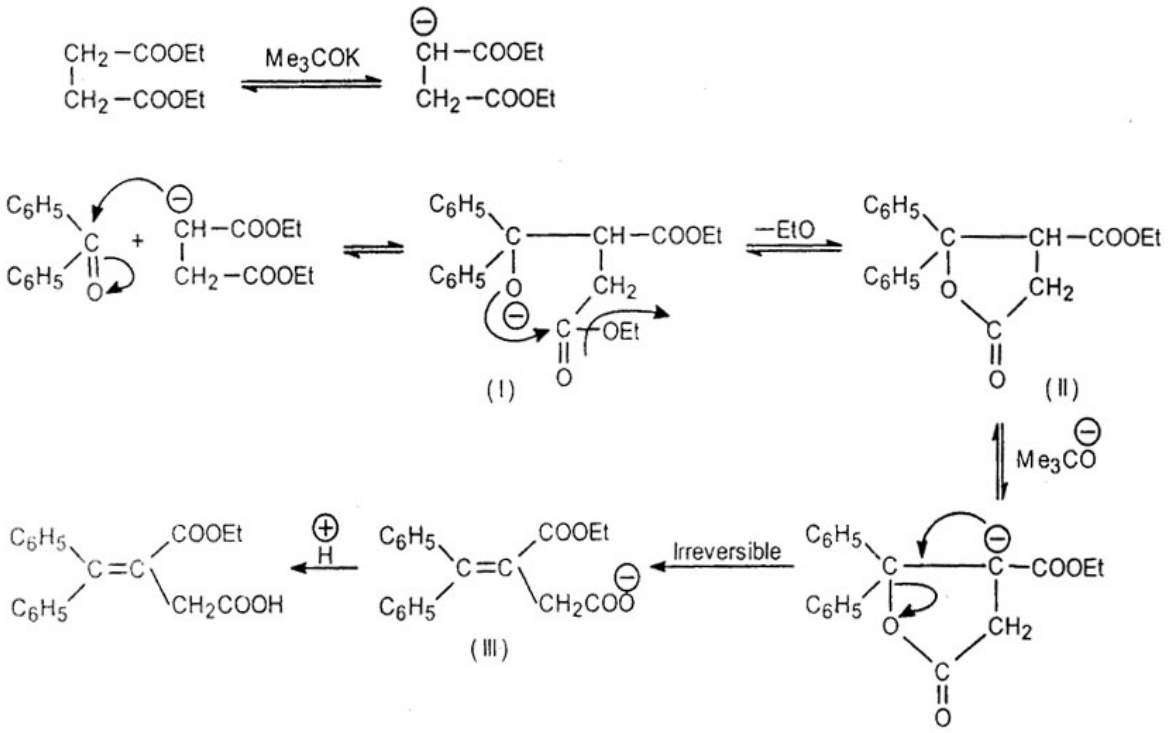
(a) Aliphatic and α,β-unsaturated aldehydes
(b) Aliphatic, aromatic, alicyclic and cyanoketones as also ketoesters.

However, ketones are more often used than aldehydes. In practice, the reaction mixture –ketone, diethyl succinate and ether solution of sodium ethoxide – is allowed to stand at room temperature for several days and then the product is recovered by acidification. The yield is improved and the reaction time is reduced on using potassium tertiary butoxide in tertiary butyl alcohol as base.

Mechanism

The mechanism of Stobbe condensation is not very clear. According to the accepted mechanism, the base accepts a proton from one of the methylene groups of succinic ester. The succinic ester carbanion then adds to the carbonyl carbon of the substrate to give (I). The adduct (I) then undergoes cyclization (ester-lactone interchange) generating alkoxide ion from the more remote ester group. The cyclized product (II) is a lactone. Subsequent base-catalysed elimination causes irreversible ring opening to produce a salt of unsaturated half ester (III).

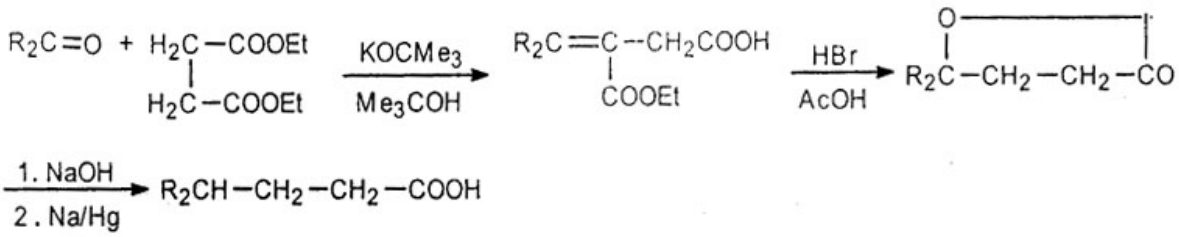
Lactones have been isolated from the reaction mixture in some cases, which support the mechanism.



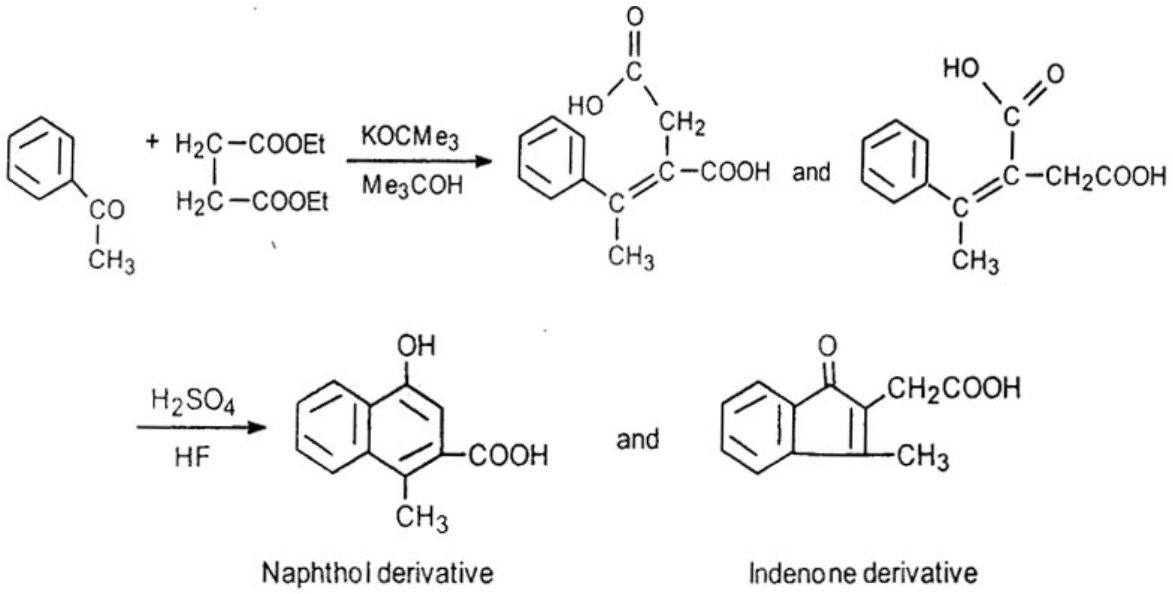
Applications

Stobbe condensation has been used to prepare a large number of varieties of unsaturated and saturated acids. The condensation has also been useful for the synthesis of many types of polycyclic ring systems. It has also been used during the synthesis of estrone. Some of its synthetic applications are given below.

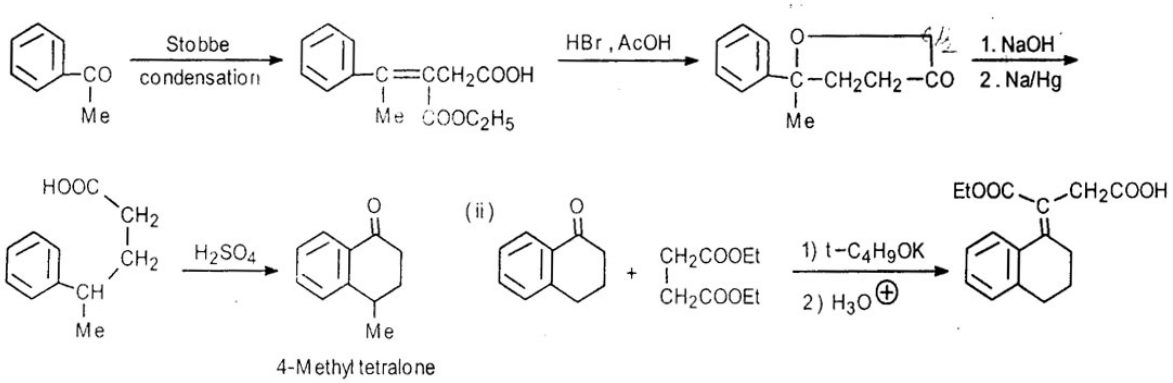
1. Synthesis of acids



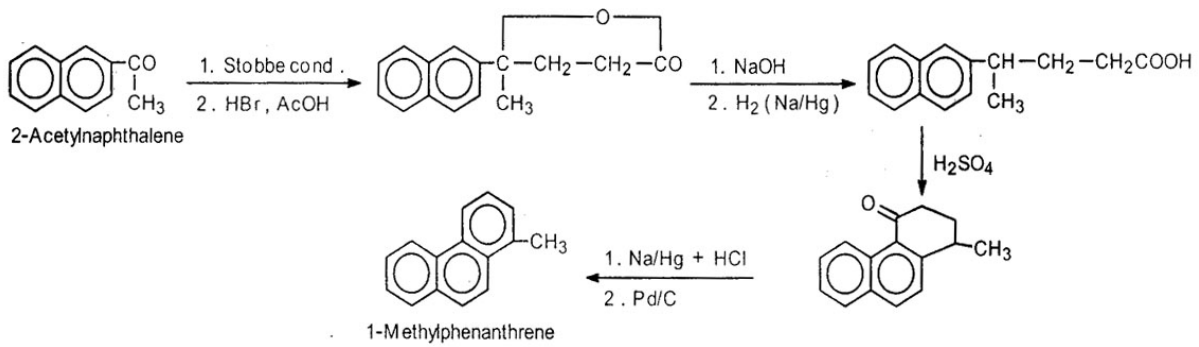
2. **Synthesis of polycyclic rings** (a) Naphthol and indenone derivatives–Stobbe condensation product with aryl ketones on cyclodehydration gives polycyclic rings. Since Stobbe condensation product is a substituted olefin, the aryl group may be cis to CH_2COOH group or to COOH group so that two products may be obtained on cyclodehydration.



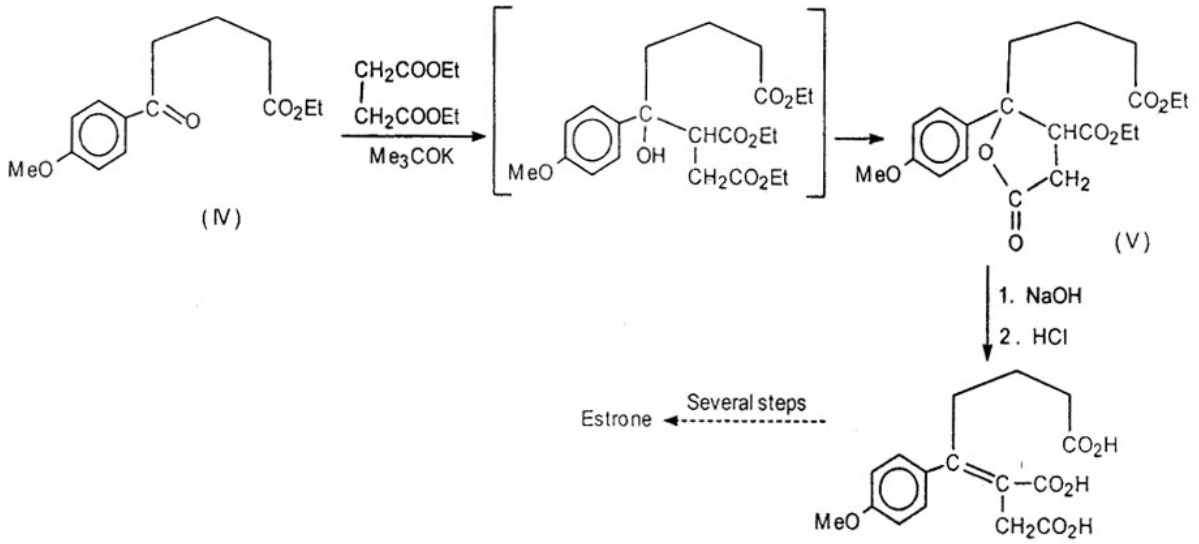
(b) Tetralone derivative:



(b) Phenanthrene derivative:

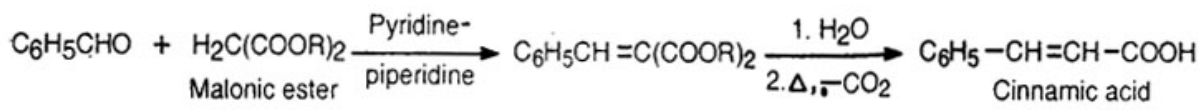


3. **In the synthesis of estrone** In the synthesis of estrone, the intermediate (iv) obtained by Friedel-Crafts acylation between methylphenyl ether and glutaric anhydride was subjected to Stobbe condensation to obtain the lactone (v) which was further processed (several steps) to get estrone.



Knoevenagel Reaction

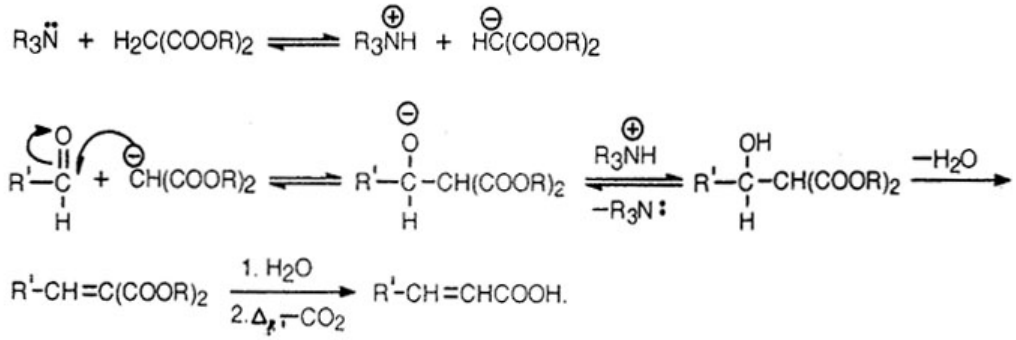
Condensations of aldehydes and ketones with compounds having active methylene group in the presence of basic catalyst to form, α, β-unsaturated compounds is called Knoevenagel reaction. The basic catalysts may be ammonia or its derivatives. Thus, primary, secondary or tertiary amines, e.g., aniline, di- or tri-alkyl amines, pyridine, piperidine, etc., are used.



Mechanism

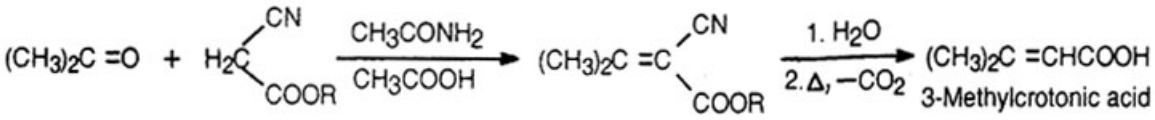
The initial stage of the reaction is base-catalysed aldol condensation with subsequent dehydration.

In the first step the base removes a proton form the active methylene group to generate a carbanion. The carbanion then attacks the carbonyl carbon of the substrate to form an alkoxide ion which abstracts the proton from the protonated catalyst to form a hydroxy compound. Subsequent dehydration gives the α,β-unsaturated compound which is hydrolysed and decarboxylated to obtain, α, β-unsaturated acid. The reaction with a malonic ester is as shown:

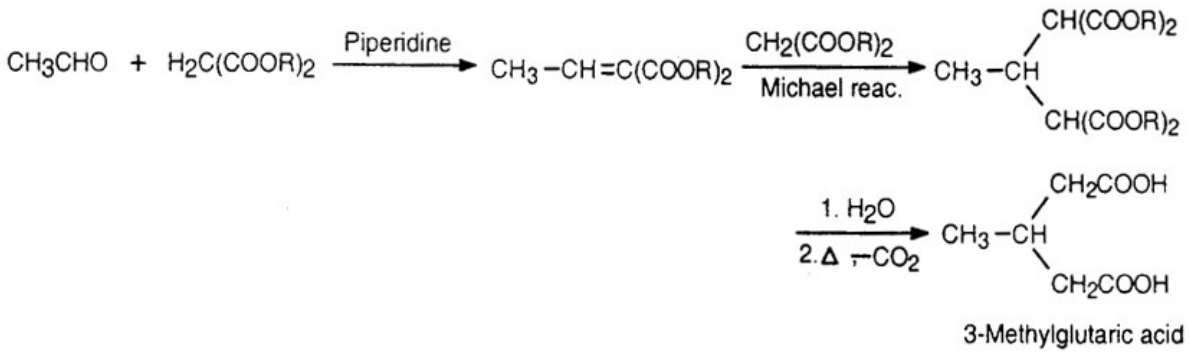


High reactivity of the methylene group of the active methylene compound prevents self-condensation of the aldehyde.

Both aromatic and aliphatic aldehydes give this reaction. For steric and electronic reasons ketones are less reactive than aldehydes. Hence, ketones react with compounds having powerful active methylene group only, e.g., ethyl acetoacetate, cyanoacetic acid and its ester but not usually with malonic ester for which stronger bases have to be used.



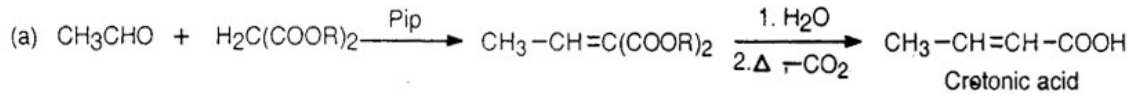
The intermediate unsaturated product formed during the course of reaction with aldehydes tends further to undergo Michael reaction especially in the presence of excess of the active methylene compound. The Michael condensation product may be hydrolysed and decarboxylated to obtain dibasic acid.

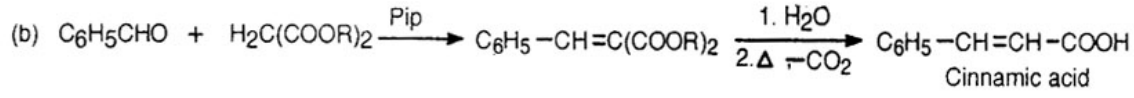


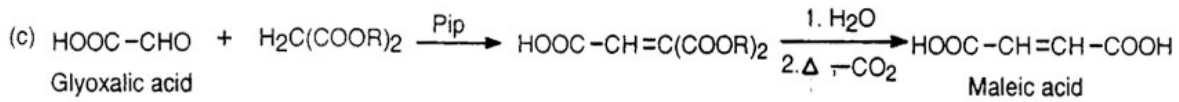
Hence, Knoevenagel reaction best proceeds with aromatic aldehydes.

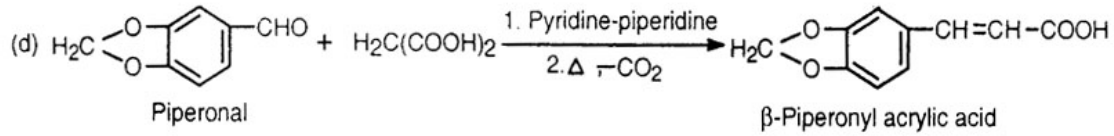
Applications

1. Various α, β-unsaturated acids such as crotonic, cinnamic, fumaric and β-piperonly acrylic acids can be prepared.

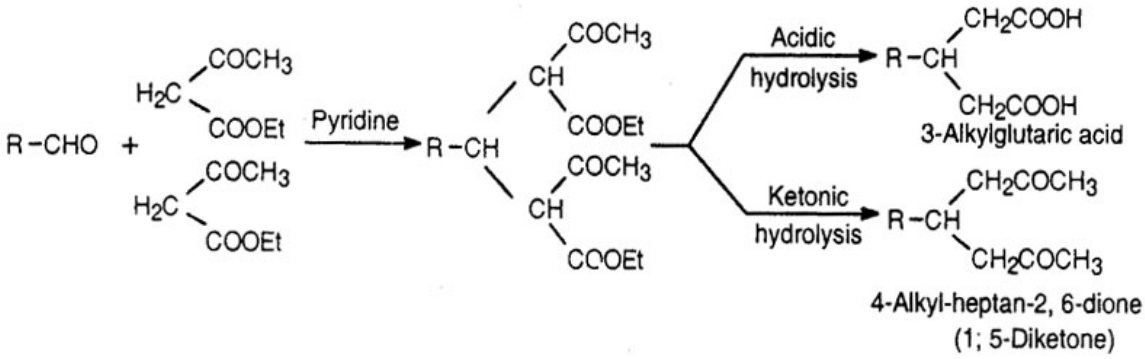




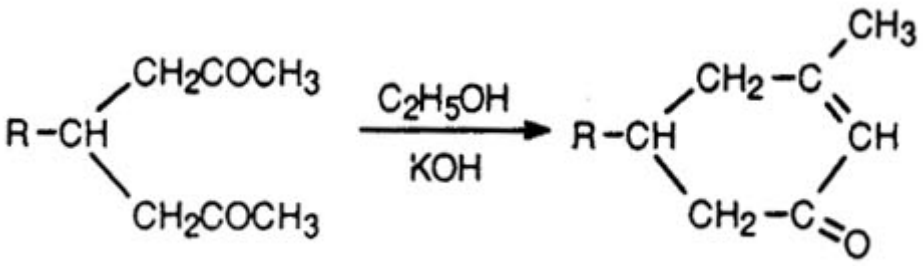




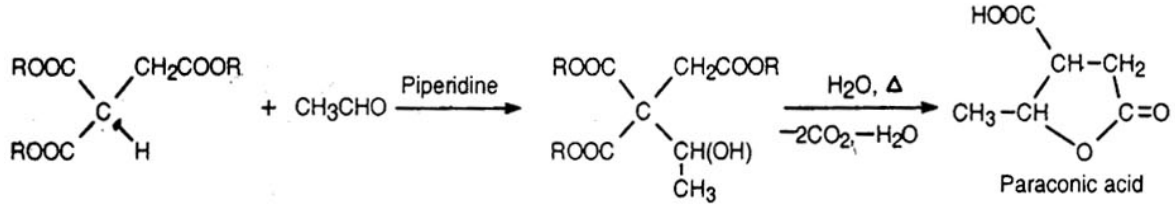
2. By reacting aldehyde with active methylene compound in 1:2 molar proportions, various dibasic acids and diketones can be prepared.



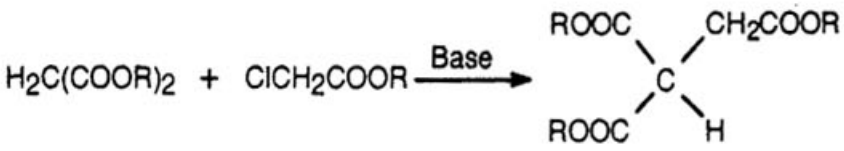
The 1:5 diketones may be cyclised by the treatment with alcoholic alkali to obtain cyclohexene derivatives.



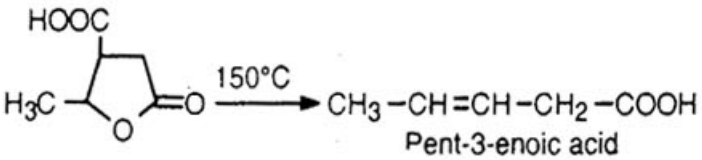
3. Cyclic compounds may also be prepared from suitably selected compounds having one active hydrogen. The reaction proceeds up to aldol stage and then the aldol is cyclised to paraconic acid.



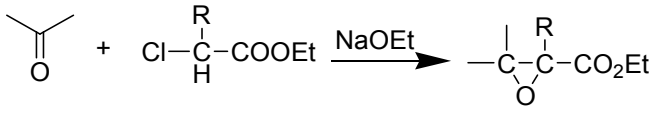
The starting product can be prepared form malonic ester and chloroacetic ester.



When paraconic acid is heated to 150°C it gives β,γ-unsaturated acid.

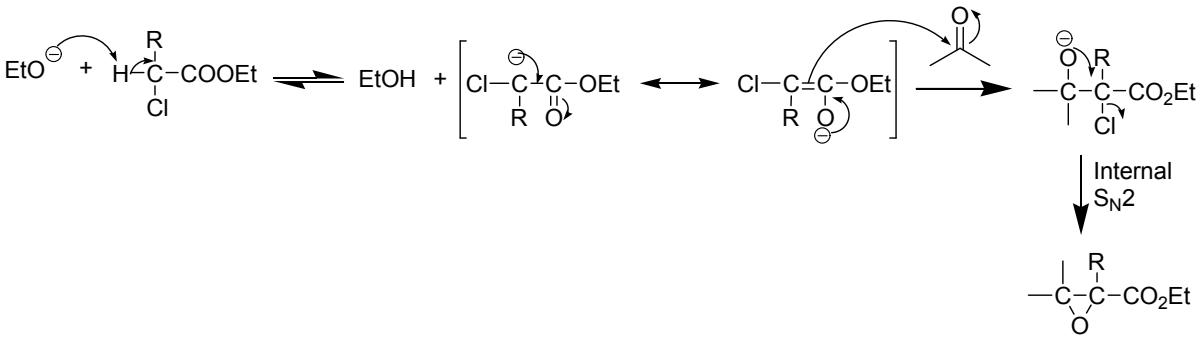


Darzens condensation



Aldehydes and ketones condense with α -halo esters in the presence of bases to give α, β-epoxy esters, called *glycidic esters*. This is called the *Darzens condensation*. The reaction consists of an initial Knoevenagel-type reaction, followed by an internal S_N2 reaction.

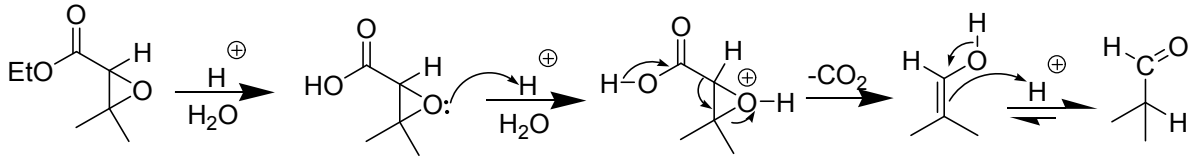
Mechanism



Although the intermediate halo alkoxide is generally not isolated, it has been done, not only with α-fluoro esters (since fluorine is such a poor leaving group in nucleophilic substitutions), but also with α -chloro esters. This is only one of several types of evidence that rule out a carbene intermediate. Sodium ethoxide is often used as the base, though other bases, including sodium amide, are sometimes used. Aromatic aldehydes and ketones give good yields, but aliphatic aldehydes react poorly. However, the reaction can be made to give good yields (~80%) with simple aliphatic aldehydes, as well as with aromatic aldehydes and ketones by treatment of the α-halo ester with the base lithium bis(trimethylsilyl) amide, $LiN(SiMe_3)_2$, in THF at -78°C (to form the conjugate base of the ester) and addition of the aldehyde or ketone to this solution. If a preformed dianion of an α-halo carboxylic acid $Cl\text{-}C^{e}R\text{-}COO^{e}$ is used instead, α,β-epoxy acids are produced directly. The Darzens reaction has also been carried out on α-halo ketones, α-halo nitriles, α-halo sulfoxides and sulfones, α-halo *N*,*N*-disubstituted amides, α-halo ketimines, and even on allylic and benzylic halides. Phase-transfer catalysis has been used. Note that the reaction of a β-bromo-α-oxo ester and a Grignard reagent leads to the glycidic ester. Acid catalyzed Darzens reactions have also been reported.

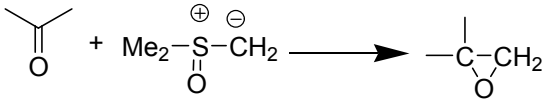
The Darzens reaction has been performed enantioselectively, by coupling optically active α-bromo-β-hydroxy esters with aldehydes. Chiral phase-transfer agents have been used to give epoxy ketones with modest enantioselectivity. Chiral additives have proven to be effective.

Glycidic esters can easily be converted to aldehydes. The reaction has been extended to the formation of analogous aziridines by treatment of an imine with an α-halo ester or an α-halo *N*,*N*-disubstituted amide and *t*-BuOK in the solvent 1,2-dimethoxyethane. However, yields were not high.



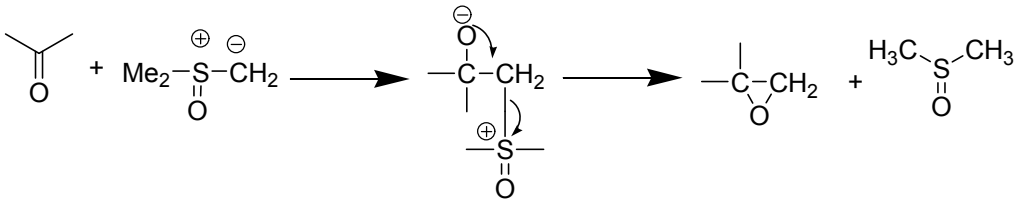
Application

The formation of epoxides from aldehydes and ketones.

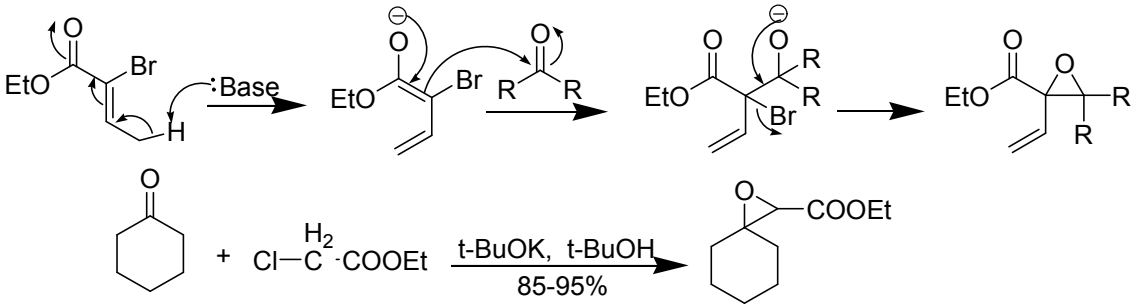


Aldehydes and ketones can be converted to epoxides in good yields with the sulfur ylides dimethyloxosulfonium methylidene.

Mechanism

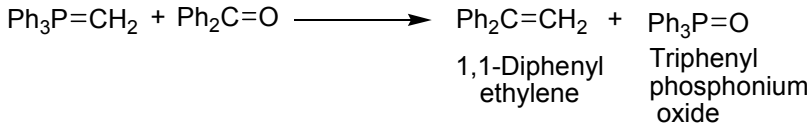


In a reaction with enones:

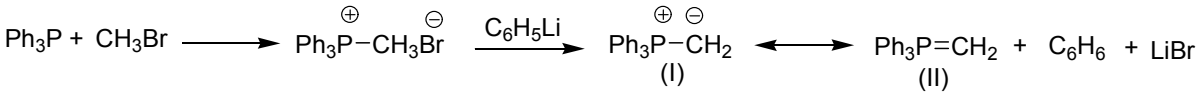


Wittig Reaction

Wittig reaction affords an important and useful method for the synthesis of alkenes by the treatment of aldehydes of ketones with alkylidenetriphenylphosphorane ($Ph_3P{=}CR_2$) or simply known as phosphorane.



The Wittig reagent, alkylidenetriphenylphosphorane, is prepared by treating trialkyl or triarylphosphine usually the latter with an alkyl halide in ether solution. The resulting phophonium salt is treated with a strong base (such as C_6H_5Li, BuLi, $NaNH_2$, NaH, C_2H_5ONa etc.) which removes a halacid to give the reagent, methylenetriphenyl phosphorane (II).

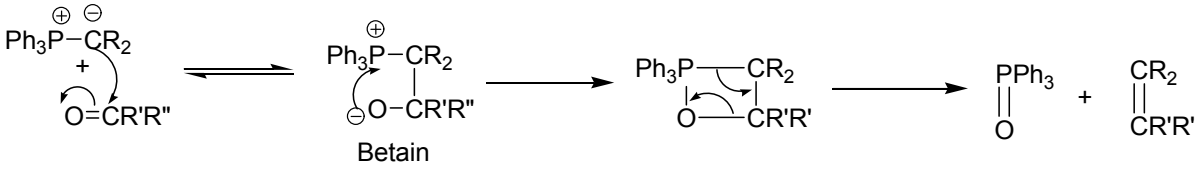


In the alkyl halide hydrogen is necessary on the halogen–bearing carbon. Alkylidene-triphenylphosphoranes are also called ylids due to the presence of opposite formal charges on adjacent atoms as in one of the resonance structures (I). The methylene structure (II) has a dπ -pπ bond between phosphorus and carbon. The ylid may be considered as a carbanion stabilized by the adjacent phosphonium cation.

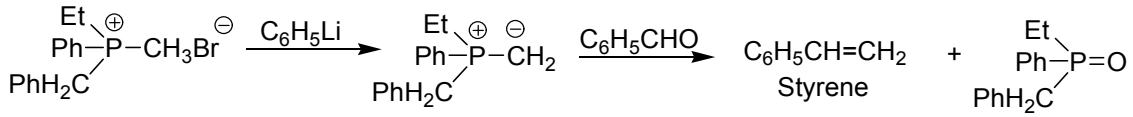
The carbonyl compound is directly treated with the ethereal solution of the reagent.

Mechanism:

The reaction probably proceeds by the nucleophilic attack of the ylid on the carbonyl carbon. The dipole complex (betain) so formed decomposes to olefin and triphenylphosphine oxide via a four-centered transition state.

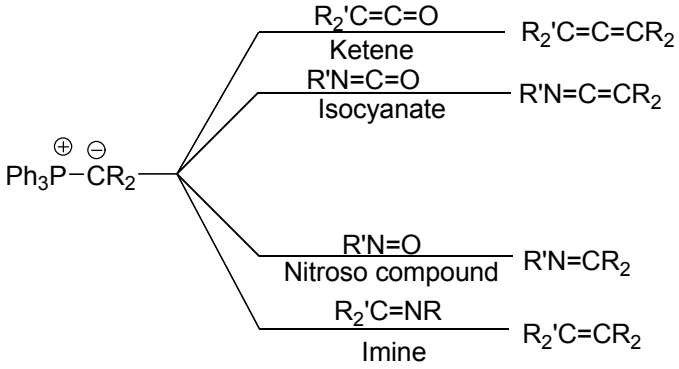


The mechanism is supported by the fact that an optically active phosphonium salt reacts to produce a phosphine oxide with retention of configuration.



Since desired alkyl groups can be introduced in the alkyl halide and the carbonyl compound, it is extremely useful for the synthesis of desired substituted alkenes. Double or triple bonds even when conjugated with the carbonyl group (>C=O) does not interfere. The reaction with the carbonyl group of esters is very slow and does not interfere.

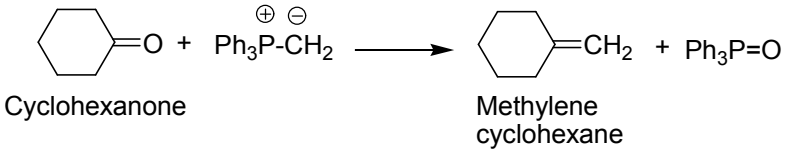
Phosphorous ylids react in the same manner with the >C=O group of ketenes and isocyanates as also with the -N=O and >C=N groups of nitroso and imine compounds respectively.



Applications:

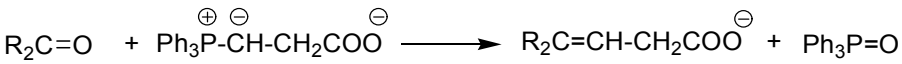
The reaction has many useful synthetic applications. Many natural products which are otherwise difficult to prepare can be synthesized by Wittig reaction.

1. Formation of exocyclic methylene group



This method of introducing exocyclic methylene group is extremely valuable and has been widely used in the preparation of methylene steroids.

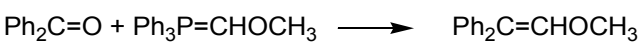
2. Preparation of β, γ -unsaturated acids



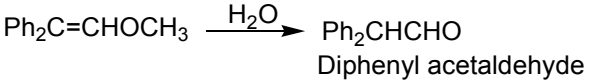
In all other methods isomerisation to α, β-unsaturated acids results.

3. Synthesis of ethers

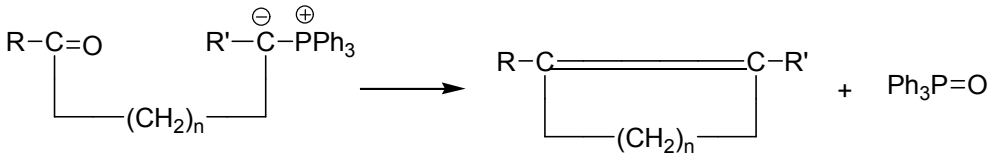
Methoxymethylenetriphenylphosphorane reacts with carbonyl compounds to give diphenyl-substituted vinyl methyl ethers.



Hydrolysis of the product gives aldehyde.

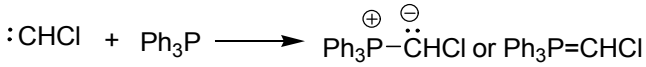


4. Formation of large rings containing 5 to 16 carbons

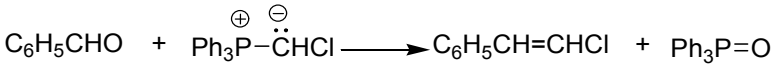


5. Synthesis of vinyl halides

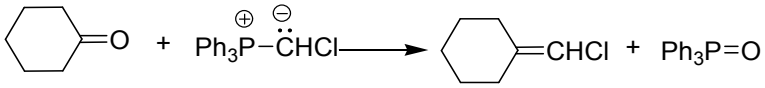
Chloromethylenephenylphosphorane ($Ph_3P{=}CCl$) required for this synthesis is prepared by reacting chlorocarbene with triphenylphosphine.



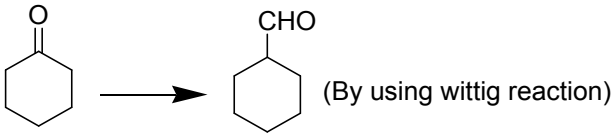
(i)



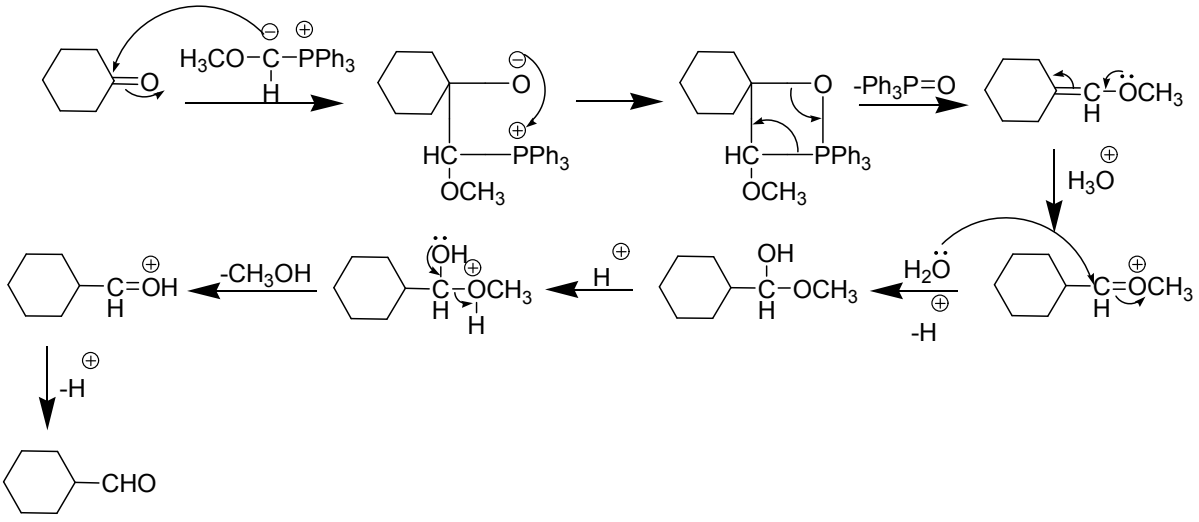
(ii)



1. Write the mechanism of the following conversion.

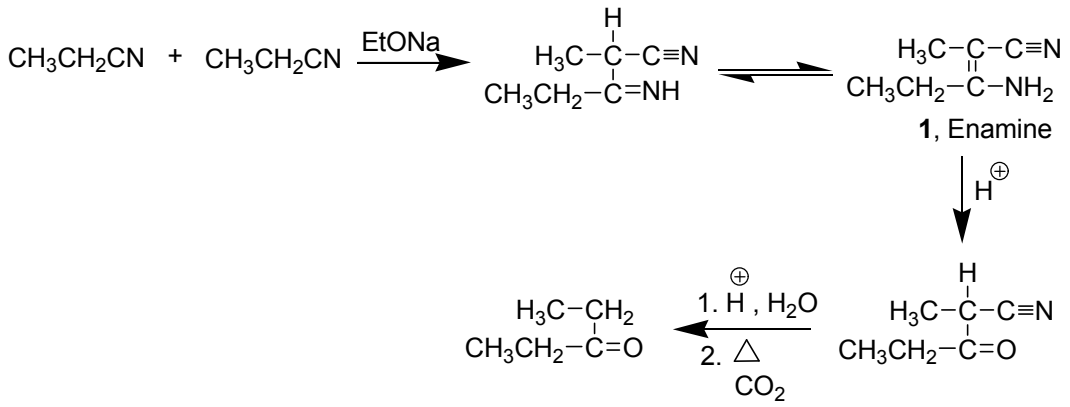


Solution:

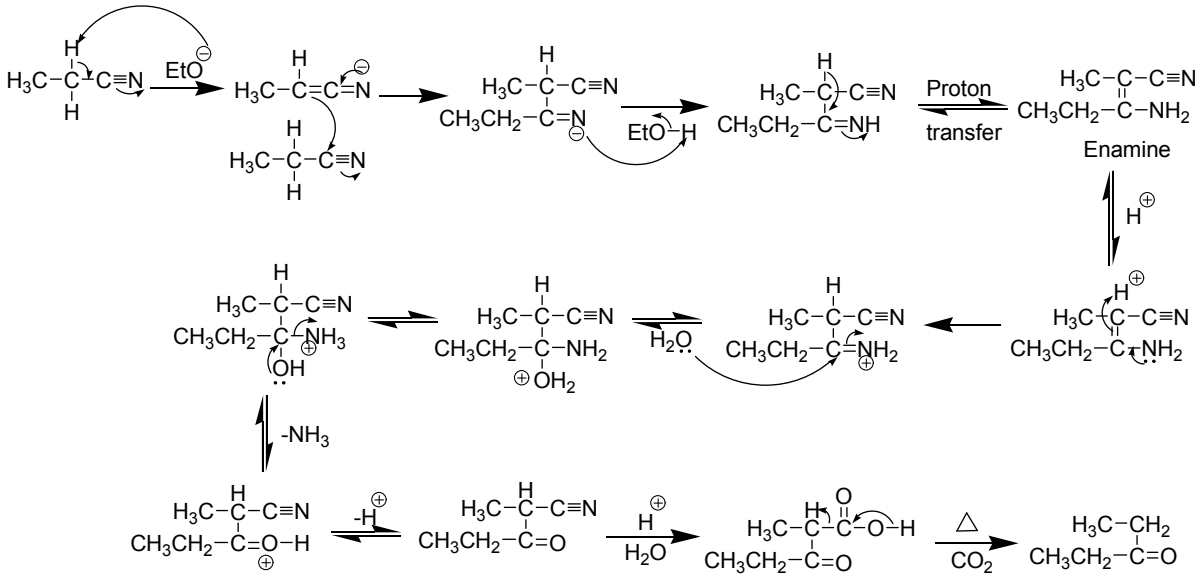


Thorpe reaction

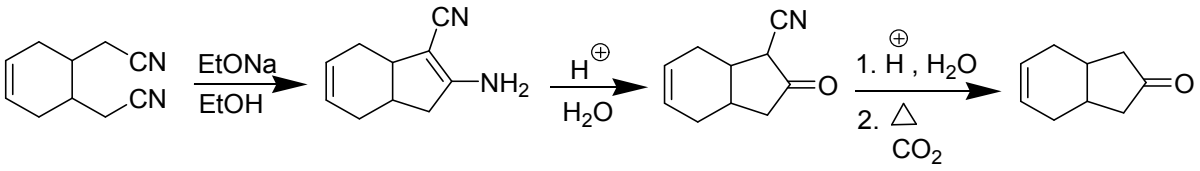
In the *Thorpe reaction*, the α–carbon of the nitrile molecule is added to the CN carbon of another, so this reaction is analogous to the aldol reaction. The C=NH bond is, of course, hydrolyzable, so β-keto-nitrile can be prepared in this manner.



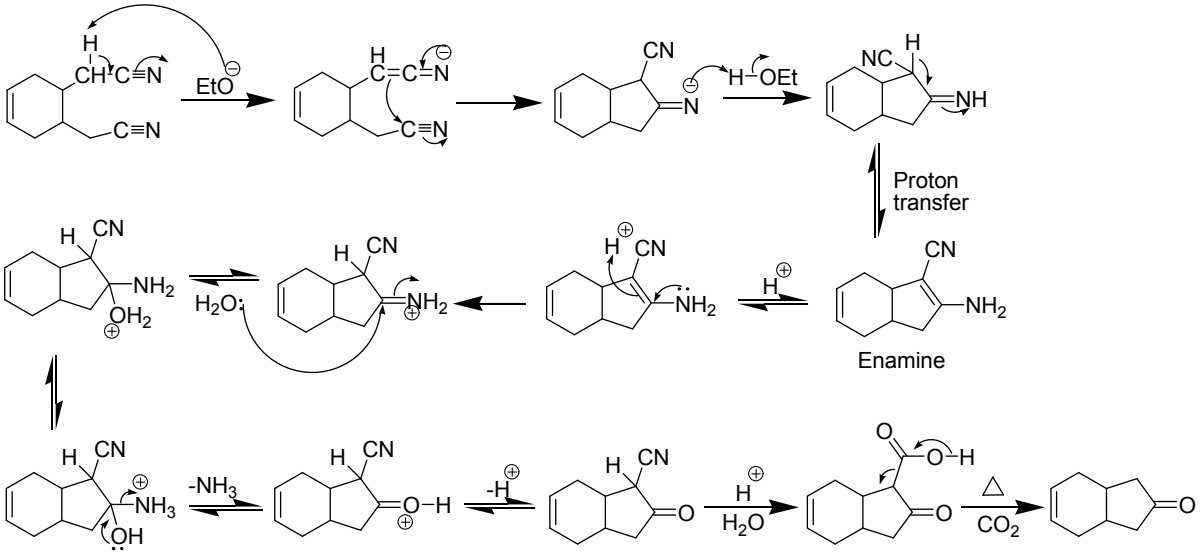
Mechanism



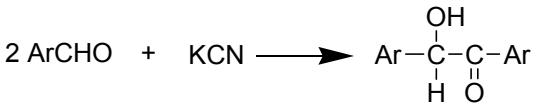
The Thorpe reaction can be done intramolecularly, in which case it is called the *Thorpe-Ziegler reaction*. This is a useful method for closing large rings. Yields are high for five- to eight-membered rings, fall off to about zero for rings of nine to thirteen members, but are high again for fourteen-membered and larger rings, if high-dilution techniques are employed. The product in the Thorpe–Ziegler reaction is not the imine, but the tautomeric enamine, for example, **1**; if desired this can be hydrolyzed to an α-cyano ketone, which can in turn be hydrolyzed and decarboxylated. Other active-hydrogen compounds can also be added to nitriles.



Mechanism

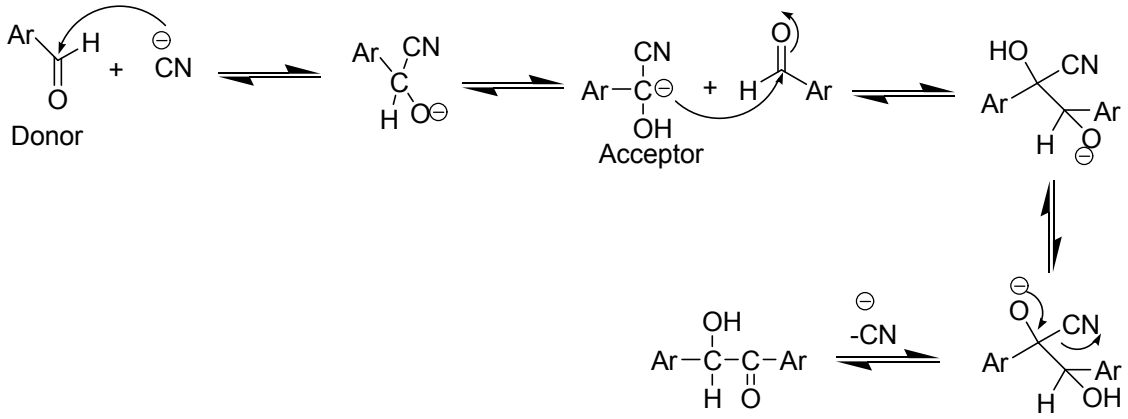


Benzoin condensation



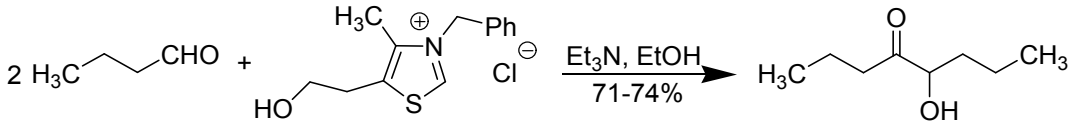
When certain aldehydes are treated with cyanide ion, *benzoins* are produced in a reaction called the *benzoin condensation*. The condensation can be regarded as involving the addition of one molecule of aldehyde to the C=O group of another. The reaction only occurs with aromatic aldehydes, but not for all of them and for glyoxals RCOCHO. The two molecules of aldehyde obviously perform different functions. The one that no longer has a C-H bond in the product is called the *donor*, because it has "donated" its hydrogen to the oxygen of the other molecule, the *acceptor*. Some aldehydes can perform only one of these functions and hence cannot be self-condensed, though they can often be condensed with a different aldehyde. For example, p–dimethylaminobenzaldehyde is not an acceptor but only a donor. Thus it cannot condense with itself, but it can condense with benzaldehyde, which can perform both functions, but is a better acceptor than it is a donor.

The following is the accepted mechanism for this reversible reaction, which was originally proposed by Lapworth in 1903.



The key step, the loss of the aldehydic proton, can take place because the acidity of this C-H bond is increased by the electron-withdrawing power of the CN group. Thus, cyanide is a highly specific catalyst for this reaction, because, almost uniquely, if can perform three conditions: (1) It acts as a nucleophile; (2) its electron-withdrawing ability permits loss of the aldehydic proton; and (3) having done this, if then acts as a leaving group.

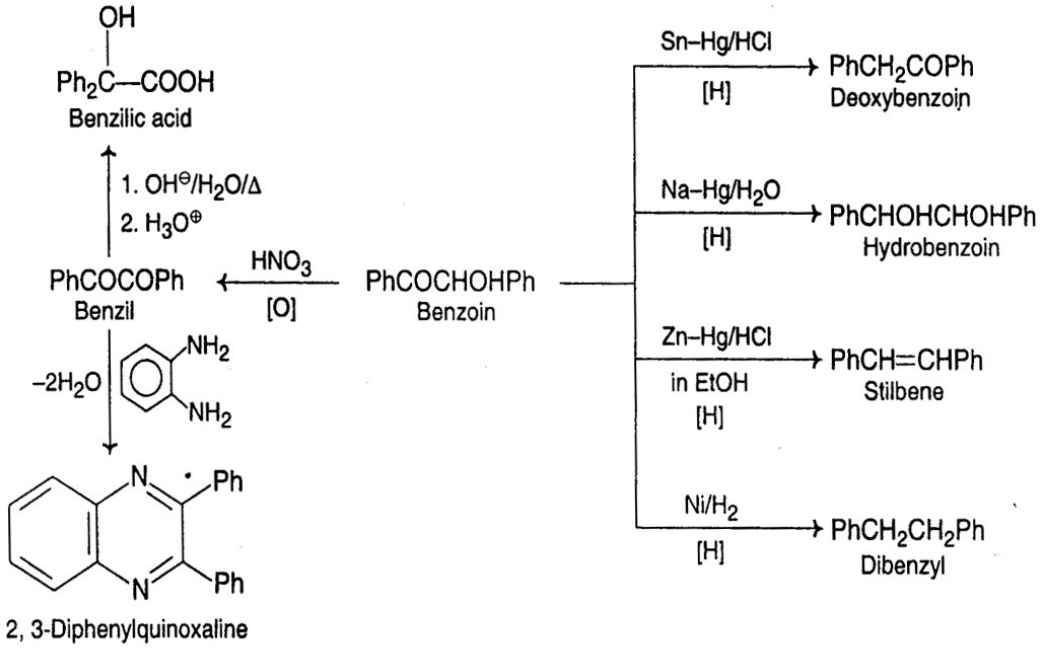
Certain thiazolium salts can also catalyze the reaction. In this case, aliphatic aldehydes can also be used (the products are called *acyloins*) and mixtures of aliphatic and aromatic aldehydes give mixed α-hydroxy ketones.



In these reactions a thiazolium salt forms an ion that participates much like cyanide. The reaction has also been carried out without cyanide, by using the benzoylated cyanohydrins as one of the components in a phase-transfer catalyzed process. By this means, products can be obtained from aldehydes that normally fail to self-condense.

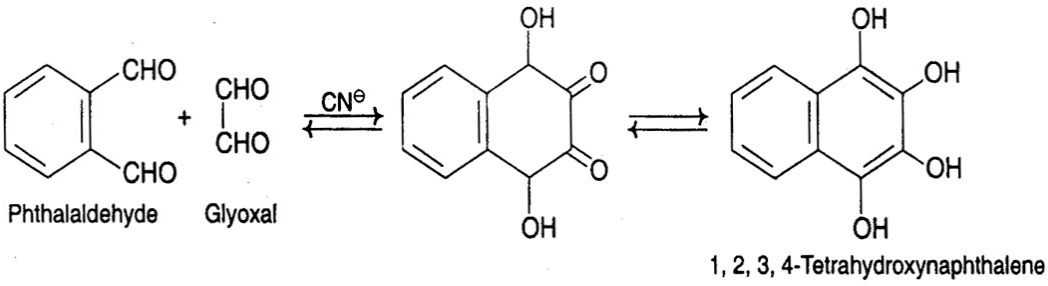
1. Mention some applications of benzoin condensation.

Benzoins the products of benzoin condensation, are useful intermediates for the synthesis of other important compounds because they can be easily oxidized to 1,2-diones and reduced to various products depending upon the reaction. For example:



Benzils may be converted to α-hydroxy acids (by benzilic acid rearrangement) and quinoxalines.

The crossed benzoin condensation may be used to synthesis polynuclear compounds. For example,

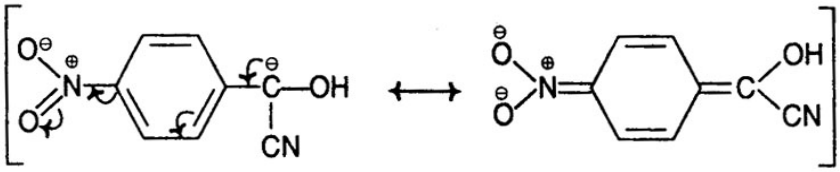


2. Explain the concept of umpolung in benzion condensation.

In benzoin condensation the usual mode of reaction of an aldehyde is reversed. Normally the carbonyl, carbon atom of an aldehyde is partially positive; it is electrophilic and consequently it reacts with nucleophiles. When $CN^{\ominus}$ adds to the aldehyde and the aldehydic hydrogen migrates to the anionic oxygen, the same carbon atom becomes negatively charged and reacts with electrophiles. This reversal of polarity of the carbonyl carbon atom is called umpolung (German for polarity reversal).

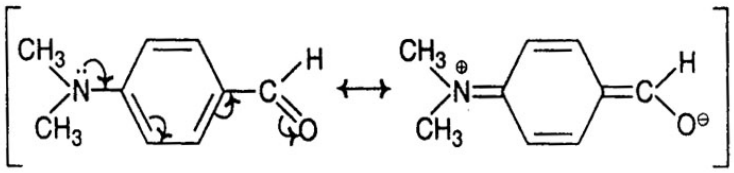
3. Explain why *p*-nitrobenzeldehyde and p-dimethylaminobenzaldehyde do not undergo benzoin condensation.

The *p*-nitro group stabilizes the intermediate carbanion (obtained from *p*-nitrobenzaldehyde) but delocalizing the negative charge. As a result, the nucleophilicity of the carbanion decreases to such an extent that it cannot attack the carbonyl carbon of a second molecule of aldehyde. So this compound cannot be self-condensed.



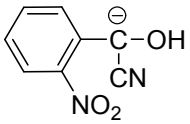
Resonance stabilized carbanion

In *p*-dimethylaminobenzaldehyde, the $-NMe_2$ group lowers the positive character of the carbonyl carbon atom through resonance to such an extent that addition of the cyanohydrin carbanion fails to take place. Thus, *p*-dimethylaminobenzaldehyde does not acts as on acceptor, i.e., if cannot be self condensed.



p-Dimethylaminobenzaldehyde

[It is to be noted that *o*-nitrobenzeldehyde undergoes the benzoin condensation. In the case of *o*-isomer, steric inhibition of resonance occurs and this makes the anionic carbon of



a stronger nucleophile than that of the *p*-isomer – so the reaction takes place.]

Text Book:

1. Smith, M. B. (2015). *March's Advanced Organic Chemistry: Reactions, Mechanisms, and Structure* (VII Edition). New Jersey: John Wiley & Sons, Inc., Hoboken.

Reference Books:

1. Tewari, N. (2011). *Advanced Organic Reaction Mechanism* (III Edition). Kolkata: Books and Allied (P) Ltd.

2. Sanyal, S. N. (2014). *Reactions, Rearrangements and Reagents* (IV Edition). New Delhi: Bharathi Bhawan (Publishers and Distributors).

POSSIBLE QUESTIONS

PART- A – Multiple Choice Questions

(Each Question Carry One Mark)

1. An atom or group of atoms possessing an odd electron is called

A) ions B) **free radical** C) anion D) cation

2. A covalent bond breaks uniformly and is known as

A) heterolytic fission B) nuclear fission C) nuclear fusion D) **homolytic fission**

3. The stability of carbocation is

A) 1° > 2° > 3° B) 2° > 1° >3° C) **3° > 2° > 1°** D) 1° > 2° >3°

4. A reaction in which the substrate and the reagent add up to form product is called

A) **addition reaction** B) rearrangement reaction

C) elimination reaction D) substitution reaction

5. The electron-releasing group conjugated to carbon-carbon multiple bonds promote

A) electrophilic addition reaction B) free radical reaction

C) **nucleophilic addition reaction** D) electrophilic substitution reaction

6. The conjugation of electron-withdrawing group activates the carbon-carbon multiple bonds towards

A) electrophilic addition reaction B) free radical reaction

C) **nucleophilic addition reaction** D) electrophilic substitution reaction

7. The example for good leaving group is

A) OH B) CN C) NO_2 D) SOR

8. The electrophilic addition of 1-propene with HI gives

A) **2-iodo propane** B) 1-iodo propane C) 1-propyne D) 1-propanol

9. The recombination of radicals results in

A) rearrangement B) **radical coupling** C) free radical reaction D) initiation

10. The addition of HBr to 1-bromocyclohexene is regioselective in that it gave only

A) trans-1,2-dibromocyclohexane B) **cis-1,2-dibromocyclohexane**

C) meso-1,2-dibromocyclohexane D) racemic 1,2-dibromocyclohexane

11. Double bond can be hydrated by treatment with

A) **water and an acid catalyst** B) water and an base catalyst

C) methanol and an base catalyst D) mercuric acetate and an base catalyst

12. 2-Methyl-1-butene treated with mercuric acetate followed by sodium borohydride gave

A) 2-methyl-1-butanol B) methyl-2-butanol

C) 1-methyl-2-butanol D) **2-methyl-2-butanol**

13. The addition of water to enol ethers causes hydrolysis to

A) acids B) **aldehydes** C) amides D) amines

14. Ketenes add water in the presence of acid gives

A) **acids** B) aldehydes C) amides D) amines

15. Decomposition of benzoyl peroxide in aromatic solvents leads to the generation of

A) benzoyl radical B) ethyl radical C) **phenyl radical** D) methyl radical

16. The conversion of acetylene into aldehyde is effected by

A) $Hg(OAC)_2/H_2O$ B) H_2O/H^+ **C)** $HgSO_2/H_2O$ D) **$HgSO_4/H_2O$**

17. The carboxylic acid is made by acid calalysed hydration of acetylenic ethers without a

A)acid catalyst B) **mercuric catalyst** C) base catalyst D) mercuric acetate catalyst

18. The most common reagent for the conversion of alkenes into cis-diol is

A) **OsO_4** B) SeO_2 C) $Hg(OAC)_2/H_2O$ D) I_2/PhCOOAg

19. The olefin is converted into trans diol can be achieved treatment with

A) O_sO_4 B) **H_2O_2/HCOOH** C) I_2, AgOAc/H_2O, H+ D) alkaline $KMnO_4$

20. Prevost anti hydroxylation, the alkene is treated with iodine and silver benzoate in a

A) 1:1 molar ratio B) 2:1 molar ratio C) **1:2 molar ratio** D) 3:2 molar ratio

21. Which reagent is used for Prevost anti hydroxylation

A) **I_2/PhCOOAg** B) I_2, AgOAc/H_2O, H+ C) O_sO_4 D) alkaline $KMnO_4$

22. The compounds having an active methylene group or having relatively acidic hydrogens are called

A) Acceptors B) receptors C) activators D) **donors**

23. The compounds having an activated olefinic bond are called

A) **Acceptors** B) receptors C) activators D) donors

24. Malonic ester is an example of

A) Acceptors B) receptors C) activators D) **donor**

25. The base catalysed addition of compounds having active methylene group to an activated olefinic bond of the type -C=C-Z is classified as

A) Aldol reaction B) **Michael reaction** C) Wittig reaction D) Mannich reaction

26. The hydration of triple bonds is generally carried out with

A) **mercuric ion salts as catalyst** B) HCl as catalyst

C) NaOH as catalyst D) mercuric ion salts as catalyst

27. Michael reaction is also called as

A) 1,2-addition B) 2,4-addition C) **1,4-addition** D) 3,4-addition

28. Aconitic acid is used in the preparation f medicines for

A) **Analgesic** B) antioxidant C) anticancer D) anti-HIV

29. The epoxidation reaction readily takes place in

A) polar solvent B) **nonpolar solvent** C) aprotic solvent D) protic solvent

30. The epoxidation addition is

A) regioselective B) regiospecific C) **stereo specific** D) stereo selective

31. The epoxidation of α,β-unsaturated ketones with hydrogen peroxide under basic conditions is known as the

A) **Waits-Scheffer epoxidation** B) harpless asymmetric epoxidation

C) Baeyer-Villiger oxidation D) Dakin oxidation

32. Which reagent is used for Sharplesss asymmetric epoxidatioon reaction?

A) peroxyacids B) **t-Bu-O-OH, Ti(Oi-Pr)4/diethyl tartrate**

C) H_2O_2/OH^- D) dimethyldioxrane

33. The condensation of a compound containing active methylene hydrogen with formaldehyde and ammonia or 1°or 2° amines usually as their hydrochlorides to form aminoethyl or substituted aminoethyl derivatives is known as

A) Aldol reaction B) Michael reaction C) Wittig reaction D) **Mannich reaction**

34. The Mannich reaction which amines do not responds

A) 1° amines B) 2° amines C) **aryl amines** D) 3° amines

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

A) Aldol reaction B) Michael reaction C) Wittig reaction D) **Mannich reaction**

36. Which amines is highly preferred for Mannich reaction

A) 1° amines B) **2° amines** C) aryl amines D) 3° amines

37. Tutocaine, a commercially useful anesthetic is prepared from

A) Aldol reaction B) Michael reaction C) Wittig reaction D) **Mannich reaction**

38. The amino acid, tryptophan is synthesized from the quaternary salt of

A) atropine B) **gramine** C) tropinone D) indole acetic acid

39. The reduction of aldehydes or ketones to alcohols by treatment with aluminium isopropoxide in excess of isopropyl alcohol is known as

A) **MPV reduction** B) Michael reaction C) Oppenauer oxidation D) Mannich reaction

40. The reverse reaction MPV reduction is called as

A) MPV reduction B) Michael reaction

C) **Oppenauer oxidation** D) Mannich reaction

41. Which catalyst is used for MPV reduction?

A) aluminium chloride B) aluminium t-butoxide

C) **aluminium isopropoxide** D) aluminium hydroxide

42. Ketones with high enol content is failed for

A) Oppenauer oxidation B) **MPV reduction**

C) Mannich reaction D) Michael reaction

43. The synhthesis of chloromycetin from

A) Oppenauer oxidation B) **MPV reduction**

C) Mannich reaction D) Michael reaction

44. Grignard reagents are

A) organomanganase halides B) organoaluminium halides

C) **organomagnesium halides** D) organocopper halides

45. The formation of Grignard reagent involves the

A) **Single electron transfer** B) double electron transfer

C) triple electron transfer D) no electron transfer

46. The Grignard reagents behaves as

A) free radical B) ions C) **carbanion** D) carbocation

47. A Grignard reagent reacts with carbon dioxide to give a

A) alcohol B) aldehyde C) ketone D) **carboxylic acid**

48. A Grignard reagent reacts with ethyl formate to give an

A) alcohol B) **aldehyde** C) ketone D) carboxylic acid

49. A Grignard reagent reacts with an orthoester to give a

A) alcohol B) aldehyde C) **ketone** D) carboxylic acid

50. The Grignard reagents is a powerful

A) Electrophile B) free radical C) ions D) **nucleophile**

51. Esters having α-hydrogen on treatment with a strong base undergo self condensation to produce β-ketoesters is called as

A) Aldol condensation B) Stobbe condensation

C) **Claisen condensation** D) Dieckmann condensation

52. Intramolecular Claisen condensation in dibasic acid esters is called

A) Aldol condensation B) Stobbe condensation

C) Claisen condensation D) **Dieckmann condensation**

53. Aldehydes and ketones condense with the esters of succinic acid in the presence of base such as sodium ethoxide to give the salts of α,β-unsaturated half ester is known as

A) Aldol condensation B) **Stobbe condensation**

C) Claisen condensation D) Dieckmann condensation

54. Condensation of aldehydes and ketones with compounds having active methylene group in the presence of basic catalyst to form α,β-unsaturated compounds is called

A) Aldol condensation B) Stobbe condensation

C) **Knoevenagel condensation** D) Dieckmann condensation

55. Aldehydes and ketones condense with α-halo esters in the presence of bases to give α,β-epoxy esters called

A) **Darzens condensation** B) Stobbe condensation

C) Knoevenagel condensation D) Dieckmann condensation

56. Wittig reaction is very useful method for the synthesis of

A) Esters B) acids C) **alkenes** D) ketones

57. When certain aldehydes are treated with cyanide ion, benzoins are produced in a reaction called the

A) Darzens condensation B) **Benzoin condensation**

C) Knoevenagel condensation D)Dieckmann condensation

58. The reversible of polarity of carbonyl carbon is called

A) **Umpolung** B) nucleophile C) synthon D) synthetic equivalent

59. The compounds containing -OH, -NH_2, SH, -COOH or -SO3H Grignard reagents is fail due to

A) Grignard is a very powerful free radical B) Grignard is a very ions

C) **Grignard is a very strong base** D) Grignard is a very strong acid

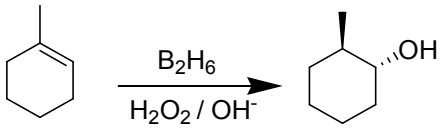
60. Grignard reagents cannot be prepared organic halide having a

A) **CN** B) OCH_3 C) SCH_3 D) SO_2Cl

PART-B (Each Question Carry Two Mark)

61. What is Claisen condensation?

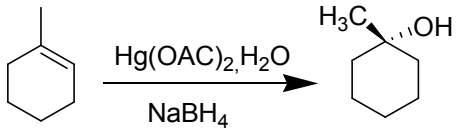
62. Write the mechanism of the following conversion.



63. Write a note on electroplilic addition.

64. What is Thorpe reaction?

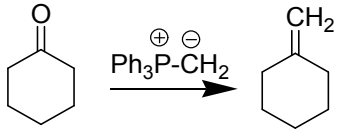
65. Explain the mechanism of the following conversion.



66. What is epoxidation reaction?

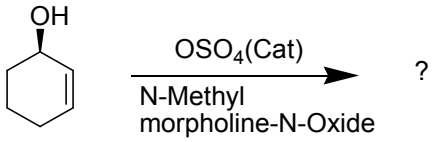
67. What is Benzoin condensation?

68. Write the mechanism of the following conversion.

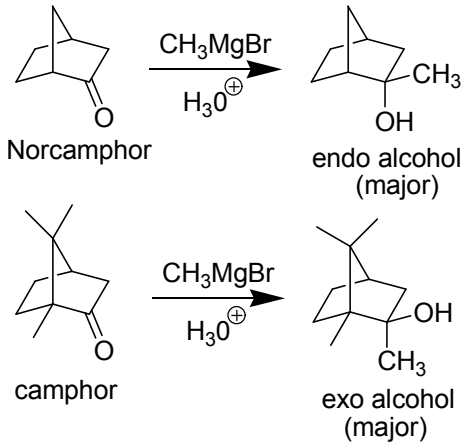


69. What is Darzen reaction?

70. Complete the following reaction. Provide the mechanism.



71. Explain the following observations:



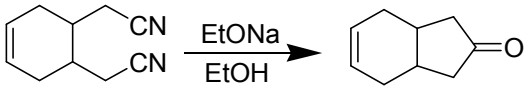
PART-C (Each Question Carry Six Mark)

72. Give an account on i) Hydroxylation ii) Epoxidation iii) Hydroboration

73. Discuss the mechanism of the following:

(i) Meerwein pondroff-verley reduction (ii) Wittig reaction.

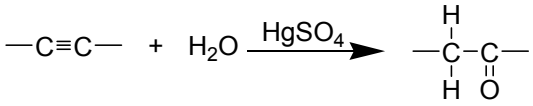
74. (i) Explain the mechanism of the following conversion.



(ii) Mention some applications of Benzoin condensation.

75. (i) What is Claisen condensation?

(ii) Write the mechanism of the following conversion.



76. Explain the Michael addition reaction with mechanism and application.

77. (i) Discuss the mechanism of Mannich reaction.

(ii) Mention some important applications of the Mannich reaction.

78. Write notes on Stobbe condensation.

79. (i) What are Grignard reagents? How are they prepared? Give the plausible mechanism by which the Grignard reagents are formed.

(ii) Discuss the Grignard synthesis of (a) alcohols, (b) carboxylic acids, (iii) aldehydes and (iv) ketones.

80. Write notes on (i) Darzen reaction (ii) Knovenagel condensation.

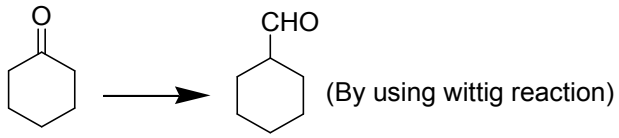
81. (i) What is meant by a addition reaction? Give examples.

(ii) Give the mechanism for electrophilic addition reaction.

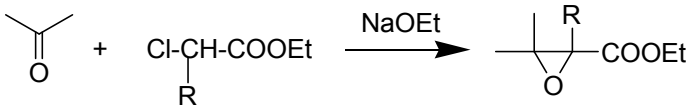
(iii) Give the mechanism for nucleophilic addition reaction.

PART-D (Each Question Carry Ten Mark)

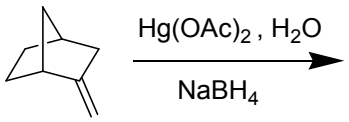
82. (i) Write the mechanism of the following conversion.



(ii) Write the mechanism of the following conversion.



(iii) Complete the following reaction. Provide mechanism.



KARPAGAM ACADEMY OF HIGHER EDUCATION
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DEPARTMENT OF CHEMISTRY

UNIT-II

ADDITION REACTIONS

PART-A–Multiple Choice Questions
(Each Question Carry One Mark) (Online Examinations)

1. An atom or group of atoms possessing an odd electron is called

A) ions B) **free radical** C) anion D) cation

2. A covalent bond breaks uniformly and is known as

A) heterolytic fission B) nuclear fission C) nuclear fusion D) **homolytic fission**

3. The stability of carbocation is

A) 1° > 2° > 3° B) 2° > 1° >3° C) **3° > 2° > 1°** D) 1° > 2° >3°

4. A reaction in which the substrate and the reagent add up to form product is called

A) **addition reaction** B) rearrangement reaction

C) elimination reaction D) substitution reaction

5. The electron-releasing group conjugated to carbon-carbon multiple bonds promote

A) electrophilic addition reaction B) free radical reaction

C) **nucleophilic addition reaction** D) electrophilic substitution reaction

6. The conjugation of electron-withdrawing group activates the carbon-carbon multiple bonds towards

A) electrophilic addition reaction B) free radical reaction

C) **nucleophilic addition reaction** D) electrophilic substitution reaction

7. The example for good leaving group is

A) OH B) CN C) NO_2 D) SOR

8. The electrophilic addition of 1-propene with HI gives

A) **2-iodo propane** B) 1-iodo propane C) 1-propyne D) 1-propanol

9. The recombination of radicals results in

A) rearrangement B) **radical coupling** C) free radical reaction D) initiation

10. The addition of HBr to 1-bromocyclohexene is regioselective in that it gave only

A) trans-1,2-dibromocyclohexane B) **cis-1,2-dibromocyclohexane**

C) meso-1,2-dibromocyclohexane D) racemic 1,2-dibromocyclohexane

11. Double bond can be hydrated by treatment with

A) **water and an acid catalyst** B) water and an base catalyst

C) methanol and an base catalyst D) mercuric acetate and an base catalyst

12. 2-Methyl-1-butene treated with mercuric acetate followed by sodium borohydride gave

A) 2-methyl-1-butanol B) methyl-2-butanol C) 1-methyl-2-butanol D) **2-methyl-2-butanol**

13. The addition of water to enol ethers causes hydrolysis to

A) acids B) **aldehydes** C) amides D) amines

14. Ketenes add water in the presence of acid gives

A) **acids** B) aldehydes C) amides D) amines

15. Decomposition of benzoyl peroxide in aromatic solvents leads to the generation of

A) benzoyl radical B) ethyl radical C) **phenyl radical** D) methyl radical

16. The conversion of acetylene into aldehyde is effected by

A) $Hg(OAC)_2/H_2O$ B) H_2O/H^+ **C)** $HgSO_2/H_2O$ D) **$HgSO_4/H_2O$**

17. The carboxylic acid is made by acid calalysed hydration of acetylenic ethers without a

A)acid catalyst B) **mercuric catalyst** C) base catalyst D) mercuric acetate catalyst

18. The most common reagent for the conversion of alkenes into cis-diol is

A) **OsO_4** B) SeO_2 C) $Hg(OAC)_2/H_2O$ D) I_2/PhCOOAg

19. The olefin is converted into trans diol can be achieved treatment with

A) O_sO_4 B) **H_2O_2/HCOOH** C) I_2, $AgOAc/H_2O$, H+ D) alkaline $KMnO_4$

20. Prevost anti hydroxylation, the alkene is treated with iodine and silver benzoate in a

A) 1:1 molar ratio B) 2:1 molar ratio C) **1:2 molar ratio** D) 3:2 molar ratio

21. Which reagent is used for Prevost anti hydroxylation

A) **I_2/PhCOOAg** B) I_2, $AgOAc/H_2O$, H+ C) O_sO_4 D) alkaline $KMnO_4$

22. The compounds having an active methylene group or having relatively acidic hydrogens are called

A) Acceptors B) receptors C) activators D) **donors**

23. The compounds having an activated olefinic bond are called

A) **Acceptors** B) receptors C) activators D) donors

24. Malonic ester is an example of

A) Acceptors B) receptors C) activators D) **donor**

25. The base catalysed addition of compounds having active methylene group to an activated olefinic bond of the type -C=C-Z is classified as

A) Aldol reaction B) **Michael reaction** C) Wittig reaction D) Mannich reaction

26. The hydration of triple bonds is generally carried out with

A) **mercuric ion salts as catalyst** B) HCl as catalyst

C) NaOH as catalyst D) mercuric ion salts as catalyst

27. Michael reaction is also called as

A) 1,2-addition B) 2,4-addition C) **1,4-addition** D) 3,4-addition

28. Aconitic acid is used in the preparation f medicines for

A) **Analgesic** B) antioxidant C) anticancer D) anti-HIV

29. The epoxidation reaction readily takes place in

A) polar solvent B) **nonpolar solvent** C) aprotic solvent D) protic solvent

30. The epoxidation addition is

A) regioselective B) regiospecific C) **stereo specific** D) stereo selective

31. The epoxidation of α,β-unsaturated ketones with hydrogen peroxide under basic conditions is known as the

A) **Waits-Scheffer epoxidation** B) harpless asymmetric epoxidation

C) Baeyer-Villiger oxidation D) Dakin oxidation

32. Which reagent is used for Sharplesss asymmetric epoxidatioon reaction?

A) peroxyacids B) **t-Bu-O-OH, Ti(Oi-Pr)4/diethyl tartrate**

C) H_2O_2/OH^- D) dimethyldioxrane

33. The condensation of a compound containing active methylene hydrogen with formaldehyde and ammonia or 1°or 2° amines usually as their hydrochlorides to form aminoethyl or substituted aminoethyl derivatives is known as

A) Aldol reaction B) Michael reaction C) Wittig reaction D) **Mannich reaction**

34. The Mannich reaction which amines do not responds

A) 1° amines B) 2° amines C) **aryl amines** D) 3° amines

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

A) Aldol reaction B) Michael reaction C) Wittig reaction D) **Mannich reaction**

36. Which amines is highly preferred for Mannich reaction

A) 1° amines B) **2° amines** C) aryl amines D) 3° amines

37. Tutocaine, a commercially useful anesthetic is prepared from

A) Aldol reaction B) Michael reaction C) Wittig reaction D) **Mannich reaction**

38. The amino acid, tryptophan is synthesized from the quaternary salt of

A) atropine B) **gramine** C) tropinone D) indole acetic acid

39. The reduction of aldehydes or ketones to alcohols by treatment with aluminium isopropoxide in excess of isopropyl alcohol is known as

A) **MPV reduction** B) Michael reaction C) Oppenauer oxidation D) Mannich reaction

40. The reverse reaction MPV reduction is called as

A) MPV reduction B) Michael reaction C) **Oppenauer oxidation** D) Mannich reaction

41. Which catalyst is used for MPV reduction?

A) aluminium chloride B) aluminium t-butoxide

C) **aluminium isopropoxide** D) aluminium hydroxide

42. Ketones with high enol content is failed for

A) Oppenauer oxidation B) **MPV reduction**

C) Mannich reaction D) Michael reaction

43. The synhthesis of chloromycetin from

A) Oppenauer oxidation B) **MPV reduction**

C) Mannich reaction D) Michael reaction

44. Grignard reagents are

A) organomanganase halides B) organoaluminium halides

C) **organomagnesium halides** D) organocopper halides

45. The formation of Grignard reagent involves the

A) **Single electron transfer** B) double electron transfer

C) triple electron transfer D) no electron transfer

46. The Grignard reagents behaves as

A) free radical B) ions C) **carbanion** D) carbocation

47. A Grignard reagent reacts with carbon dioxide to give a

A) alcohol B) aldehyde C) ketone D) **carboxylic acid**

48. A Grignard reagent reacts with ethyl formate to give an

A) alcohol B) **aldehyde** C) ketone D) carboxylic acid

49. A Grignard reagent reacts with an orthoester to give a

A) alcohol B) aldehyde C) **ketone** D) carboxylic acid

50. The Grignard reagents is a powerful

A) Electrophile B) free radical C) ions D) **nucleophile**

51. Esters having α-hydrogen on treatment with a strong base undergo self condensation to produce β-ketoesters is called as

A) Aldol condensation B) Stobbe condensation

C) **Claisen condensation** D) Dieckmann condensation

52. Intramolecular Claisen condensation in dibasic acid esters is called

A) Aldol condensation B) Stobbe condensation

C) Claisen condensation D) **Dieckmann condensation**

53. Aldehydes and ketones condense with the esters of succinic acid in the presence of base such as sodium ethoxide to give the salts of α,β-unsaturated half ester is known as

A) Aldol condensation B) **Stobbe condensation**

C) Claisen condensation D) Dieckmann condensation

54. Condensation of aldehydes and ketones with compounds having active methylene group in the presence of basic catalyst to form α,β-unsaturated compounds is called

A) Aldol condensation B) Stobbe condensation

C) **Knoevenagel condensation** D) Dieckmann condensation

55. Aldehydes and ketones condense with α-halo esters in the presence of bases to give α,β-epoxy esters called

A) **Darzens condensation** B) Stobbe condensation

C) Knoevenagel condensation D) Dieckmann condensation

56. Wittig reaction is very useful method for the synthesis of

A) Esters B) acids C) **alkenes** D) ketones

57. When certain aldehydes are treated with cyanide ion, benzoins are produced in a reaction called the

A) Darzens condensation B) **Benzoin condensation**

C) Knoevenagel condensation D) Dieckmann condensation

58. The reversible of polarity of carbonyl carbon is called

A) **Umpolung** B) nucleophile C) synthon D) synthetic equivalent

59. The compounds containing -OH, $-NH_2$, SH, -COOH or $-SO_3H$ Grignard reagents is fail due to

A) Grignard is a very powerful free radical B) Grignard is a very ions

C) **Grignard is a very strong base** D) Grignard is a very strong acid

60. Grignard reagents cannot be prepared organic halide having a

A) **CN** B) OCH_3 C) SCH_3 D) SO_2Cl

UNIT-III

Electrophilic substitution reactions: Aromatic electrophilic substitution reactions-formylations–Gattermann, Gattermann Koch, Riemer Tiemann and Vilsmeier-Haack reactions. Kolbes, Bischler-Napieralski and Hofmann-Martius reactions. Friedel crafts alkylation and acylations.

Aliphatic electrophilic substitution reactions - mechanisms- SE1, SE2 and SEi - structure reactivity relationship, typical electrophilic substitution reactions - Friedel crafts acylation at olefinic carbon, Stork enamine reaction and decarboxylation of aliphatic acids.

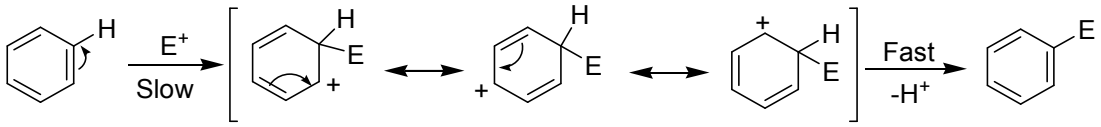
ELECTROPHILIC SUBSTITUTION REACTIONS

Introduction

Electrophilic substitution reactions, unlike nucleophilic substitutions proceed by a common bimolecular mechanism, via the formation of an intermediate which constitutes the rate determining step. The attacking species may be produced in various ways, even for the same reaction. Herein, the same reaction may produce different attacking species under different experimental conditions of temperature, concentration, and catalyst. It is important to find that what is happening to the benzene ring is practically the same in all the cases.

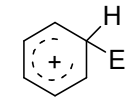
Mechanism of electrophilic substitution in benzene

The attacking electrophilic attacks the benzene ring, removes a pair of electrons from the aromatic sextet and forms a carbonium ion as shown below:



In the formation of carbonium ion, the carbon atom, which is attacked, changes its state of hybridization from sp^2 (trigonal) to sp^3 (tetrahedral) and thus this carbon atom cannot participate in the conjugation of the benzene ring. This type of carbonium ion is called a σ-complex.

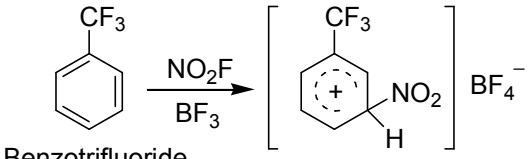
Though the intermediate (σ-complex) is not benzenoid, it still contains two conjugated double bonds which can stabilize it by resonance. This stabilization is, however, lesser than that present in a perfect benzenoid structure and, therefore, its stabilization energy is comparatively lower. The three canonical forms represented in the first step of the above reaction can also be represented by the resonance hybrid:



σ–complex

The second step, involving the expulsion of a proton, is generally very fast as compared to the first step (the formation of carbonium ion).

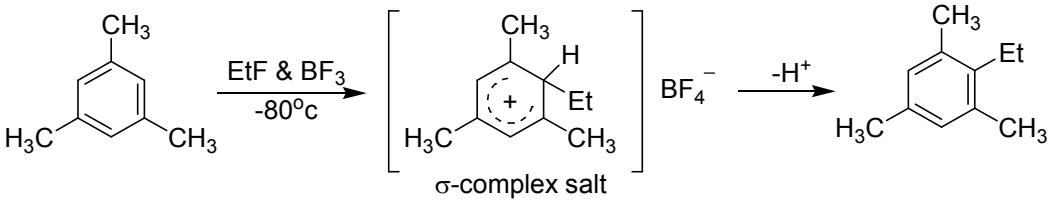
The carbonium ion described above has been given several names e.g., *benzenium cation*, *cyclohexadienyl cation*, *Wheland intermediate*, etc. This σ-complex or carbonium ion is very unstable and thus cannot be isolated. In special cases, such as the nitration of benzotrifluoride with nitryl fluoride (NO_2F) and boron trifluoride at low temperatures, this intermediate can also be isolated.



Benzotrifluoride

Crystalline salt at very low terperature

The σ-complex has also been isolated as a salt in the following reaction:



σ-complex salt

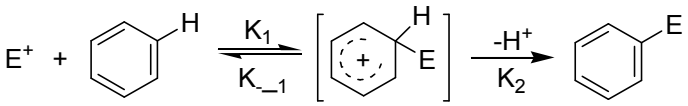
The above σ-complex salt is a solid (m. pt -15°C) and it decomposes on heating to give the product. The relative stabilities of the above adducts are associated with the stability of the fluoroborate anion. The isolation of σ-complex in such cases supports the above mechanism.

This mechanism is very much different from the common S_N1 mechanism (which also involves the carbonium ion formation) because it has been shows by isotopic studies that in this case the leaving group does not depart before the arrival of the attacking species.

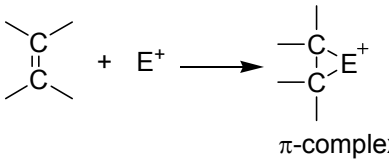
The σ-complex mechanism is further supported by the isotopic studies. As in this mechanism, the C—H bond is not broken in the rate determining step, no isotopic effect should be observed on replacing H by D. This has actually been confirmed by taking a deuterated substrate, when it is seen that the deuterated substance undergoes substitution at

exactly the same rate as the non-deuterated one. In most of the cases, especially in the nitration and bromination of aromatic compounds, no such isotope effect has been observed.

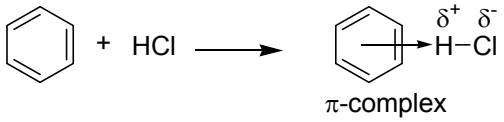
However, in some cases, isotope effect have been observed, e.g., in the sulphonation reactions. In such cases, the values of isotope effects are much lower than expected by any of the mechanisms other than the σ-complex mechanism and the reason for the observed isotopic effect should be looked somewhere else in the process. Existence of a small isotope effect, thus does not rule out the σ-complex mechanism. The σ-complex mechanism of electrophilic aromatic substitution may be summarized:



Comparison of addition complexes formed by olefins and arenes. When an electrophilic substitution attacks an olefin, it forms an adduct known as π-complex.



A similar situation may also be visualized in the case of an aromatic electrophilic substitution reaction. An electrophilic attacks the benzene ring and initially forms this type of a π-complex, before actually removing in electron pair from the ring to form a σ-complex. In the reaction of toluene and HCl, such a complex has been observed spectroscopically.



The π-complex would represent an energy maximum on the energy diagram of the reaction. If the leaving group also forms a similar complex before it finally leaves the environment of the ring, the energy profile of the reaction would appear as in Figure 1 or 2 depending upon the stability of the π-complex.

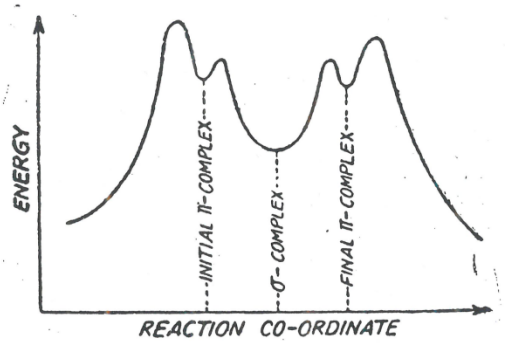


Figure 1

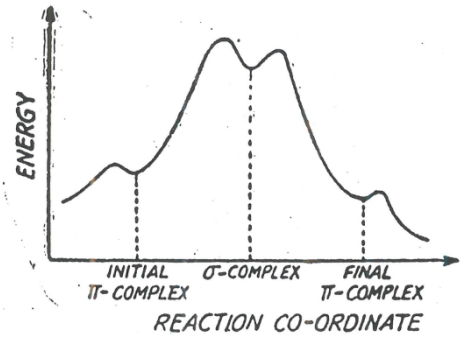
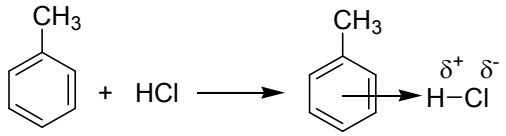
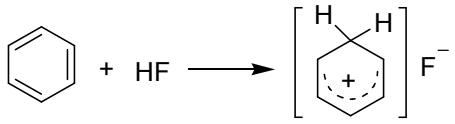


Figure 2

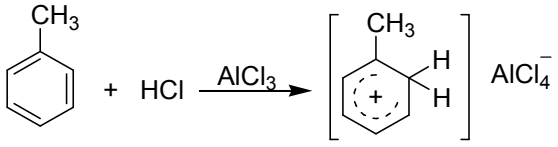
The stabilities of the π-complexes have been compared relative to the equilibrium constant of the reaction,



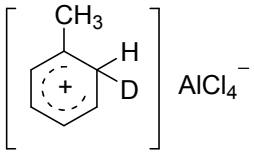
whereas the stabilities of the σ-complexes have been determined by the relative basicity of the substrate towards HF.



In should be noted that when an electron deficient compound, capable of occupying an electron pair is also present in the reaction mixture, σ-complexes are formed instead of π-complexes, as in the reaction of toluene with HCl in the presence of $AlCl_3$.



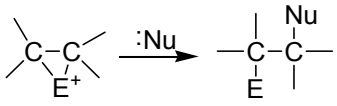
This proved y the significant change in the absorption spectrum when the reaction is carried out with DCl instead of HCl, because actual bonding takes place between the carbon of the benzene ring and D^+ in this case.



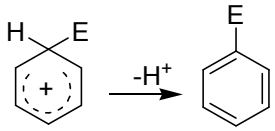
In the case of a π-complex, however, this bond formation does not occur as evidenced by the absence of a significant change in the absorption spectrum and the isotopic effect is also absent. Conductivity measurements also support the same view that a σ-complex is

formed when an electron deficient compound is present in the reaction medium. Thus the presence of a Lewis acid will increase the rate of formation of a σ-complex and will facilitate electrophilic aromatic substitution. This has been confirmed by careful experimental observations.

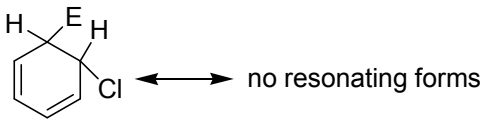
The basic difference in the electrophilic addition to olefins and the electrophilic substitution in arenes lies in the second step. In the case of olefins, the reaction is completed by the addition of a nucleophile,



whereas in arenes, the concluding step is the expulsion of a proton,



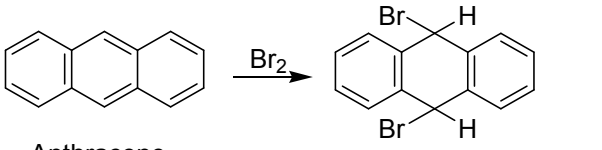
In aromatic compounds, the second step is an elimination reaction rather than the addition of a nucleophile; because removal of the proton provides the stabilization energy whereas in the case of addition as the concluding steps, whatever stabilization energy of the cation due to resonance of the positive charge over two conjugated double bond is there, is also lost as shows below.



This is way the addition of one mole of H_2 benzene is endothermic, whereas reduction of ethylene is exothermic by about 33 kcal/mole. Thus aromatic compounds, in general are characterized by their undergoing substitution reactions just as olefins are characterized by addition reactions.

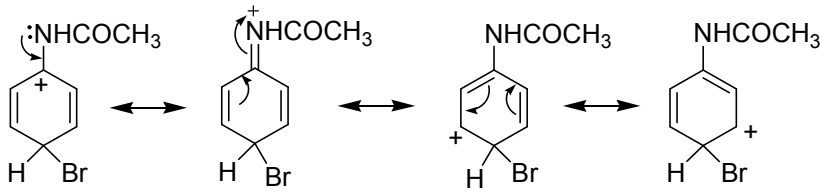
Aromatic compounds react less rapidly than olefins with a given electrophile. For example, benzene is hardly affected by Br_2 whereas ethylene readily reacts with it. This is because addition to benzene leads to more endothermic reaction than that to ethylene as in benzene, the intermediate carbonium ion is accompanied by the loss of aromatic stabilization energy, which is not completely offset by the delocalization energy of the resulting ion.

Although benzene and its simple derivatives are inert to addition; compounds in which two benzene rings are fused together are often quite susceptible to addition. For example, addition of bromine to anthracene is a well-known reaction.

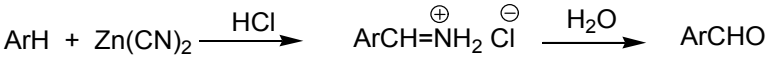


Anthracene 9, 10-Dibromoanthracene

Some substituted benzenes react very rapidly with electrophiles, e.g., dimethylaniline and acetanilide undergo bromination more readily than benzene. This is because certain substituents are able to stabilize the carbonium ion intermediate and hence the preceding transition state. This extra stabilization acquired is due to the contribution of more canonical structures, e.g., in the case of acetanilide, the positive charge is also delocalized over nitrogen in addition to three nuclear carbon atoms of the benzene nucleus.



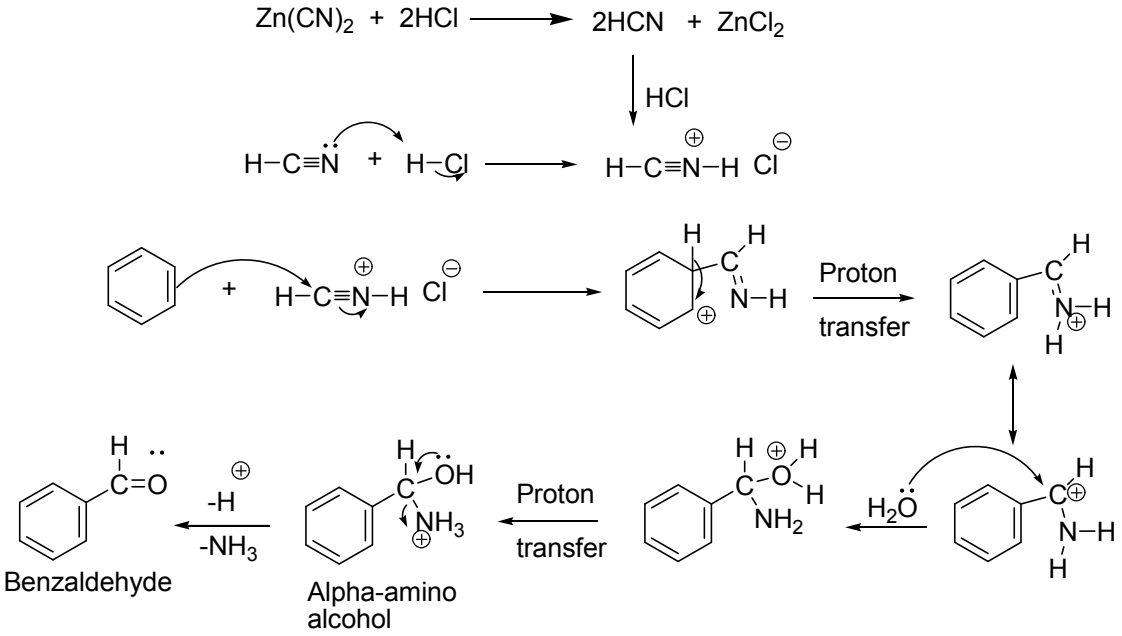
Gattermann reaction



Formylation with $Zn(CN)_2$ and HCl is called the *Gattermann reaction*. It can be applied to alkylbenzenes, phenols and their ethers, and many heterocyclic compounds. However, it cannot be applied to aromatic amines. In the original version of this reaction the substrate was treated with HCN, HCl, and $ZnCl_2$, but the use of $Zn(CN)_2$ and HCl (HCN and $ZnCl_2$ are generated *in situ*) makes the reaction more convenient to carry out and yields are not diminished.

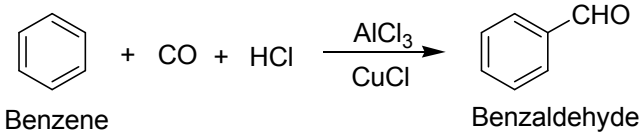
The mechanism of the Gattermann reaction has not been investigated very much, but it is known that an initially formed but not isolated nitrogen-containing product is hydrolyzed to aldehyde. This product is presumed to be $ArCH=NH_2^+Cl^-$, as shown. When benzene was treated with NaCN under superacid conditions (F_3CSO_2OH-SbF_5), a good yield of product was obtained, leading to the conclusion that the electrophile in this case was $^+C(H)=N^+H_2$.

Mechanism

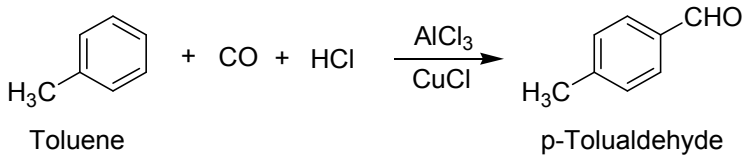


Gattermann–Koch reaction

Formylation of benzene and alkylbenzene with carbonmonoxide (CO) and hydrogen chloride (HCl) in the presence of aluminium chloride ($AlCl_3$) and cuprous chloride (CuCl) is known as the Gattermann-Koch reaction.



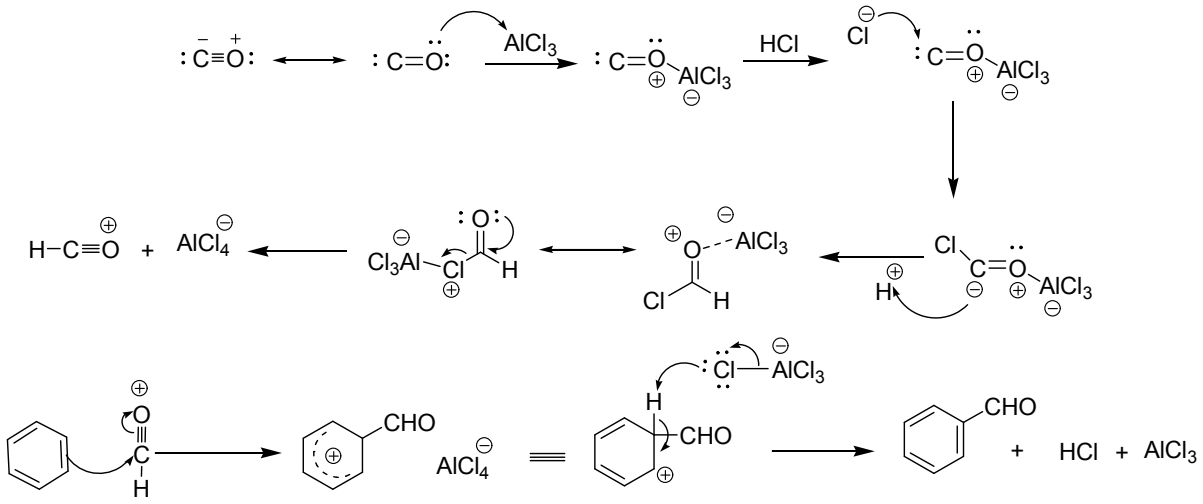
Usually, nitrobenzene or ether is used as solvent. In the case of alkylbenzene, the aldehyde group is introduced into the para position only. This method is used industrially to prepare arylaldehydes.



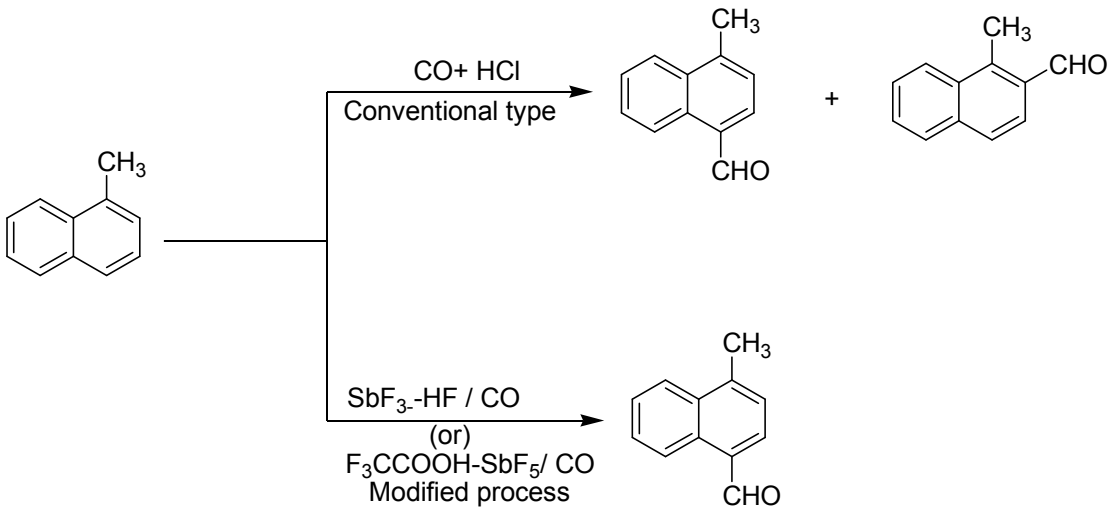
The Gattermann-Koch aldehyde synthesis is not applicable to phenols or their ethers, amino aromatic species and also when the aromatic ring is strongly deactivated (nitrobenzene).

Mechanism

The Gattermann-Koch formylation is considered as a typical elelctrophilic aromatic substitution with high para regioselectivity .The most likely electrophile is the acylium ion [H-$^{+}$C=O] in the ion pair [HCO]$^{+}$ [AlCl4]$^{-}$. Common factors such as electron density of the aromatic substrate, reactivity of electrophile, stability of reaction intermediates, and steric factors may influence the regioselectivity.



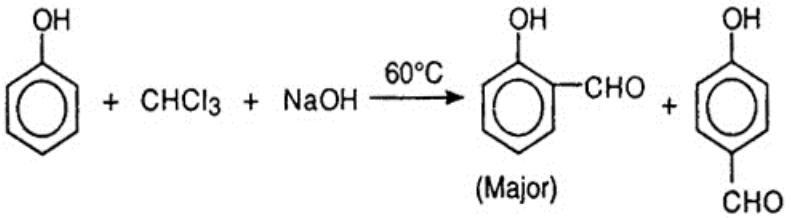
Application

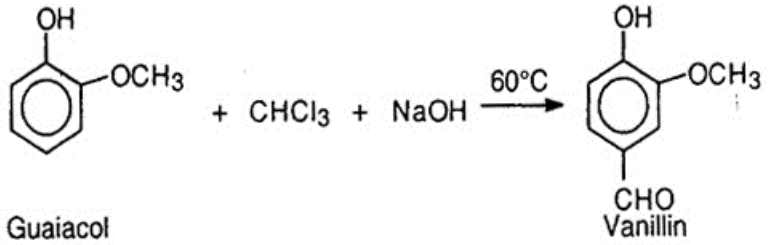


Reimer–Tiemann Reaction

Formylation of phenols with chloroform in alkaline solution is known as Reimer-Tiemann reaction (RTR). The method is applicable to phenols and some heterocyclic compounds.

A mixture of ortho- and para-isomers is obtained in which the ortho isomer predominates. If one of the ortho positions is occupied, the para-isomer is the major product.

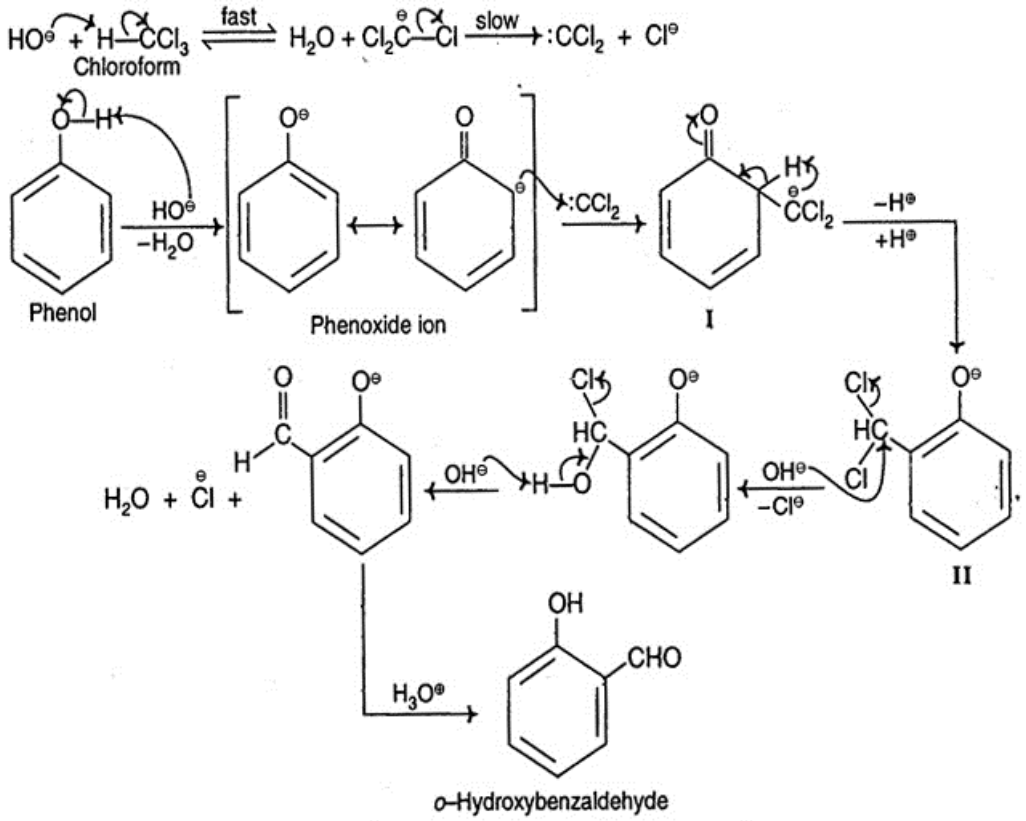




The reaction is carried out by refluxing an alkaline solution of phenol and chloroform at 60ºC for sometime (1/2 h). Excess chloroform is distilled off, the mixture acidified with sulphuric acid and steam distilled. Unreacted phenol and the ortho-isomer distil over leaving behind the para-isomer. The two isomers are further purified by sodium bisulphite. The yield is low.

Mechanism

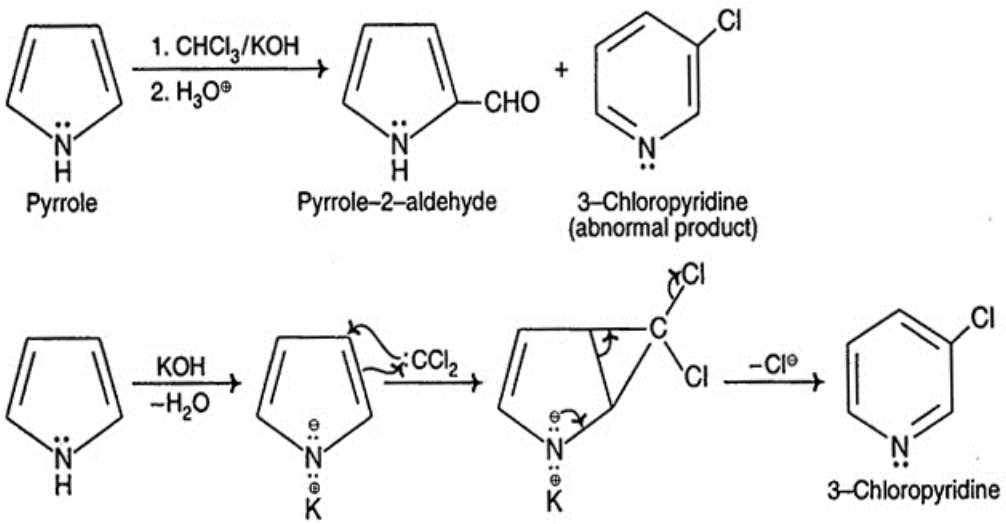
The mechanism of the reaction involves electrophilic substitution on the highly reactive phenoxide ring by dichlorocarbene, $:CCl_2$, the electrophilic reagent generated from chloroform by the action of alkali through an α-elimination reaction. The mechanistic pathway of the reaction may be sketched as follows:



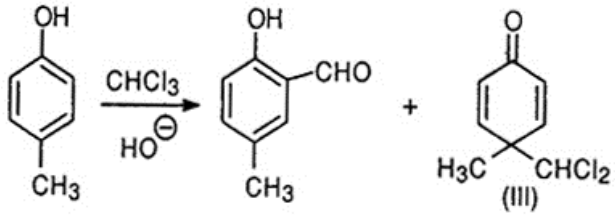
The highly electrophilic dichlorocarbene attacks the activated ortho-position of the phenoxide ring to form an unstable intermediate (I) which by a proton-shift is converted into a phenoxide ion containing a dichloromethyl group (II). Alkaline hydrolysis of the resulting dichloro compound followed by acidification gives the corresponding aldehyde (salicylaldehyde). The para-isomer is obtained through a similar pathway.

That the reacting species is dichlorocarbene is supported by the following:

(i) Dichlorocarbene is known to cause ring expansion which is observed in the reaction of pyrrole with chloroform and alkali.

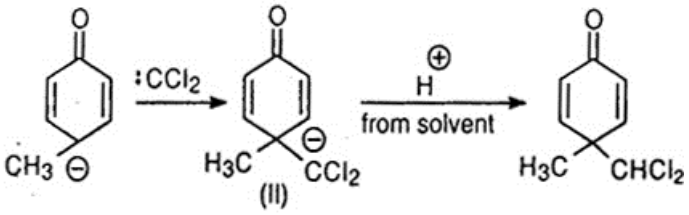


(ii) When p-cresol instead of phenol is used besides the normal aldehyde, a ketone (III) with dichloromethyl group is obtained as a by-product.



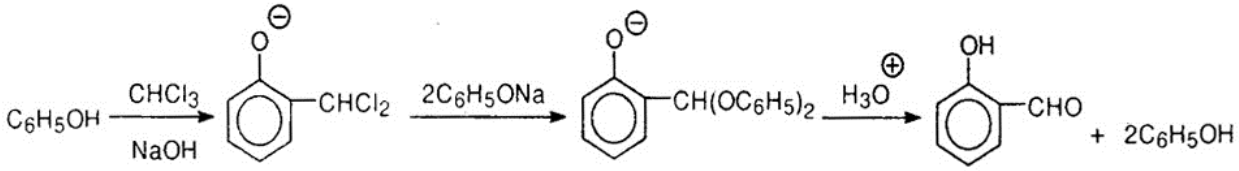
The compound (III) may be explained to be formed by the attack of some $:CCl_2$ at the para position and subsequent gain of a proton form the solvent. As this para position has no ring H that can be lost as proton to re-aromatise the ring, the reaction does not proceed further.

Due to its insolubility in basic aqueous medium and crowding around chlorine atoms, the dichloro compound (III) is not hydrolysed.



The presence of negative groups such as CN, COOH, NO_2, SO_3H, etc., decreases the yield.

The yield is nearly 50% and a large amount of phenol remains unreacted. This is probably due to the formation of diphenylacetal derivative.

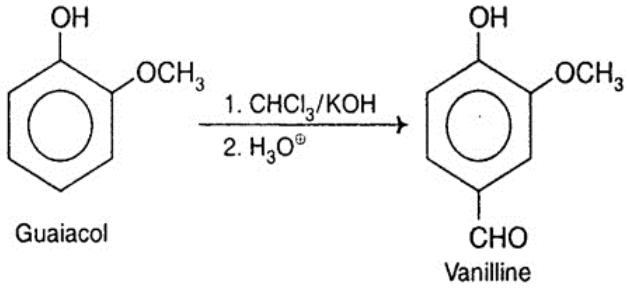


Carbon tetrachloride in placed of chloroform under RTR condition gives salicylic acid.

Applications

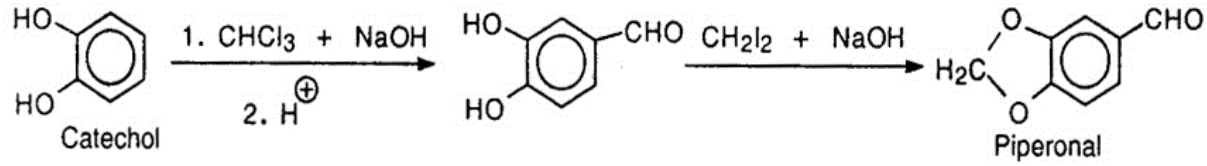
The reaction affords a good method for introducing aldehyde or carboxyl group in phenols.

(i) Preparation of vanilline



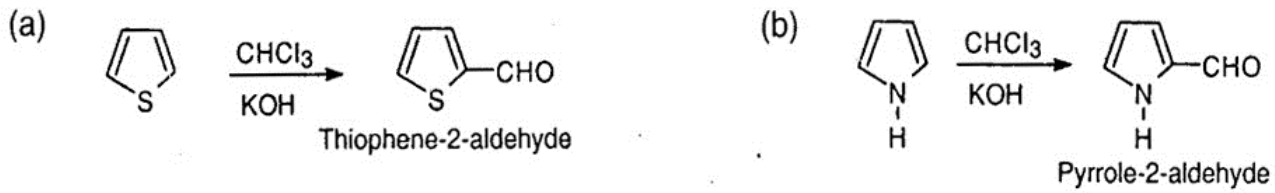
Vanilline has long been used for flavouring different kinds of foods and perfumes.

(ii) Preparation of piperonal

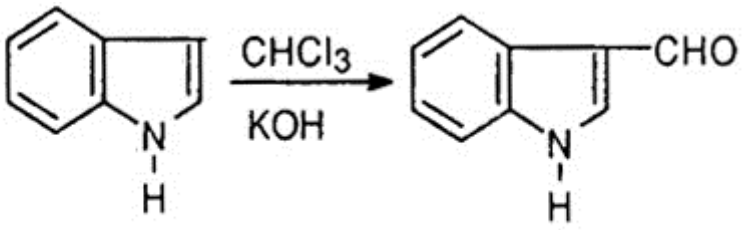


This 3,4-dihydroxybenzaldehyde is used to synthesize piperonal which provides a floral and spicy sweetness to perfumes.

(iii) Formylation of heterocyclic compounds



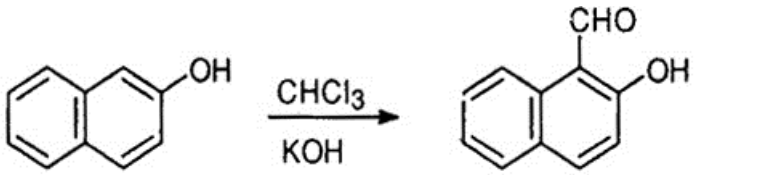
(c)



β-Indole-aldehyde

Indole-3-aldehyde has been used to synthesize the essential amino acid, tryptophan.

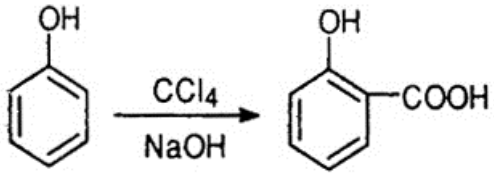
(iv) Formylation of naphthol



2-Naphthol 2-Hydroxy-1-naphthaldehyde

(v) Preparation of acid

When carbon tetrachloride in place of chloroform is used, a carboxyl group is introduced.



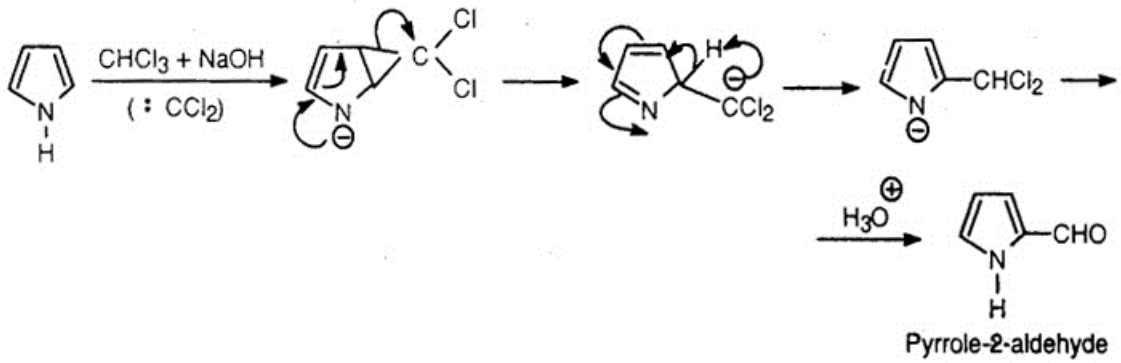
Salicylic acid

Salicylic acid is used to synthesize the pain killer drugs aspirin and methyl salicylate.

(vi) Abnormal Reimer–Tiemann reaction

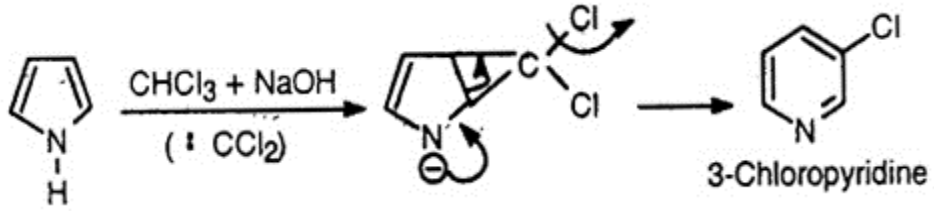
1. Pyrrole undergoes normal and abnormal RTR

Normal reaction-



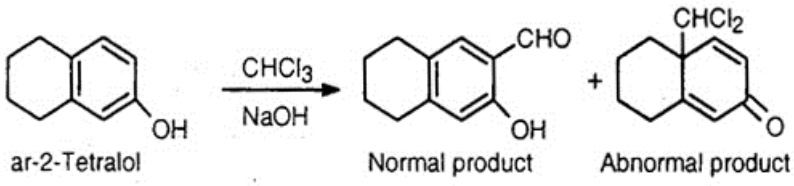
Pyrrole-2-aldehyde

Abnormal reaction (ring expansion)-

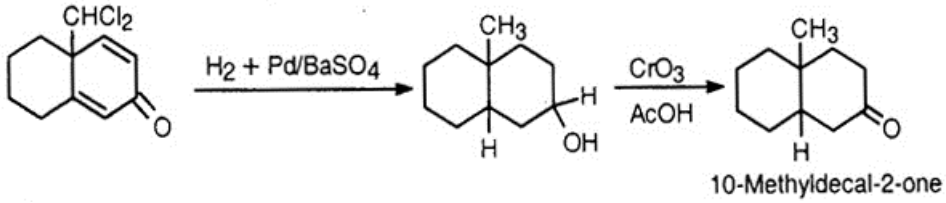


The reaction has been used to prepare pyridine and its derivatives.

(vii) Certain phenolic compounds also exhibit normal and abnormal RTR



The abnormal product may be reduced and then oxidized to give a product with angular methyl group. The process has been utilized in steroid chemistry.

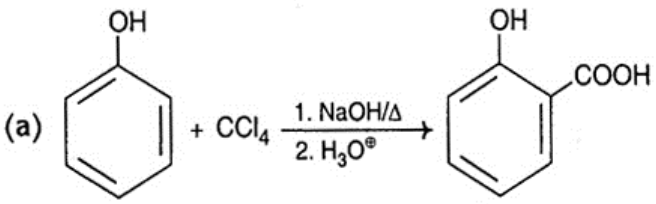


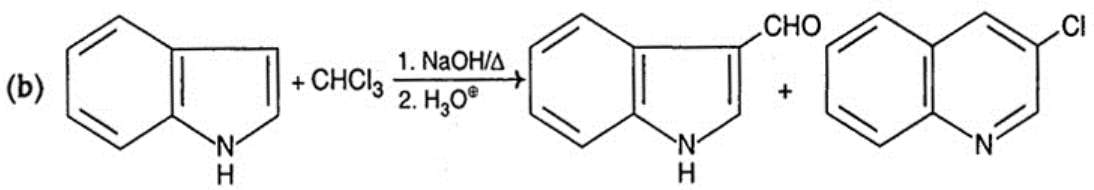
(1) How is *o*-hydroxybenzaldehyde (salicyladehyde) isolated from the product mixture?

Solution:

The *o*-hydroxybenzaldehyde is separated from the *p*-isomer by steam distillation and that is because the former is appreciably volatile in steam due to intramolecular hydrogen bonding. The distillate containing the *o*-isomer plus some unreacted phenol is then treated with saturated sodium bisulphite solution. The bisulphite addition compound on decomposition with dilute sulphuric acid gives *o*-hydroxybenzaldehyde.

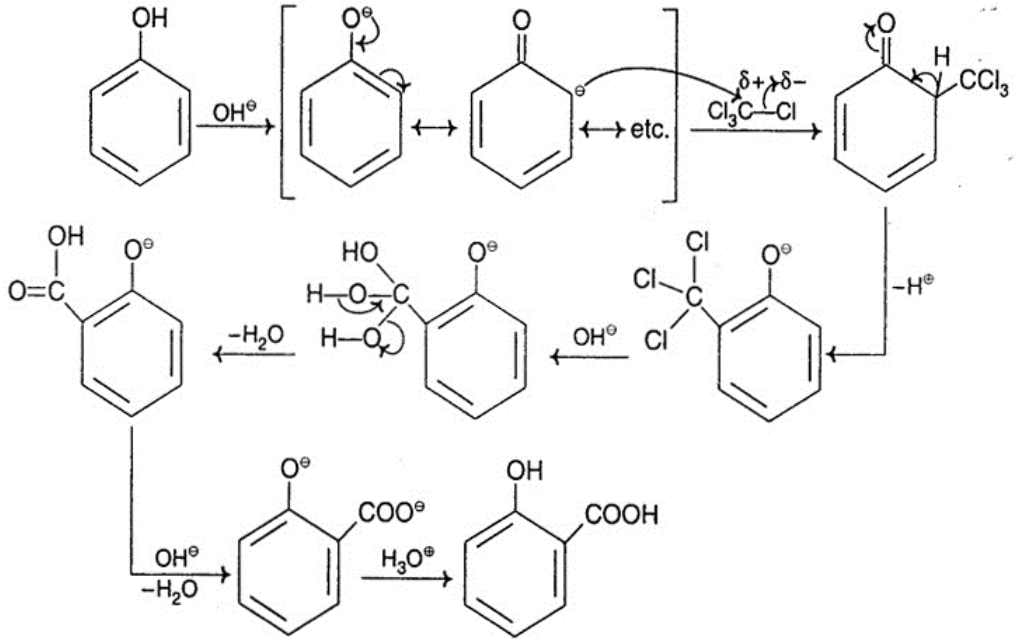
(2) Sketch the mechanistic steps of the following reactions:



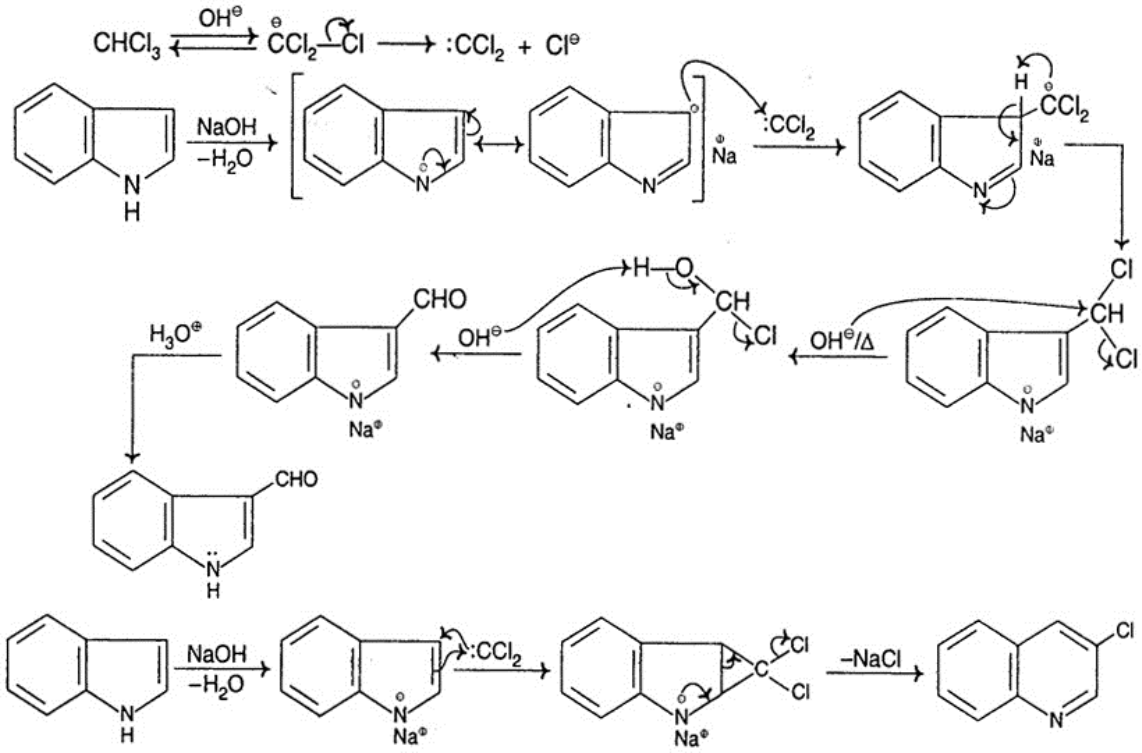

(b)
+ CHCl3
1. NaOH/Δ
2. H3O⊕
CHO
Cl
N
H

Solution:

(a)

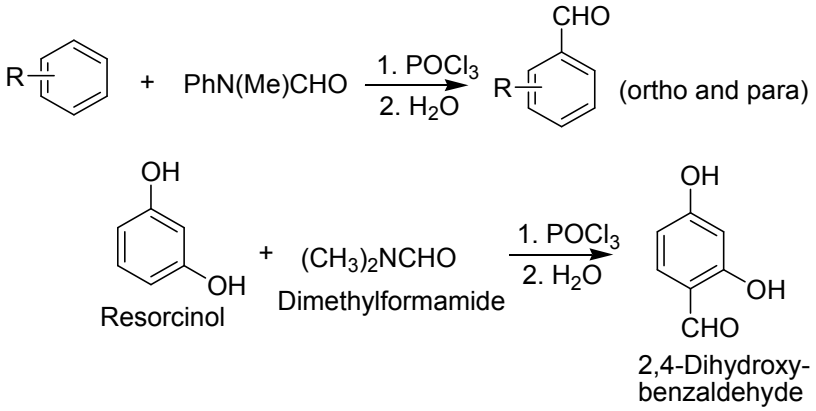

OH
OH⊖
etc.
δ+ δ−
Cl3C—Cl
CCl3
−H⊕
OH⊖
−H2O
HO
COO⊖
COOH
H3O⊕

(b)


CHCl3
OH⊖
:CCl2 + Cl⊖
NaOH
−H2O
Na
:CCl2
CCl2
CHO
OH⊖
OH⊖/Δ
H3O⊕
Cl
CH
Na⊕
−NaCl

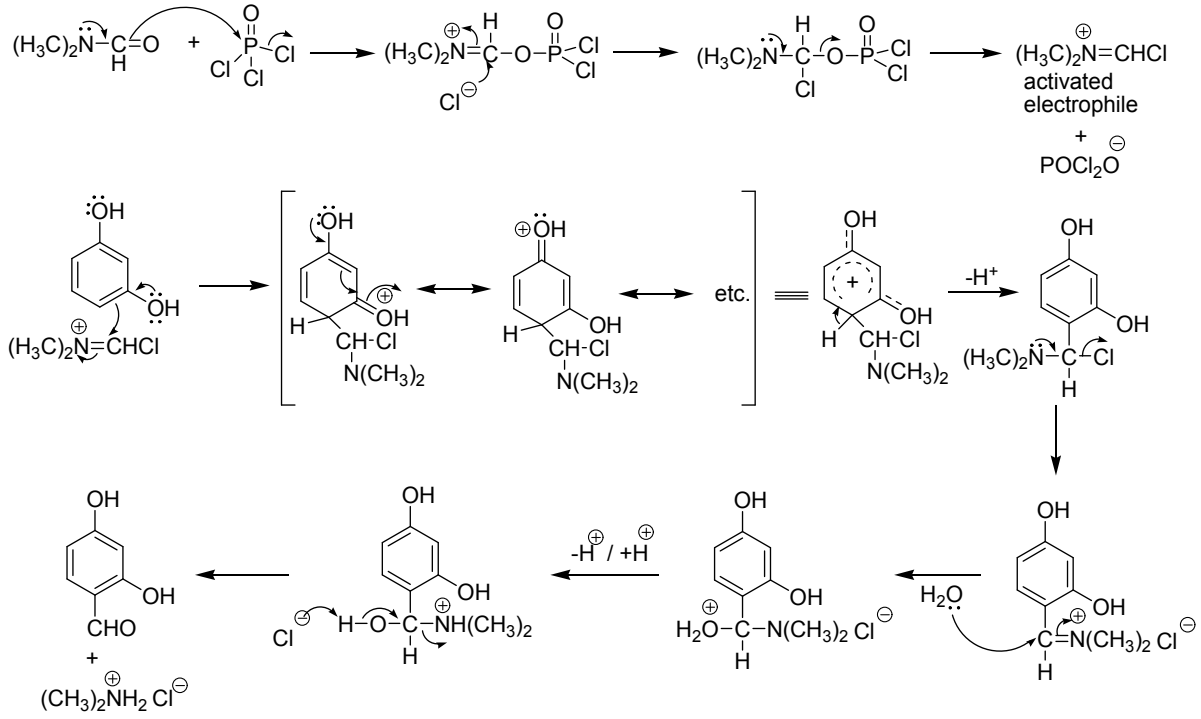
Vilsmeier-Haack reaction

Formylation of electron-rich (i.e., activated) aromatic or heterocyclic compounds with *N*,*N*-disubstituted formamides and phosphorus oxychloride is known as Vilsmeier-Haack reaction. *N*-Phenyl-*N*-methylformamide is a common reagent, although other arylallkyl amides and dialkylamides are also in use. Aromatic hydrocarbons and heterocycles, which are more active than simple benzene can also be formylated by this process. For example:

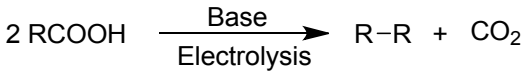


Mechanism

N,*N*-Dimethylformamide reacts with phosphorus oxychloride to give the active electrophile, Me_2N^+=CHCl (chloriminium ion), which in turn reacts with the activated substrate to give, after hydrolysis, 2,4-dihydroxybenzaldehyde. The mechanism of the reaction is given below.

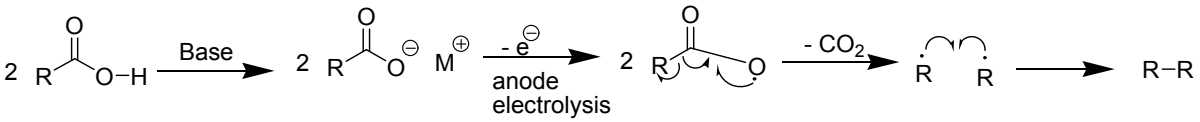


Kolbe reaction



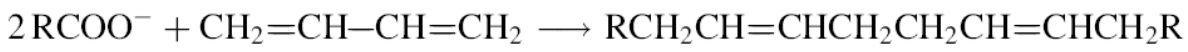
Electrolysis of carboxylate ions, results in decarboxylation and combination of the resulting radicals to give the coupling product R-R. This coupling reaction is called the *Kolbe reaction* or the *Kolbe electrosynthesis*. It is used to prepare symmetrical R-R, where R is straight chained, since little or no yield is obtained when there is a branching. The reaction is not successful for R= aryl. Many functional groups may be present, though many others inhibit the reaction. Unsymmetrical RR' have been made by coupling mixtures of acid salts.

A free-radical mechanism is involved:



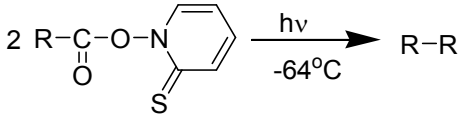
There is much evidence for this mechanism, including side products (RH, alkenes) characteristic of free-radical intermediates and the fact that electrolysis of acetate ion in the presence of styrene caused some of the styrene to polymerize to polystyrene (such polymerizations can be initiated by free radicals). Other side products (ROH, RCOOR) are sometimes found, stemming from further oxidation of the radical $R^{\bullet}$ to a carbocation R^{+}.

When the reaction is conducted in the presence of 1,3-dienes, additive dimerization can occur:



The radical $R^{\bullet}$ adds to the conjugated system to give $RCH_2CH{=}CHCH_2^{\bullet}$, which dimerizes. Another possible product is $RCH_2CH{=}CHCH_2R$, from coupling of the two kinds of radicals.

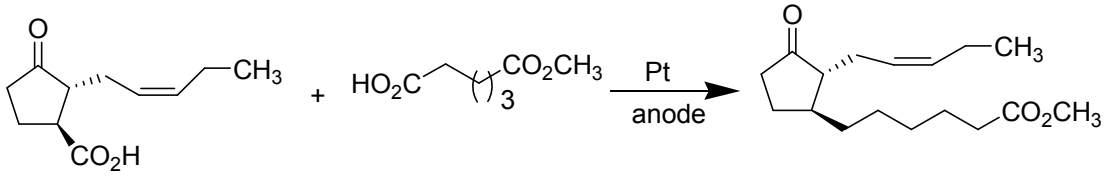
In a nonelectrolytic reaction, which is limited to R = primary alkyl, the thiohydroxamic esters **40** give dimers when irradiated at -64°C in an argon atmosphere:



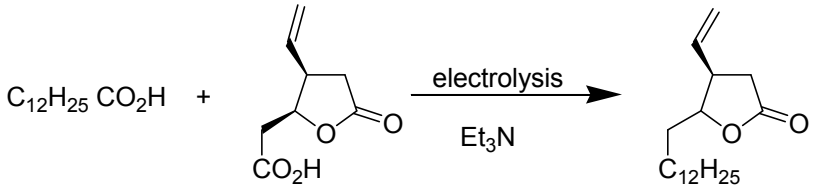
In another nonelectrolytic process, aryl acetic acids are converted to *vic*-diaryl compounds $2ArCR_2COOH \rightarrow ArCR_2CR_2Ar$ by treatment with sodium persulfate $Na_2S_2O_8$ and a catalytic amount of $AgNO_3$. Photolysis of carboxylic acids in the presence of Hg_2F_2 leads to the dimeric alkane via decarboxylation. Both of these reactions involve dimerization of free radicals. In still another process, electrondeficient aromatic acyl chlorides are dimerized to biaryls ($2\ ArCOCl \rightarrow Ar\text{-}Ar$) by treatment with a disilane R_3SiSiR_3 and a palladium catalyst.

Examples

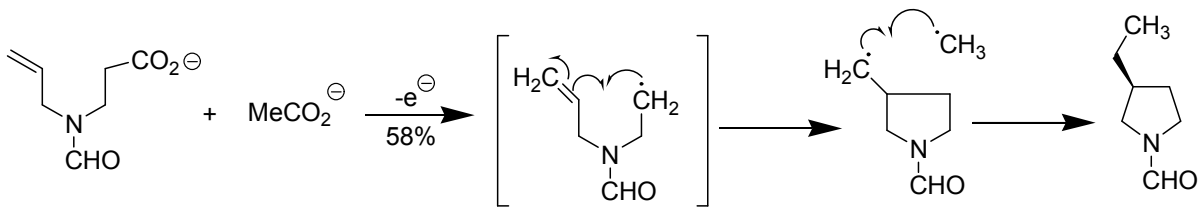
1.



2.



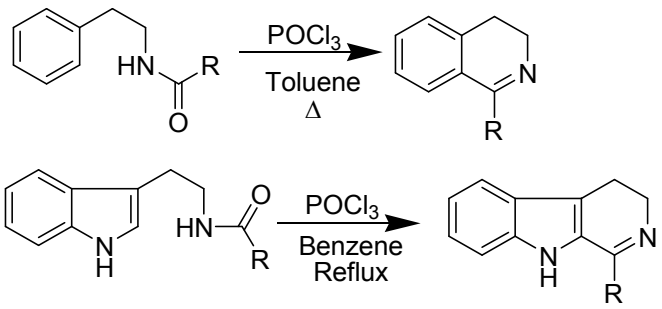
3.



Bischler–Napieraski reaction

The Bischler–Napieralski reaction is an intramolecular electropilic aromatic substitution reaction that allows for the cyclization of β-arylethylamides or β-arylethyl carbamates. It was first discovered in 1893 by August Bischler and Bernard Napieralski in affiliation with Basle chemical works and the University of Zurich.

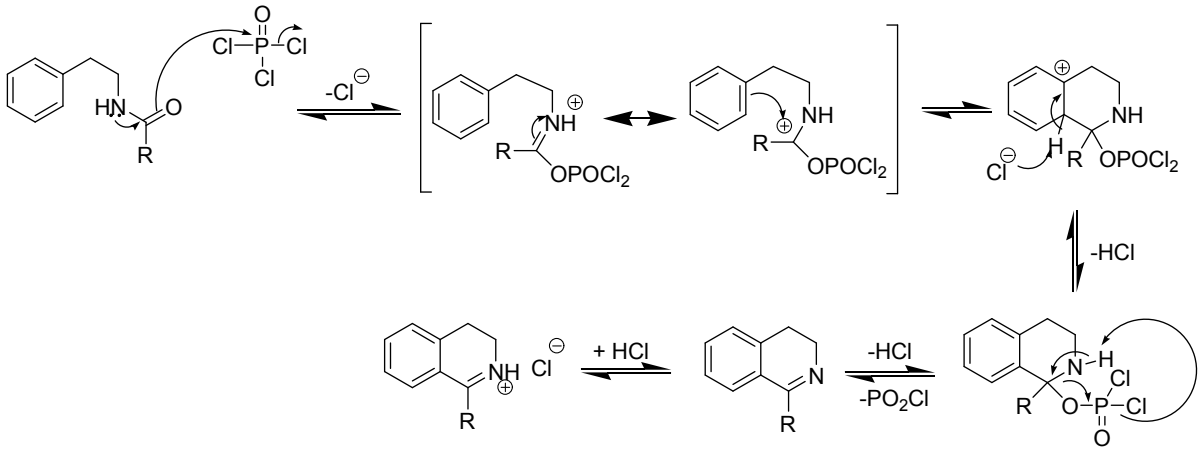
The reaction is most notably used in the synthesis of dihydroisoquinolines which can be subsequently dehydrated to isoquinolines.



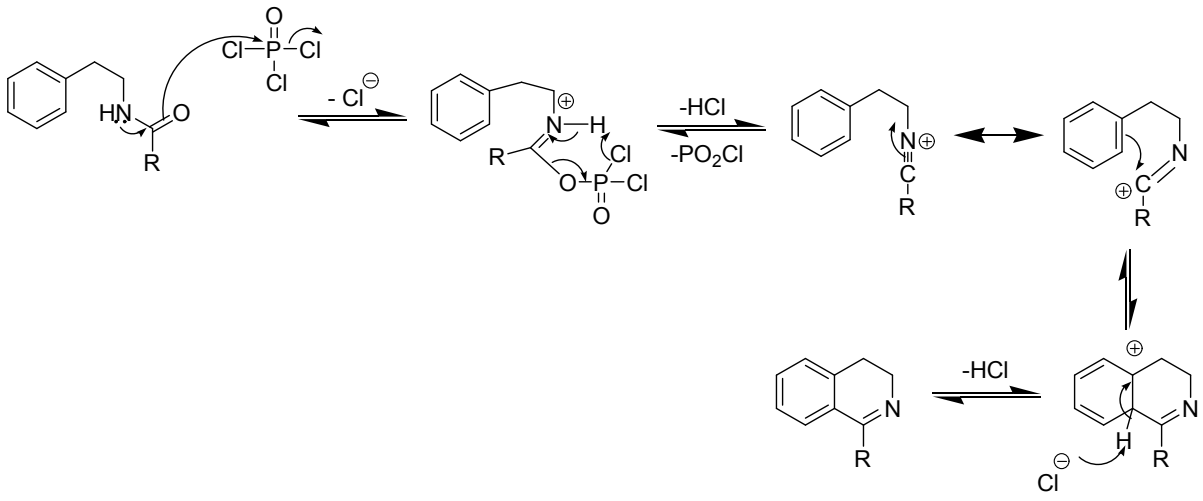
Mechanism

Two types of mechanisms have appeared in literature for the Bischler-Napieralski reaction. Mechanism I involves a dichlorophosphoryl imine-ester intermediate while mechanism II involves a nitrilium ion intermediate.

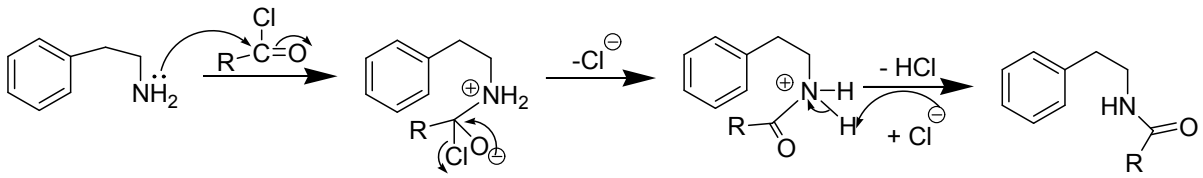
Mechanism I



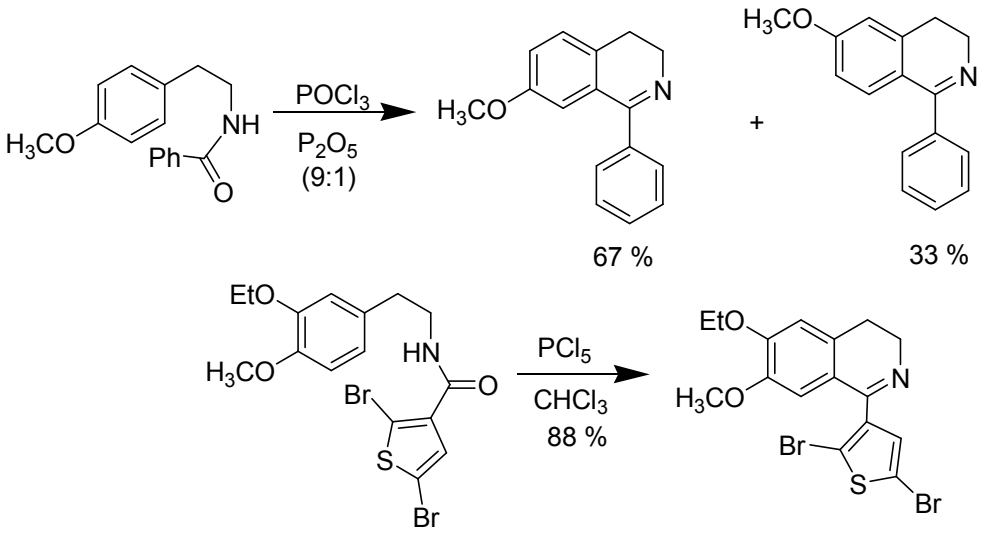
Mechanism II



Starting material preparation

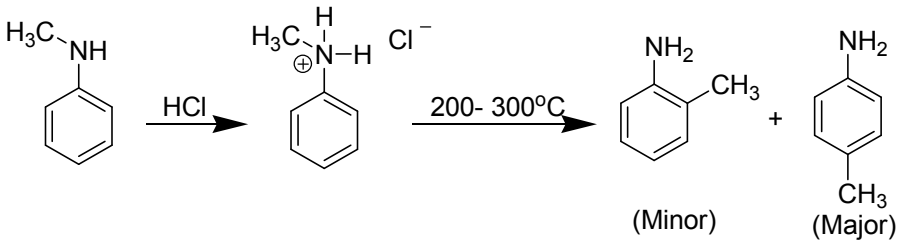


Examples



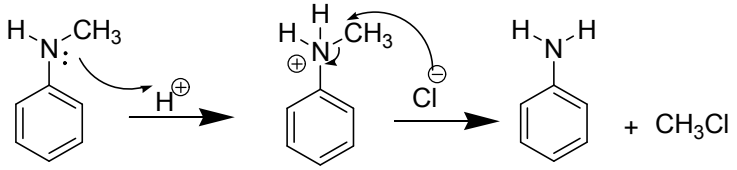
Hofmann- Martius reaction

When HCl salts of arylalkylamines are heated at ~200–300°C, migration occurs in what is called the *Hofmann–Martius reaction*.

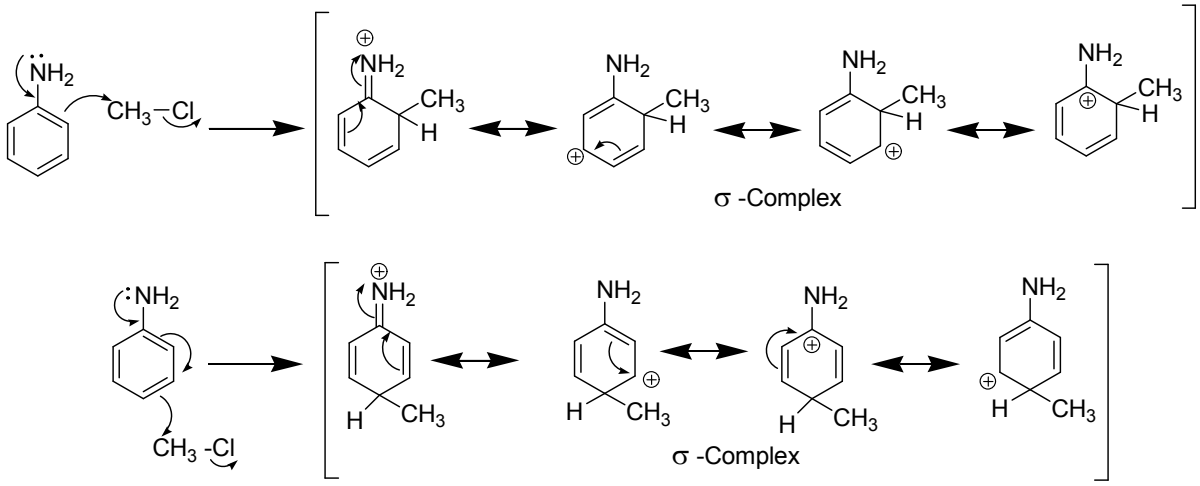


Mechanism

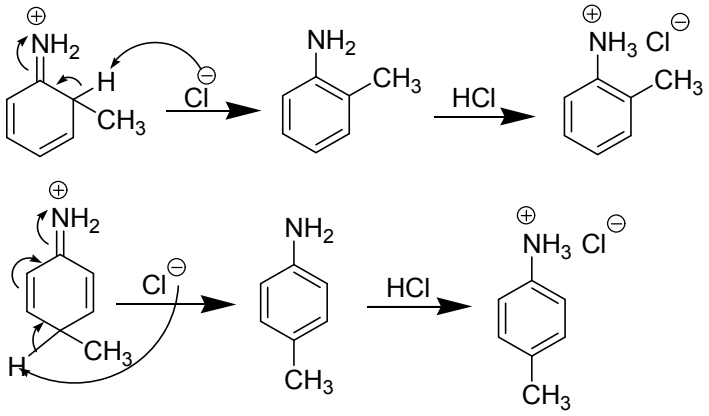
Step 1: The hydrochloride salt of *N*-methyl aniline decomposes to give aniline and CH_3Cl by an S_N2 process.



Step 2: Electrophilic attack occurs at the ortho and para–position of the aniline molecule by the positive end of the $CH_3^{\delta+}$-$Cl^{\delta-}$ dipole to form a σ–complex.

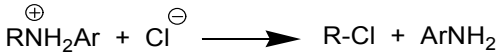


Step 3: The σ–complex undergo aromatization to give the hydrochloride salts of *o*- and *p*–toluidine.



It is an intermolecular reaction, since crossing is found. For example, methylanilinium 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 isomerization when R is primary.

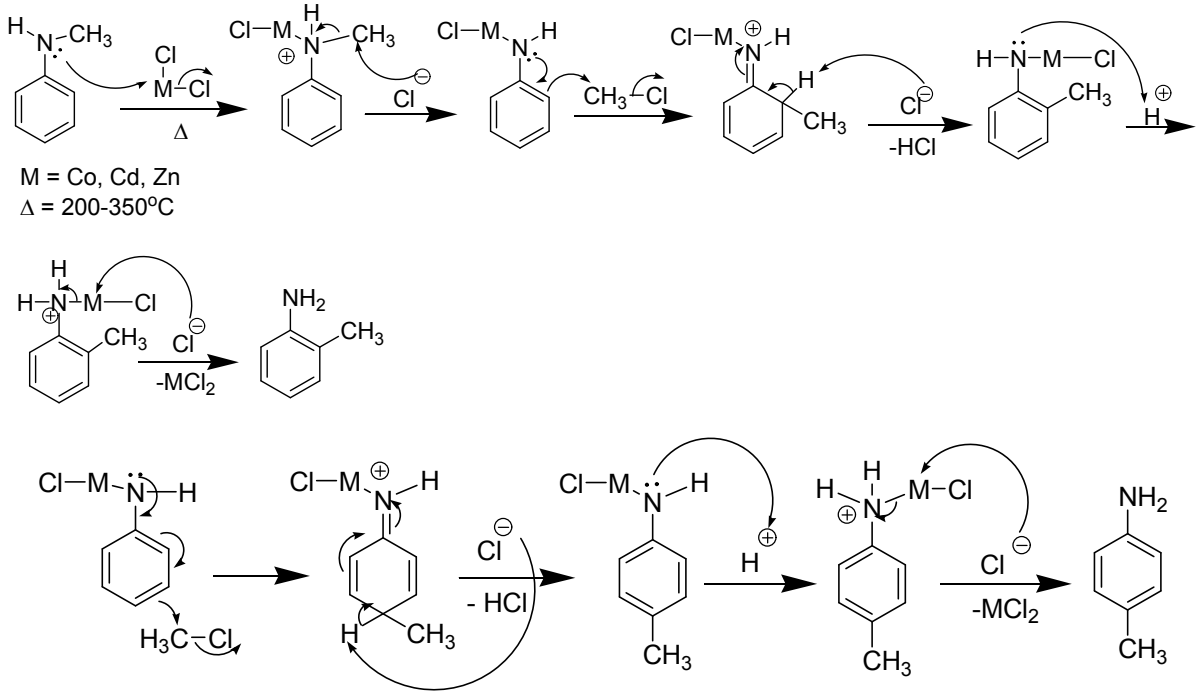
With primary R, the reaction probably goes through the alkyl halide formed initially in an S_N2 reaction:



Evidence for this view is that alkyl halides have been isolated from the reaction mixture and that Br^- , Cl^-, and 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 not

rearranged (as would be expected if they are formed by an S_N2 mechanism), even though the alkyl groups in the ring are rearranged. Once the alkyl halide is formed, it reacts with the substrate by a normal Friedel–Crafts alkylation process, accounting for the rearrangement. When R is secondary or tertiary, carbocations may be directly formed so that the reaction does not go through the alkyl halides.

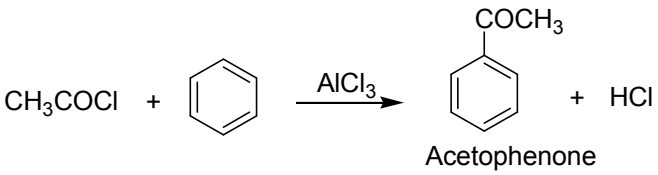
It is also possible to carry out the reaction by heating the amine (not the salt) at a temperature between 200 and 350°C with a metal halide, such as $CoCl_2$, $CdCl_2$, or $ZnCl_2$. When this is done, the reaction is called the *Reilly–Hickinbottom rearrangement*. Primary R groups larger than ethyl give both rearranged and unrearranged products. The reaction is not generally useful for secondary and tertiary R groups, which are usually cleaved to alkenes under these conditions.



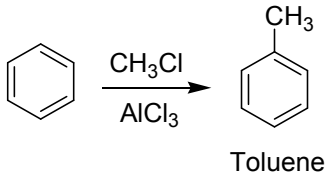
When acylated arylamines are photolyzed, migration of an acyl group takes place in a process that resembles the Photo-Fries reaction.

Friedel-Crafts reaction

Friedel-Crafts reaction involves the introduction of an alkyl or acyl group into the benzene ring by using a Lewis acid as a catalyst, e.g., acetophenone can be obtained by the Friedel-Crafts acylation of benzene with CH_3COCl and $AlCl_3$,



and toluene can be obtained from benzene by Friedel-Crafts alkylation of benzene with CH_3Cl and $AlCl_3$.



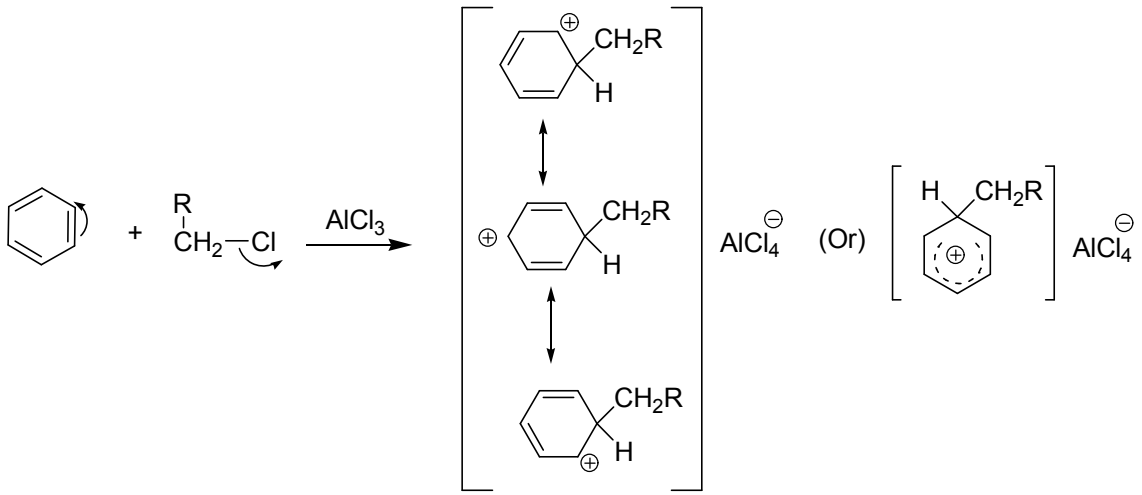
Friedel-Crafts Alkylation reactions:

Aliphatic compounds which can be used as alkylating agents are alkyl halides, alcohols, ethers, esters, olefins, aldehydes and ketones. Reactions of the first four classes of compounds are usually catalysed by Lewis acid and those of the later three are catalysed by protonic acids.

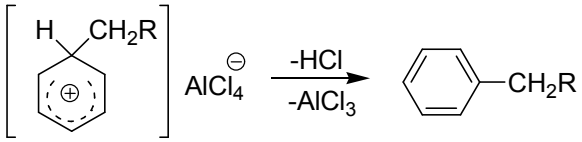
For alkylation, commonly used reagents are alkyl halides and commonly used catalyst is $AlCl_3$.

The reaction of benzene with primary and secondary alkyl halides occurs by the S_N2 mechanism in which nucleophilic attack by benzene on the aliphatic carbon is aided by the removal of halide ion by the Lewis acid (step 2).

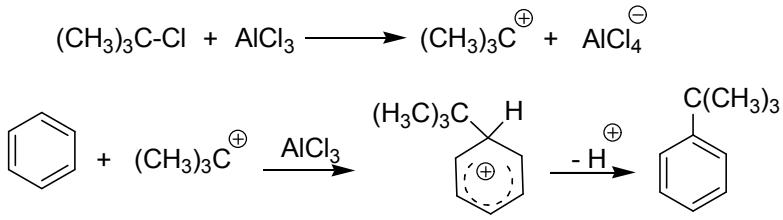
Step 1:



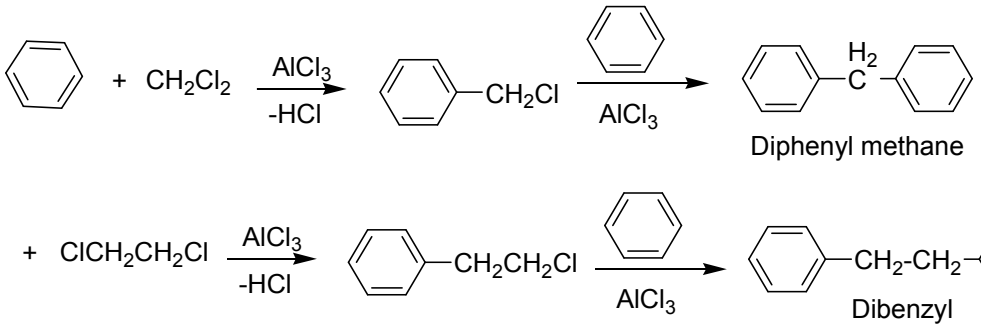
Step 2:



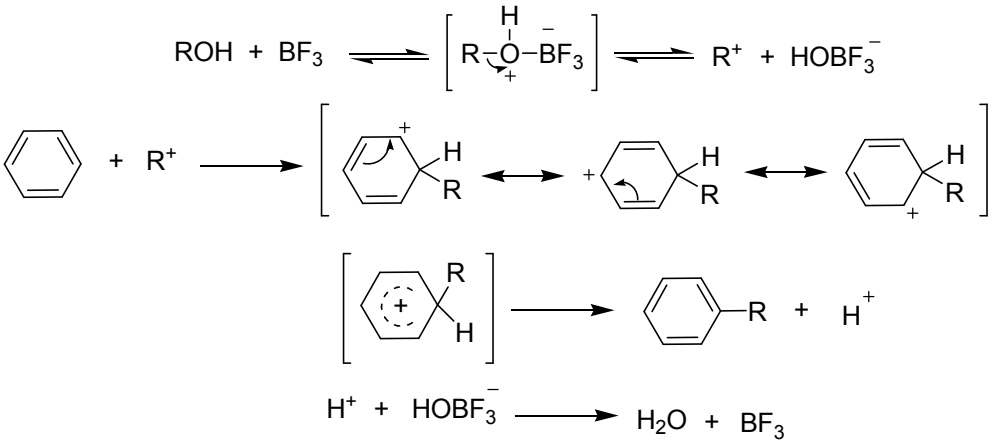
In the case of *t*-alkyl halides, alkylation occurs by S_N1 mechanism, since the *t*-carbonium ion is more stable, e.g.,



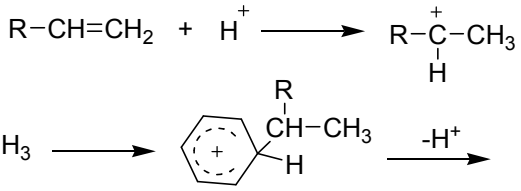
The use of di- and polyhalides leads to successive alkylation, e.g., benzene reacts with CH_2Cl_2 and ethylene dichloride in the presence of $AlCl_3$ to give diphenyl methane and dibenzyl, respectively.



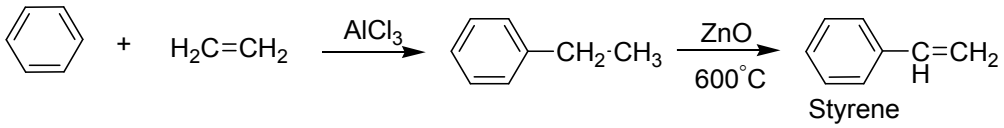
Alcohols, ethers and esters also react in a manner similar to halides:



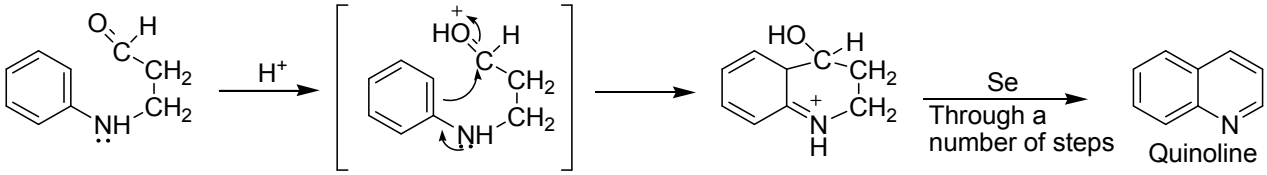
In the presence of protonic acids, olefins react via carbonium ions, which they form with protonic acids.



A commercially important compound, styrene can be prepared by alkylation of benzene using ethylene as alkylating agent in the presence of $AlCl_3$ to give ethyl benzene which on dehydrogenation with zinc oxide at 600°C gives styrene.

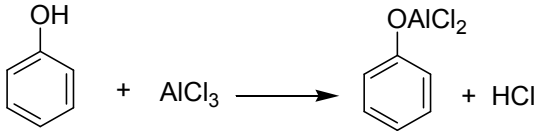


Aldehydes and ketones, in the presence of protonic acids can also act as alkylating agents but the reaction does not complete favourably with acid catalysed self-condensation of these carbonyl compounds except when alkylation is intramolecular and stereochemically favoured, e.g., the **Skraup's synthesis** of quinoline involves the acid catalysed intramolecular alkylation.



It should be noted that Friedel-Crafts alkylation reactions are rendered difficult when the benzene nucleus is highly activated or highly deactivated and smooth reaction occurs in the case of benzene or compounds of comparable reactivity. Thus whereas chlorobenzene can undergo alkylation reactions, nitrobenzene is inert and is often used as a solvent.

Phenols react very slowly and unsatisfactorily because they react with Lewis acid to give complex compounds, which are only slightly soluble in the reaction medium.



Similar is the case of amines, which also form complex with the catalyst and, therefore, are not suitable for alkylation. However, if the phenols and amines are first acetylated, alkylation reaction can successfully be carried out at low temperatures.

The choice of a suitable catalyst is also very important. The primary halides require a stronger catalyst such as $AlCl_3$ whereas tert. Alkyl halides need only a mild catalyst like $FeCl_3$. It is better to use milder catalysts because strong catalysts may bring about several other changes such as isomerization, etc.

The alkylation reactions with compounds such as alcohols can be catalysed both by protonic as well as Lewis acid and amongst them, BF_3 is the reagent of choice because of its strong tendency to form a complex with oxygen.

The order catalytic activity of various Lewis acids is as follows:

$$AlBr_3 > AlCl_3 > GaCl_3 > FeCl_3 > SbCl_3 > ZrCl_4 > SnCl_4 > BCl_3 > BF_3$$

The protonic acids used as catalysts are HF, H_2SO_4 and phosphoric acid. Sulphuric acid is generally not used because of its high sulphonation capacity rather than its catalysing effect.

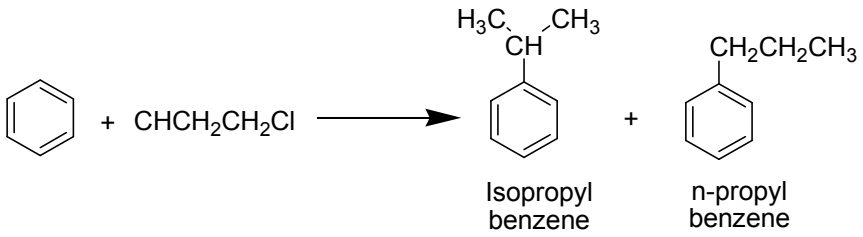
The most common solvents for Friedel-Crafts reaction are carbon disulphide, nitrobenzene, etc.

The overall reaction, however, depends upon the nature of the substrate, the reagent and the experimental conditions.

Limitations of Alkylation reactions

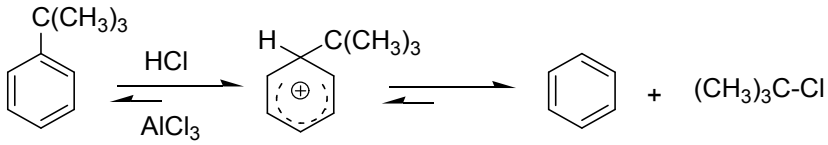
Since alkyl group are activating groups, the product of alkylation is more reactive than the starting material and therefore, further alkylation of the alkylated product inevitably occurs. For example, alkylation of benzene with CH_3Cl and $AlCl_3$ gives a mixture of mono- di and poly-methyl benzenes. So it is very difficult to get monosubstituted product as a result of alkylation reactions. In order to get a monoalkyalated product, an excess of the aromatic compound must be used.

Another important synthetic limitation of Friedel-Crafts alkylation is that the electrophilic reagent generally undergoes a rearrangement. For example, benzene when heated with n-propyl chloride, gives isopropyl benzene as the major product along with a small amount of the expected product, *n*-propyl benzene.

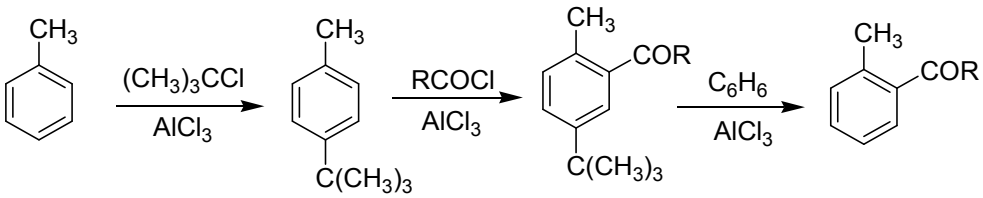


Rearrangement usually occurs in the order primary⟶ secondary⟶ tertiary, owing to the greater stability of the tertiary carbonium ion.

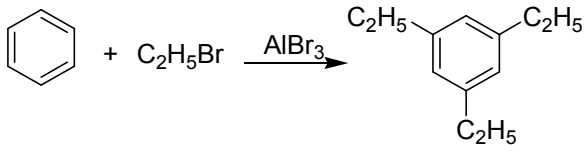
Just as tertiary alkyl groups are more readily introduced in the benzene nucleus, they are also very easily removed by the reverse reaction.



The *t*-butyl group can thus be used to protect the most reactive positions in a given compound in order to effect reaction elsewhere, as it can be easily removed by addition of excess of benzene which shift the equilibrium towards right. Thus ortho acyl toluene can be obtained by first protecting the *p*-position by *t*-butyl group followed by acylation and the removal of *t*-butyl group.



Further, since alkylation is a reversible process, the reaction is thermodynamically controlled. For example, a monosustituted benzene gives mainly the meta-alkyl derivatives because of its greater thermodynamic stability than that of the ortho/para isomer. Thus excess of ethyl bromide in the presence of $AlBr_3$ reacts with benzene to give 1, 3, 5-triethyl benzene.

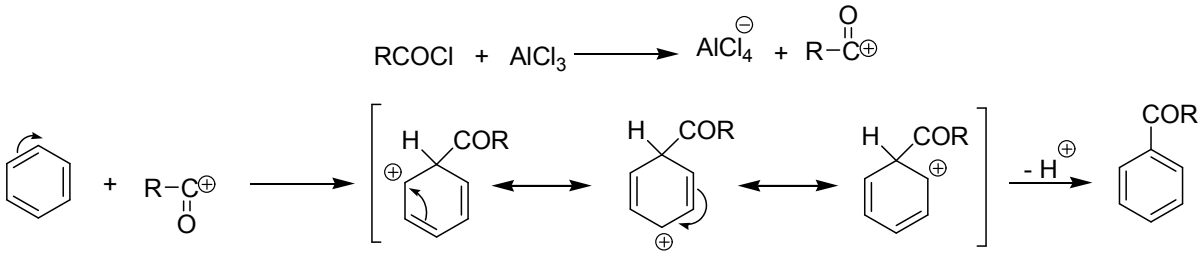


Friedel-Crafts acylation reactions

The acylation of aromatic rings can be brought about by an acid chloride or anhydride in the presence of an Lewis acid. Two mechanisms have been suggested for acylation reactions.

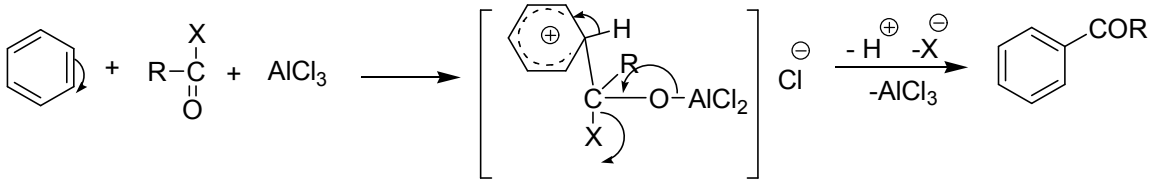
a) Ionic mechanism

The Lewis acid ionizes the acyl chloride to give the acylium cation which then reacts with aromatic compound to give the product by a mechanism analogous to that of alkylation.

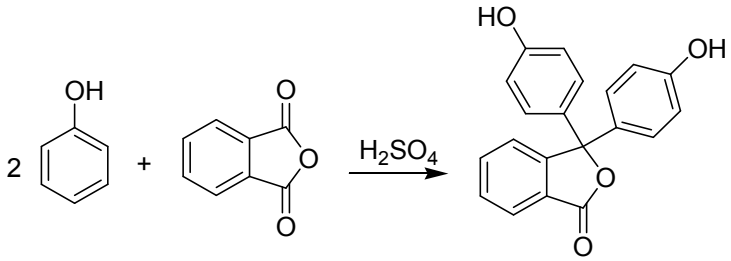


b) Substitution mechanism

In this mechanism, the alkylating agent is polarized through oxygen, thereby enhancing the activity of the carbonyl carbon to nucleophilic reaction.



The aromatic compound which can be alkylated can also be acylated. Deactivated molecules such as benzaldehyde, benzonitrile and nitrobenzene are inert to such an extent that nitrobenzene is often used as solvent for Friedel-Crafts reactions. For reactive compounds such as phenols the reaction can be carried out either at a low temperature or by using an acid as the condensing catalyst to get the required product, e.g., the formation of phenolphthalein from phenol.



Friedel-Crafts reaction of pyridine is difficult whereas thiophene, furan etc. can be alkylated or acylated to give the α-derivatives, when a weak catalyst likes $SnCl_4$ is used. The reason for the unreactivity of pyridine is the same as that for no acylation of nitro-benzene.

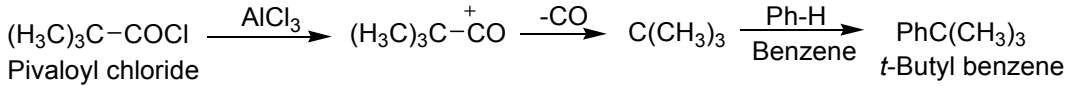
Advantages of acylation over alkylation reactions

Since the acylation product (acyl derivatives) is less reactive than the starting material, poly substitution, commonly observed in alkylation reactions, is obscure in this case. Therefore, the monoalkyl derivatives can be obtained in a better yield by Friedel-Crafts acylation since the resulting keto compound can be conveniently reduced to give the alkyl derivative.

The alkylation reactions do not require stochiometric quantities of the Lewis acid, since it is regenerated in the last step but in acylation reactions, greater amounts of catalyst (more than molar amounts) are needed because the resulting ketone combines with the Lewis acid to form a complex.

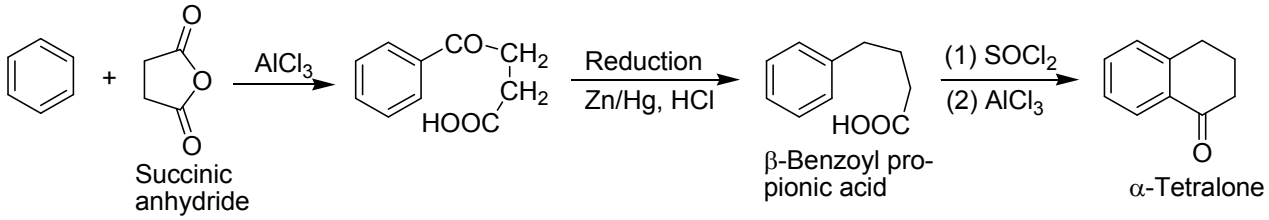
In acylation reactions, the rearrangement and isomerization, so characteristic of Friedel- Crafts alkylation, do not occur.

In spite of all these advantages of acylation over alkylation, there is one disadvantage also. When the acylation reaction is carried out with tertiary acid chlorides, unexpected alkylation takes place. For example, benzene, when treated with pivaloyl chloride, gives *t*-butyl benzene.

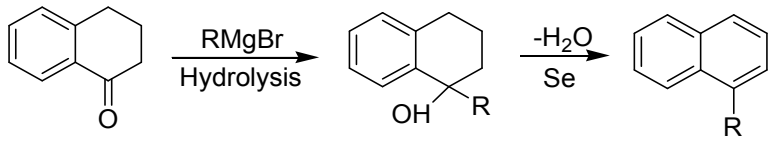


Further, since the complex of the acylation agent and Lewis acid is bulky, ortho and para directing monosubstituted benzene gives very little of the ortho product. For example, toluene, which gives 60% of ortho derivative on nitration, gives negligible amount of *o*-methyl acetophenone on acylation and the *p*-isomer is obtained in over 85% yield.

Intermolecular Friedel-Crafts acylations are of great value in building up cyclic systems, dibasic acid anhydrides are widely used in these reactions, e.g.,

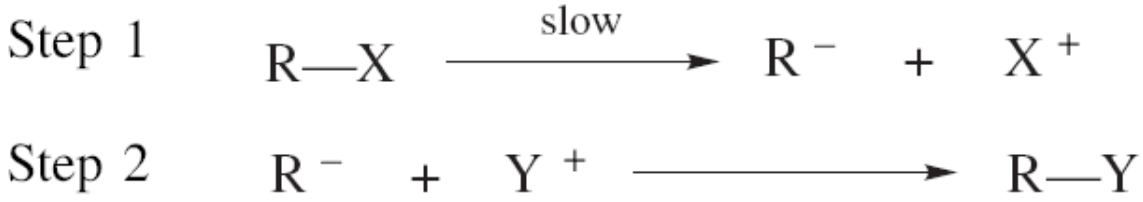


α-Tetralone can be utilized for obtaining substituted naphthalene.

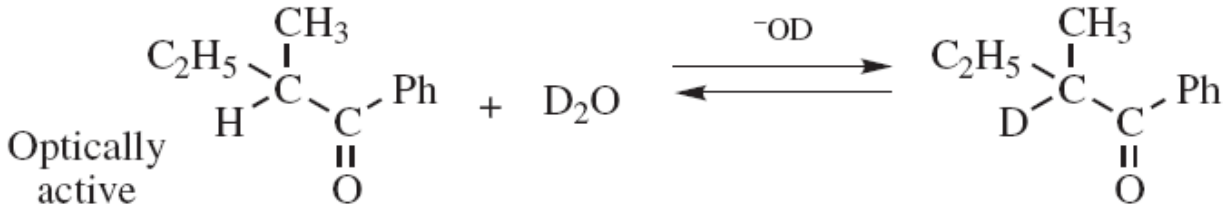


THE S_E1 MECHANISM

The S_E1 mechanism is analogous to the S_N1. It involves two steps: a slow ionization and a fast combination.



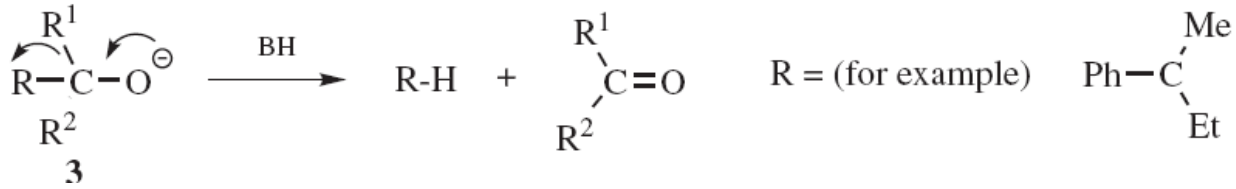
The IUPAC designation is $D_E + A_E$. First-order kinetics are predicted and many such examples have been found. Other evidence for the S_E1 mechanism was obtained in a study of base-catalyzed tautomerization. In the reaction the rate of deuterium exchange was the same as the rate of racemization and there was an isotope effect.



It is known that S_N1 reactions do not proceed at strained bridgehead carbons (e.g., in [2.2.1] bicyclic systems) because planar carbocations cannot form at these carbons. However, carbanions not stabilized by resonance are probably not planar, and S_E1 reactions readily occur with this type of substrate. Indeed, the question of carbanion structure is intimately tied into the problem of the stereochemistry of the S_E1 reaction. If a carbanion is planar, racemization should occur. If it is pyramidal and can hold its structure, the result should be retention of configuration. On the other hand, even a pyramidal carbanion will give racemization if it cannot hold its structure, that is, if there is pyramidal inversion as with amines. Unfortunately, the only carbanions that can be studied easily are those stabilized by resonance, which makes them planar, as expected. For simple alkyl carbanions, the main

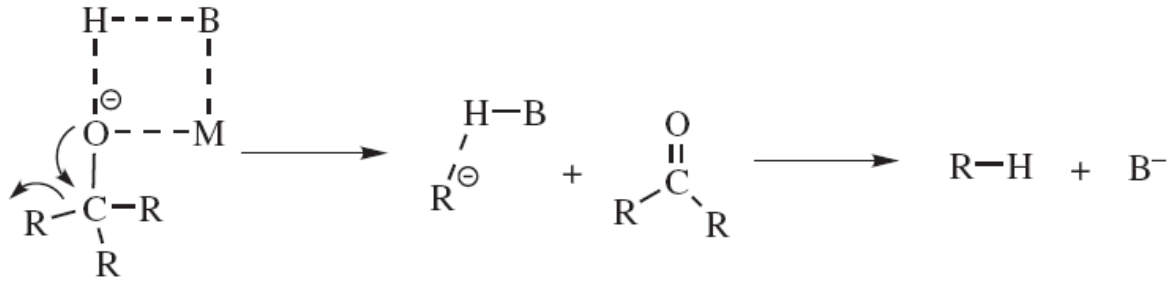
approach to determining structure has been to study the stereochemistry of S_E1 reactions rather than the other way around. Racemization is almost always observed, but whether this is caused by planar carbanions or by oscillating pyramidal carbanions is not known. In either, case racemization occurs whenever a carbanion is completely free or is symmetrically solvated.

However, even planar carbanions need not give racemization. Cram found that retention and even inversion can occur in the alkoxide (see **3**) cleavage reaction:

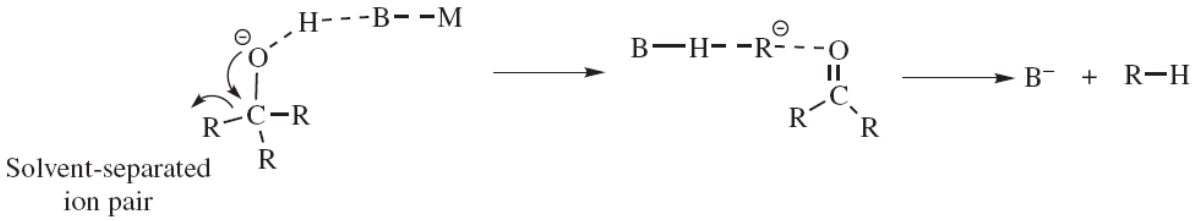


3

which is a first-order S_E1 reaction involving resonance-stabilized planar carbanions (here designated R^-). By changing the solvent, Cram was able to produce products ranging from 99% retention to 60% inversion and including complete racemization. These results are explained by a carbanion that is not completely free but is solvated. In nondissociating, nonpolar solvents (e.g., benzene or dioxane), the alkoxide ion exists as an ion pair, solvated by the solvent BH:

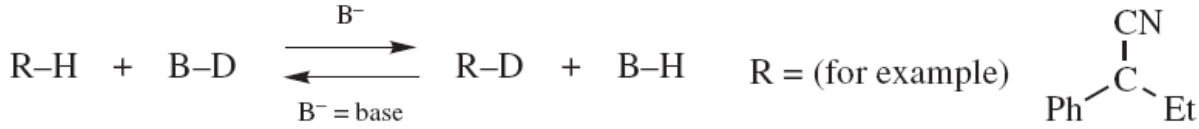


In the course of the cleavage, the proton of the solvent moves in to solvate the newly forming carbanion. As is easily seen, this solvation is asymmetrical since the solvent molecule is already on the front side of the carbanion. When the carbanion actually bonds with the proton, the result is retention of the original configuration. In protic solvents (e.g., diethylene glycol), a good deal of inversion is found. In these solvents, the leaving group solvates the carbanion, so the solvent can solvate it only from the opposite side:

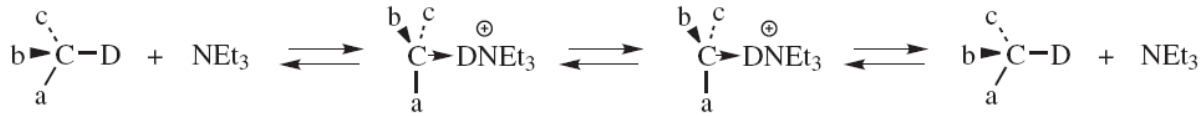


When C–H bond formation occurs, the result is inversion. Racemization occurs in polar aprotic solvents (e.g., DMSO). In these solvents, the carbanions are relatively long lived (because the solvent has no proton to donate) and symmetrically solvated.

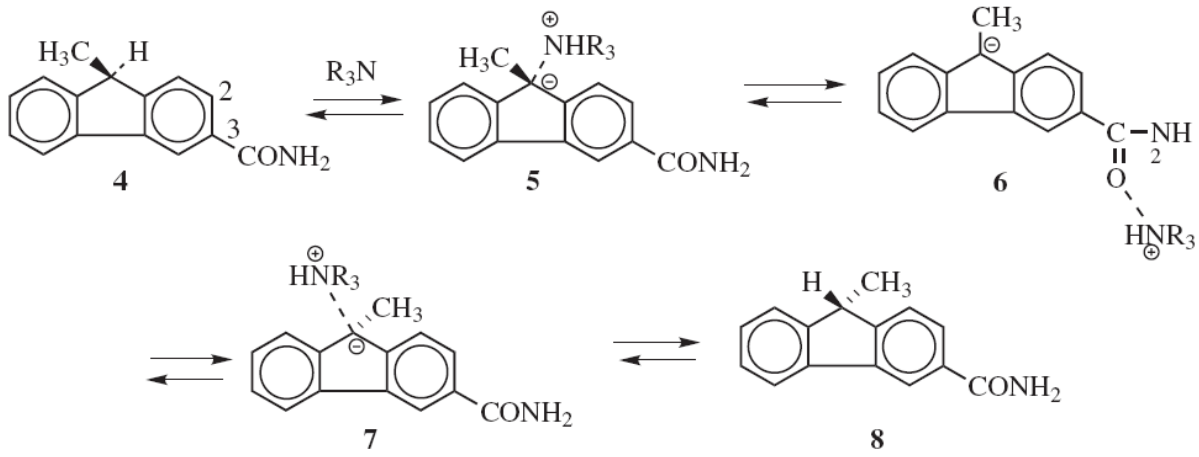
Similar behavior was found for carbanions generated by base-catalyzed hydrogen exchange reaction.



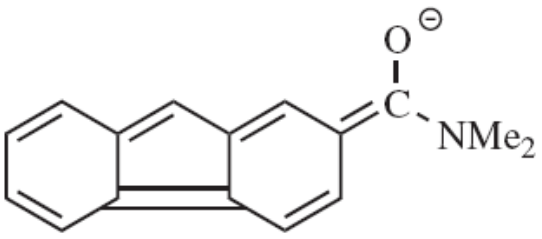
In this case, information was obtained from measurement of the ratio of k_e (rate constant for isotopic exchange) to k_a (rate constant for racemization). A k_e/k_a ratio substantially >1 means retention of configuration, since many individual isotopic exchanges are not producing a change in configuration. A k_e/k_a ratio of ~1 indicates racemization and a ratio of 1/2 corresponds to inversion. All three types of steric behavior were found, depending on R, the base, and the solvent. As with the alkoxide cleavage reaction, retention was generally found in solvents of low dielectric constant, racemization in polar aprotic solvents, and inversion in protic solvents. However, in the proton-exchange reactions, a fourth type of behavior was encountered. In aprotic solvents, with aprotic bases like tertiary amines, the k_e/k_a ratio was found to be less than 0.5, indicating that racemization took place *faster* than isotopic exchange (this process is known as *isoracemization*). Under these conditions, the conjugate acid of the amine remains associated with the carbanion as an ion pair. Occasionally, the ion pair dissociates long enough for the carbanion to turn over and recapture the proton:



Thus, inversion (and hence racemization, which is produced by repeated acts of inversion) occurs without exchange. A single act of inversion without exchange is called *isoinversion*.



The isoinversion process can take place by a pathway in which a positive species migrates in a stepwise fashion around a molecule from one nucleophilic position to another. For example, in the exchange reaction of 3-carboxamido-9-methylfluorene (**4**) with Pr_3N in *t*-BuOH, it has been proposed that the amine removes a proton from the 9 position of **4** and conducts the proton out to the C═O oxygen (**6**), around the molecule, and back to C-9 on the opposite face of the anion. Collapse of **7** gives the inverted product **8**. Of course, **6** could also go back to **4**, but a molecule that undergoes the total process **4**→ **5**→ **6**→ **7**→ **8** has experienced an inversion without an exchange. Evidence for this pathway, called the *conducted tour mechanism*, is that the 12-carboxamido isomer of **4** does not give isoracemization. In this case, the negative charge on the oxygen atom in the anion corresponding to **6** is less, because a canonical form in which oxygen acquires a full negative charge (**9**) results in disruption of the aromatic sextet in both benzene rings (**10** where one benzene ring is intact). Whether the isoracemization process takes place by the conducted tour mechanism or a simple nonstructured contact ion-pair mechanism depends on the nature of the substrate (e.g., a proper functional group is necessary for the conducted tour mechanism) and of the base.



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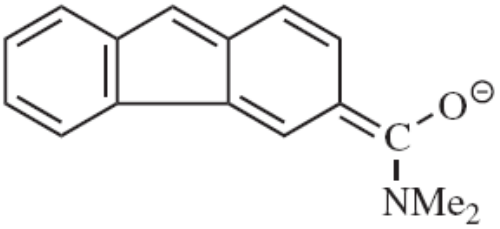
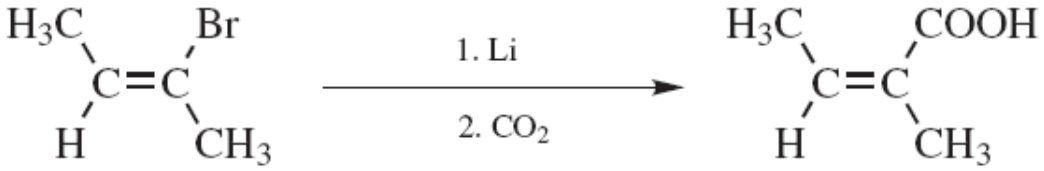


10

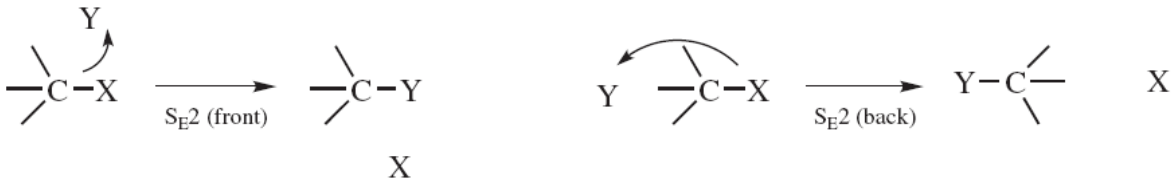
It is known that vinylic carbanions can maintain configuration, so that S_E1 mechanisms should produce retention, which is the case. there. For example, trans-2-bromo-2-butene was converted to 64-74% angelic acid:



Only ~5% of the cis isomer, (tiglic acid), was produced. In addition, certain carbanions in which the negative charge is stabilized by *d*-orbital overlap can maintain configuration and S_E1 reactions involving them proceed with retention of configuration.

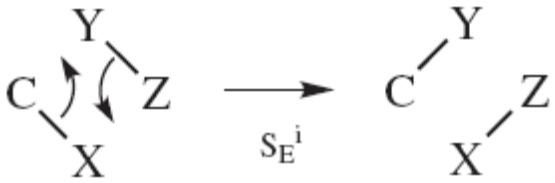
Bimolecular Mechanisms: S_E2 and S_Ei

The bimolecular mechanisms for electrophilic aliphatic substitution are analogous to the S_N2 mechanism in that the new bond forms as the old one breaks. However, in the S_N2 mechanism the incoming group brings with it a pair of electrons, and this orbital can overlap with the central carbon only to the extent that the leaving group takes away its electrons; otherwise the carbon would have more than eight electrons at once in its outer shell. Since electron clouds repel, this means also that the incoming group attacks backside, at a position 180º from the leaving group, resulting in inversion of configuration. When the nucleophilic species attacks (donates electrons to) an electrophile, it brings only a vacant orbital, predicting the direction of the attack is not as straightforward. We can imagine two main possibilities: delivery of the electrophile to the front, which we call S_E2 (front), and delivery of the electrophile to the rear, which we call S_E2 (back). The possibilities can be pictured (charges not shown):

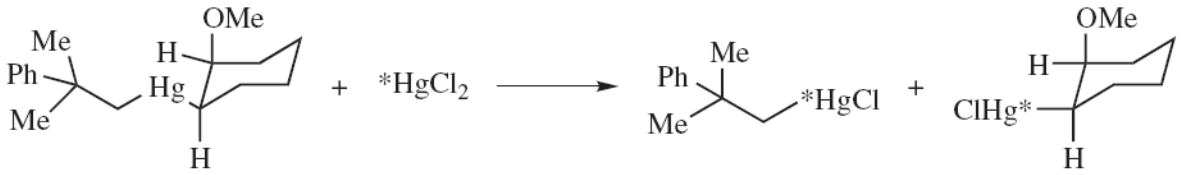


Both the S_E2 (front) and S_E2 (back) mechanisms are designated D_EA_E in the IUPAC system. With substrates in which these possibilities may be distinguished, the former mechanism should result in retention of configuration and the latter results in inversion. The reaction of allylsilanes with adamantyl chloride and $TiCl_4$, for example, gives primarily the antiproduct via a S_E2' reaction. When the electrophile reacts from the front, there is a third

possibility. A portion of the electrophile may assist in the removal of the leaving group, forming a bond with it at the same time that the new C–Y bond is formed:

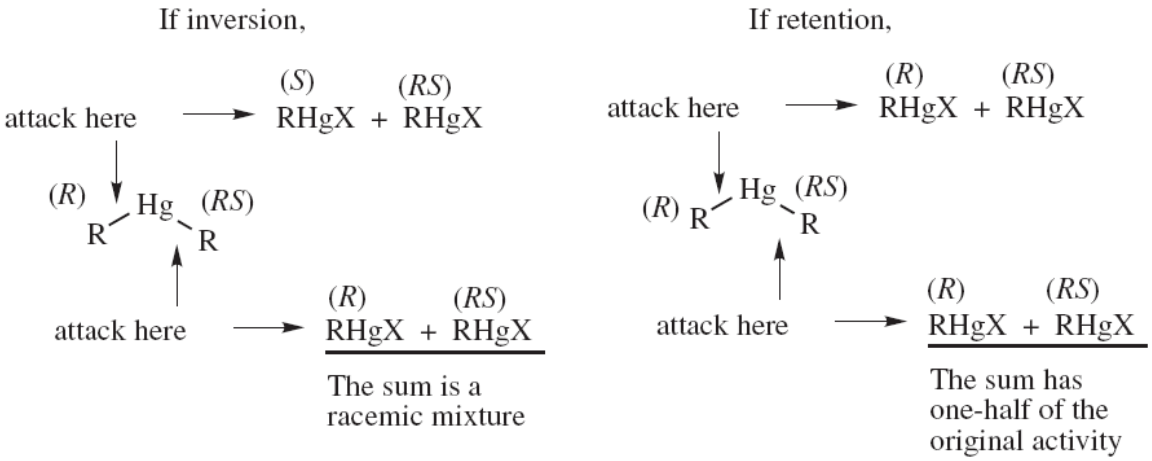


This mechanism, which is called the S_Ei mechanism (IUPAC designation: *cyclo*-$D_EA_ED_nA_n$), also results in retention of configuration. Plainly, where a second order mechanism involves this kind of internal assistance, backside attack is impossible.

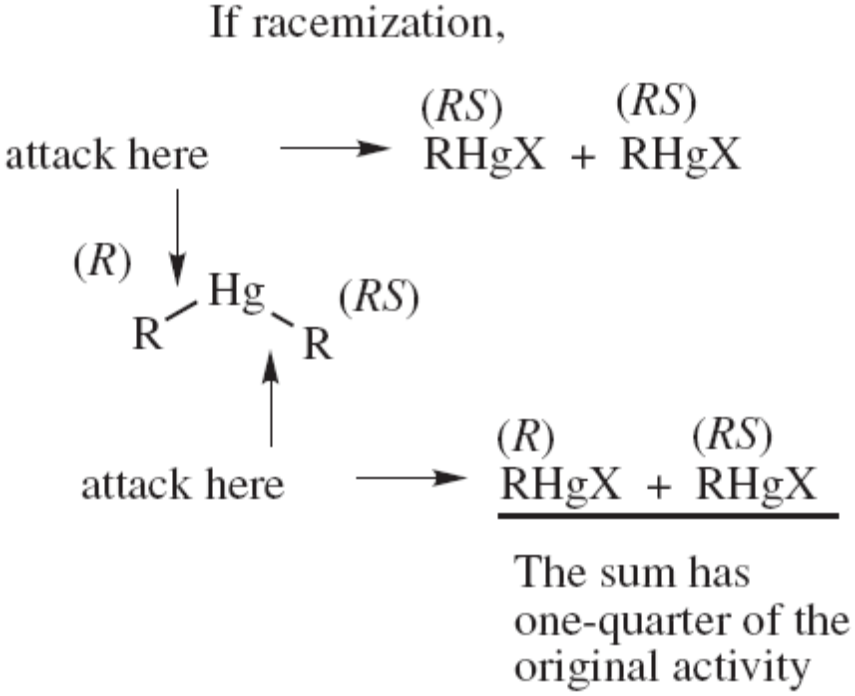


1 **2**

It is evident that these three mechanisms are not easy to distinguish. All three mechanisms give second-order kinetics and two mechanisms results in retention of configuration. In fact, although much work has been done on this question, there are few cases in which one of these three can be unequivocally established to demonstrate that another is not actually taking place. Clearly, a study of the stereochemistry can distinguish between S_E2 (back) on the one hand and S_E2 (front) or S_Ei on the other. Many such investigations have been made. In the overwhelming majority of second-order electrophilic substitutions, the result has been retention of configuration or some other indication of frontside attack, indicating an S_E2 (front) or S_Ei mechanism. For example, when *cis*-**1** was treated with labeled mercuric chloride, the **2** produced was 100% cis. The bond between the mercury and the ring must have been broken (as well as the other Hg–C bond), since each of the products contained about half of the labeled mercury. Another indication of frontside attack is that second-order electrophilic substitutions proceed very easily at bridgehead carbons. Still another indication is the behavior of neopentyl as a substrate. S_N2 reactions at neopentyl are extremely slow, because attack from the rear is blocked and the transition state for the reaction lies very high in energy. The fact that neopentyl systems undergo electrophilic substitution only slightly more slowly than ethyl is further evidence for frontside attack. One final elegant experiment may be noted.



The compound di-*sec*-butylmercury was prepared with one sec-butyl group optically active and the other racemic. This was accomplished by treatment of optically active *sec*-butylmercuric bromide with racemic *sec*-butylmagnesium bromide. The di-*sec*-butyl compound was then treated with mercuric bromide to give 2 eqiuivalents of *sec*-butylmercuric bromide. The steric course of the reaction could then be predicted by the following analysis, assuming that the bonds between the mercury and each carbon have a 50% chance of breaking. The original activity referred to is the activity of the optically active *sec*-butylmercuric bromide used to make the dialkyl compound. The actual result was that, under several different sets of conditions, the product had one-half of the original activity, demonstrating retention of configuration.

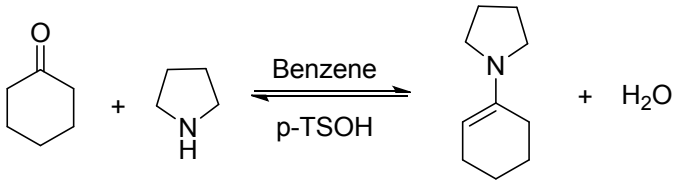


However, inversion of configuration has been found in certain cases, demonstrating that the S_E2 (back) mechanism can take place. For example, the reaction of optically active *sec*-butyltrineopentyltin with bromine gives inverted *sec*-butyl bromide. A number of other organometallic compounds have also been shown to give inversion when treated with halogens, although others do not. So far, no inversion has been found with an organomercury substrate. It may be that still other examples of backside

attack exist, but have escaped detection because of the difficulty in preparing compounds with a configurationally stable carbon–metal bond. Compounds that are chiral because of a stereogenic carbon at which a carbon–metal bond is located are often difficult to resolve and once resolved are often easily racemized. The resolution has been accomplished most often with organomercury compounds, and most stereochemical investigations have therefore been made with these substrates. Only a few optically active Grignard reagents have been prepared (i.e., in which the only stereogenic center is the carbon bonded to the magnesium). Because of this, the steric course of electrophilic substitutions at the C–Mg bond has not often been determined. However, in one such case, the reaction of both the exo and endo isomers of the 2-norbornyl Grignard reagent with $HgBr_2$ (to give 2-norbornylmercuric bromide) has been shown to proceed with retention of configuration. It is likely that inversion takes place only when steric hindrance prevents reaction on the frontside and when the electrophile does not carry a Z group.

Stork-enamine reaction

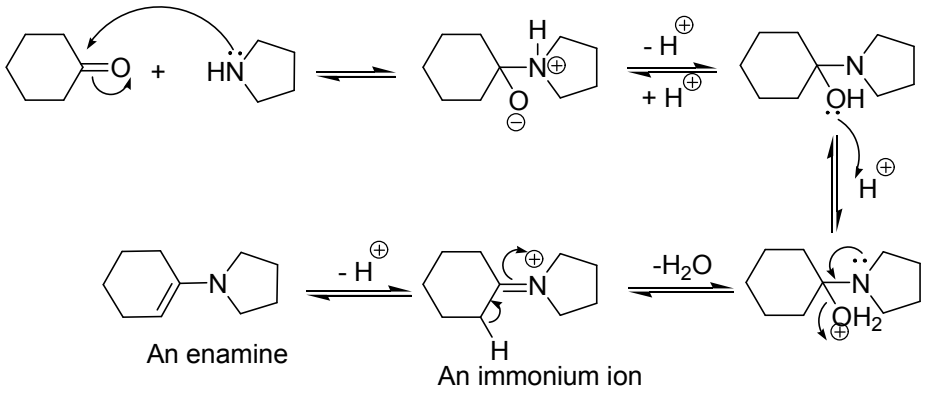
Aldehydes and ketones react with secondary amines in the presence of a trace of an acid to form compound containing structure unit C=C-N rather than C-C=N and these α,β- unsaturated amines are known as enamine (alkene+amine) which are useful synthetic intermediate. For example, pyrrolidine reacts with cyclohexanone in the presence of *p*-toluenesulphonic acid to form an enamine.



1. Sketch a step-by-step mechanism for this reaction.

Solution:

Mechanism:



Pyrrolidine adds to cyclohexanone to form a compound that loses OH to form an immonium or iminium ion. This ion then loses a proton from a carbon β to the nitrogen atom to yield an enamine.

2. In the preparation of enamine why is it necessary to remove water from the reaction mixture?

Solution:

An enamine formation, like many other addition reactions, is readily reversible and when hydrolyzed with dilutes aqueous acid, enamines regenerate the carbonyl compound. For this reason, to obtain a better yield of enamine, removal of water from the reaction mixture is necessary.

3. How is water eliminated in the above reaction?

Solution:

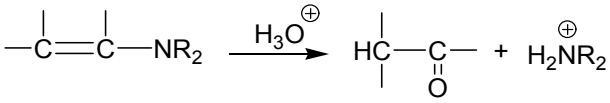
In the above reaction water is eliminated by azeotropic distillation with benzene.

4. Why is a cyclic amine generally used as the secondary amine in the enamine synthesis?

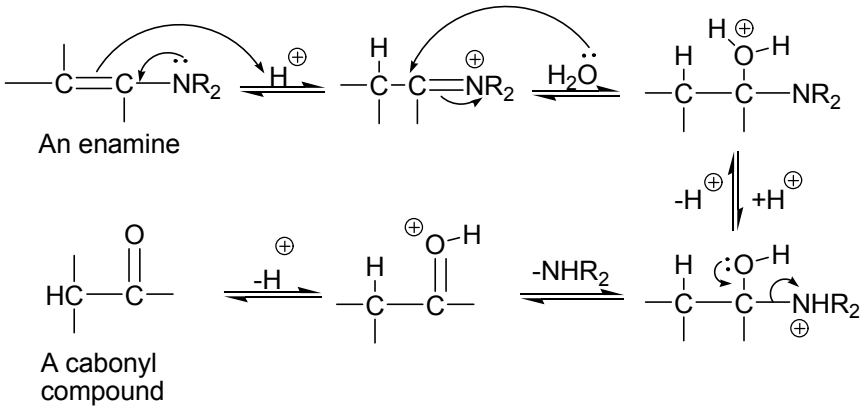
Solution:

In the cyclic amines, the carbon atoms attached with nitrogen atom are held back by the ring system. So, they have less steric crowding around nitrogen than an open chain amine and because of this, cyclic amines are generally used in enamine synthesis.

5. Sketch a step-by-step mechanism for the acid-catalyzed hydrolysis of enamines:

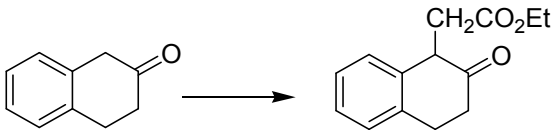


Solution:



6. Show how you could carry out each of the following transformation by way of an enamine (Stork-enamine reactions):

(a)



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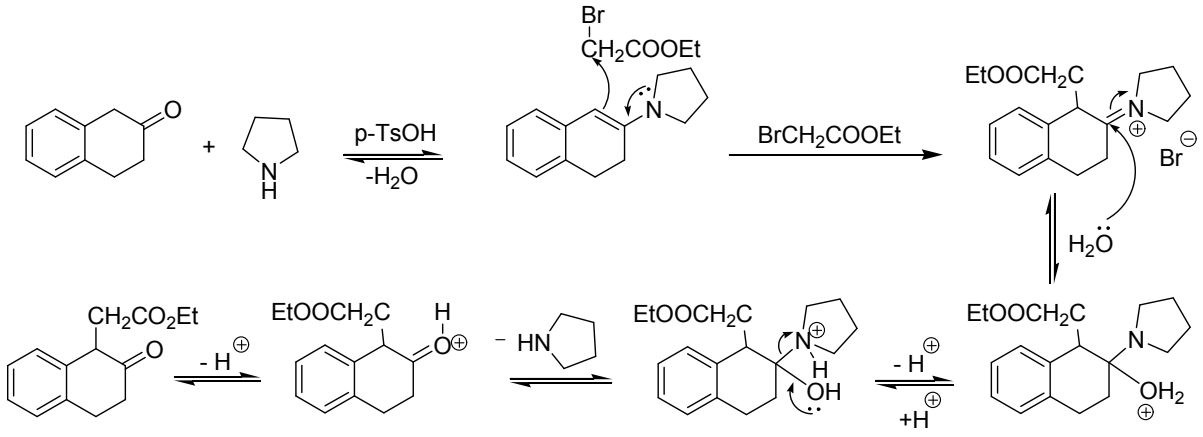
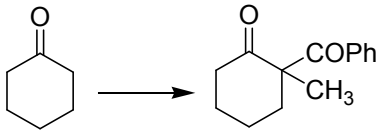


(b)



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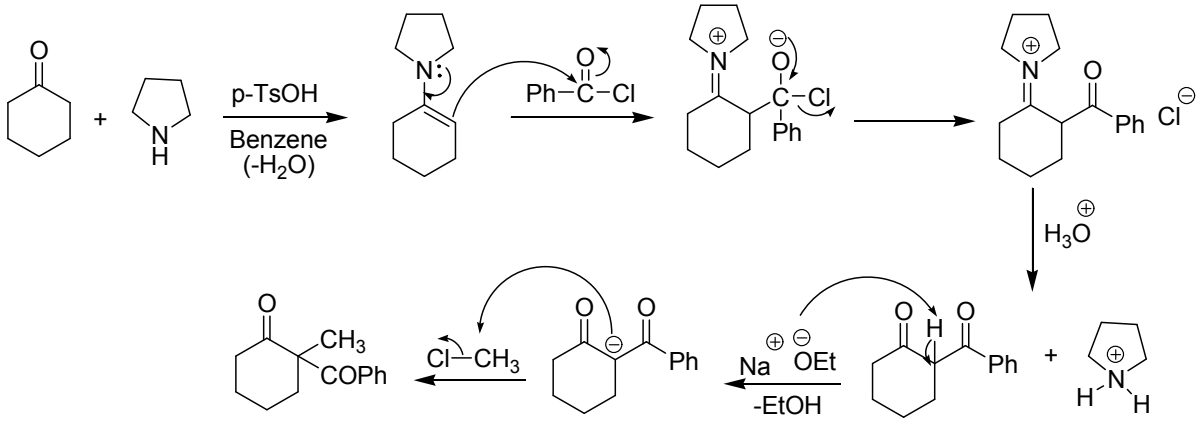
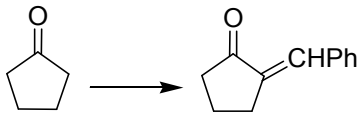


(c)



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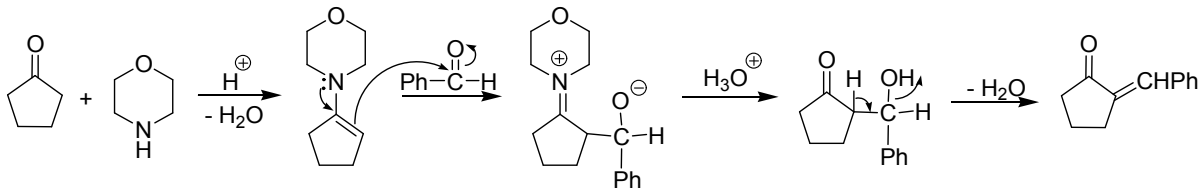
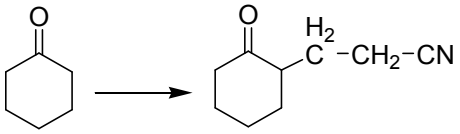
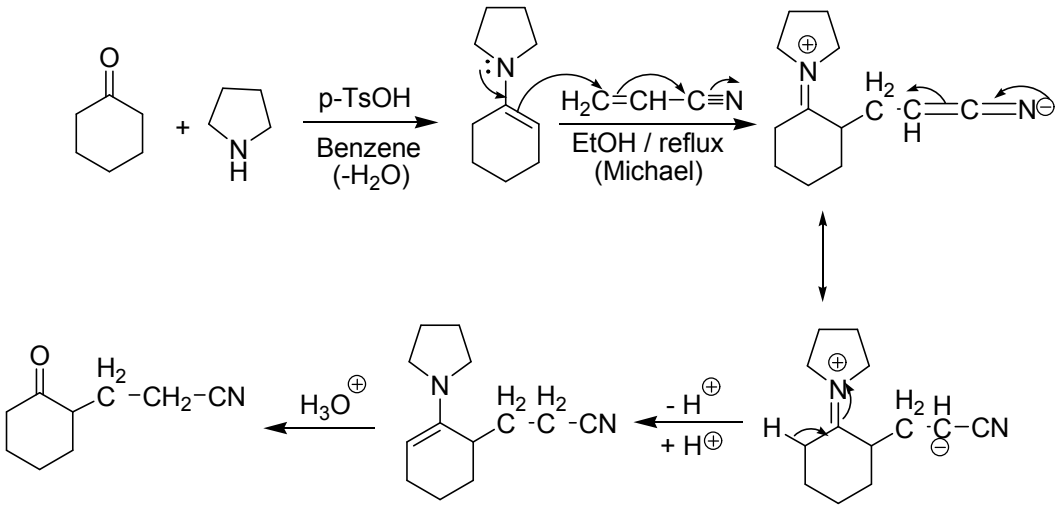


(d)

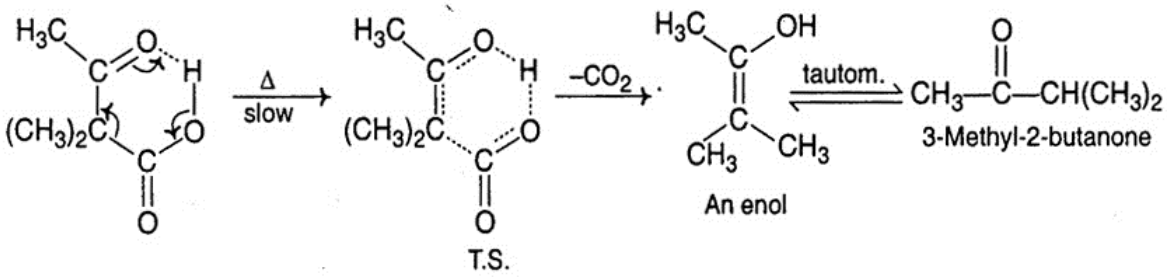


Solution:

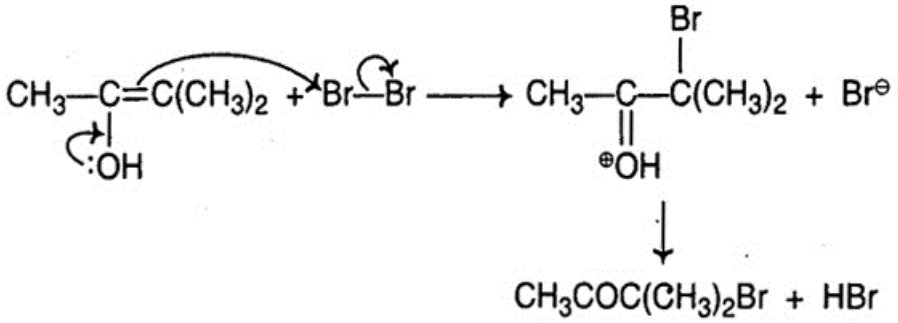


Decarboxylation of aliphatic acids

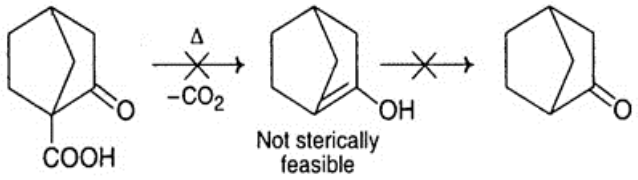
The decarboxylation of a β-keto acid proceeds via a six membered cyclic transition state and the decarboxylation is promoted by the incipient proton transfer to the keto group through hydrogen bonding. The first formed product is an enol which readily tautomerizes to the more stable keto form. For example, the decarboxylation of 2,2–dimethyl-3-oxobutanoic acid. $CH_3COC(CH_3)_2COOH$ may be shown as follows.



The intermediacy of the enol form is demonstrated by trapping it with halogens. When the decarboxylation of 2,2–dimethyl -3-oxobutanoic acid is carried out in the presence of bromine, 3-bromo-3methyl-2-burtanone, $CH_3COC(CH_3)_2Br$ is obtained. Since 3-methyl-2-butanone remains unaffected by bromine under the condition of decarboxylation as also is the starting keto acid, the isolation of $CH_3COC(CH_3)_2Br$ is a clear evidence for the existance of an enol which forms in the rate-determining step.



A mechanism of decarboxylation is also consistant with the resistance of bridgetead bicyclic β-keto acids to decarboxylation and this is because strain prevents formation of a double bond at the bridge head position (Bredt's rule).



Text Book:

1. Smith, M. B. (2015). *March's Advanced Organic Chemistry: Reactions, Mechanisms, and Structure* (VII Edition). New Jersey: John Wiley & Sons, Inc., Hoboken.

Reference Books:

1. Tewari, N. (2011). *Advanced Organic Reaction Mechanism* (III Edition). Kolkata: Books and Allied (P) Ltd.

2. Sanyal, S. N. (2014). *Reactions, Rearrangements and Reagents* (IV Edition). New Delhi: Bharathi Bhawan (Publishers and Distributors).

POSSIBLE QUESTIONS

PART- A – Multiple Choice Questions

(Each Question Carry One Mark)

1. Formylation with zinc cyanide and HCl is called the

A) **Gattermann reaction** B) Gattermann-Koch reaction

C) Reimer-Tiemann reaction D) Kolbe reaction

2. Gattermann reaction method is applicable to

A) Esters B) **phenols** C) amines D) acids

3. Gattermann reaction method cannot be applicable to

A) Alkylbenzenes B) phenols C) **amines** D) ethers

4. Formylation of benzene and alkyl benzene with carbon monoxide and HCl in the presence of $AlCl_3$ and CuCl is known as the

A) Gattermann reaction B) **Gattermann-Koch reaction**

C) Reimer-Tiemann reaction D) Kolbe reaction

5. Gattermann-Koch reaction which solvent is generally used

A) benzene B) chloroform C) **nitrobenzene** D) ethyl acetate

6. Gattermann-Koch method is used industrially to prepare

A) ketones B)acids C) amides D) **arylaldehydes**

7. The Gattermann-Koch aldehydes synthesis is not applicable to

A) Alkyl benzenes B) **phenols** C) acids D) esters

8. The nitrobenzene is failed for

A) Gattermann reaction B) **Gattermann-Koch reaction**

C) Reimer-Tiemann reaction D) Kolbe reaction

9. Formylation of phenols with chloroform in alkaline solution is known as

A) Gattermann reaction B) Gattermann-Koch reaction

C) **Reimer-Tiemann reaction** D) Kolbe reaction

10. Reimer-Tiemann reaction is applicable to

A) Alkyl benzenes B) **phenols** C) amines D) ethers

11. A mixture of ortho and para-isomers is obtained from Reimer-Tiemann in which the ortho isomer predominates due to

A) ionic bond B) intra-molecular hydrogen bonding

C) Vander walls force D) **inter-molecular hydrogen bonding**

12. The dichlorocarbene generated from chloroform by the action of

A) **base** B) acid C) salt D) ions

13. The Gattermann-Koch formylation as a typical

A) nucleophilic aromatic substitution B) **electrophilic aromatic substitution**

C) electrophilic aliphatic substitution D) nucleophilic aliphatic substitution

14. The reaction of pyrrole with chloroform and alkali to produce 3-chloropyridine is an example for

A) **Reimer-Tiemann reaction** B) Gattermann reaction

C) Gattermann-Koch reaction D) Kolbe reaction

15. Carbon tetrachloride in placed of chloroform under Reimer-Tiemann reaction condition gives

A) benzoic acid B) o-hydroxybenzaldehyde C) **salicyclic acid** D) piperonal

16. Pyrrole undergoes Reimer-Tiemann reaction to produces

A) pyrrole-2-aldehyde B) pyridine C) **3-chloropyridine** D) piperonal

17. When carbon tetrachloride in place of chloroform is used Reimer-Tiemann reaction condition gives

A) Aldehyde B) amide C) **acid** D) ketone

18. The o-hydroxybenzaldehyde is separated from the p-hydroxybenzaldehyde by

A) vaccum distillation B) **steam distillation** C) adsorption D) recrystalation

19. Electrolysis of carboxylate ions, results in decarboxylation and combination of the resulting radicals to give the coupling product is called the

A) Gattermann reaction B) Gattermann-Koch reaction

C) Reimer-Tiemann reaction D) **Kolbe reaction**

20. The Kolbe reaction is a

A) addition reaction B) elimination reaction C) **coupling reaction** D) substitution reaction

21. Kolbe reaction is used for the preparation of

A) **aliphatic compounds** B) aromatic compounds

C) heterocyclic compounds D) bicyclic compounds

22. Conversion of an amide to a heterocyclic system using $POCl_3$ is called

A) Gattermann reaction B) Jacobson reaction

C) **Bischler-Napieralski reaction** D) Kolbe reaction

23. The first step in the formation of nucleophilic addition to C=C bond is the formation of

A) Carbocation B) free radical C) **carbanion** D) carbene

24. Ene reaction is similar to

A) polyene synthesis B) Hunsdiecker synthesis

C) Dieckmann condensation D) **Diels- Alder reaction**

25. Michael reaction involves

A) substituted addition B) commuted addition

C) **conjugated addition** D) concerted addition

26. Bischler-Napieralski reaction is an

A) intramolecular nucleophilic aliphatic substitution reaction

B) intramolecular electrophilic aliphatic substitution reaction

C) intramolecular nuclophilic aromatic substitution reaction

D) **intramolecular electrophilic aromatic substitution reaction**

27. The conversion of $2ArCR_2COOH$ into $ArCR_2CR_2Ar$ by the treatment with

A) base/electrolysis B) **$Na_2S_2O_8/AgNO_3$** C) disilane/Pd D) $DMF/POCl_3$

28. The electron deficient aromatic acyl chlorides are dimerized to biaryls by treatment with a

A) base/electrolysis B) $Na_2S_2O_8/AgNO_3$ C) **disilane/Pd** D) $DMF/POCl_3$

29. Bischler-Napieralski reaction is mainly used for synthesis of

A) Quinoline B) **isoquinoline** C) indole D) pyrrole

30. Which type of intermediate involved in Bischler-Napieralski reaction is

A) amino ester B) enol ether C) dichlorocarbene D) **nitrilium ion**

31. When HCl salts of arylalkylamines are heated at 200-300°C, migration occurs is called as

A) Hunsdiecker synthesis B) Gattermann reaction

C) **Hofmann-Martius reaction** D) Reimer-Tiemann reaction

32. The hydrochloride salts of N-methyl aniline decomposes to give

A) **aniline and methyl chloride** B) benzene and methyl chloride

C) phenol and methyl chloride D) anilinium ion and methyl chloride

33. The hydrochloride salts of N-methyl aniline decomposes to give aniline and methyl chloride by an

A) S_N1 process B) **S_N2 process** C) S_Ni process D) E1 process

34. The Hofmann-Martius reaction the major product is

A) 2-methyl aniline B) 3-methyl aniline C) **4-methyl aniline** D) aniline

35. The Hofmann-Martius reaction is an

A) intermolecular reaction B) **intermolecular process**

C) addition reaction D) elimination reaction

36. The reaction by heating the amine at a temperature between 200-350°C with metal halides is known as

A) Fries rearrangement B) Claisen rearrangement

C) **Reilly-Hickinbottom rearrangement** D) Hofmann-Martius reaction

37. The commonly catalyst used for Vilsmeir reaction is

A) $AlCl_3$ B) **$POCl_3$** C) PCl_5 D) P_2O_5

38. The introduction of an alkyl or acyl group into the benzene ring is known as

A) Hofmann-Martius reaction B) Reimer-Tiemann reaction

C) Kolbe reaction D) **Friedel-Crafts reaction**

39. The Lewis acid catalyst is used for

A) Kolbe reaction B) **Friedel-Crafts reaction**

C) Reimer-Tiemann reaction D) Hofmann-Martius reaction

40. Acetophenone can be obtained by the Friedel-Crafts acylation of benzene with

A) **CH_3COCl and $AlCl_3$** B) $Ac_2O$and $AlCl_3$

C) CH_3COCl and HCl D) CH_3Cl and $AlCl_3$

41. Toluene can be obtained by the Friedel-Crafts acylation of benzene with

A) CH_3COCl and $AlCl_3$ B) $Ac_2O$and $AlCl_3$

C) CH_3COCl and HCl D) **CH_3Cl and $AlCl_3$**

42. For alkylation commonly used reagents are alkyl halides and commonly used catalyst is

A) HCl B) **$AlCl_3$** C) $ZnCl_2$ D) H_2SO_4

43. In the case of t-alkyl halides, alkylation occurs by

A) **S_N1 mechanism** B) S_N2 mechanism C) S_Ni mechanism D) E1 mechanism

44. The pyridine molecule is failure for

A) Kolbe reaction B) **Friedel-Crafts reaction**

C) Reimer-Tiemann reaction D) Hofmann-Martius reaction

45. The Friedel-Crafts acylation of furan and thiophene can be acylated with CH_3COCl and

A) HCl B) $AlCl_3$ C) **$SnCl_4$** D) H_2SO_4

46. The phenolphthalein is obtained from

A) phthalic acid and phenol B) **phthalic anhydride and phenol**

C) phthalic anhydride and resorcinol D) phthalic anhydride and catechol

47. The SE1 mechanism follows

A) second order kinetics B) third order kinetics

C) zero order kinetics D) **first order kinetics**

48. The Friedel-Crafts acylation reaction is failure in

A) Benzene B) phenol C) **nitrobenzene** D) anisole

49. Aldehydes and ketones react with secondary amines in the presence of a trace of an acid to form compound containing structure is -C=C-N rather than -C-C=N and these α,β-unsaturated amines are known as

A) enamine B) amino alcohol C) imine D) imino ketone

50. Which type of intermediate involved in enamine reaction is

A) Amine B) ketone C) aminol D) **iminium ion**

51. The enamine reaction water is eliminated by

A) **azeotropic distillation with benzene** B) steam distillation with benzene

C) vaccum distillation D) chromatography separation

52. Why is a cyclic amine generally used as the secondary amine in the enamine synthesis?

A) more steric crowding in open chain amine

B) more steric crowding around nitrogen in cyclic amine

C) **less steric crowding around nitrogen in cyclic amine**

D) more steric crowding in acyclic amine

53. Which amines is highly preferred for enamine reaction

A) primary amines B) **secondary amines** C)tertiary amines D) ammonia

54. The acid-catalzed hydrolysis of enamines gives

A) nitro compound B) cyano compound C) **carbonyl compound** D) sulphur compound

55. The conversion of cyclohexanone into 2-benzoyl cyclohaxanone is effected by

A) **enamine reaction** B) Mannich reaction C) Michael reaction D)Wittig reaction

56. *p*-Hydroxy benzaldehyde can be prepared by

A) **Reimer-Tiemann reaction** B) Kolbe reaction

C) Friedel Crafts alkylation D) Friedel Crafts acylation

57. Which of the following is not used as a reagent in Friedel Crafts acylation

A) acyl halide B) carboxylic acid C)anhydrides D) **halogen**

58. 3,4-Dihydroxybenzaldehyde is used to synthesize

A) Vanilline B) indole-aldehyde C) **piperonal** D) 3-chloropyridine

59. Indole-3-aldehyde has been used to synthesize the essential amino acid,

A) Proline B) phenylalanine C) phenylglycine D) **tryptophan**

60. Salicyclic acid is used to synthesize the pain killer drugs

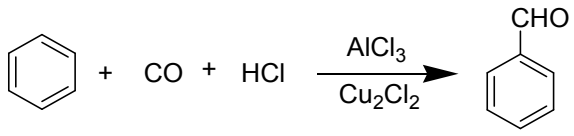
A) **Aspirin** B) sulphafurazole C) sulphadiazine D) chloromycetin

PART-B (Each Question Carry Two Mark)

61. What is Gattermann reaction? Provide the mechanism.
62. What is Kolbe's reaction?
63. β-keto acids undergo decayboxylation fast why.
64. Write the mechanism of Gattermann Koch reaction.
65. Explain Hoffmann Martius reaction with mechanism.
66. What is an enamine? Give examples.
67. Write the mechanism of Bischler-Napieraski reaction.
68. Write the mechanism of Friedel crafts alkylations.

PART-C (Each Question Carry Six Mark)

69. Write a note on Friedel Crafts alkylation and acylation. Compare their advantages and limitations.
70. (i) Discuss about the Stork enamine reaction.
    (ii) Explain Gattermann koch reaction with mechanism.
71. Explain the mechanism of the following reactions.
    (i)



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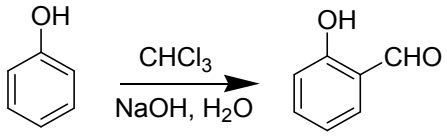

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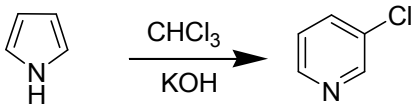
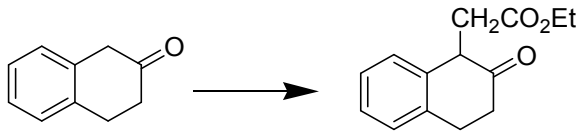


72. (i) Write notes on SE_1 mechanism.
    (ii) Explain Gattermann reaction with mechanism.

73. Show how you would carry out each of the following transformations by way of an enamine (Stork enamine reaction).

(i)



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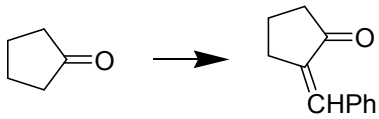

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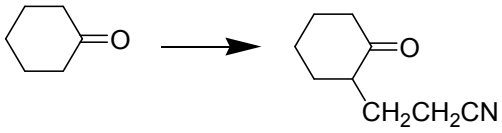
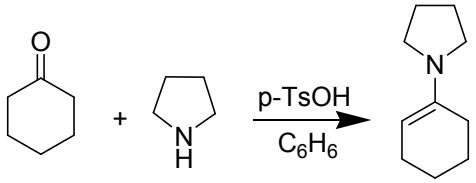
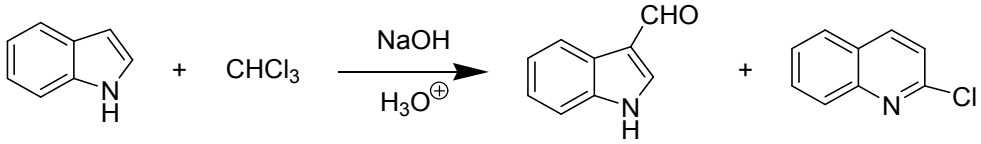


74. (i) Write the mechanism of the following conversion.



(ii) Explain the mechanism of the following reaction.

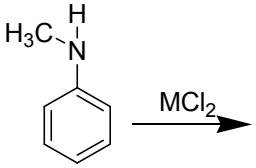


(iii) Give two important applications of the Reimer-Tiemann reaction.

75. Write notes on SE_i mechanism.

76. (i) Explain the Reimer-Tiemann reaction.

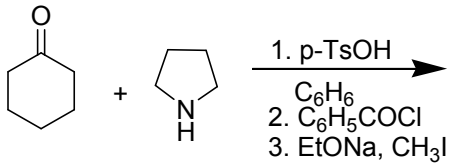
(ii) Complete the following reaction. Provide the mechanism.



77. Sketch a step-by-step mechanism for the acid catalyzed hydrolysis of enamines.

78. Complete the following conversions. Provide the mechanism.

(i)



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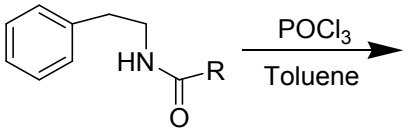

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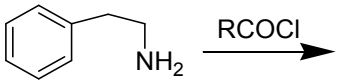
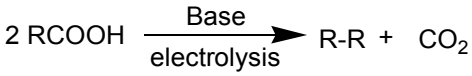


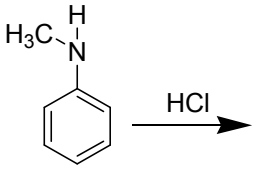
PART-D (Each Question Carry Ten Mark)

79. (i) Give the mechanism of decarboxylation of β-keto acids. Give evidence in favour of the mechanism.

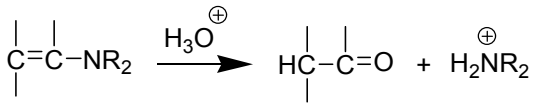
(ii) Write the mechanism of the following conversion.



(iii) Complete the following reaction. Provide the mechanism.



(iv) Write the mechanism of the following conversion.



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DEPARTMENT OF CHEMISTRY

UNIT-III

ELECTROPHILIC SUBSTITUTION REACTIONS

PART-A–Multiple Choice Questions
(Each Question Carry One Mark) (Online Examinations)

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A) **Gattermann reaction** B) Gattermann-Koch reaction

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C) Reimer-Tiemann reaction D) Kolbe reaction

5. Gattermann-Koch reaction which solvent is generally used

A) benzene B) chloroform C) **nitrobenzene** D) ethyl acetate

6. Gattermann-Koch method is used industrially to prepare

A) ketones B)acids C) amides D) **arylaldehydes**

7. The Gattermann-Koch aldehydes synthesis is not applicable to

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8. The nitrobenzene is failed for

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A) Alkyl benzenes B) **phenols** C) amines D) ethers

11. A mixture of ortho and para-isomers is obtained from Reimer-Tiemann in which the ortho isomer predominates due to

A) ionic bond B) intra-molecular hydrogen bonding

C) Vander walls force D) **inter-molecular hydrogen bonding**

12. The dichlorocarbene generated from chloroform by the action of

A) **base** B) acid C) salt D) ions

13. The Gattermann-Koch formylation as a typical

A) nucleophilic aromatic substitution B) **electrophilic aromatic substitution**

C) electrophilic aliphatic substitution D) nucleophilic aliphatic substitution

14. The reaction of pyrrole with chloroform and alkali to produce 3-chloropyridine is an example for

A) **Reimer-Tiemann reaction** B) Gattermann reaction

C) Gattermann-Koch reaction D) Kolbe reaction

15. Carbon tetrachloride in placed of chloroform under Reimer-Tiemann reaction condition gives

A) benzoic acid B) o-hydroxybenzaldehyde C) **salicyclic acid** D) piperonal

16. Pyrrole undergoes Reimer-Tiemann reaction to produces

A) pyrrole-2-aldehyde B) pyridine C) **3-chloropyridine** D) piperonal

17. When carbon tetrachloride in place of chloroform is used Reimer-Tiemann reaction condition gives

A) Aldehyde B) amide C) **acid** D) ketone

18. The o-hydroxybenzaldehyde is separated from the p-hydroxybenzaldehyde by

A) vaccum distillation B) **steam distillation** C) adsorption D) recrystalation

19. Electrolysis of carboxylate ions, results in decarboxylation and combination of the resulting radicals to give the coupling product is called the

A) Gattermann reaction B) Gattermann-Koch reaction

C) Reimer-Tiemann reaction D) **Kolbe reaction**

20. The Kolbe reaction is a

A) addition reaction B) elimination reaction C) **coupling reaction** D) substitution reaction

21. Kolbe reaction is used for the preparation of

A) **aliphatic compounds** B) aromatic compounds

C) heterocyclic compounds D) bicyclic compounds

22. Conversion of an amide to a heterocyclic system using $POCl_3$ is called

A) Gattermann reaction B) Jacobson reaction

C) **Bischler-Napieralski reaction** D) Kolbe reaction

23. The first step in the formation of nucleophilic addition to C=C bond is the formation of

A) Carbocation B) free radical C) **carbanion** D) carbene

24. Ene reaction is similar to

A) polyene synthesis B) Hunsdiecker synthesis

C) Dieckmann condensation C) **Diels- Alder reaction**

25. Michael reaction involves

A) substituted addition B) commuted addition C) **conjugated addition** D) concerted addition

26. Bischler-Napieralski reaction is an

A) intramolecular nucleophilic aliphatic substitution reaction

B) intramolecular electrophilic aliphatic substitution reaction

C) intramolecular nuclophilic aromatic substitution reaction

D) **intramolecular electrophilic aromatic substitution reaction**

27. The conversion of $2ArCR_2COOH$ into $ArCR_2CR2Ar$ by the treatment with

A) base/electrolysis B) **$Na_2S_2O_8/AgNO_3$** C) disilane/Pd D) $DMF/POCl_3$

28. The electron deficient aromatic acyl chlorides are dimerized to biaryls by treatment with a

A) base/electrolysis B) $Na_2S_2O_8/AgNO_3$ C) **disilane/Pd** D) $DMF/POCl_3$

29. Bischler-Napieralski reaction is mainly used for synthesis of

A) Quinoline B) **isoquinoline** C) indole D) pyrrole

30. Which type of intermediate involved in Bischler-Napieralski reaction is

A) amino ester B) enol ether C) dichlorocarbene D) **nitrilium ion**

31. When HCl salts of arylalkylamines are heated at 200-300°C, migration occurs is called as

A) Hunsdiecker synthesis B) Gattermann reaction

C) **Hofmann-Martius reaction** D) Reimer-Tiemann reaction

32. The hydrochloride salts of N-methyl aniline decomposes to give

A) **aniline and methyl chloride** B) benzene and methyl chloride

C) phenol and methyl chloride D) anilinium ion and methyl chloride

33. The hydrochloride salts of N-methyl aniline decomposes to give aniline and methyl chloride by an

A) S_N1 process B) **S_N2 process** C) S_Ni process D) E1 process

34. The Hofmann-Martius reaction the major product is

A) 2-methyl aniline B) 3-methyl aniline C) **4-methyl aniline** D) aniline

35. The Hofmann-Martius reaction is an

A) intermolecular reaction B) **intermolecular process**

C) addition reaction D) elimination reaction

36. The reaction by heating the amine at a temperature between 200-350°C with metal halides is known as

A) Fries rearrangement B) Claisen rearrangement

C) **Reilly-Hickinbottom rearrangement** D) Hofmann-Martius reaction

37. The commonly catalyst used for Vilsmeir reaction is

A) $AlCl_3$ B) **$POCl_3$** C) PCl_5 D) P_2O_5

38. The introduction of an alkyl or acyl group into the benzene ring is known as

A) Hofmann-Martius reaction B) Reimer-Tiemann reaction

C) Kolbe reaction D) **Friedel-Crafts reaction**

39. The Lewis acid catalyst is used for

A) Kolbe reaction B) **Friedel-Crafts reaction**

C) Reimer-Tiemann reaction D) Hofmann-Martius reaction

40. Acetophenone can be obtained by the Friedel-Crafts acylation of benzene with

A) **CH_3COCl and $AlCl_3$** B) $Ac_2O$and $AlCl_3$ C) CH_3COCl and HCl D) CH_3Cl and $AlCl_3$

41. Toluene can be obtained by the Friedel-Crafts acylation of benzene with

A) CH_3COCl and $AlCl_3$ B) $Ac_2O$and $AlCl_3$ C) CH_3COCl and HCl D) **CH_3Cl and $AlCl_3$**

42. For alkylation commonly used reagents are alkyl halides and commonly used catalyst is

A) HCl B) **$AlCl_3$** C) $ZnCl_2$ D) H_2SO_4

43. In the case of t-alkyl halides, alkylation occurs by

A) **S_N1 mechanism** B) S_N2 mechanism C) S_Ni mechanism D) E1 mechanism

44. The pyridine molecule is failure for

A) Kolbe reaction B) **Friedel-Crafts reaction**

C) Reimer-Tiemann reaction D) Hofmann-Martius reaction

45. The Friedel-Crafts acylation of furan and thiophene can be acylated with CH_3COCl and

A) HCl B) $AlCl_3$ C) **$SnCl_4$** D) H_2SO_4

46. The phenolphthalein is obtained from

A) phthalic acid and phenol B) **phthalic anhydride and phenol**

C) phthalic anhydride and resorcinol D) phthalic anhydride and catechol

47. The SE1 mechanism follows

A) second order kinetics B) third order kinetics C) zero order kinetics D) **first order kinetics**

48. The Friedel-Crafts acylation reaction is failure in

A) Benzene B) phenol C) **nitrobenzene** D) anisole

49. Aldehydes and ketones react with secondary amines in the presence of a trace of an acid to form compound containing structure is -C=C-N rather than -C-C=N and these α,β-unsaturated amines are known as

A) enamine B) amino alcohol C) imine D) imino ketone

50. Which type of intermediate involved in enamine reaction is

A) Amine B) ketone C) aminol D) **iminium ion**

51. The enamine reaction water is eliminated by

A) **azeotropic distillation with benzene** B) steam distillation with benzene

C) vaccum distillation D) chromatography separation

52. Why is a cyclic amine generally used as the secondary amine in the enamine synthesis?

A) more steric crowding in open chain amine

B) more steric crowding around nitrogen in cyclic amine

C) **less steric crowding around nitrogen in cyclic amine**

D) more steric crowding in acyclic amine

53. Which amines is highly preferred for enamine reaction

A) primary amines B) **secondary amines** C)tertiary amines D) ammonia

54. The acid-catalzed hydrolysis of enamines gives

A) nitro compound B) cyano compound C) **carbonyl compound** D) suphur compound

55. The conversion of cyclohexanone into 2-benzoyl cyclohaxanone is effected by

A) **enamine reaction** B) Mannich reaction C) Michael reaction D)Wittig reaction

56. p-hydroxy benzaldehyde can be prepared by

A) **Reimer-Tiemann reaction** B) Kolbe reaction

C) Friedel Crafts alkylation D) Friedel Crafts acylation

57. Which of the following is not used as a reagent in Friedel Crafts acylation

A) acyl halide B) carboxylic acid C)anhydrides D) **halogen**

58. 3,4-Dihydroxybenzaldehyde is used to synthesize

A) Vanilline B) indole-aldehyde C) **piperonal** D)3-chloropyridine

59. Indole-3-aldehyde has been used to synthesize the essential amino acid,

A) Proline B) phenylalanine C) phenylglycine D) **tryptophan**

60. Salicyclic acid is used to synthesize the pain killer drugs

A) **Aspirin** B) sulphafurazole C) sulphadiazine D) chloromycetin

UNIT-IV

Nucleophilic substitution reactions: Aliphatic nucleophilic substitution reactions-mechanisms - SN1, SN2, ion pair and SNi- substitution at vinyl carbon. Stereochemistry of nucleophilic substitution reaction - effect of substrate structure - solvent effects - leaving group effect – nucleophilicity, ambident nucleophiles and ambident substrates- neighbouring group participation.

Aromatic nucleophilic substitution reactions - benzyne mechanism, intermediate complex mechanism and SN1 mechanism, structure reactivity relationship.

Ziegler alkylation and Chichibabin reaction.

NUCLEOPHILIC SUBSTITUTION REACTIONS

Aliphatic Nucleophilic Substitution

Introduction

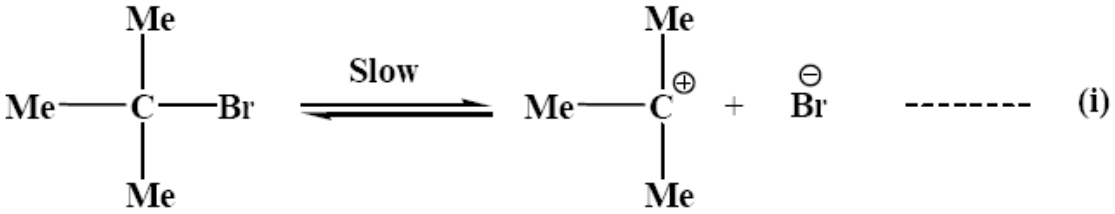
Nucleophilic substitution reaction involves the displacement of a nucleophile by another. These reactions have great synthetic importance. A classic example is the hydrolysis of alkyl halides.

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.

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 α $[R_3CX]$. 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 **$[OH^-]$**, it is interpreted that the halide undergoes slow ionization in the first step producing carbocation intermediate. In the second step a rapid attack of **OH^-** on the carbocation completes the hydrolysis.

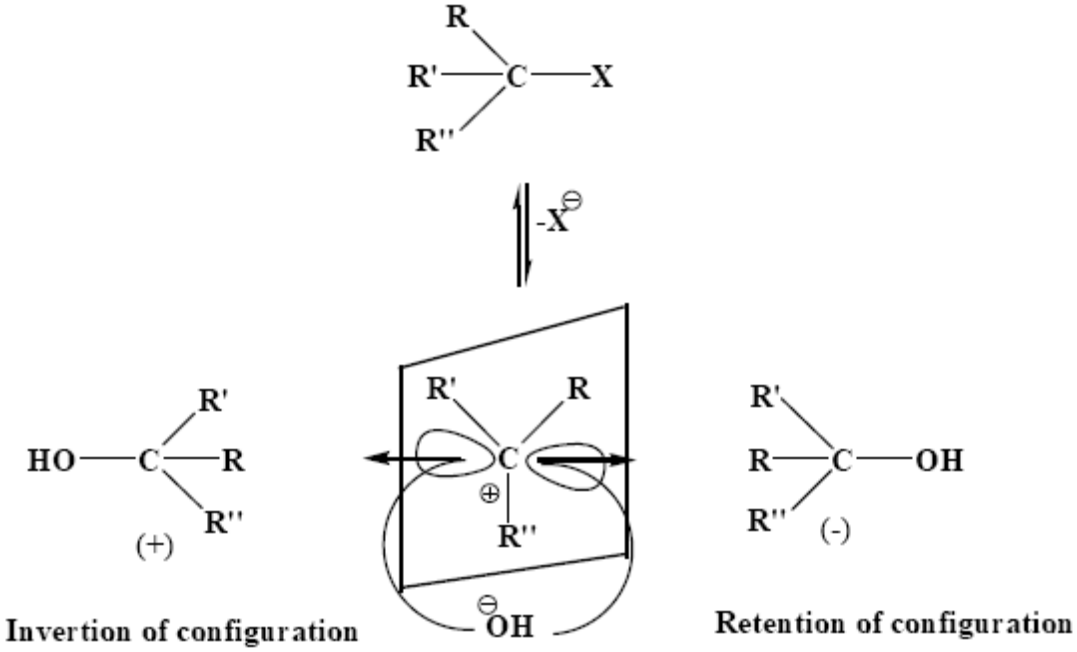


The energy required for the ionization of the halide is supplied by the energy of solvation of the ions. Since a carbocation is formed in the slowest step, the alkyl halide which can most easily form a stable carbocation will favor hydrolysis by S_N1 path. Hence, the order of hydrolysis of alkyl halides by S_N1 path is:

Allyl, Benzyl > 3^0 > 2^0> 1^0 > CH_3X

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.

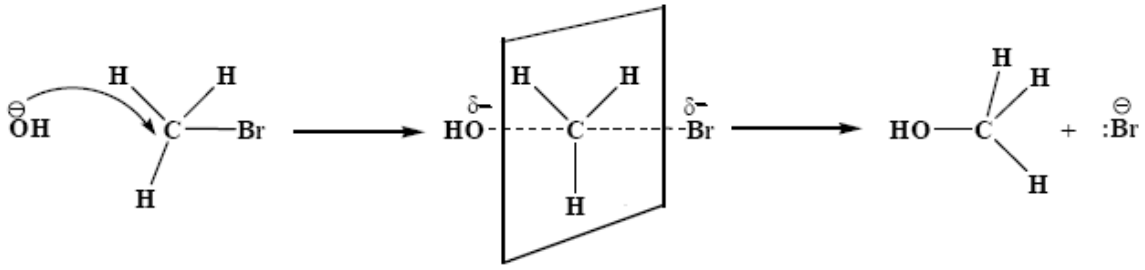
S_N2 Mechanism

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.,

the rate α $[CH_3Br]$ $[OH^-]$

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 backside 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 nonparticipating 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.



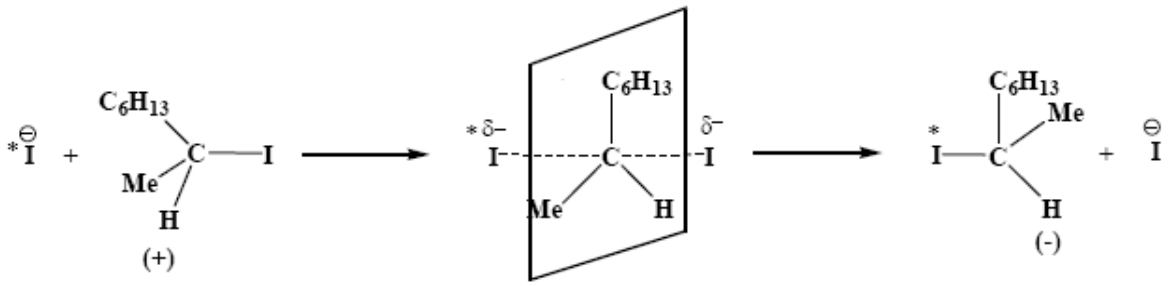
Transition state

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 Eact 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.

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 ptically 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.

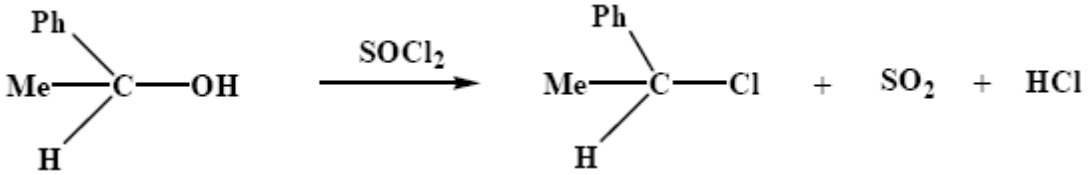
An elegant method has been suggested (Huges and Ingold) to establish the inversion of configuration in S_N2 reaction. The method involves the conversion of (+2) iodooctane with potassium radioiodide ($K^{128}I$) in acetone to (-) 2 -iodooctane. The reaction was found to be bimolecular (S_N2), i.e. rate α $[C_6H_{13}CHICH_3]$ [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.



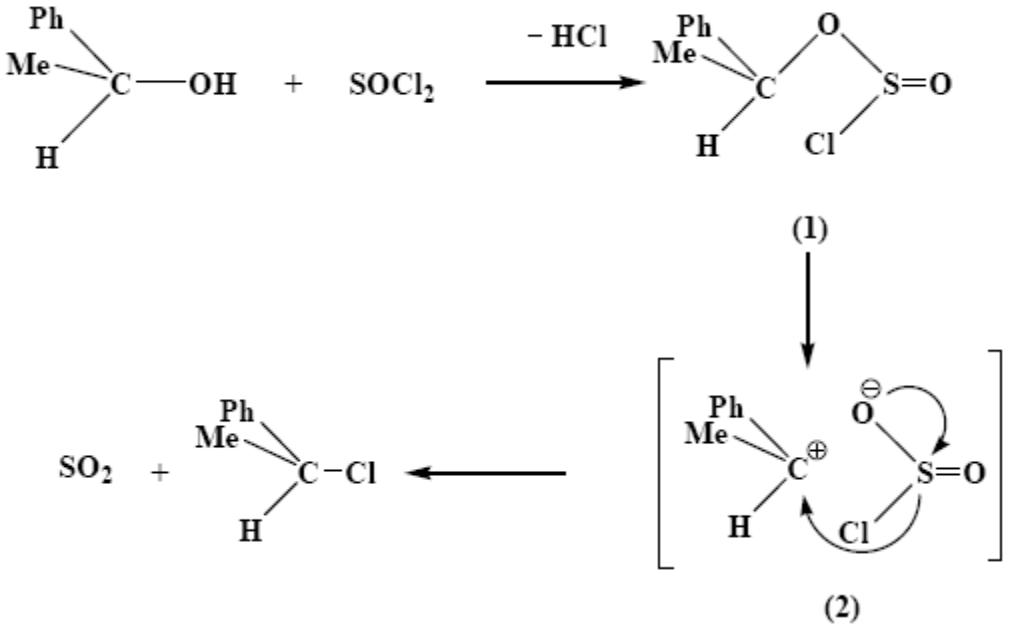
The rate of loss of optical activity (i.e. racemisation) was found to be twice the rate of iodine exchange (i.e. inversion) - one (+) molecule is inverted and another (+) molecule pairs with it to form a (±) modification. The above formulated mechanism of S_N2 reaction is therefore established. Inversion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

S_Ni Mechanism

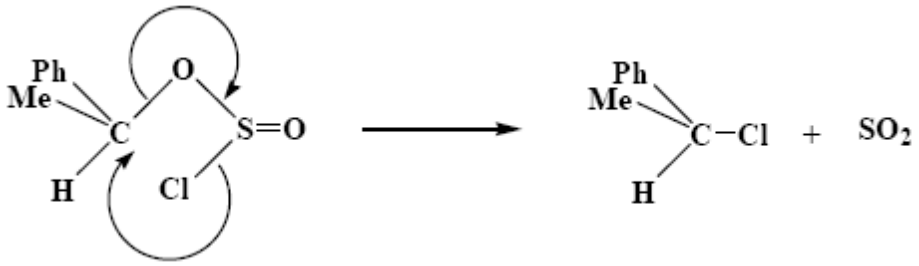
It means Substitution Nucleophilic Internal mechanism. This follows second-order kinetics and yet with no change in the configuration of the product is identified as S_Ni. Thus, the esterification of chiral alcohols with thionyl chloride results in the retention of configuration of the product.



The rate of the reaction is found to be dependent on both the reactants, i.e., rate α [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.

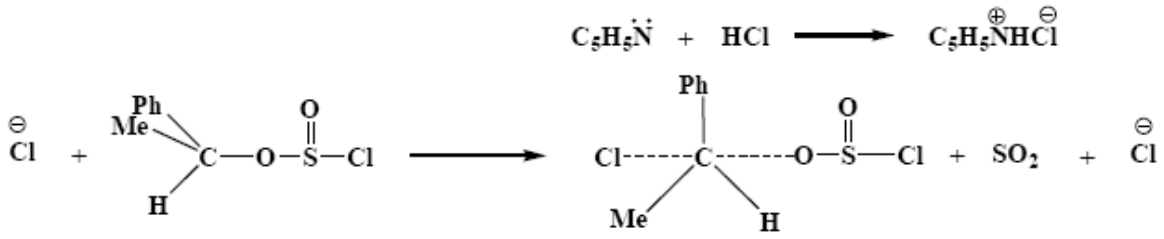


The overall reaction may be considered as an internal attack.



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 SN2 reaction with inversion of configuration.



Factors affecting nucleophilic substitution

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.

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.

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

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

A Strong bases such as $\mathbf{\overset{\ominus}{O}H}$, $\mathbf{\overset{\ominus}{O}R}$, $\mathbf{R_2\overset{\ominus}{N}}$, 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.

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

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 $\mathbf{I^- < Br^- < Cl^- < F^-}$. Therefore, the rate of hydrolysis of the alkyl halides is RI > RBr > RCl by either S_N2 path.

Substrate

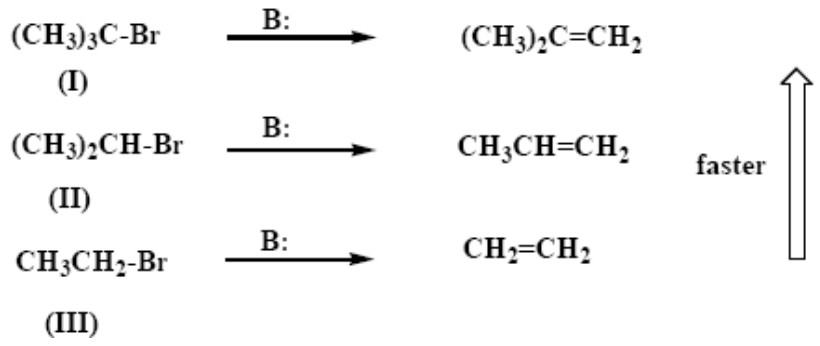
(a) For S_N2 reactions

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 bserved. Table 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 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 55^0C (**Scheme 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, $(CH_3)_2C = CH_2$.

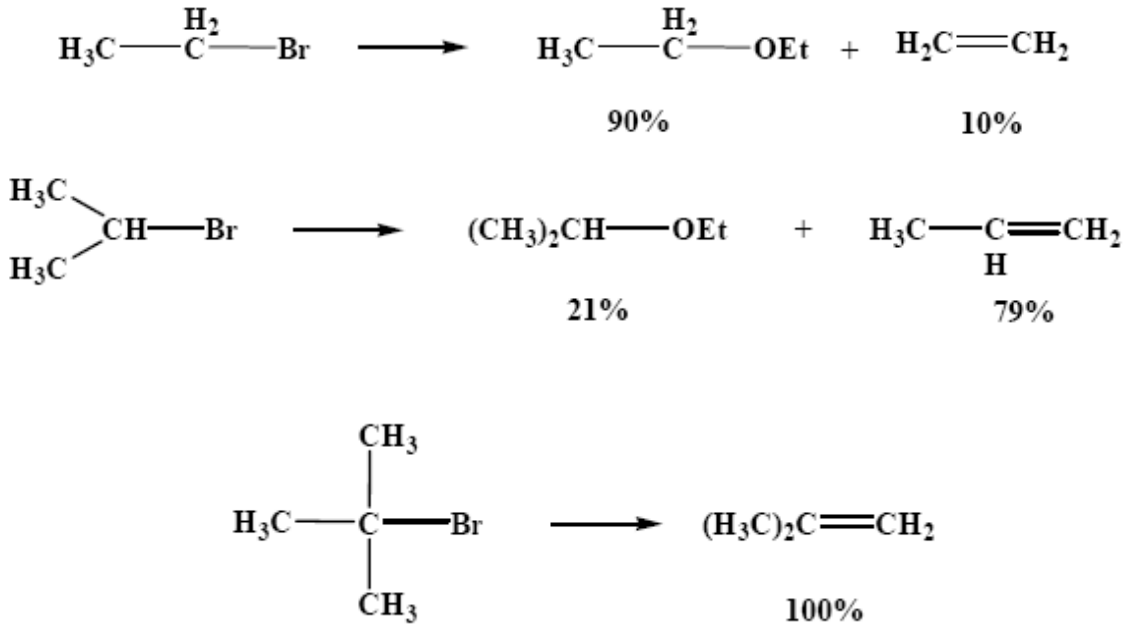
Table: Relative rates of reactions of alkyl halides in S_N2 reactions

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



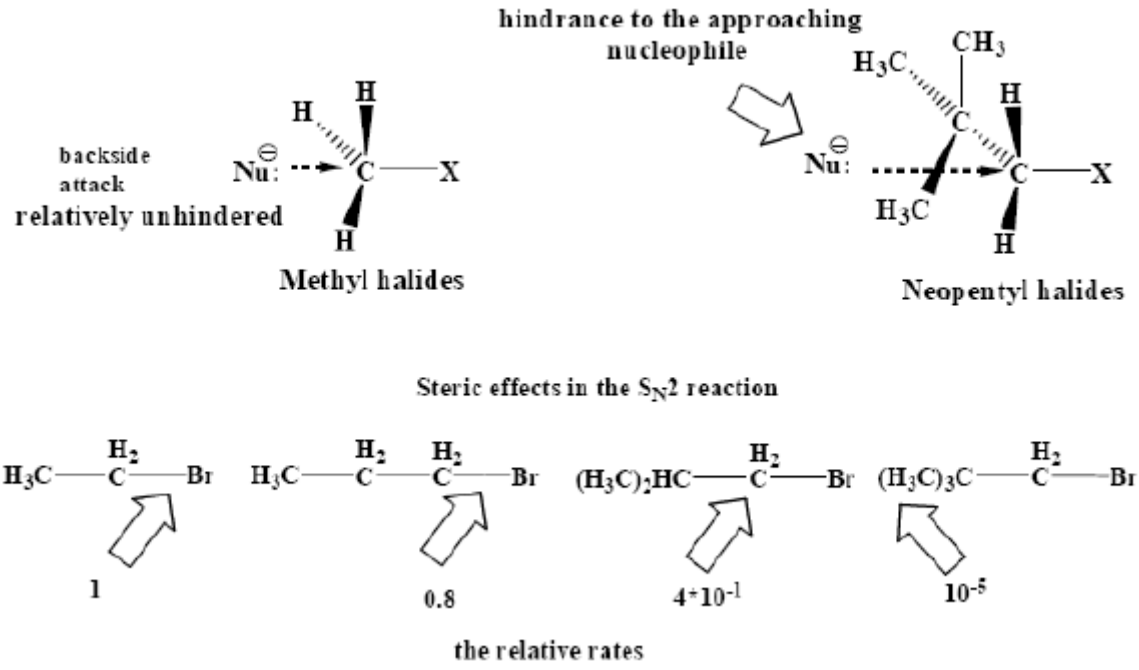
Scheme 1

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 restarted 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 3**, good yields of neopentyl iodide can be obtained via Grignard reagent, see **Scheme 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.

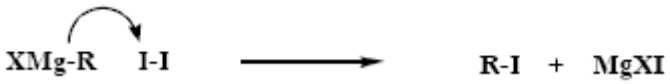


Scheme 2

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** 3).



Scheme 3

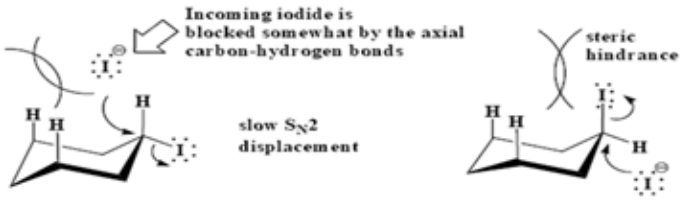


Scheme 4

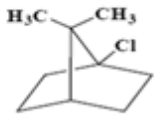
The halocycloalkanes display significant rate differences during S_N2 reactions depending on the size of the ring**.** Halocyclohexanes although seemingly more capable of attaining sp^2 hybridization at the reacting carbon are somewhat slower in S_N2 reaction (see Table).When a nucleophile approaches 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 5**). In a conformation where the leaving group is axial, then its exit its encounters steric hindrance.

Table: 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 5



(apocamphyl chloride)

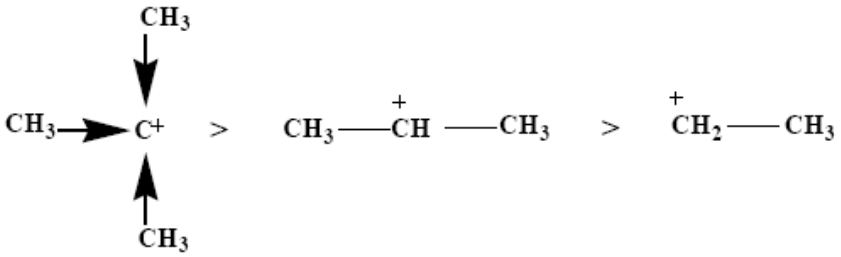
1-chloro-7,7-dimethylbicyclo[2.2.1]heptane

Scheme 6

A bridgehead halide (**Scheme 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

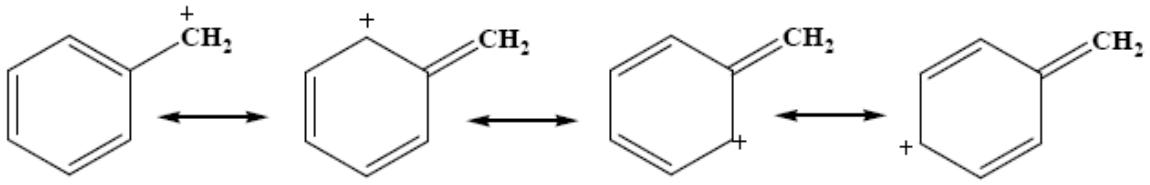
The major structural features necessary for a substrate to undergo S_N1 substitution is the presence of substituents which stabilize the carbocation derived from it. These are the substituents which have +*I* and or +*M* effects. Among alkyl halides, for all practical purposes only tertiary halides react by S_N1 mechanism. A tertiary carbocation being stabilized by three electron releasing groups (see, **Scheme 7**). Allylic and benzylic halides can also react by an S_N1 mechanism since these substrates can form relatively stable carbocations (see e.g., **Scheme 8**).



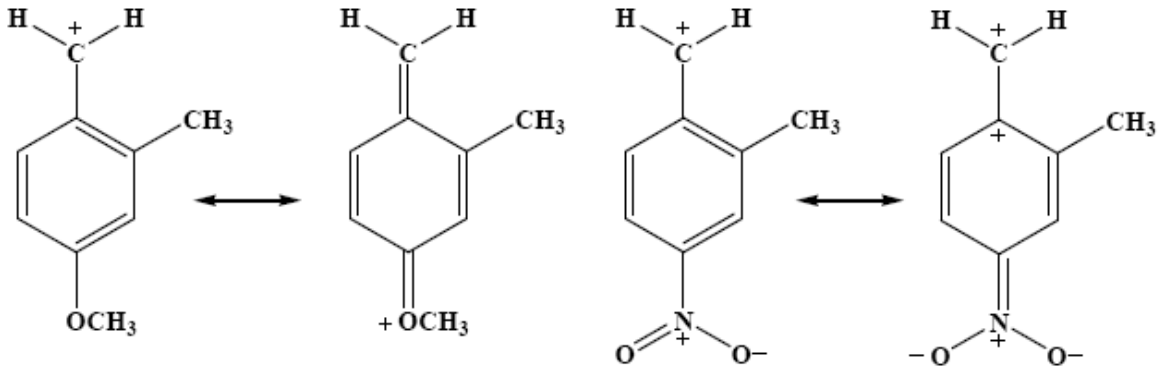
Stability of carbocations $\overset{\circ}{3} > \overset{\circ}{2} > \overset{\circ}{1} > \overset{+}{C}H_3$

Electron release: Disperses charge, stabilizes ion

Scheme 7

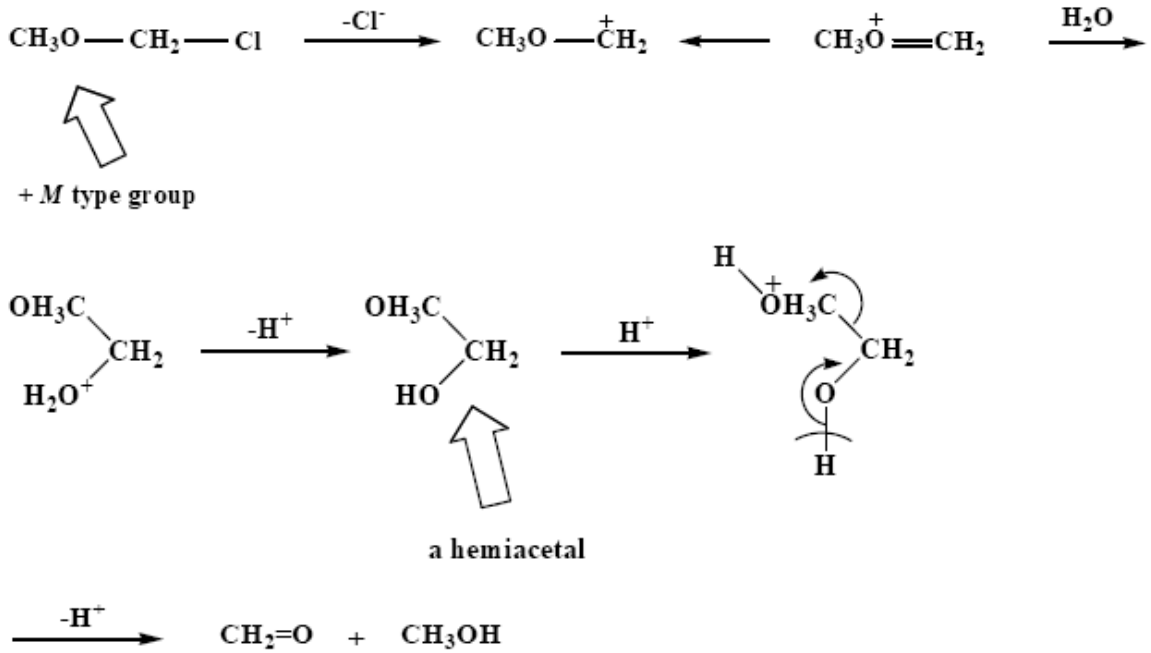


benzylic cation
greater stability
positive carbon is in conjugation with a double bond positive charge is spead over due to resonance



Scheme 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 9**).

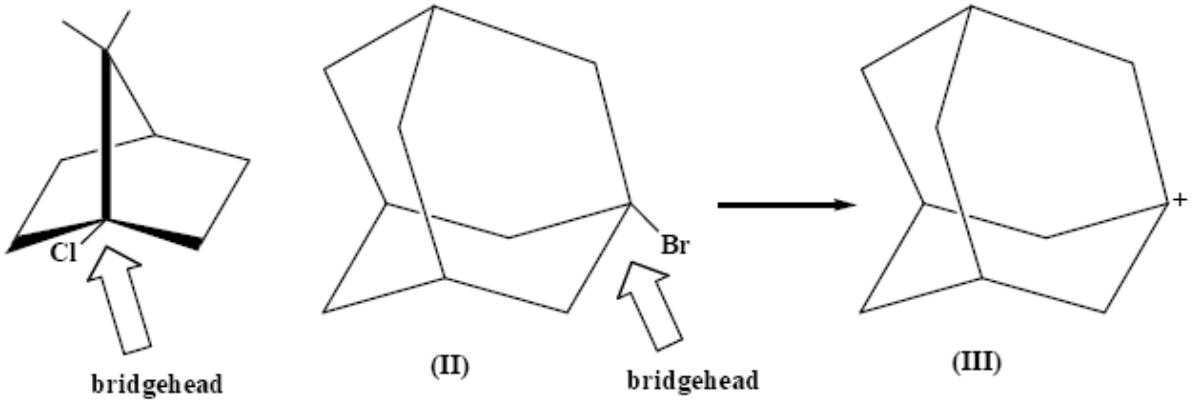


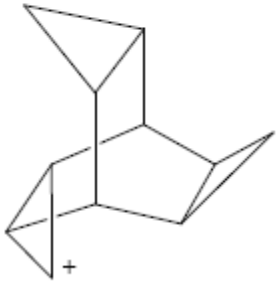
Scheme 9

B strain and I strain effects are observed in many substrates and these effect the rate of SN1 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 10**).





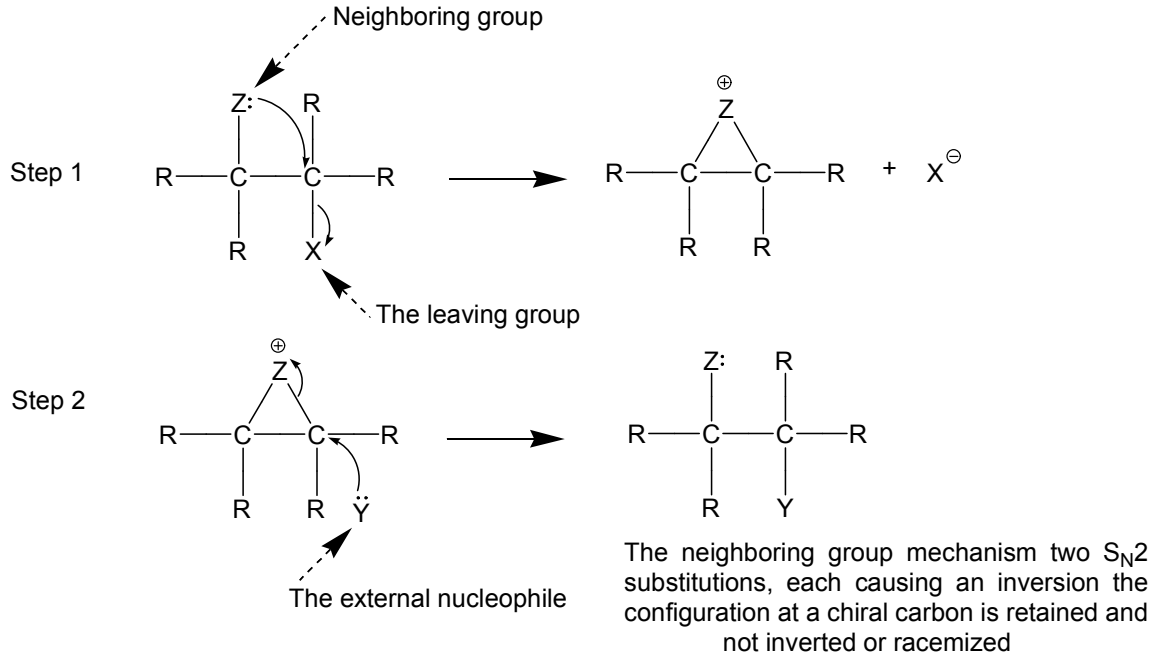
the 1-trishomobarrelyl cation
(IV)

Scheme 10

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 11**) 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 11**) 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.

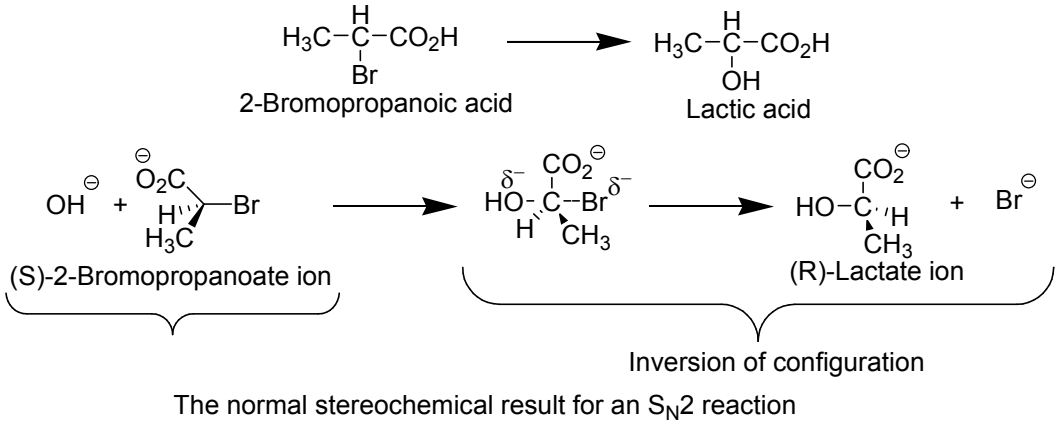


Scheme 11

A graphic example of neighboring group participation is found in the conversion of 2-bromopropanoic acid into lactic acid (**Scheme 12**). In the presence of concentrated sodium hydroxide, (S)-2-bromopropanoic acid (shown as its ion, **Scheme 12**) 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 13**).

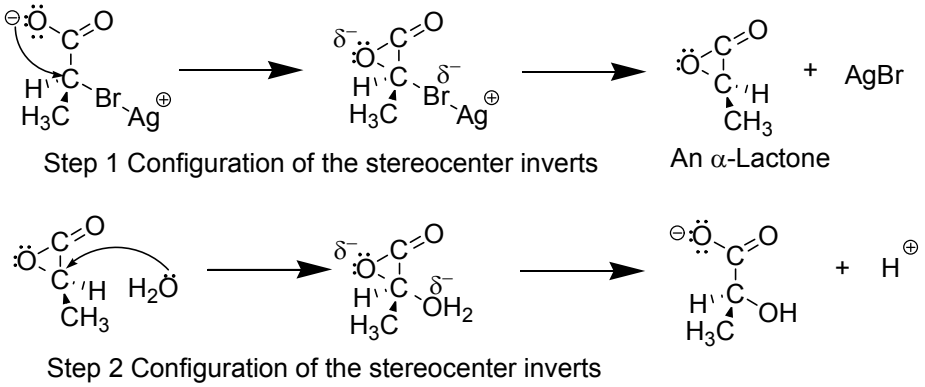
The reaction now involves two steps, in the first step the carboxylate group acts as a neighboring group to displace bromide ion via backside attack on the chiral center. The silver ion here acts as an electrophilic catalyst and aids the removal of bromine. In the second step, the α–lactone is attacked 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.



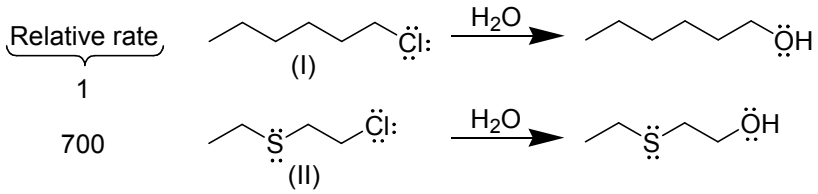
The normal stereochemical result for an S_N2 reaction

Scheme 12



Scheme 13

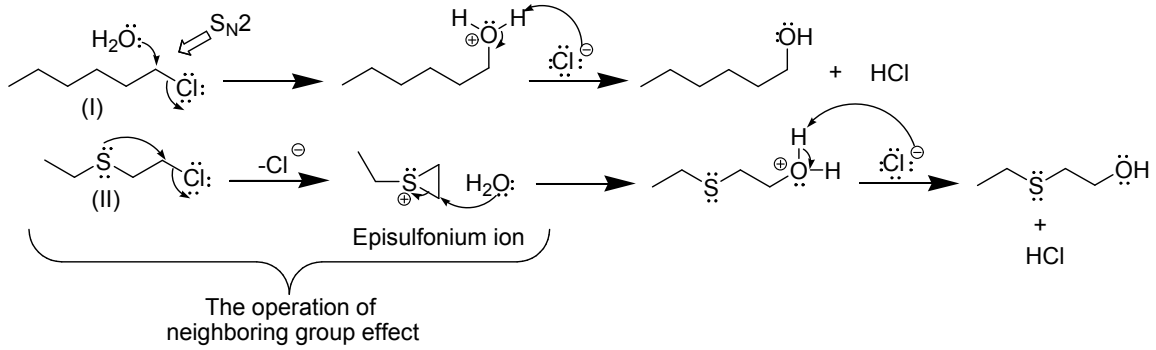
When the neighboring group participation operates during the rate determinating step of a reaction, the reaction rate is usually markedly increased. This effect is then termed anchimeric assistance. Sulfur atoms act as powerful nucleophiles and the participation of sulfur as a neighboring group is common. On reaction with water both hexyl chloride (**Scheme 14**) and 2-chloroethyl-ethylsulfide (II) give their corresponding alcohols.



Scheme 14

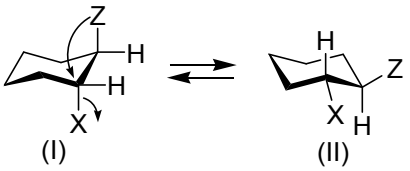
However the rate of reaction of sulfur containing compound (II) is much greater than that of the alkyl chloride. The reaction in the case of (I) is a simple S_N2 displacement of chloride with water, while in the case of sulfide, it is the sulfur atom, which displaces the leaving group and acts as a neighboring 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 15**).

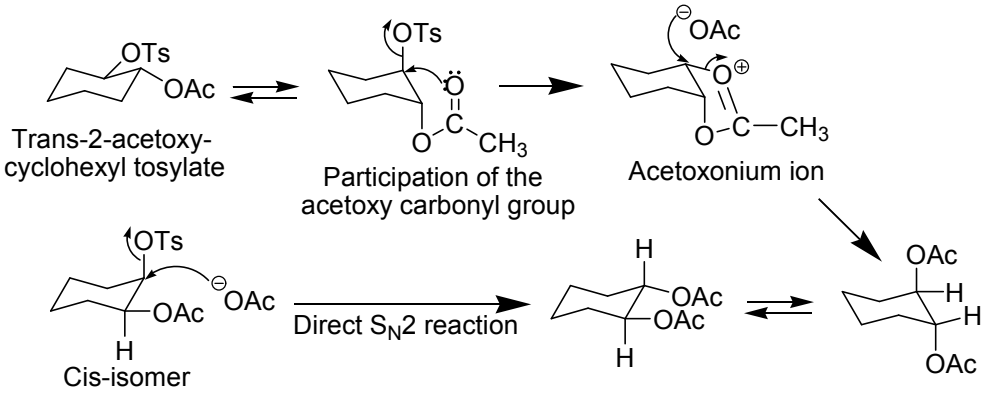


Scheme 15

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 16**). 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 17**) which give the same product I.



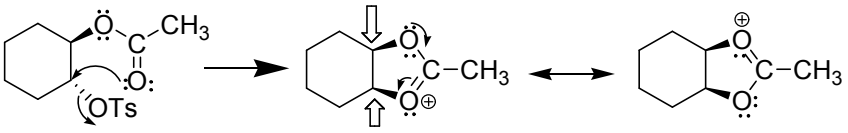
Scheme 16



Scheme 17

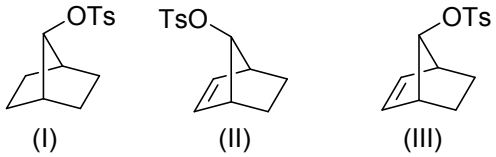
The *cis* isomer reacts via a direct S_N2 mechanism and the trans isomer reacts (about 700 times faster) via neighboring group participation by involving an acetoxonium ion (II, **Scheme 17**).The acetoxonium ion (the resonance hybrid structure) from the trans isomer is, symmetrical achiral (**Scheme 18**) 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.



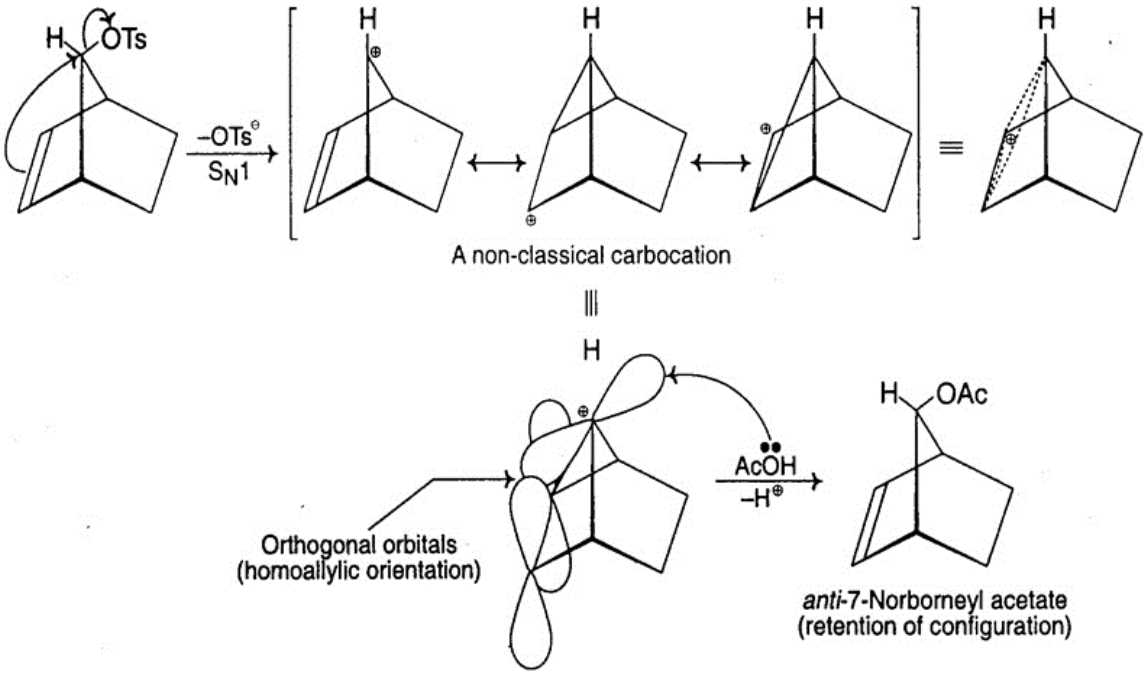
Scheme 18

Among the norbornyl derivatives (on acetolysis) the anti tosylate (III,**Scheme** 19) reacts 10^{11} times faster than (I) while (II) has 10^4 times reactivity compared to (I).

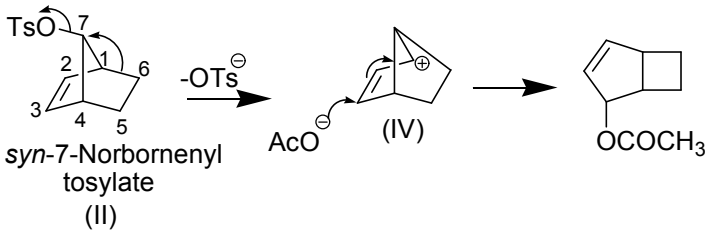


Scheme 19

The fastest rate of acetolysis of anti-tosylate (III) compared to (I, **Scheme 19**) 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 20**). In the syn-isomer (II, **Scheme 19**) 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 21**) 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.



Scheme 20



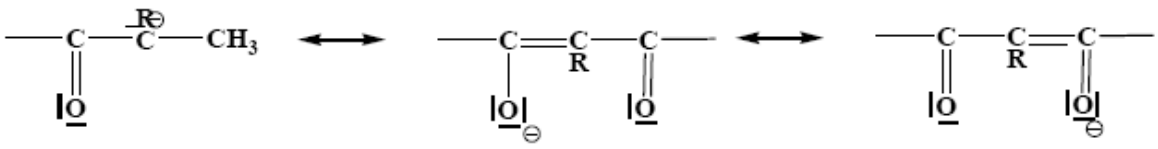
Scheme 21

Ambident nucleophile

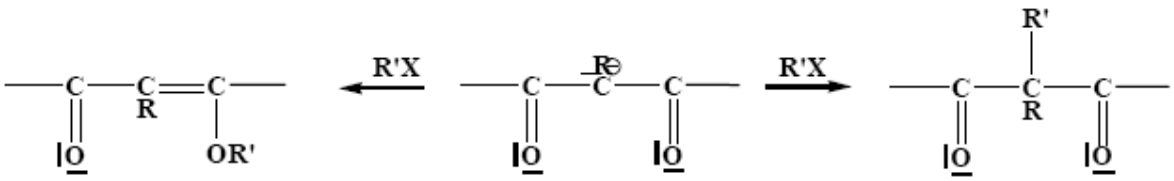
Some nucleophiles have a pair of electrons on each of two or more atoms, or canonical forms can be drawn in which two or more atoms bear an unshared pair. In these cases the nucleophile may attack in two or more ways to give different products. Such reagents are called ambident nucleophiles.

Some important ambident nucleophiles are:

1. Ions of the type **-CO-C-R$^{(-)}$-CO-** . These ions, which are derived by removal of a proton from malonic esters, β–keto esters, β–diketones, etc., are resonance hybrids:

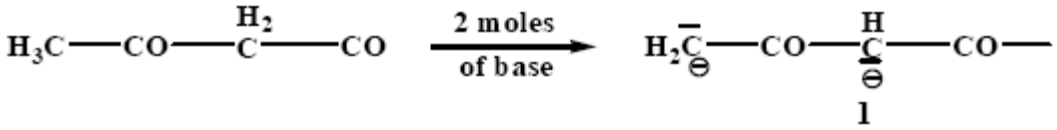


They can thus attack a saturated carbon with their carbon atoms (C-alkylation) or with their oxygen atoms (O-alkylation):



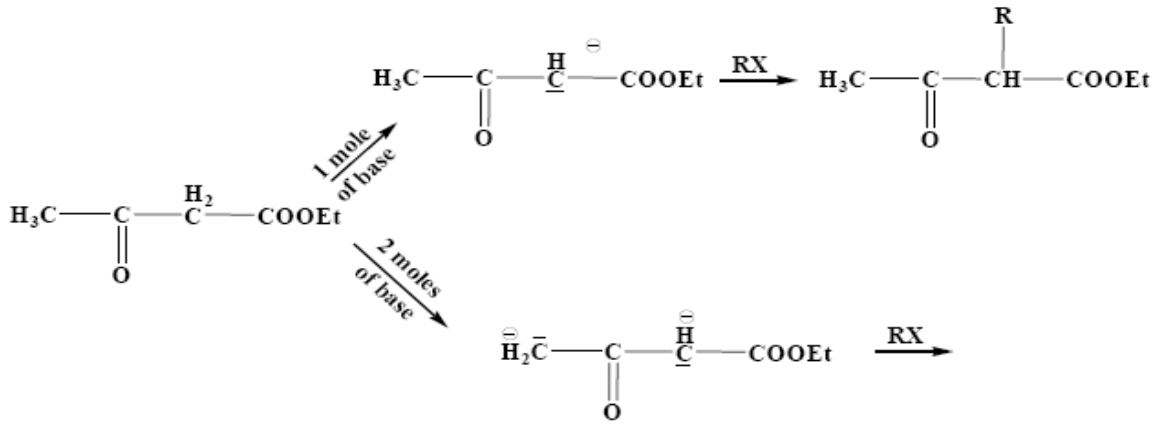
With unsymmetrical ions, three products are possible, since either oxygen can attack with a carbonyl substrate the ion can analogously undergo C-alkylation or O-alkylation.

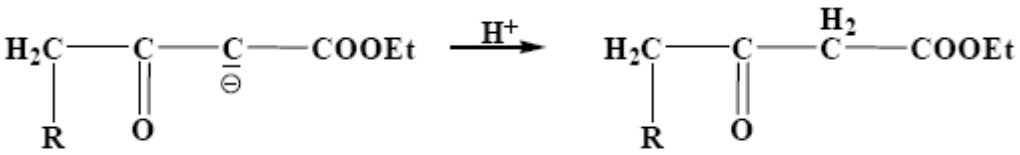
2. Compounds of the type $CH_3CO\text{-}CH_2\text{-}CO$- can give up two protons, if treated with two moles of a strong enough base, to give dicarbanions:



1

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.

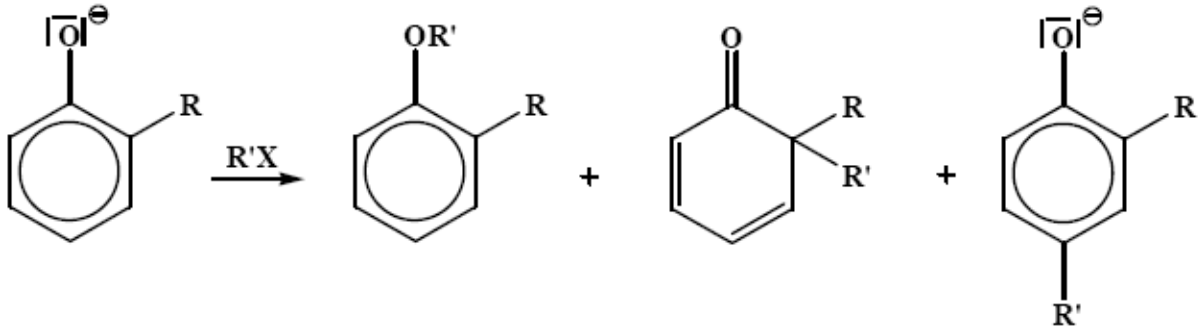




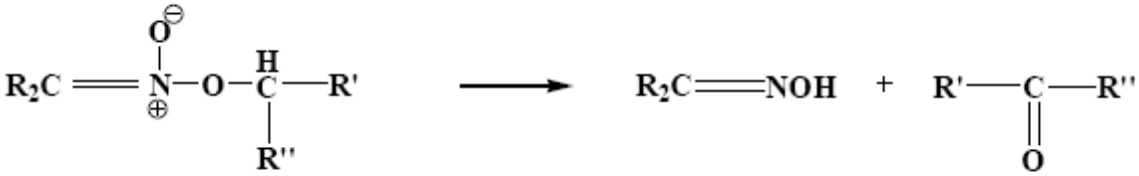
3. The CN^- ion. This nucleophile can give nitrites **RCN** or isocyanides **RN≡C.**

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:



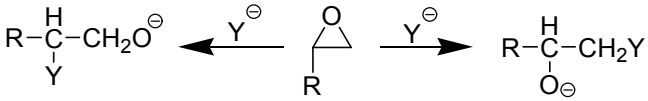
6. Removal of a proton from an aliphatic nitro compound gives a carbanion $\mathbf{R_2C^{\ominus}\text{-}NO_2}$ that can be alkylated at oxygen or carbon. O-alkylation gives nitronic esters, which are generally unstable to heat but break down to give an oxime and an aldehyde or ketone.



There are many other ambident nucleophiles.

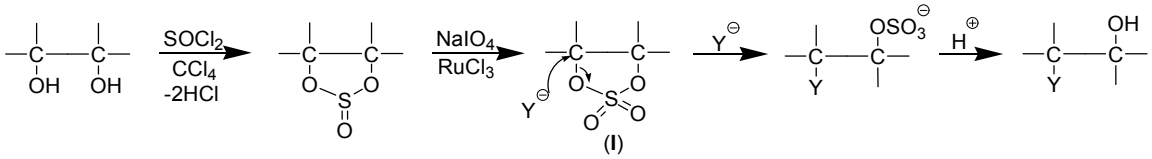
Ambident substrates

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:

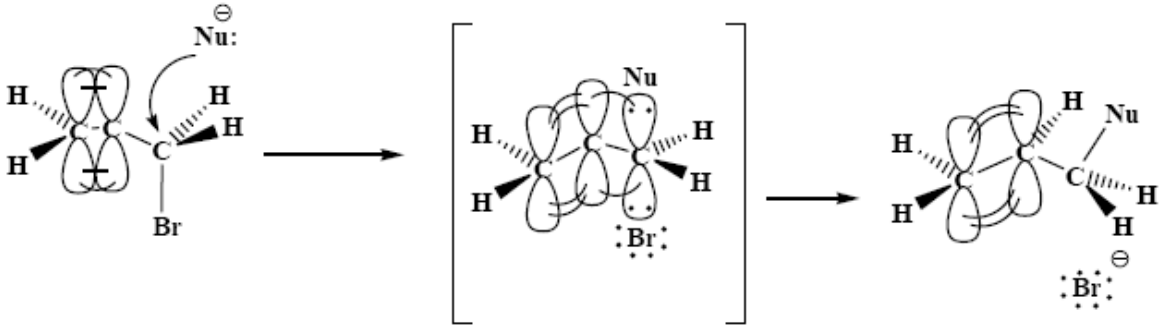


Nucleophilic substitution at vinylic carbon

S_N2 Reactions with allylic and vinylic systems

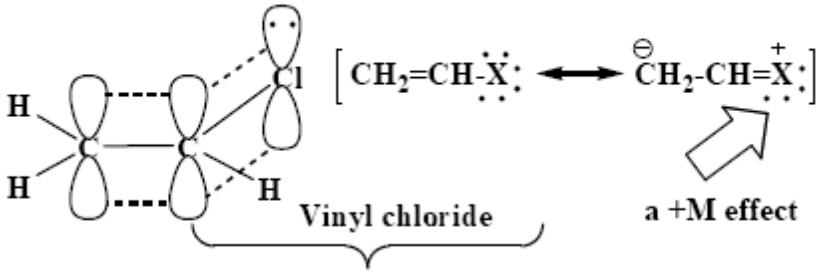
The allylic systems are prone to react by S_N1 mechanism since these form delocalized allylic carbocations easily. However, the synthetic utility of these reactions is limited due to the allylic shift of the double bond. It is possible to have suitable reaction conditions under which allylic bromides 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 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

Scheme 1



Scheme 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 (see also **Scheme** 2).

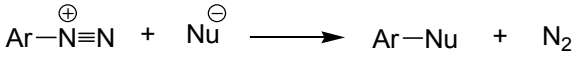
Aromatic nucleophilic substitution reactions

Aromatic nucleophilic substitution reactions are found to occur mainly by the following three mechanistic courses.

(a) The S_N1 mechanism
(b) The addition-elimination mechanism (or) S_N Ar mechanism
(c) The elimination–addition (or) benzyne mechanism

(a) The S_N1 mechanism

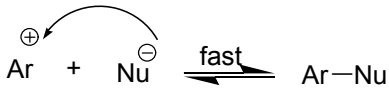
The most common example of an aromatic S_N1 reaction is the displacement of N_2 in the reactions of diazonium salts.



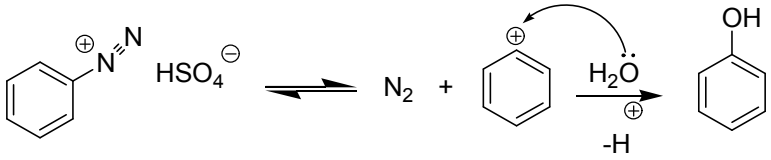
The reaction proceeds through the steps as follows:

Step 1: Formation of an aryl cation by reversible decomposition of the diazonium cation.

Step 2: Attack by the nucleophile on the positive ring carbon of Ar^+ to yield the substitution product.



Benzene diazonium sulphate for example when boiled or steam distilled gives phenol:

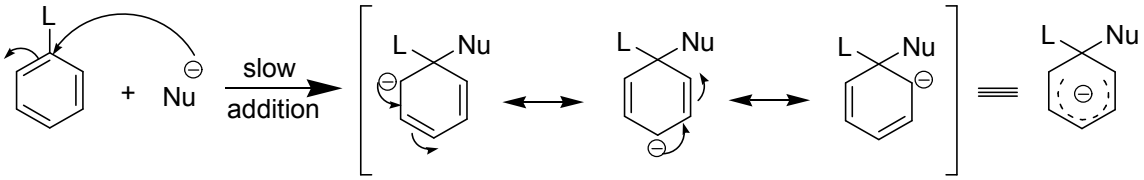


(b) The addition–elimination (or) S_NAr mechanism (or) Intermediate complex mechanism

This is the most important mechanism for aromatic nucleophilic substitution. The reactions following this mechanism involve displacement of groups such $X^{\ominus}$ (X = F, Cl, Br, I), $SO_3^{2\ominus}$, $H^{\ominus}$ etc. The attacking nucleophiles are usually $RO^{\ominus}$, $NH_2^{\ominus}$, $OH^{\ominus}$, piperidine etc.

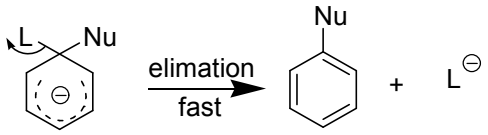
The mechanism consists of two steps:

Step 1: Attack by the nucleophile on the ring carbon bearing the leaving group to form a resonance–stabilised carbanion (I). This is the slow (rate determining) step of the reaction. Formation of the anion results in destruction of aromaticity of the substrate. The carbon undergoing nucleophilic attack changes its hybridisation from sp^2 (planer) to sp^3 (tetrahedral).

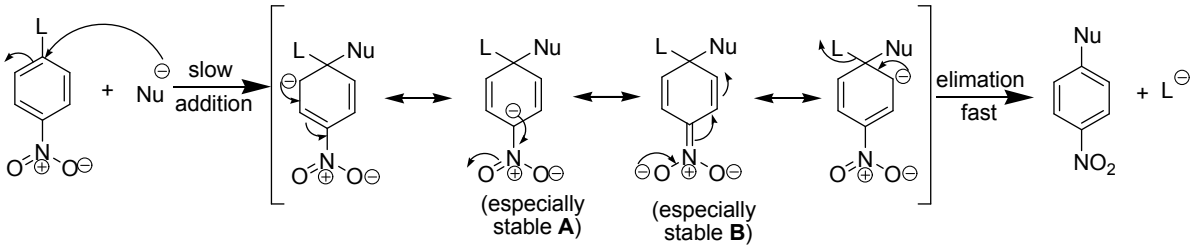


Since the transition state of this slow addition-step involves both the nucleophile and the substrate, the reaction is bimolecular.

Step 2: Loss of $L^{\ominus}$ from the intermediate carbanion to yield the substituted product.



The formation of the benzene anion intermediate is not possible unless some group (e.g., -NO_2, -CN etc) capable of accommodating the negative charge is present in the ortho or para position. Such groups decrease the electron density in the benzene ring making it more favourable for nucleophilic attack and stabilize the intermediate hexadienyl anion by dispersing the negative charge. A substrate containing a –NO_2 group para to the leaving groups undergoes substitution as follows.

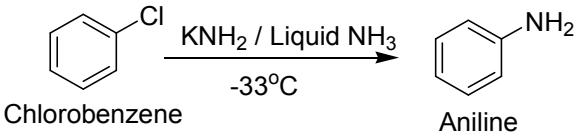


The resonance structures **A** and **B** are especially stable because in **A** the negative charge is on the carbon bearing the electron–withdrawing -NO_2 group and in **B** the negative charge is accommodates by highly electronegative oxygen atom of the -NO_2 group.

Due to presence of these two especially stable structures the carbanion resonance hybrid becomes very stable and the reaction occurs smoothly.

c) The elimination–addition (or) benzyne mechanism

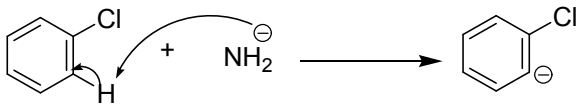
The simple aryl halides are too unreactive to undergo nucleophilic displacement (S_NAr) by usual nucleophiles. However, they react with strongly basic nucleophiles (e.g. $NaNH_2$ or KNH_2 in liquid NH_3) or with usual nucleophiles under drastic conditions. Chlorobenzene for example, when treated with KNH_2 in liquid NH_3 produces aniline by this mechanistic pathway.



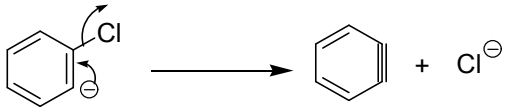
This is a two-stage reaction involving benzyne as an intermediate. The mechanism of the reaction may be given as follows:

Ist Stage: A two-steps elimination of HX and formation of a highly reactive intermediate called benzyne.

Step 1: Abstraction of an ortho hydrogen by $NH_2^{\ominus}$ to form a phenyl anion.

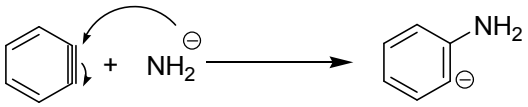


Step 2: Loss of $Cl^{\ominus}$ from the phenyl anion to form the intermediate, benzyne.

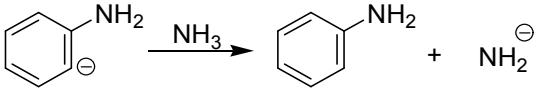


2 nd Stage: A two-step addition of NH_3 to benzyne and formation of aniline.

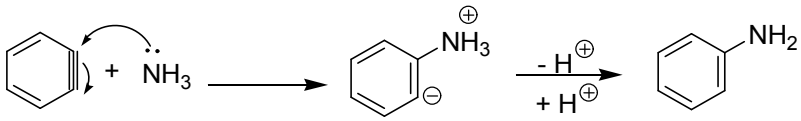
Step 3: Nucleophilic attack by $NH_2^{\ominus}$ at any one of the triple-bonded C-atoms of benzyne.



Step 4: Protonation of the carbanion by NH_3 to form aniline.



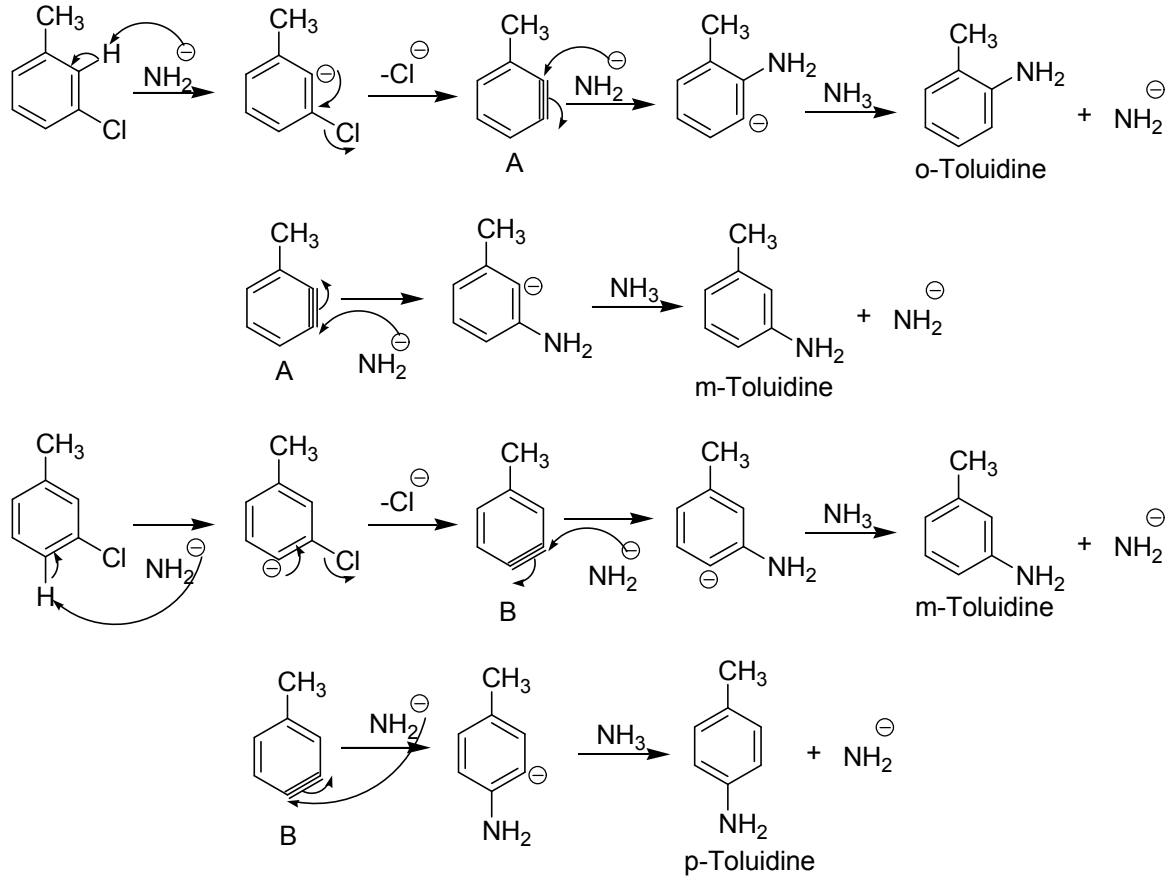
Amination of benzyne may also take place as follows:



Account for the following observations:

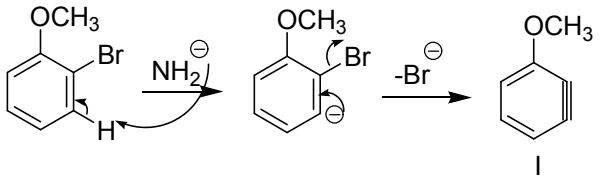
(1) When m-chlorotoluene is treated with KNH_2 in liquid ammonia, a mixture of o- and m- and p-toluidine is obtained.

Since the hydrogens ortho to chlorine are non-equivalent m-chlorotoluene leads to the formation of two arynes (A and B) when treated with KNH_2 in liquid ammonia. These arynes is turn give all the three toluidines.

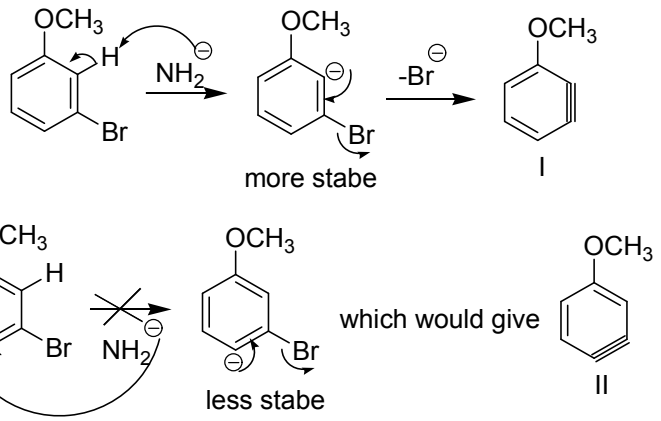


(2) Both o-bromoanisole and m-bromoanisole react with KNH_2 in liquid ammonia to produce m-anisidine.

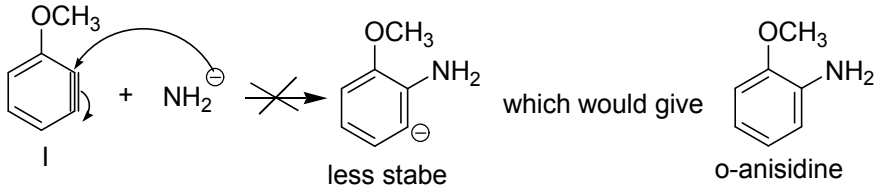
In the presence of KNH_2, o-bromoanisole yields only one aryne (I) and that is because it contains only one ortho hydrogen with respect to bromine.



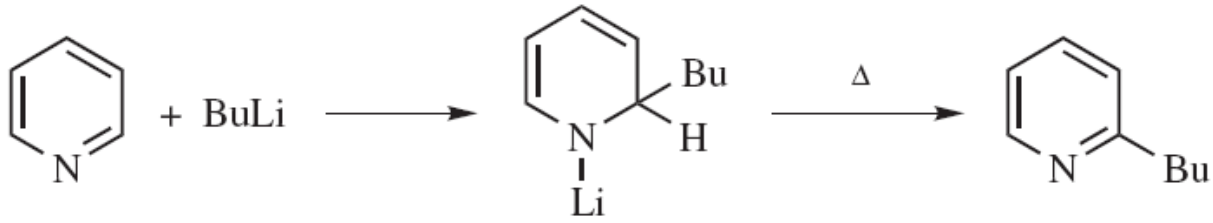
In m-bromoanisole, there are two ortho hydrogens with respect to bromine and so, two arynes (I and II) are expected to be formed. But the actual aryne involved in this reaction is I and that is due to the fact that the carbanion leading to I is more stable than that leading to II.



Since the electron pair of a phenyl anion is out of the plane of the π electron system, the charge cannot be delocalized by resonance. The stability of such a carbanion depends only on the inductive effect of the substituent already present in the ring. Since a methoxy group has an electron-withdrawing inductive effect, the carbanion where the negative charge is closer to the $–OCH_3$ group is more stable than that where it is further from $–OCH_3$. So, the carbanion leading to II is less stable than the carbanion leading to I. Therefore, both the isomeric anisoles generate the same aryne (I) and for the same basic reason, this aryne undergoes nuclephilic attack by NH_2^{Θ} to give a relatively stable carbanion which on protonation gives m-anisidine.



Ziegler alkylation

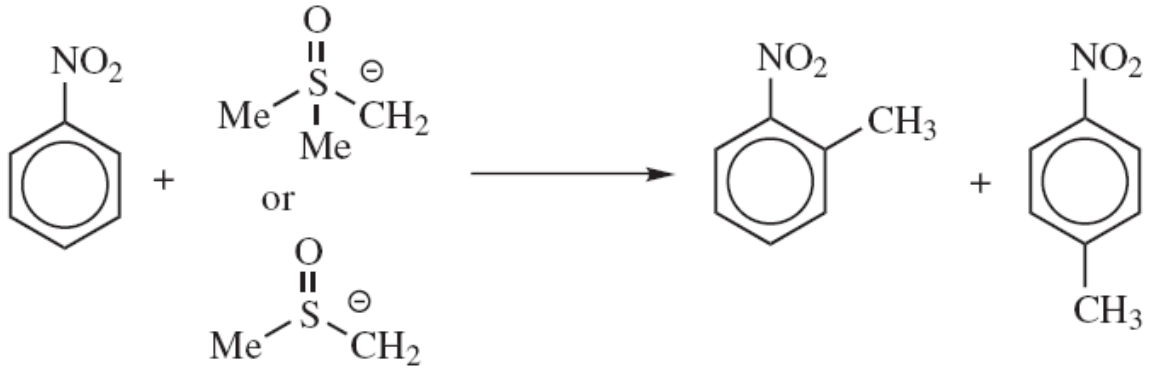


The alkylation of heterocyclic nitrogen compounds with alkyllithium reagents is called *Ziegler alkylation*. Aryllithium reagents give arylation. The reaction occurs by an addition–elimination mechanism and the adduct can be isolated. Upon heating of the adduct, elimination of LiH occurs and an alkylated product is obtained. With respect to the 2-carbon the first step is the same as that of the S_NAr mechanism. The difference is that the unshared pair of electrons on the nitrogen combines with the lithium, so the extra pair of ring electrons has a place to go: it becomes the new unshared pair on the nitrogen. Heteroaromatic

compounds can be alkylated. Pyrrole, for example, reacts with an allylic halide and zinc to give primarily the 3-substituted pyrrole.

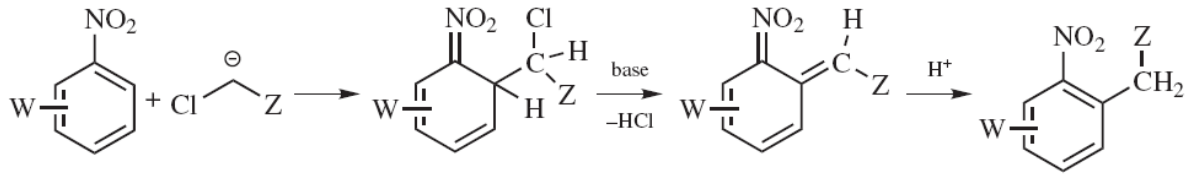
Mercuration of aromatic compounds can be accomplished with mercuric salts, most often $Hg(OAc)_2$ to give ArHgOAc. This is ordinary electrophilic aromatic substitution and takes place by the arenium ion mechanism. Aromatic compounds can also be converted to arylthallium bis(trifluoroacetates) $ArTl(OOCCF_3)_2$ by treatment with thallium(III) trifluoroacetate in trifluoroacetic acid. These arylthallium compounds can be converted to phenols, aryl iodides or fluorides, aryl cyanides, aryl nitro compounds, or aryl esters. The mechanism of thallation appears to be complex, with electrophilic and electron-transfer mechanisms both taking place. Transient metalated aryl complexes can be formed that react with another aromatic compound. Aryl iodides reacted with benzene to form a biaryl in the presence of an iridium catalyst. Aniline derivatives reacted with $TiCl_4$ to give the para-homo coupling product (R_2N-Ar-Ar-NR_2).

Aromatic nitro compounds can be methylated with dimethyloxosulfonium methylid or the methylsulfinyl carbanion (obtained by treatment of DMSO with a strong base):



The latter reagent also methylates certain heterocyclic compounds (e.g., quinoline) and certain fused aromatic compounds (e.g., anthracene, phenanthrene). The reactions with the sulfur carbanions are especially useful, since none of these substrates can be methylated by the Friedel–Crafts procedure. It has been reported that aromatic nitro compounds can also be alkylated, not only with methyl but with other alkyl and substituted alkyl groups as well, in ortho and para positions, by treatment with an alkyllithium compound (or, with lower yields, a Grignard reagent), followed by an oxidizing agent, such as Br_2 or DDQ.

A different kind of alkylation of nitro compounds uses carbanion nucleophiles that have a chlorine at the carbanionic carbon. The following process takes place:

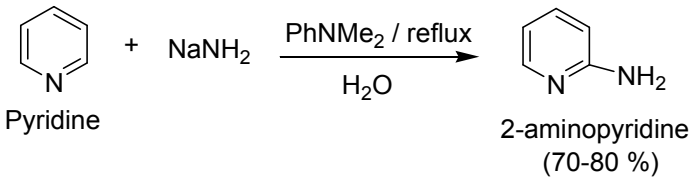


This type of process is called *vicarious nucleophilic substitution of hydrogen*. The Z group is electron-withdrawing (e.g., SO_2R, SO_2OR, SO_2NR_2, COOR, or CN); it stabilizes the negative charge. The carbanion attacks the activated ring ortho or para to the nitro group. Hydride ion ($H^{\ominus}$) is not normally a leaving group, but in this case the presence of the adjacent Cl allows the hydrogen to be replaced. Hence, Cl is a ‘‘vicarious’’ leaving group. Other leaving groups have been used (e.g., OMe, SPh), but Cl is generally the best. Many W groups in the ortho, meta, or para positions do not interfere. The reaction is also successful for di- and trinitro compounds, for nitronaphthalenes, and for many nitro heterocycles, Z-$^{\ominus}$CR-Cl may also be used. When $Br_3C^{\ominus}$ or $Cl_3C^{\ominus}$ is the nucleophile the product is $ArCHX_2$, which can easily be hydrolyzed to ArCHO.

Replacement of an amino group is possible. When aniline derivatives were treated with allyl bromide and *tert*-butyl nitrite (t-BuONO), the aryl–allyl coupling product was formed (Ar-NH_2 → Ar-$CH_2CH{=}CH_2$).

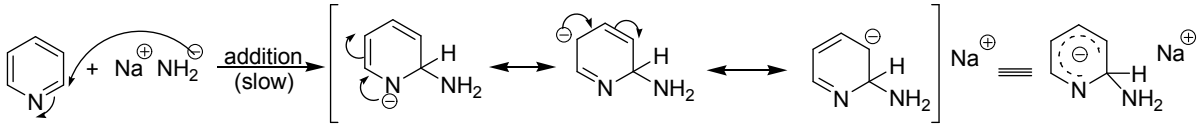
Chichibabin reaction

Amination of pyridine with an alkali metal amide ($NaNH_2$ or KNH_2) is called the Chichibabin reaction.

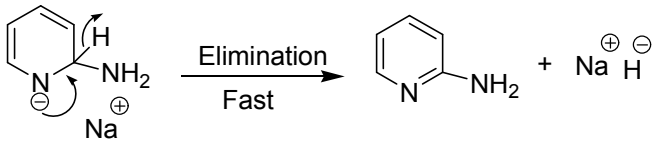


Mechanism

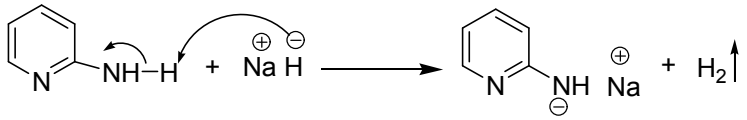
Step 1: Nucleophilic attack by $NH_2^{\ominus}$ at the 2-position of pyridine to yield a resonance stabilized intermediate carbanion.



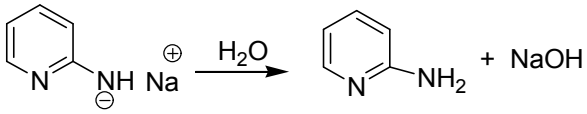
Step 2: Elimination of $H^{\ominus}$ to yield 2-aminopyridine. The driving force for hydride elimination is the re-aromatization of the intermediate.



In practice, a subsequent reaction occur in which the hydride ion abstracts a proton from 2-aminopyridine to form a sodio salt and H_2.



Finally, the sodio salt is converted to 2-aminopyridine by adding cold water to the reaction mixture.



1.Explain the following observation:

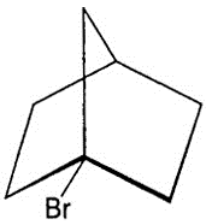
(a) The rate of solvolysis with water (hydrolysis) increase as the following series is traversed:

$PhCH_2Cl$ Ph_2CHCl Ph_3CCl

(b) The rate of reaction (S_N2) of the following bromides with EtO^- in EtOH decreases as the following series is traversed.

	CH_3CH_2Br Ethyl bromide	$CH_3CH_2CH_2Br$ n-Propyl bromide	$(CH_3)_2CHCH_2Br$ Isobutyl bromide	$(CH_3)_3CCH_2Br$ Neopentyl bromide
Relative rate:	1	0.4	0.03	0.00001

(c) The following bicyclic compound is exceedingly unreactive towards nucleophilic substitution either by the S_N1 or S_N2 mechanism.



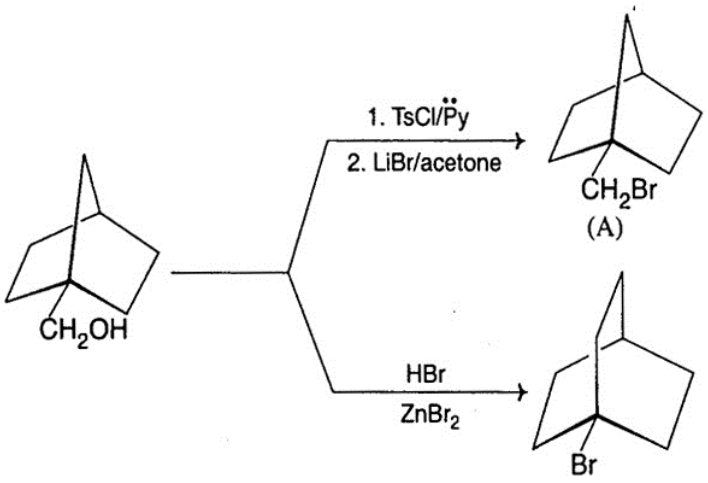
1-Bromobicyclo[2,2,1]heptane

(d) Allyl bromide, CH_2=CH–CH_2Br, undergoes S_N2 reactions slightly more rapidly than does ethyl bromide.

(e) Neopentyl chloride cannot be prepare from neopentyl alcohol by the following reaction:

$$(CH_3)_3CCH_2OH + HCl \not\longrightarrow (CH_3)_3CCH_2Cl + H_2O$$

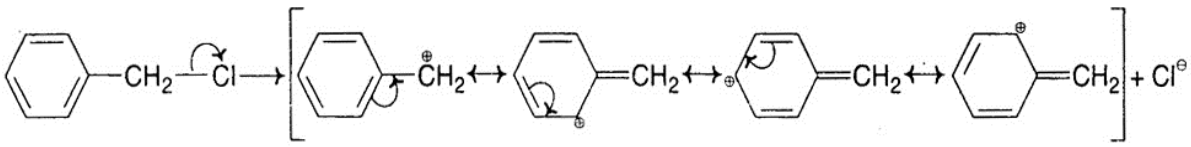
(f)



(g) tert-Butylamine cannot be prepared by Gabriel synthesis.

Solution:

(a) Charge delocalization makes the carbocation derived from benzyl chloride reasonably stable. Because of this, benzyl chloride ionizes readily in water (a polar protic solvent), i.e., it undergoes ready hydrolysis by the S_N1 mechanism.



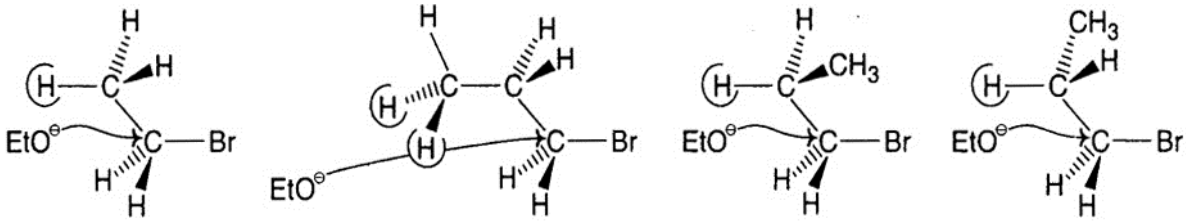
As the number of phenyl groups on the reacting carbon increases, resonance stabilization of the corresponding carbocation increases and consequently, the rate of hydrolysis increases as the series is traversed.

Stability order:

$$Ph_3\overset{\oplus}{C} > Ph_2\overset{\oplus}{C}H > Ph\overset{\oplus}{C}H_2$$

(b) The differences in inductive effect (+I) of the methyl groups at the β-carbon through two saturated carbon atoms is too small to make any detectable difference in the S_N2 reaction rate. It is the steric effect which is responsible for the rate differences. As the number of methyl groups at the β-position increases, it becomes progressively more difficult

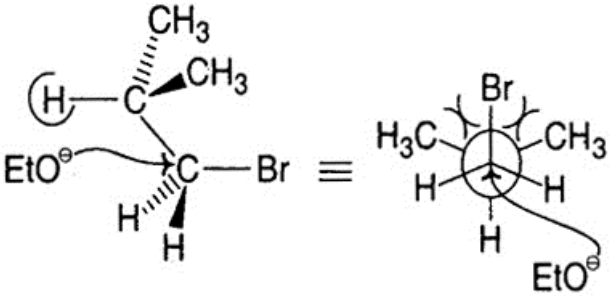
sterically for $EtO^{\ominus}$ to attack on the carbon bearing bromine from the backside and consequently, the S_N2 reaction rate decreases across the series of bromides. It becomes more clear from conformational analysis. In one conformation (a), the backside of a n-propyl carbon is seriously blocked, whereas in other two conformations (b and c) the situation is no worse than ethyl. Consequently, n-propyl bromide undergoes S_N2 reactions only slightly less readily than does ethyl bromide.



S_N2 attack on ethyl bromide (a) (b) (c)

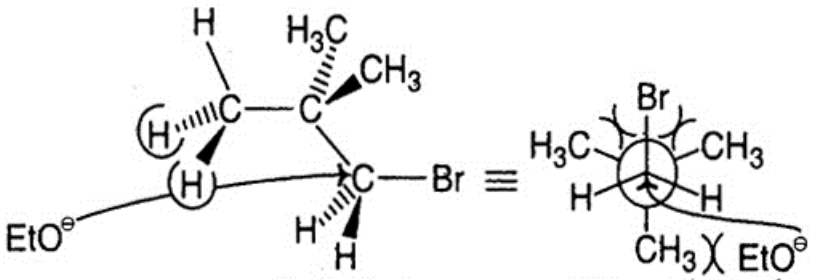
S_N2 attack on n-propyl bromide

In the case of isopropyl bromide, it is possible to rotate both the β-methyl groups out of the way of the attacking nucleophile, but the resulting conformation is highly congested and therefore, has relatively high energy. Consequently, isobutyl bromide is much less reactive than either ethyl or n-propyl bromides.



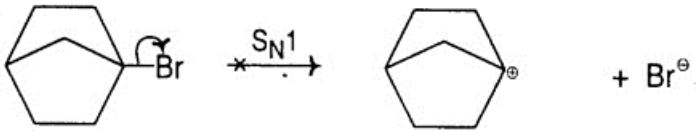
S_N2 attack on isobutyl bromide

In the case of neopentyl bromide, however, there is no conformation in which the nucleophile can avoid a blocking methyl group. Thus, neopentyl bromide is practically unreactive in S_N2 reactions (except under very drastic conditions).



S_N2 attack on neopentyl bromide

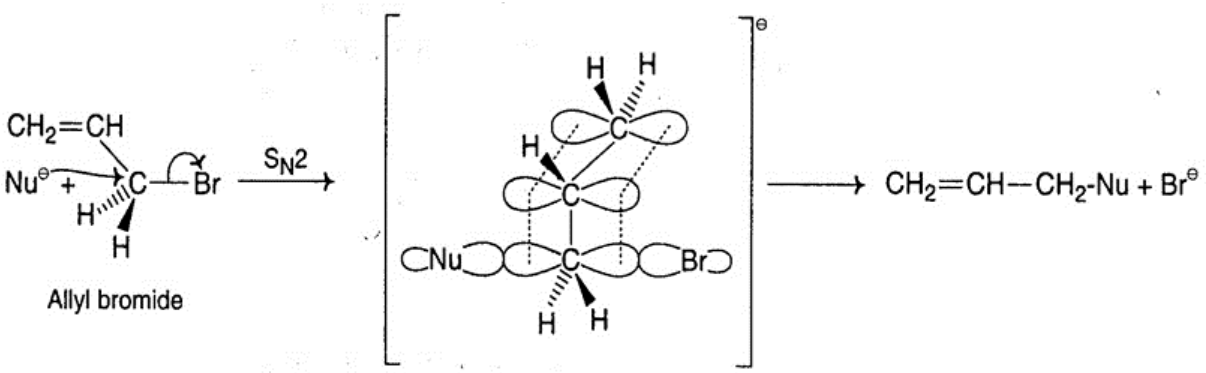
(c) Because of extremely rigid cage-like structure, the bridgehead carbocation cannot assume its usual planar trigonal orientation of bonds and for this, it is highly unstable. So, ionization of 1-bromobicyclo[2.2.2]heptane leading to the formation of an unstable bridgehead carbocation does not take place, i.e., the compound is unreactive towards S_N1 reaction.



1-Bromobicyclo[2,2,1]heptane A nonplanar carbocation (unstable)

The compound is unreactive towards S_N2 reaction because the backside attack on the carbon bearing bromine is prevented sterically by its cage-like structure and also by the impossibility of assuming the required planar distribution of bonds to the bridgehead carbon atom.

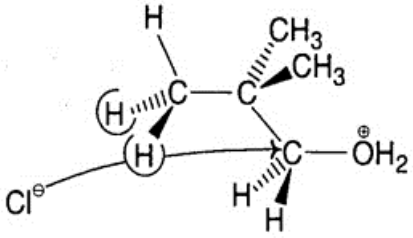
(d) The S_N2 attack on allyl bromide occurs at a faster rate than on ethyl bromide because the unhybridized p orbital involved in the transition state interacts with the π-orbital system of the allyl group and thereby, makes the transition state much stable.



Allyl bromide

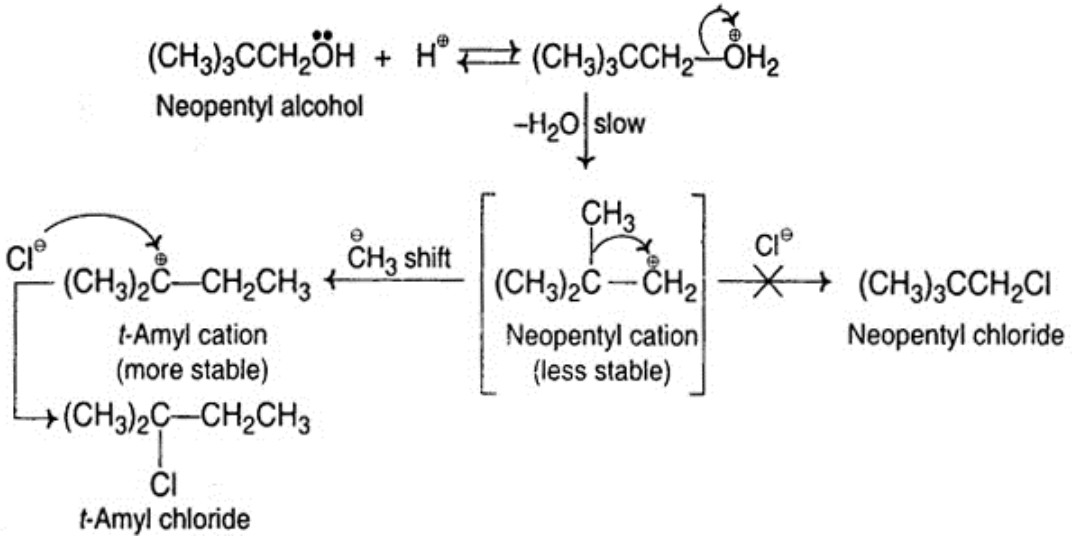
Transition state (stabilized by π overlap)

(e) Although neopentyl is a primary group, because of steric reason, neopentyl alcohol reacts with HCl to give neopentyl chloride by an S_N2 mechanism very slowly.

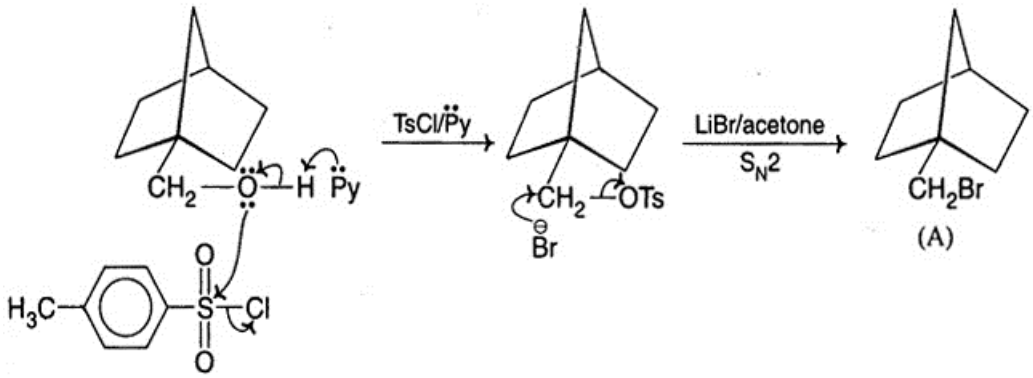


S_N2 attack on the conjugate acid of neopentyl alcohol

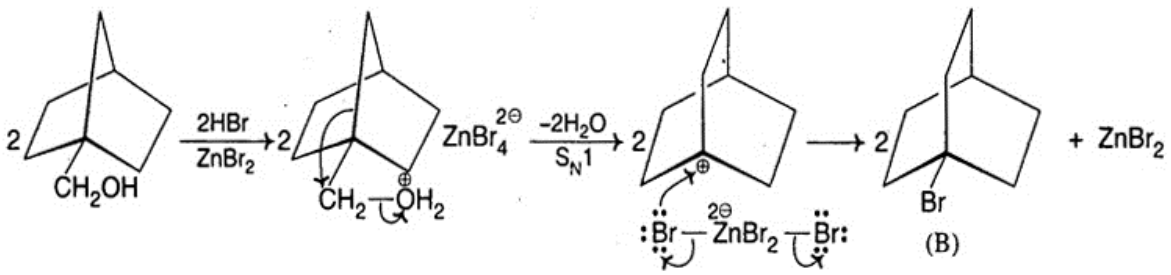
The reaction proceeds by an S_N1 mechanism because the formation of neopentyl cation, although slow, is much faster than the alternative S_N2 reaction. However, the neopentyl cation, being a primary one, undergoes ready rearrangement to form relatively stable *tert*-amyl cation and results in the formation of *tert*-amyl chloride almost exclusively. Neopentyl chloride thus cannot be prepared by the reaction of neopentyl alcohol with HCl.



(f)

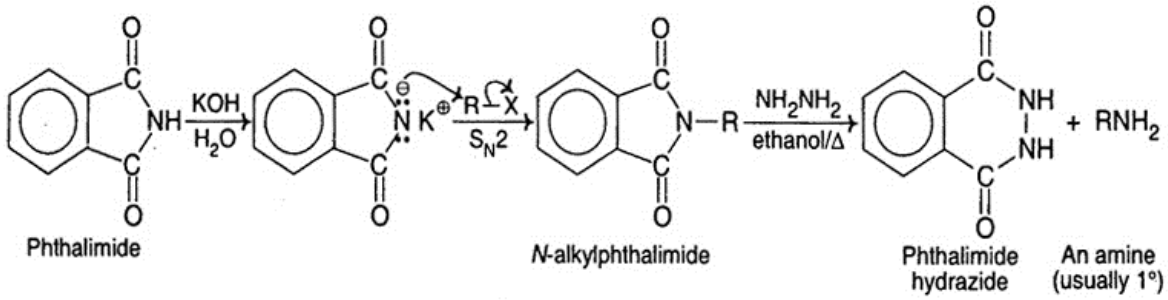


Although the intermediate tosylate is a neopentyl type of substrate, displacement of $OTs^{\ominus}$ by $Br^{\ominus}$ occurs under S_N2 conditions to form A. This is because the groups on the 3º bridgehead carbon are tied back and do not interfere sterically with the incoming nucleophile $Br^{\ominus}$.



Under S_N1 conditions ($HBr/ZnBr_2$), the bridge methylene group migrates to bond with the incipient carbocation that forms as H_2O (a good leaving group) is lost. The resulting 3º bridgehead carbocation then undergoes nucleophilic attack by $Br^{\ominus}$ to give B.

(g) The Gabriel synthesis of an amine (usually 1º) may be outlined as follows:



To get *tert*-butyl amine we have to use *tert*-butyl halide in step II. But a tertiary substrate cannot be used in the step because this step involves an S_N2 reaction. For this reason, *tert*-butylamine cannot be prepared by Gabriel synthesis.

2. Explain the following observations:

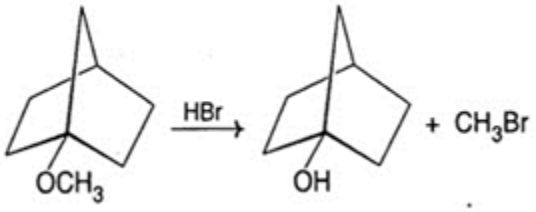
(a) Chloroacetone, CH_3COCH_2Cl, undergoes S_N2 reaction faster than does n-propyl chloride, but it undergoes S_N1 reaction much more slowly.

(b) Chloromethyl methyl ether, $ClCH_2OCH_3$, undergoes ready S_N1 solvolysis reactions, even though it is a primary substrate.

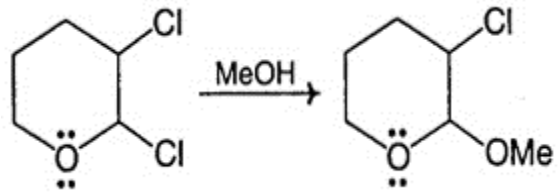
(c) Halocyclopropanes are unreactive towards S_N2 reactions.

(d) Halocyclohexanes react slowly by the S_N2 mechanism

(e)

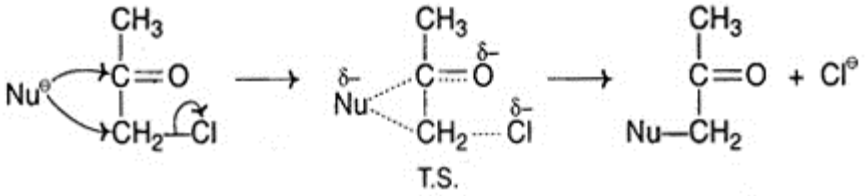


(f)



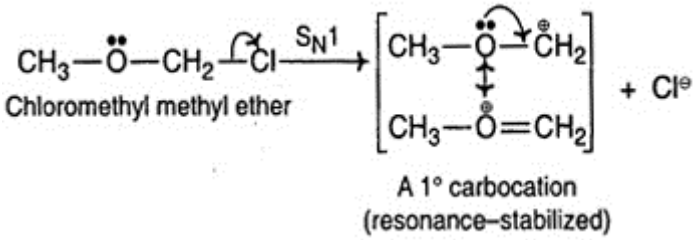
Solution:

(a) Chloroacetone, CH_3COCH_2Cl, undergoes S_N2 reaction faster than does n-propyl chloride because the α-carbonyl group accepts some of the charge of the nucleophile and thereby facilitates the nucleophilic attack.



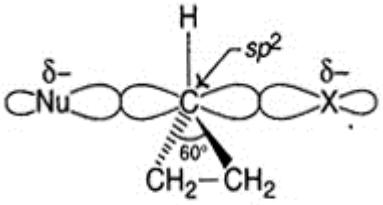
The electron-withdrawing carbonyl group destabilizes the carbocation involved in an S_N1 reaction by intensifying the charge. So, this haloketone undergoes S_N1 reaction even more slower than does n-propyl chloride.

(b) Since the carbocation obtained from CH_3OCH_2Cl on C-Cl bond cleavage is resonance stabilized, it undergoes S_N1 reaction, even though it is a primary substrate.



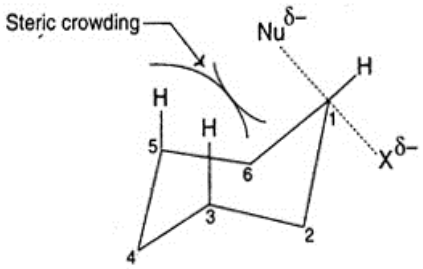
(c) At the transition state of a S_N2 reaction, the central carbon becomes sp^2-hybridized in which the normal bond angle is 120º. In a cyclopropyl system, the bond angle strain increases (from 109.5º – 60º = 49.5º to 120º -60º = 60º) with change in hybridization of the

central carbon. The energy of the transition state, therefore, becomes too high to make halocyclopropanes unreactive towards S_N2 reactions.



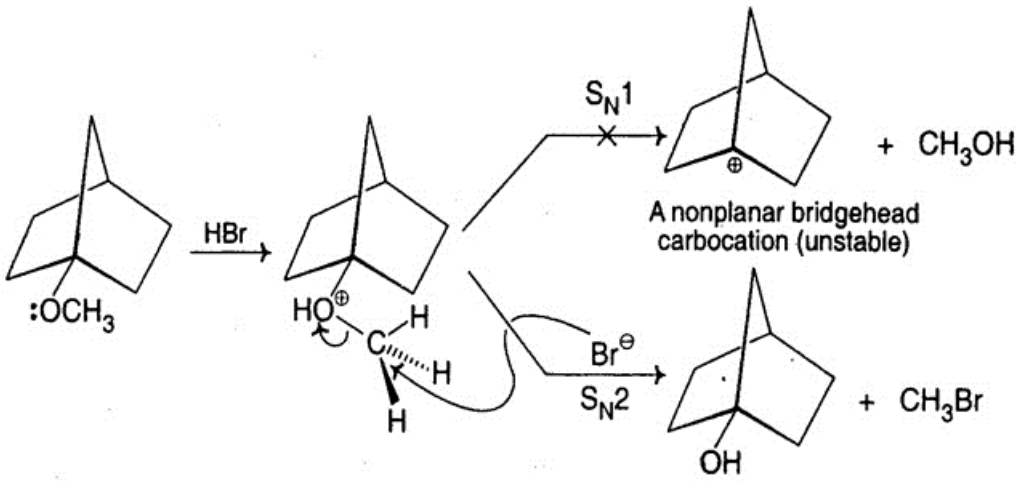
Transition state for an S_N2 attack on a cyclopropyl halide (destabilized by angle strain)

(d) Halocyclohexanes undergo S_N2 reactions *via* the relatively stable equatorial conformation. Ring strain does not appear to be an important factor in this case. However, the axial hydrogens at C-3 and C-5 interfere sterically with the attacking nucleophile and make the transition state relatively unstable. Because of this, halocyclohexanes react by the S_N2 mechanism rather slowly.



Transition state for S_N2 reaction of a cyclohexyl halide involving the axial approach of the nucleophile for an equatorial leaving group.

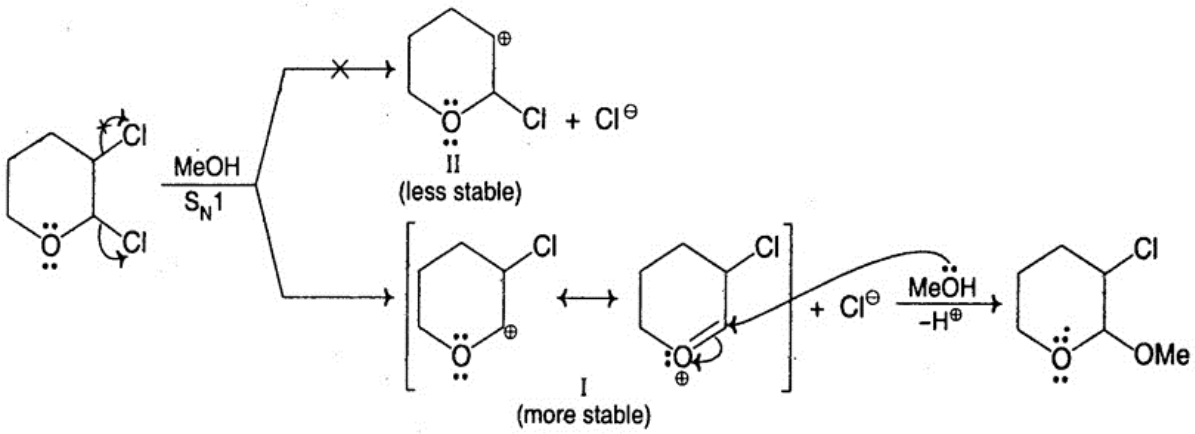
(e)



Because of formation of an unstable bridgehead carbocation, the reaction does not proceed through the S_N1 pathway to give the corresponding products. The reaction actually

proceeds through the S_N2 pathway involving nucleophilic attack by $Br^{\ominus}$ on the methyl carbon of the protonated ether to give the corresponding bicyclic alcohol and CH_3Br.

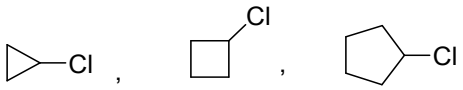
(f)



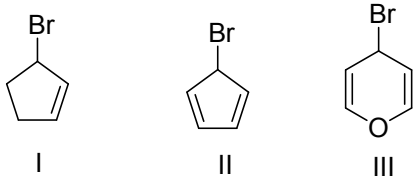
Since the carbocation I (resonance–stabilized) is more stable than the carbocation II, the compounds undergoes solvolysis (S_N1) through the formation of carbocation I to give the corresponding product.

3. Arrange the following compounds in order of increasing S_N1 reactivity:

(a)



(b)

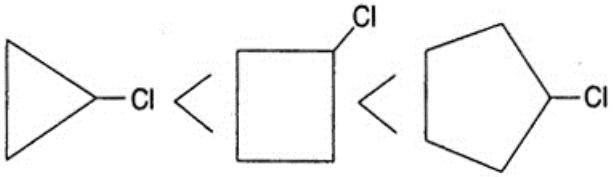


Develop your reasons:

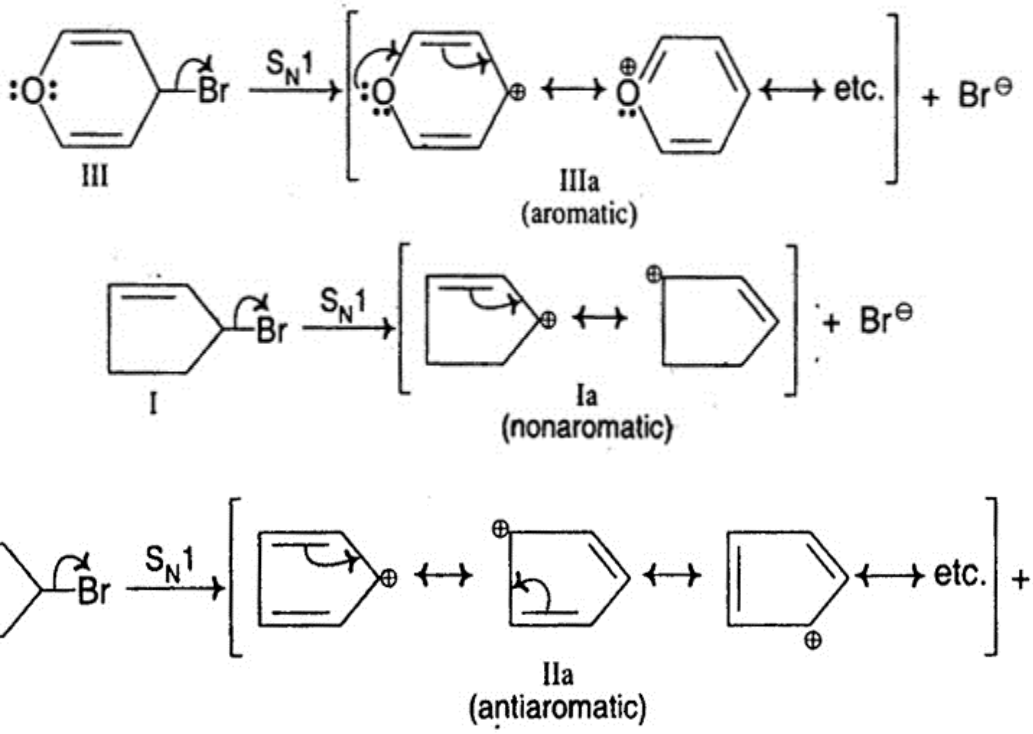
Solution:

(a) An S_N1 reaction proceeds through the rate-determining formation of a planar carbocation in which the angle between any two bonds is 120º. The normal bond angles of three-, four-, and five- membered rings are of the order of 60º, 90º and 108º respectively. These represent deviations of 60º, 30º and 12º respectively from the trigonal angle. The bond-angle strain in cycloalkyl carbocations thus increases in the order cyclopentyl cation < cyclobutyl cation < cyclopropyl cation. Also, in the cyclopentane system, change of hybridization from sp^3 to sp^2 involves relief of four bond oppositions. Therefore, the stability

of the carbocations increases in the order cyclopropyl cation < cyclobutyl cation < cyclopentyl cation. Since S_N1 reactivity depends on the stability of the carbocation, the reactivity order of these chlorocycloalkanes is as follows:



(b) The compound III on ionization produces a carbocation which is aromatic [(4n + 2) π electron system, where n = 1]. The compound I on ionization produces a carbocation which is nonaromatic and the compound II on ionization produces a carbocation which is antiaromatic (a 4nπ electron system, where n = 1).



Therefore, the increasing order of stability of the resulting carbocations is: (least stable) IIa < la < IIIa (most stable). Since, the S_N1 reactivity depends on the stability of the intermediate carbocation, the order of increasing S_N1 reactivity of these compounds is: II < I < III.

4. Explain each of the following:

(a) Trimethylamine, $(CH_3)_3N$, is a good nucleophile while tris(trifluoromethyl)amine, $(CF_3)_3N$, is completely nonnucleophilic.

(b) Quinuclidine is a better nucleophile than triethylamine.

(c) In the following reaction, the order of nucleophilicity for the various halides is $I^{\ominus} > Br^{\ominus} > Cl^{\ominus}$ when LiX is used, but the order is $Cl^{\ominus} > Br^{\ominus} > I^{\ominus}$ when $Bu_4N^+X^{\ominus}$ is used.

$$CH_3CH_2CH_2CH_2OBs + \overset{\ominus}{X} \xrightarrow{\text{acetone}} CH_3CH_2CH_2CH_2X + BsO^{\ominus}$$

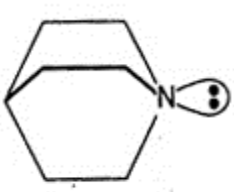
(d) In the gas phase, the order of reactivity of halide ions towards bromomethane is $F^{\ominus} > C1^{\ominus} > Br^{\ominus} > I^{\ominus}$.

(e) In a weakly polar solvent, such as acetone, the nucleophilicity of $F^{\ominus}$ increases in the order: LiF < KF < CsF.

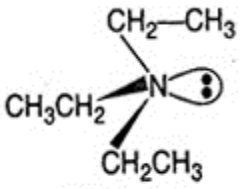
Solution:

(a) In trimethylamine, the electron-donating (+I) methyl groups increase the electron density on nitrogen and thereby increase the availability of its unshared electron pair. Because of this, trimethylamine acts as a good nucleophile. In tris(trifluoromehtyl)amine, however, the powerfully electron-withdrawing (-I) $–CF_3$ groups highly decrease the electron density on nitrogen and thereby decrease the availability of the unshared pair markedly. For this reason, $(CF_3)_3N$ is completely nonnucleophilic.

(b) Since the carbon atoms in quinuclidine are held back by its cage-like structure, the nitrogen atom is more exposed and its approach towards carbon from the backside is not sterically hindered. On the other hand, the alkyl groups in triethylamine hinder sterically its close approach towards carbon. Quinuclidine is, therefore, a better nucleophile than triethylamine.



Quinuclidine



Triethylamine

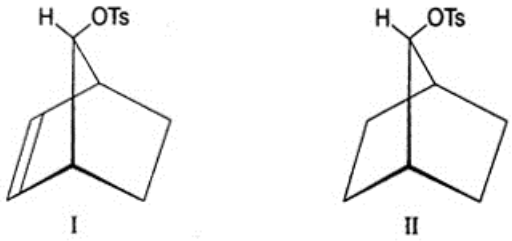
(c) There is considerable ion pairing in the weakly ionizing solvent acetone and the electrostatic attraction between the concentrated charges on two smaller ions is strongest. The small Li^+ ion, therefore, forms tight ion pair with a small halide ion and makes it less reactive as a nucleophile. In the presence of Li^+, then, the order of nucleophilicity is the same as that observed in protic solvents, i.e., $I^{\ominus} > Br^{\ominus} > Cl^{\ominus}$ and for much the same reason. The large quaternary ion, with its charge shielded by the bulky alkyl groups, forms only very loose ion pairs. The halide ions are then relatively free and their reactivity order is same as their basicity order, i.e., $Cl^{\ominus} > Br^{\ominus} > I^{\ominus}$.

(d) In the gas phase where solvation effects are absent, the smaller anion having its negative charge spread out over a comparatively small volume is more energetic than the larger anion and tends to be a better nucleophile. Therefore, in the gas phase, the order of reactivity of halide ions towards bromomethane is $F^{\ominus} > Cl^{\ominus} > Br^{\ominus} > {}^{\ominus}I$, which reflects the strength of the C-X bond being formed.

(e) As the alkali metal cation gets smaller, ion-pairing to $F^{\ominus}$ gets stronger and as a result, its nucleophilicity diminishes. Since, Cs^{+} is the largest and Li^{+} is the smallest cation, $F^{\ominus}$ in CsF is the most nucleophilic and $F^{\ominus}$ in LiF is the least nucleophilic.

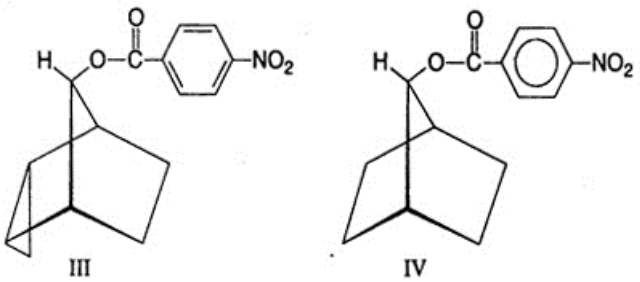
5. Explain the following observations:

(a) Acetolysis of anti-7-norbornenyl tosylate (I) is very much (10^{11} times) faster than that of its saturated analog (II).



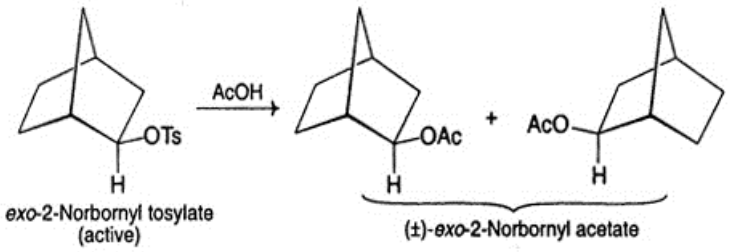
I II

(b) Acetolysis of endo-anti-tricyclo-[3.2.1.$0^{2,4}$] octan-8-yl- p-nitrobenzoate (III) is very much (10^{14} times) faster than that of the p-nitrobenzoate of 7-hydroxybicyclo [2,2,1] heptane (IV).



III IV

(c)



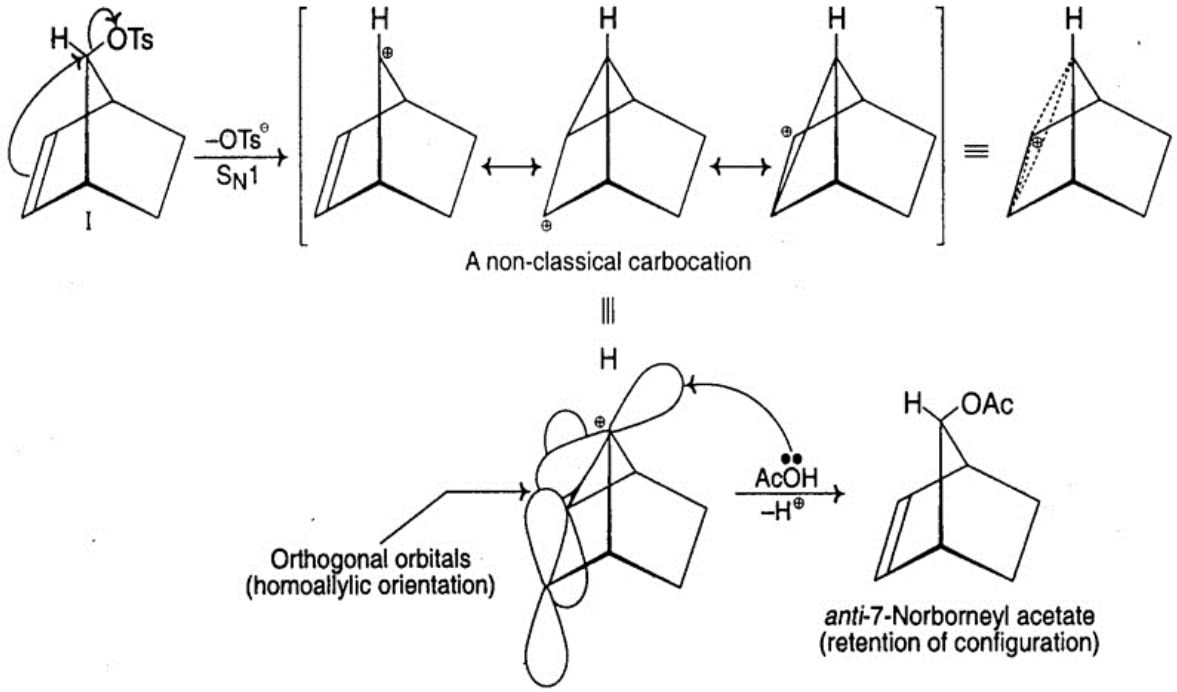
exo-2-Norbornyl tosylate (active)

(±)-*exo*-2-Norbornyl acetate

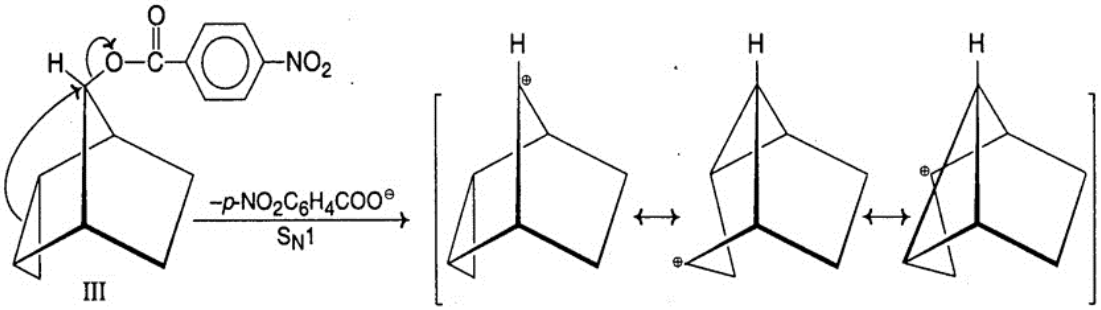
(d) What is the required conformation of a 1,2-disubstituted cyclohexane for the neighbouring group participation to be operative.

Solution:

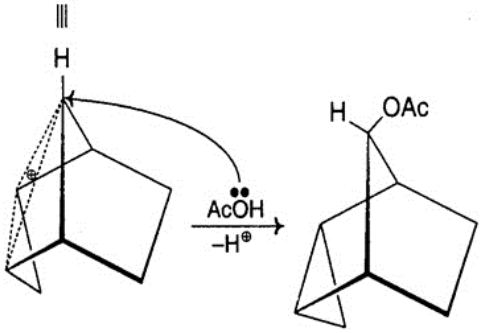
(a) The properly situated (favourable position for backside attack) C=C group acts as an effective neighbouring group in the acetolysis of anti-7-norbornenyl tosylate and assists in the departure of the –OTs. So, this compound undergoes acetolysis faster than that of its saturated analog where participation is absent. The resulting non-classical or bridged carbocation then reacts with AcOH from the side opposite to the neighbouring C=C group to form the corresponding acetate with retention of configuration.



(b) In compound III the suitably placed cyclopropyl ring acts as a very effective neighbouring group and assists in the departure of *p*-$NO_2C_6H_4COO^{\ominus}$. So, this compound undergoes acetolysis very much faster than the compound IV where such participation is absent. The resulting non-classical carbocaiton then undergoes nucleophilic attack by AcOH from the side opposite to the neighbouring cyclopropyl group to form the corresponding acetate with retention of configuration.

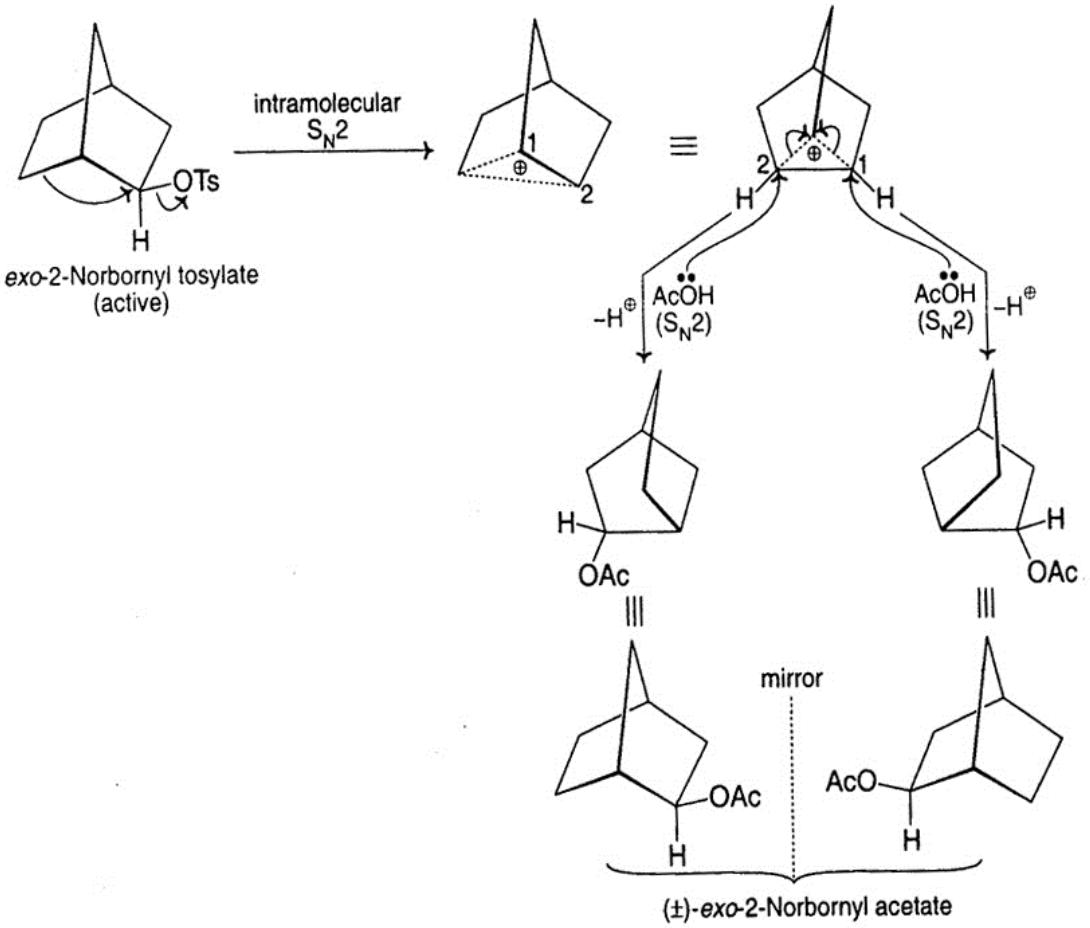


A non-classical carbocation



endo-anti-Tricyclo-[3.2.1.$0^{2,4}$] octan-8-yl acetate. (retention of configuration)

(c)

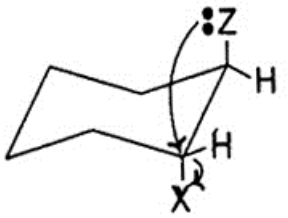


exo-2-Norbornyl tosylate (active)

(±)-*exo*-2-Norbornyl acetate

The exo-2-norbornyl tosylate undergoes α-bond assisted ionization (a neighbouring group participation) to give a cyclic bridged ion. The bridged ion then undergoes nucleophilic attack by AcOH with equal probability on two equivalent carbons to give both enantiomers of exo-2-norbornhyl acetate.

(d) For neighbouring group participation to be operative in a 1,2-disubstituted cyclohexane, a trans diaxial arrangement of the departing and participating groups is necessary and this is because such conformation is very suitable for backside attack.



trans diaxial conformation
(good geometry for anchimeric assistance)

Text Book:

1. Smith, M. B. (2015). *March's Advanced Organic Chemistry: Reactions, Mechanisms, and Structure* (VII Edition). New Jersey: John Wiley & Sons, Inc., Hoboken.

Reference:

1. Tewari, N. (2011). *Advanced Organic Reaction Mechanism* (III Edition). Kolkata: Books and Allied (P) Ltd.

POSSIBLE QUESTIONS

PART- A – Multiple Choice Questions

(Each Question Carry One Mark)

1. The rate of the reaction is dependent on one of the reactants, the reaction is a

A) second order reaction B) **first order reaction**

C) third order reaction D) zero order reaction

2. Nucleophilic substitution reaction which follows first order kinetics is designated

A) S_Ni B) **S_N1** C) S_N2 D) SE2

3. In SN1 reaction the rate of the reaction is

A) dependent of nucleophile C) remains constant of nucleophile

B) **independent of nucleophile** D) same

4. Identify the ambident nucleophile from the following

A) OH^- B) Br^- C) CN^- D) NH_2^-

5. The conversion of R- CH=CH–CH_2–OH in presence of $SOCl_2$ to give R-CH=CH–CH_2–Cl in dry ether involves the mechanism of

A) **S_Ni** B) S_N1 C) S_N2 D) SE2

6. In SN2 mechanism when the nucleophilicity of the nucleophile decreases, the rate of the reaction

A) **decreases** B) increases C) no change D) first increase and then decrease

7. Which one of the following statements is wrong for an SN1 reaction?

A) **for a neutral substrate more polar solvent slower the reaction**

B) for a neutral substrate more polar solvent faster the reaction

C) tertiary halides react faster than primary halide

D) SN1 reaction proceed with more racemisation for an optically active substrate

8. Good leaving group among the halides are

A) F^- B) Cl^- C) Br^- D) **I^-**

9. Stereochemistry of S_N2 reaction is

A) retention of configuration B) inversion of configuration

C) **racemization of configuration** D) no stereochemistry involved

10. In nucleophilic substitution reactions, highly reactive halide ion is

A) F^- B) Cl^- C) Br^- D) **I^-**

11. CN^- is an example for

A) powerful nucleophile B) weak nucleophile

C) **ambident nucleophile** D) powerful electrophile

12. The order of reactivity in S_N2 reaction is

A) **methyl> primary> secondary> tertiary** B) secondary> methyl> primary > tertiary

C) tertiary> primary> methyl> secondary D) primary> secondary> tertiary>methyl

13. Pick out the nucleophile which is not ambient

A) $CN^{(-)}$ **B) $NCO^{(-)}$** C) $OCH_3^{(-)}$ D) $R_2C^{(-)}– NO_2$

14. Nucleophilic substitution with allylic rearrangement is taking place in

A) S_Ni B**)** **S_N1** C) S_N2 D) SE2

15. CH_3Br on treatment with $OH^{(-)}$ gives CH3OH. This reaction is an example of

A**)** S_N1 B) **S_N2** C) E1 D) E2

16. Meisenheimer salts are formed in which of the following mechanisms

A) **S_NAr** B) S_N1 C) S_N2 D) benzyne

17. Which one alkyl halides is hydrolysis faster in S_N1

A) **allyl halides** B) tertiary halides C) secondary halides D) primary halides

18. In polar aprotic solvents the relative nucleophilicity is in the order

A) F> Cl > Br > I B) **I > Br > Cl > F** C) Br > I > F >Cl D) Cl > F>I > Br

19. S_N2 reactions are favored by

A) **strong nucleophiles** B) mild nucleophiles C) weak nucleophiles D) nucleophiles

20. Nucleophile may attack in two or more different ways to get different products are called

A) **ambident nucleophiles** B) strong nucleophiles C) weak nucleophiles D) nucleophiles

21. Involvement of a functional group with a reaction in a molecule leading to reaction via cyclic intermediate is called

A) cyclisation B) cycloaddition reaction

C) **neighbouring group participation** D) rearrangement

22. Some substrates can be attacked at two or more positions and the substrates is called as

A) ambident nucleophiles B) **ambident substrates**

C) polar substrates D)non-polar substrates

23. Amination of pyridine with an alkali metal amide ($NaNH_2$ or KNH_2) is called the

A) Wittig reaction B) **Chichibabin reaction** C) Zeigler reaction D) Darzen reaction

24. Which is the best leaving group?

A) **I^-** B) OH^- C) OR^- D) R_2N^-

25. Strongly polar solvents slightly down the rate of

A) S_NAr reaction B) S_N1 reaction C) **S_N2 reaction** D) SE2

26. Solvent nature will affect the

A) reactant B) **rate** C) product D) catalyst

27. Chlorobenzene when treated with KNH_2 in liquid NH_3 produces aniline is known as

A) **Benzyne mehanism** B) Chichibabin reaction

C) Zeigler reaction D) Claisen rearrangement

28. Benzyne mechanism is also called

A) addition reaction B) elimination reaction

C) **elimination-addition reaction** D) rearrangement reaction

29. S_N2 reaction proceeds through

A) **walden inversion** B) retention C) racemisation D) meso

30. S_N1 reaction proceeds through

A) Walden inversion B) retention C) **racemisation** D) meso

31. In S_N1 reaction the intermediate formed is

A) **Carbocation** B) carbanion C) free radical D) carbene

32. S_N2 reaction takes place in

A) **basic conditions** B) acidic conditions

C) neutral conditions D) very acidic conditions

33. S_N2 reaction follows

A) first order kinetics B) **second order kinetics**

C) zero order kinetics D) pseudo first order kinetics

34. When excess of soda lime is used in chichibabin reaction the product formed is

A) **2,6 diamino pyridine** B) 2,5 diamino pyridine

C) 1,2 diamino pyridine D) 2,4 diamino pyridine

35. S_Ni mechanism gives

A) racemised of configuration B) **retention of configuration**

C) inversion of configuration D) no stereochemistry involved

36. Neighbouring group mechanism results in

A) racemised of configuration B) **retention of configuration**

C) inversion of configuration D) no stereochemistry involved

37. The reaction in which solvent act as a nucleophilic reagent is known as

A) **solvolysis** B) hydrolysis C) ozonolysis D) hydrogenation

38. Primary alkyl halide prefers to

A) S_Ni type of reaction B) S_N1 type of reaction

C) **S_N2 type of reaction** D) neighbouring group participation

39. Both S_N1 and S_N2 reaction takes place in

A) **secondary alkyl halide** B) primary alkyl halide C) tertiary alkyl halide D) alkenes

40. Which is called carbonium ion process?

A) S_Ni B) **S_N1** C) S_N2 D) SE2

41. S_N1 reaction is also known as

A) carbanion process B) free radical process

C) **carbonium ion process** D) carbene process

42. S_N2 reaction is also known as

A) direct elimination process B) **direct displacement process**

C) indirect displacement process D) direct addition process

43. S_N2 reaction proceeds with stereochemical inversion usually referred to

A) **Walden inversion** B) Walden retention C) racemisation D) retention

44. Back side attack possible in

A) S_N1 B) **S_N2** C) S_Ni D) SE2

45. The result of inversion and retention configuration is

A) enantiomer B) isomerisation C) **racemisation** D) polarization

46. The example for ambident substrate is

A) **1,3-dichlorobutane** B) chlorobutane C) ethyl bromide D) bromobutane

47. S_NAr mechanism is also called as

A) elimination-addition mechanism B) **addition-elimination mechanism**

C) aromatic S_N1 mechanism D) vinylic mechanism

48. Hybridisation of carbon atom in carbonium ion is

A) sp^3 B) **sp^2** C) sp D) dsp^2

49. Which step is rate determining step in S_N1 mechanism

A) formation of free radical B) ion-pair destruction

C) **formation of carbocation** D) formation of product

50. Benzene diazonium sulphate when boiled with water gives

A) **Phenol** B) aniline C) benzene D) benzene radical

51. Conversion of benzene diazonium sulphate into phenl is an example for

A) S_Ni reaction B) **aromatic S_N1 reaction** C) S_N2 reaction D) SE2 reaction

52. The 1-bromobicyclo[2.2.1]heptane is unreactive towards S_N2 reaction because

A) inductive effect B) **steric hindrance** C) resonance effect D)mesomeric effect

53. In cyclohexane derivative S_N2 rate becomes slow due to

A) **steric hindrance** B) hyperconjucation C) inductive effect D) mesomeric effect

54. In S_N2 attack on allyl bromide occurs at a faster rate than on ethyl chloride because the

A) **transition state stabilized by π overlap of allyl group**

B) transition state unstabilized by π overlap of allyl group

C) transition state stabilized by π overlap of ethyl group

D) transition state stabilized by σ bond of ethyl group

55. The reaction of neopentyl alcohol with HCl gives

A) neopentyl chloride B) pentyl chloride C) **t-amyl chloride** D) t-amyl alcohol

56. The Gabriel synthesis of an

A) **primary amine** B) secondary amine C) tertiary amine D) quaternary amine

57. The akylation of heterocyclic nitrogen compounds with akyllithium reagents is called

A) Friedel Crafts alkylation B) Friedel Crafts acylation

C) thio alkylation D) **ziegler alkylation**

58. Ziegler alkylation follows the

A) elimination-addition mechanism B) **addition-elimination mechanism**

C) aromatic S_N1 mechanism D) vinylic mechanism

59. Pyrrole reacts with an allylic halide and zinc to gives

A) 1-substituted pyrrole B) **3-substituted pyrrole**

C) 5-substituted pyrrole D) 4-substituted pyrrole

60. What is the required conformation of a 1,2-disubstituted cyclohexane for the neighbouring group participation?

A) **trans diaxial conformation** B) trans diequtorial conformation

C) cis axial-equatorial conformation D) cis equatorial-axial conformation

PART-B (Each Question Carry Two Mark)

61. Mention the any three examples of ambident nucleoplies.

62. Explain the Ziegler alkylation.

63. Explain why halocyclohexanes react slowly by the S_N2 mechanism.

64. The following bicyclic compound is exceedingly unreactive towards nuclophilic substitution either by the S_N1 or S_N2 mechanism.

65. Account for the following observation:

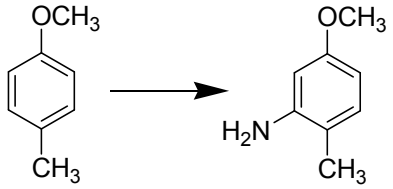
    When m-chlorotoluene is treated with KNH_2 in liquid ammonia, a mixture of o-, m- and p-toludine is obtained.

66. What is called cine-substitution? Give an example.

67. Account for the following observation:

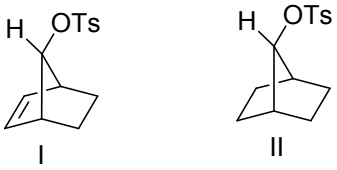
    Both o-bromoanisole and m-bromoanisole react with KNH_2 in liquid ammonia to produce m-anisidine.

68. How would you convert the compound **A** into its derivative **B?**



69. Explain the following observation:

    Acetolysis of anti-7-norborneyl tosylate (**I**) is very much (10^{11} times) faster than that of its saturted analog (**II**).



PART-C (Each Question Carry Six Mark)

70. (i) Discuss the Benzyne mechanism for the aromatic nucleophilic substitution reaction. Mention the evidences for this mechanism.

    (ii) What is Chichibabin reaction?

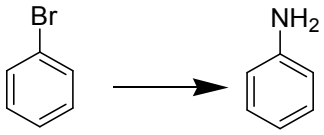
71. (i) Write notes on neighboring group participation.

    (ii) Explain the ambident substrates.

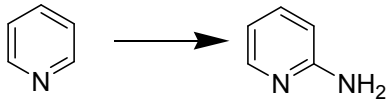
72. Discuss the mechanism for the following aliphatic nucleophilic substitution reaction (i) S_N1 (ii) S_N2

73. Write notes on factors affecting the nuclophilic substitution in effect of substrate.

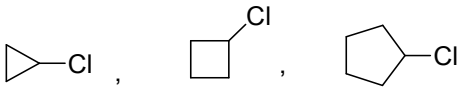
74. (i) Suggest suitable reagent for the following transformation. Provide the mechanism.



(ii) Indicate the reagent to bring about the following transformation. Provide the mechanism.



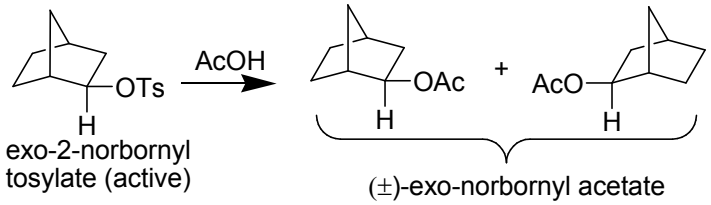
(iii) Arrange the following compounds in the order of increasing S_N1 reactivity:



Suggest your reasons.

75. Explain the following observations:

(i)

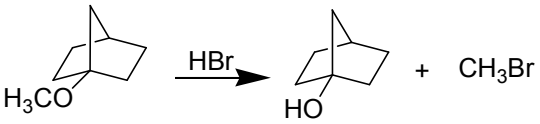


(ii) Quinuclidine is a better nucleophile than triethylamine.

76. Explain the following observations:

(i) Chloroacetone, CH_3COCH_2Cl, undergoes S_N2 reaction faster than does n-propyl chloride, but it undergoes S_N1 reaction much more slowly.

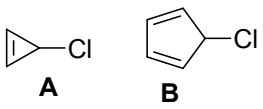
(ii)



(iii) Trimethylamine, $(CH_3)_3N$, is a good nucleophile while tris(trifluoromethyl)-amine, $(CF_3)_3N$, is completely nonnucleophilic.

77. (i) Explain why allyl bromide, CH_2=CH-CH_2-Br, undergoes S_N2 reactions rapidly than does ethyl bromide.

(ii) Explain why the compound **A** undergoes solvolysis in ethanol more readily than the compound **B**.



(iii) Explain why halocyclopropanes are unreactive towards S_N2 reactions.

78. (i) Explain what are Ambident nuclophiles.

(ii) Explain the following observations:

(a) The rate of reaction (S_N2) of the following bromides with EtO^- in EtOH decreases as the following series is traversed.

	CH_3CH_2Br Ethyl bromide	$CH_3CH_2CH_2Br$ Propyl bromide	$(CH_3)_2CHCH_2Br$ Isobutyl bromide	$(CH_3)_3CCH_2Br$ Neopentyl bromide
Relative rate:	1	0.4	0.03	0.0001

(b) Tert-butylamine cannot be prepared by Gabriel synthesis.

79. Aromatic nucleoplilic substitution reactions are found to occur mainly by the following three mechanistic courses:

(i) The S_N1 mechanism.

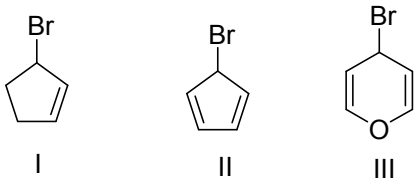
(ii) The addition-eliminations or S_NAr mechanism.

(iii) The elimination-addition or benzyne mechanism.

Discuss these mechanisms with examples.

PART-D (Each Question Carry Ten Mark)

80. (i) Arrange the following compounds in the order of increasing S_N1 reactivity:



Justify your reasons.

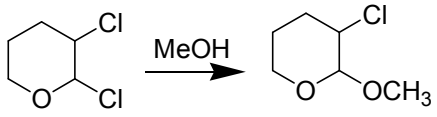
(ii) Explain the following observation:

The rate of solvolysis with water (hydrolysis) increase as the following series is traversed:

$PhCH_2Cl$ Ph_2CHCl Ph_3CCl

(iii) Explain why halocyclohexanes react slowly by the S_N2 mechanism.

(iv) Write the mechanism of the following conversion.



KARPAGAM ACADEMY OF HIGHER EDUCATION
(*Deemed to be University Established Under Section 3 of UGC Act 1956*)
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DEPARTMENT OF CHEMISTRY

UNIT-IV

NUCLEOPHILIC SUBSTITUTION REACTIONS

PART-A–Multiple Choice Questions
(Each Question Carry One Mark) (Online Examinations)

1. The rate of the reaction is dependent on one of the reactants, the reaction is a

A) second order reaction B) **first order reaction**

C) third order reaction D) zero order reaction

2. Nucleophilic substitution reaction which follows first order kinetics is designated

A) S_Ni B) **S_N1** C) S_N2 D) SE2

3. In SN1 reaction the rate of the reaction is

A) dependent of nucleophile C) remains constant of nucleophile

B) **independent of nucleophile** D) same

4. Identify the ambident nucleophile from the following

A) OH^- B) Br^- C) CN^- D) NH_2^-

5. The conversion of R- $CH=CH–CH_2–OH$ in presence of $SOCl_2$ to give R-$CH=CH–CH_2$ –Cl in dry ether involves the mechanism of

A) **S_Ni** B) S_N1 C) S_N2 D) SE2

6. In SN2 mechanism when the nucleophilicity of the nucleophile decreases, the rate of the reaction

A) **decreases** B) increases C) no change D) first increase and then decrease

7. Which one of the following statements is wrong for an S_N1 reaction?

A) **for a neutral substrate more polar solvent slower the reaction**

B) for a neutral substrate more polar solvent faster the reaction

C) tertiary halides react faster than primary halide

D) SN1 reaction proceed with more racemisation for an optically active substrate

8. Good leaving group among the halides are

A) F^- B) Cl^- C) Br^- D) **I^-**

9. Stereochemistry of S_N2 reaction is

A) retention of configuration B) inversion of configuration

C) **racemization of configuration** D) no stereochemistry involved

10. In nucleophilic substitution reactions, highly reactive halide ion is

A) F^- B) Cl^- C) Br^- D) **I^-**

11. CN^- is an example for

A) powerful nucleophile B) weak nucleophile

C) **ambident nucleophile** D) powerful electrophile

12. The order of reactivity in S_N2 reaction is

A) **methyl> primary> secondary> tertiary** B) secondary> methyl> primary > tertiary

C) tertiary> primary> methyl> secondary D) primary> secondary> tertiary>methyl

13. Pick out the nucleophile which is not ambient

A) $CN^{(-)}$ **B) $NCO^{(-)}$** C) $OCH_3^{(-)}$ D) $R_2C^{(-)}– NO_2$

14. Nucleophilic substitution with allylic rearrangement is taking place in

A) S_N^i B**)** **S_N1** C) S_N^2 D) SE2

15. CH_3Br on treatmnet with $OH^{(-)}$ gives CH_3OH. This reaction is an example of

A**)** S_N^1 B) **S_N2** C) E1 D) E2

16. Meisenheimer salts are formed in which of the following mechanisms

A) **S_NAr** B) S_N1 C) S_N2 D) benzyne

17. Which one alkyl halides is hydrolysis faster in SN1

A) **allyl halides** B) tertiary halides C) secondary halides D) primary halides

18. In polar aprotic solvents the relative nucleophilicity is in the order

A) F> Cl > Br > I B) **I > Br > Cl > F** C) Br > I > F >Cl D) Cl > F>I > Br

19. S_N2 reactions are favored by

A) **strong nucleophiles** B) mild nucleophiles C) weak nucleophiles D) nucleophiles

20. Nucleophile may attack in two or more different ways to get different products are called

A) **ambident nucleophiles** B)strong nucleophiles C)weak nucleophiles D)nucleophiles

21. Involvement of a functional group with a reaction in a molecule leading to reaction via cyclic intermediate is called

A) cyclisation B) cycloaddition reaction

C) **neighbouring group participation** D) rearrangement

22. Some substrates can be attacked at two or more positions and the substrates is called as

A) ambident nucleophiles B) **ambident substrates**

C) polar substrates D)non-polar substrates

23. Amination of pyridine with an alkali metal amide ($NaNH_2$ or KNH_2) is called the

A) Wittig reaction B) **Chichibabin reaction** C) Zeigler reaction D) Darzen reaction

24. Which is the best leaving group?

A) **I^-** B) OH^- C) OR^- D) R_2N^-

25. Strongly polar solvents slightly down the rate of

A) S_NAr reaction B) S_N1 reaction C) **S_N2 reaction** D) SE2

26. Solvent nature will affect the

A) reactant B) **rate** C) product D) catalyst

27. Chlorobenzene when treated with KNH_2 in liquid NH_3 produces aniline is known as

A) **Benzyne mehanism** B) Chichibabin reaction C) Zeigler reaction D) Claisen rearrangement

28. Benzyne mechanism is also called

A) addition reaction B) elimination reaction

C) **elimination-addition reaction** D) rearrangement reaction

29. S_N2 reaction proceeds through

A) **walden inversion** B) retention C) racemisation D) meso

30. S_N1 reaction proceeds through

A) Walden inversion B) retention C) **racemisation** D)meso

31. In S_N1 reaction the intermediate formed is

A) **Carbocation** B) carbanion C) free radical D) carbene

32. S_N2 reaction takes place in

A) **basic conditions** B) acidic conditions C) neutral conditions D) very acidic conditions

33. S_N2 reaction follows

A) first order kinetics B) **second order kinetics**

C) zero order kinetics D) pseudo first order kinetics

34. When excess of soda lime is used in chichibabin reaction the product formed is

A) **2,6 diamino pyridine** B) 2,5 diamino pyridine

C) 1,2 diamino pyridine D) 2,4 diamino pyridine

35. S_Ni mechanism gives

A) racemised of configuration B) **retention of configuration**

C) inversion of configuration D) no stereochemistry involved

36. Neighbouring group mechanism results in

A) racemised of configuration B) **retention of configuration**

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37. The reaction in which solvent act as a nucleophilic reagent is known as

A) **solvolysis** B) hydrolysis C) ozonolysis D) hydrogenation

38. Primary alkyl halide prefers to

A) S_Ni type of reaction B) S_N1 type of reaction

C) **S_N2 type of reaction** D) neighbouring group participation

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UNIT-V

Elimination reactions: Mechanisms - E1, E2, Ei and E1cB mechanisms- stereochemistry of eliminations. Hofmann rule-Saytzeff rule-Bredts rule – Substitution versus Elimination. Typical elimination reaction - Chugaev reaction, Hofmann degradation and Cope elimination.

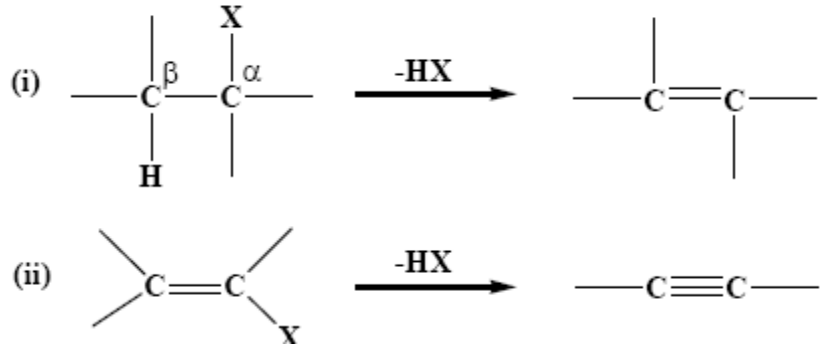
Carbenes and nitrenes - structure, generation and reactions.

ELIMINATION REACTIONS

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.

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

(2) Dehydration of alcohols by acids.

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

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

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

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

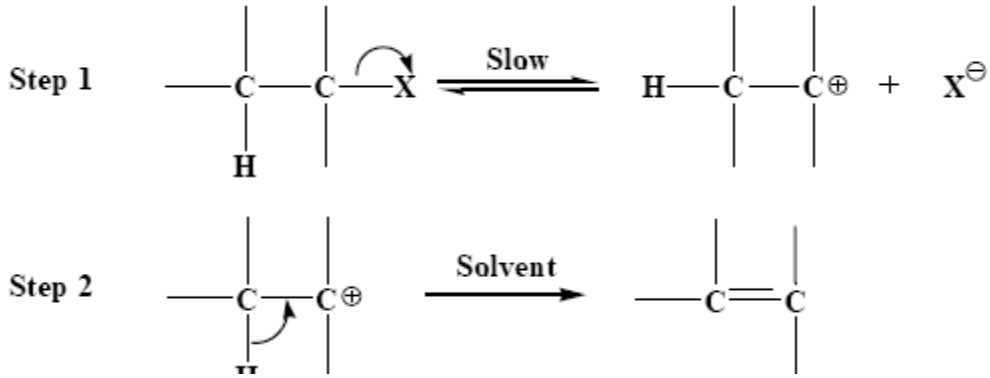
(a) Stability of the olefin formed

(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 substituent can be relieved on the formation of olefin since the bond angles increase from 109.5° in the substrate (sp^3 hybridized) to 120° 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.

E1 Mechanism

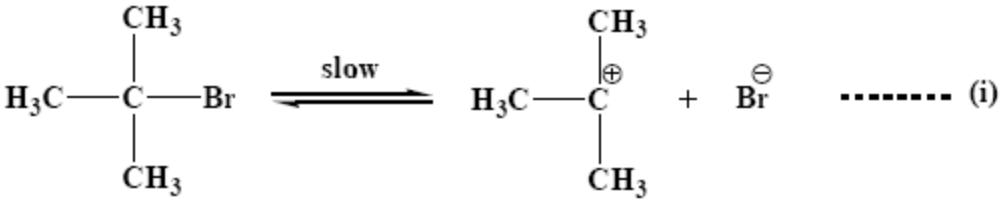
The E1 mechanism is a two step process in which the rate determining step is ionization of the substrate to give a carbocation that rapidly loses a β-proton to a base.

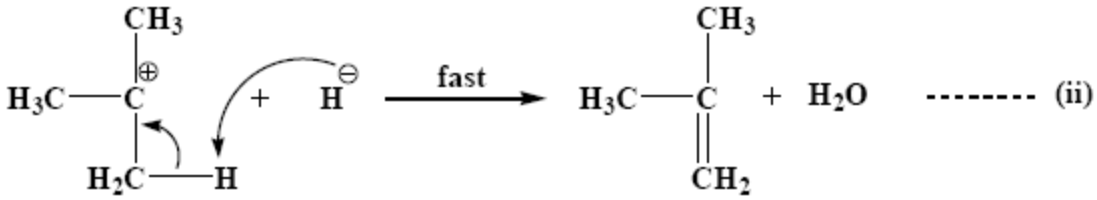


E1 mechanism reaction the product should be completely nonstereospecific, since the carbocation is free to adopt its most stable conformation.

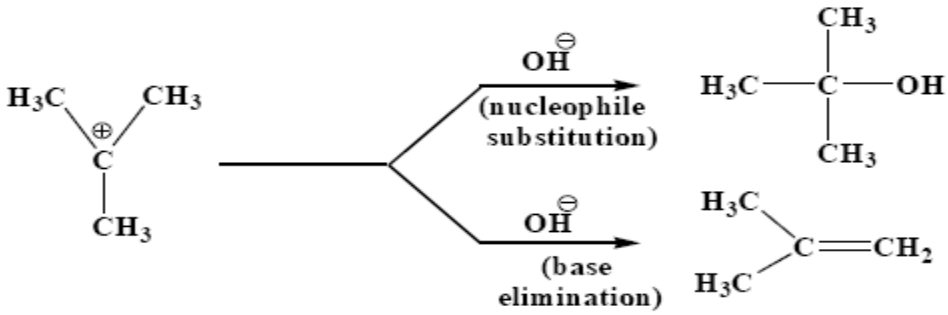
Dehydrohalogenation of alkyl halides

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.

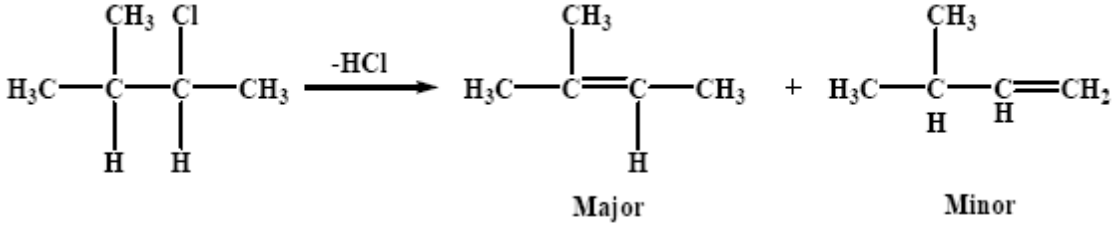




The carbocation is formed in the first step in E1 reaction. Hence the reagent can attack the carbon to give substitution product and also can accept a proton to give elimination product. In practice both alcohol and alkene are obtained on hydrolysis of Me_3CBr.



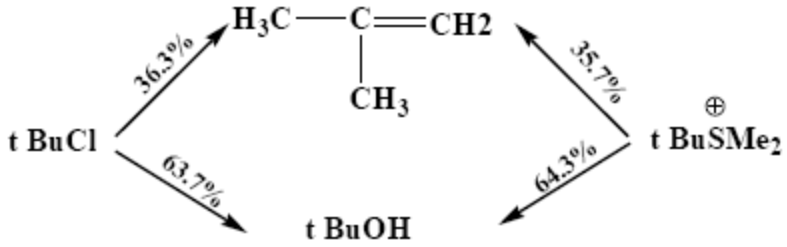
When more than one alkene can be formed, the alkene will predominate which has large number of alkyl groups on the double-bonded carbons – this is Saytzev's rule. This is understandable since the substituted alkyl groups will stabilize the alkene by hyperconjugation.



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.

E1 reaction is facilitated by:

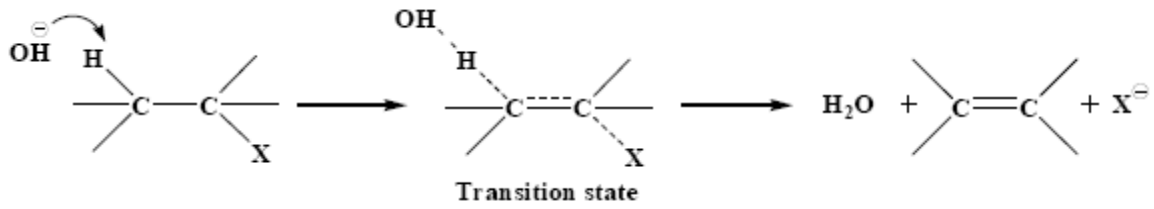
(i) Branching at the α and β carbons of the substrate – for the stability of the olefin.

(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.

E2 Mechanism

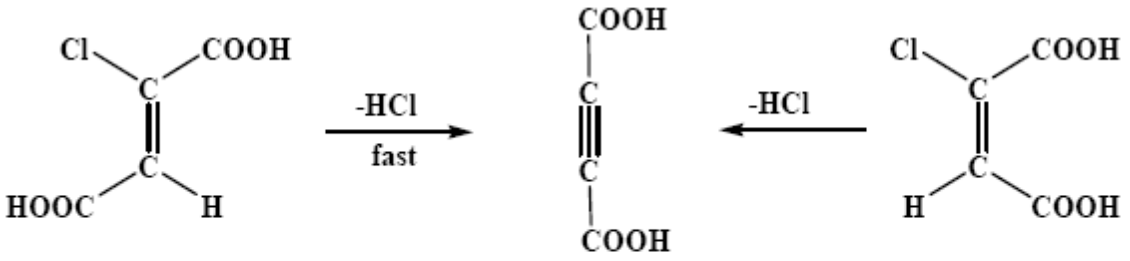
When the rate of elimination reaction is dependent on both the substrate and the reagent the reaction is kinetically second order or bimolecular.



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 a nd 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)

Evidences for the existence of E2 mechanism

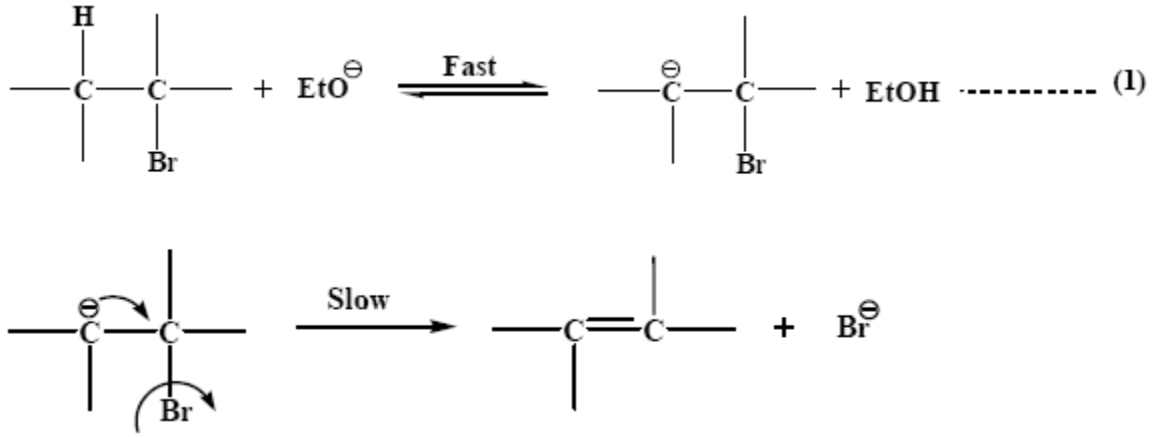
1. The reaction displays the proper second-order kinetics.
2. When the leaving hydrogen is replaced by deuterium in second order elimination there is an isotope effect with breaking of cis bond in the rate determining step. This result proves that E2 mechanism. E2 is stereospecific it is found from stereochemical studies.

E2 reaction is facilitated by:

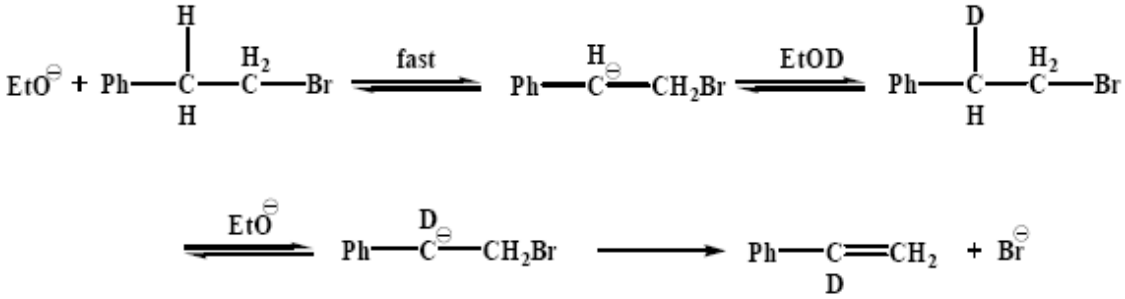
1. branching at α and β carbons since more stable olefins is formed.
2. Strong base of high concentration since a strong C-H bond has to break.
3. Solvent of low polarity.

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.



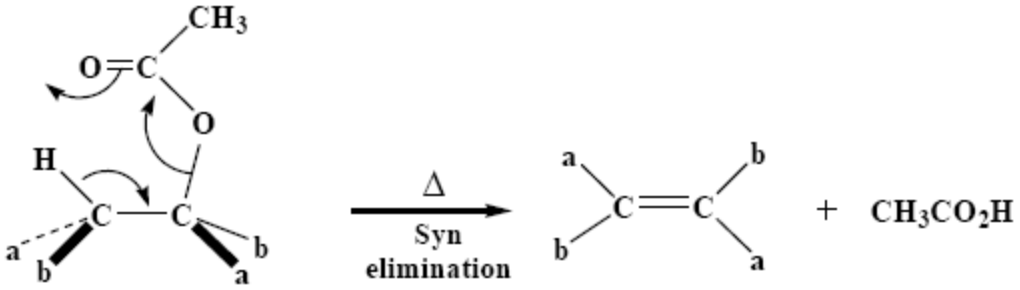
The overall rate of this reaction is thus dependent on the concentration of the conjugate base of the substrate. Hence this designated as E1CB.To distinguish between E2 and E1CB mechanism, deuterium exchange experiment was performed. For this 2-phenyl ethyl bromide was treated with sodium ethoxide in 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 E2 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 $Cl_2CH\text{-}CF_3$.

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.



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.

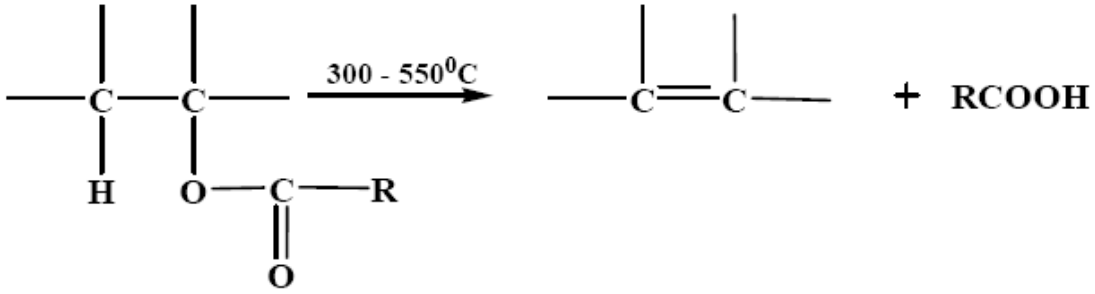
4. ^{14}C isotope effects for the cope elimination show that both the $C-H$ and $C-N$ bonds have been exclusively broken in the transition state.
5. Some of these reactions have been shown to exhibit negative entropies of activation, indicating that the molecules are more restricted on geometry in the 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.

Hydroacyloxy elimination

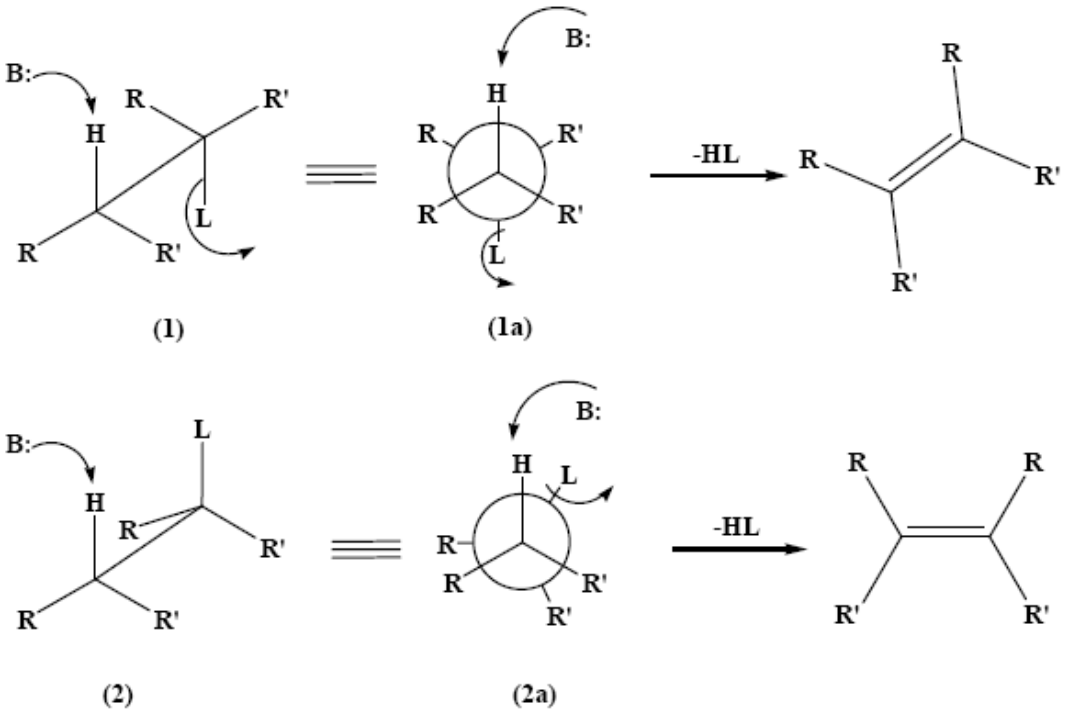


Ester in which the alkyl group has a β-hydrogen can be pyrolyzed. Most often in the gas phase to give the corresponding acid an olefin. No solvent is required. For higher olefins a better method is to pyrolyze the alcohol in the presence of acetic anhydride. The mechanism is Ei. Lactones can be pyrolyzed to give unsaturated acids, provided that six membered transition state required for Ei is available. Amides give a similar reaction but require higher temperatures.

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:



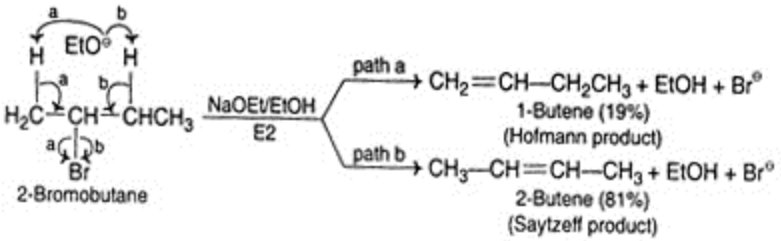
From the Newman projection of the *trans* a n d *cis* conformations the elimination is expected to be more facile from the trans conformation 1(a) than from the cis conformation 2(a). This is because in 1(a) the attacking base approaches from the farthest side o the leaving group, while in 2(a) the attack 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.

Saytzeff rule and Hofmann rule

The saytzeff rule states that neutral substrates (alkyl halides and sulphonates) possessing two different types of β-hydrogens yield predominantly the more highly substituted alkene.

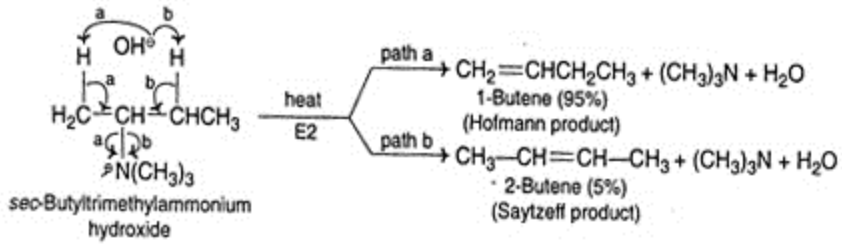
The Hofmann rule states that eliminations produce predominantly the less-substituted alkene if the leaving group is positively charged.

The dehydrobromination of 2-bromobutane with ethoxide ion, for example, follows the Saytzeff rule, since it produces 81% of the more substituted alkene, 2-butene and 19% of the less-substituted alkene, 1-butene.



Compounds containing uncharged leaving group undergo the ideal E2 elimination in which both the C-H and C-L bonds are being broken and the carbon-carbon double bond is being formed at the same time. Because of this, the transition state possesses considerable double bond character. Consequently, any effect that stabilizes the product alkene also stabilizes the transition state. The stability of a double bond increases progressively with the increase in the number of alkyl groups bonded to it and this increasing stabilization arises from the operation of the hyperconjugative effect. The disubstituted alkene, 2-butene, is, therefore, more stable than the monosubstituted alkene, 1-butene. It thus follows that the transition state leading to 2-butane (path b) is more stable than the transition state leading to 1-butene (path a) and so, 2-butene is formed more rapidly than 1-butene, i.e., the reaction produces predominance of the more–substituted alkene, 2-butene.

When sec-butyltrimethylammonium hydroxide, $(CH_3)_3{}^+NCH(CH_3)CH_2CH_3OH^\ominus$, is heated, it produces 95% of the less-substituted alkene, 1-butene and 5% of the more substituted alkene, 2-butene. The reaction thus follows the Hofmann rule.



There are three different views to explain the predominance of the Hofmann product:

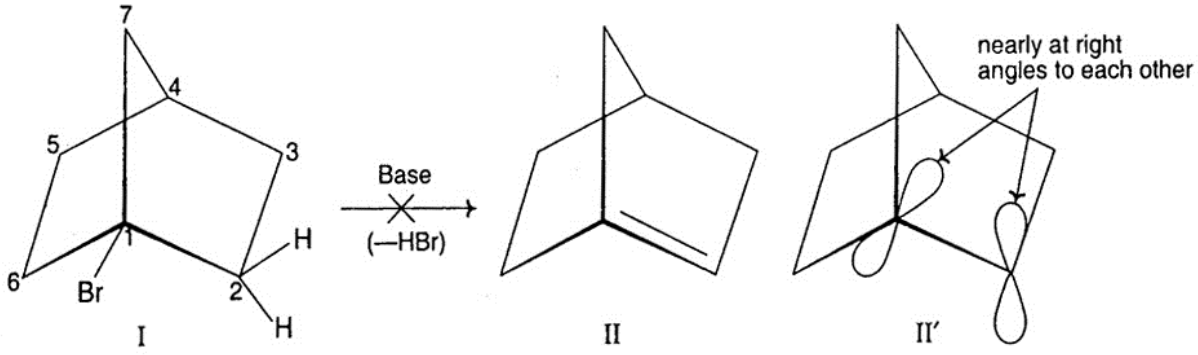
(i) Compounds containing charged leaving groups undergo the E2 elimination in which the breaking of C-H bond starts well before th breaking of C-L bond. Because of this, the transition state possesses little alkene character but considerable carbanion character. Thus, any actor that stabilizes a carbanion also stabilizes the transition state. The stabilities of carbanions decrease progressively with increase in the number of alkyl group attached to the

central carbon atom, i.e., the order of carbanion stability is primary > secondary > tertiary. It thus follows that abstraction of β-hydrogen by base takes place preferentially from the methyl group (the primary carbon), since that leads to the formation of a more stable carbanion-like transition state. The reaction thus produces a predominance of the less-substituted alkene, 1-butene.

(ii) A strong electron-withdrawing positively charged leaving group causes development of partial positive charges on all the neighbouring carbon atoms. This renders the β-hydrogens acidic so that they can be easily abstracted by a base. However, two different types of β-hydrogens are not comparable in acidity. The presence of an electron-releasing alkyl group at a β-carbon makes its hydrogen less acidic. Consequently, the base abstracts preferably the more acidic β-hydrogen (the $–CH_3$ hydrogen) and results in predominant formation of the Hofmann product.

Bredt's rule

Bredt's rule states that it is not possible to introduce a double bond (C=C or C=N) at the bridgehead position in bridged bicyclic compounds with small rings. For example, 1-bromobicyclo[2,2,1]-heptane (I) does not undergo base-promoted dehydrobromination to give bicyclo [2,2,1] hept-1-ene (II).



The p orbitals of a bridgehead double bond are not coplanar and in fact, these are virtually at right angles to each other (II'). Significant orbital overlap is, therefore, not possible and formation of a double bond is not allowed. To bring the orbitals in one plane, a condition required for maximum overlap, the system is to be distorted. But such distortion resulting in severe strain in the rigid molecule is not permitted energetically.

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:

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.

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.

Nature of solvent

A less polar solvent not only favors bimolecular reaction but also E2 over S_N2. 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.

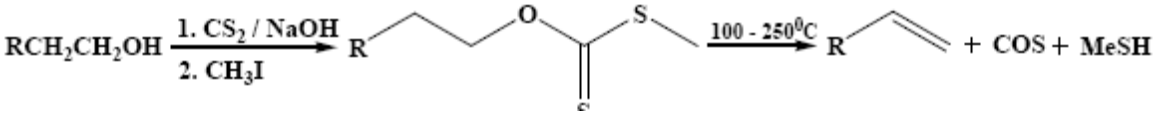
Effect of temperature

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.

Typical elimination reactions

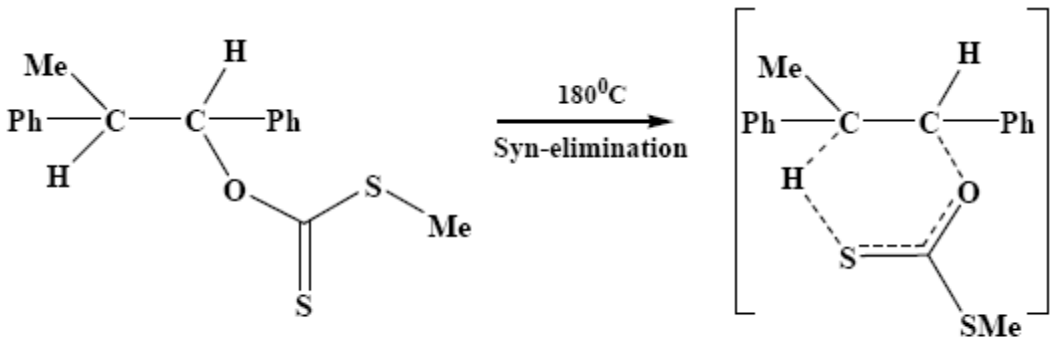
Chugaev reaction

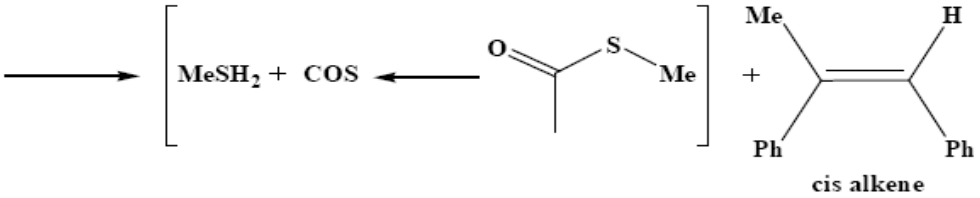
The thermal decomposition of xanthates prepared from alcohols involving stereo specific elimination to yield alkenes is called the Chugaev reaction. The reaction is advantageous because it requires relatively lower temperature and leads to the predominant formation of unrearranged terminal alkenes.



Mechanism:

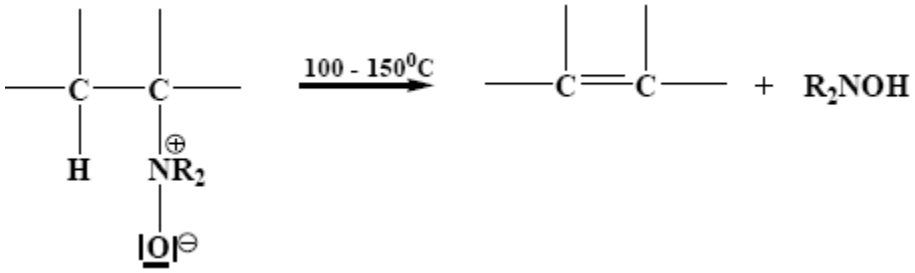
The reaction involves a six membered cyclic transition state, and proceeds through Ei mechanistic pathway.





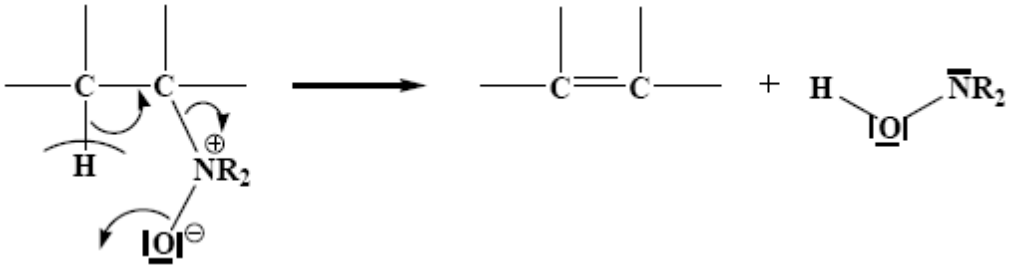
Cope reaction

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.

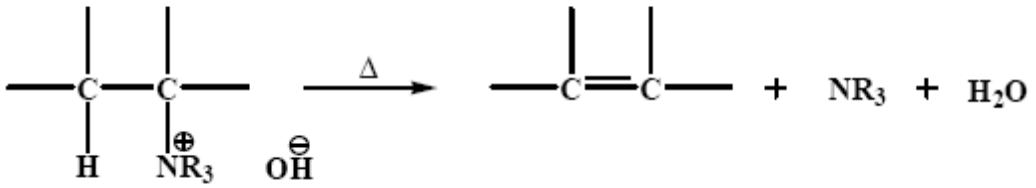
The reaction is thus useful for preparation of many olefins. The elimination is a stereo selective syn process and the five membered Ei mechanisms operate.



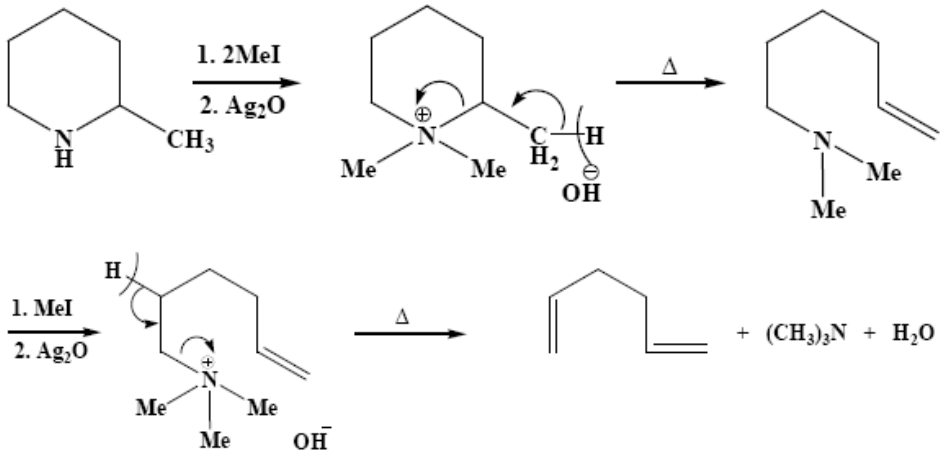
Evidences indicate that the transition state must be planar. The stereoselectivity of this reaction and lack of rearrangement of the product, it is useful for the formation of trans cyclo-olefins.

Hofmann degradation

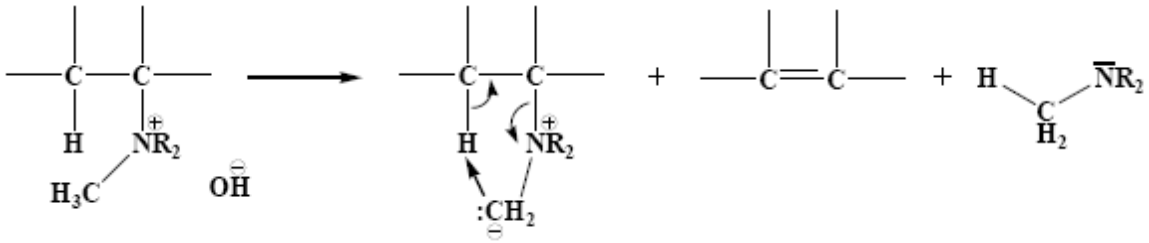
Cleavage of quaternary ammonium hydroxide is the final step of the process known as Hofmann degradation.



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 E_i mechanism.

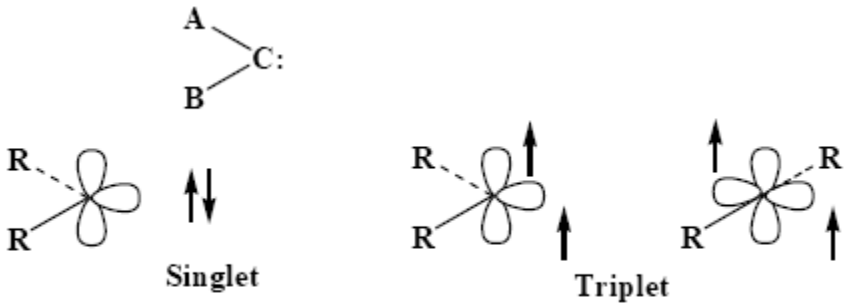


E1and E2 mechanisms are distinguished by the use of deuterium labeling. For example, if the reaction is carried out on a quaternary hydroxide deuterated on the β-carbon then the rate of deuterium indicates the mechanism. If the E2 mechanism is in operation, the trimethylamine produced would contain no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

Carbenes and nitrenes

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.

CARBENES

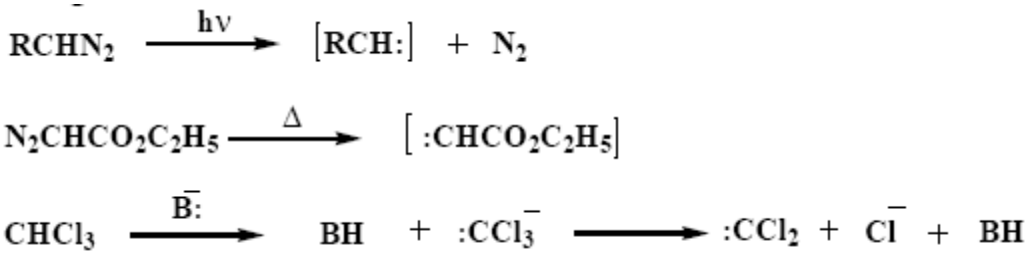
STRUCTURE

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.

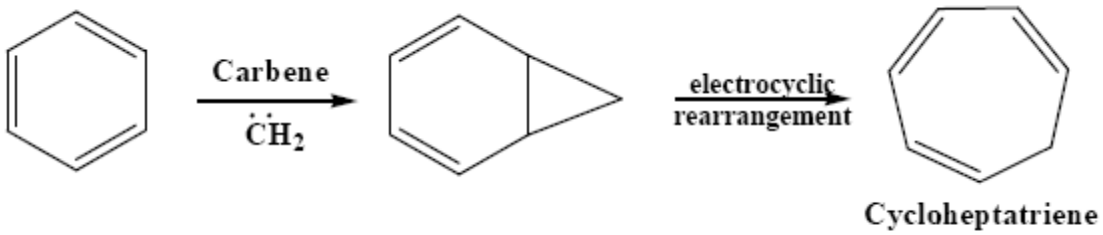
Generation

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.

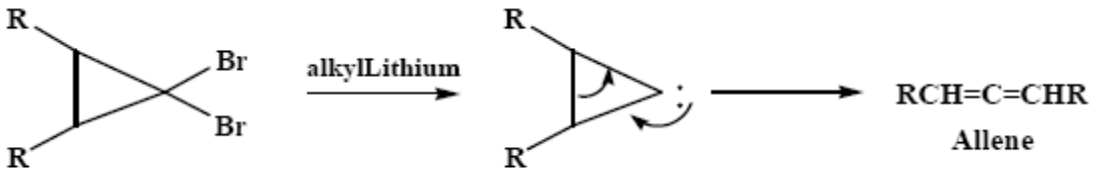


Reactions

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



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



Nitrenes

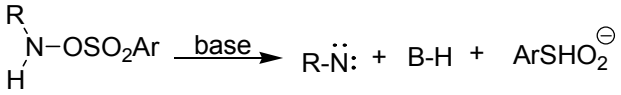
Structure

The nitrenes $R-N$ represent the nitrogen analogs of carbenes and may be generated in the singlet (R-N: or triplet R-N·)

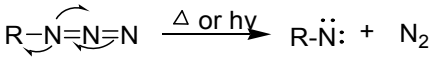
Generation

The two principal means of generating nitrenes are analogous to those used to form carbenes.

1. *Elimination.* An example is



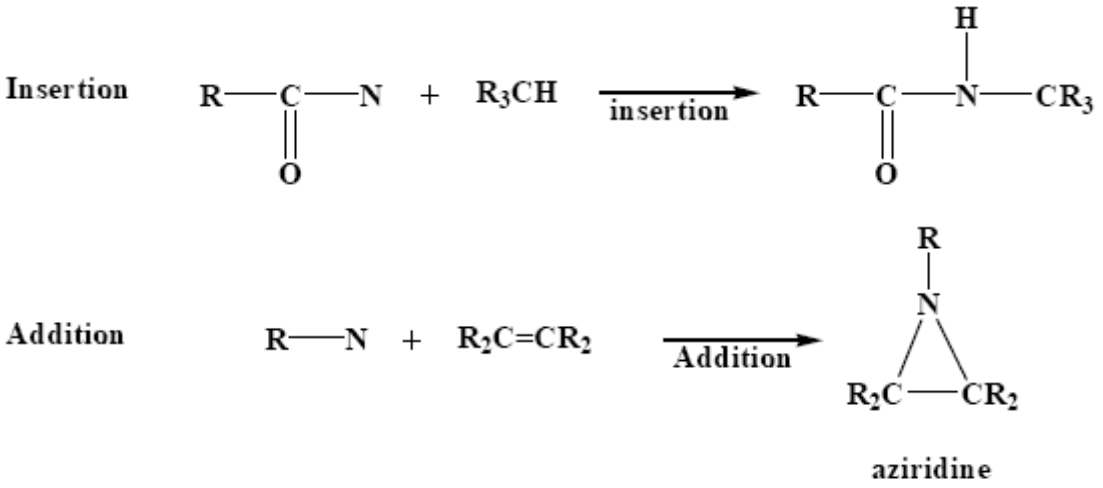
2. *Breakdown of certain double-bond compounds*. The most common method of forming nitrenes is photolytic or thermal decomposition of azides,



The unsubstituted nitrene (NH) has been generated by photolysis of electric discharge through NH_3, N_2H_4 or HN_3.

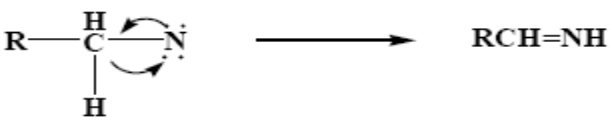
Reactions

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.

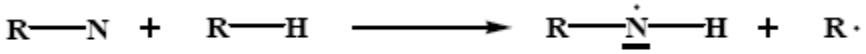


Rearrangements:

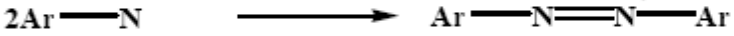
Alkyl nitrenes do not generally give either of two proceeding reaction because the rearrangement is more rapid.



Abstraction: (eg)



Dimerization: NH dimerizes to diimide N_2H_2

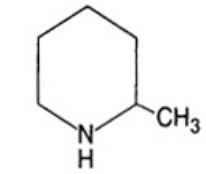


The dimerization is more important for nitrines than carbenes.

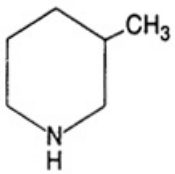
1. (a) What is the Hofmann elimination reaction?

(b) Discuss the steps involved in Hofmann exhaustive methylation or Hofmann degradation, a process which is widely used for structure determination of alkaloids.

(c) Give the steps involved in the complete Hofmann degradation of the following cyclic amines:



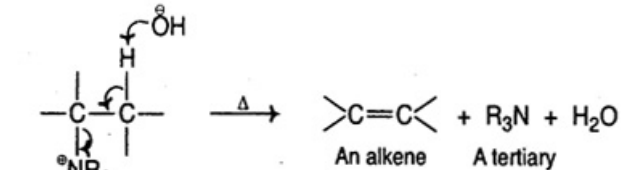
2-Methylpiperidine



3-Methylpiperidine

Solution:

(a) The Hofmann elimination is a specific E2 reaction in which a quaternary ammonium hydroxide undergoes thermal decomposition to yield an alkene, a tertiary amine, and water.

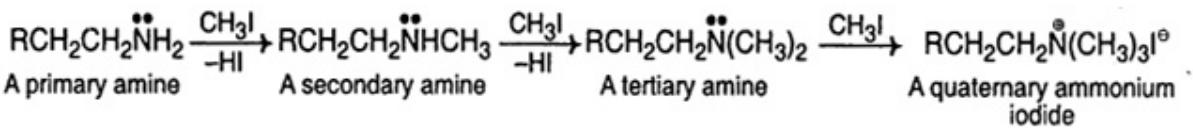


A quaternary ammonium hydroxide

An alkene

A tertiary amine

(b) Hofmann exhaustive methylation is a three-step process. In the first step, a primary, secondary or tertiary amine is converted to a quaternary ammonium iodide by treatment with excess methyl iodide.



A primary amine

A secondary amine

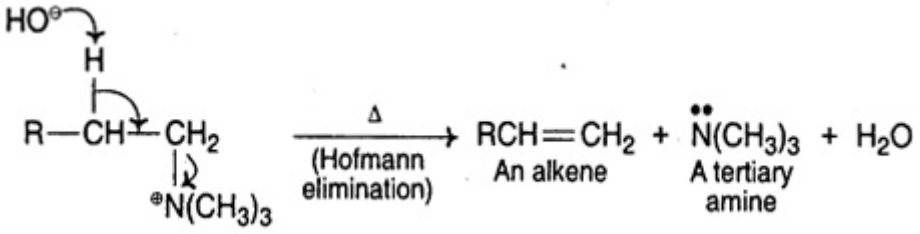
A tertiary amine

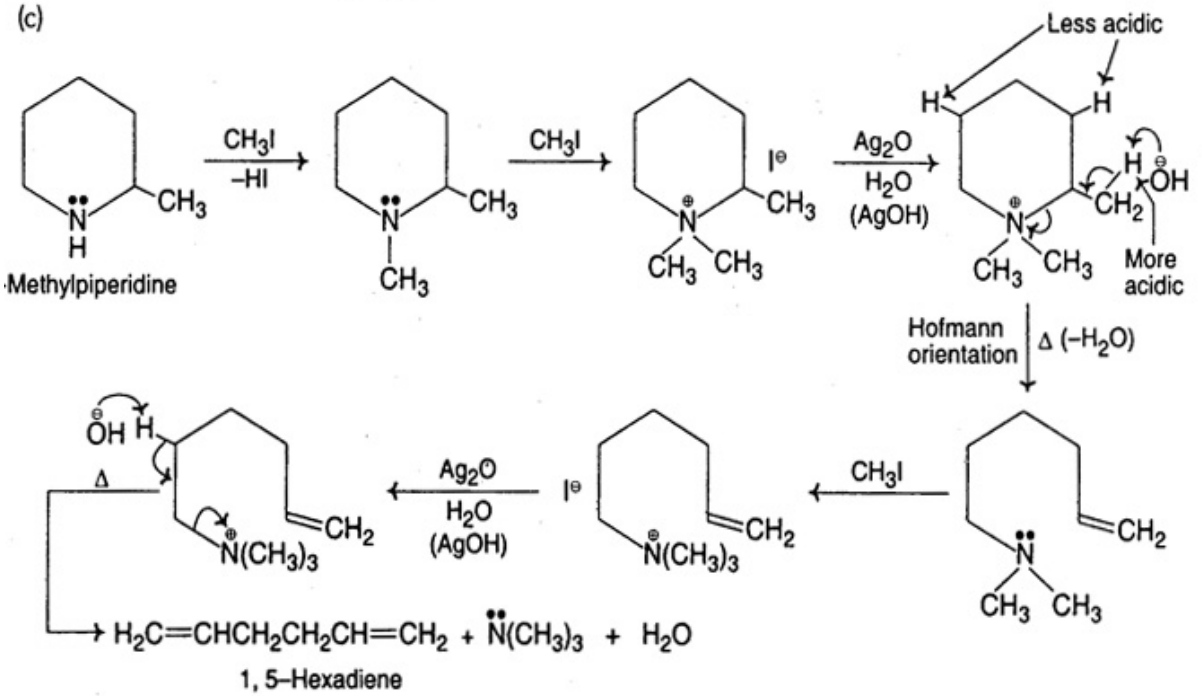
A quaternary ammonium iodide

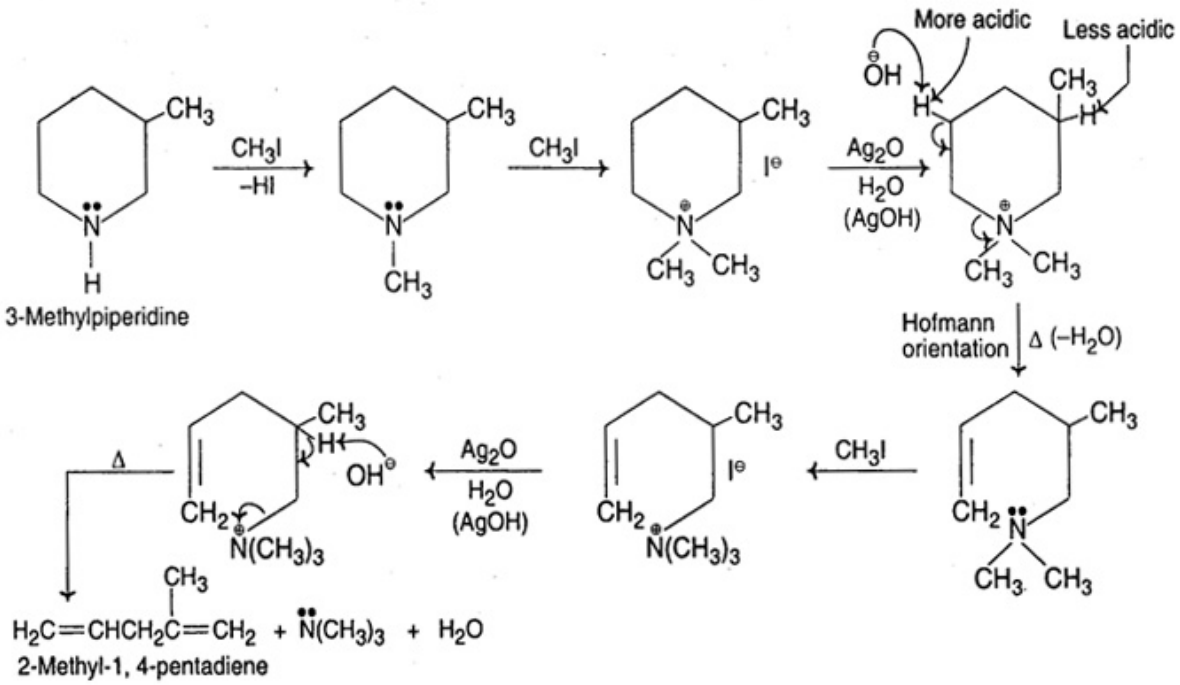
In the second step, the iodide salt is treated with moist silver oxide to give the corresponding hydroxide.

$$2\,RCH_2CH_2\overset{\oplus}{N}(CH_3)_3I^{\ominus} + Ag_2O + H_2O \longrightarrow 2\,RCH_2CH_2\overset{\oplus}{N}(CH_3)_3OH^{\ominus} + 2\,AgI$$

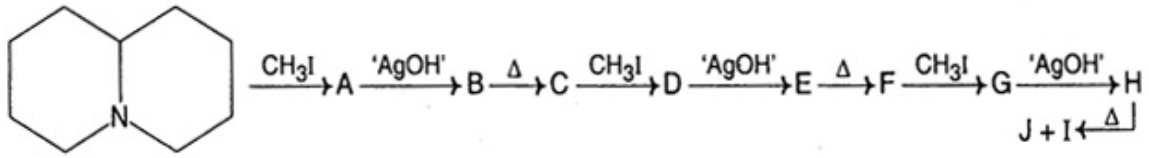
In the final step, thermal decomposition of the hydroxide to form an alkene, a tertiary amine, and water is carried out by distilling its aqueous or alcoholic solution.



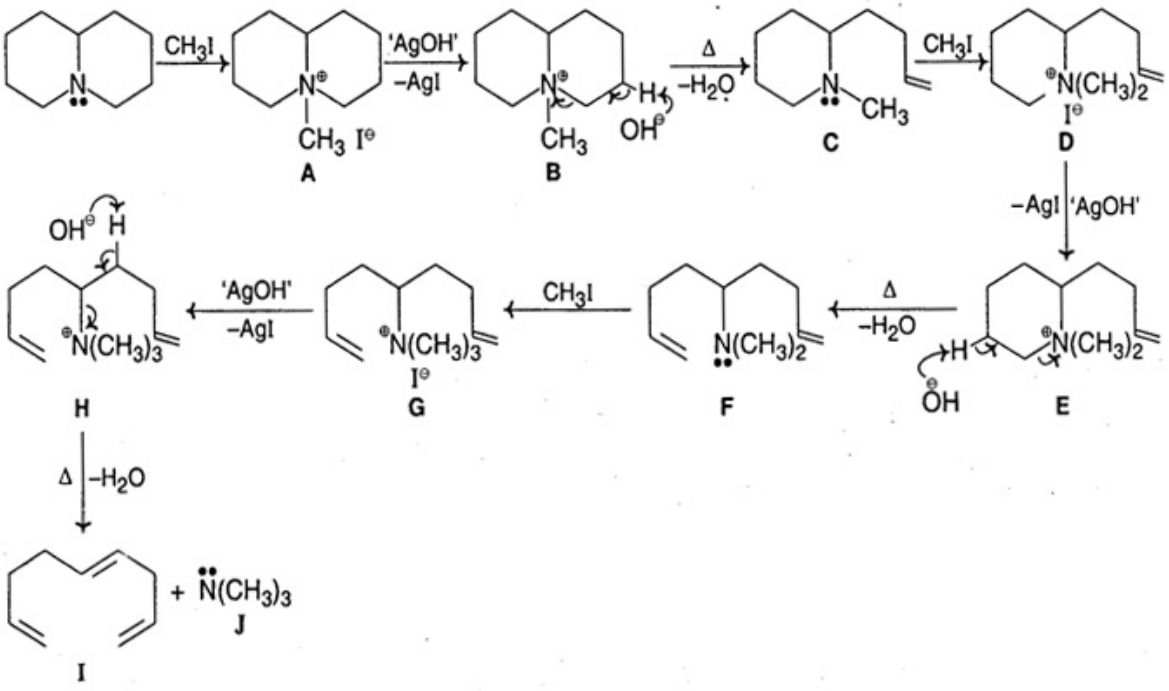




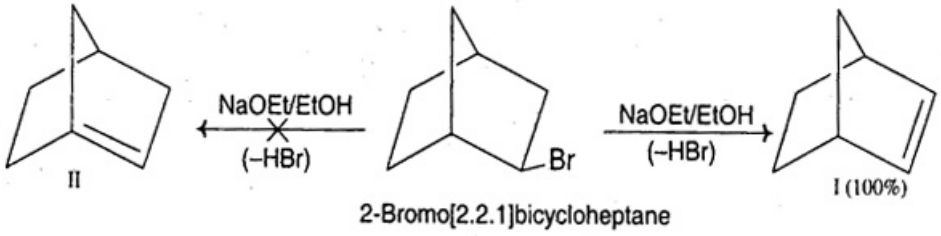
2. Identify the products in the following reaction sequence:



Solution:

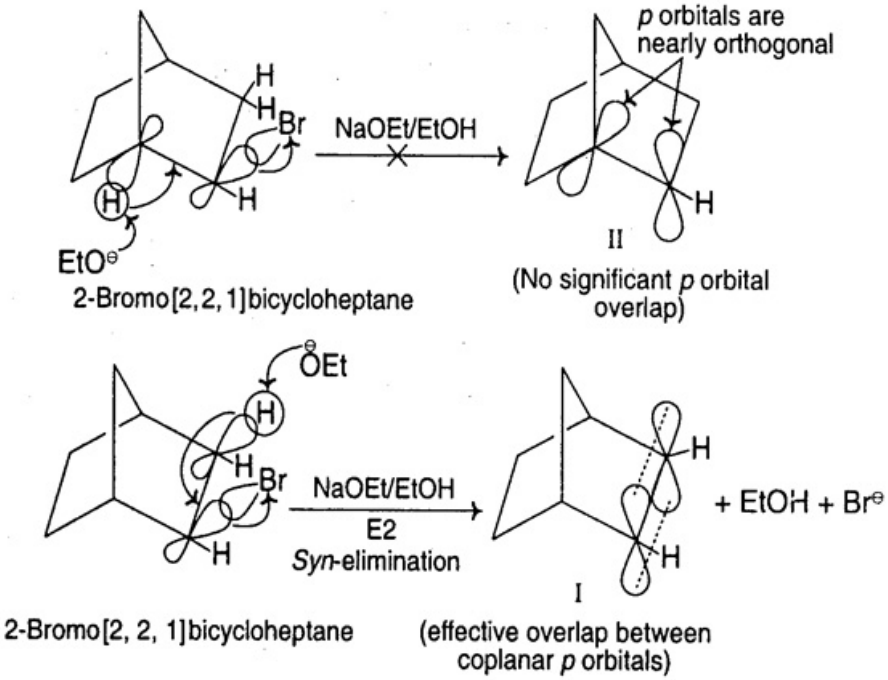


3. Explain the following observation:

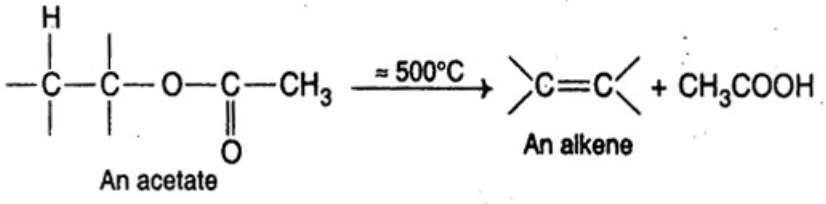


Solution:

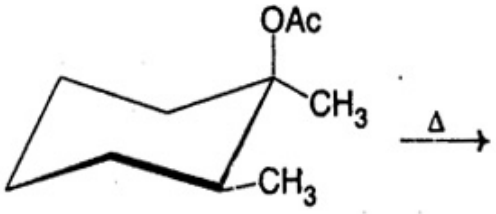
In small bicyclic systems, a double bond cannot be formed at the bridgehead position (Bredt's rule) and this is because the developing p orbitals cannot become coplanar (virtually at right angles to each other). For this reason, 2-bromo[2.2.1]bicycloheptane undergoes dehydrobromination to give the alkene I exclusively, even though II is the more substituted alkene (the Saytzeff product).



4. (a) Certain organic compounds (e.g. esters, amine oxides, etc.) undergo pyrolytic elimination in the absence of an external reagent. These reactions are often referred to as Ei eliminations (elimination, internal). Discuss the mechanism and stereochemistry of the following Ei reaction:

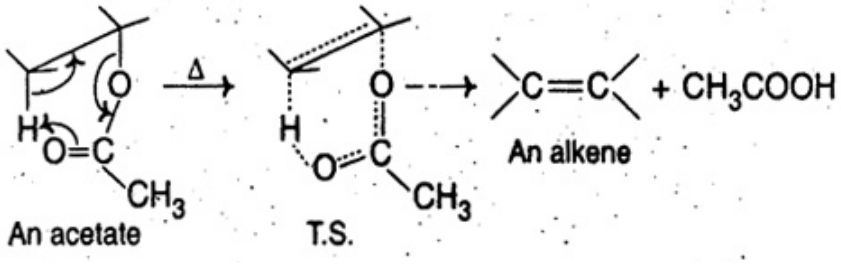


(b) Predict the major product and suggest a mechanism of the following reaction:

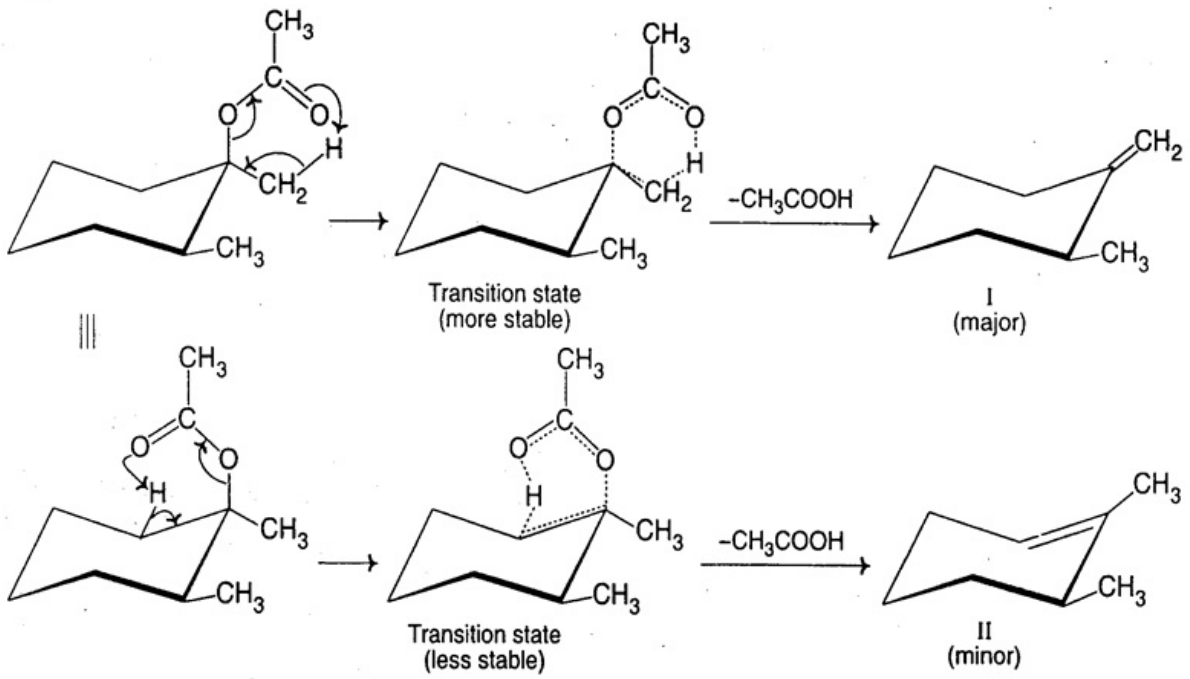


Solution:

(a) The pyrolytic elimination of an acetate containing a β-hydrogen atom proceeds in a concerted fashion through a six-membered cyclic transition state. The cyclic pathway requires a syn-periplanar arrangement of the departing groups and so the reaction is a stereospecific syn-eliminaiton.



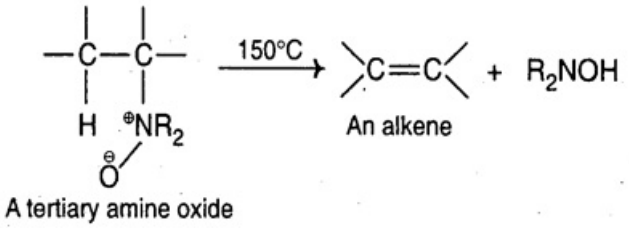
(b) The acetate undergoes pyrolytic syn-elimination to give the alkene I as the major product and this is because the six-membered cyclic transition state leading to the formation of I is planar and geometrically more favourable.



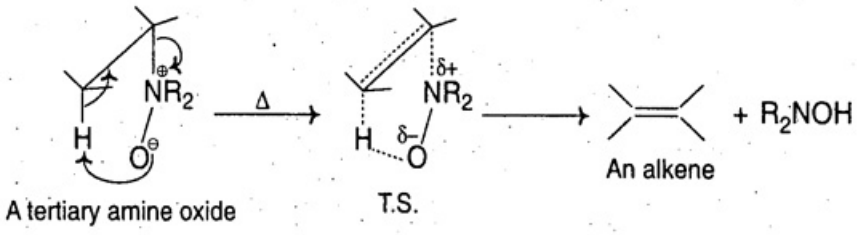
5. What is Cope reaction? Discuss the mechanism and stereochemistry of this reaction. Why is the reaction very useful for the preparation of many olefins?

Solution:

Thermal decomposition of tertiary amine oxides containing at least one β-hydrogen atom to produce an alkene and a hydroxylamine is known as the Cope reaction.

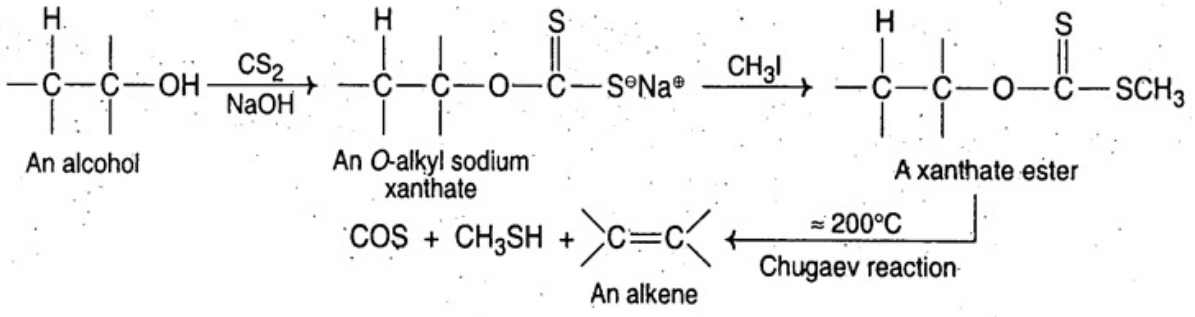


In this Ei reaction, the amine oxide attacks the β-hydrogen intramolecularly and the reaction proceeds through a planar five-membered cyclic transition state. The mechanistic pathway requires the departing groups to be coplanar on the same side of the molecule and so the reaction gives syn-elimination product stereospecifically.



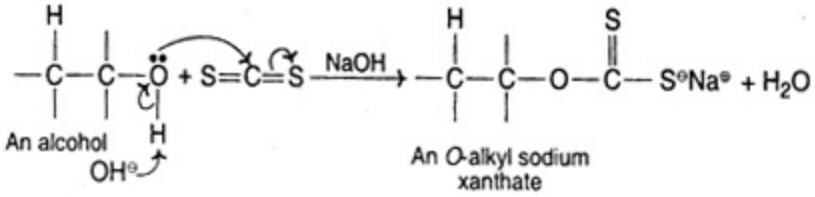
Since the reaction temperature is relatively low, possible isomerization of the resulting olefin is minimized and also because of mild conditions, side reactions are few. For these reasons, the reaction is very useful for the preparation of many olefins.

6. Give the mechanism of each step of the following reaction sequence which offers an indirect method of dehydration of an alcohol:

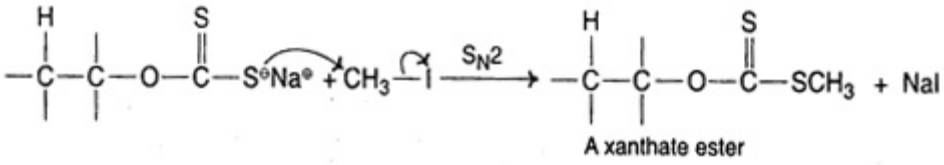


Solution:

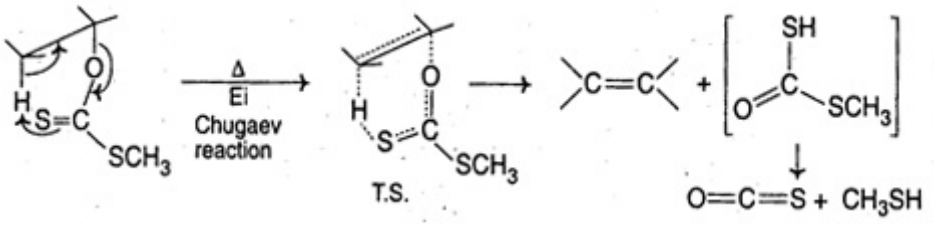
In the first step of this reaction sequence, the alcohol reacts with carbon disulphide in the presence of alkali to give an O-alkyl sodium xanthate:



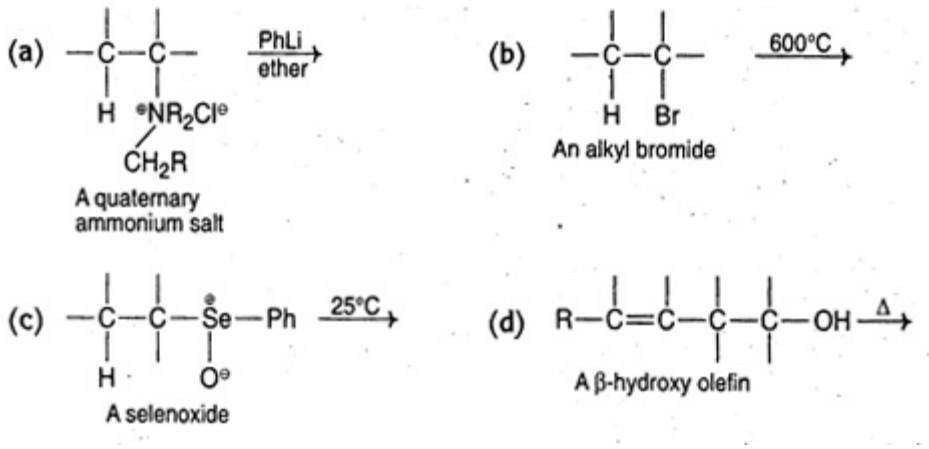
In the second step, the O-alkyl sodium xanthate reacts with methyl iodide by an S_N2 mechanism to yield a xanthate ester.



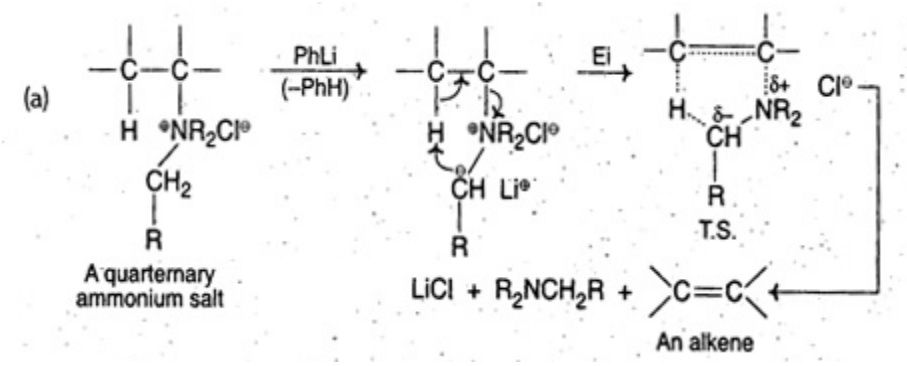
In the third step, the xanthate ester undergoes pyrolytic elimination (Ei reaction) to give an alkene. This one-step reaction proceeds through a six-membered cyclic transition state.

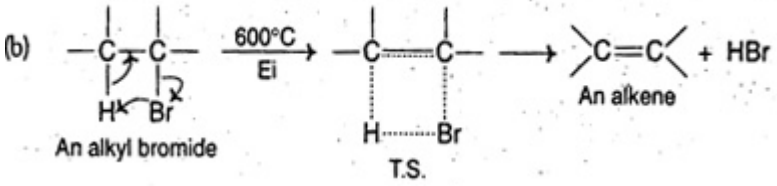


7. Write a mechanism for each of the following Ei reactions:

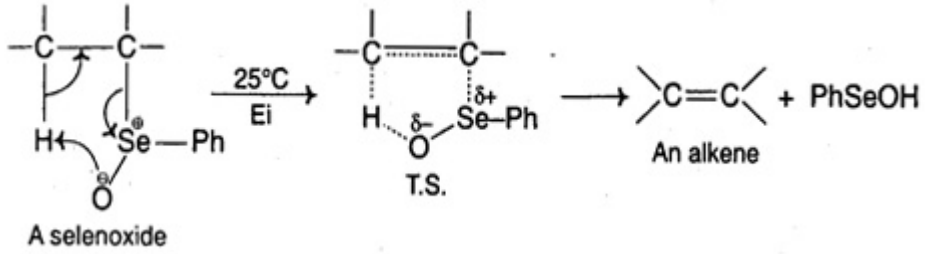


Solution:

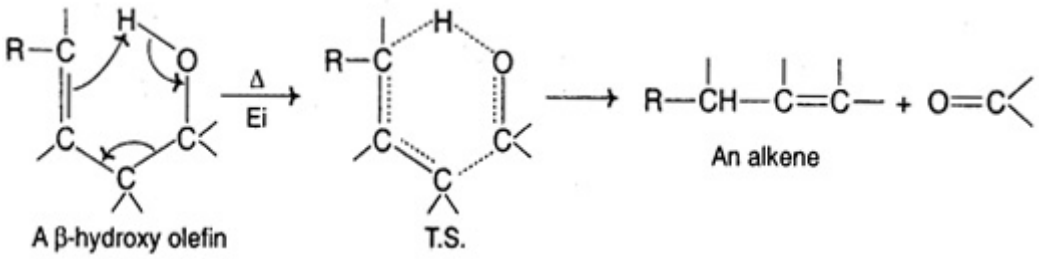




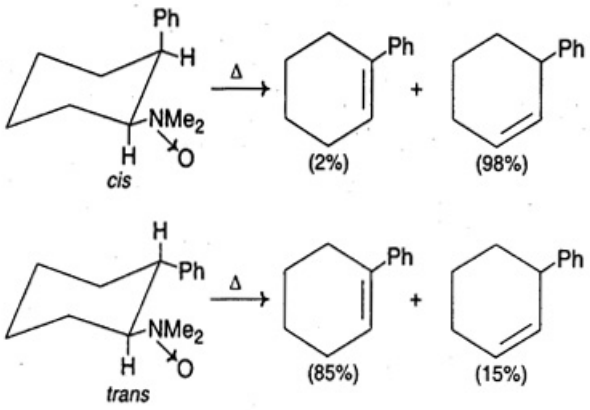
(c)



(d)

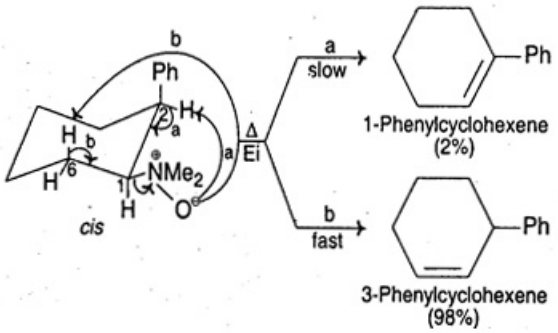


8. Explain the following observations:

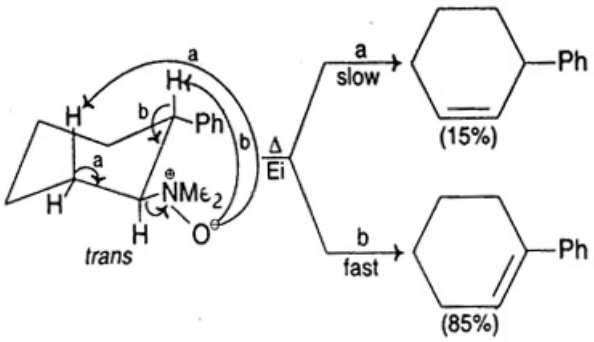


Solution:

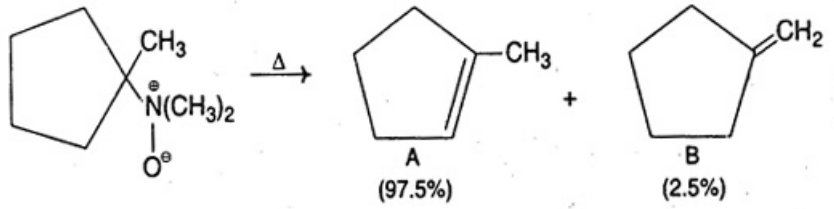
The five-membered cyclic transition state involved in the pyrolytic elimination of a tertiary amine oxide must be completely coplanar. Since it is easier to force an axial and an equatorial bond into a plane than two equatorial bonds, an equatorial and an axial substituent (hence cis to each other) undergo pyrolytic elimination more readily than two equatorial substituents (hence trans to each other). The formation of 1-phenylcyclohexene from the cis-isomer of the amine oxide involves an unfavourable trans elimination of the equatorial $–NMe_2 \rightarrow O$ group and the equatorial hydrogen at C-2, whereas the formation of 3-phenylcyclohexene form the same isomer involves a favourable cis-elimination of the equatorial $–NMe_2 \rightarrow O$ group and the axial hydrogen at C-6. Because of this, 3-phenylcyclohexene is formed almost entirely in this case.



The formation of both 1- and 3-phenylcyclohexene from the trans-amine oxide involve a favourable cis-elimination of an equatorial $–NMe_2 \rightarrow O$ group and an axial hydrogen (at C-2 or C-6). This isomer is, therefore, expected to yield 50% of each olefin. In fact, 1-phenylcyclohexene is formed predominantly and this is because 1-phenylcyclohexene, being a conjugated olefin, is thermodynamically more stable than 3-phenylcyclohexene.

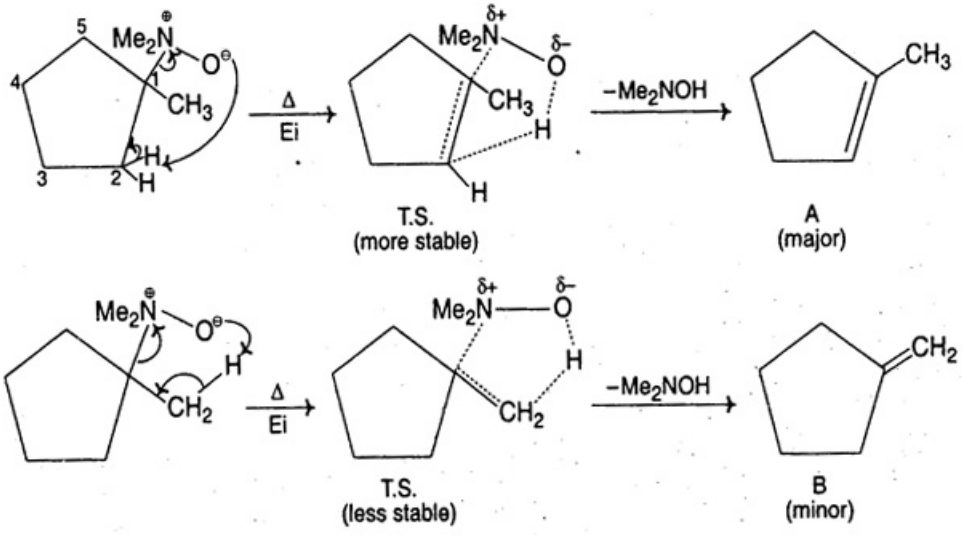


9. Explain the following observations:

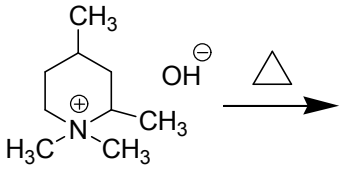


Solution:

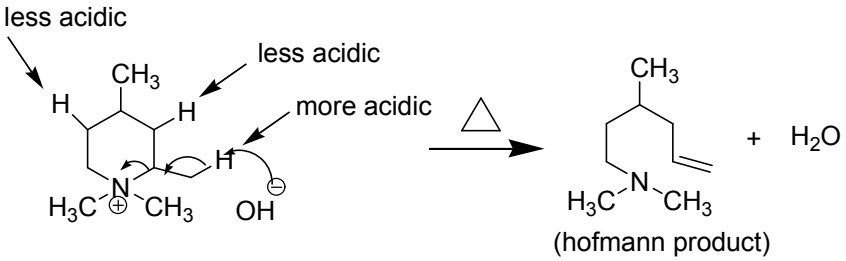
The five-membered cyclic transition state involved in the pyrolytic elimination of a tertiary amine oxide must be completely coplanar. In this 3° amine oxide, the $–N^+Me_2–O^-$ group can form a planar transition state not only with a methyl hydrogen but also with a cis β-hydrogen at C-2 or C-5 of the ring. Thus, the amine oxide is expected to yield nearly equal amount of each alkene. In fact, the alkene A in which the double bond is endocyclic is obtained predominantly. This is because the alkene A, being a highly substituted one, is thermodynamically more stable than the isomeric alkene B in which the double bond is exocyclic to the ring.



10. Give the structure of the major product of the following reaction and explain its formation.



Solution:



Text Book:

1. Smith, M. B. (2015). *March's Advanced Organic Chemistry: Reactions, Mechanisms, and Structure* (VII Edition). New Jersey: John Wiley & Sons, Inc., Hoboken.

Reference:

1. Tewari, N. (2011). *Advanced Organic Reaction Mechanism* (III Edition). Kolkata: Books and Allied (P) Ltd.

POSSIBLE QUESTIONS

PART- A – Multiple Choice Questions

(Each Question Carry One Mark)

1. Carbenes are

A) electron deficient species B) **electron rich species** C) bases D) acids

2. Carbenes are

A) carbocation intermediate B) **neutral intermediates**

C) carbanion intermediate D) free radical intermediate

3. Chugaev reaction is the conversion of

A) **xanthate to olefin** B) amine oxide to olefin

C) carboxylic ester to olefin D) quaternary ammonium hydroxide to olefin

4. The product in Chugaev reaction is

A) alcohol B) ester C) **alkene** D)carboxylic acid

5. E2 elimination is a

A) syn elimination B) **anti elimination** C) 1,1 elimination D) 1,2-elimination

6. Anti- elimination requires dihedral angle of

A) 60˚ B) 90˚ C) **180˚** D) 360˚

7. The dehydrohalogenation of 2,2-dichloro 1,1,1-trifluro ethane is failure in

A) E1 elimination B) E2 elimination C) **$E1_{CB}$ elimination** D) S_N1 elimination

8. E1 reaction is faciliated by

A) **strong polar solvent** B) low polar solvent

C) high concentration of base D)low temperature

9. In E2 elimination, some compounds follow Hofmann's rule which means

A) the double bond goes to the most substituted position

B) the compound is resistant to elimination

C) **the double bond goes to the least substituted position**

D) the double bond goes to the terminal carbon

10. The singlet carbene two electrons are

A) spin free B) parallel C) **spin paired** D) unpaired

11. The cleavage of amine oxides to produce an alkene and hydroxylamine is called

A) Chugaev reaction B) **Cope reaction** C) Hofmann reaction D) Sayteff rule

12. Carbenes are trapped as

A) **cyclopropane derivative** B) Diel's alder adduct

C) oxidative product D) hydroxylamine derivative

13. In Hofmann degradation, there must be

A) **β-hydrogen** B) α- hydrogen C) γ- hydrogen D) δ-hydrogen

14. The predominant product of elimination of HBr from 3-bromo-2,3-dimethyl pentane is

A) 3,4-dimethyl-2-pentene B) **2,3- dimethyl-2-pentene**

C) 2-ethyl-3-methyl-1-butene D) 3,4-dimethyl-1-pentene

15. The double bond does not go to the bridge head carbon .This rule is called

A) Zaitsev's rule B) Hoffmann rule C) **Bredt's rule** D) Blanc's rule

16. Cope elimination involves

A) pyrolysis of esters B) **syn elimination is observed**

C) In the transition state C-H and C-X bond are cleaved to the same extent

D) cleavage of ethers to olefins

17. The Hofmann degradation of 2-methylpyridine gives

A) **1,5-hexadiene** B) 2-methyl-1,4-pentadiene

C) 1,4-hexadiene D) 1-methyl-1,4-pentadiene

18. E1 mechanism is

A) **first order** B) second order C)third order D) zero order

19. $E1_{CB}$ reaction

A) **proceeds through an anion intermediate**

B) is a single step process C) is stereospecific D) is of unknown mechanism

20. The Hofmann exhaustive methylation of 3-methylpyridine gives

A) 1,5-hexadiene B) 2-methyl-1,4-pentadiene

C)1,4-hexadiene D) **1-methyl-1,4-pentadiene**

21. Considering the mechanism of elimination reaction, which of the following statement are true?

A) E1, E2 and E1CB reactions are stereospecific

B) E1 and E1CB reactions are stereospecific

C) E2 reaction alone is stereospecific

D) **E2 and $E1_{CB}$ reactions are stereospecific**

22. The singlet carbene is

A) paramagnetic B) **diamagnetic** C) ferromagnetic D) same spin species

23. The triplet carbene is

A) sp^2 hybridized B) **sp hybridized** C) sp^3 hybridized D) dsp^2 hybridized

24. The Hofmann elimination is related to

A) **E2 reaction** B) E1 reaction C) E1CB reaction D) Ei reaction

25. Photochemical decomposition of diazoalkanes gives

A) alkanes B) carbanions C) alkynes D) **carbenes**

26. E1CB mechanism is also called

A) **carbanion mechanism** B) carbene mechanism

C) carbonium ion mechanism D) benzyne mechanism

27. Which mechanism is normally found in substrates which have a poor nucleophile and an acidic hydrogen?

A) E1 B) E2 C) **$E1_{CB}$** D) E1 followed by E2

28. On adding double bonds to carbenes gives

A) **cyclic compounds** B) open chain compounds

C) aromatic compound D)conjugated system

29. E1 reactions are favored by

A) **polar solvents** B) non-polar solvents C) aprotic solvents D) amphoteric solvents

30. E1 reactions are favored by

A) **–I effect** B) high pressure C) steric effect D) hyperconjugation

31. Intermediate formed in E1CB mechanism is

A) **carbanoin** B) carbonium C) free radical D) carbene

32. Intermediate formed in E1 mechanism is

A) carbanoin B) **carbonium ion** C) cyclic transition state D) carbene

33. Certain organic compounds (e.g. esters, amine oxides etc.) undergo pyrolytic elimination in the absence of an external reagent. These reactions are often referred to as

A) E2 elimination B) E1 elimination C) E1CB elimination D) **Ei elimination**

34. The example for simplest carbene is

A) ethylene B) **methylene** C) formylene D) propylene

35. Not possible to introduce a double bonds at a bridgehead position in bridged bicyclic cmpounds with smal rings is called

A) **Bredt's rule** B) Saytzeff rule C) Hofmann rule D) Chugaev reaction

36. Charged substrates yield predominately the least substituted alkene. The rule is called

A) Bredt's rule B) Saytzeff rule C) **Hofmann rule** D) Chugaev reaction

37. Nitrenes also called as

A) **Imidogen** B) imides C) Imines D) amines

38. Nitrene is a

A) monovalent electrophilic species B) monovalent nucleophilic species

C) divalent electrophilic species D) **divalent nucleophilic species**

39. The acetate undergoes pyrolytic syn-elimination to give the

A) alkane B) alkyne C) **alkene** D) alcohol

40. In Cope reaction the tertiary amine oxides containing at least one

A) α-hydrogen atom B) δ-hydrogen atom C) **β-hydrogen atom** D) γ-hydrogen atom

41. In Chugave reaction the alcohol reacts with carbon disulphide in the presence of alkali too give an

A) tertiary amine oxide B) **xanthate** C) acetates D) quaternary ammonium hydroxide

42. Anti elimination is generally favoured in

A) E1 elimination B) **E2 elimination** C) E1CB elimination D) E1 & E2 elimination

43. If the two atoms or groups are lost from the adjacent carbon atoms it is called

A) **1,2-elimination** B) 1,1-elimination C) 1,3-elimination D) 1,5-elimination

44. Which elimination reactions solvent is not required

A) E1 elimination B) E2 elimination C) E1CB elimination D) **Ei elimination**

45. A selenoxide to gives alkene is effected by

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46. How many non bonded atom present in carbine

A) 3 B) **2** C) 4 D)5

47. The conversion of β-hydroxy olefin into alkene is effected by

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49. Photochemistry reactions are useful method for

A) **carbene** B) nitrene C) alkene D) ketone

50. The elimination produce predominantly the less-substituted alkene if the leaving group is positively charged is called as

A) Bredt's rule B) Saytzeff rule C) **Hofmann rule** D) Chugaev reaction

51. Important application of carbenes are

A) dying B) textile C) **synthetic** D) detergents

52. In which type of reaction involve in ion pair

A) **E1 reaction** B) E2 reaction C) E1CB reaction D) Ei reaction

53. The conversion of benzene into cycloheptatriene is effected by

A) Cope reaction B) Hoffman reaction C) **carbene reaction** D) nitrene reaction

54. Cope reaction is useful for the formation of

A) **trans cyclo-olefins** B) cis cyclo-olefins C) cis olefins D) trans olefins

55. Highly reactive species are

A) carbon B) halogen C) **carbene** D) carbocation

56. Which one of the following does not undergo dimerisation

A) **carbene** B) alkene C) nitrene D)alcohol

57. Which halides favour the elimination mostly?

A) primary B)secondary C) **tertiary** D)chlorohydrin

58. Which one halides favour the elimination leastly

A) **primary** B)secondary C)tertiary D)chlorohydrin

59. Hoffman exhaustive methylation process which is widely used for structure determination of extremely useful in the

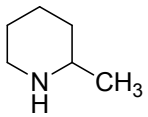
A) Steroids B) proteins C) terpenoids D) **alkaloids**

60. Hoffman exhaustive methylation is a

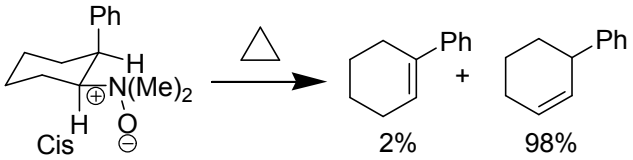
A) one-step process B) **three-step process** C) two-step process D) four-step process

PART-B (Each Question Carry Two Mark)

61. What is the Hofmann elimination reaction?
62. Write the structure of singlet and triplet carbenes.
63. Discuss the steps involved in Hofmann degradation process which is widely used for structural determination of alkaloids.
64. Write the generation of carbenes.
65. Give the steps involved in the complete Hofmann degradation of the following cyclic amine.

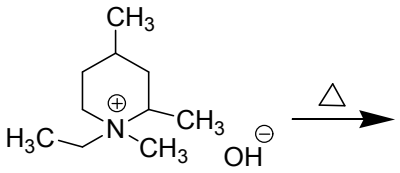


66. Explain the following observation:



67. Illustrate the reactions of nitrenes with suitable examples.

68. Predict the product of the following reaction:

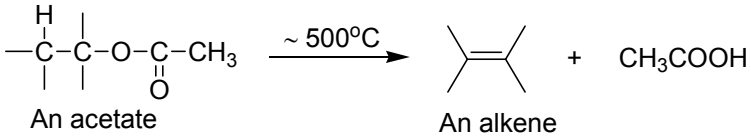


PART-C (Each Question Carry Six Mark)

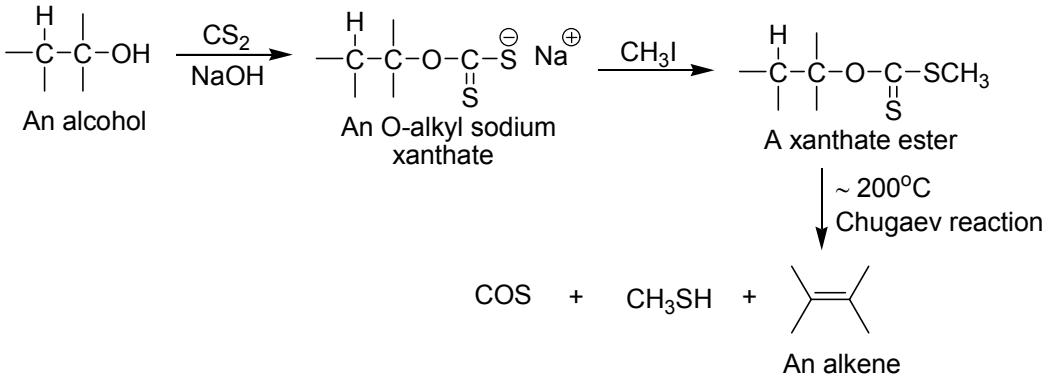
69. (i)How will you generate nitrenes? Give an account of their structure and stability.

(ii) Explain the Bredts rule.

70. (i) Discuss the mechanism and stereochemistry of the following Ei reaction:



(ii) Give the mechanism of each step of the following reaction sequence which offers an indirect method of dehydration of an alcohol.



71. Write the structure, generation and reactions of carbenes and nitrenes.

72. Discuss about (i) Hofmann rule (ii) Elimination Vs substitution.

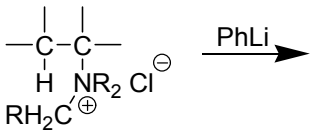
73. (i) Explain the E_2 mechanism with examples.

(ii) Explain the Chugaev elimination reactions.

74. Discuss about (i) Saytzeff rule (ii) Cope elimination.

75. (i) Explain the E_{1CB} mechanism with examples.

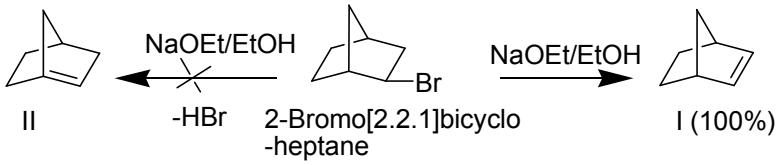
(ii) Write mechanism of the following E_i reaction.



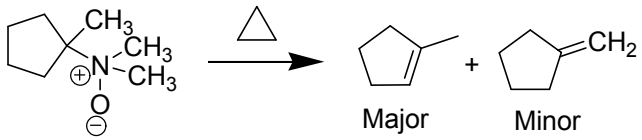
76. What are the evidences for the existence of E_1, E_2 and E_{1CB} mechanisms?

77. (i) Explain the E_1 mechanism with example.

(ii) Explain the following observation:

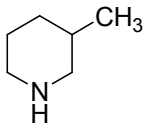


78. (i) Explain the following observation:



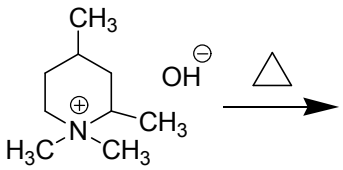
(ii) How nitrenes are generated.

(iii) Give the steps involved in the complete Hofmann degradation of the following cyclic amine.

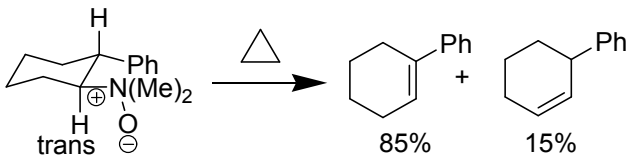


PART-D (Each Question Carry Ten Mark)

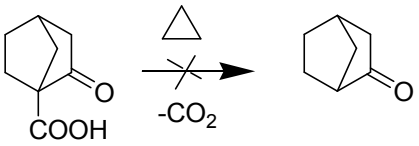
79. (i) Give the structure of the major product of the following reaction and explain its formation.



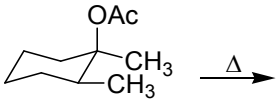
(ii) Explain the following observation:



(iii) Explain why this β-keto acid does not readily undergo decarboxylation.



(iv) Predict the major product and suggest a mechanism of the following reaction:



KARPAGAM ACADEMY OF HIGHER EDUCATION
(*Deemed to be University Established Under Section 3 of UGC Act 1956*)
Pollachi Main Road, Eachanari Post, Coimbatore–641021.

DEPARTMENT OF CHEMISTRY

UNIT-V

ELIMINATION REACTIONS

PART-A–Multiple Choice Questions
(Each Question Carry One Mark) (Online Examinations)

1. Carbenes are

A) electron deficient species B) **electron rich species** C) bases D) acids

2. Carbenes are

A) carbocation intermediate B) **neutral intermediates**

C) carbanion intermediate D) free radical intermediate

3. Chugaev reaction is the conversion of

A) **xanthate to olefin** B) amine oxide to olefin

C) carboxylic ester to olefin D) quaternary ammonium hydroxide to olefin

4. The product in Chugaev reaction is

A) alcohol B) ester C) **alkene** D)carboxylic acid

5. E2 elimination is a

A) syn elimination B) **anti elimination** C) 1,1 elimination D) 1,2-elimination

6. Anti- elimination requires dihedral angle of

A) 60˚ B) 90˚ C) **180˚** D) 360˚

7. The dehydrohalogenation of 2,2-dichloro 1,1,1-trifluro ethane is failure in

A) E1 elimination B) E2 elimination C) **$E1_{CB}$ elimination** D) S_N1 elimination

8. E1 reaction is faciliated by

A) **strong polar solvent** B) low polar solvent

C) high concentration of base D)low temperature

9. In E2 elimination, some compounds follow Hofmann's rule which means

A) the double bond goes to the most substituted position

B) the compound is resistant to elimination

C) **the double bond goes to the least substituted position**

D) the double bond goes to the terminal carbon

10. The singlet carbene two electrons are

A) spin free B) parallel C) **spin paired** D) unpaired

11. The cleavage of amine oxides to produce an alkene and hydroxylamine is called

A) Chugaev reaction B) **Cope reaction** C) Hofmann reaction D) Sayteff rule

12. Carbenes are trapped as

A) **cyclopropane derivative** B) Diel's alder adduct

C) oxidative product D) hydroxylamine derivative

13. In Hofmann degradation, there must be

A) **β-hydrogen** B) α- hydrogen C) γ- hydrogen D) δ-hydrogen

14. The predominant product of elimination of HBr from 3-bromo-2,3-dimethyl pentane is

A) 3,4-dimethyl-2-pentene B) **2,3- dimethyl-2-pentene**

C) 2-ethyl-3-methyl-1-butene D) 3,4-dimethyl-1-pentene

15. The double bond does not go to the bridge head carbon .This rule is called

A) Zaitsev's rule B) Hoffmann rule C) **Bredt's rule** D) Blanc's rule

16. Cope elimination involves

A) pyrolysis of esters B) **syn elimination is observed**

C) In the transition state C-H and C-X bond are cleaved to the same extent

D) cleavage of ethers to olefins

17. The Hofmann degradation of 2-methylpyridine gives

A) **1,5-hexadiene** B) 2-methyl-1,4-pentadiene

C) 1,4-hexadiene D) 1-methyl-1,4-pentadiene

18. E1 mechanism is

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Reg. No.....

KARPAGAM ACADEMY OF HIGHER EDUCATION

(Deemed University Established Under Section 3 of UGC Act 1956)

COIMBATORE-641 021

(For the candidates admitted from 2017 & onwards)

PG DEGREE EXAMINATION, AUGUST 2017

FIRST SEMESTER

INTERNAL TEST-I

CHEMISTRY

ORGANIC CHEMISTRY-I (Reaction Mechanisms)

Time: 2 hours **Maximum: 50 marks**
Date: 28-8-2017 (AN) **Subject code: 17CHP101**

PART- A (20 x 1=20 Marks)
Answer All the Questions

1. Cyclooctatetraene is

a) aromatic compound b) antiaromatic compound

c) non aromatic compound d) aliphatic compound

2. Which of the following compound is called a sandwich compound?

a) ferrocene b) azulene c) annulene d) naphthalene

3. Compounds having one or more sp^3 hybridized carbon atom in an conjugated cycle are called as

a) homo-aromatic compounds b) non-aromatic compounds

c) anti-aromatic compounds d) aromatic compounds

4. Hammett equation is not applicable to

a) *o*-substituted aromatic system b) *p*-substituted aromatic system

c) *m*-substituted aromatic system d) aliphatic system

5. A cyclic compound that does not have a continuous, overlapping ring of p orbital is said to be

a) anti-aromatic compound b) non-aromatic compound

c) aromatic compound d) heterocyclic compound

6. Azulene is aromatic due to

a) charge separated structures b) both rings are aromatic

c) both rings having 6π electrons d) two Kekule structures

7. The change in the rate of a reaction observed due to replacement of one isotope of an element for another is called

a) non-kinetic isotopic effect b) kinetic isotopic effect

c) isotopic labeling d) cross over experiment

8. The nitronium ion involved in nitration of benzene has been detected by

a) NMR spectrum b) UV spectrum c) Raman spectrum d) ESR spectrum

9. A reaction in which the substrate and the reagent add up to form product is called

a) addition reaction b) rearrangement reaction

c) elimination reaction d) substitution reaction

10. Double bond can be hydrated by treatment with

a) water and an acid catalyst b) water and an base catalyst

c) methanol and an base catalyst d) mercuric acetate and an base catalyst

11. The base catalysed addition of compounds having active methylene group to an activated olefinic bond of the type -C=C-Z is classified as

a) Aldol reaction b) Michael reaction c) Wittig reaction d) Mannich reaction

12. Which reagent is used for Prevost anti hydroxylation reaction?

a) I_2/PhCOOAg b) I_2, AgOAc/H_2O, H^+ c) O_sO_4 d) alkaline $KMnO_4$

13. Aldehydes and ketones condense with the esters of succinic acid in the presence of base such as sodium ethoxide to give the salts of α,β-unsaturated half ester is known as

a) Aldol condensation b) Stobbe condensation

c) Claisen condensation d) Dieckmann condensation

14. Aldehydes and ketones condense with α-halo esters in the presence of bases to give α,β-epoxy esters called as

a) Darzens condensation b) Stobbe condensation

c) Knoevenagel condensation d) Dieckmann condensation

15. When certain aldehydes are treated with cyanide ion, benzoins are produced in a reaction called the

a) Darzens condensation b) Benzoin condensation

c) Knoevenagel condensation d) Dieckmann condensation

16. The reversible of polarity of carbonyl carbon is called the

a) umpolung b) nucleophile c) synthon d) synthetic equivalent

17. Formylation with zinc cyanide and HCl is called the

a) Gattermann reaction b) Gattermann-Koch reaction

c) Reimer-Tiemann reaction d) Kolbe reaction

18. Gattermann-Koch reaction which solvent is generally used?

a) benzene b) chloroform c) nitrobenzene d) ethyl acetate

19. The commonly used catalyst for Vilsmeier Haack reaction is

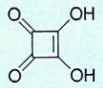
a) $AlCl_3$ b) $POCl_3$ c) PCl_5 d) P_2O_5

20. Pyrrole undergoes Reimer-Tiemann reaction to produces

a) pyrrole-2-aldehyde b) pyridine c) 3-chloropyridine d) piperonal

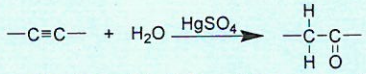
PART- B (3 x 2= 6 Marks)
Answer All the Questions

21. The following cyclic diol (squaric acid) is almost strong an acid as H_2SO_4. Explain why?



Squaric acid

22. Write the mechanism of the following conversion.

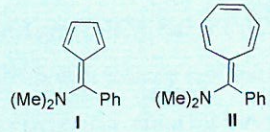


23. Give two important applications of the Reimer-Tiemann reaction.

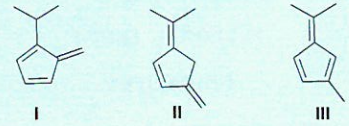
PART- C (3 x 8= 24 Marks)
Answer All the Questions

24. (a) Provide an explanation for each of the following observations:

(i) The amine **II** is more basic than the amine **I**.



(ii) One of the following hydrocarbons is much more acidic than the others.



(Or)

(b) What do you understand by kinetic isotope effect? What are primary and secondary isotope effects? Illustrate these techniques of elucidation of reaction mechanisms with suitable examples.

25. (a) Explain the conditions for a compound to be aromatic, non-aromatic and anti aromatic with examples.

(Or)

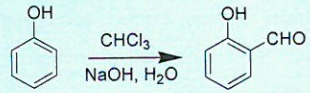
(b) Explain the Michael addition reaction with mechanism and application.

26. (a) Give an account on i) Hydroxylation ii) Epoxidation.

(Or)

(b) (i) Explain Gattermann and Gattermann Koch reactions with mechanism.

(ii) Explain the mechanism of the following reaction.



Reg. No……..

KARPAGAM ACADEMY OF HIGHER EDUCATION

(Deemed University Established Under Section 3 of UGC Act 1956)

COIMBATORE-641 021

(For the candidates admitted from 2017 & onwards)

PG DEGREE EXAMINATION, AUGUST 2017

FIRST SEMESTER

INTERNAL TEST-I ANSWER KEY

CHEMISTRY

ORGANIC CHEMISTRY-I (Reaction Mechanisms)

Time: 2 hours **Maximum: 50 marks**
Date: 28-8-2017 (AN) **Subject code: 17CHP101**

PART- A (20 x 1=20 Marks)

1. Cyclooctatetraene is

a) aromatic compound b) antiaromatic compound

c) non aromatic compound d) aliphatic compound

Answer: c) non aromatic compound

2. Which of the following compound is called a sandwich compound?

a) ferrocene b) azulene c) annulene d) naphthalene

Answer: a) ferrocene

3. Compounds having one or more sp^3 hybridized carbon atom in an conjugated cycle are called as

a) homo-aromatic compounds b) non-aromatic compounds

c) anti-aromatic compounds d) aromatic compounds

Answer: a) homo-aromatic compounds

4. Hammett equation is not applicable to

a) *o*-substituted aromatic system b) *p*-substituted aromatic system

c) *m*-substituted aromatic system d) aliphatic system

Answer: a) *o*-substituted aromatic system

5. A cyclic compound that does not have a continuous, overlapping ring of p orbital is said to be

a) anti-aromatic compound b) non-aromatic compound

c) aromatic compound d) heterocyclic compound

Answer: b) non-aromatic compound

6. Azulene is aromatic due to

a) charge separated structures b) both rings are aromatic

c) both rings having 6π electrons d) two Kekule structures

Answer: a) charge separated structures

7. The change in the rate of a reaction observed due to replacement of one isotope of an element for another is called

a) non-kinetic isotopic effect b) kinetic isotopic effect

c) isotopic labeling d) cross over experiment

Answer: b) kinetic isotopic effect

8. The nitronium ion involved in nitration of benzene has been detected by

a) NMR spectrum b) UV spectrum c) Raman spectrum d) ESR spectrum

Answer: c) Raman spectrum

9. A reaction in which the substrate and the reagent add up to form product is called

a) addition reaction b) rearrangement reaction

c) elimination reaction d) substitution reaction

Answer: a) addition reaction

10. Double bond can be hydrated by treatment with

a) water and an acid catalyst b) water and an base catalyst

c) methanol and an base catalyst d) mercuric acetate and an base catalyst

Answer: a) water and an acid catalyst

11. The base catalysed addition of compounds having active methylene group to an activated olefinic bond of the type -C=C-Z is classified as

a) Aldol reaction b) Michael reaction c) Wittig reaction d) Mannich reaction

Answer: b) Michael reaction

12. Which reagent is used for Prevost anti hydroxylation reaction?

a) I_2/PhCOOAg b) I_2, AgOAc/H_2O, H^+ c) O_sO_4 d) alkaline $KMnO_4$

Answer: a) I_2/PhCOOAg

13. Aldehydes and ketones condense with the esters of succinic acid in the presence of base such as sodium ethoxide to give the salts of α,β-unsaturated half ester is known as

a) Aldol condensation b) Stobbe condensation

c) Claisen condensation d) Dieckmann condensation

Answer: b) Stobbe condensation

14. Aldehydes and ketones condense with α-halo esters in the presence of bases to give α,β-epoxy esters called as

a) Darzens condensation b) Stobbe condensation

c) Knoevenagel condensation d) Dieckmann condensation

Answer: a) Darzens condensation

15. When certain aldehydes are treated with cyanide ion, benzoins are produced in a reaction called the

a) Darzens condensation b) Benzoin condensation

c) Knoevenagel condensation d) Dieckmann condensation

Answer: b) Benzoin condensation

16. The reversible of polarity of carbonyl carbon is called the

a) umpolung b) nucleophile c) synthon d) synthetic equivalent

Answer: a) umpolung

17. Formylation with zinc cyanide and HCl is called the

a) Gattermann reaction b) Gattermann-Koch reaction

c) Reimer-Tiemann reaction d) Kolbe reaction

Answer: a) Gattermann reaction

18. Gattermann-Koch reaction which solvent is generally used?

a) benzene b) chloroform c) nitrobenzene d) ethyl acetate

Answer: c) nitrobenzene

19. The commonly used catalyst for Vilsmeier Haack reaction is

a) $AlCl_3$ b) $POCl_3$ c) PCl_5 d) P_2O_5

Answer: b) $POCl_3$

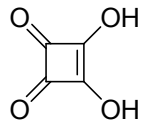
20. Pyrrole undergoes Reimer-Tiemann reaction to produces

a) pyrrole-2-aldehyde b) pyridine c) 3-chloropyridine d) piperonal

Answer: c) 3-chloropyridine

PART- B (3 x 2= 6 Marks)

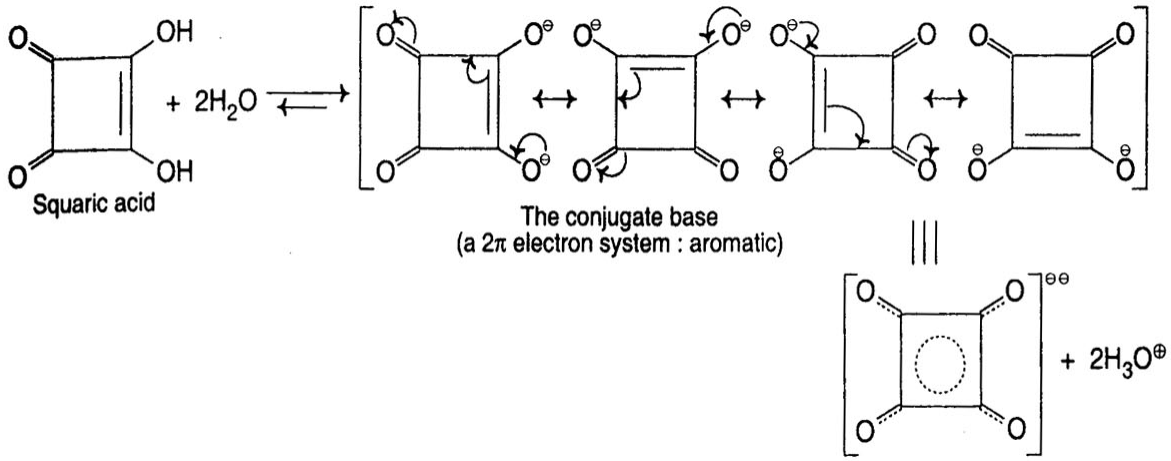
21. The following cyclic diol (squaric acid) is almost strong an acid as H_2SO_4. Explain why?



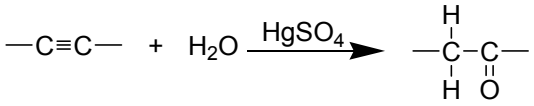
Squaric acid

Answer:

The dianionic conjugate base of this cyclic diol is very much stable because it is a cyclic resonance system of (4n +2) π (n=0) electrons (aromatic) and for this reason, the compound is almost as strong an acid as H_2SO_4.

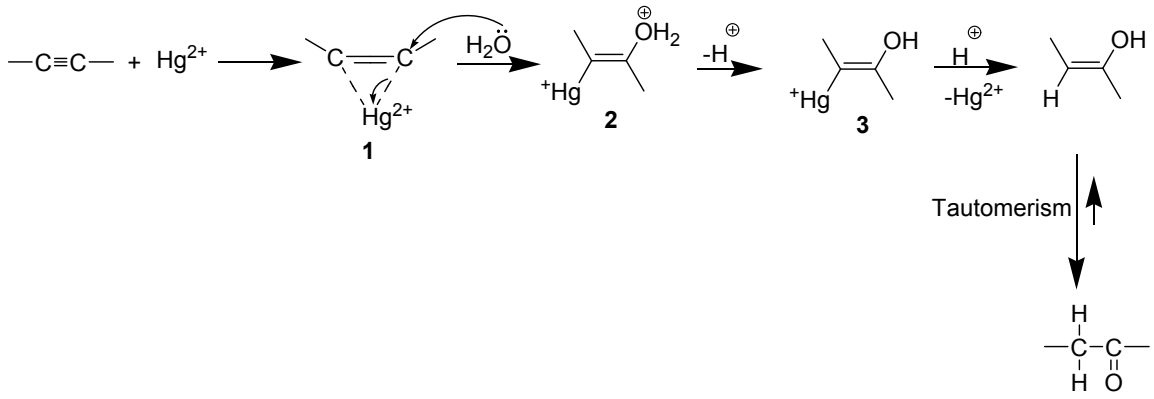


22. Write the mechanism of the following conversion.



Answer:

The first step of the mechanism is formation of a complex (**1**) (ions like Hg^{2+} form complexes with alkynes). Water then attacks in an S_N2-type process to give the intermediate **2,** which loses a proton to give **3**. Hydrolysis of **3** gives the enol, which tautomerizes to the product. A spectrum of the enol was detected by flash photolysis when phenyl acetylene was hydrated photolytically.

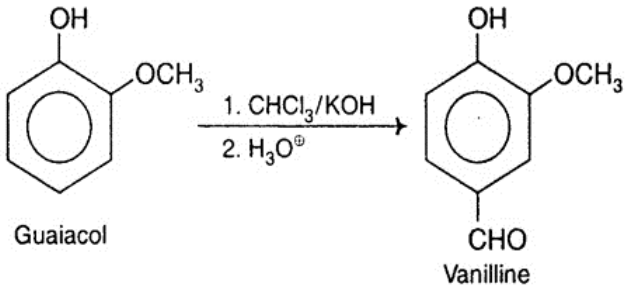


23. Give two important applications of the Reimer-Tiemann reaction.

Answer:

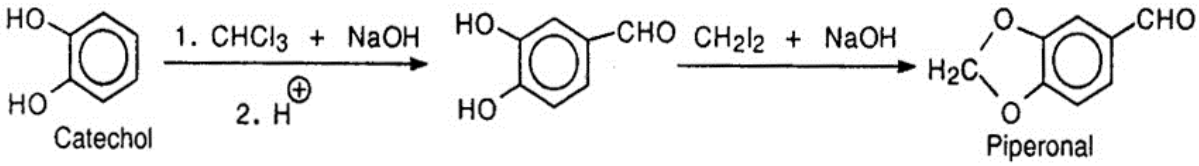
The reaction affords a good method for introducing aldehyde or carboxyl group in phenols.

(i) Preparation of vanilline



Vanilline has long been used for flavouring different kinds of foods and perfumes.

(ii) Preparation of piperonal

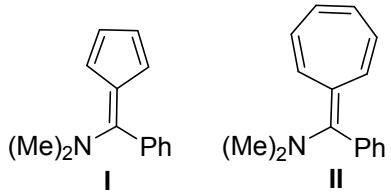


This 3,4-dihydroxybenzaldehyde is used to synthesize piperonal which provides a floral and spicy sweetness to perfumes.

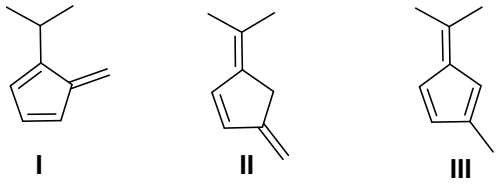
PART- C (3 x 8= 24 Marks)

24. (a) Provide an explanation for each of the following observations:

(i) The amine **II** is more basic than the amine **I**.

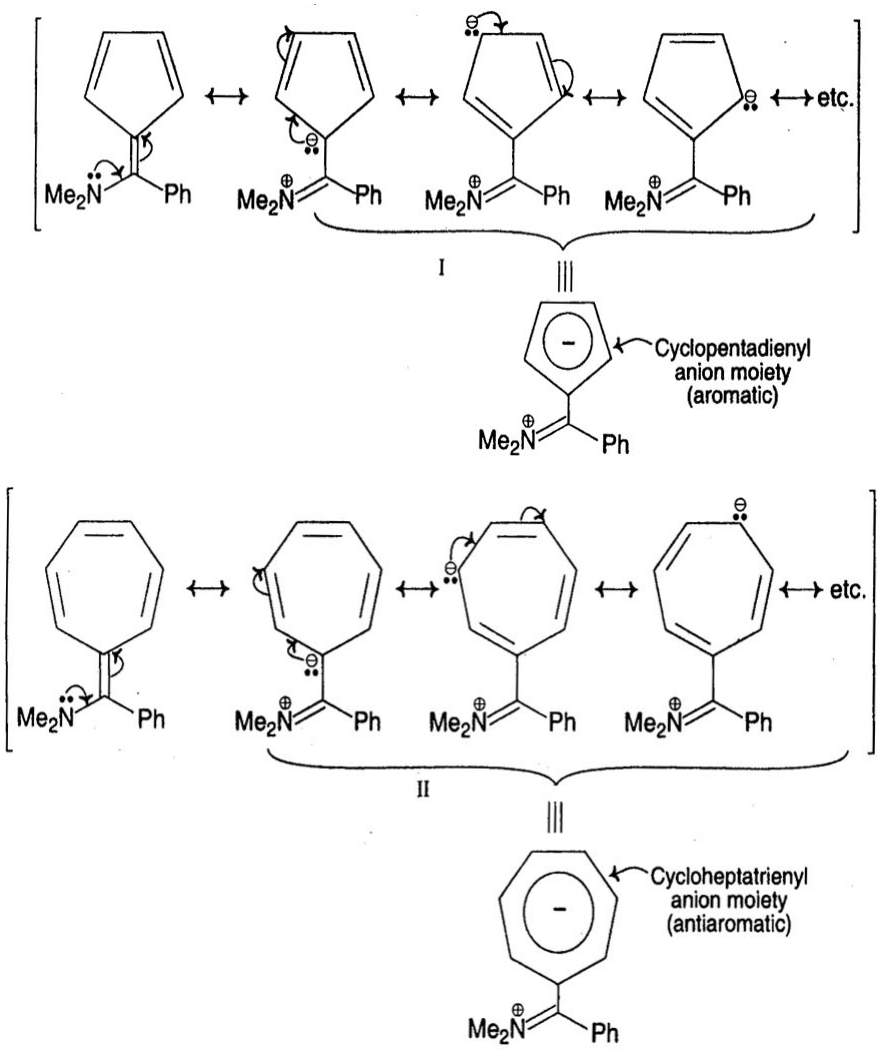


(ii) One of the following hydrocarbons is much more acidic than the others.

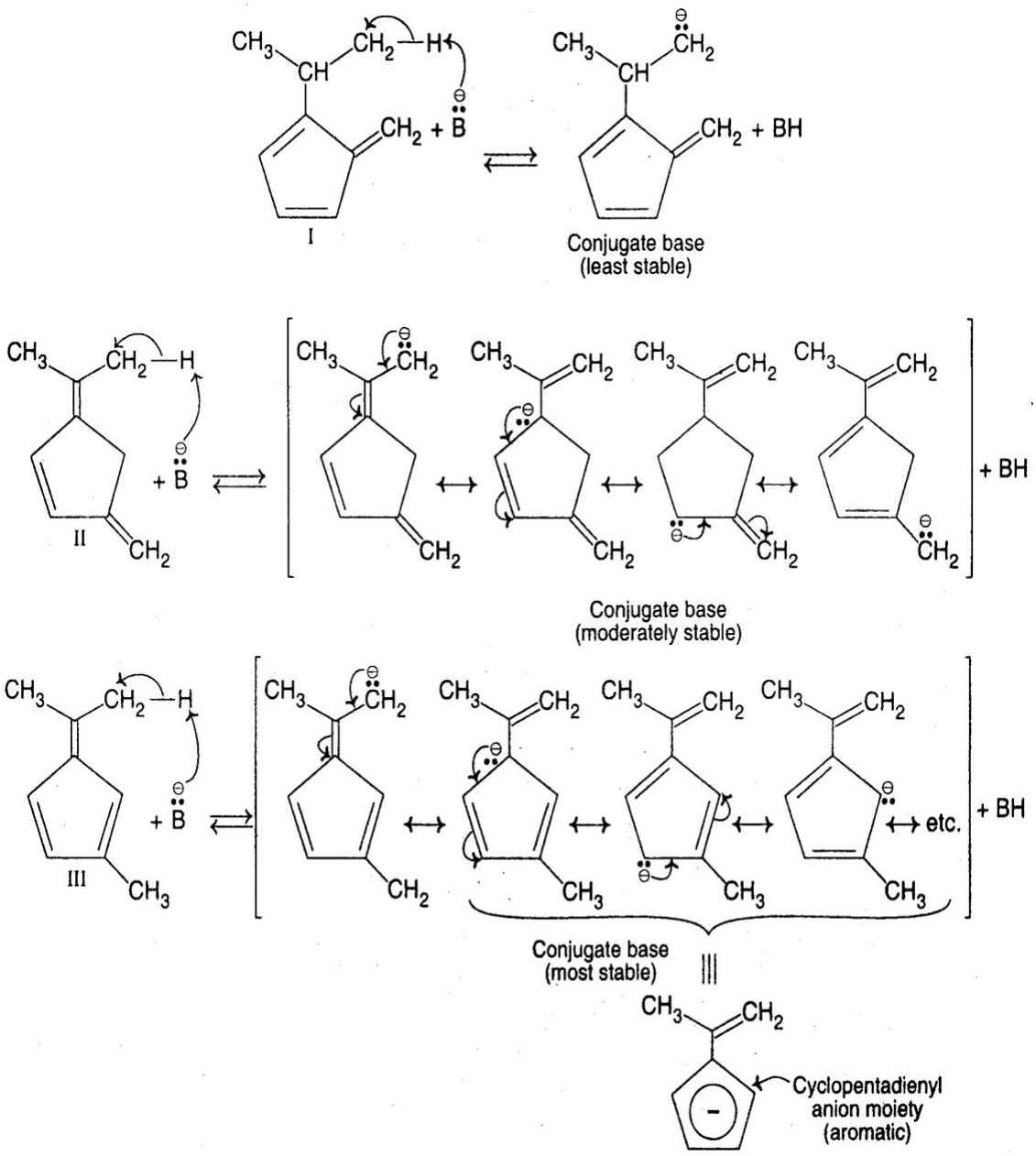


Answer:

(i) The unshared electron pair on nitrogen in the amine **I** is well delocalized because the charge separated structure constitute a stable aromatic system [cyclopentadienyl anion with (4n+2) π electron where n=1]. On the other hand, the unshared electron pair on nitrogen in the amine **II** is not at all delocalized because the charge separated structure constitute an unstable antiaromatic system (cycloheptatrienyl anion with 4nπ electron, where n=2). Therefore, the availability of the lane pair of electrons on nitrogen in **II** is greater than in **I**. Consequently, **II** is more basic than **I**.



(ii) Due to lack of conjugation the conjugate base of the compound **I** is not resonance stabilized. The conjugate base of **II** is resonance-stabilized because the negative charge on carbon is in proper conjugation with the double bonds. The conjugate base of **III** is also resonance-stabilized. However, because of constituting an aromatic system [(4n+2) π, n =1], it is much more stable than either the conjugate base of **I** or the conjugate base of **II**. For this reason, the hydrocarbon **III** is much more acidic than the others.



(Or)

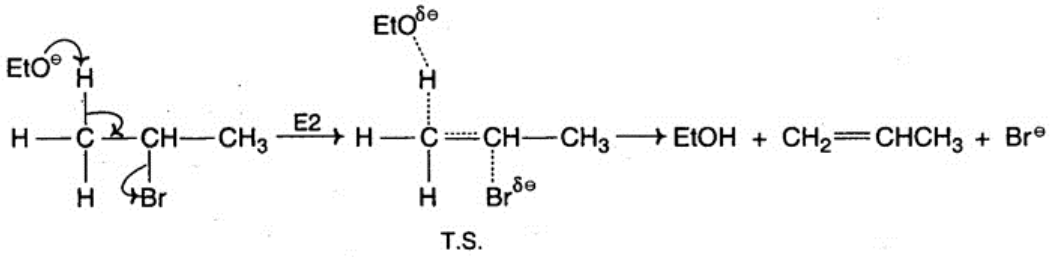
(b) What do you understand by kinetic isotope effect? What are primary and secondary isotope effects? Illustrate these techniques of elucidation of reaction mechanisms with suitable examples.

Answer:

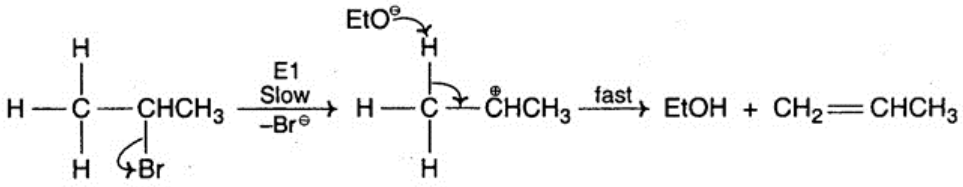
The change in the rate of a reaction observed due to replacement of one isotope of an element for another is called kinetic isotope effect.

A large difference in the rate of a reaction is observed when one of the atoms of a bond that breaks in the rate determining step is replaced by its isotope. This is called primary isotope effect. If a C-H bond breaks in the rate-determining step of a reaction, substitution of D for H results in decrease in reaction rate and that is because a C-D bond is stronger than a C-H bond. For example, the rate of elimination of HBr from 2-bromopropane on treatment with sodium ethoxide has been found to be slowed down when the hydrogens in the methyl group of the alkyl halide are replaced by deuteriums. A large kinetic isotope effect (k_H/k_D = 6.7) is observed. This observation strongly suggests that the rate-determining step of the reaction involves the cleavage of the C-H (or C-D) bond, i.e., the reaction proceeds through the mechanistic pathway **I** and not through the pathway **II**.

Pathway I:



Pathway II:



Deuterium isotope effects have also been observed in reactions in which the C-H bond does not break at all. Such effects are known as secondary isotope effects, secondary because it is a bond other than that carrying the isotope label that is being broken. For example, the rate of solvolysis of tert-butylchloride in 60% aqueous ethanol is found to be faster than the rate of solvolysis of its nonadeuterio analog. The k_H/k_D ratio was found to be 2.32.

$$(CH_3)_3CCl \xrightarrow[k_H]{EtOH/H_2O} (CH_3)_3COEt + (CH_3)_3COH$$

$$(CD_3)_3CCl \xrightarrow[k_D]{EtOH/H_2O} (CD_3)_3COEt + (CD_3)_3COH$$

This secondary isotope effect indicates that the $-CH_3$ (or $-CD_3$) groups by hyperconjugative electron-release stabilize the transition state (of the rate-determining step) which has considerable carbenium ion character. The reaction is thus expected to proceed through the rate-determining formation of tert-butyl cation.

$$(CH_3)_3C{-}Cl \xrightarrow[-Cl^{\ominus}]{Slow} (CH_3)_3C^{\oplus} \xrightarrow{EtOH/H_2O} (CH_3)_3C{-}OEt + (CH_3)_3COH$$
$$S_N1$$

25. (a) Explain the conditions for a compound to be aromatic, non-aromatic and anti aromatic with examples.

Answer:

Aromaticity

Benzene and compounds that resemble benzene in chemical behaviour possess unusual stability. This quality which renders these compounds especially stable is referred to as aromaticity.

Conditions for aromaticity

The necessary conditions for a compound to possess aromatic character (aromaticity) are as follows:

(i) The structure must be cyclic.

(ii) Each atom in the ring must have an unhybridized p orbital.

(iii)These p orbitals must be parallel, so that they can overlap to form a continuous ring of parallel orbitals. In most cases the structure must be planer (or nearly planer) for effective overlap to occur.

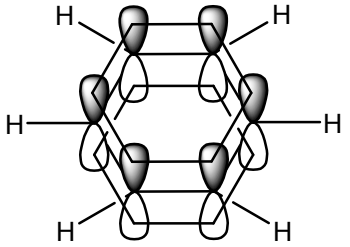
(iv)The overlapping π system must have $(4n + 2)\pi$ electrons, where n = 0,1,2, etc. (Huckel's rule) and therefore all the bonding orbitals must be completely filled.

(v) Delocalization of the π electrons over the ring must lower the electronic energy, i.e., the species must be stabilized by delocalization.

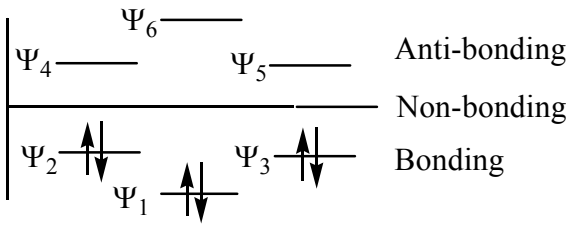
Conditions for antiaromaticity

An antiaromatic compound is one that meets the first three criteria, but the overlapping π system must have 4nπ electrons, where, n=1, 2, 3 etc., and delocalization of the π electrons over the ring must increases the electronic energy, i.e., the species must be destabilized by delocalization.

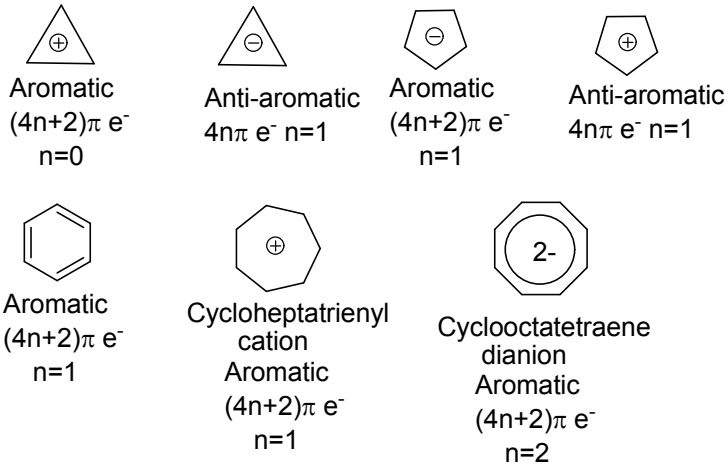
Benzene is the best known example of compounds possessing aromatic character, since this molecule is planer (effective overlap of p orbitals occurs) and it has a closed shell of six π electrons [(4n + 2)π electrons, when n=1], i.e., all the occupied bonding orbitals are completely filled.



Planar benzene molecule



Molecular orbitals of benzene

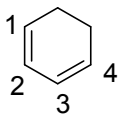


Cyclobutadiene is an example of antiaromatic compound, since this molecule is planer (effective overlap of p orbitals occurs) and it has a closed shell of four π electrons i.e., 4nπ electrons, where n=1.

Cyclobutadiene
4π electrons system:
antiaromatic

Conditions for nonaromaticity

A cyclic compound that does not have a continuous, overlapping ring of p orbitals is said to be nonaromatic (or aliphatic). 1,3-Cyclohexadiene is an example of nonaromatic compound.



1,3-Cyclohexadiene

Cyclopentadienyl
radical

[A (4n + 2)π electron system that have a continuous ring of p orbitals is also nonaromatic if overlapping of orbitals is inhibited due to nonplanarity.]

Modern definition of aromaticity

The modern definition of aromaticity is the ability to sustain an induced ring current by a planer or nearly planer cyclic system with (4n+2) delocalized π electrons, where n = 0, 1, 2, 3.....etc.

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 an NMR spectrum depends on the electron density of its bond; the greater the electron density of the electron cloud surrounding or partially surrounding a proton, the more upfield is its chemical shift (a lower value of δ).

However, this rule has several exceptions; one is for protons in the vicinity of an aromatic ring. When an external magnetic field is imposed upon an aromatic ring (as in

an NMR instrument), 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 **Fig. 1**, this induced field curves around and in the area of the proton is parallel to the external field, so the field 'seen' by the aromatic proton is greater than it would have been in the absence of diamagnetic ring current. The protons are moved downfield (to higher δ) compared to where they would be if electron density were the only factor. Thus ordinary alkene hydrogens are found at ~5-6 δ, which the hydrogens of benzene rings are located at about ~7-8 δ.

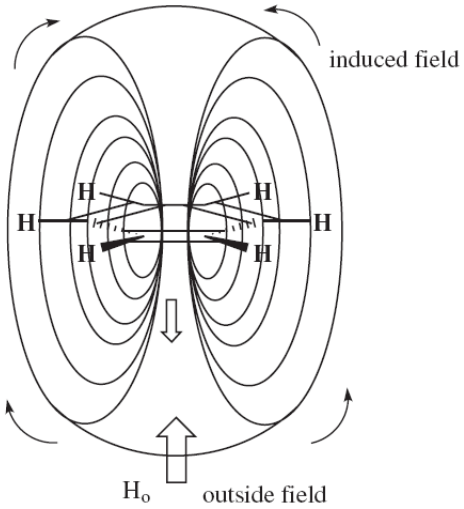


Fig. 1. Ring current in benzene.

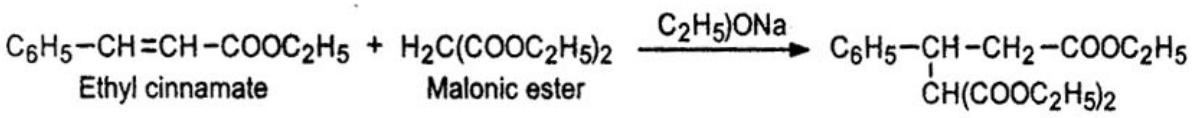
It follows that aromaticity can be determined from an NMR spectrum. If the protons attached to the ring are shifted downfield from the normal alkene region, we can conclude that the molecule is diatropic, and hence aromatic. In addition, if the compound has protons above or within the ring, then if the compound is diatropic, these will be shifted upfield. One drawback to this method is that it cannot be applied to compounds that have no protons in either category, for example, the dianion of squaric acid.

(Or)

(b) Explain the Michael addition reaction with mechanism and application.

Answer:

The base-catalysed addition of compounds having active methylene group (or relatively acidic hydrogens) to an activated olefinic bond of the type –C=C–Z (Z = electron–withdrawing) is classified as Michael reaction.



The compounds having an active methylene group or having relatively acidic hydrogens are called *donors* and the compounds having an activated olefinic bond are called *acceptors*. A large variety of donors and acceptors are employed in Michael reaction.

The donors include malonic ester, cyanoacetic ester, acetoacetic ester, phenylacetic acid ester, cyanoacetamide, aliphatic nitro compounds, benzyl cyanide, sulphones, cyclopentadienes, indenes, fluorenes, etc.

The acceptors include (a) Aldehydes, e.g., acraldehyde, CH_2=CH–CHO; cinnamaldehyde, C_6H_5CH=CHCHO.

(b) Ketones, e.g., benzylideneacetone, C_6H_5CH=CHCOCH$_3$; mesityloxide, $(CH_3)_2$C = CHCOCH$_3$; quinones, etc.

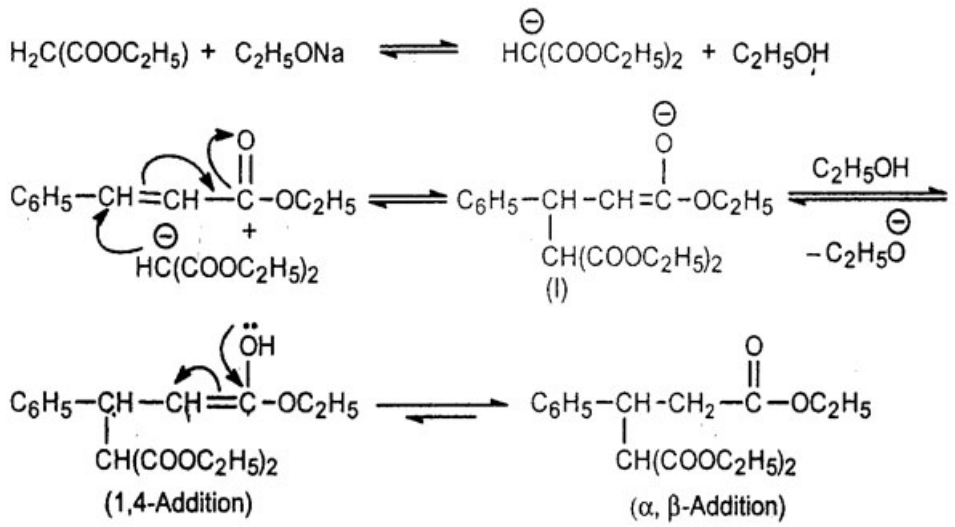
(c) Nitriles, e.g., acrylonitrile, CH_2=CH-CN.

(d) Esters of α, β-unsaturated acids, e.g., C_6H_5-CH=CH-COOC$_2$H$_5$.

Various types of basic catalysts are used. Most commonly used are alkali metal alkoxides, such as sodium or potassium ethoxides, potassium tertiary butoxide, potassium isopropoxide, etc. Mild basic catalysts such as 2° amines, 3° amines, piperidine and pyridine have been used with success.

Mechanism

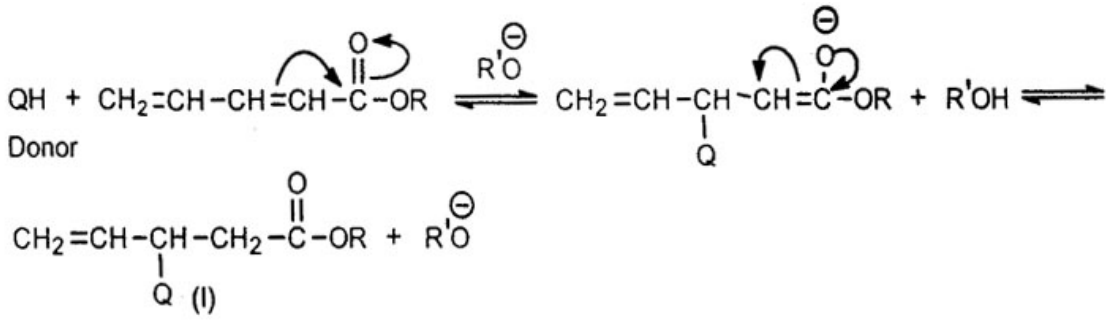
The base generates a carbanion from the donor, malonic ester. The carbanion then adds to the β-carbon of the α, β-unsaturated ester acceptor, ethyl cinnamate to yield the anion (I) which takes up a proton form alcohol to produce an enol. The enol then tautomerises to the more stable product, ketone.



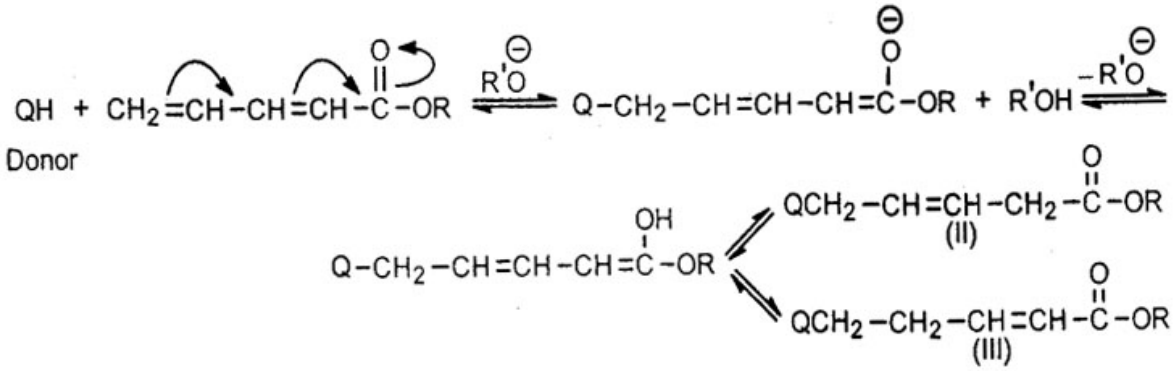
The electron-attracting group -$COOC_2H_5$ (Z) facilitates the attack by stabilizing the intermediate anion (I) by dispersal of the charge. It is seen that although 1,4-addition occurs initially, the final result is addition to the α, β-unsaturated carbons. This is because the enol reverts to the more stable ketone (recall that vinyl alcohol is unknown). In the presence of strong base, the product may undergo cyclisation. No cyclisation occurs with mild bases such as 2° or 3° amines and piperidine.

Compounds with two double bonds in conjugation with the electron-withdrawing group may undergo nucleophilic attack at β-carbon or δ-carbon to give three products. Thus:

(a) On attack at β-carbon



(b) On attack at δ-carbon



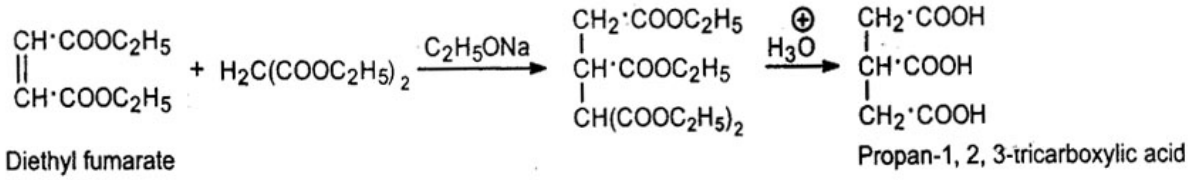
Since the double bond is conjugated in (III), it is the most stable of the three products. Hence it is the predominant product.

Applications

The reaction is of great synthetic importance since a variety of organic compounds can be synthesized with the help of this reaction.

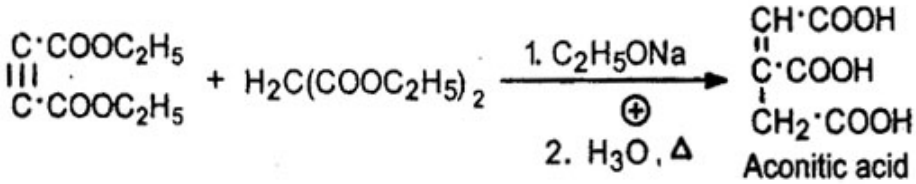
1. Synthesis of polybasic acids

(a) Tricarboxylic acids



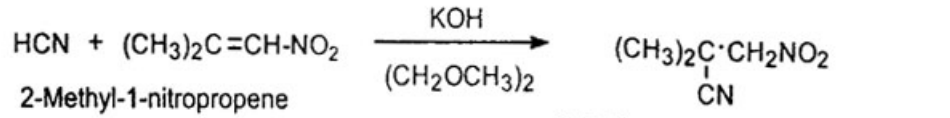
Esters of tricarboxylic acids are used as plasticisers.

(b) Aconitic acid



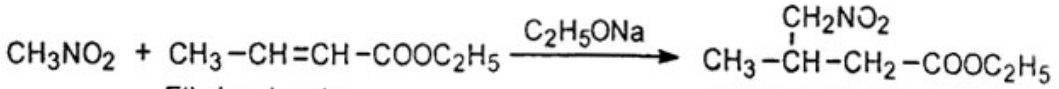
Aconitic acid is used in the preparation of medicines for relieving pain (analgesic) and reducing fever (febrifuge). Its esters are used as plasticisers.

2. Preparation of cyano and nitro compounds



2-Methyl-1-nitropropene

2, 2-Dimethyl-3-nitropropanonitrile.

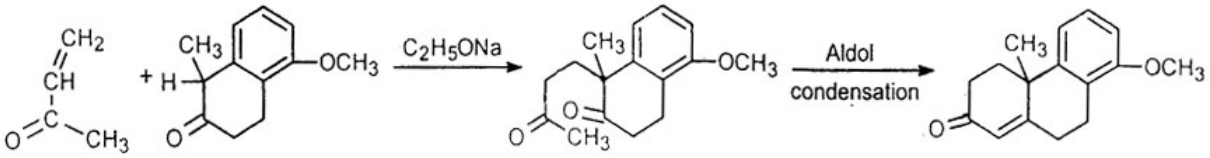


Ethyl crotonate

Ethyl 3-methyl-4-nitrobutyrate

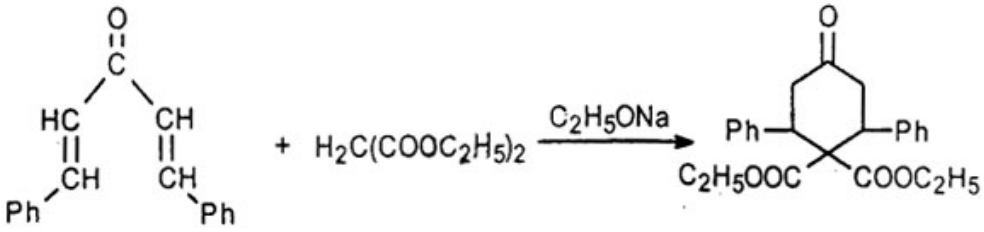
3. **Building of ring system**

(a) Condensed alicyclic ring

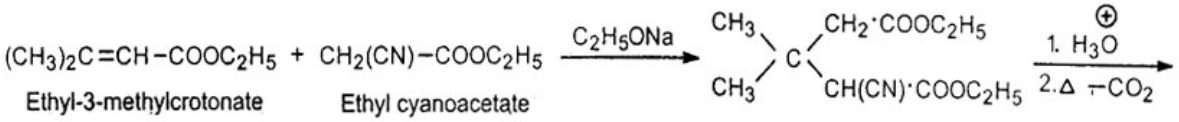


This method has been employed during the synthesis of cholesterol to build the ring system.

(b) Double Michael addition for ring formation

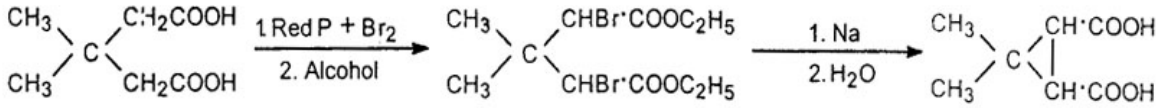


(c) Cyclopropane derivative-Caronic acid



Ethyl-3-methylcrotonate

Ethyl cyanoacetate

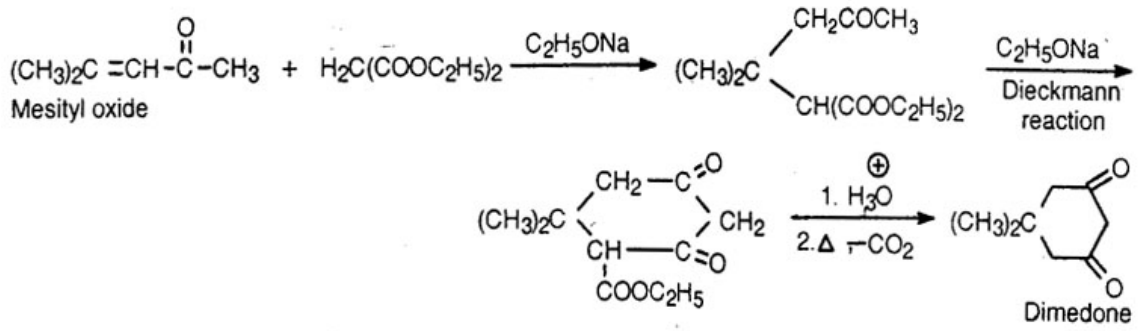


β, β-Dimethyl glutaric acid

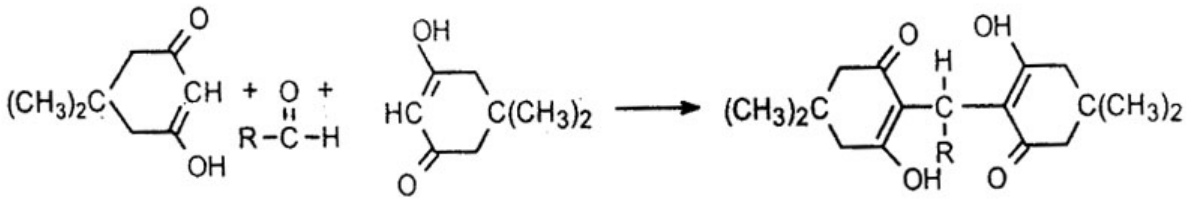
Caronic acid

4. **Synthesis of dimedone**

Dimedone is a reagent for the identification of aldehydes in the presence of ketones.

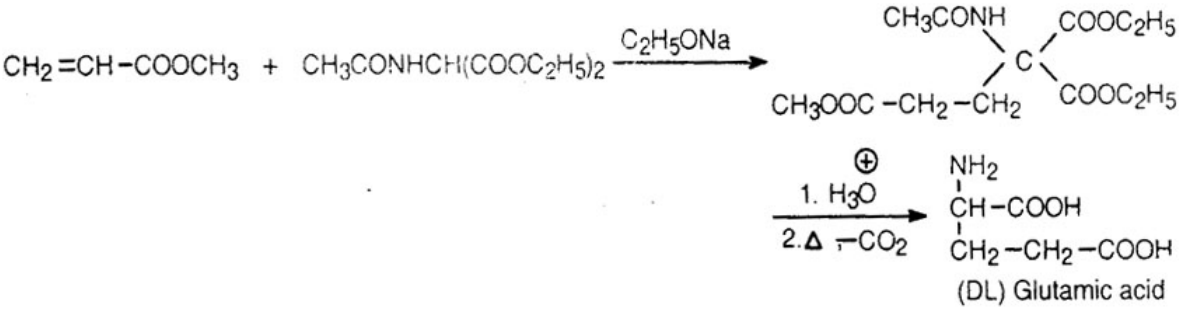


Dimedone is also employed for the separation of aldehydes from ketones because it reacts only with aldehydes.



Reaction with formaldehyde is quantitative and hence, the reagent is used for the quantitative estimation of formaldehyde.

5. Synthesis of amino acids



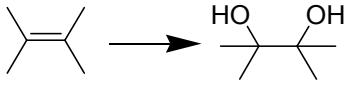
Michael reaction has been employed to synthesize anthracene from naphthalene.

26. (a) Give an account on i) Hydroxylation ii) Epoxidation.

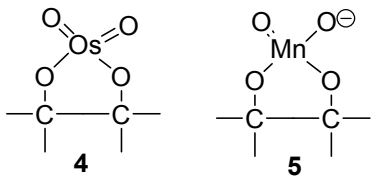
Answer:

(i) **Hydroxylation (Addition of Oxygen, Oxygen)**

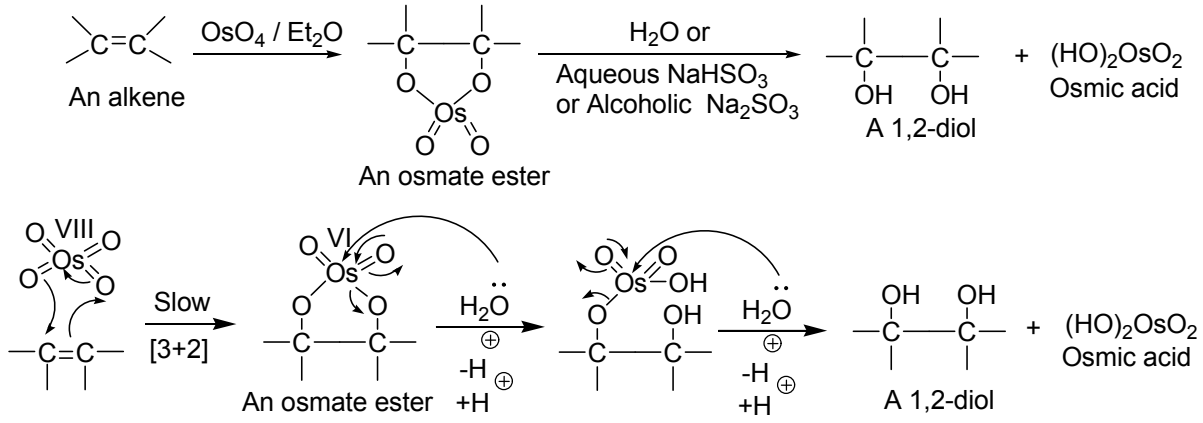
Dihydroxy-addition



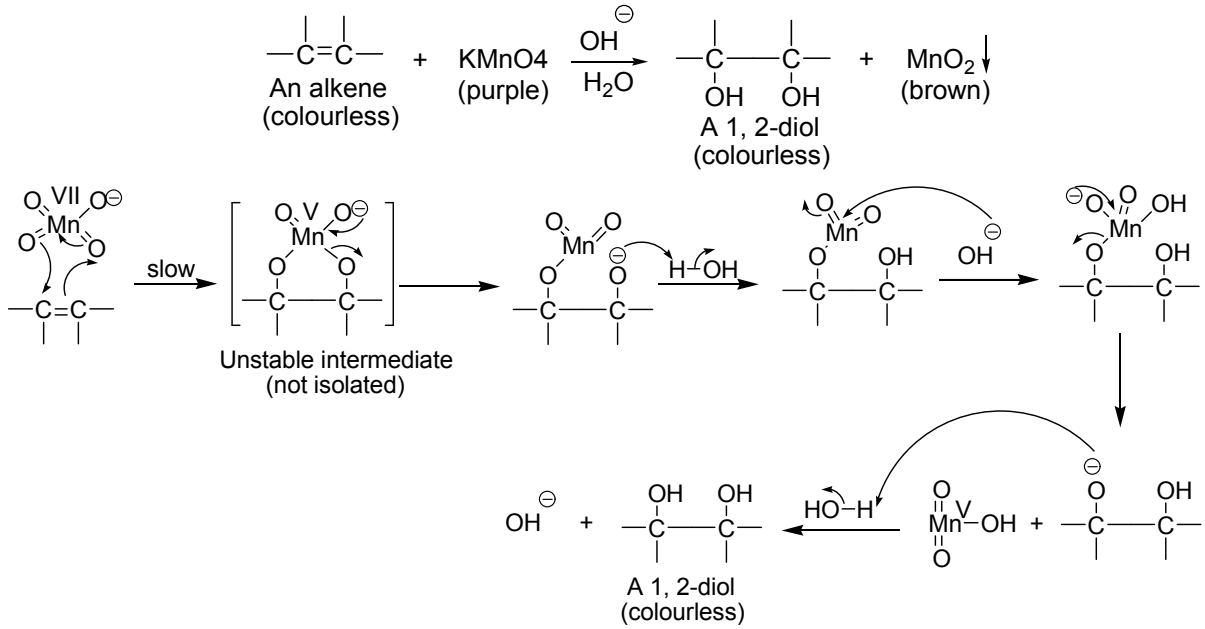
There are many reagents that add two OH groups to a double bond. The most common are OsO_4 and alkaline KMnO4, which give syn addition from the less-hindered side of the double bond. Less substituted double bonds are oxidized more rapidly than more substituted alkenes. Permanganate adds to alkenes to form an intermediate manganate ester (**5**), which is decomposed under alkaline conditions. Bases catalyze the decomposition of **5** by coordinating with the ester. Osmium tetroxide adds rather slowly but almost quantitatively to form a cyclic ester, such as **4**, as an intermediate, which can be isolated, but is usually decomposed solution, with sodium sulfite in ethanol or other reagents. The chief drawback to the use of OsO_4 is expensive and highly toxic, but the reaction is made catalytic in OsO_4 by using *N*-methylmorpholine-*N*-oxide (NMO), *tert*-butyl hydroperoxide in alkaline solution, H_2O_2, peroxyacid, flavin and TEAA, $K_3Fe(CN)_6$ and non-heme iron catalysts. Polymer-bound OsO_4, and encapsulated OsO_4 have been shown to give the diol in the presence of NMO, as well as OsO_4^{2-} on an ion exchange resin. Dihydroxylation has also been reported in ionic liquids, and with fluorous osmium tetroxide. A catalytic amount of K_2OsO_4 with a Cinchona alkaloid on a ordered inorganic support, in the presence of $K_3Fe(CN)_6$, gives the cis-diol. Oxidation of pent-4-en-1-ol to valerolactone was accomplished with Oxone and a catalytic amount of OsO_4 in DMF.



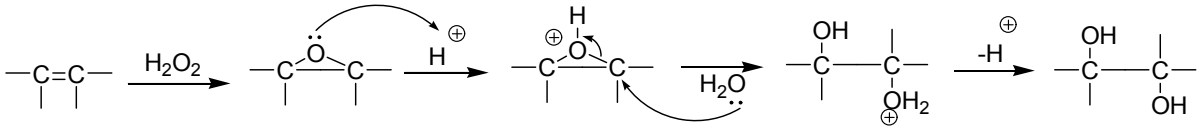
4 **5**



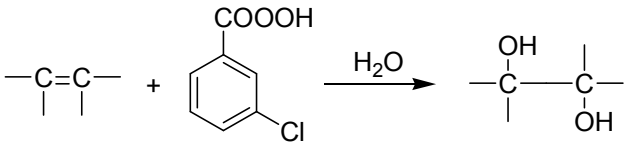
The end-product of the reaction of either potassium permanganate or osmium tetroxide under the conditions described above is a 1,2-diol. Potassium permanganate is a strong oxidizing agent and can oxidize the glycol product. In acid and neutral solution it always does so; hence glycols must be prepared with alkaline permanganate, but the conditions must be mild. Even so, yields are seldom >50%, although they can be improved with phase-transfer catalysis or increased stirring. The use of ultrasound with permanganate dihydroxylation has resulted in good yields of the diol. There is evidence that cyclic esters (**5**) are intermediates for OsO_4 dihydroxylation. This reaction is the basis of the *Baeyer test* for the presence of double bonds. The oxidation is compatible with a number of functional groups, including trichloroacetamides.



Anti hydroxylation can be achieved by treatment with H_2O_2 and formic acid. In this case, epoxidation occurs first, followed by an S_N2 reaction, which results in overall anti addition:



The same result can be achieved in one step with *m*-chloroperoxybenzoic acid and water.

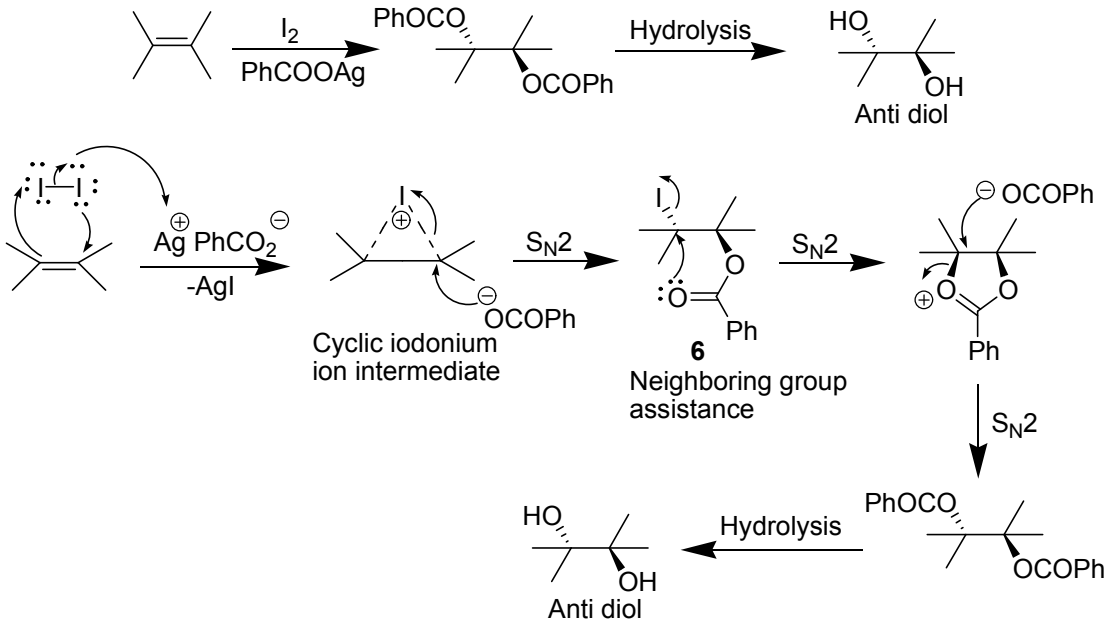


Anti diol

Overall anti addition can also be achieved by the method of Prevost (the *Prevost reaction*).

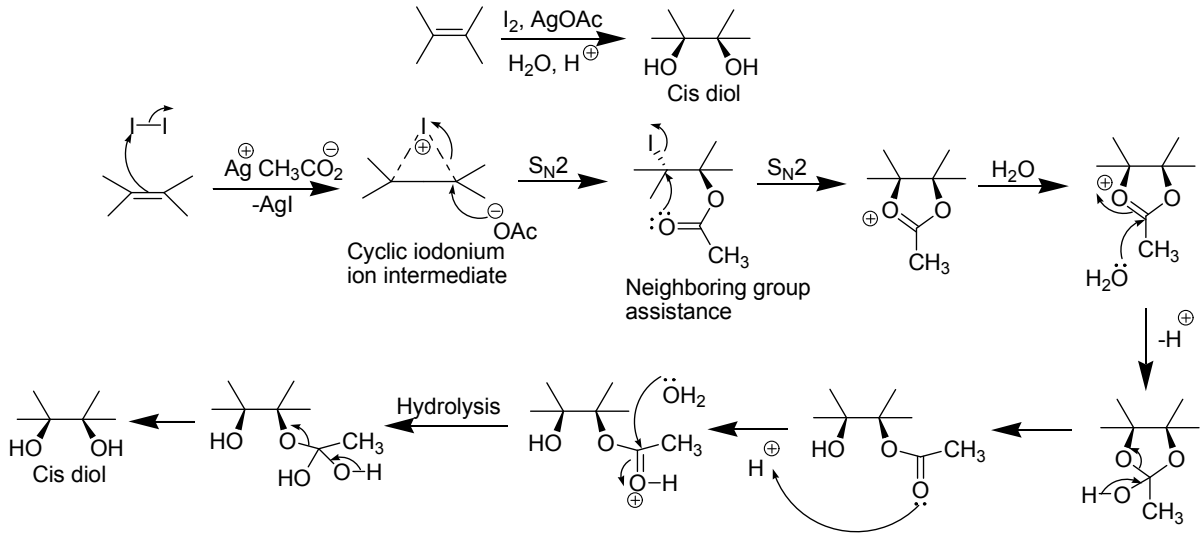
Prevost anti hydroxylation

In this method, the alkene is treated with iodine and silver benzoate in a 1:2 molar ratio. The initial addition is anti and results in a β-halo benzoate (**6**). These can be isolated, and this represents a method of addition of IOCOPh. However, under the normal reaction conditions, the iodine is replaced by a second PhCOO group. This is a nucleophilic substitution reaction, and it operates by the neighboring-group mechanism, so the groups are still anti:

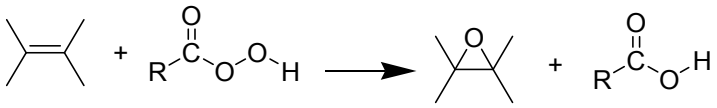


Woodward's cis (or) syn hydroxylation

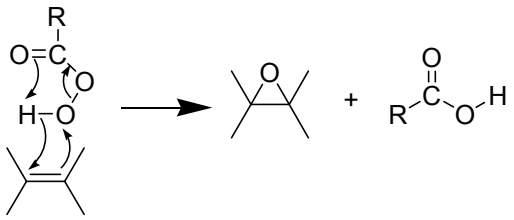
The alkene is treated with iodine and silver acetate in a 1:1 molar ratio in acetic acid containing water. Here again, the initial product is a β-halo ester; the addition is anti and a nucleophilic replacement of the iodine occurs. However, in the presence of water, neighboring-group participation is prevented or greatly decreased by solvation of the ester function, and the mechanism is the normal S_N2 process, so the monoacetate is syn and hydrolysis gives the glycol that is the product of overall syn addition. Although the Woodward method results in overall syn addition, the product may be different from that with OsO_4 or $KMnO_4$, since the overall syn process is from the more-hindered side of the alkene. Both the Prevost and the Woodward methods have also been carried out in high yields with thallium (I) acetate and thallium (I) benzoate instead of the silver carboxylates. Note that cyclic sulfates can be prepared from alkenes by reaction with PhIO and SO_3.DMF.



(ii) **Epoxidation**



Alkenes can be epoxidized with many peroxyacids, of which *m*-chloroperoxybenzoic has been the most often used. The reaction, called the *Prilezhaev reaction*, has wide utility. Alkyl, aryl, hydroxyl, ester, and other groups may be present, although not amino groups, since these are affected by the reagent. Electron-donating groups increase the rate, and the reaction is particularly rapid with tetraalkyl alkenes. Conditions are mild and yields are high. Other peroxyacids, especially peroxyacetic and peroxybenzoic, are also used; trifluoroperoxyacetic acid and 3,5-dinitroperoxybenzoic acid are particularly reactive ones. Transition metal catalysts can facilitate epoxidation of alkenes at low temperatures or with alkenes that may otherwise react sluggishly. Magnesium monoperoxyphthalate (MMPP) is commercially available, and has been shown to be a good substitute for *m*-chloroperoxybenzoic acid in a number of reactions.



7

The one-step mechanism involving a transition state, such as 7, was proposed by Bartlett:

Evidence for this concerted mechanism is as follows:

(1) The reaction is second order. If ionization were the rate-determining step, it would be first order in peroxyacid.

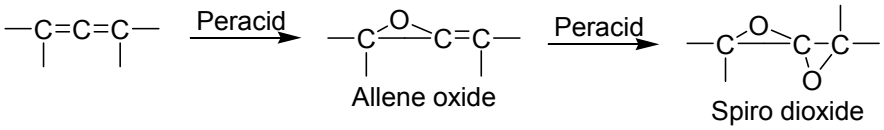
(2) The reaction readily takes place in nonpolar solvents, where formation of ions is inhibited.

(3) Measurements of the effect on the reaction rate of changes in the substrate structure show that there is no carbocation character in the transition state.

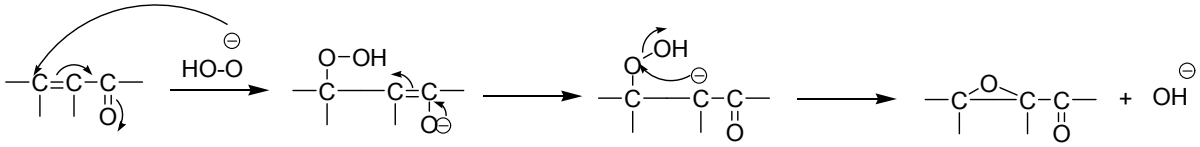
(4) The addition is stereospecific (i.e., a trans-alkene gives a trans-epoxide and a cis-alkene a cis epoxide) even in cases where electron-donating substituents would stabilize a hypothetical carbocation intermediate.

However, where there is an OH group in the allylic or homoallylic position, the stereospecificity diminishes or disappears, with both cis and trans isomers giving predominantly or exclusively the product where the incoming oxygen is syn to the OH group. This probably indicates a transition state in which there is hydrogen bonding between the OH group and the peroxy acid.

Conjugated dienes can be epoxidized (1,2-addition), though the reaction is slower than for corresponding alkenes, but α,β-unsaturated ketones do not generally give epoxides when treated with peracids. However, α,β-unsaturated esters react normally to give glycidic esters. When a carbonyl group is in the molecule but not conjugated with the double bond, the Baeyer-Villiger oxidation may compete. Allenes are converted by peracids to allene oxides or spiro dioxides both of which species can in certain cases be isolated but more often are unstable under the reaction conditions and react further to give other products.



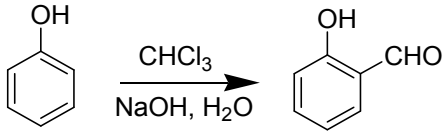
The epoxidation of α,β-unsaturated ketones with hydrogen peroxide under basic conditions is known as the *Waits–Scheffer epoxidation*, discovered in 1921. This fundamental reaction has been extended to α,β -unsaturated ketones (including quinones), aldehydes, and sulfones. This is a nucleophilic addition by a Michael-type mechanism, involving attack by HO_2^-.



(Or)

(b) (i) Explain Gattermann and Gattermann Koch reactions with mechanism.

(ii) Explain the mechanism of the following reaction.



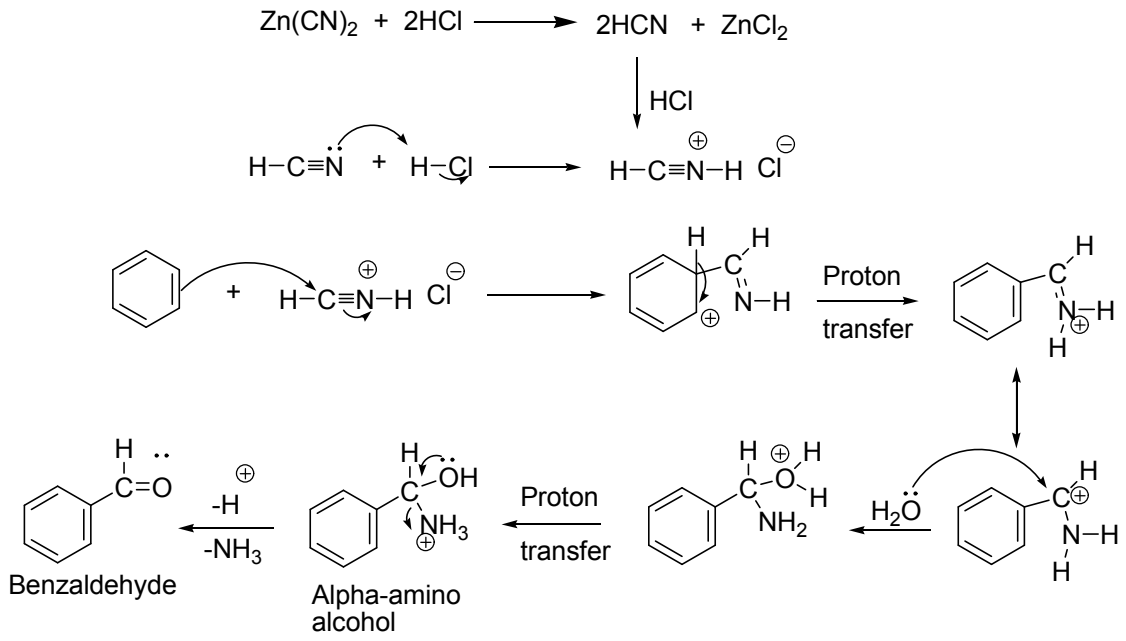
Answer:

(i) **Gattermann reaction**

Formylation with $Zn(CN)_2$ and HCl is called the *Gattermann reaction*. It can be applied to alkylbenzenes, phenols and their ethers, and many heterocyclic compounds. However, it cannot be applied to aromatic amines. In the original version of this reaction the substrate was treated with HCN, HCl, and $ZnCl_2$, but the use of $Zn(CN)_2$ and HCl (HCN and $ZnCl_2$ are generated *in situ*) makes the reaction more convenient to carry out and yields are not diminished.

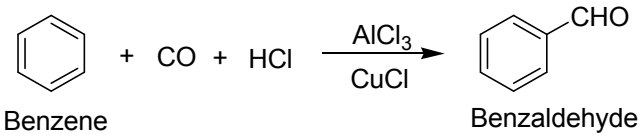
The mechanism of the Gattermann reaction has not been investigated very much, but it is known that an initially formed but not isolated nitrogen-containing product is hydrolyzed to aldehyde. This product is presumed to be $ArCH=NH_2^+Cl^-$, as shown. When benzene was treated with NaCN under superacid conditions (F_3CSO_2OH-SbF_5), a good yield of product was obtained, leading to the conclusion that the electrophile in this case was $^+C(H)=N^+H_2$.

Mechanism

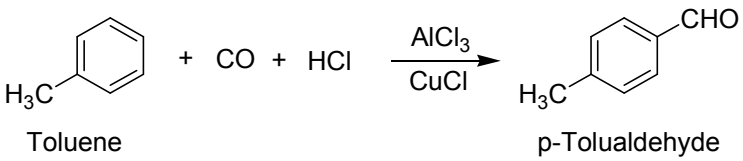


Gattermann–Koch reaction

Formylation of benzene and alkylbenzene with carbonmonoxide (CO) and hydrogen chloride (HCl) in the presence of aluminium chloride ($AlCl_3$) and cuprous chloride (CuCl) is known as the Gattermann-Koch reaction.



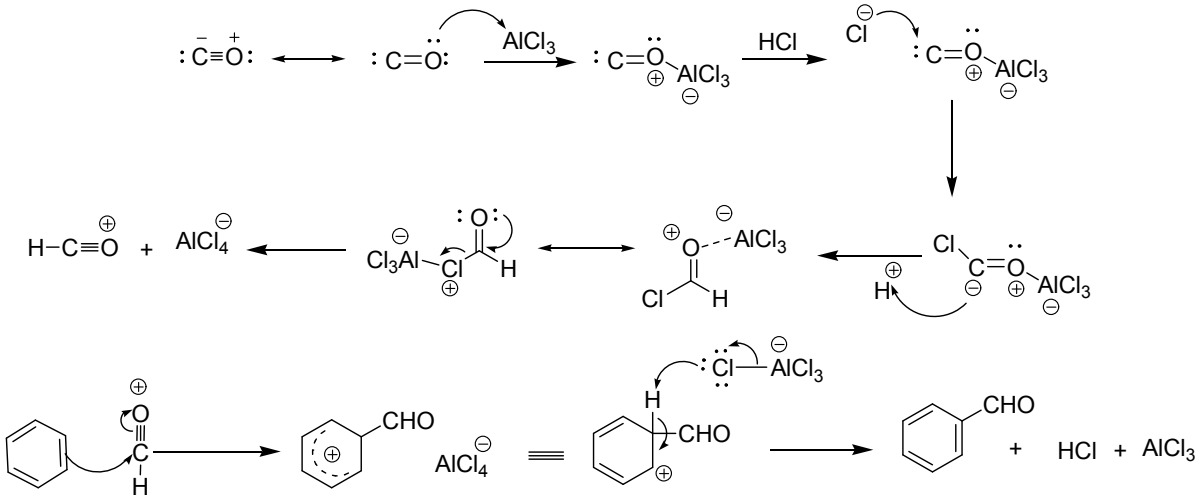
Usually, nitrobenzene or ether is used as solvent. In the case of alkylbenzene, the aldehyde group is introduced into the para position only. This method is used industrially to prepare arylaldehydes.



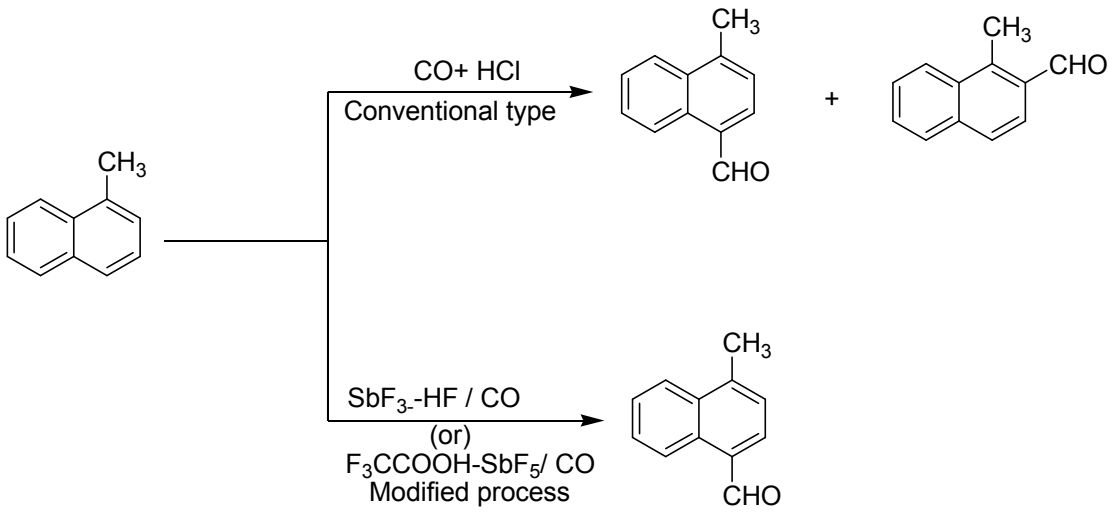
The Gattermann-Koch aldehyde synthesis is not applicable to phenols or their ethers, amino aromatic species and also when the aromatic ring is strongly deactivated (nitrobenzene).

Mechanism

The Gattermann-Koch formylation is considered as a typical elelctrophilic aromatic substitution with high para regioselectivity .The most likely electrophile is the acylium ion [H-$^{+}$C=O] in the ion pair [HCO]$^{+}$ [AlCl4]$^{-}$. Common factors such as electron density of the aromatic substrate, reactivity of electrophile, stability of reaction intermediates, and steric factors may influence the regioselectivity.

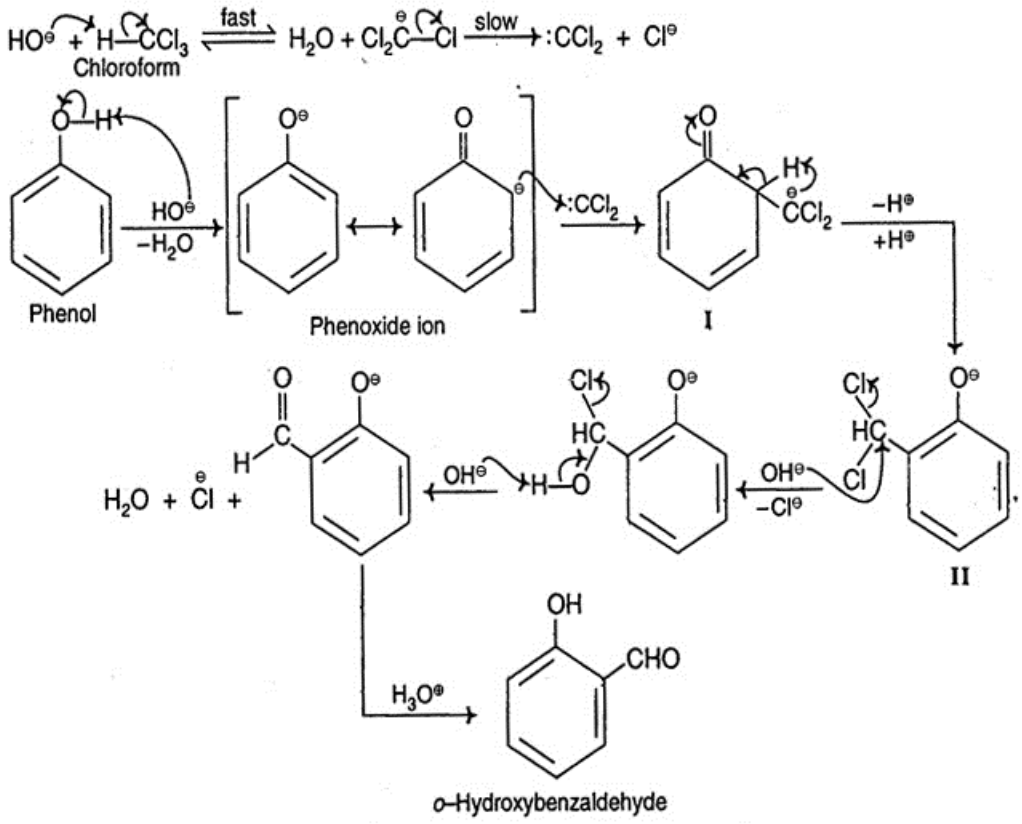


Application



(ii) **Mechanism**

The mechanism of the reaction involves electrophilic substitution on the highly reactive phenoxide ring by dichlorocarbene, $:CCl_2$, the electrophilic reagent generated from chloroform by the action of alkali through an α-elimination reaction. The mechanistic pathway of the reaction may be sketched as follows:



The highly electrophilic dichlorocarbene attacks the activated ortho-position of the phenoxide ring to form an unstable intermediate (I) which by a proton-shift is converted into a phenoxide ion containing a dichloromethyl group (II). Alkaline hydrolysis of the resulting dichloro compound followed by acidification gives the corresponding aldehyde (salicylaldehyde). The para-isomer is obtained through a similar pathway.

Reg. No.....

KARPAGAM ACADEMY OF HIGHER EDUCATION

(Deemed University Established Under Section 3 of UGC Act 1956)

COIMBATORE-641 021

(For the candidates admitted from 2017 & onwards)

PG DEGREE EXAMINATION, OCTOBER 2017

FIRST SEMESTER

INTERNAL TEST-II

CHEMISTRY

ORGANIC CHEMISTRY-I (Reaction Mechanisms)

Time: 2 hours **Maximum: 50 marks**
Date: 23-10-2017 (AN) **Subject code: 17CHP101**

PART- A (20 x 1=20 Marks)
Answer All the Questions

1. The Kolbe reaction is a
a) addition reaction b) elimination reaction
c) coupling reaction d) substitution reaction
2. Conversion of an amide to a heterocyclic system using $POCl_3$ is called
a) Gattermann reaction b) Jacobson reaction
c) Bischler-Napieralski reaction d) Kolbe reaction
3. When HCl salts of arylalkylamines are heated at 200-300°C, migration occurs is called as
a) Hunsdiecker synthesis b) Gattermann reaction
c) Hofmann-Martius reaction d) Reimer-Tiemann reaction
4. The enamine reaction water is eliminated by
a) azeotropic distillation with benzene b) steam distillation with benzene
c) vaccum distillation d) chromatography separation
5. The conversion of R-CH=CH–CH_2–OH in presence of $SOCl_2$ to give R-CH=CH–CH_2–Cl in dry ether involves the mechanism of
a) S_Ni b) S_N1 c) S_N2 d) SE2
6. In nucleophilic substitution reactions, highly reactive halide ion is
a) F^- b) Cl^- c) Br^- d) I^-
7. CN^- is an example for
a) powerful nucleophile b) weak nucleophile
c) ambident nucleophile d) powerful electrophile
8. Meisenheimer salts are formed in which of the following mechanisms
a) S_NAr b) S_N1 c) S_N2 d) benzyne
9. Amination of pyridine with an alkali metal amide ($NaNH_2$ or KNH_2) is called the
a) Wittig reaction b) Chichibabin reaction c) Zeigler reaction d) Darzen reaction
10. Chlorobenzene when treated with KNH_2 in liquid NH_3 produces aniline is known as
a) Benzyne mehanism b) Chichibabin reaction
c) Zeigler reaction d) Claisen rearrangement
11. S_Ni mechanism gives
a) racemised of configuration b) retention of configuration
c) inversion of configuration d) no stereochemistry involved
12. The reaction in which solvent act as a nucleophilic reagent is known as
a) solvolysis b) hydrolysis c) ozonolysis d) hydrogenation
13. Carbenes are
a) carbocation intermediate b) neutral intermediates
c) carbanion intermediate d) free radical intermediate
14. Chugaev reaction is the conversion of
a) xanthate to olefin b) amine oxide to olefin
c) carboxylic ester to olefin d) quaternary ammonium hydroxide to olefin
15. In the singlet carbene two electrons are
a) spin free b) parallel c) spin paired d) unpaired
16. The cleavage of amine oxides to produce an alkene and hydroxylamine is called
a) Chugaev reaction b) Cope reaction c) Hofmann reaction d) Sayteff rule
17. Not possible to introduce a double bond at bridgehead position in bridged bicyclic compounds with small rings this is called
a) Bredt's rule b) Saytzeff rule c) Hofmann rule d) Chugaev reaction
18. The neutral substrate (alkyl halides and sulphonates) possessing two different types of β-hydrogen yielding predominantly the more highly substituted alkene is known as
a) Bredt's rule b) Saytzeff rule c) Hofmann rule d) Chugaev reaction

19. Hoffman exhaustive methylation process which is widely used for structure determination is extremely useful in the

a) Steroids b) proteins c) terpenoids d) alkaloids

20. Nitrene is a

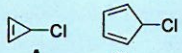
a) monovalent electrophilic species b) monovalent nucleophilic species

c) divalent electrophilic species d) divalent nucleophilic species

PART- B (3 x 2= 6 Marks)
Answer All the Questions

21. β-keto acids undergo decayboxylation faster why.

22 Explain why the compound **A** undergoes solvolysis in ethanol more readily than the compound **B**.



A B

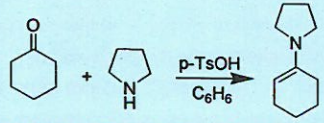
23. What is the Hofmann elimination reaction?

PART- C (3 x 8= 24 Marks)
Answer All the Questions

24. (a) Write a note on Friedel Crafts alkylation and acylation. Compare their advantages and limitations.

(Or)

(b) (i) Write the mechanism of the following conversion.

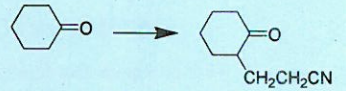


(ii) Show how would you carry out each of the following transformations by way of an enamine (Stork enamine reaction).

(a)

(b)

(c)



25. (a) (i) Discuss the Benzyne mechanism for the aromatic nucleophilic substitution reaction. Mention the evidences for this mechanism.

(ii) What is Chichibabin reaction?

(Or)

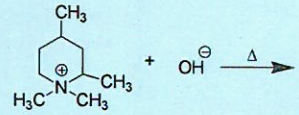
(b) (i) Write notes on neighboring group participation.

(ii) Explain the ambident substrates.

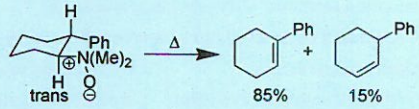
26. (a) Write the structure, generation and reactions of carbenes and nitrenes.

(Or)

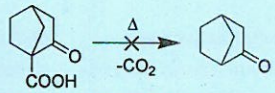
(b) (i) Give the structure of the major product of the following reactions and explain its formation.



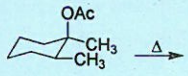
(ii) Explain the following observation:



(iii) Explain why this β-keto acid does not readily undergo decarboxylation.



(iv) Predict the major product and suggest a mechanism of the following reaction:



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FIRST SEMESTER

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PART- A (20 x 1=20 Marks)

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a) addition reaction b) elimination reaction

c) coupling reaction d) substitution reaction

Answer: c) coupling reaction

2. Conversion of an amide to a heterocyclic system using $POCl_3$ is called

a) Gattermann reaction b) Jacobson reaction

c) Bischler-Napieralski reaction d) Kolbe reaction

Answer: c) Bischler-Napieralski reaction

3. When HCl salts of arylalkylamines are heated at 200-300°C, migration occurs is called as

a) Hunsdiecker synthesis b) Gattermann reaction

c) Hofmann-Martius reaction d) Reimer-Tiemann reaction

Answer: c) Hofmann-Martius reaction

4. The enamine reaction water is eliminated by

a) azeotropic distillation with benzene b) steam distillation with benzene

c) vacuum distillation d) chromatography separation

Answer: a) azeotropic distillation with benzene

5. The conversion of R-CH=CH–CH_2–OH in presence of $SOCl_2$ to give R-CH=CH–CH_2 –Cl in dry ether involves the mechanism of

a) S_Ni b) S_N1 c) S_N2 d) SE2

Answer: a) S_Ni

6. In nucleophilic substitution reactions, highly reactive halide ion is

a) F^- b) Cl^- c) Br^- d) I^-

Answer: d) I^-

7. CN^- is an example for

a) powerful nucleophile b) weak nucleophile

c) ambident nucleophile d) powerful electrophile

Answer: c) ambident nucleophile

8. Meisenheimer salts are formed in which of the following mechanisms

a) S_NAr b) S_N1 c) S_N2 d) benzyne

Answer: a) S_NAr

9. Amination of pyridine with an alkali metal amide ($NaNH_2$ or KNH_2) is called the

a) Wittig reaction b) Chichibabin reaction c) Zeigler reaction d) Darzen reaction

Answer: b) Chichibabin reaction

10. Chlorobenzene when treated with KNH_2 in liquid NH_3 produces aniline is known as

a) Benzyne mehanism b) Chichibabin reaction

c) Zeigler reaction d) Claisen rearrangement

Answer: a) Benzyne mehanism

11. S_Ni mechanism gives

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Answer: b) retention of configuration

12. The reaction in which solvent act as a nucleophilic reagent is known as

a) solvolysis b) hydrolysis c) ozonolysis d) hydrogenation

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14. Chugaev reaction is the conversion of

a) xanthate to olefin b) amine oxide to olefin

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Answer: a) xanthate to olefin

15. In the singlet carbene two electrons are

a) spin free b) parallel c) spin paired d) unpaired

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16. The cleavage of amine oxides to produce an alkene and hydroxylamine is called

a) Chugaev reaction b) Cope reaction c) Hofmann reaction d) Sayteff rule

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17. Not possible to introduce a double bond at bridgehead position in bridged bicyclic compounds with small rings this is called

a) Bredt's rule b) Saytzeff rule c) Hofmann rule d) Chugaev reaction

Answer: a) Bredt's rule

18. The neutral substrate (alkyl halides and sulphonates) possessing two different types of β-hydrogen yielding predominantly the more highly substituted alkene is known as

a) Bredt's rule b) Saytzeff rule c) Hofmann rule d) Chugaev reaction

Answer: b) Saytzeff rule

19. Hoffman exhaustive methylation process which is widely used for structure determination is extremely useful in the

a) Steroids b) proteins c) terpenoids d) alkaloids

Answer: d) alkaloids

20. Nitrene is a

a) monovalent electrophilic species b) monovalent nucleophilic species

c) divalent electrophilic species d) divalent nucleophilic species

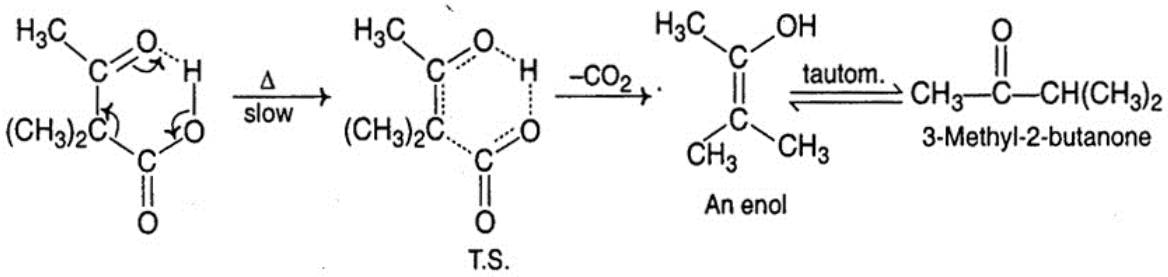
Answer: d) divalent nucleophilic species

PART- B (3 x 2= 6 Marks)

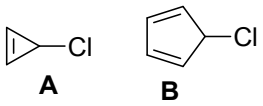
21. β-keto acids undergo decayboxylation faster why.

Answer:

The decarboxylation of a β-keto acid proceeds via a six membered cyclic transition state and the decarboxylation is promoted by the incipient proton transfer to the keto group through hydrogen bonding. The first formed product is an enol which readily tautomerizes to the more stable keto form. For example, the decarboxylation of 2,2–dimethyl-3-oxobutanoic acid. $CH_3COC(CH_3)_2COOH$ may be shown as follows.

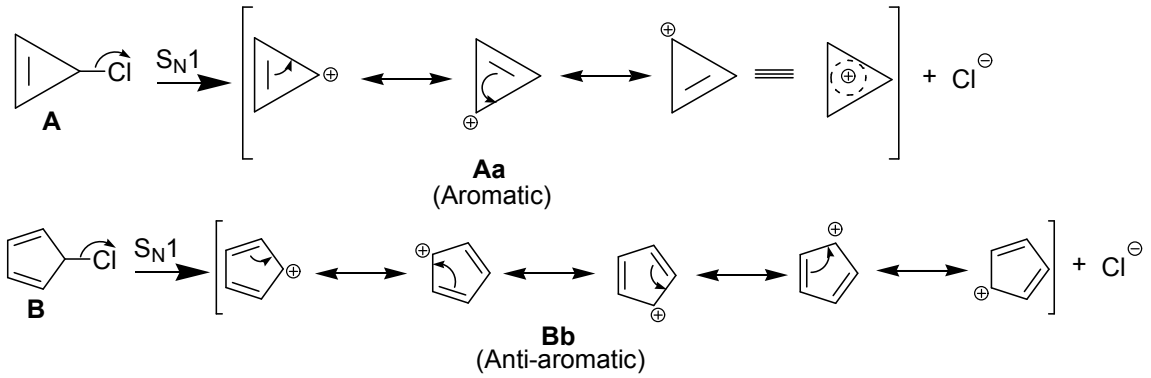


22 Explain why the compound **A** undergoes solvolysis in ethanol more readily than the compound **B**.



Answer:

The compound **A** on ionization produces a carbocation which is aromatic [(4n + 2) π electron system, where n=0]. The compound **B** on ionization produces a carbocation which is antiaromatic (a 4nπ electron system, where n = 1).

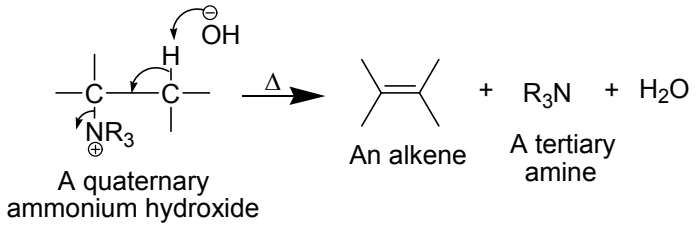


Therefore, the increasing order of stability of the resulting carbocations is: (least stable) **B** < **A** (most stable). Since, the S_N1 reactivity depends on the stability of the intermediate carbocation, the order of increasing S_N1 reactivity of these compounds is: **B** < **A.**

23. What is the Hofmann elimination reaction?

Answer:

The Hofmann elimination is a specific E2 reaction in which a quaternary ammonium hydroxide undergoes thermal decomposition to yield an alkene, a tertiary amine, and water.



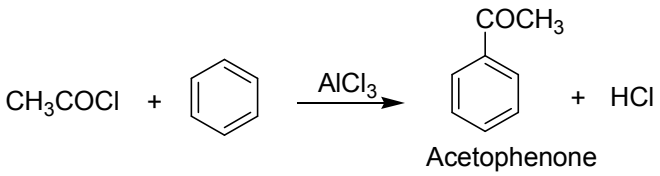
PART- C (3 x 8= 24 Marks)

24. (a) Write a note on Friedel Crafts alkylation and acylation. Compare their advantages and limitations.

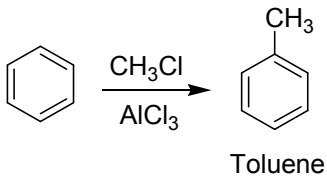
Answer:

Friedel-Crafts reaction

Friedel-Crafts reaction involves the introduction of an alkyl or acyl group into the benzene ring by using a Lewis acid as a catalyst, e.g., acetophenone can be obtained by the Friedel-Crafts acylation of benzene with CH_3COCl and $AlCl_3$,



and toluene can be obtained from benzene by Friedel-Crafts alkylation of benzene with CH_3Cl and $AlCl_3$.



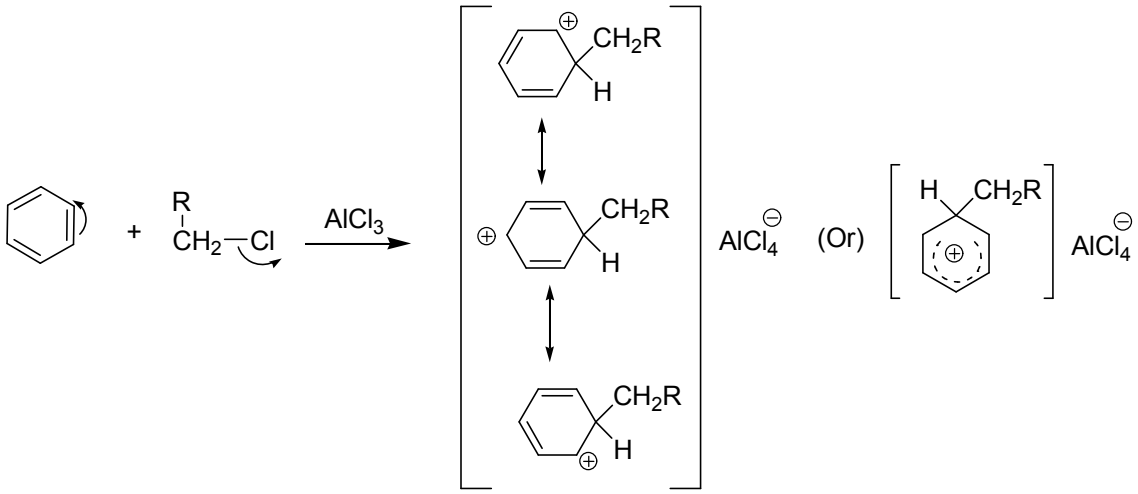
Friedel-Crafts Alkylation reactions:

Aliphatic compounds which can be used as alkylating agents are alkyl halides, alcohols, ethers, esters, olefins, aldehydes and ketones. Reactions of the first four classes of compounds are usually catalysed by Lewis acid and those of the later three are catalysed by protonic acids.

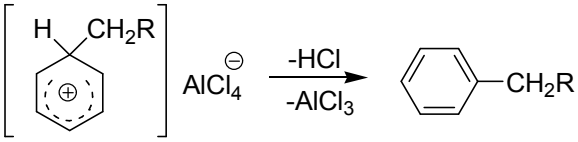
For alkylation, commonly used reagents are alkyl halides and commonly used catalyst is $AlCl_3$.

The reaction of benzene with primary and secondary alkyl halides occurs by the S_N2 mechanism in which nucleophilic attack by benzene on the aliphatic carbon is aided by the removal of halide ion by the Lewis acid (step 2).

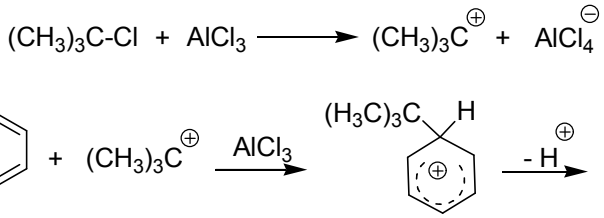
Step 1:



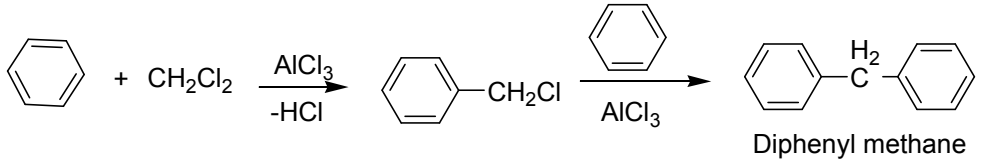
Step 2:

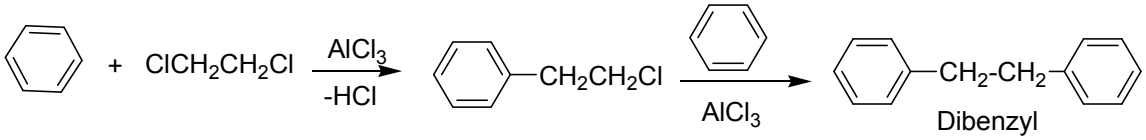


In the case of *t*-alkyl halides, alkylation occurs by S_N1 mechanism, since the *t*-carbonium ion is more stable, e.g.,

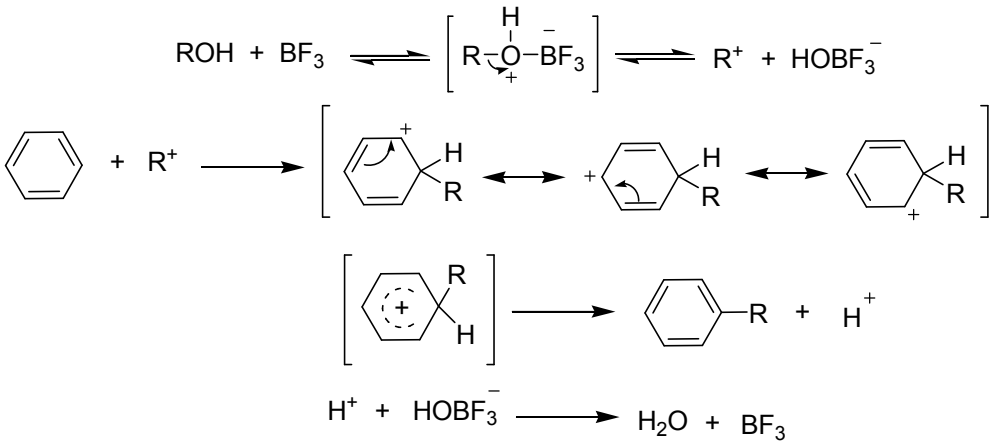


The use of di- and polyhalides leads to successive alkylation, e.g., benzene reacts with CH_2Cl_2 and ethylene dichloride in the presence of $AlCl_3$ to give diphenyl methane and dibenzyl, respectively.

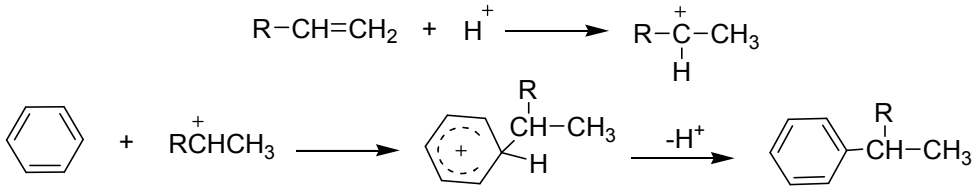




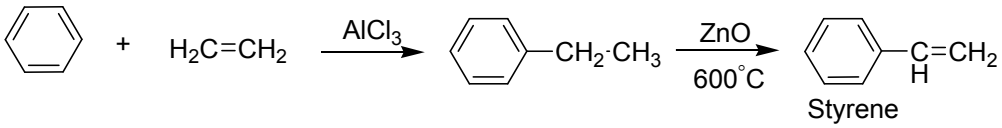
Alcohols, ethers and esters also react in a manner similar to halides:



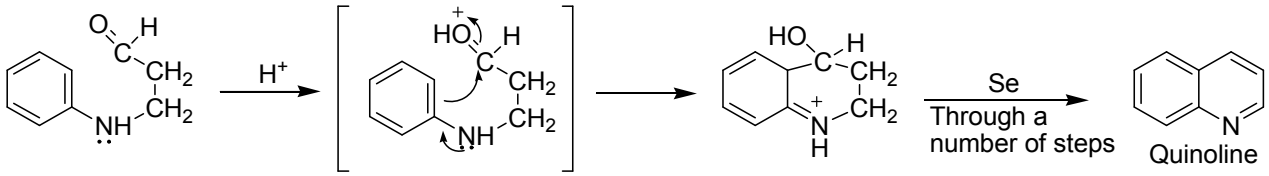
In the presence of protonic acids, olefins react via carbonium ions, which they form with protonic acids.



A commercially important compound, styrene can be prepared by alkylation of benzene using ethylene as alkylating agent in the presence of $AlCl_3$ to give ethyl benzene which on dehydrogenation with zinc oxide at 600°C gives styrene.

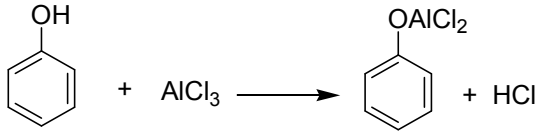


Aldehydes and ketones, in the presence of protonic acids can also act as alkylating agents but the reaction does not complete favourably with acid catalysed self-condensation of these carbonyl compounds except when alkylation is intramolecular and stereochemically favoured, e.g., the **Skraup's synthesis** of quinoline involves the acid catalysed intramolecular alkylation.



It should be noted that Friedel-Crafts alkylation reactions are rendered difficult when the benzene nucleus is highly activated or highly deactivated and smooth reaction occurs in the case of benzene or compounds of comparable reactivity. Thus whereas chlorobenzene can undergo alkylation reactions, nitrobenzene is inert and is often used as a solvent.

Phenols react very slowly and unsatisfactorily because they react with Lewis acid to give complex compounds, which are only slightly soluble in the reaction medium.



Similar is the case of amines, which also form complex with the catalyst and, therefore, are not suitable for alkylation. However, if the phenols and amines are first acetylated, alkylation reaction can successfully be carried out at low temperatures.

The choice of a suitable catalyst is also very important. The primary halides require a stronger catalyst such as $AlCl_3$ whereas tert. Alkyl halides need only a mild catalyst like $FeCl_3$. It is better to use milder catalysts because strong catalysts may bring about several other changes such as isomerization, etc.

The alkylation reactions with compounds such as alcohols can be catalysed both by protonic as well as Lewis acid and amongst them, BF_3 is the reagent of choice because of its strong tendency to form a complex with oxygen.

The order catalytic activity of various Lewis acids is as follows:

$$AlBr_3 > AlCl_3 > GaCl_3 > FeCl_3 > SbCl_3 > ZrCl_4 > SnCl_4 > BCl_3 > BF_3$$

The protonic acids used as catalysts are HF, H_2SO_4 and phosphoric acid. Sulphuric acid is generally not used because of its high sulphonation capacity rather than its catalysing effect.

The most common solvents for Friedel-Crafts reaction are carbon disulphide, nitrobenzene, etc.

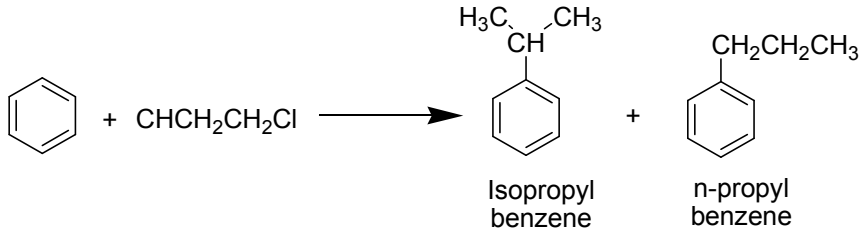
The overall reaction, however, depends upon the nature of the substrate, the reagent and the experimental conditions.

Limitations of Alkylation reactions

Since alkyl group are activating groups, the product of alkylation is more reactive than the starting material and therefore, further alkylation of the alkylated product inevitably occurs. For example, alkylation of benzene with CH_3Cl and $AlCl_3$ gives a mixture of mono- di and poly-methyl benzenes. So it is very difficult to get

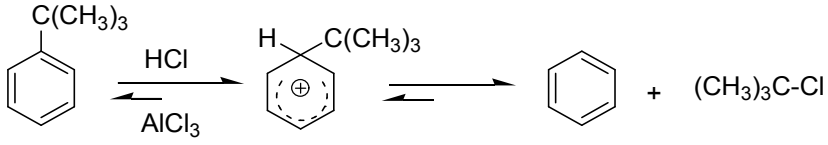
monosubstituted product as a result of alkylation reactions. In order to get a monoalkyalated product, an excess of the aromatic compound must be used.

Another important synthetic limitation of Friedel-Crafts alkylation is that the electrophilic reagent generally undergoes a rearrangement. For example, benzene when heated with n-propyl chloride, gives isopropyl benzene as the major product along with a small amount of the expected product, *n*-propyl benzene.

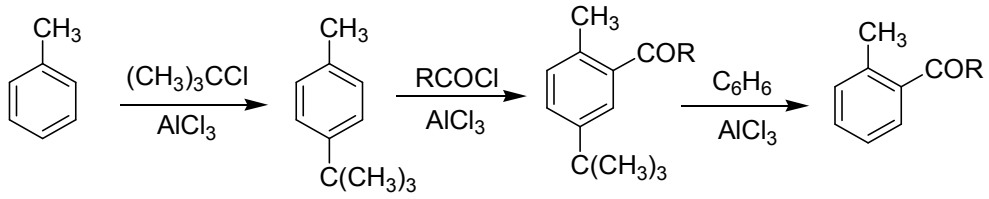


Rearrangement usually occurs in the order primary→ secondary→ tertiary, owing to the greater stability of the tertiary carbonium ion.

Just as tertiary alkyl groups are more readily introduced in the benzene nucleus, they are also very easily removed by the reverse reaction.

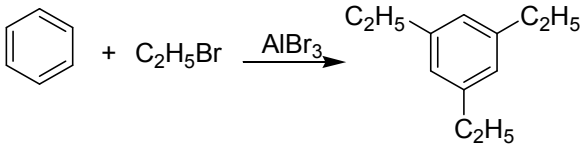


The *t*-butyl group can thus be used to protect the most reactive positions in a given compound in order to effect reaction elsewhere, as it can be easily removed by addition of excess of benzene which shift the equilibrium towards right. Thus ortho acyl toluene can be obtained by first protecting the *p*-position by *t*-butyl group followed by acylation and the removal of *t*-butyl group.



Further, since alkylation is a reversible process, the reaction is thermodynamically controlled. For example, a monosustituted benzene gives mainly the meta-alkyl

derivatives because of its greater thermodynamic stability than that of the ortho/para isomer. Thus excess of ethyl bromide in the presence of $AlBr_3$ reacts with benzene to give 1, 3, 5-triethyl benzene.

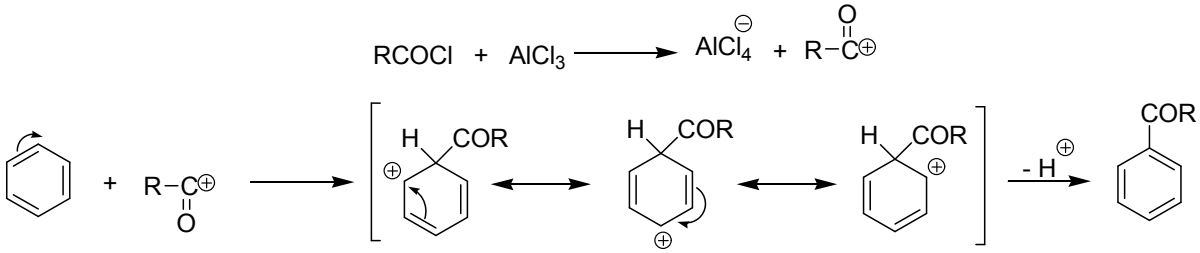


Friedel-Crafts acylation reactions

The acylation of aromatic rings can be brought about by an acid chloride or anhydride in the presence of an Lewis acid. Two mechanisms have been suggested for acylation reactions.

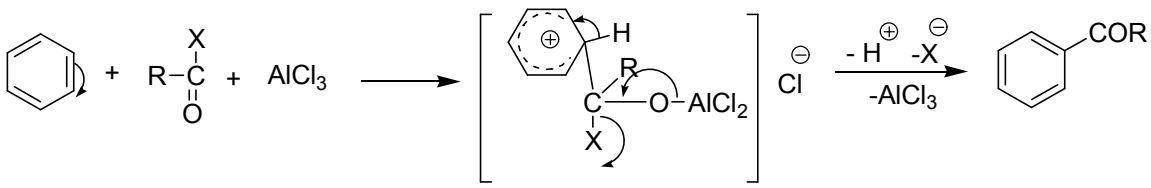
a) Ionic mechanism

The Lewis acid ionizes the acyl chloride to give the acylium cation which then reacts with aromatic compound to give the product by a mechanism analogous to that of alkylation.

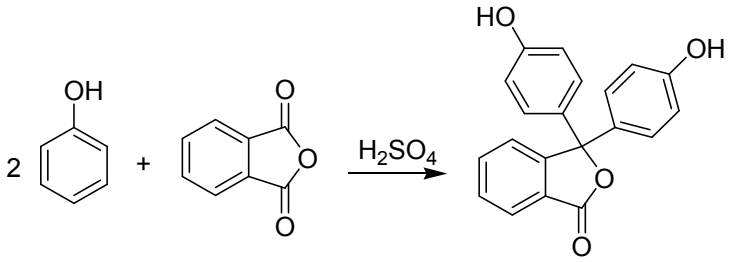


b) Substitution mechanism

In this mechanism, the alkylating agent is polarized through oxygen, thereby enhancing the activity of the carbonyl carbon to nucleophilic reaction.



The aromatic compound which can be alkylated can also be acylated. Deactivated molecules such as benzaldehyde, benzonitrile and nitrobenzene are inert to such an extent that nitrobenzene is often used as solvent for Friedel-Crafts reactions. For reactive compounds such as phenols the reaction can be carried out either at a low temperature or by using an acid as the condensing catalyst to get the required product, e.g., the formation of phenolphthalein from phenol.



Friedel-Crafts reaction of pyridine is difficult whereas thiophene, furan etc. can be alkylated or acylated to give the α-derivatives, when a weak catalyst likes $SnCl_4$ is used. The reason for the unreactivity of pyridine is the same as that for no acylation of nitro-benzene.

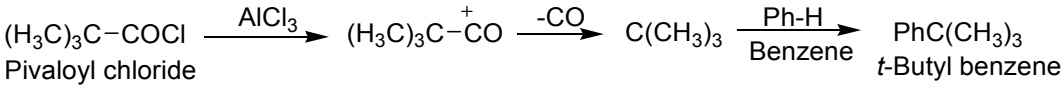
Advantages of acylation over alkylation reactions

Since the acylation product (acyl derivatives) is less reactive than the starting material, poly substitution, commonly observed in alkylation reactions, is obscure in this case. Therefore, the monoalkyl derivatives can be obtained in a better yield by Friedel-Crafts acylation since the resulting keto compound can be conveniently reduced to give the alkyl derivative.

The alkylation reactions do not require stochiometric quantities of the Lewis acid, since it is regenerated in the last step but in acylation reactions, greater amounts of catalyst (more than molar amounts) are needed because the resulting ketone combines with the Lewis acid to form a complex.

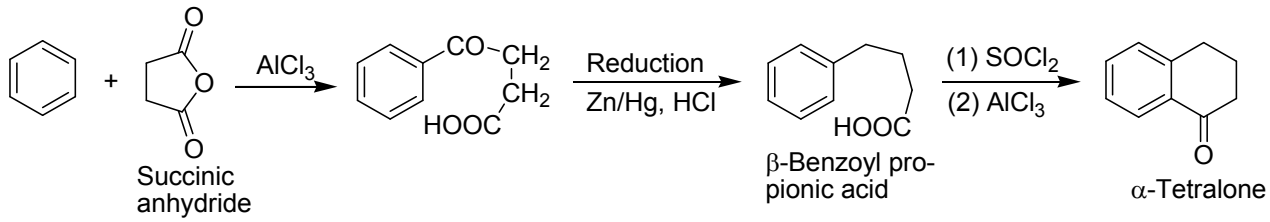
In acylation reactions, the rearrangement and isomerization, so characteristic of Friedel- Crafts alkylation, do not occur.

In spite of all these advantages of acylation over alkylation, there is one disadvantage also. When the acylation reaction is carried out with tertiary acid chlorides, unexpected alkylation takes place. For example, benzene, when treated with pivaloyl chloride, gives *t*-butyl benzene.

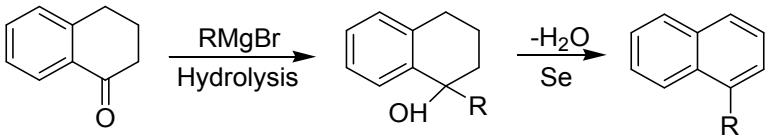


Further, since the complex of the acylation agent and Lewis acid is bulky, ortho and para directing monosubstituted benzene gives very little of the ortho product. For example, toluene, which gives 60% of ortho derivative on nitration, gives negligible amount of *o*-methyl acetophenone on acylation and the *p*-isomer is obtained in over 85% yield.

Intermolecular Friedel-Crafts acylations are of great value in building up cyclic systems, dibasic acid anhydrides are widely used in these reactions, e.g.,

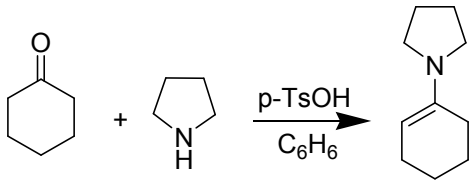


α-Tetralone can be utilized for obtaining substituted naphthalene.



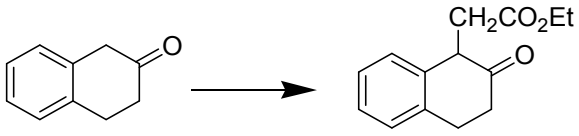
(Or)

(b) (i) Write the mechanism of the following conversion.

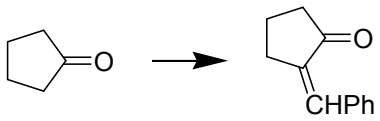


(ii) Show how would you carry out each of the following transformations by way of an enamine (Stork enamine reaction).

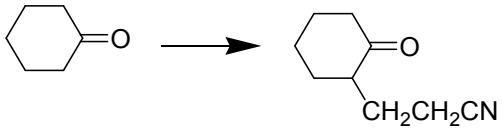
(a)



(b)

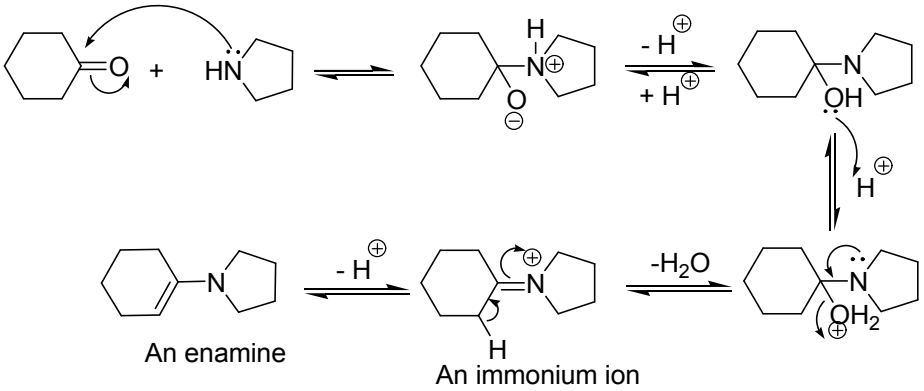


(c)

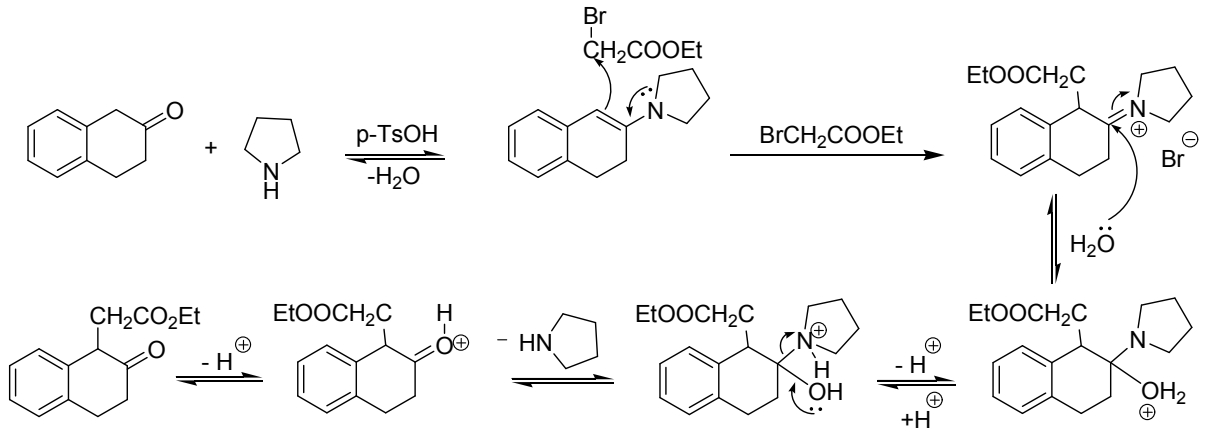


Answer:

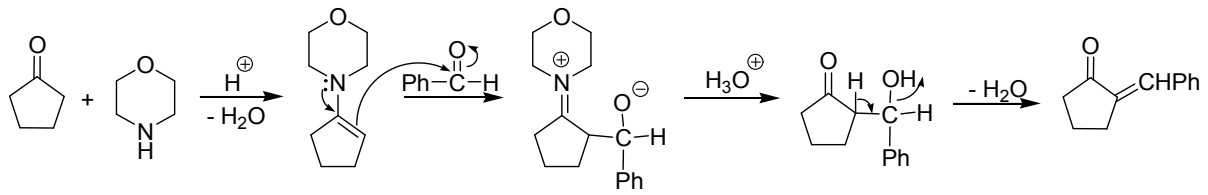
(i) Pyrrolidine adds to cyclohexanone to form a compound that loses OH to form an immonium or iminium ion. This ion then loses a proton from a carbon β to the nitrogen atom to yield an enamine.



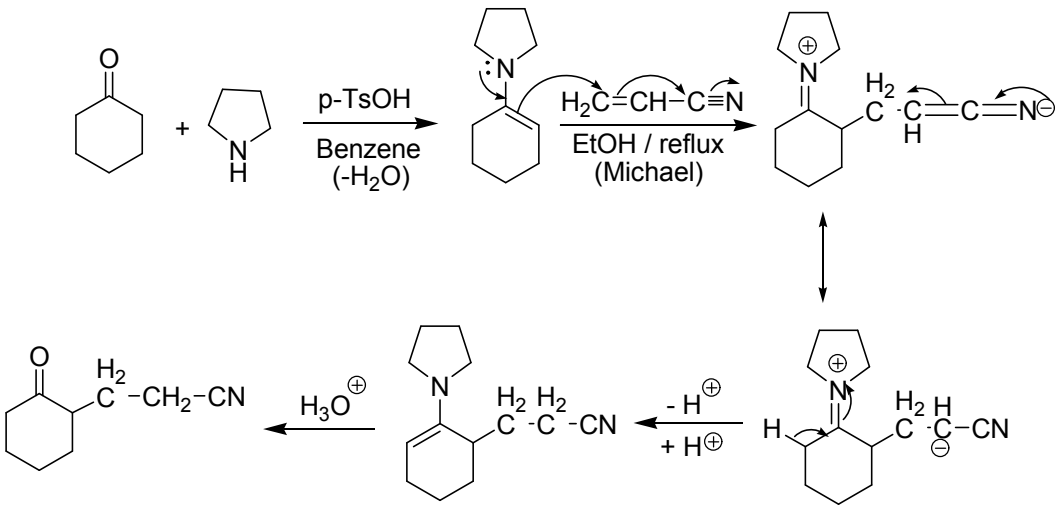
(ii) (a)



(b)



(c)



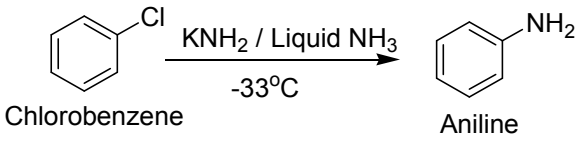
25. (a) (i) Discuss the Benzyne mechanism for the aromatic nucleophilic substitution reaction. Mention the evidences for this mechanism.

(ii) What is Chichibabin reaction?

Answer:

(i) **The elimination–addition (or) benzyne mechanism**

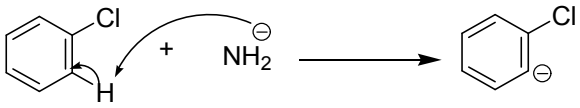
The simple aryl halides are too unreactive to undergo nucleophilic displacement (S_NAr) by usual nucleophiles. However, they react with strongly basic nucleophiles (e.g. $NaNH_2$ or KNH_2 in liquid NH_3) or with usual nucleophiles under drastic conditions. Chlorobenzene for example, when treated with KNH_2 in liquid NH_3 produces aniline by this mechanistic pathway.



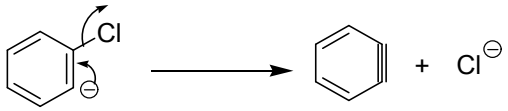
This is a two-stage reaction involving benzyne as an intermediate. The mechanism of the reaction may be given as follows:

Ist Stage: A two-steps elimination of HX and formation of a highly reactive intermediate called benzyne.

Step 1: Abstraction of an ortho hydrogen by $NH_2^{\ominus}$ to form a phenyl anion.

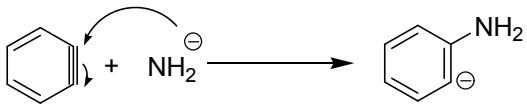


Step 2: Loss of $Cl^{\ominus}$ from the phenyl anion to form the intermediate, benzyne.

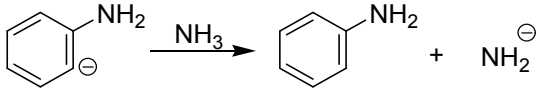


2nd Stage: A two-step addition of NH_3 to benzyne and formation of aniline.

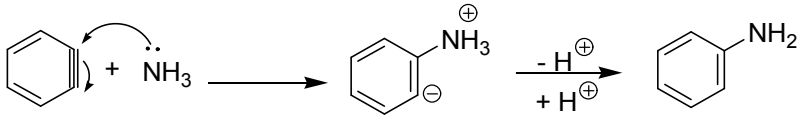
Step 3: Nucleophilic attack by $NH_2^{\ominus}$ at any one of the triple-bonded C-atoms of benzyne.



Step 4: Protonation of the carbanion by NH_3 to form aniline.



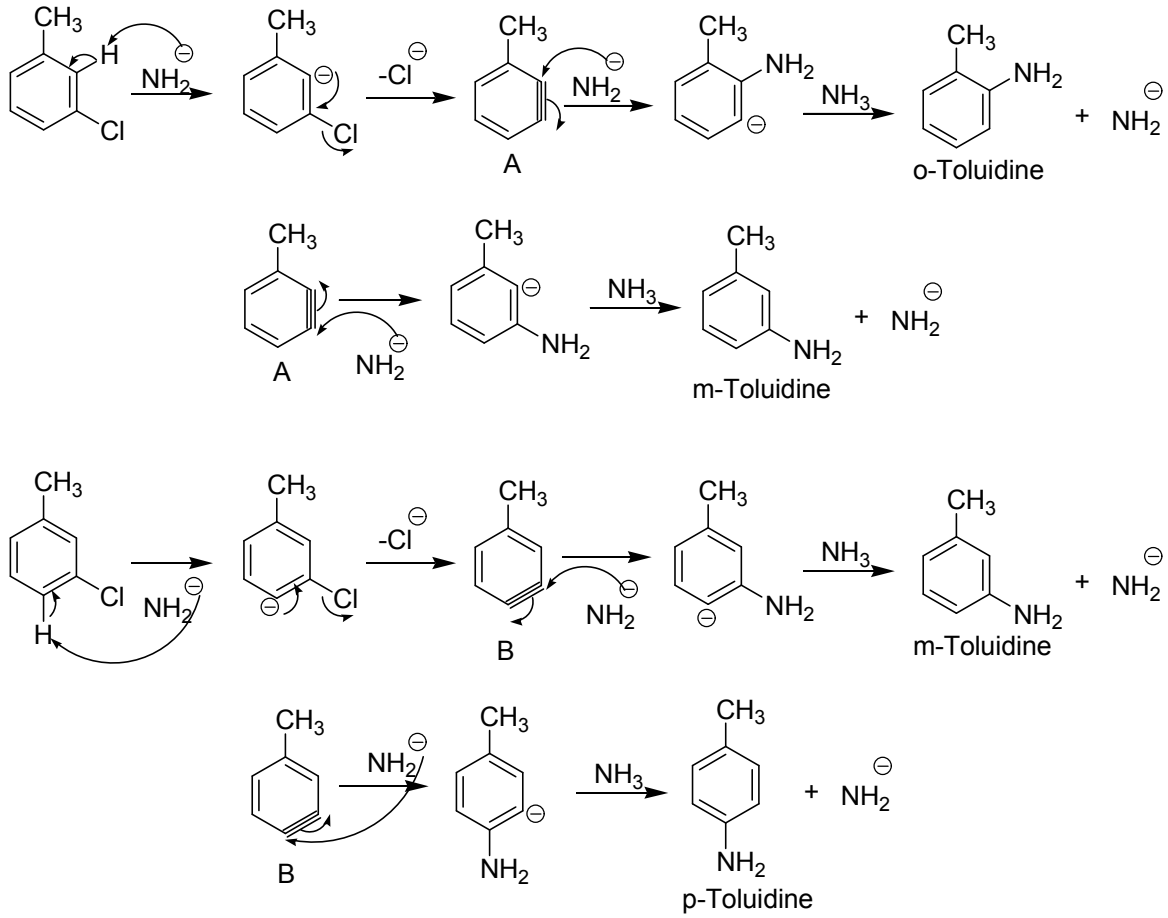
Amination of benzyne may also take place as follows:



Account for the following observations:

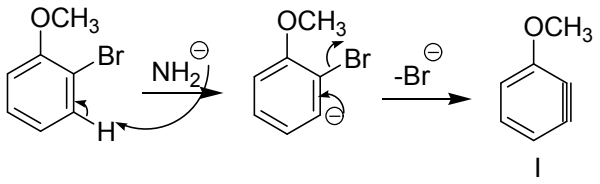
(1) When m-chlorotoluene is treated with KNH_2 in liquid ammonia, a mixture of *o*-and *m*-and *p*-toluidine is obtained.

Since the hydrogens ortho to chlorine are non-equivalent *m*-chlorotoluene leads to the formation of two arynes (A and B) when treated with KNH_2 in liquid ammonia. These arynes is turn give all the three toluidines.

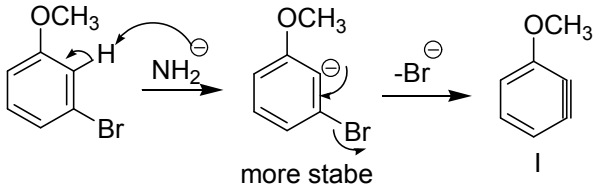


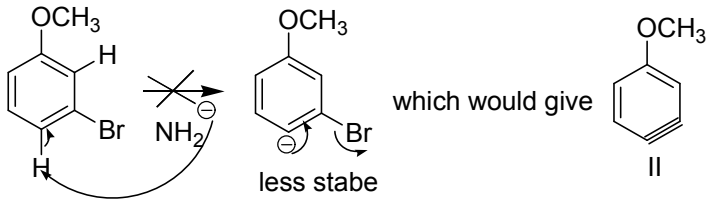
(2) Both *o*-bromoanisole and *m*-bromoanisole react with KNH_2 in liquid ammonia to produce *m*-anisidine.

In the presence of KNH_2, *o*-bromoanisole yields only one aryne (I) and that is because it contains only one ortho hydrogen with respect to bromine.

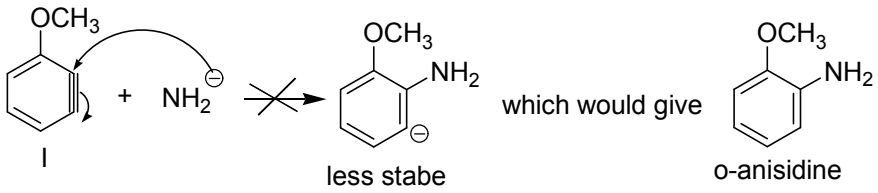


In *m*-bromoanisole, there are two ortho hydrogens with respect to bromine and so, two arynes (I and II) are expected to be formed. But the actual aryne involved in this reaction is I and that is due to the fact that the carbanion leading to I is more stable than that leading to II.



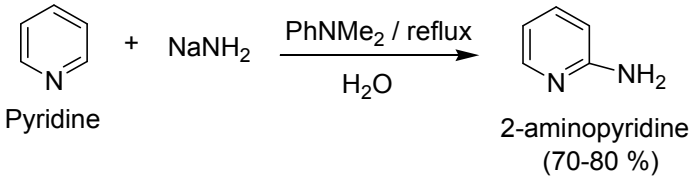


Since the electron pair of a phenyl anion is out of the plane of the π electron system, the charge cannot be delocalized by resonance. The stability of such a carbanion depends only on the inductive effect of the substituent already present in the ring. Since a methoxy group has an electron-withdrawing inductive effect, the carbanion where the negative charge is closer to the $–OCH_3$ group is more stable than that where it is further from $–OCH_3$. So, the carbanion leading to II is less stable than the carbanion leading to I. Therefore, both the isomeric anisoles generate the same aryne (I) and for the same basic reason, this aryne undergoes nuclephilic attack by $NH_2^{\ominus}$ to give a relatively stable carbanion which on protonation gives *m*-anisidine.



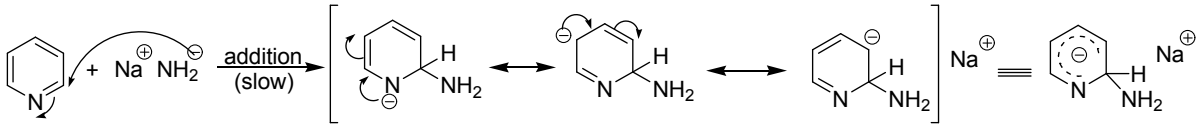
(ii) **Chichibabin reaction**

Amination of pyridine with an alkali metal amide ($NaNH_2$ or KNH_2) is called the Chichibabin reaction.

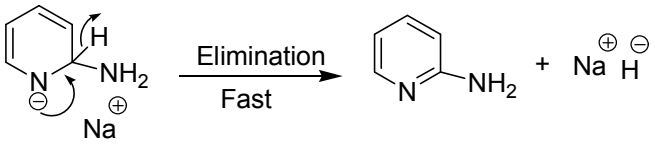


Mechanism

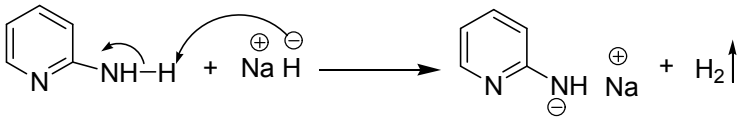
Step 1: Nucleophilic attack by $NH_2^{\ominus}$ at the 2-position of pyridine to yield a resonance stabilized intermediate carbanion.



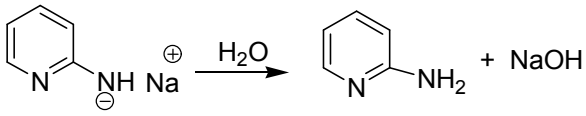
Step 2: Elimination of $H^{\ominus}$ to yield 2-aminopyridine. The driving force for hydride elimination is the re-aromatization of the intermediate.



In practice, a subsequent reaction occur in which the hydride ion abstracts a proton from 2-aminopyridine to form a sodio salt and H_2.



Finally, the sodio salt is converted to 2-aminopyridine by adding cold water to the reaction mixture.



(Or)

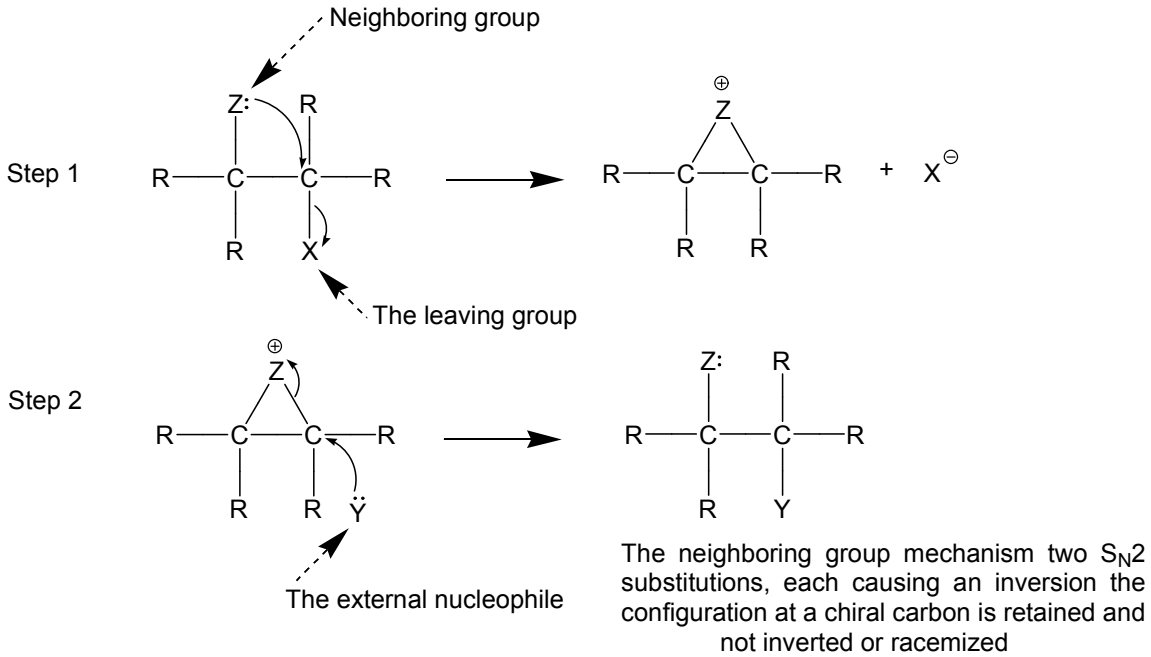
(b) (i) Write notes on neighboring group participation.

(ii) Explain the ambident substrates.

Answer:

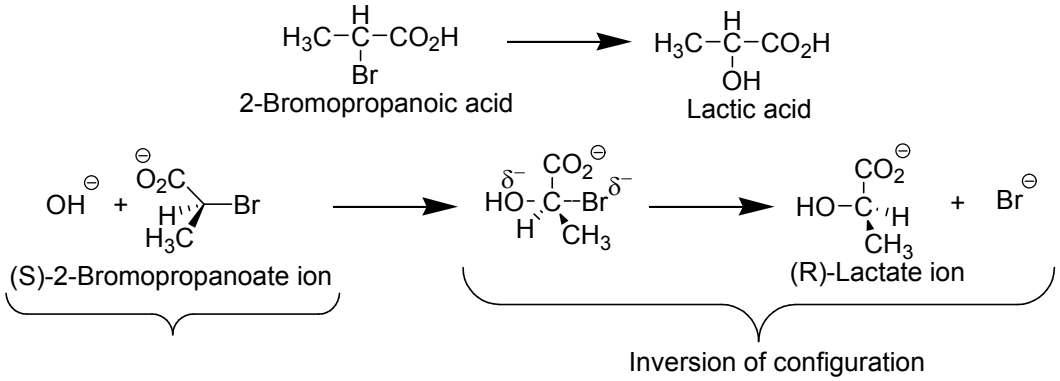
(i) **Neighboring group participation**

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 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 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.



Scheme 1

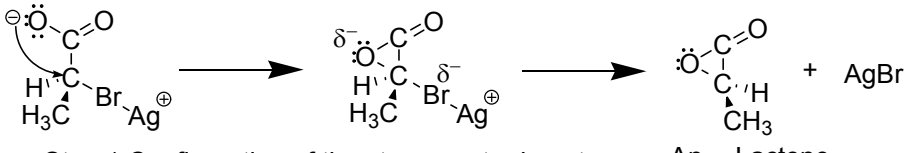
A graphic example of neighboring group participation is found in the conversion of 2-bromopropanoic acid into lactic acid (**Scheme 2**). In the presence of concentrated sodium hydroxide, (S)-2-bromopropanoic acid (shown as its ion, **Scheme 2**) undergoes a bimolecular displacement with inversion of configuration as expected from the normal S_N2 reaction.



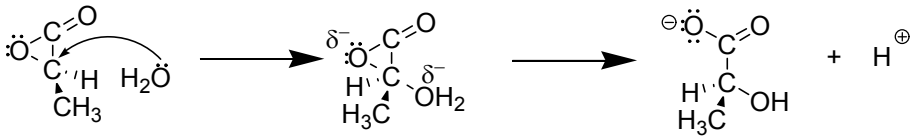
The normal stereochemical result for an S_N2 reaction

Scheme 2

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 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.



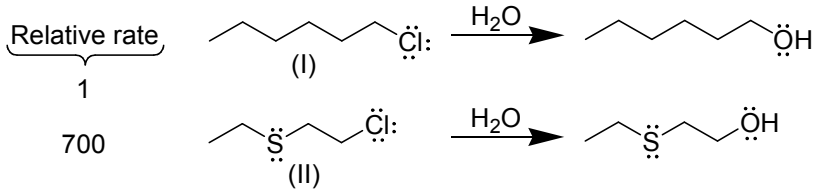
Step 1 Configuration of the stereocenter inverts



Step 2 Configuration of the stereocenter inverts

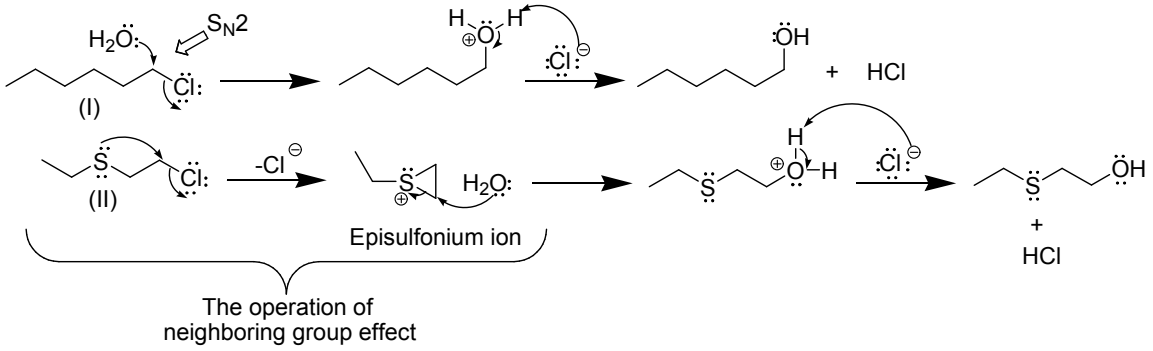
Scheme 3

When the neighboring group participation operates during the rate determining 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 (**Scheme 4**) and 2-chloroethyl-ethylsulfide (II) give their corresponding alcohols.



Scheme 4

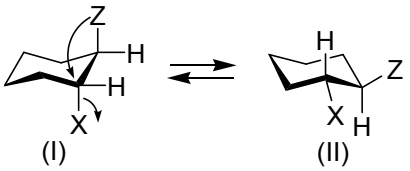
However the rate of reaction of sulfur containing compound (II) is much greater than that of the alkyl chloride. The reaction in the case of (I) is a simple S_N2 displacement of chloride with water, while in the case of sulfide, it is the sulfur atom, which displaces the leaving group and acts as a neighboring 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 5**).



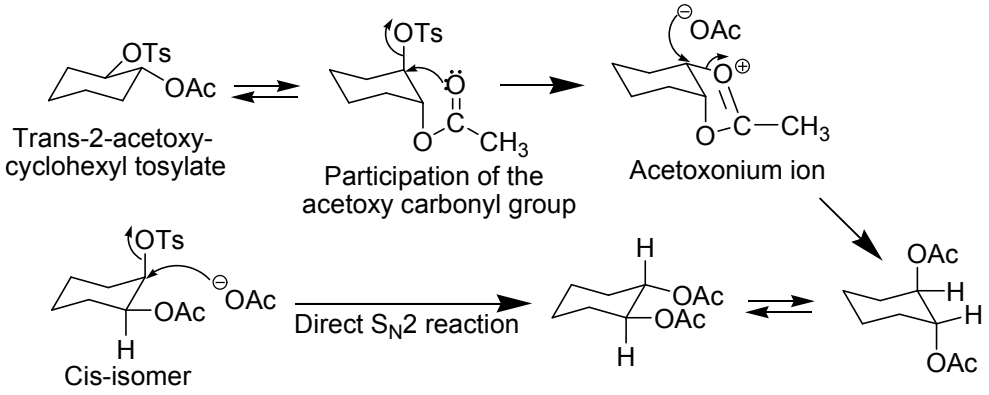
Scheme 5

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 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**) which give the same product I.

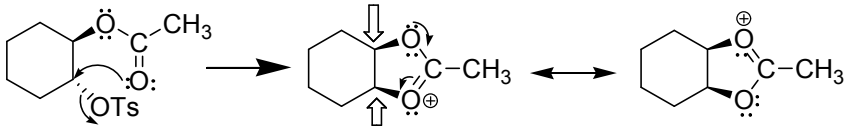


Scheme 6



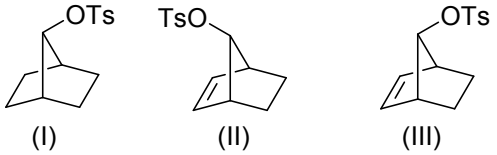
Scheme 7

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**).The acetoxonium ion (the resonance hybrid structure) from the trans isomer is, symmetrical achiral (**Scheme 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.



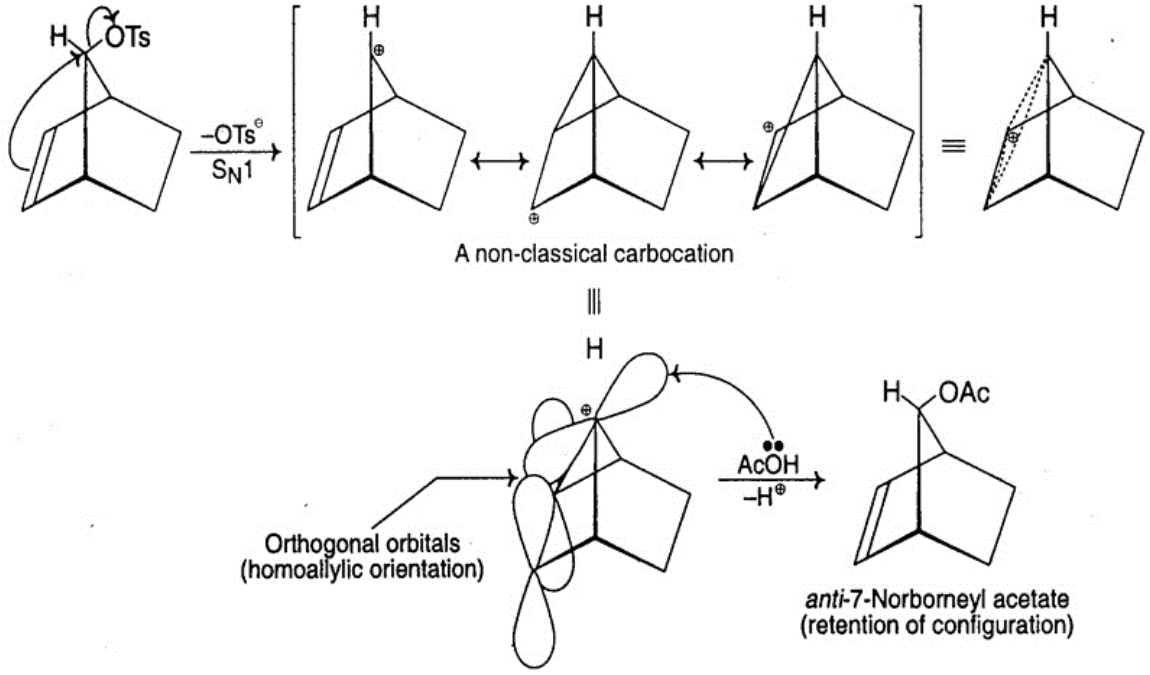
Scheme 8

Among the norbornyl derivatives (on acetolysis) the anti tosylate (III, **Scheme 9**) reacts 10^{11} times faster than (I) while (II) has 10^4 times reactivity compared to (I).

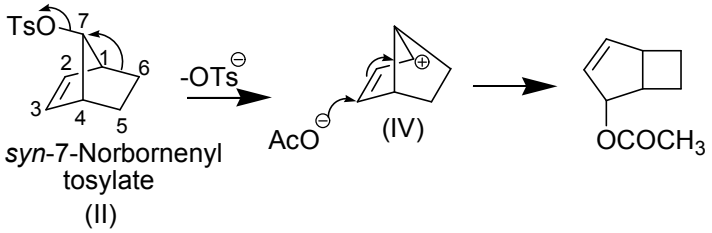


Scheme 9

The fastest rate of acetolysis of anti-tosylate (III) compared to (I, **Scheme 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 10**). In the syn-isomer (II, **Scheme 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 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.



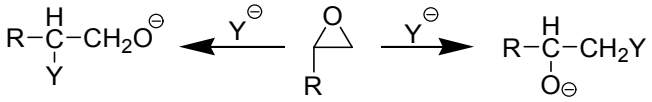
Scheme 10



Scheme 11

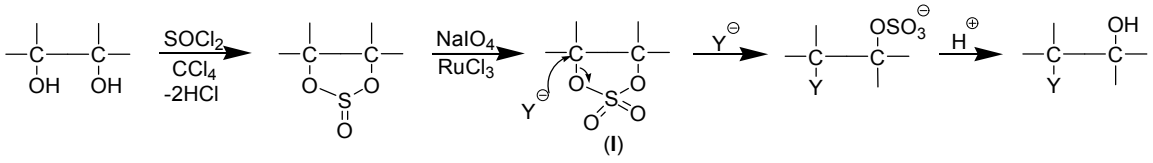
(ii) **Ambident substrates**

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:



26. (a) Write the structure, generation and reactions of carbenes and nitrenes.

Answer:

Carbenes

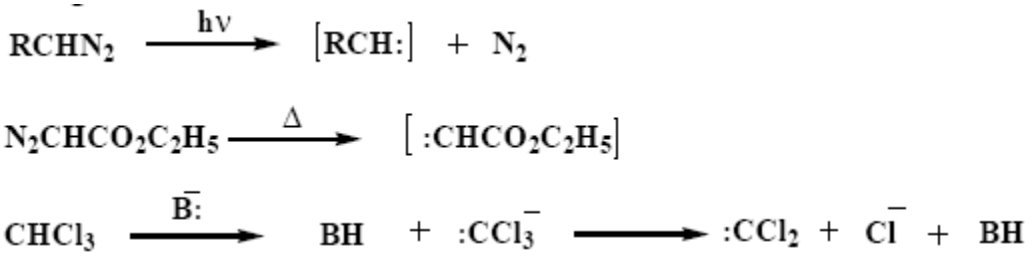
Structure

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.

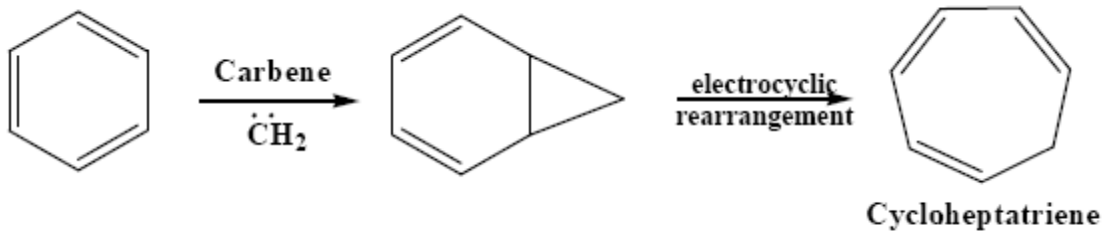
Generation

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.

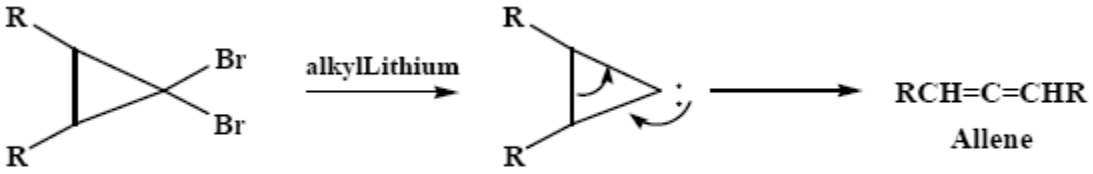


Reactions

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



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



Nitrenes

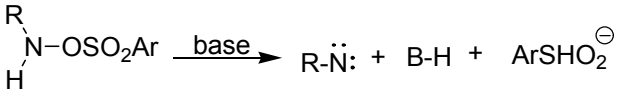
Structure

The nitrenes *R– N* represent the nitrogen analogs of carbenes and may be generated in the singlet (R-N: or triplet R-N·)

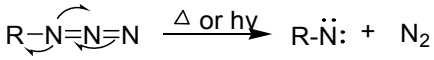
Generation

The two principal means of generating nitrenes are analogous to those used to form carbenes.

1. *Elimination.* An example is



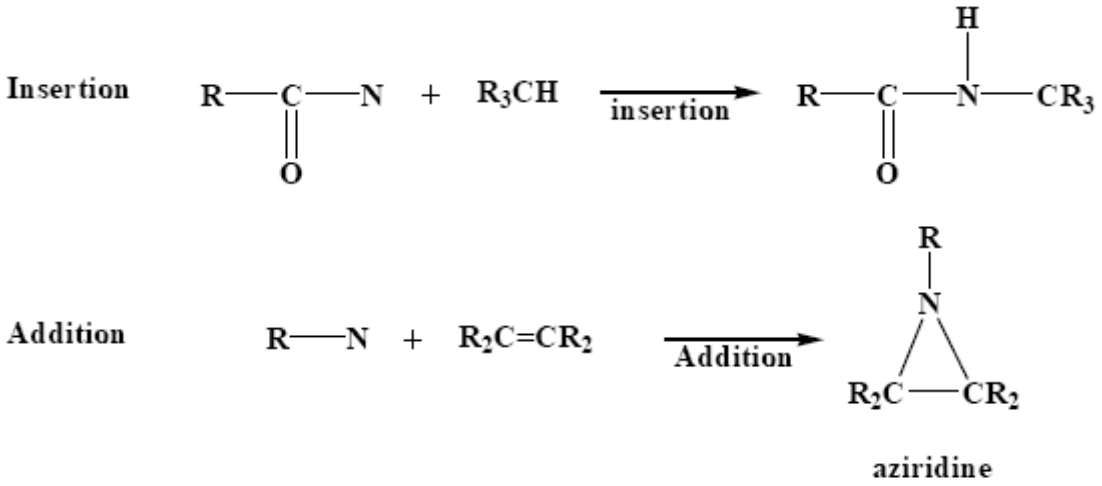
2. *Breakdown of certain double-bond compounds*. The most common method of forming nitrenes is photolytic or thermal decomposition of azides,



The unsubstituted nitrene (NH) has been generated by photolysis of electric discharge through NH_3, N_2H_4 or HN_3.

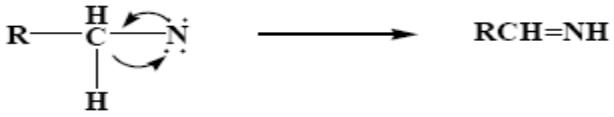
Reactions

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.

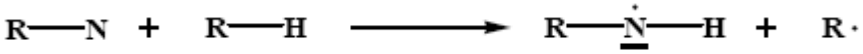


Rearrangements:

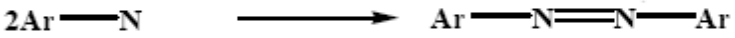
Alkyl nitrenes do not generally give either of two proceeding reaction because the rearrangement is more rapid.



Abstraction: (eg)



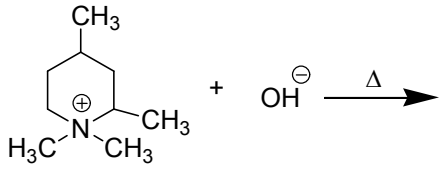
Dimerization: NH dimerizes to diimide N_2H_2



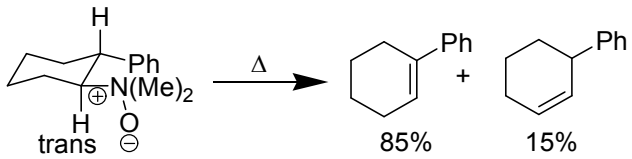
The dimerization is more important for nitrines than carbenes.

(Or)

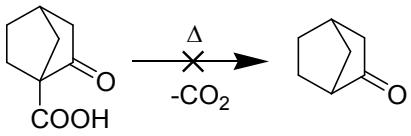
(b) (i) Give the structure of the major product of the following reactions and explain its formation.



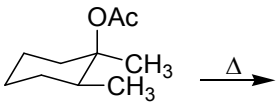
(ii) Explain the following observation:



(iii) Explain why this β-keto acid does not readily undergo decarboxylation.

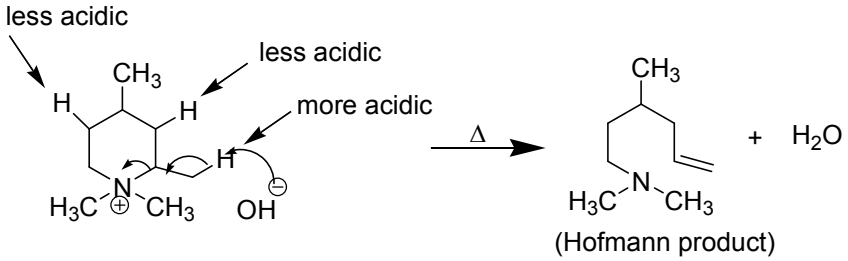


(iv) Predict the major product and suggest a mechanism of the following reaction:

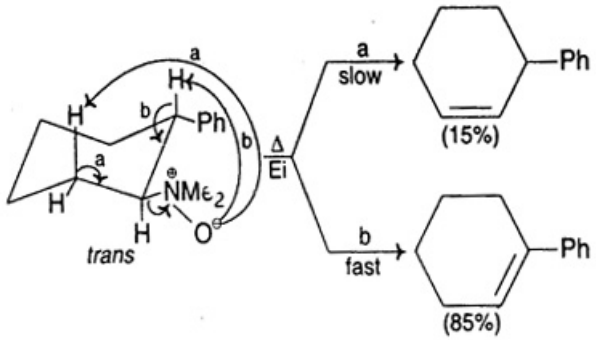


Answer:

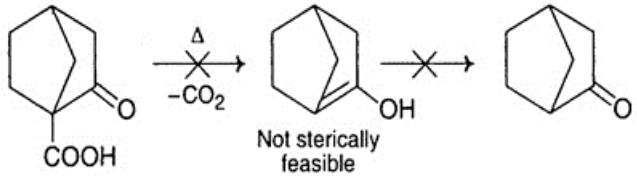
(i)



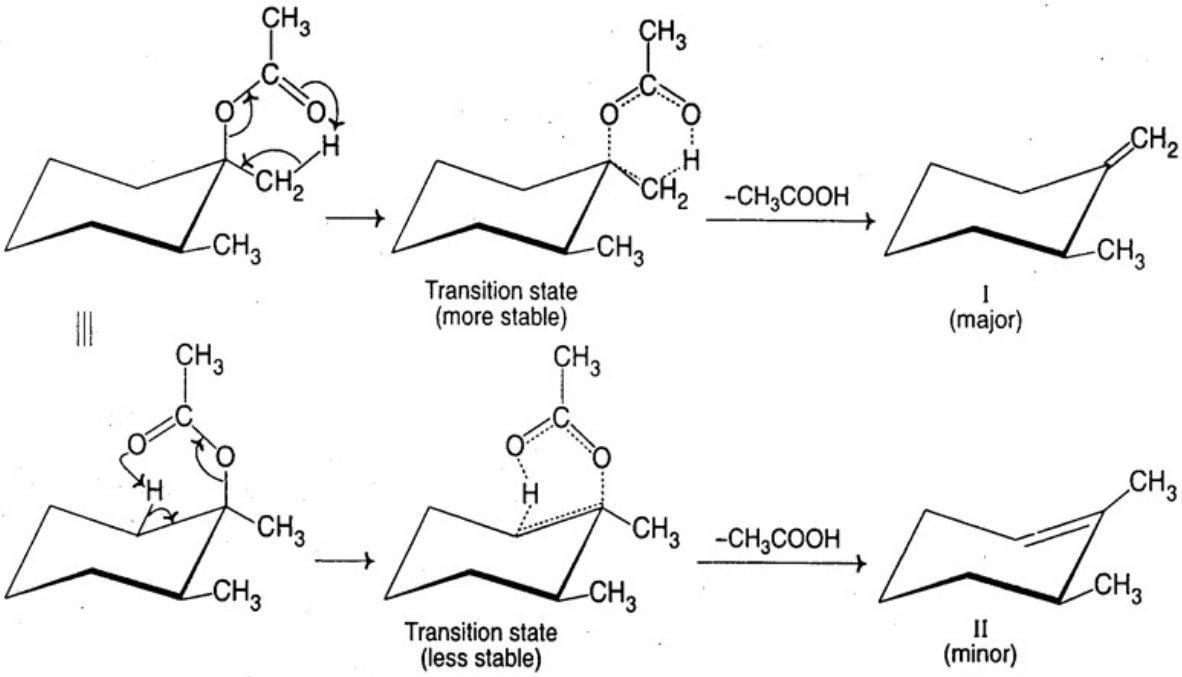
(ii)The formation of both 1- and 3-phenylcyclohexene from the trans-amine oxide involve a favourable cis-elimination of an equatorial $-NMe_2 \rightarrow O$ group and an axial hydrogen (at C-2 or C-6). This isomer is, therefore, expected to yield 50% of each olefin. In fact, 1-phenylcyclohexene is formed predominantly and this is because 1-phenylcyclohexene, being a conjugated olefin, is thermodynamically more stable than 3-phenylcyclohexene.



(iii) A mechanism of decarboxylation is also consistant with the resistance of bridgetead bicyclic β-keto acids to decarboxylation and this is because strain prevents formation of a double bond at the bridge head position (Bredt's rule).



(iv) The acetate undergoes pyrolytic syn-elimination to give the alkene I as the major product and this is because the six-membered cyclic transition state leading to the formation of I is planar and geometrically more favourable.



Reg. No.....

[16CHP101]

KARPAGAM UNIVERSITY

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COIMBATORE – 641 021
(For the candidates admitted from 2016 onwards)

M.Sc., DEGREE EXAMINATION, NOVEMBER 2016

First Semester

CHEMISTRY

ORGANIC CHEMISTRY I
(Reaction Mechanisms)

Time: 3 hours Maximum : 60 marks

PART – A (20 x 1 = 20 Marks) (30 Minutes)
(Question Nos. 1 to 20 Online Examinations)

(Part - B & C 2 ½ Hours)

PART B (5 x 6 = 30 Marks)
Answer ALL the Questions

21. a. State Huckel's Rule of aromaticity.
Or
b. Describe the Hammett and Taft equation.

22. a. Write the following addition reactions.
(i) Michael Addition (ii) Thorpe reaction (iii) Mannich Reaction
Or
b. Describe the hydroxylation and epoxidation reactions.

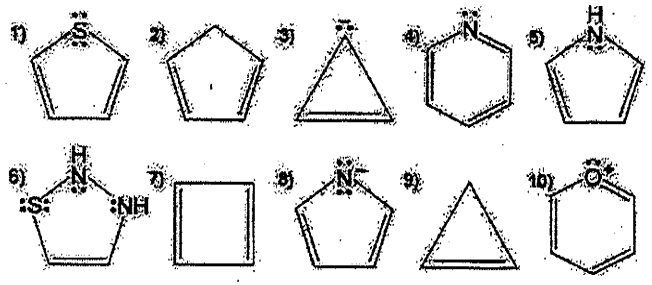
23. a. Discuss the following electrophilic substitution reaction
(i) Bischler-Napieralski Reaction (ii) Hofmann–Martius Reaction
Or
b. (i) Give the mechanism of Bimolecular aliphatic electrophilic substitution (S_E^2)
(ii) Write the Stork enamine reaction

24. a. (i) Explain the benzyne mechanism. ii) Write the Chichibabin reaction.
Or
b. Give a brief account on neighbouring group participation.

25. a. Give the Stereochemistry of E_2 Reaction
Or
b. Write in brief about Cope elimination and Bredts rule.

PART C (1 x 10 = 10 Marks)
(Compulsory)

26. Using the criteria for aromaticity, determine if the following molecules are aromatic



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First Semester

CHEMISTRY

ORGANIC CHEMISTRY I
(Reaction and Mechanism)

Time: 3 hours Maximum : 60 marks

PART – A (20 x 1 = 20 Marks) (30 Minutes)
(Question Nos. 1 to 20 Online Examinations)

(Part - B & C 2 ½ Hours)

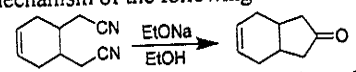
PART B (5 x 6 = 30 Marks)
Answer ALL the Questions

21. (a) (i) Explain the Huckel's rule with example.
(ii) Write a note on fulvenes.

Or

(b) (i) Explain the following observation:
Azulene, an isomer of naphthalene, possesses dipole moment (1.0 D) and electrophilic substitution in it occurs at 1-position of the five-membered ring.
(ii) Explain the Hammonds postulate.

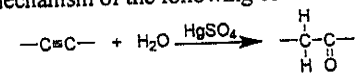
22. (a) (i) Explain the mechanism of the following conversion.



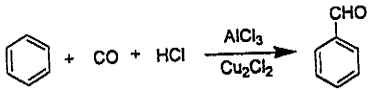
(ii) Mention some applications of Benzoin condensation.

Or

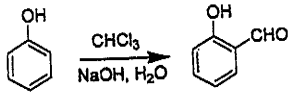
(b) (i) What is Claisen condensation?
(ii) Write the mechanism of the following conversion.



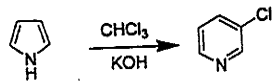
23. (a) Explain the mechanism of the following reactions.
(i)



(ii)



(iii)



Or

(b) (i) Write notes on SE_1 mechanism.
(ii) Explain Gattermann reaction with mechanism.

24. (a) Discuss the mechanism for the following aliphatic nucleophilic substitution reaction (i) S_N1 (ii) S_N2

Or

(b) Write notes on factors affecting the nuclophilic substitution in effect of substrate.

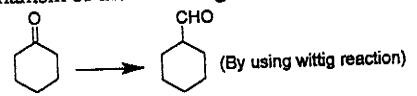
25. (a) Write the structure, generation and reactions of carbenes and nitrenes.

Or

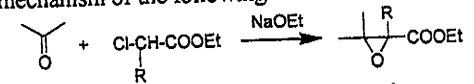
(b) Discuss about (i) Hofmann rule (ii) Elimination Vs substitution.

PART C (1 x 10 = 10 Marks)
(Compulsory)

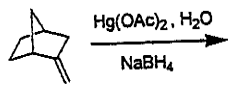
26. (i) Write the mechanism of the following conversion.



(ii) Write the mechanism of the following conversion.



(iii) Complete the following reaction. Provide mechanism.



Reg. No.....

[14CHP101]

KARPAGAM UNIVERSITY

(Under Section 3 of UGC Act 1956)
COIMBATORE – 641 021
(For the candidates admitted from 2014 onwards)

M.Sc. DEGREE EXAMINATION, JANUARY 2015

First Semester

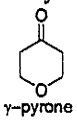
CHEMISTRY

ORGANIC CHEMISTRY – I (Reaction Mechanism)

Time: 3 hours Maximum : 60 marks

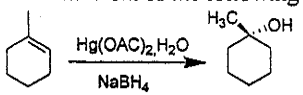
PART – A (10 x 2 = 20 Marks)
Answer any TEN Questions

1. Explain why carbonyl oxygen of γ-pyrone is more basic than the ring oxygen.



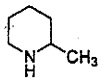
γ–pyrone

2. Write a note on microscopic reversibility.
3. Explain the aromatic nature of ferrocene.
4. Write a note on electroplilic addition.
5. What is Thorpe reaction?
6. Explain the mechanism of the following conversion.



7. Write the mechanism of Gattermann Koch reaction.
8. Explain Hoffmann Martius reaction with mechanism.
9. Give the mechanism of decarboxylation of β-keto acids. Give evidence in favour of the mechanism.
10. Explain why halocyclopropanes are unreactive towards S_N2 reactions.
11. Explain the Ziegler alkylation.
12. Explain the following observation:
    The rate of solvolysis with water (hydrolysis) increase as the following series is traversed:
    $PhCH_2Cl$ Ph_2CHCl Ph_3CCl
13. Discuss the steps involved in Hofmann degradation process which is widely used for structural determination of alkaloids.

14. Write the generation of carbenes.
15. Give the steps involved in the complete Hofmann degradation of the following cyclic amine.



PART B (5 X 8= 40 Marks)
Answer ALL the Questions

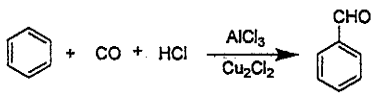
16. a. i. Explain the Huckel's rule with example.
    ii. Write a note on fulvenes.

    Or

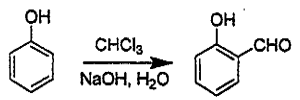
    b. i. Explain the following observation:
    Azulene, an isomer of naphthalene, possesses dipole moment (1.0 D) and electrophilic substitution in it occurs at 1-position of the five-membered ring.
    ii. Explain the Hammonds postulate.

17. a. Explain the mechanism of the following reactions.

(i)



(ii)



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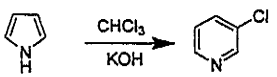

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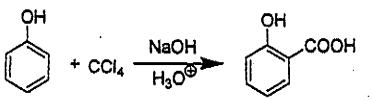


Or

b. i. Write notes on SE_1 mechanism.
ii. Explain Gattermann reaction with mechanism.

18. a. Discuss the mechanism for the following aliphatic nucleophilic substitution reaction (i) S_N1 (ii) S_N2

Or

b. Write notes on factors affecting the nuclophilic substitution in effect of substrate.

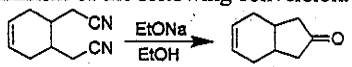
19. a. Write the structure, generation and reactions of carbenes and nitrenes.

Or

b. Discuss about (i) Hofmann rule (ii) Elimination Vs substitution.

20. **Compulsory : -**

i. Explain the mechanism of the following conversion.



ii. Mention some applications of Benzoin condensation.

Reg. No.....

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KARPAGAM UNIVERSITY

(Under Section 3 of UGC Act 1956)
COIMBATORE – 641 021
(For the candidates admitted from 2014 onwards)

M.Sc. DEGREE EXAMINATION, NOVEMBER 2014

First Semester

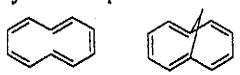
CHEMISTRY

ORGANIC CHEMISTRY – I (Reaction Mechanism)

Time: 3 hours Maximum : 60 marks

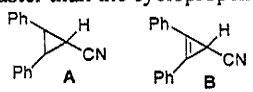
PART – A (10 x 2 = 20 Marks)
Answer any TEN Questions

1. Write a note on isotopic labeling.
2. Explain why the compound **II** is more stable than the compound **I**.



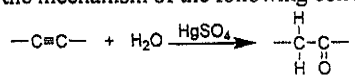
I II

3. The cyclopropane (**A**) loses its proton in hydrogen-exchange reaction ≈10, 000 times faster than the cyclopropene (**B**). Explain.

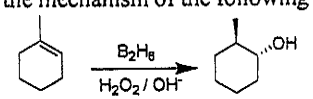


A B

4. What is Claisen condensation?
5. Write the mechanism of the following conversion.

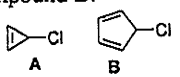


6. Write the mechanism of the following conversion.



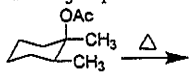
7. What is Gattermann reaction? Provide the mechanism.
8. What is Kolbe's reaction?
9. β-keto acids undergo decayboxylation fast why.
10. Mention the any three examples of ambident nucleoplies.
11. Explain why allyl bromide, CH_2=CH-CH_2-Br, undergoes S_N2 reactions rapidly than does ethyl bromide.

12. Explain why the compound **A** undergoes solvolysis in ethanol more readily than the compound **B**.



A B

13. What is the Hofmann elimination reaction?
14. Write the structure of singlet and triplet carbenes.
15. Predict the major product and suggest a mechanism of the following reaction:



PART B (5 X 8= 40 Marks)
Answer ALL the Questions

16. (a) Give an account on i) Hydroxylation ii) epoxidation iii) Hydroboration

Or

(b) Discuss the mechanism of the following:
(i) Meerwein pondroff-verley reduction (ii) Wittig reaction.

17. (a) Write a note on Friedel Crafts alkylation and acylation. Compare their advantages and limitations.

Or

(b) (i) Discuss about the Stork enamine reaction.
(ii) Explain Gattermann koch reaction with mechanism.

18. (a) (i) Discuss the Benzyne mechanism for the aromatic nucleophilic substitution reaction. Mention the evidences for this mechanism.
(ii) What is Chichibabin reaction?

Or

(b) (i) Write notes on neighboring group participation.
(ii) Explain the ambident substrates.

19. (a) (i) How will you generate nitrenes? Give an account of their structure and stability.
(ii) Explain the Bredts rule.

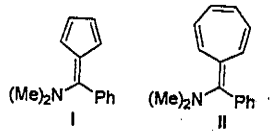
Or

(b) Discuss about E_1, E_2 and E_i mechanisms with suitable examples.

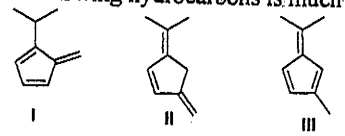
20. **Compulsory : -**

Provide an explanation for each of the following observations:

(i) The amine **II** is more basic than the amine **I**.



(ii) One of the following hydrocarbons is much more acidic than the others.



Reg. No.....

[11CHP101]

KARPAGAM UNIVERSITY

(Under Section 3 of UGC Act 1956)
COIMBATORE – 641 021
(For the candidates admitted from 2011 onwards)

M.Sc. DEGREE EXAMINATION, APRIL 2012

First Semester

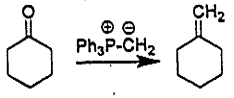
CHEMISTRY

ORGANIC CHEMISTRY – I (REACTION MECHANISMS)

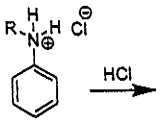
Time: 3 hours Maximum : 100 marks

PART – A (15 x 2 = 30 Marks)
Answer ALL the Questions

1. Explain the conditions for anti aromatic with some examples.
2. Write a note on identification of products.
3. Pyrrole is a much weaker base than pyridine.
4. What is epoxidation reaction?
5. Differentiate hydroxylation and hydroboration reaction.
6. Write the mechanism of the following conversion.

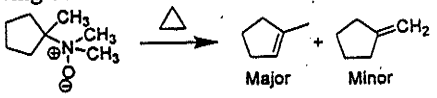


7. Write the mechanism of Kolbe's reaction.
8. Complete the following reactions. Provide mechanisms.

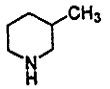


9. Write the mechanism of Stork enamine reaction.
10. What is Chichibabin reaction?
11. Explain the ambident substrate.
12. The following bicyclic compound is exceedingly unreactive towards nuclophilic substitution either by the S_N1 or S_N2 mechanism.

13. Explain the following observation:



14. Write the generation of nitrenes.
15. Give the steps involved in the complete Hofmann degradation of the following cyclic amine.



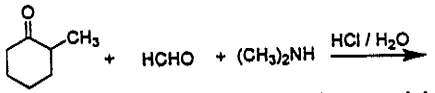
PART B (5 X 14= 70 Marks)
Answer ALL the Questions

16. (a) (i) Explain the aromaticity of non-benzenoid aromatic compounds.
(ii) Explain the resonance structure of cyclopropenyl cation and cyclopentadiene cation

(Or)

(b) Explain the non-kinetic methods of study of reaction mechanism.

17. (a) (i) Discuss the mechanism of mannich reaction.
(ii) Predict the major product in the following reaction and give you reasoning:



(iii) Mention some important applications of the mannich reaction.

(Or)

(b) Write notes on (i) Stobbe condensation (ii) Dieckmann reaction.

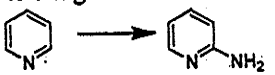
18. (a) Explain the following reactions.
(i) Gattermann reaction (ii) Reimer Tiemann reaction
(iii) Gattermann Koch reaction

(Or)

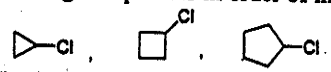
(b) Write notes on SE_i mechanism.

19. (a) (i) Suggest suitable reagent for the following transformation.

(ii) Indicate the reagent to bring about the following transformation.



(iii) Arrange the following compounds in order of increasing S_N1 reactivity:



Develop your reasons.

(Or)

(b) Write notes on neighbouring group participation.

20. (a) (i) Explain the E_1 mechanism with example.

(ii) Explain the Bredts rule.

(Or)

(b) Discuss about (i) Saytzeff rule (ii) Cope elimination
