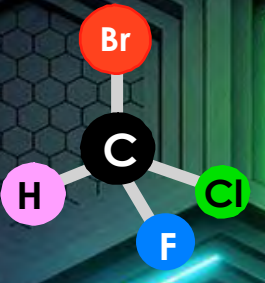
First Edition

Basic Concepts of Organic Chemistry



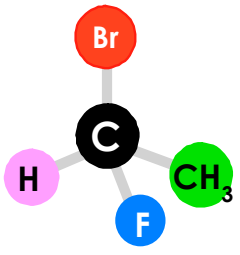
Muhammad Sohail
Lecturer Chemistry

Textbook on

Basic Concepts of Organic Chemistry

By

Muhammad Sohail



Basic Concepts of Organic Chemistry
Muhammad Sohail
First Edition 2025

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Preface

Organic chemistry offers tricky experience. Students feel it difficult to attempt. Many think it a science of complexity and confusion. In my teaching experience, students who learn the subject conceptually and practice it thoroughly, they love the science. Those who skip it or force themselves to memorize it for exam purpose suffer since they never try to understand the basic of the subject. Organic chemistry is interesting science which require concepts, problem solving and reasoning its application. Concepts are built by passionate and dedicated teachers whose devotion could inspire students to learn and practice. Reading standard textbooks and hardworking equip students to master the science. In fact, practice and problem solving boost confidence to tackle the subject with clarity and conception. Once concepts and practice are combined, students take it privilege to apply the science for practical utility whether it be their research, exams or explaining the real world of organic chemistry around them.

Organic chemistry is ever emerging science with vast vistas of knowledge that encompasses almost every facet of life and technology. As an instructor, I can say, organic chemistry is not about memorization but it requires problem solving, consistent practice and wide reading exposure to master the science. Most students are used to descriptive examination. When they encounter my paper, they feel it troublesome to solve. But those who prepare the subject with consistent reading and problem solving take great pleasure in handling varied dimensions of organic chemistry. It takes them few moments to solve whole paper. This is what I want to impart organic chemistry as a medium of education to my students because we need shift from traditional mode of examination towards more pragmatic and applicable pattern of science utilization.

Author of the book is MS degree holder in Organic Synthesis. He did his MSc in chemistry from Quaid-i-Azam University Islamabad. The author teaches chemistry for the past ten years. Based on his teachings experience, he brings this book with intent to inspire students, teachers and researchers with updated contents on organic chemistry. The author has also written textbook on Fundamental of Intermediate Chemistry. Basic Concepts in Organic Chemistry is another attempt. The author managed this book single handedly since neither any editor facilitated it nor any reviewer collaborated. Writing a science book is an uphill task since it requires multiple tiers of assistance to complete with all graphics, formatting, sketches, reactions and figures etc. This book helps students, teachers, researchers and general readers to evolve the fundamental concepts of organic chemistry. In fact, these concepts occurs throughout organic chemistry. I hope, my writing will assist you in mastering your course. For any error or omission, kindly reach me on the following address so that comings edition of the book would be presented with updated and precise information.

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Introduction

Basic Concepts of Organic Chemistry brings concepts, practice and applications in one go so that it could present better reading experience. Organic chemistry does not offer detailed explanation or in depth insights when it comes to examine the students. Instead, students are examined about its brief applications which could only be successfully attempted when both concepts and practice are mastered. To do away with the task, I presented both concepts and their practice in this book. Students are required to learn concepts and practice it by frequent problem solving. This book is an attempt to cover my experience regarding basics of organic chemistry. Teaching the science taught me to present it in my own way. This book is reflection of my urge so that my student could read and explore standard material.

Basics Concepts of Organic Chemistry is first such edition which is covered in seven sections. First section imbibes all basic concepts of organic chemistry which help students to build foundation. Organometallics portion has added in the section 1.17 with an aim to equip students with fundamental knowledge of this domain. Second section is about nomenclature of organic molecules. Both simple and heterocyclic molecules have been briefly addressed. Most text books don't focus this section. Either the section is skipped or merged in relevant functional group chemistry. I have combined whole nomenclature in a single section so that students find it easy to study at one place. Third section concerns functional groups chemistry. This section involves properties, synthesis and reactions of each functional group. In section four, I have addressed basic biochemistry. Fifth section presents fundamental aspects of stereochemistry. Sixth section explains spectroscopy that cover techniques such as IR, UV, MS and NMR. The last technique covers proton and carbon NMR in detail. Section seven covers an introductory insight into synthetic organic chemistry. It contains some of my research experiences besides enlisting some basic experiments in organic chemistry. The last section has added to enable students so that they could build better understanding of practical work in organic chemistry. I hope the book will help readers with intent to master the basics of organic chemistry.

Teaching chemistry offers an interesting experience because not only students are taught how chemistry works in defining life around us but also boost self-interest to explore the discipline more and more so that it could be presented in more fascinating manner.

Muhammad Sohail
Lecturer Chemistry

Contents

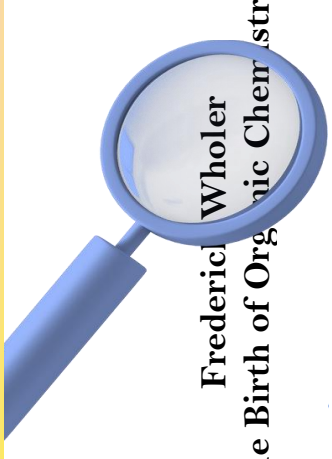
Dedicated to My Students

Fundamental Concepts In Organic Chemistry

Section 1 Basic Concepts

1.1 History of Organic Chemistry

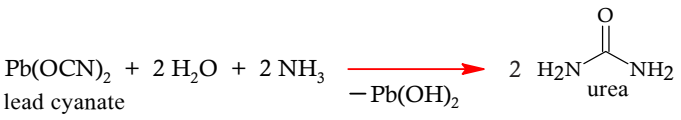
Organic chemistry emerged with Fredrick Wholer, a German Chemist, who transformed inorganic compound such as ammonium cyanate into an organic ones as urea. Prior to this development, there was general misconception about organic compounds such as sugar, fats, coal and petroleum and they were believed that only living organisms could produce them. In fact, the term "organic" at that time was meant to represent something 'living' or 'formed' by living system. The term 'organic' was first coined in 1807 by a Swedish chemist Jöns Jakob Berzelius.



Frederick Wholer challenged and refuted vitalism which stated that organic compounds could only be synthesized by some mysterious force of nature. He was German chemist (1800-1882) with specialties in both organic and inorganic chemistry. Wholer was student of Jacob Berzelius who is regarded as the father of modern chemistry through his spectacular contribution of determining atomic weights, inventing chemical symbols and introducing electrochemical theory. In 1828, he synthesized urea, an organic compound, from inorganic ones such as ammonium cyanate in urine of animal. This was his second groundbreaking experiment. Earlier in 1827, he ventured the most difficult task of isolating aluminum from its compound and he got successful. As ammonium cyanate and urea were two isomers of different properties, Wholer brought the science of isomerism into work. In fact, two years later, his mentor Berzelius defined and introduced the term isomerism. Wholer was best friend of Liebig because both published same compounds with different properties which were isomers. Their worked got accepted published. Since then they became friends. Wholer work led to

1. Rejection of vitalism
2. Inception of organic chemistry
3. Opened new science
4. Opened doors to isomerism

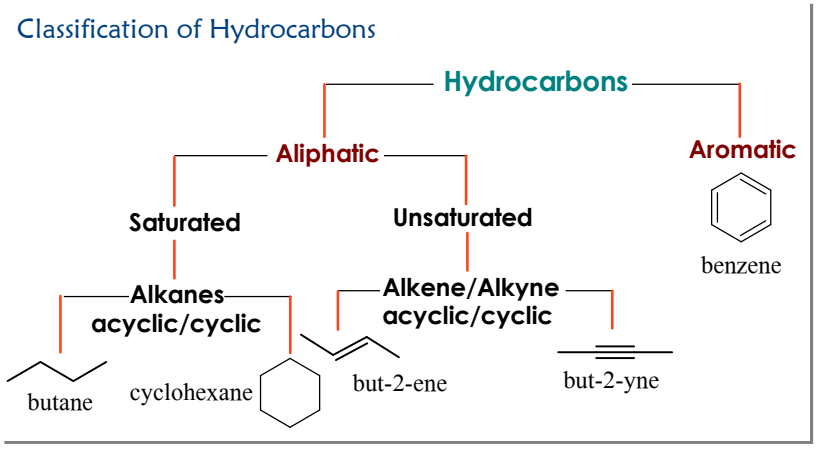
The concept about organic chemistry before Wholer's synthesis was based on "vitalism" that referred to force present in plants and animals responsible for synthesis of organic compounds. However, the general disbelief about organic chemistry buried with the following reaction when Wholer, 27 years old German physician, succeeded in 1828 to transform inorganic compound into organic through a simple heating reaction.



On account of Wholer's efforts, today he is regarded as the father of organic chemistry because he pioneered the discipline with his amazing laboratory synthesis of urea. To begin with organic chemistry, lets first define the field and shed some light on the distinction between organic and inorganic compounds.

1.2 Definition

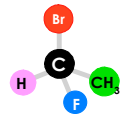
The study of carbon compounds which are covalently bonded to hydrogen or some other heteroatoms such as oxygen, nitrogen or halogens is known as organic chemistry. The oxides of carbon, carbonates, cyanides and metallic carbides are not taken as organic compounds but classed as inorganic compounds instead. Inorganic compounds containing carbon is not bonded to hydrogen such as CO, CO_2 and Na_2CO_3 etc.



In essence, organic chemistry is the study of just one element, carbon, whereas inorganic chemistry is the study of rest of the 117 elements of the periodic table. Organic compounds based on carbon and hydrogen only are termed as hydrocarbons. These compounds are classified as alkanes, alkenes, alkynes and aromatic compounds. Organic compounds are most prevalent in nature as compared to inorganic ones which are characterized by ionic instead of covalent bond. For instance, there are ten million known organic compounds as compared to just 1.5 million inorganic compounds. Organic compounds accounts for approximately 85% of all known compounds.

Organic Compounds	Inorganic Compounds
1. Bonding is covalent	1. Bond is ionic
2. Exist as solid, liquid and gas	2. Usually solid
3. Insoluble in water	3. Soluble in water
4. Soluble in organic solvents	4. Insoluble in organic solvents
5. Don't conduct electricity in aqueous solution	5. Conduct electricity in aqueous solution due to ions
6. Burn and decompose	6. Few burn
7. React slowly	7. React fast

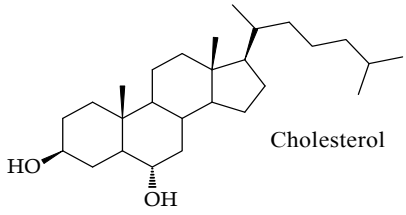
Hydrocarbons (HCs) are compounds of carbon and hydrogen which are divided into two broad categories: saturated and unsaturated HCs. Saturated hydrocarbons are



those with C – C single bond. In other words, HCs in which all four valencies of carbons are satisfied by four hydrogen or other atoms are termed as saturated HCs. Alkanes represent the class of saturated HCs. The next division of HCs is unsaturated compounds in which four valencies of the carbon atoms are not satisfied by four hydrogen or other atoms. Compounds with double bond (alkenes) or triple bond (alkynes) are referred as unsaturated HCs. Aromatic hydrocarbons are compound of benzene and its derivatives. Presence of benzene unit is the characteristic of this class of compounds. Alkenes, alkynes and aromatics HCs are examples of unsaturated HCs.

1.3 Features

Carbon is unique feature of organic compounds. Almost all such compounds are based on carbon atom skeleton. Carbon is tetravalent in character. It makes four bonds by sharing four of its valence electrons either with itself or with other atoms.



Cholesterol

Carbon not only forms single bond as in alkanes but also makes double and triple bonds as in alkenes and alkynes. The most important feature of carbon atom in organic chemistry is to catenate, the tendency which enables carbon atoms to link in a chains of numerous carbon atoms. Comparatively, C—C bond is shorter than Si—Si bond, which equips the atom to catenate, a property of catenation that makes carbon unique over silicon. In fact, this property makes carbon possible to bond itself in a chain of varied lengths. Silicon also makes bond with itself but due to rich prevalence and affinity for oxygen as Si—O bond is stronger than Si—Si, therefore, most of the silicon establishes compounds based on Si—O linkage instead of Si—Si. Contrary, C—C bond strength is 347kJ/mol, which is almost equal to C—O bond (359kJ/mol). The similarity in bond strength makes compounds based on C—C relatively stable in oxygen environment.

1.31 Organic Formulas

In dealing with organic chemistry, formulas are represented in different ways. In preliminary classes, we usually relied on simple structural formulas in which different atoms were clearly depicted. Besides, ball and stick model formulas help us to evolve a conceptual realization of atoms in space. Similarly, line and angle formulas are simple and most easy to draw. Unlike structural formulas, line and angle formulas are simply drawn with the help of plain line. Stereochemical formulas give us mental realization of atoms in three dimensional space. In these formulas, we us lines for atoms laying on plane of paper, a solid wedge for bond directing above the plane and dotted wedge or dashed line for bond directing below the plane of paper. A wavy line shows the bond can either be above or below the plan of paper. Consider the formula of methane below:

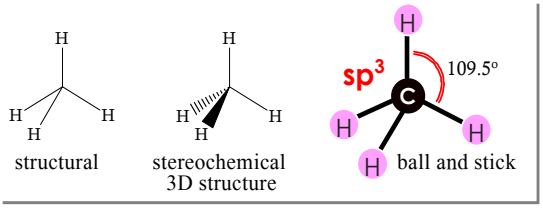


Fig 1.1 Methane has shown in three different formats: structural formula which shows bond angle and position of atoms, stereochemical formula which gives information about spatial arrangements of atoms and ball and stick model.

In methane, two C—H bonds lay on the plan because they are drawn by simple lines. One C—H has shown by dotted wedge which means the bond directs below the plan of paper whereas one C—H bond is shown by solid wedge which means the bond directs above the plan of paper. As a whole, methane is tetrahedral molecule. Consider the following table in which molecules have represented by different type of formulas used in organic chemistry.

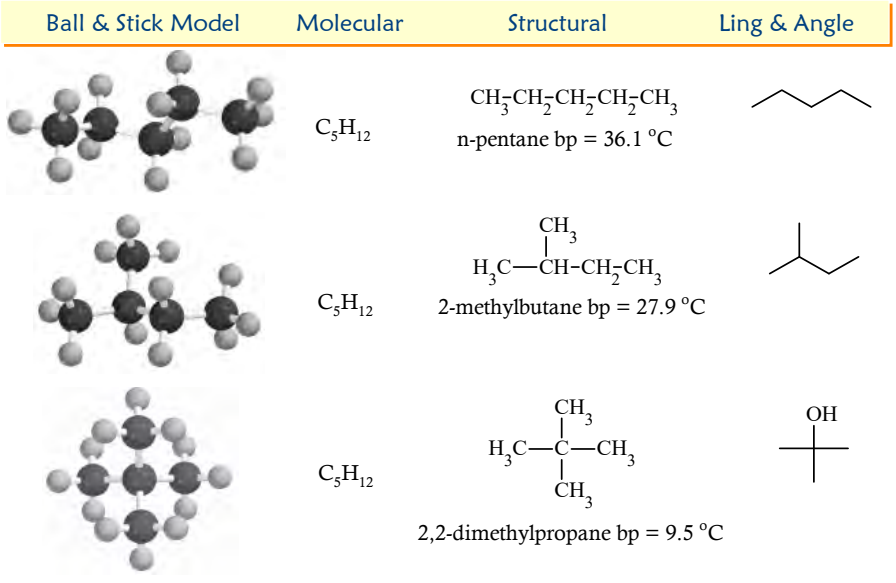
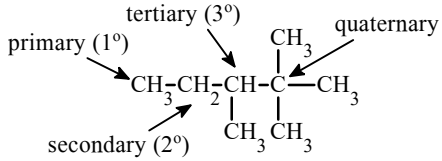


Fig 1.2 Different types of formula used in organic chemistry for representation of molecules.

1.32 Structural Nature of Carbon in Organic Compounds

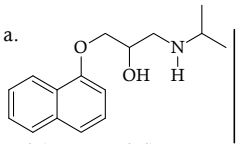
Carbon atoms in organic compounds can be primary, secondary, tertiary or quaternary. A primary carbon is attached to one other carbon atom. Carbon atoms at the ends of an alkane chain are always primary carbons. The hydrogen atoms attached to a primary carbon atom are known as primary hydrogen atoms, and an alkyl group formed by removing a primary hydrogen atom is a primary alkyl group. A secondary carbon is attached to two other carbon atoms, and a tertiary carbon, to three other carbon atoms. Their hydrogen atoms are labeled similarly. Removal of a secondary hydrogen results in the formation of a secondary alkyl group, and such removal from tertiary carbon results in



a tertiary alkyl group. Finally, a carbon attached to four other carbon atoms is known as quaternary carbon atom.

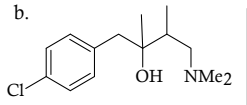
Problem 1.1 State the type of formulas used for representation of the following molecules.

a.



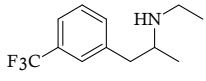
Inderal (propranolol)

b.



Clobutinol

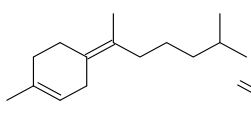
c.

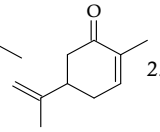


Fenfluramine

Problem 1.2 Point out the number of primary, secondary and tertiary carbons atoms in the following molecules.

1. Bisabolene

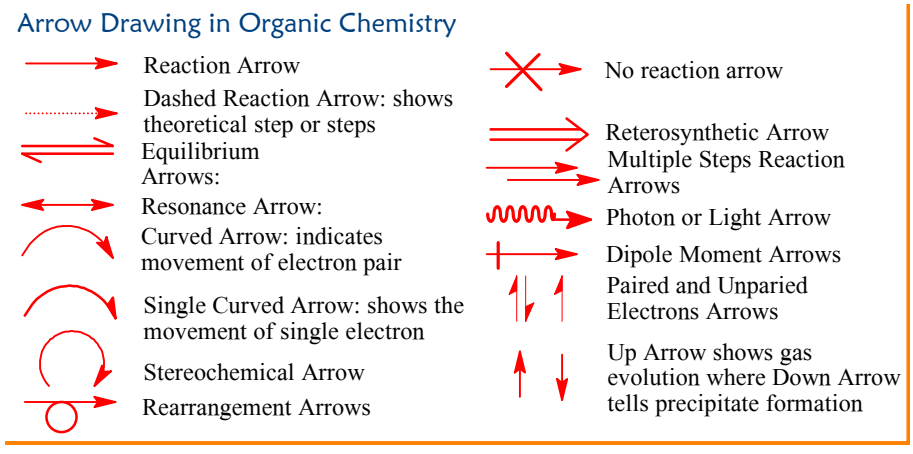




2.Carvone

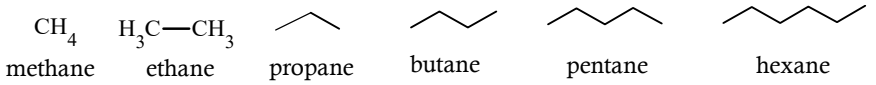
1.33 Arrow Drawing in Organic Chemistry

All reactions proceed from reactants towards products either in a single or multiple steps. The direction of reactions is shown by arrows. Stepwise representation of a reaction is known as mechanism which is illustrated by arrow drawing. Ordinary reaction uses straight arrow from reactants towards product. Movement of electron is represented by curved arrows with a tail emerging from electrons or negative charge (nucleophile) towards proton or positive charge (electrophile) species. The following table depicts different arrows used in organic chemistry.

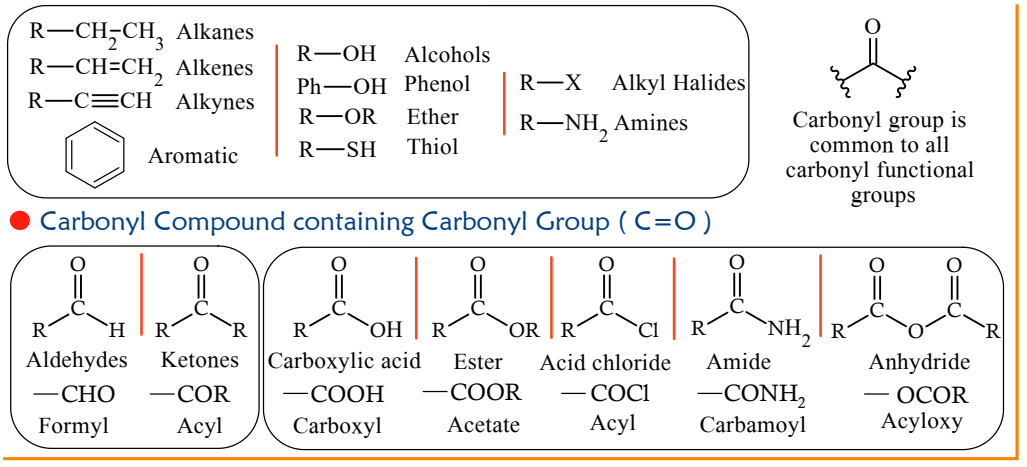


1.34 Homologous Series & Functional Group

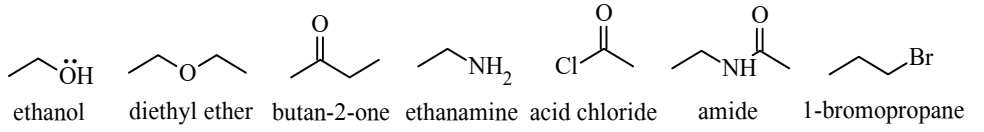
A series of compounds which are differed only by the number of methylene (–CH_2–) groups, is known as homologous series. Each individual member of the series is termed as homolog. For example, butane is a homolog of propane.

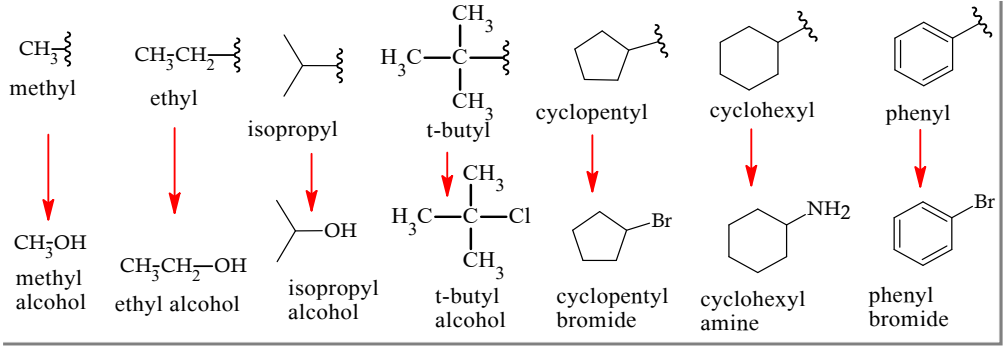


An atom or group of atom which characterizes organic molecules with peculiar set of physical and chemical properties is known as functional group. For example, double bond is functional group of alkene, triple bond of alkynes and carboxyl group (—COOH) is functional group of carboxylic acids. The ensuing table enlists different functional groups prevalent in organic chemistry.



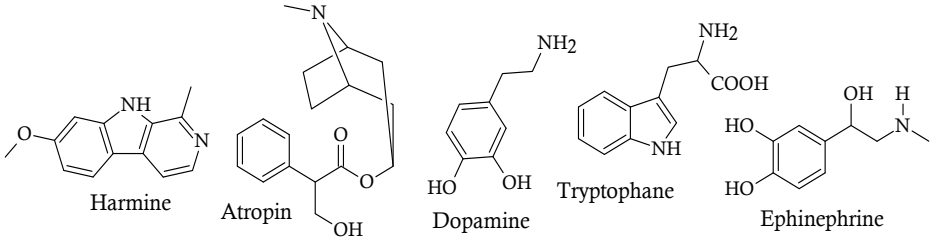
Consider the following molecules with different functional groups frequently encountered in organic chemistry.





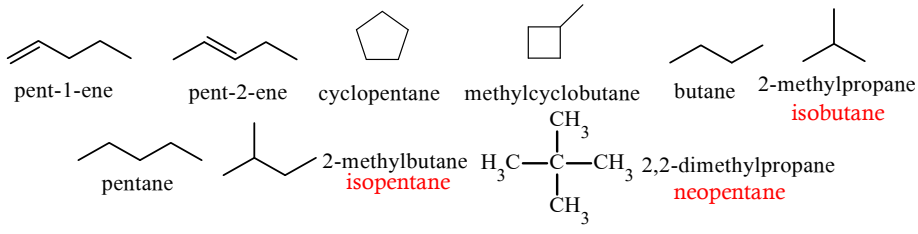
A group of atoms forms by removing hydrogen from alkane is known as alkyl group. We get methyl group from methane after removing one of its hydrogen atom, ethyl group from ethane and propyl group from propane after. With alkenes, we get alkenyl group, alkynes give alkynyl group and aromatic compounds give aryl or phenyl groups.

Problem 1.3 Point out the number of functional groups in the following alkaloids.

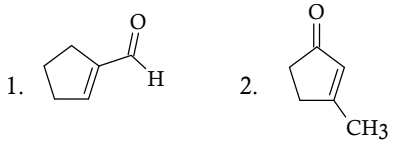


1.4 Isomerism

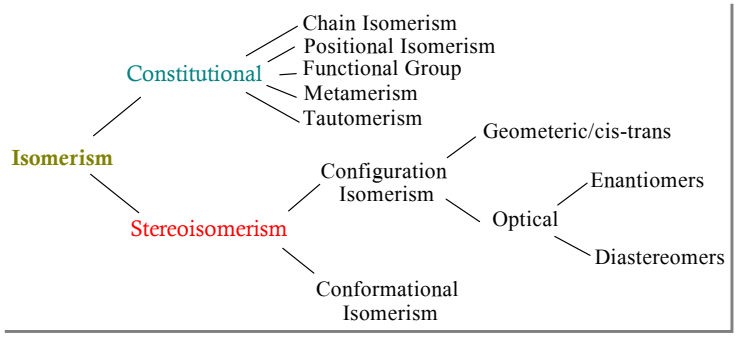
Isomers are different compounds that have same molecular formulas but different structural formulas. When molecules are differed by structure or constitution, the type of isomerism emerges is known as structural or constitutional isomerism.



Problem 1.4 Are the following two molecules are isomers? If yes, state which type of isomerism they exhibit.



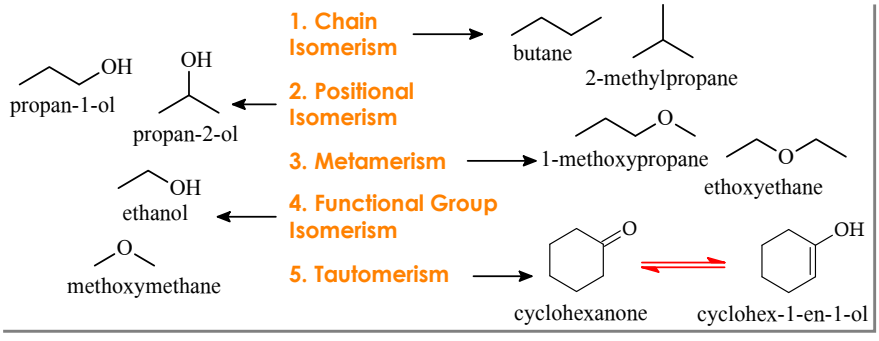
A simplified classification of different types of isomerism has given below:



Constitutional isomerism is classified into chain, functional group, metamerism and positional isomerism. Isomers from each category have different physical and chemical properties. For instance, butane boils at – 0.5 °C whereas its chain or structural isomer 2 – Methylpropane boils at – 11.6 °C.

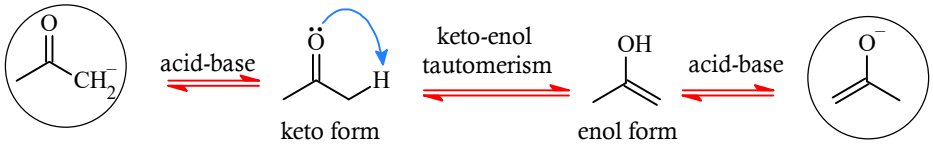
2-Bromobutane	R	S
Boiling Point (°C)	91.2	91.2
Melting Point (°C)	– 112	– 112
Density	1.253	1.253
Refractive Index	1.436	1.436

Isomerism in which same divalent or trivalent (multivalent) atom is linked to different alkyl group is regarded as metamerism. Another type of isomerism is known is tautomerism, which is characterized by shift of proton coupled with corresponding adjustment of double bond. The most common example of tautomerism is keto-enol tautomerism. Stereoisomerism will be dealt in separate section of stereochemistry.

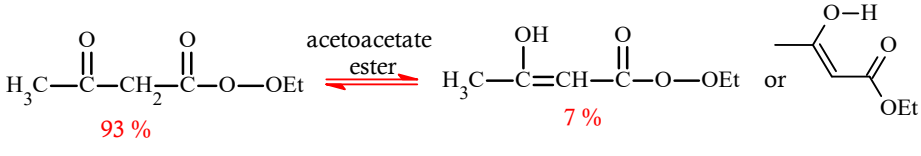


1.41 Tautomerism

Isomerism in which same molecule exists in two different forms that are obtained through the movement of hydrogen followed by corresponding adjustment of double bond is referred as tautomerism (Greek: 'tauto' means same and 'meros' stands for parts). Each of the forms is known as tautomer which interconverts rapidly in an equilibrating mixture. Tautomers can't be separated easily. The position of equilibrium depends upon the structure of either form and is associated stabilization.



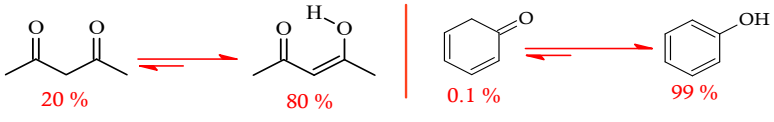
Acetone has α proton that moves toward carbonyl oxygen giving hydroxyl group and double bond between carbon and α carbon atom. We call one tautomer as keto form because it contains ketone moiety as the other form an enol form as it possesses both alkene and alcoholic moieties.



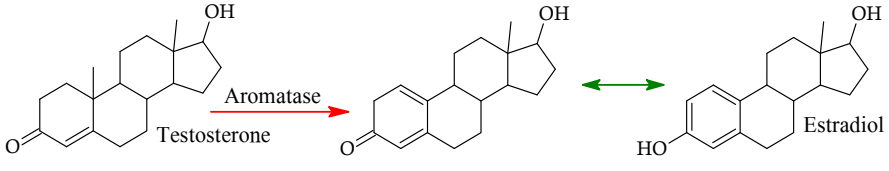
Usually, carbonyl compounds are better suited for demonstration of this phenomenon. Tautomerism was first observed by L. Knorr at university of Jena in 1911 in acetoacetate ester. He was the first to suggest that acetoacetate ester is a mixture of two compounds. The Following table shows difference between tautomerism and resonance. Both phenomenon are closely related, therefore distinction is important to address.

S.No.	Differences	Tautomerism	Resonance
1.	Atomic Nuclei	Different as H moves	Remain same
2.	Different Forms	Exist due to movement of proton	Exist due to movement of electrons
3.	Equilibrium	Dynamic equilibrium	No equilibrium
4.	Functional Groups	Different	Same
5.	Planarity	Not required	Required
6.	Characterization	Can be separated	Cannot be separated
7.	Bond Lengths	Reamin same	Different
8.	Stability	Not concern with	Concern with

Generally, keto form is more stable than enol form. The percentage of enol in acetone solution is quite low because the enol form is quite unstable. However, the enol form of acetoacetate ester exists in considerable proportion which is due to stabilization offered by hydrogen bond holding molecule in six member cyclic structure. Further, the establishment of conjugated system contributes considerable stabilization. The situation is same in following examples:

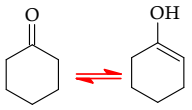


Testosterone is the most potent male sex hormone (androgen). Likewise, estradiol is the dominant female sex hormone (estrogen). Both of these hormones are synthesized in testes from cholesterol. In females, estradiol is synthesized in ovaries from testosterone. Sex hormones are responsible for maintaining secondary sex characters in both sexes. Whether testosterone or estradiol, both are found in males and females.

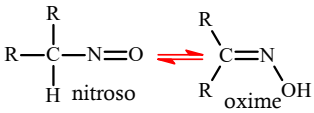


Testosterone differs from estradiol by presence of aromatic ring in the latter. In fact, both differ by ring of the steroid structures shown below. Enzyme aromatase converts testosterone to estradiol. The enzyme initially transforms testosterone to a cyclic conjugated ketone which rapidly tautomerise to estradiol. In other words, keto-enol tautomerism is exhibited by transformation of testosterone to estradiol in the presence of aromatase enzyme. The following table enlists different types of tautomerism.

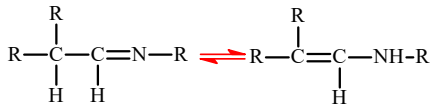
1. **Keto-Enol**



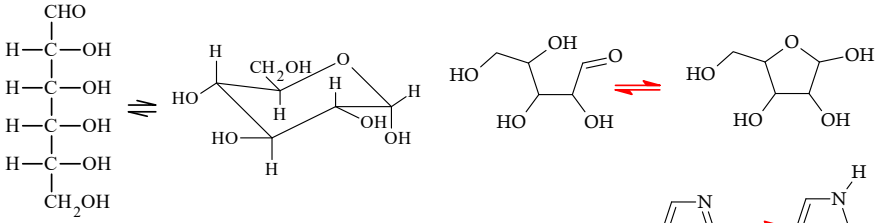
2. **Nitros-Oxime**



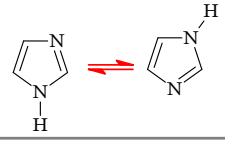
3. **Imine-Enamine**



4. **Ring-Chain**: This type involves relocation of proton which is followed by ring formation from an open chain compound.



5. **Prototrophic or Annular**: This type of tautomerism involves the relocation of proton, especially in heterocyclic system.



1.5 Intermolecular Forces

Intermolecular forces exist among molecules unlike intramolecular ones which operate within molecules such as covalent, ionic or coordinate covalent bonding. There are different types of intermolecular forces which are collectively known as van der Waals forces. All such forces are electrical in nature. Polarity is not the only feature that enables the operation of intermolecular forces because even non polar molecules exhibit liquid and solid character which reflects the physical nature of such compounds is bestowed by intermolecular forces that even operate among non-polar molecules.

In organic chemistry, we encounter thee different types of intermolecular forces: dipole-dipole forces, dispersion forces and hydrogen bond. Some organic molecules such as alkyl halides, aldehydes or ketones possess permanent dipoles because presence of C—X bond in alkyl halides or carbonyl group in carbonyl compounds render them polar in character. The dipole becomes stronger when hydrogen bonds to small and electronegative atoms such as nitrogen, oxygen or fluorine. This type of intermolecular forces is known as hydrogen bonding whose bond dissociation energies vary between 4—38 kJ/mol.

Boiling Points (°C) of Some Isomeric Alkanes

C_4H_{10}	Butane	0.5	C_6H_{14}	Hexane	68.7
	Methylpropane	11.7		3-Methylpentane	63.3
C_5H_{12}	Pentane	36.1		2-Methylpentane	60.3
	2-Methylbutane	27.9		2,3-Dimethylbutane	58
	2,2-Dimethylpropane	9.5		2,2-Dimethylbutane	49.7

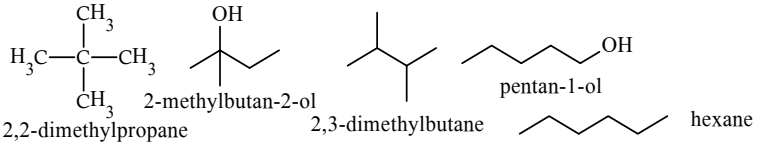
Hydrogen bonding is weak than covalent bonding but stronger than dipole-dipole interaction. Alkanes are non-polar molecules where dipole induced dipole forces exist. These forces are weak that make alkanes relatively easy to evaporate, hence incorporate low melting and boiling points to them.

Fajan's rule predicts the covalent character of molecules based on polarizability of molecules. More polarizability means more covalent character. Usually, polarization is distortion of electronic cloud in the presence of external charge that establishes strong association among molecules. For instance, carbon tetra iodide presents stronger dispersion forces as compared to carbon tetrafluoride because the CI_4 has iodine which is bigger in size and thus its electronic cloud is easy to polarize. In larger atoms, electronic clouds lie away from the strong attractive influence of nucleus, therefore they are more prone to distortion. Greater the distortion, stronger will be the covalent character which means dispersions forces would operate efficiently, thus making the overall compound high melting and high boiling point species.

Methane (CH_4), for instance, is non polar molecule. Its melting and boiling points are considerably low: -182.6 °C and -168 .8 °C respectively. At room temperature, CH_4 exists in gaseous state. However, it can be liquefied or solidified. How does this happen when CH_4 is non polar. In fact, intermolecular forces give answer. London dispersion forces operate among CH_4 molecules. Although electronic density distribution in CH_4 is uniform yet at some instance it can be distorted which incorporates a temporary dipole within a molecule. This temporary dipole induces dipole in near molecules which establishes electrostatic interaction among CH_4 molecules. This interaction tells us why CH_4 exists in liquid or solid state. Larger molecules have high surface area which means higher degree of intermolecular forces to operate among molecules. For instance, straight chain alkanes have larger surface area than branched ones. Consequently, straight chain alkanes have higher values of melting and boiling points as compared to branched analogues. Straight chain pentane (unbranched) has higher melting and boiling point (36.1°C) as compared to neopentane (branched) whose boiling point is 9.5 °C.

Solved Problem 1.1 Predict boiling point of the following molecules!

Intermolecular forces, molecular weights and surface areas are chosen to predict the boiling point of molecules. Neopentane is branched, hence its boiling point is lower than all given examples. Next, 2,3-dimethyl is bit more branched, it ranks higher in boiling point to neopentane because it is less branched as compared to neopentane, n-hexane comes next because it is straight chain which demonstrates higher intermolecular forces as compared to former two branched alkanes. Alcohols demonstrate hydrogen bonding, therefore their boiling points are higher than alkanes. Likewise, branched alcohols have lower boiling point as compared to straight chain alcohols.



On the basis of increasing boiling point, we can arrange them as follow: Neopentane (10 °C) < 2,3-dimethylbutane (58 °C) < hexane (69 °C) < 2-methylbutan-2-ol (102 °C) < pentan-1-ol (138°C)

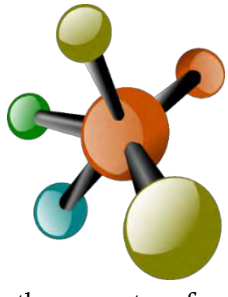
1.6 Chemical Bonding

A chemical reaction is exchange of electrons among atoms and molecules for yielding new compounds. A chemical reaction tries to establish link among atoms. This link is known as chemical bond which holds atoms together in a stable molecule. What enables these atoms to join in a stable molecule? In fact, a bond is required to establish the link among atoms and molecules. This link or bond is known as chemical bond. Atoms use valence electrons (outermost electrons) to make chemical bond. These electrons are either shared (covalent bond), lost or gained (ionic bond) or partially associated (coordinated covalent bond) for establishing chemical connectivity.

G. N. Lewis expounded the formation of bond on the basis of electronic configuration of inert gases (noble gases). His theory, Electronic Theory of Valence, explains: two or more atoms interact to achieve stable noble gas electronic configuration of duplet or octet by gaining or losing or sharing electrons. Valency is the number of electrons gained, lost or shared in the valence shell of an atom. According to Lewis, all atoms having electronic configuration other than noble gases are unstable. For stability, atoms strive to attain electronic configuration of noble gases.

1.61 Theories of Bonding

Different theories of chemical bond have been proposed with intent to explain the nature of chemical bond, its formation, shape of molecules and varied properties associated with the bonding. Three such theories are significant in our discussion: VSEPR (valence shell electron pair repulsion) theory, VBT (valence bond theory) and MOT (molecular orbital theory).



1. VSEPR Theory

VSEPR theory helps explaining the nature, shape and geometry on the basis of valence pair and bond pair of electrons around the central atom in a molecule. In fact, those electrons which participate in bonding determine the geometry. Bonding electrons are valence in character. Both bonding and lone pair of electron participate in assigning the geometry of molecules. Bond pairs of electrons are those which participate in formation of chemical bond, whereas lone pairs don't participate in chemical bond formation. Lone pair of electron influence geometry due to repulsive factor. Double and triple bonds are treated like single bond. In general, the order of repulsion among electron pairs is as follow:

Lone pair – lone pair > lone pair – bond pair > bond pair – bond pair

The above order shows that repulsion caused by lone pair – lone pair interaction is greater than all other possibilities because lone pairs are under the influence of one nuclei, therefore it occupies more space and exerts greater repulsion as compare to bond pair which occupies less space because they are under the influence of more than one nuclei. In methane, there are four bond pairs and no lone pair. The molecule has tetrahedral shape. Ethene and ethyne have three and two bond pairs respectively. None of

these molecules has lone pair. Ethene is trigonal in shape where ethyne is linear. VSEPR theory usually helps explaining the shape and geometry of inorganic molecules.

VSEPR Theory

VSEPR stands for valence shell electron pair repulsion. The theory was presented by Nevil Sidgwick and Robert Powell at Oxford University and later elaborated and developed by Gillespie and Nyhlom in 1957 at the University College London. Following are main points of the theory are:

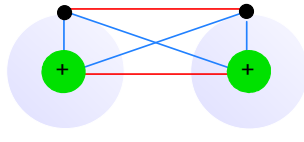
1. Electron pairs around central atom arrange in such way that minimize repulsion.
2. Non-bonding (lone pair) electron around central atom occupy more space than bonding ones.
3. The extent of repulsion between lone pair and lone pair is greater than bonded pair and bonded pair.
4. Space occupied by two or three bonded pair of electrons in double and triple bond is more than single bond.
5. Influence of bonded pair of electron decrease with increase in electronegativity of atom.

VSEPR theory chiefly tried to explain the geometries of molecules on the basis of Lewis dot theory, which was simple approximation for assessing the nature of chemical bonding. However, the theory failed to explain how atoms join or what are bond energies? For instance, VSEPR does not explain the nature of bond formation in simple molecule such as H_2 or F_2. In a bid to address the new dynamics of chemical bonding, quantum mechanics presented two important theories: valence bond theory and molecular orbital theory (MOT). VBT explains that electrons participate in chemical bonding are possessed in atomic orbitals of atoms. MOT says that atomic orbitals combine to form molecular orbitals. It is important to note that neither theory helps explaining the complete picture yet each contributes significantly in interpreting the nature of chemical bonding.

2. Valence Bond Theory (VBT)

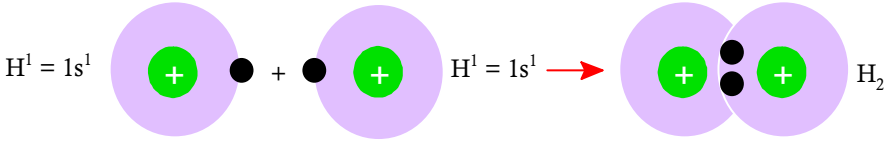
VBT was introduced by Hitler and London in 1927 and later on improved by Pauling and Slater. In fact, the theory war propounded with intent to fill up the shortcomings of VSEPR theory which failed to address: how electrons are shared when they carry similar charge, how a chemical bond forms, what is the status of energy changes during chemical bond formation and how sigma (σ) and π bonds are formed etc.

When two hydrogen atoms are far away from each other, their potential energies are higher, attractive or repulsive forces are almost non-existent. As soon as they begin to approach each other, potential energy of each hydrogen atom decreases. When both atoms are sufficiently close to each other, attractive forces establish and potential energies become negative. Six forces develops: two repulsive and four attractive, as has shown by blue and red lines in the adjoining figure. Energy is released during H_2 formation which is evident from the fact that the potential energies of each hydrogen atom decrease as they approach each other.



$$H + H \longrightarrow H_2 \qquad \Delta H = -436 \text{ kJ/mol}$$

As attractive forces are dominant, bond between the two hydrogen atoms establishes. In short, VBT tries to explain the formation of covalent bond on the basis of energetic associated with the atoms participating in chemical bond formation.



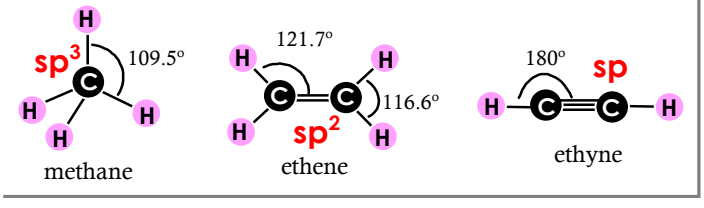
Problem 1.5 Explain the formation of H_2, N_2, H_2O, HF and F_2 molecules.

Hybridization

VBT predicts mixing of two atomic orbitals of hydrogen for formation of a covalent bond. Hybridization is mixing of atomic orbitals of different size, shape and energy to form new set of uniform molecular orbitals of same size, shape and energy. These molecular orbitals are known as hybrid orbitals which establish bonding in a molecule. The number of hybrid orbitals is always equal to the number of atomic orbitals. Hybridization is essential and it takes place before the formation of a bond. Consider the following table where number of hybrid orbitals and their geometries and bond angles are listed:

Hybrid orbitals	Hybridization	Geometry	Bond angle
2	s + p = sp	Linear	180°
3	s + p + p = sp^2	Trigonal	120°
4	s + p + p + p = sp^3	Tetrahedral	109.5°

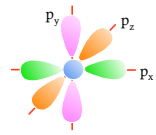
Hybridization is an important feature for predicting geometry of molecules. Besides, it also influences certain physical and chemical properties of organic molecules. For instance, acetylenic hydrogen is acidic in character due to sp hybridization of carbon atom. In organic chemistry, we usually deal with three types of hybridization.



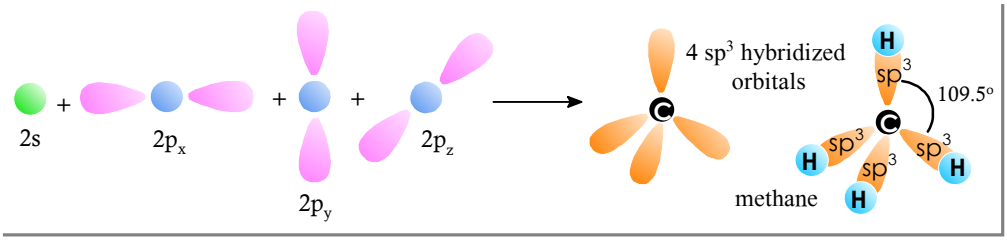
1. Tetrahedral Hybridization (sp^3)

When one s and three p atomic orbitals mix up with one another to give four sp^3 hybridized orbitals is known as sp^3 hybridization. Consider the formation of methane molecule.

$C^6 = 1s^2\ 2s^2\ 2p^2$ or $1s^2\ 2s^2\ 2p_x^1\ 2p_y^1\ 2p_z^0$ **Ground state** electronic configuration
$C^6 = 1s^2\ 2s^1\ 2p^3$ or $1s^2\ 2s^1\ 2p_x^1\ 2p_y^1\ 2p_z^1$ **Excited state** electronic configuration



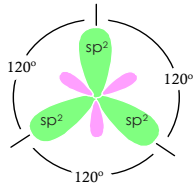
From above configuration, we can assume that in methane one carbon and four hydrogen mix up to form the molecule. In other words, one s and three p orbitals of carbon mix up to form four equivalent sp^3 hybridized orbitals.



Atomic orbitals interact to form new molecular orbitals. For instance, in methane, one atomic orbital of carbon atom mixes up with three p atomic orbitals of carbon atom to form four hybridized sp^3 molecular orbitals which orient four hydrogen atoms towards the corner of regular tetrahedron. Remember, all hybridized orbitals form sigma bonds. In methane, we have four hybridized orbitals, therefore it establish four sigma bonds orienting at angle of 109.5°.

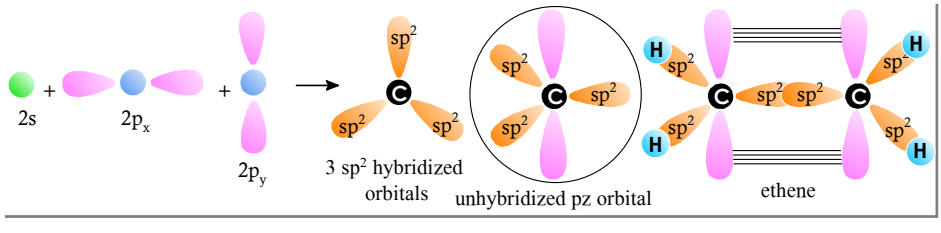
2. Trigonal Hybridization (sp^2)

In sp^2 hybridization, one s and two p orbitals combine to form three sp^2 hybridized orbitals. Two such hybrid orbitals form two σ bonds with two hydrogen atoms, where the third hybridized orbital forms another σ bond with carbon. This hybridization gives rise to one unhybridized p orbital which remains parallel to the plane formed by the three hybridized sp^2 orbitals. The unhybridized p orbital has one unpaired electron. In case of ethene, two unhybridized p orbital on two adjacent carbon atoms establish lateral overlap for π bond formation. The double bond between two carbon atoms in ethene is σ and π by nature. Bond angle between three sp^2 hybridized orbitals in ethene is 120° which make the structure trigonal planar.



$C^6 = 1s^2\ 2s^2\ 2p^2$ or $1s^2\ 2s^2\ 2p_x^1\ 2p_y^1\ 2p_z^0$ **Ground state** electronic configuration
$C^6 = 1s^2\ 2s^1\ 2p^3$ or $1s^2\ 2s^1\ 2p_x^1\ 2p_y^1\ 2p_z^1$ **Excited state** electronic configuration

We can assume that in ethene one carbon and two hydrogen mix up to form the molecule. In other words, one s and two p orbitals of carbon mix up to form three equivalent sp^2 hybridized orbitals in which two overlap with two hydrogen atoms and one with another sp^2 hybridized orbital of another carbon atom for giving ethene molecule.



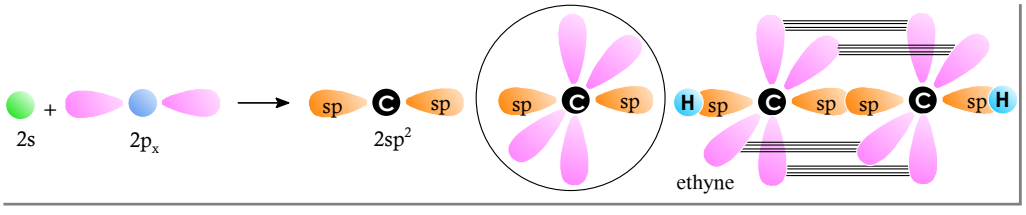
Sigma bond is stronger than π one because the former forms through head on overlap between hybridized orbitals unlike the latter which forms through weak lateral overlap that operates through space. Thus, we can say, π bond is more reactive and less stable than σ bond. As general rule, double bond reflects sp^2 hybridization. Molecules with double bond between two carbon atoms are regarded as alkenes. In other words, double bond is functional group of alkenes, an important class of organic compound represented by general formula of $C_n(H_2O)_n$.

3. Linear Hybridization (sp)

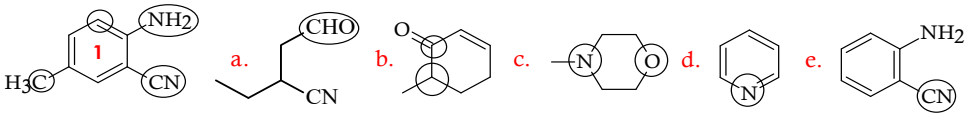
In acetylene, we find sp hybridization that is characterized by linear geometry orienting the two sigma bonds at 180°. Unlike ethene, acetylene or ethyne has two unhybridized orbitals which form two π bonds through lateral overlap. The triple bond in alkyne has two π and one σ bond. Consider the formation of ethyne molecule.

$C^6 = 1s^2\ 2s^2\ 2p^2$ or $1s^2\ 2s^2\ 2p_x^1\ 2p_y^1\ 2p_z^0$ **Ground state** electronic configuration
$C^6 = 1s^2\ 2s^1\ 2p^3$ or $1s^2\ 2s^1\ 2p_x^1\ 2p_y^1\ 2p_z^1$ **Excited state** electronic configuration

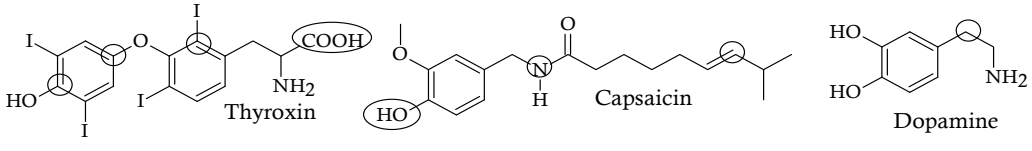
From above configuration, we can assume that in ethyne one carbon and two hydrogen mix up to form the molecule. In other words, one s and one p orbitals of carbon mix up to form two equivalent sp hybridized orbitals. Notice, the encircled figure reflects an sp hybridized carbon which contains two sp hybridized orbitals directed at 180° and two unhybridized p orbitals that form two π bonds via lateral overlap. The two hybridized orbitals form two sigma bonds.

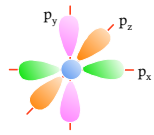


Problem 1.6 Point out type of hybridization in encircled atoms in the following molecule.



Problem 1.7 Point out type of hybridization in encircled atoms in the following molecule.



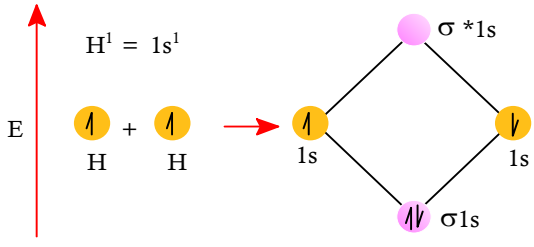


3. Molecular Orbital Theory

Multiple questions aroused when remained unanswered by VSEPR and VBT theories, though both contributed significantly in elaborating the nature of chemical bonding. Questions such as paramagnetism, multiple bond formation and existence of molecules hadn't yet been answered until molecular orbital theory (MOT) was propounded by Hund and Mullikan in 1932. According to this theory, molecules are formed by linear combination of atomic orbitals (LCAO). The number of molecular orbital (MO) is equal to the number of atomic orbitals (AO). Molecular orbitals are of two types: bonding molecular orbitals (BMO) and anti-bonding molecular orbitals (ABMO). BMOs are lower in energy and stable unlike ABMOs which are unstable because they are higher in energy. BMOs are formed by constructive overlap (interference) of AO where ABMOs are formed through destructive overlap of AO. In order to apply this theory, we consider the formation of the following molecules.

Hydrogen Molecule

Hydrogen molecule is formed by combination of two hydrogen atoms. Atomic orbital of one hydrogen atom overlap with atomic orbital of another hydrogen atom. Two atomic orbital overlap which give rise to formation of two molecular orbitals: one is BMO and another is ABMO. Each hydrogen atom has one electron. Thus both hydrogen atoms contribute two electrons which are placed in BMO in increasing order of energy. In fact, the lower energy orbital i.e. BMO is first filled as per Auf Bau principle (electrons are being filled in increasing order of energy). The ABMO remains empty. Bond order for the molecule is one which reflects the existence of H_2 molecule unlike He_2 molecule where bond order is zero.



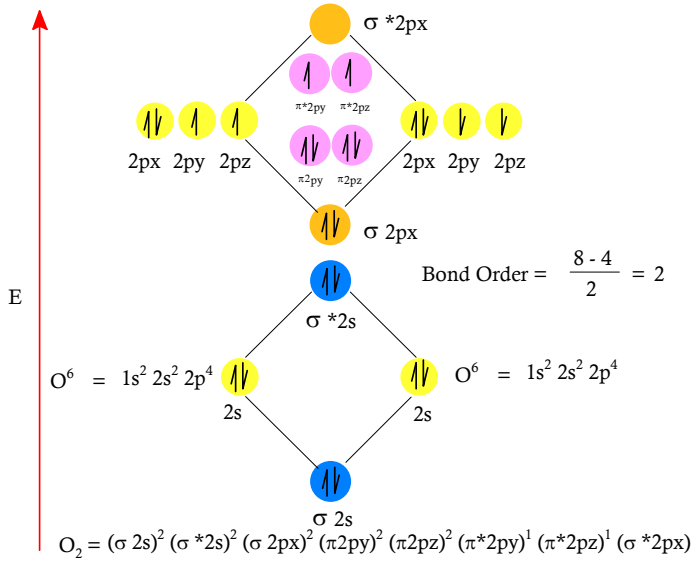
$$\text{Bond Order} = \frac{\text{es in BMO} - \text{es in ABMO}}{2} = \frac{2-0}{2} = 1$$

Bond order for hydrogen molecule is one which reflects a single covalent bond between two hydrogen atoms. MOT diagram for O_2 molecule is given below:

Oxygen Molecule

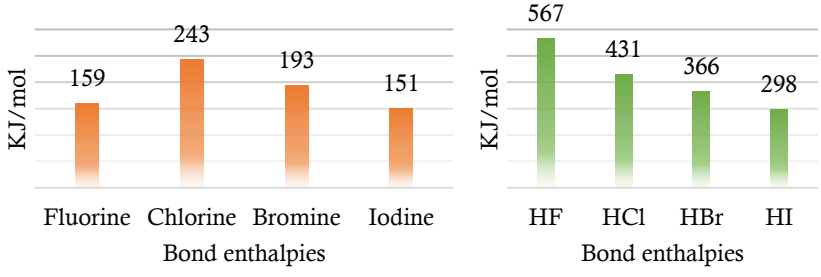
MOT tells us whether oxygen has single or double bond. It also improves our knowhow about magnetic properties of the molecule. Let's represent O_2 molecule diagrammatically in the following illustration. Bond order for O_2 is 2 which reflects a double bond in the molecule. One is sigma, another is π bond. Moreover, the molecule is paramagnetic due to presence of unpaired electrons in π *2py and π *2pz. The two orbitals

are anti-bonding, hence both unpaired electrons are delocalized over the O_2 molecule. Each oxygen atom holds two lone pair of electrons in O_2 molecule and both are paired. The unpaired electrons are not the part of lone pairs.

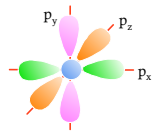


1.62 Bond Characteristics

As stated in VBT, bond formation is accompanied by release of energy. When two atoms come close to each other, they lose potential energy and become associates with each other at close distance required for electronic association. In other words, bond making is exothermic process because energy is released during the process. Contrary, bond breaking is endothermic process because it requires energy to separate atoms from each other. The strength of bond determines the extent of energy released or absorbed. Different bonds have different strengths. Even the strength of bond formed by same atom with different atom is different. For instance, the covalent bond formed by hydrogen with halogen is different in nature.



Bond energy is the amount of heat required to break one mole of covalent bond to give individual atoms. It is also termed as bond enthalpy which is measured in kJ/mol. Among halogens which are diatomic molecules, with exception of fluorine, bond enthalpy decrease down the group because atoms get larger in size which make the bond weaker, hence low energy is required to break them off. In case of fluorine, the two atoms are so small that electronic cloud around each F atom gets too closer to repeal each other. This



repulsion makes the covalent bond weak. Hence, low energy is required to break it off. Bond enthalpies in hydrogen halides decrease down the group on account of weak bonds. Down the group, size increase, hence bond length increase. Lengthy bonds are weaker.

1.63 Dipole Moment

Dipole moment is the quantitative measure of bond polarity. The product of charge and distance between two ions is known as dipole moment. It is denoted byμ. Mathemcatically, $\mu = q \times r$, Where q is the charge on each ion and r is the distance between two ions. Dipole moment is vector quantity. It is represented by drawing an arrow from least electronegative atoms toward more electronegative atom.

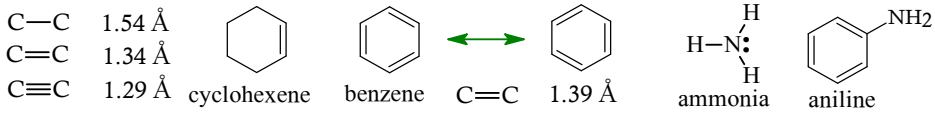
Dipole moment is usually expressed in unit Debye (D).

$$1\ D = 3.336 \times 10^{-30}\ Cm$$

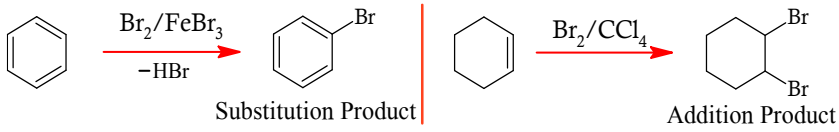
Hetero diatomic molecules have some value of dipole moment unlike homo diatomic molecule where the value of μ is zero. Dipole moment tells us about useful features of molecules. For instance, tri atomic molecules such as CO could be assessed for its geometry whether it has linear or bent structure. If the value of dipole moment for CO_2 is zero, the molecule is confirmed linear. If it has some value of dipole moment, we can assume the structure for the molecule is somewhat bent. Dipole moment for cis molecule has some value unlike trans where individual bond moment cancel each other. Thus, we can point out from value of μ whether particular molecule has cis or trans conformation.

1.7 Resonance

A covalent bond is formed through sharing of two electrons. When shared pair of electrons is under the influence of only two nuclei, the bond is said to be localized. For example, in methane, each bond between carbon and hydrogen is localized because the two bonded pair of electrons in each C—H bond is confined to carbon and hydrogen alone. Similarly, a lone pair of electron which is attracted by only one atom is said to be localized. For example, in ammonia, lone pair of electron on nitrogen atom is localized. The lone pair cannot spread over rest of molecule which contains three hydrogen atoms. However, when the shared pair of electrons (π bond) is under the influence, says attracted by more than two nuclei, the bond it forms is known as delocalized chemical bonding. In benzene, each of the double bond is delocalized because all six π electrons are spread over entire molecule. Similarly, the lone pair on nitrogen of aniline is delocalized unlike ammonia, because it is spread over whole aromatic ring.



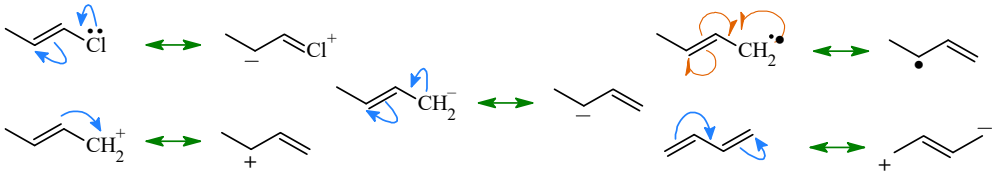
Delocalization of electrons is interesting property that renders many features of molecules altered. For instance, benzene presents different chemical behavior than alkenes although both are common by possessing carbon—carbon double bond. Aromatic compounds on account of its unusual stability give substitution products unlike alkenes that give addition products.



In fact, benzene is quite stable and does not show the reactions of alkenes on account of high stability which is due to its resonance. Resonance is delocalization of electrons be it sigma bond (hyperconjugation or no bond resonance), π bond, lone pair of electrons, free radical or negative charge.

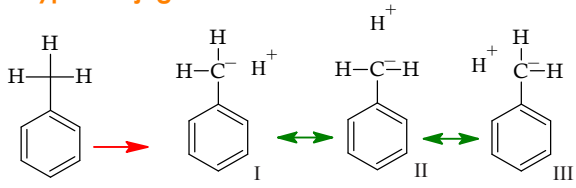
1.71 Delocalization of Double Bond

A double bond or triple bond can be delocalized when it is in conjugation with lone pair of electrons, positive or negative charge, unpaired electron (free radical) or another double or triple bond. Movement of electron on account of resonance forms different resonating structures. All these structures contribute to real structure of the molecule. We call these structures as canonical forms. One of the canonical structures is most stable and is known as resonance hybrid.

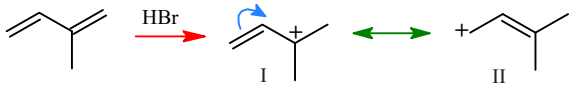


● Examples of Resonance

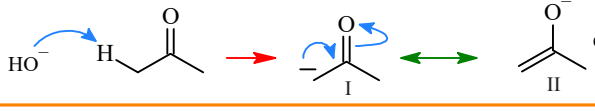
1. Hyperconjugation in Toluene



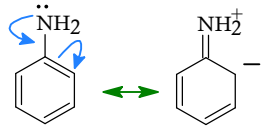
2. Resonance of Carbocation



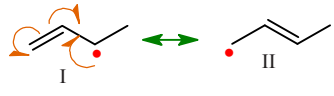
3. Resonance of Carbanion



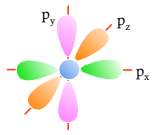
4. Resonance of Electron Pair



5. Resonance of Free Radical



allylic free radical

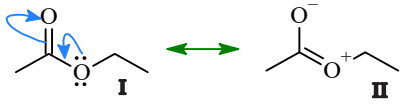


The phenomenon of resonance plays crucial role in determining the physical and chemical features of molecules. The difference in energy between the resonance hybrid and the lowest contributing structure (most unstable) is termed as resonance energy. Due to resonance, three double bonds in benzene swiftly move all over molecule: a C—C bond is double and single for a moment. In fact, all six carbon—carbon bonds in benzene are neither purely double nor purely single. This is how the bond length of each C—C bond is 1.39 Å which is shorter than normal C— C single bond (1.54 Å) and longer than carbon—carbon double bond (1.34 Å).

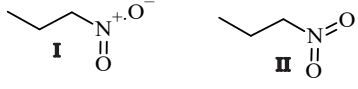
1.72 Rules of Resonance

Resonance is delocalization of electrons which can be lone pair, free electron, negative charge, π electrons, sigma bond or positive charge as shown in above examples. Existence of same molecule in different resonance structures brings stability and incorporates remarkable properties to organic molecules. Each of the resonating structure is known as canonical form. All canonical forms contribute to a resonance hybrid which is weighted average of all structures and consequent representation of a molecule. Some canonical forms contribute less, others more; depending upon the relative stability of particular canonical form. A canonical form which is stable contributes more to the resonance hybrid. Following are some rules which help us to predict which canonical form exist or which contributes less or more.

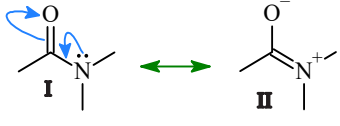
1. All resonance structures have same connectivity of atoms.



2. All canonical forms must be valid Lewis structures. Second row elements must follow the rule of octet. Structure II is not a resonance structure because it is not a valid Lewis structure. Nitrogen has ten instead of 8 valence electrons.

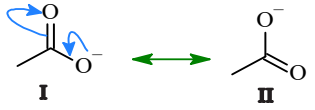


3. All resonance structures must have same charge. Structure II is neutral like I, hence both have same charge.

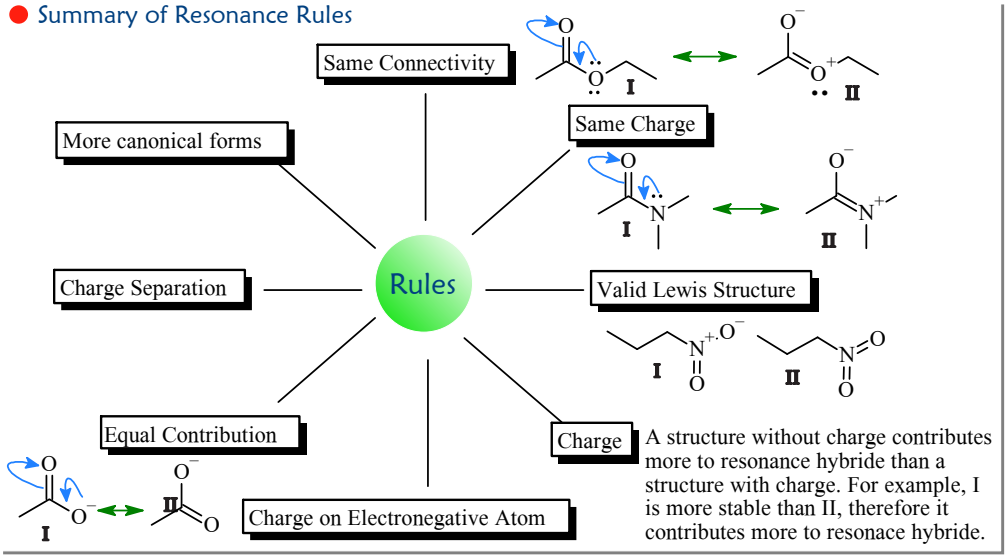


4. A structure without charge is more stable than a structure with charge.
5. A structure in which negative charge resides on more electronegative atom is more stable than one in which negative charge resides on less electronegative atom.

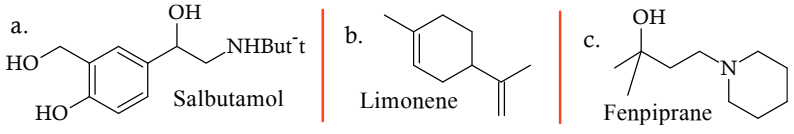
6. A structure where charge separation is less contributes more than one where charge separation is large.
7. Two structures which contribute equally enhance stability such as both resonance structures of acetate ion make the anion stable and parent species more acidic.



● Summary of Resonance Rules



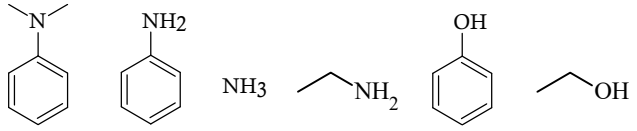
Problem 1.8 Comment which of the following molecule shows resonance and state whether the resonance is confined to one or more positions.



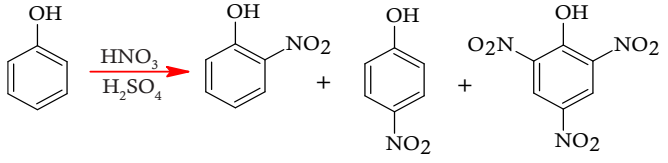
1.73 Resonance Effect: Mesomeric effect

Resonance or mesomeric effect has profound effect on physical and chemical properties of molecules. Not only resonance offers stabilizing phenomenon but it also influences properties such as acidic and basic behavior, reactivity and orientation in aromatic system. The changes in properties of molecules due to delocalization of electron is known as resonance or mesomeric effect. Consider the basicity of NH_3 and aniline. Both molecules have lone pair of electron on N atom which makes it basic in character. Aniline is less basic than ammonia due to resonance effect because lone pair on nitrogen atom delocalizes over aromatic ring, hence not available for free donation as in case of ammonia. Amides are less basic than primary amines because lone pair of electron on nitrogen of amide is delocalized unlike localized lone pair of electron on nitrogen of primary or

secondary amines. Similarly, phenol is more acidic than alcohols because resonance stabilized phenoxide ion more than alkoxide once proton is lost to yield a conjugate base.

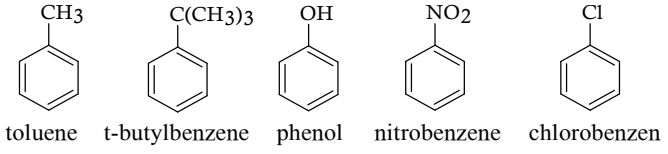


Hydroxyl group on aromatic ring as in phenol makes it more reactive than benzene because lone pair on oxygen atom delocalizes over aromatic ring. Group like hydroxyl one which enhance electronic density on aromatic ring activate the system for ortho/para orientation. In other words, such groups are known as o/p director. They are electron donating groups (EDG) which increase electronic density on the ring.

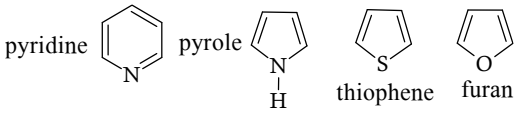


1.74 Outcomes of Resonance Effect

a. Toluene reacts 25 than benzene.
b. t-butyl benzene reacts 16 times faster than benzene but less reactive than toluene.
c. Phenol undergoes nitration 10^3 times faster than benzene.
d. Nitrobenzene undergoes nitration 10^4 times slower than benzene.
e. Chlorobenzene undergoes nitration 30 times slower than benzene?



Pyridine is more basic than pyrrole because lone pair of electron on nitrogen atom of pyridine is not involved in resonance like pyrrole. If we look at the basicity, thiophene is more basic than pyrrole which is in turn more basic than furan.



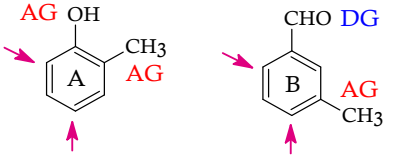
1.75 Orientation of Benzene Ring Containing Two Substituents

If benzene ring has just one substituent, it is easy to predict whether the upcoming second substituent will go to ortho, para or meta position because we decide according to the nature of the group already present whether it is electron withdrawing or donating in character. For example, nitration of toluene gives dominant o/p isomers as compared to meta as methyl group is electron donating in character. The situation becomes difficult

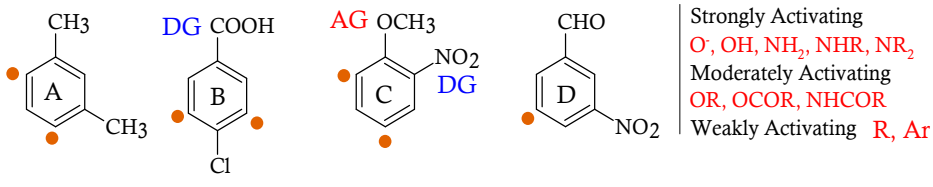
when two substituents are already present on the ring and we are supposed to decide the fate of the third substituent on the ring. Following are some rules that help us in dealing with the difficulty.

Rules of Orientations

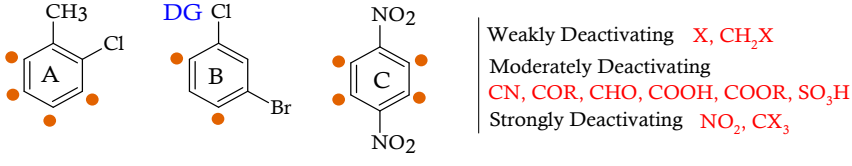
1. When two groups oppose the effect of each other, the group which is strongly activating will orient upcoming substituent. We represent activating group by AG and deactivating group by DG in the following examples. In case of example a both groups are activating yet OH is strongly activating as compared to methyl group, therefore it will lead the orientation of upcoming substituent. In example B, one group is activating and another is deactivating, thus in such cases AG will control orientation.



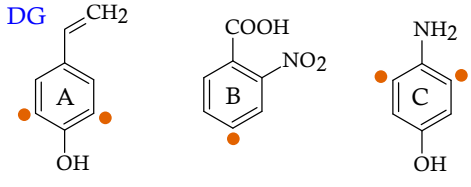
2. The position of orientation on ring when both groups direct the upcoming substituent to the same position is easy to predict. In the following example, as in case of A, both methyl groups direct upcoming substituent to position spotted by red dot. Each position is reinforced by both groups.



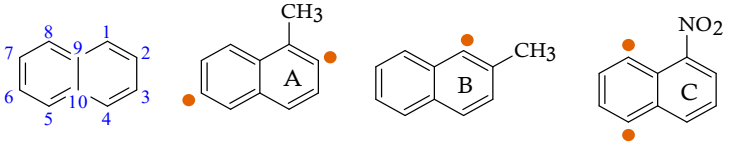
3. When both groups have the same directing potential, the upcoming substituent can occupy any position on the ring.



4. As stated in rule 1 when two groups are activating, the stronger will orient the upcoming substituent. Similarly, when both groups are deactivating, the stronger one will control orientation as in case of B, nitro is stronger deactivating group than carboxyl group. Amino, NH_2 is stronger activating group than OH.



5. In case of naphthalene, when AG is linked to position 1, it will orient coming substituent to position 2 or 4 as in case of example A. However, if AG is present on position 2, it will orient coming substituent towards position 1 as in case of B. When DG is attached to either position 1 or 2, it will orient coming substituent toward position 5 or 8 as in case of C.



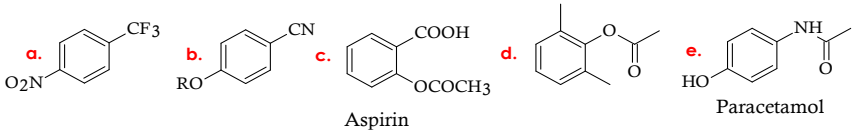
Alkyl Group is Electron Withdrawing

A new research in Cardiff University, UK, published in November 2024 experimentally proven that alkyl group has electron withdrawing inductive effect. This is contrary to the traditional understandings of electron donating behavior as maintained in school and college textbooks and taught by teachers. The new research found that replacing hydrogen with methyl group increases positive charge on adjacent carbon atom. Had the alkyl group electron donating, the positive charge on the adjacent carbon atom would have been decreased. But this is not the case which has scientifically been proven by computational studies using DFT (density functional theory) and charge analysis methods.

The electron withdrawing effect of alkyl group is small as compared to the effects of hyperconjugation, solvent, polarization or steric considerations. For instance, tertiary carbocation is stabilized by hyperconjugation, not by electron donating effect of alkyl groups. In toluene, electronic density from benzene ring is inductively withdrawn by methyl group but compensated by hyperconjugation. The electron withdrawing inductive effect of alkyl group is noticed in isolated or computation system where hyperconjugation and solvent effects are absent. New textbook on chemistry will revise its position on alkyl group and teachers will teach students both traditional and new understanding on alkyl group so that they could evolve critical thinking about understanding chemistry.

In solution, methanol is more acidic than t-butyl alcohol since methoxide anion is more stable than t-butoxide anion which isn't due to alkyl group but solvation of solvent because in gaseous state t-butoxide is more stable than methoxide anion that reflects t-butyl group is bulky and it enhances polarization of negative charge on oxygen as compared to methyl group. Here, alkyl group assists polarization rather –ve inductive effect for stabilizing the alkoxide. In short, teachers like you now convince students not about inductive effect of alkyl group but its polarizability, steric and hyperconjugation features that decide its properties.

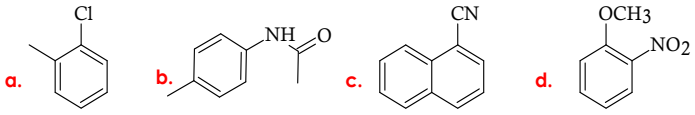
Problem 1.9 Point out relevant position of orientation for upcoming electrophile on each of the following molecule.



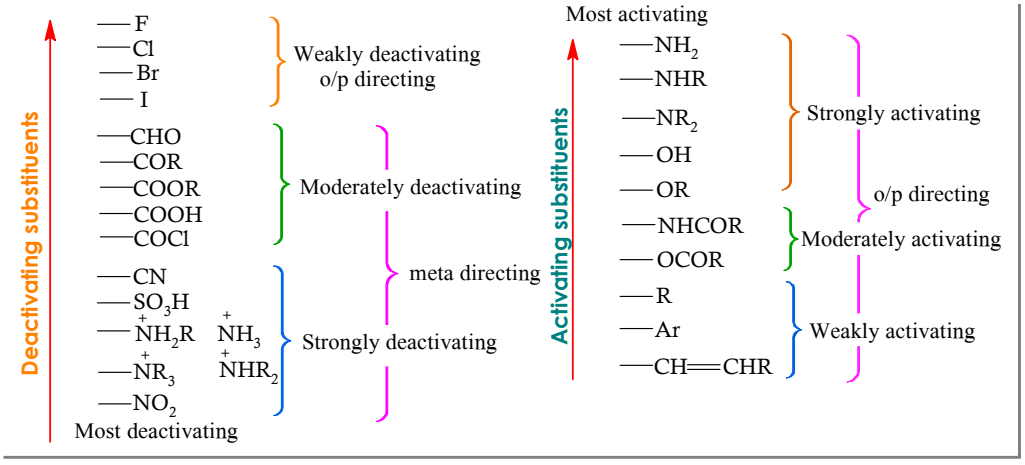
Aspirin

Paracetamol

Problem 1.10 Point out position for upcoming electrophile in any three of the following molecules.



In the following table, different groups have listed on account of their capacity to donate or withdraw electron density from aromatic ring.



1.8 Hydrogen Bonding

Hydrogen bonding is electrostatic force of interaction between hydrogen and an electronegative atom such as fluorine, oxygen or nitrogen. Besides, F, O and N, chloroform also forms hydrogen bonding with oxygen of carbonyl compounds. This bond is represented by dotted lines between the two atoms. Hydrogen acts as a bridge between two electronegative atoms: one in linked by covalent bond where the other by hydrogen bonding. Hydrogen itself attaches to one heteroatom by covalent bond which is of low polarizability and high electronegativity such as oxygen in water or fluorine in HF.

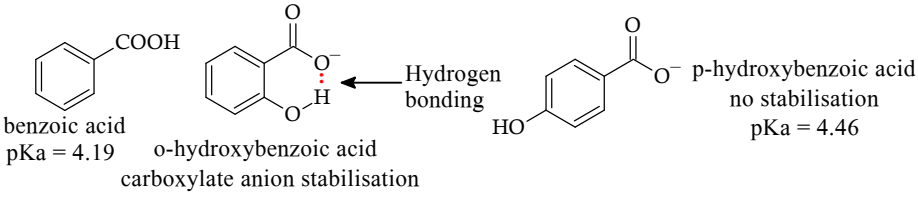
Remember H bond is stronger than all intermolecular bonding but weaker than intramolecular bonding. In fact, H bond is some 20 times weaker than ordinary covalent bond. This difference can be visualized by bond length: O—H bond length in water is 0.96 A° but its Hydrogen bond length is 2.07 A°. The strength of H bond depends upon the electronegativity of the atom attached: fluorine being highly electronegative forms strongest hydrogen bond. Moreover, the acidity of hydrogen atom or the basicity of the atom to which hydrogen atom attaches determines the strength of Hydrogen bond. For instance, the strength of Hydrogen bond in HF is 41.84 kJ/mole. In water, the value reduces to 29.3 kJ/mol, which is further declined to 8.35 kJ/mol in ammonia.

Problem 1.11: Which one would have higher boiling point, butane or acetone? State your reason!

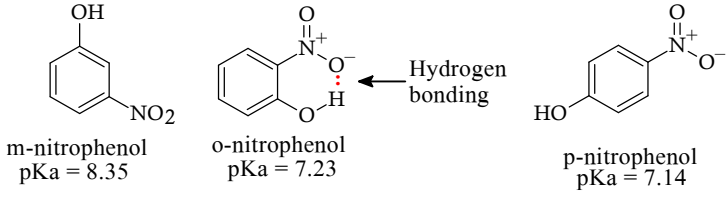
Problem 1.12: Boiling points for CCl_4 and ethanol are 76 and 78 °C. State why ethanol has higher boiling point than CCl_4.

Many important properties of molecules are influenced by hydrogen bonding which acts as significant feature that transforms the chemistry of compounds bearing hydrogen bonding. For instance, hydrogen bonding enable water molecule to boil at 100 °C. If we compare the molecular formula of diethyl ether and ethanol, one finds no difference because both have same formula, that is, C_2H_6O. However, their properties such as boiling points are remarkably different: ethanol boils at 78 °C where diethyl ether boils at 37 °C. This difference can be attributed to hydrogen bonding in ethanol which holds individual molecules tightly enough to be broken apart by temperature less than 78 °C. Diethyl ether exhibits no hydrogen bonding, therefore, it doesn't require higher temperature to evaporate. Water, though lower in molecular weight than the two examples, yet its boiling point is greater than both because water demonstrates sufficient high degree of hydrogen bonding: four hydrogen bonds per water molecule unlike two in HF although fluorine in more electronegative than oxygen of water.

Ortho hydroxybenzoic acid is more acidic (40 times, pKa = 2.16) and has lower boiling point than its para isomer (pKa = 3.41). In ortho case, the conjugate carboxylate anion is better stabilized by hydrogen bonding. Due to intramolecular hydrogen bonding, the ortho isomer demonstrate remarkable depression of boiling point (196 °C) as compared to para one 240 °C). Chelation offered by hydrogen bonding helps cyclization of molecules that makes it easy to get volatile.



Intramolecular hydrogen bonding reduces solubility of ortho nitrophenol as compared to para isomer. Besides, their acidities are influenced by intramolecular hydrogen bonding. Consider the following examples:



Applications of Hydrogen Bonding

Water is liquid due to hydrogen bonding but H_2S and H_2Se are gases due to lack of the bonding. Hydrogen bonding plays significant role. Our body is made of proteins that constitute the structure of our hair, nails and muscles. These proteins are long chain of

amino acids that are linked by hydrogen bonding. Most importantly, our genetic material, DNA helical structure is linked by hydrogen bonding. Ice occupies 9% more volume than liquid water because of tetrahedral arrangements of water molecules in ice.

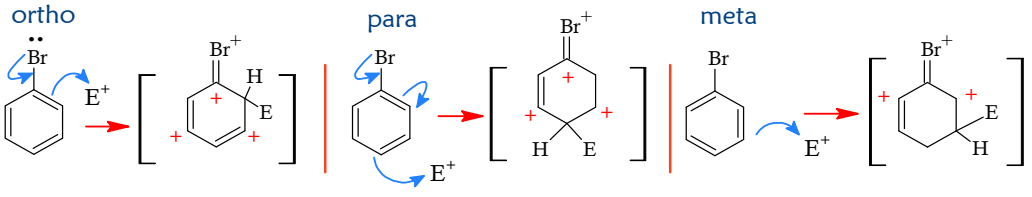
1.9 Electronic Effects

1.91 Inductive Effect

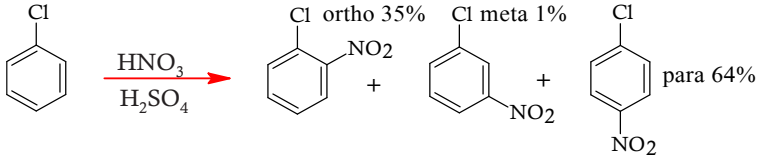
If halogen substituent is present on aromatic ring, it creates strange effect because both inductive and resonance effects are observed. What exactly is inductive effect? The polarization of bond through adjacent polar bond is known as inductive effect which is due to electronegative difference that creates a sort of polarity within molecules by withdrawing electronic density from less electronegative atom towards more electronegative atoms along covalent bond. Halogens are the most electronegative elements of the periodic table. Via inductive effect, halogens withdraw electronic density from aromatic ring, thus render it deactivated. Lone pair of electron present on the halogen atom makes it liable to trigger resonance phenomenon which activates aromatic ring. Which effect is dominant because both operate in opposite directions? One effect is activating whereas the other is deactivating.

Solved Problem 1.2 Halogens are deactivating yet they are o/p directors: How?

Consider the stability of the following halonium ion which forms after electrophilic aromatic substitution reaction on aromatic ring.



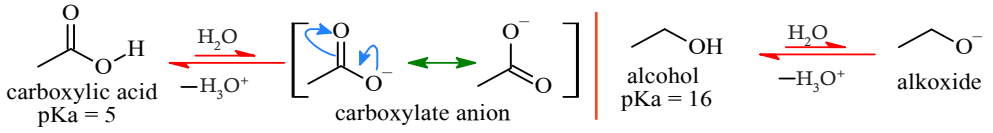
Reason for o/p directions: Halonium or sigma complex obtained from ortho or para attack is more stable than the one obtained from meta attack because in both o/p cases, one of the canonical form has positive charge on the ipso carbon atom (aromatic carbon to which substituent is attached) where it is stabilized by delocalisation of lone pair on halogen atom. This stabilization makes halogen o/p director. Remember, here we have sketched weighted average of all three sigma complexes to show where positive charge forms. You can draw them separately.



1.92 Acidity of Carboxylic Acids

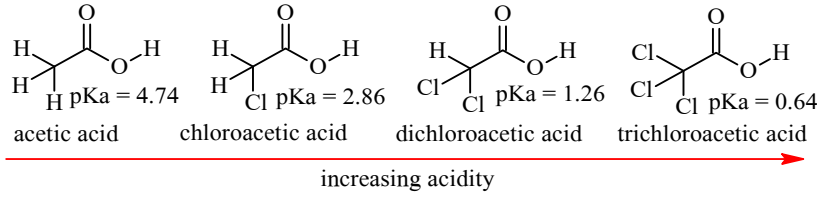
Carboxylic acids are stronger acids than alcohols. For example, pKa value for acetic acid is 5 and 16 for ethanol. Lower the pKa value, higher is acidity. Acids are

stronger because their carboxylate anion (conjugate base) is resonance stabilized unlike alkoxide anion of alcohols where there is no such resonance for stabilization. Both resonance forms of acetic acid are equivalent with negative charge on oxygen atoms, therefore both contribute equally, making parent acid stronger.

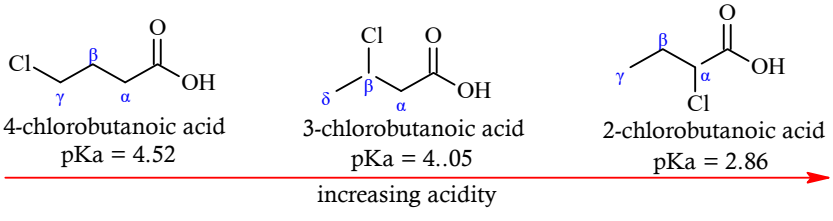


Chloroacetic Acid Derivatives

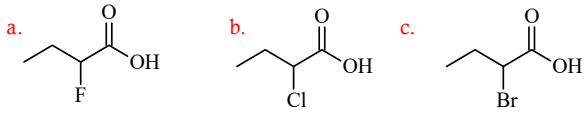
Consider substitution pattern of acetic acid with chlorine atom. As halogen atom is electronegative, it withdraws electronic density from the negative charged carboxylate anion once it forms after loss of proton from the parent acid. This renders the anion stable because halogen atom snatches some of electronic density through inductive effect. Greater the number of halogen atom, higher will be the stability.



If distance of halogen atom increases from negative anion, the influence of inductive effect decreases. Consider the following examples in which chlorine atom is linked to alpha, beta and gamma positions. The closer the chlorine atom linked to carboxylate group, the higher will be the influence of inductive effect. Consequently, the anion will be stabilized and the parent acid will be stronger.



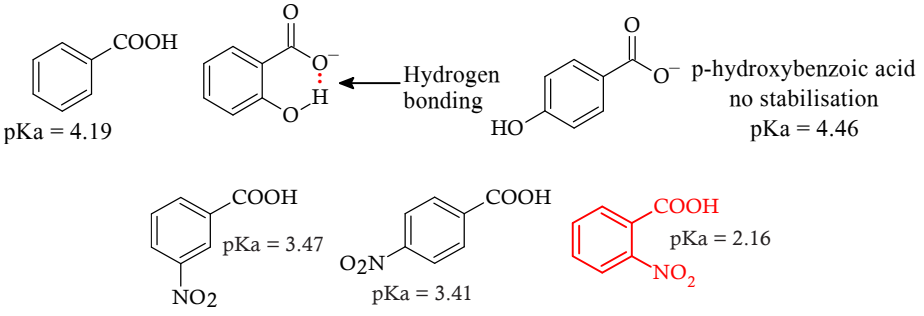
Problem 1.13 Which of the following compounds is more acidic? Justify your answer



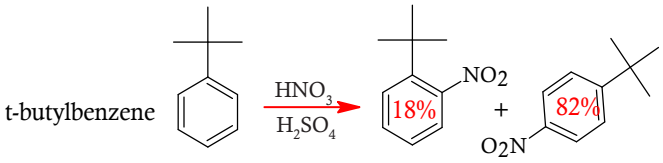
1.93 Field, Steric & Ortho Effects

Ortho nitrobenzoic acid is more acid than its para isomer due to ortho effect. When two bulky groups locate next to each other as in case of ortho nitrobenzoic acid,

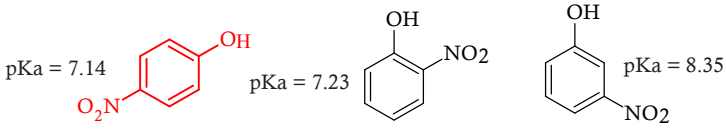
they exert spatial impact (field effect or steric effect) over each other. For instance, in ortho isomer, nitro group pushes carboxyl group out of planarity. Once this happens, carboxyl group no longer remains in resonance with aromatic ring. This effect is known as ortho effect which makes the ortho isomer more acidic than para one. When proton is lost, the size of the carboxylate anion reduces which is no longer bulky enough to be influenced by ortho effect. This turns the negative anion in resonance with the ring.



Sterically, t-butylbenzene gives predominantly p-isomer upon nitration because t-butyl is bulky group and it blocks ortho position for nitro ligand to attach. This effect is known as steric effect.

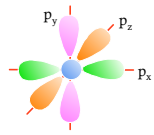


When electron withdrawing group (EWG) is present on the ring, it reduces electronic density at ortho and para positions. In other words, EWGs reduce electronic density at ortho and para sites that render these positions positively charged. As carboxylate anion is present on ortho position, therefore positive charge on the carbon bearing the negative group helps in stabilization of the carboxylate anion. Unlike ortho nitrobenzoic acid, para nitrophenol is more acidic than its ortho isomer. Here, low acidity of ortho isomer is reflected by intramolecular hydrogen bonding that traps hydrogen from free release. Hydroxyl group is small, so no ortho effect is observed here.



1.94 Solvent Effect

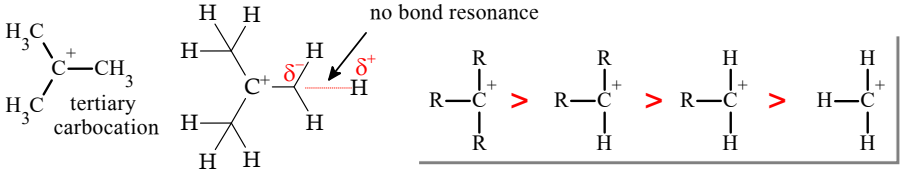
Solvent plays crucial role in organic chemistry. Majority of organic reactions are solvent dependent. The chemistry of solvent is not only limited to reactions but almost all chromatographic techniques require solvent for separation, purification and identification of organic compounds. The effect with which solvent influence the chemistry of molecules or reactions is known as solvent effect. Solvent effects are very broad in organic chemistry. A solvent engages in salvation, affects rate of reaction, acts a catalyst as acid catalyzed



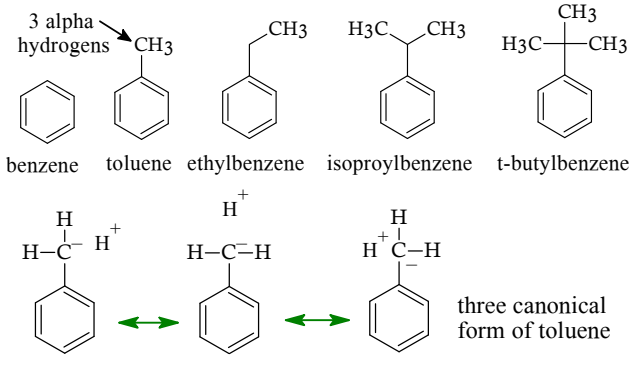
reactions, influences equilibrium of a reaction, induces rearrangement, influences stereochemistry, effect solubility and leaves pronounced impacts on acidic and basic character of organic molecules.

1.10 Hyperconjugation

Hyperconjugation, also known as no bond resonance, is type of resonance that involves sigma electrons to delocalize. Usually, C—H bond of alkyl group demonstrates a situation where no bond situation exists between carbon and hydrogen leaving positive charge on hydrogen and negative charge on carbon atom. The partial deposition of negative charge enhances electron donating capacity of carbon atom to delocalize over connected resonance system. Consequently, the effect makes alkyl group electron donating in character. For instance the methyl group of toluene is electron donating due to hyperconjugation. Methyl group exhibits three canonical forms because it has three C—H bonds. Tertiary carbocation gives nine canonical forms due to hyperconjuation. As per resonance rules, greater the number of canonical forms, higher will be the stability. Tertiary carbocation is more stable than secondary and primary ones.



If we compare the reactivity of benzene, toluene, ethyl benzene, isopropyl benzene and tertiary butyl benzene, we can point out toluene as the most reactive species because it has three alpha (α) hydrogen atoms which deposit more electron density due to hyperconjugation on methyl carbon as compared to ethyl benzene where the number of α hydrogens are two, isopropyl benzene where α hydrogen is one and no α hydrogen in tertiary butyl benzene. Higher electronic density on the alkyl carbon immediately attached to benzene ring means more delocalization of negative charge on the aromatic system that makes the reactivity of aromatic ring enhanced.

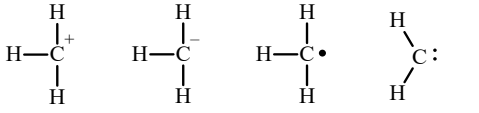


Hyperconjugation plays important role in explaining the stability of substituted alkenes: tetra substituted alkenes are more stable than tri substituted analogues, which are more stable than di substituted alkenes. Mono substituted alkenes or ethene are least stable.

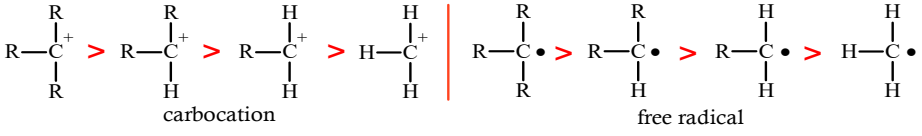
A methyl group attaches to alkene carbon provides for extra sp^2 hybridized carbon due to hyperconjugation that enable overlap with the p system of the double bond, thus rendering the double bond delocalized and stable. A methyl carbon is sp^3 but once it acquires negative charge on account of hyperconjugation, it gets sp^2 which enables delocalization with adjacent double bond.

1.11 Carbocation

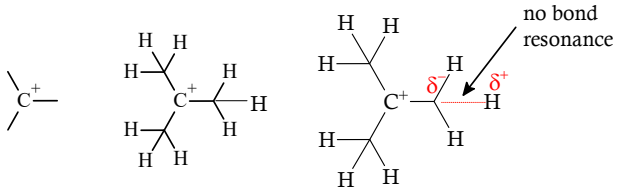
Carbocation is important reactive intermediate in organic chemistry besides carbanion, free radical and carbene. Reactive intermediates are short lived species which are never present in high concentrations because they react as quickly as they are formed. In most cases, reactive intermediates are fragments of molecules (like free radicals), often having atoms with unusual numbers of bonds.



A carbocation is a species with positive charge on carbon atom that has deficit of two electrons before it completes its octet. The charge species is trigonal planar with sp^2 hybridization of the carbon atom bearing positive charge. Three hybridized orbitals in carbocation lie in plane with 120° bond angle which form three bonds. The unhybridized orbital lies perpendicular to the plane. It is this unhybridized orbital that bears positive charge. Unlike carbocation, the geometry of free radical is different because the single unpaired electrons in unhybridized sp^2 orbital pushes the three bonds (three hybridized orbitals) close toward one another thus giving pyramidal geometry. Carbocation is charged species unlike free radical which is neutral species. In both reactive intermediate, the carbon atoms bearing positive charge or unpaired electron are sp^2 hybridized. Free radical has one electron short of octet completion. The order of stability is same for both species. Tertiary carbocation is more stable than secondary which is more stable than primary. Free radicals exhibit similar order in stability trend.

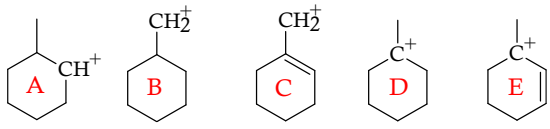


A tertiary carbocation has three alkyl groups that stabilize the ion through hyperconjugation, a phenomenon in which electronic density of C–H bond in alkyl group is donated to the positive charge through inductive effect. In fact, we call hyperconjugation a no bond resonance because one of the C–H bonds in alkyl group partially exists that with partial positive charge on hydrogen and partial negative charge on carbon atom of the alkyl group. In the following structure of carbocation, we have sketched just one canonical form for one C–H bond of the alkyl group. We can draw eight more canonical forms this way. Thus, a tertiary carbocation with three methyl group can yield nine canonical forms. As per rule of resonance, greater the number of canonical forms, higher will be the stability.



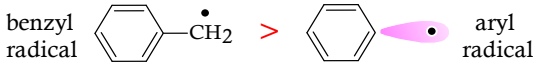
Comparatively, a free radical should be more stable than carbocation because deficit of one electron can be easily compensated by hyperconjugation as compared to the deficit of two electrons. Another factor that supports the stability of free radical over carbocation is that methyl radical can form as we encounter it during free radical substitution of alkanes but we don't find this possibility for methyl carbocation because its formation would be highly unfavorable. One of the most stable free radicals known is the triphenylmethyl radical. It was discovered by Moses Gomberg in 1900. In the absence of oxygen, this radical is indefinitely stable at room temperature. Moreover, carbocation undergoes rearrangement but free radical doesn't which demonstrates that free radicals are relatively more stable than carbocation.

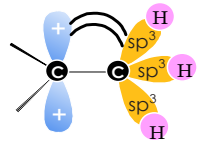
Problem 1.14 List the following carbocation in increasing order of stability



Solved Problem 1.3: Is benzyl or aryl radical stable?

Benzyl radical is stable than aryl because the former has the freedom to resonate over aromatic ring unlike the latter where the unpaired electron lie in unhybridized orbital of the carbon atom constituting benzene ring. The unhybridized orbital lies in the plane of the ring that does not find a change to resonate with the pi electrons in perpendicular orbitals of aromatic ring.

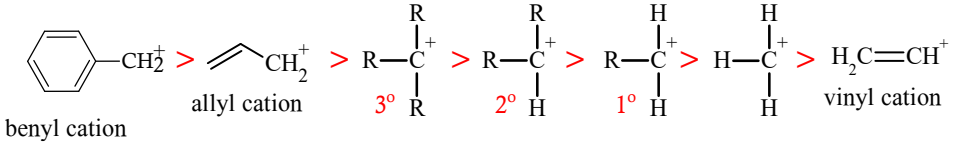




Contrary to alkyl group that stabilizes carbocation through hyperconjugation, a π bond next to positive charge has considerable influence on stability because the π electrons are free to resonate unlike partial negative charge in case of hyperconjugation. Besides, both reactive intermediates are stabilized by atom or group of atoms with lone pair of electrons lying next to positive charge of carbocation or unpaired electron of free radical. For example, amino and hydroxyl group have stabilizing tendency. A carbocation (shown above) is stabilized by alkyl in two ways: inductive effect and partial overlap with the C–H bond in alkyl group.

Solved Problem 1.4: Is benzyl or tertiary carbocation stable?

The question whether benzyl or tertiary carbocation is stable could be answered from the preceding facts cited above. As π bond demonstrates considerable freedom to resonate, therefore its stabilization influence is more pronounced as compared to hyperconjugation. On the basis of this argument, we can say that benzyl carbocation is stable than tertiary carbocation. We can arrange different carbocations in the following order of decreasing stability. Vinyl cation is highly unstable because positive charge on sp^2 carbon is highly unstable. In fact, an sp^2 carbon is more electronegative than sp^3 which makes the positive charge more unstable.

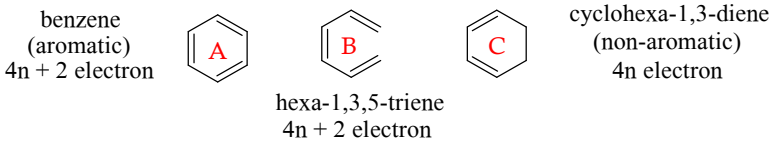


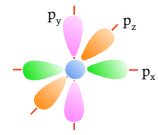
1.12 Aromaticity

Aromatic compounds show exceptional stability and remarkable physical and chemical properties. In fact, aromatic character is associated with peculiar behavior of such compounds. While dealing with aromatic functional group in organic chemistry, we need to learn about whether a particular compound is aromatic or not. What is the criterion for a compound to be declared as aromatic? There are few guidelines which are necessary to learn before we equip ourselves with skills to identify a compound for aromatic character. Following are some significant features that should be present in a molecule before we label it as aromatic.

1. The system must be **conjugated** and **planner** in conformation.
2. It must be **cyclic**.
3. Each carbon of the cycle must be **sp^2 hybridized**
4. Each carbon of the cycle must have one parallel **unhybridized orbital** that could facilitate lateral overlapping.
5. The system must demonstrate **delocalization** of electrons that increases the stability by lowering the energy of the system.
6. The system must obey **Huckel number** i.e. it must contain $4\pi + 2$ electrons.

Contrary to aromatic compound, if a system has 4n number of electrons, delocalization of π electrons does not induce stability. The system is known as anti-aromatic. A cyclic conjugated compound that does not have continuous overlapping ring of p orbitals cannot be aromatic or anti aromatic. Such compounds are regarded as non-aromatic or aliphatic. On the basis of this information, we take following examples to realize the significance of above theory.





cycloocta-1,3,5,7-tetraene (neither aromatic nor anti-aromatic)

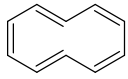
cyclobuta-1,3-diene (anti-aromatic) 4n electron

Cyclic conjugated polyenes containing alternate single and double bonds are known as annulene. For example, benzene is [6] annulene.

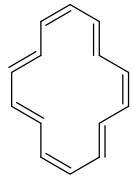
[4] Annulene

[6] Annulene

[8] Annulene



[10] Annulene



[14] Annulene

The number enclosed in square bracket reflects the total number of carbon atoms. Example D is [8] where E is [4] annulene.

1.121 Huckel's Rule

The rule was devised by Eric Huckel to predict whether a compound is aromatic or anti-aromatic. He tried to resolve the issue by a number known as Huckel number. The rule is applied only to system when there is continuous ring of overlapping p orbital in planner conformation. This number is: (4n + 2) where n = 0,1,2,3… For a compound to obey this number would be aromatic. For example, benzene is aromatic because we get the 6π electrons by putting 1 as the value of n in Huckel number. Common aromatic systems have 2, 6 and 10 π electrons for value of n = 0, 1 and 2 respectively. If a compound has 4n π electrons, the system will be regarded as anti-aromatic. For example, cyclobutadiene, example E, is anti-aromatic because it has 4n π electrons i.e. for n =1, we get 4π electrons of the molecule.

Common anti-aromatic systems have 4, 8 and 12 π electrons for value of n = 1, 2 and 3 respectively. Anti-aromaticity is associated with instability and high reactivity. In case of above examples noted as A, B, C, D and E, A is aromatic because it follows Huckel number. Example B follows the criterion of Huckel number yet it is not aromatic because the molecule is not cyclic. Example C reflects non-aromatic character because it has 4n electron yet the molecule does not have continuous conjugation. Example D has 4n π electrons yet it is not anti-aromatic because cyclooctatetrene is stable molecule and reacts like alkenes. The molecule has tub shaped structure that minimizes the chance of instability. It is not unstable like anti-aromatic compounds.

1.122 Aromaticity in Ions

For rings containing 3, 7, 11, 15 and 19 π electrons, their cations will behave as aromatic whereas anion will be anti-aromatic. For rings containing 5, 9, 13, 17 and 21 π electrons, their anions will act as aromatic whereas their cations will demonstrate anti-aromatic character.

1.13 Acids & Bases

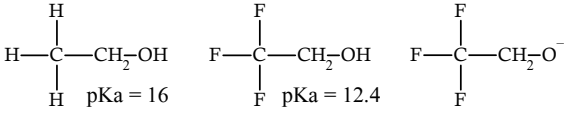
Organic acids and bases are simple to address. Unlike many different concepts or definition in elementary classes, in organic chemistry we are usually concerned with attribution of different fundamental concepts that address the nature, strength and reactivity of acids and bases. These fundamental concepts include: hyperconjugation, inductive effect, resonance effect, steric, elemental or field effect, size, hybridization, aromaticity, electronegativity, bond strength and hydrogen bonding etc. Acidity or basicity is usually estimated in pKa or pKb values. Lower the pKa value for an acid, higher will be its acidity.

Hyperconjugation

Alkyl group such as methyl is electron donating due to hyperconjugation that make toluene more reactive over benzene because more electronic density is deposited over ring when methyl group is attached to it. Methyl group has three hydrogen, hence it yields three canonical forms, is more reactive than ethyl where two such canonical forms occur. For instance, methyl amine (pKb = 3.36) is more basic than ammonia (pKb = 4.74) because methyl group donates electron density to nitrogen by hyperconjugation. Dimethyl amine (pKb = 3.28) is even more reactive than methyl amine because here another methyl group contributes additional electronic density by hyperconjugation.

Inductive Effect

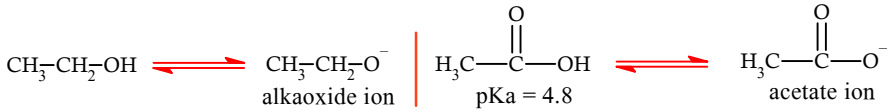
Transmission of electronic density through sigma bond is known as inductive effect. The effect is pronounced on bond near to electronegative atoms. As the distance from electronegative atom increases, inductive effect decreases. Ethanol is less acidic than 2-chloroethanol (pKa = 14.3) because alkoxide ion is better stabilized when Cl atom is attached. Electronegative atom such chlorine stabilize alkoxide anion by withdrawing –ve charge from oxygen atom by inductive effect, therefore making the charge less concentrated and stable unlike ethyl group where hyperconjugation deposits additional –ve charge on oxygen atom. Consider another example where inductive effect influences acidity is offered by carboxylic acids. Formic acid (pKa = 3.75) is more acidic than acetic acid (pKa = 4.74) due to inductive effect in the latter which destabilizes the carboxylate anion by electron donating tendency of CH_3 group. Oxalic acid (pKa = 1.27) is even stronger acid than formic acid because loss of first H^+ leaves carboxylate anion that is stabilized by attached carboxyl group which is electron withdrawing in character.



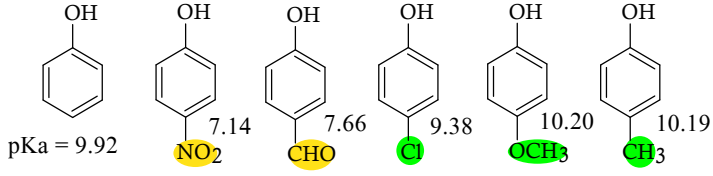
Resonance Effect

Alcohols are less acidic than phenols because phenoxide ion is more stable than alkoxide due to resonance or mesomeric effect. Remember, -OH group of phenol is electron donating in character due to positive resonance effect. Two effects operate in

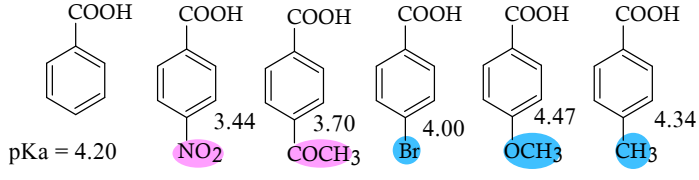
opposite directions: inductive effect withdraws electronic density from benzene ring whereas resonance effect delivers lone pair on oxygen atom to the ring. Acetic acid is stronger acid than ethanol because the conjugate base, acetate ion, is more stable than ethoxide ion since acetate ion is stabilized by resonance because the negative charge on oxygen atom is spread over three atoms unlike ethoxide where it is localized on single atom i.e. oxygen atom.



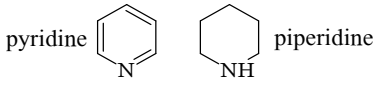
Resonance effect is dominant, hence phenol is more reactive than benzene. In case of phenoxide ion, negative charge is stabilized by delocalisation over the ring that makes phenol more acidic than alcohols. If we look at the derivatives of phenol, we can point out that EWGs increases acidity and EDGs decrease acidity. Consider their pKa values:



Increasing the strength of EWG, higher will be the acidity of —OH and —COOH groups on aromatic ring. Consider the acidity of benzoic acid derivatives.



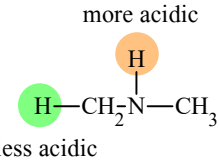
Problem 1.15 Amides are less basic than primary amines, reason and state which one of the following is more basic, reason!



Element Effect

Steric effect operates through space. For instance, 2,6-dimethyle-N,N-dimethyl aniline is more basic than N,N-dimethyl aniline due to steric effect in the former case where two ortho methyl group disturbs nitrogen planarity by interacting with two methyl groups attach to it. Once planarity is distorted, lone pair on nitrogen finds it difficult to delocalize over ring. Loss of delocalisation is tantamount to availability of lone pair that makes species more basic. Steric effect is also known as field effect as well.

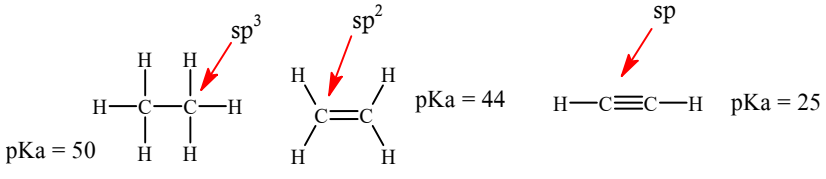
Size plays an important role in ascertaining acidity or basicity. HI is more acidic than HBr, HCl and HF due to the fact that conjugate base of HI is iodide ion where larger



size greatly helps –ve charge to accommodate for enhancing the stability of the –ve charge. Thiols such as ethane thiol (pKa = 10.5) are more acidic than alcohols such as ethanol (pKa = 15.9) because S—H bond is weak than O—H bond. Additionally, the thiolate anion is stable than alkoxide because sulfur has larger size as compared to oxygen that makes –ve charge free to delocalize over larger sulfur atom. Size coupled with resonance makes benzene thiol (pKa = 7.8) much more acidic than simple thiol due to enhanced resonance of –ve charge over benzene ring. Acidity of hydrogen depends how much loosely it bound to heteroatom. Moreover, size also plays role to tell why conjugate base of thiols is more stable than alcohols. This can also be explained on the basis of electronegativity factor as well. Hydrogen atom bond to less electronegative atom is more acidic. Stability of anion, conjugate base of acid, increase with increase in electronegativity. A negative charge on electronegative atom is stable. Moreover, size also matters. A negative charge on ions of bigger size are stable as compared to smaller size.

Hybridization

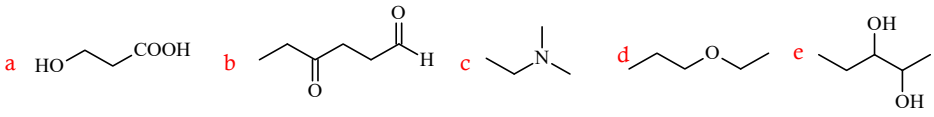
Acetylenic hydrogen is more acidic (pKa = 25) than ethylene one (pKa = 44) which is more acidic than ethane hydrogen (pKa = 50). This can be understood by viewing the stability of the conjugate base. In acetylene, after loss of hydrogen as proton, negative charge resides on sp carbon which is more electronegative with greater s character (50%) than sp^2 hybridized carbon of ethylene. Terminal alkynes act as acidic species due to sp hybridization.



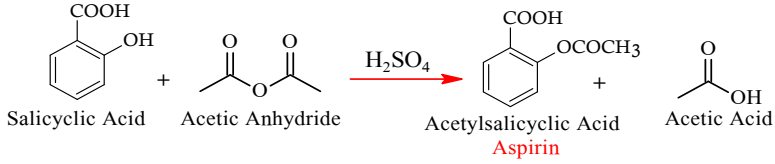
Hydrogen Bonding

Hydrogen bonding plays pivotal role in influencing acidity or basicity of organic molecules. For instance carboxylic acids (acetic acid, pKa = 4.74) are weak acids but hydrogen bonding makes them strong enough to take precedence over all organic acids. This is due to the fact the carboxylic acids form hydrogen bonding with water. The carboxylate anion is stabilized by solvation provided by hydrogen bonding in aqueous solution. Similarly, acidity of alcohols is also enhanced by hydrogen bonding: the alkoxide anion is stabilized by hydrogen bonding in aqueous solution. This makes alcohols to donate its hydroxyl hydrogen as proton. Smaller anions are better stabilized by hydrogen bonding. This explains why methanol is more acidic than ethanol. Tertiary butyl group is bigger than ethyl, therefore ethanol is more acidic than t-butyl alcohol because ethoxide anion is better solvated by hydrogen bonding than t-butoxide anion. Amines are made less basic by hydrogen bonding because lone pair is solvated that reduces its availability.

Problem 1.16 Point out most acidic hydrogen in the following molecules.



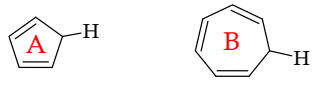
Solved Problem 1.5 Aspirin is more acidic than acetic acid, comment!



Aspirin or acetylsalicylic acid is monoprotic acid (pKa = 3.49). It has ester group on ortho position to carboxyl group. Once carboxylate anion is formed after loss of proton, the anion is stabilized both by inductive and resonance effect of ester group. Oxygen of ester group withdraws electronic density and stabilize the negative anion. The negative charge delocalize over oxygen of ester group and benzene ring. Contrary, acetic acid (pKa = 4.74) is simple acid and methyl group destabilize anion by electron donating effect.

Aromaticity

Aromaticity plays important role in determining acidity and basicity of organic molecules. For instance, shown proton in structure A, cyclopentadiene, is acidic in character because loss of proton generates a carbanion whose negative charge remains in resonance with the two double bonds, therefore it makes the structure aromatic because negative charge restored six π electrons required for aromatic character. In structure B, cycloheptatriene, shown proton is basic in character because its loss as hydride ion leaves positive charge one the carbon which means it induces a sp^2 hybridized carbon required for promoting conjugation with six π electrons. As per Huckel rule, six π electrons reflect aromatic character which is associated with stability. In short, species A acts as acid where B as base due to aromaticity.



1.14 Formal Charge

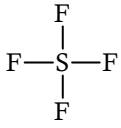
1.141 How to Draw Lewis Structures

Sometimes we are required to draw correct Lewis structure for a molecule or ion. In order to master the trick, we need to abide by some rules. We note following two rules for drawing accurate Lewis structures.

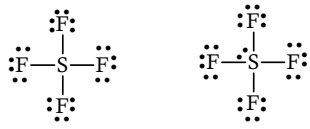
1. Calculate the number of valence electrons (steric number) in each atom of the molecule. For example, in SF_4, we have two types of atoms: sulfur and fluorine. Sulfur belongs to group 6, therefore it has six valence electrons. Fluorine belongs to group 7, hence it has seven valence electrons. There are total of 4 F, therefore the number of valence electrons for F will be 28.

$$SF_4 = 6 + 7(4) = 6 + 28 = 34$$

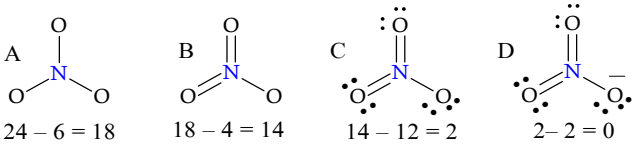
We draw the structure:



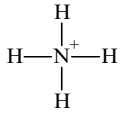
From above structure, we have used 8 out of 34 electrons in making of four sigma bond. Each bond carries two electrons: 34 – 8 = 26 Place the remaining 26 electrons on five atoms of the molecule. First, place the electrons on the terminal atoms as F in case of SF_4 and then on central atom. We have used 24 electrons in filling the valence shells of four F atoms by placing 6 on each. Now we are left with only two electrons which are placed on the central S atom.



2. Add one electron for each negative charge and subtract one electron for each positive charge. Consider NO_3^- and NH_4^+. For nitrate ion, we calculate total number of valence electrons: 5 + 3(6) = 5 + 18 = 23 + 1 = 24. We added 1 for single negative charge on the ion. Let's place these electrons first in making three sigma bonds of oxygen atoms with nitrogen in nitrate ion as shown in structure A. We are now left with 18 electrons out of which 4 are used in making two pi bonds in structure B. Out of remaining 14 electrons, 12 have used in completing the octet of three oxygen atoms. The remaining two electrons serve as negative charge on one of the oxygen atom.



For ammonium ion, NH^{4+}, we calculate the total number of electrons as: 5 + 4 = 9 – 1 = 8 the structure is simple. All 8 electrons have been used in making 4 sigma bonds. Place the positive charge on nitrogen as it has one electron deficit.

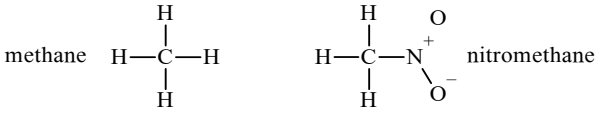


Problem 1.17 Draw Lewis structures of: HCHO, NO_2, PCl_3, N_2O, ICl_4^-, SOF_2, HNO_3 and PCl_5.

1.142 What is Formal Charge?

How electrons are shared within a molecule? Where shared electrons are according to group number or valence electrons of an atom under consideration or it exceeds or falls less than it. Formal charge gives us idea about how electrons are shared within a molecule or how a molecule remains neutral, positive or negative charged. The concept of formal charge is theoretical construct for ascertaining electron distribution within a molecule. It doesn't necessary reflect the actual charge distribution in a molecule.

Any neutral molecule like methane or nitromethane has either all neutral atoms or positive and negative charges are balanced within the molecule. Formal charges for methane and nitromethane are zero. In CH_3NO_2, N of nitro group has formal charge of +1 and one of oxygen atom of the said group has formal charge of -1, as a whole nitro group is neutral.



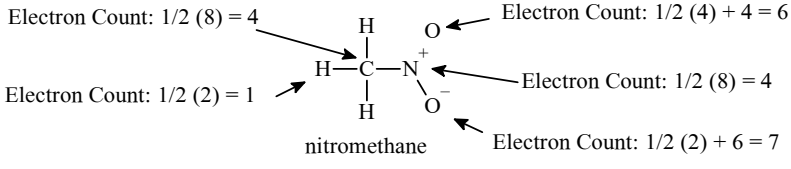
To count formal charge, we use simple formula:

Formal Charge = Group No. – Nonbonding es – ½ Shared es

Group number is the number of valence electrons of an atom, which is the group number indeed to which an element belongs. For instance, oxygen belongs to group 6. Its group number is six. In methane, carbon belongs to group 4. There is no nonbonding electron on carbon atom in methane. Carbon makes four covalent bonds with hydrogen atoms in methane. Hence, number of shared electrons are 8.

For methane, FC = 4 – 0 – ½ (8) = 0
For Nitromethane, FC for carbon is 0
For nitrogen, FC = 5 – 0 – ½ (8) = +1
For one oxygen of nitro group, FC = 6 – 4 – ½ (4) = 0
For other oxygen of nitro group, FC = 6 – 6 – ½ (2) = -1

We can simply count electrons: nitrogen of nitromethane makes four bonds (8 bonding es) and has no nonbonding electrons.



Electron count = ½ (8) = 4

This illustration means that nitrogen of nitromethane is short of one electron, hence it acquires unipositive charge. For oxygen bearing negative charge,

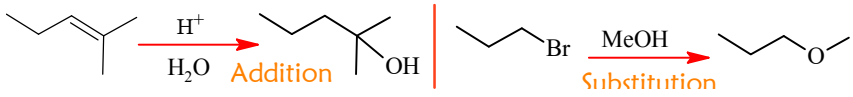
Electron count = ½ (2) + 6 = 7

This shows oxygen has acquired one extra electron than its normal group number of 6. This extra electron appears as uni-negative charge.

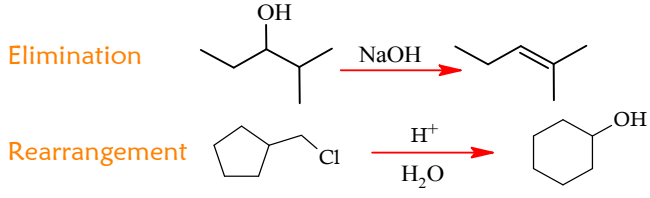
Problem 1.18 Calculate formal charge for each atom in $SOCl_2$, N_2O, O_3, H_3O, NH_4, BH_4 and N_3.

1.15 Types of Organic Reactions

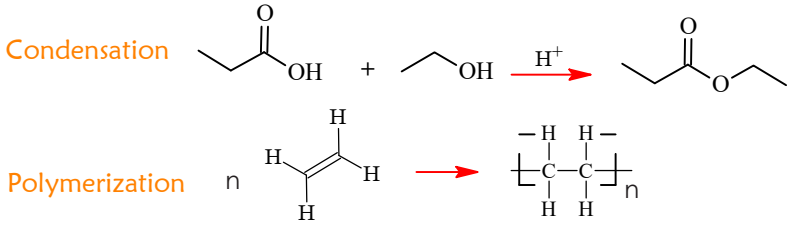
Organic molecules are covalent in nature. They react by chemical transformation of one reactant with another aided by catalysts or suitable reaction conditions. These molecules exhibit different reactions through which reactants transform into product. Organic molecules over which reaction takes place are known as substrate. An **addition reaction** involves addition of one molecule into another. For instance, water adds to alkenes which give alcohol. When a part of molecule adds by replacing a part of molecule, the reaction is known as **substitution reaction** which doesn't involve addition of whole molecule into substrate.



In **elimination reactions**, a substrate eliminates two groups on adjacent carbon atoms for yielding new molecules. **Rearrangement reactions** proceed through internal transformation of an atom or group of atoms which disconnect from one point of attachment and connect to another point for forming new molecules. For instance, the migration of alkyl or aryl group from one carbon to another carbon for giving a stable carbocation is known as Wagner-Meerwein rearrangement.

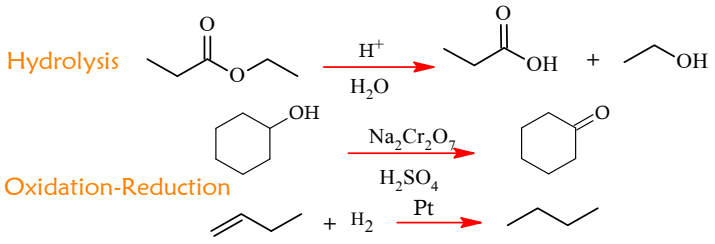


In **condensation reactions**, two or more molecules combine with elimination of small molecule such as hydrogen, nitrogen, water or alcohol to form larger molecules. Esters, amides and peptides formation occur through condensation reactions. When large molecules known as polymers form by joining high number of small molecules which are known as monomers, the type of reaction is known as **polymerization reaction**. For example, polyethylene polymer is made through polymerization reaction.

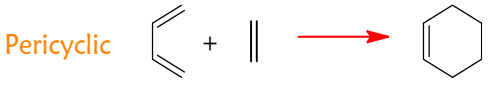


Hydrolysis reactions involve the breaking of chemical bond in water and subsequent addition to substrate. Esters are hydrolyzed back to alcohols and carboxylic acid through a hydrolysis reaction. **Oxidation** and **reduction** are important class of organic

reactions. Primary alcohols are oxidized to ketones which are reduced back to alcohols. Similarly, alkenes are reduced to alkanes.



Pericyclic reactions involve concerted reorganization of bonding electrons through a cyclic transition state. These reactions don't require the necessity of catalyst and are governed by Woodward-Hoffmann rules of orbital symmetry. Examples of pericyclic reactions include cyclo-addition reactions such as Diel-Alder reaction, electrocyclic reactions and sigmatotrophic rearrangement (Claisen and Cope rearrangement). **Photocatalytic reactions** are effected with the aid of light.

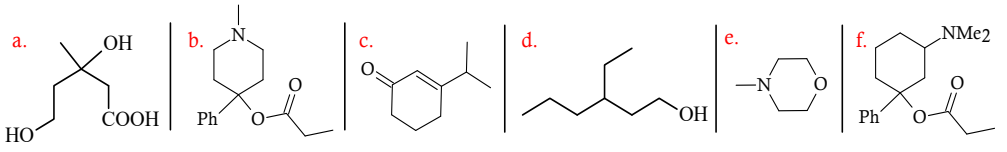


1.16 Mechanism

1.161 Electrophile and Nucleophile

An electrophile (electron loving) is electron deficient species which requires electron rich species for a reaction. Proton, H^+, carbocation and boron are examples of electrophiles which can either be positive charge or neutral molecules. Electron rich species which react with electrophile are known as nucleophiles (nucleus loving) such as neutral molecules like water and alcohols which possess lone pair of electron on oxygen atom or negative charged such as halides, hydroxide or hydride anions. Most of the organic reactions take place between electrophile and nucleophile.

Problem 1.19 Which part of the following molecules act as electrophile or nucleophile? State reason for your selection.

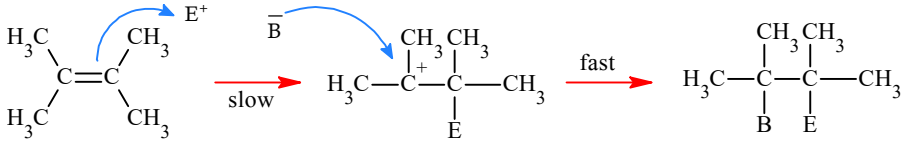


Sometimes, a part within a molecule behaves as nucleophile and electrophile at the same time. For instance, in Grignard Reagent, alkyl group acts like nucleophilic moiety due to deposition of electronic density on account of electronegative difference between carbon-metal bonds. The —MgX behaves as electrophilic entity. Similarly, in carbonyl compounds, the carbonyl group is polar. The carbonyl carbon is electrophilic because it is electron deficient due to electronegativity of oxygen where accumulation of electronic

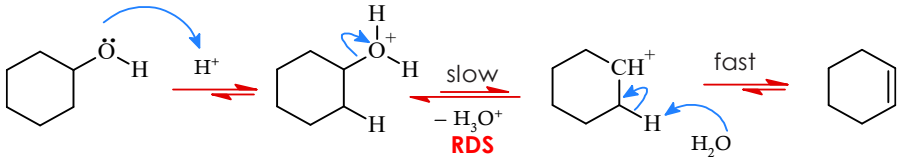
density renders oxygen nucleophilic in character. When Grignard Reagent is reacted with carbonyl compound, the alkyl group (nucleophilic) adds to carbonyl carbon (electrophilic) and the —MgX (electrophilic) part couples with oxygen (nucleophilic) of carbonyl group.

1.162 Introduction to Mechanism

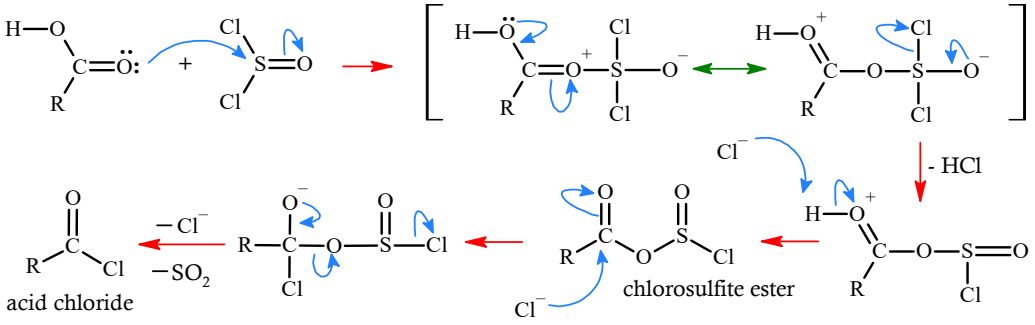
Reactions proceed from reactants to products either through single or series of steps. These steps tell us how reactants transform into product. Most of these steps have experimentally proven valid by varied mechanistic tools such as isotopic labeling, spectroscopic studies and chemical transformations. The stepwise representation of reaction is known as mechanism. Consider electrophilic addition reaction of alkenes which is two step mechanism. Double bond is electrophilic in character. First step is slow in which double bond attacks electrophile. An intermediate carbocation is formed which is prone to rearrangement. The second step is fast. Carbocation is attacked by base and product is formed.



Many reactions are concerted which transform reactants into product in single step. Many other reactions proceed through series of steps. Each of these steps is termed as elementary step. In multistep reactions, some steps are slow and others are fast. The slowest step is known as rate determining step (RDS) which can carries one (unimolecular), two (bimolecular) or three (termolecular) molecules. In fact, the number of molecules involved in rate determining step is known as molecularity of reaction. Most of the organic reactions are either unimolecular or bimolecular. Mechanism of a reaction is facilitated by curved arrows whose tail emerges from nucleophile or negative charge species and direct head towards electrophile or positive charge species. Curved arrows are used for movement of electrons. Consider the following dehydration reaction of alcohol to alkene which proceeds through unimolecular elimination reaction. The reaction involves three steps: protonation of hydroxyl group of alcohol, elimination of water molecule and subsequent formation of carbocation and the abstraction of proton by base. Elimination of water molecules which yields carbocation is slow and rate determining step of the reaction.



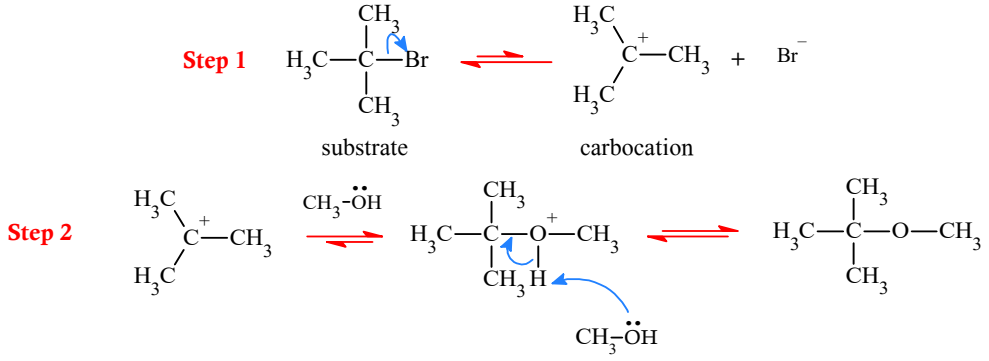
Consider the mechanism for reaction of carboxylic acids with thionyl chloride for synthesis of acid chlorides. The mechanisms of these reactions begin like the reaction of an alcohol with thionyl chloride. Either oxygen atom of the acid can attack sulfur, replacing chloride by a mechanism that looks like sulfur's version of nucleophilic acyl substitution. The product is an interesting, reactive chlorosulfite anhydride.



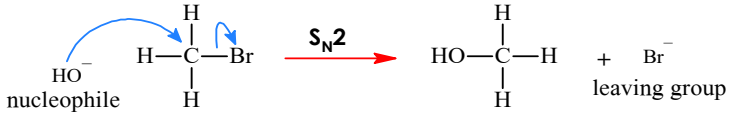
The reactive anhydride undergoes nucleophilic acyl substitution by chloride ion to give acid chloride.

1.163 Rate of Organic Reactions

Solvents effects are broad. Here, we just focus on single effect to see how solvent influences the rate of reaction. Solvents are useful for solvation purposes. The rule of thumb, like dissolves like, refers to solvent role in manipulating the chemistry of chemical reactions. As an example, we introduce two important substitution reactions (S_N1 & S_N2) to check how solvent influence their rate of reaction. S_N1 is unimolecular reaction. It is two steps process. First step involves slow ionization of substrate which is rate determining step. Ionization gives carbocation which is attacked by nucleophile in the second step. This is fast step. These reactions have extensively covered in section 3.54.



S_N2 is one step bimolecular reaction in which nucleophile attacks substrate from the side opposite to the leaving group. This reaction is concerted. It doesn't involve any formation of intermediate.



For an S_N1 reaction, we need polar solvent because the first step is rate determining which involves ionization of substrate. Only polar solvent such as water or alcohols encourages ionization of substrate. Non polar solvents are poor choices for S_N1 reactions. For S_N1 reaction, polar solvent not only enhances ionization but also stabilizes intermediate carbocation. Consequently, solvents reduces activation energy barrier by

interacting with transition state and stabilizing it. Rate of S_N1 reaction increases with increasing polarity of solvent.

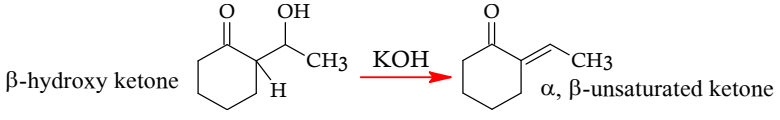
Solvent can be either polar or non-polar. Polar solvents are divided into protic and aprotic. Protic solvents are important for establishing hydrogen bonding. These solvents contain N—H, O—H or H—X groups. In protic solvents, hydrogen atom is attached to electronegative atoms such as oxygen, nitrogen or halogen. For instance, alcohols, ammonia, acetic acid, water and amines are protic solvents. Aprotic solvents don't contain above groups. Acetone, DMF, DMS, HMPA, acetonitrile and DMSO are examples of aprotic solvents. Consider the S_N1 reaction of tertiary butyl iodide in different solvents. The relative rate of reaction in DMF (aprotic) is 12.5. With methanol, the rate dramatically surges i.e. 7400,000.

For S_N2 reactions of methyl bromide in ethanol with different nucleophiles, the rate is steeply influenced by interaction of solvent with nucleophile. Polar solvent like ethanol strongly solvates charged nucleophiles, which is poor choice to stage backside attack on substrate along with chariot of ethanol molecules. Usually, polar aprotic solvents are good choices for S_N2 reactions. Small charge is strongly solvated by polar solvent unlike large size charges. For instance, in ethanol as solvent, an S_N2 reaction with fluoride nucleophile will work with slow rate of reaction as compared to chloride with which the rate of reaction is thousands times fast.

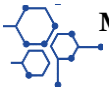
1.164 A Detailed Mechanistic Perspective

1. E1cB Mechanism

This is another important category of elimination reactions. E1 stands for unimolecular elimination where the cB stands for conjugate base. In other words, unimolecular elimination of conjugate base is known as E1cB mechanism. It is also known as carbanion mechanism.



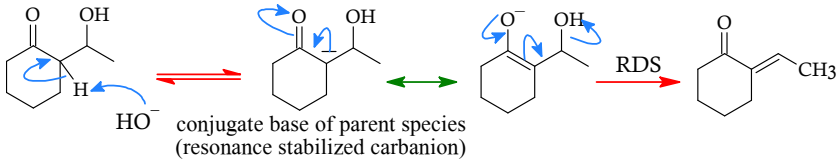
The reaction is catalyzed by strong base such as KOH. The characteristic feature of E1cB involves the presence of acidic proton adjacent to carbonyl group. The reaction operates through similar mechanism of E1 with exception that the leaving group is –OH. Besides, halogens and –OR can also act as leaving groups. β–halocarbonyl compounds are rather unstable. A combination of good leaving group and presence of acidic proton means E1cB mechanism is extremely easy.



Mechanism

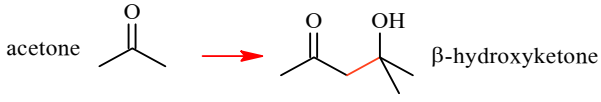
Mechanism for E1cB initiates with abstraction of acidic proton by strong base. This step leads to formation of a carbanion (conjugate base). The first step is fast and reversible. The next step involves the expulsion of leaving group which gives rise to formation of double or triple bond. This step is slow and rate determining (RDS) in kinetics. As only single molecule is involved in RDS, therefore the mechanism operates

through unimolecular kinetics. In fact, the driving force for the mechanism is the formation of conjugation though hydroxyl group is poor in leaving potential. The rate of reaction is indirectly depends upon the concentration of base because it the base that gives rise to formation of conjugate base for onward reaction.



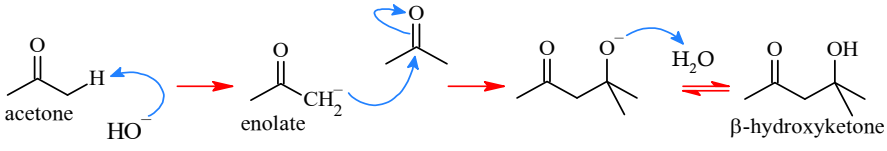
2. Aldol Condensation

It is important reaction for making β-hydroxyketones and αβ-unsaturated ketones. The reaction involves dimerization of aldehyde or ketones molecules which are catalyzed either by base or acid. The reaction proceeds through three steps mechanism:



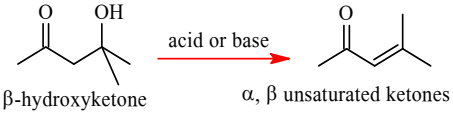
Mechanism

First step involves removal of β-proton to give an enolate ion. In second step, enolate adds to carbonyl group of another aldehyde or ketone molecule. Finally, protonation gives aldol product which is β-hydroxy alcohol.



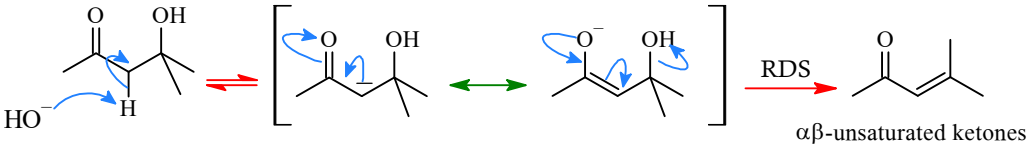
The enolate is the very stable conjugate base of the starting material, and is one of the intermediates in the reaction. The enolate acts as a nucleophile and can attack an electrophilic carbon of the carbonyl group of aldehyde or ketone.

Dehydration of Aldol Product: Aldol product is then deprotonated forming another enolate followed by the elimination of water in an E1cB dehydration reaction.



Mechanism

First step proceeds via formation of resonance stabilized enolate ion which undergoes elimination of hydroxide ion to give product. Dehydration is usually exothermic because it leads to formation of a conjugated system.

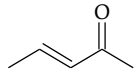


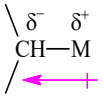
Differences among E1, E2 and E1cB Mechanisms

1. Mechanism for E1 and E1cB is stepwise whereas concerted for E2.
2. Intermediate for E1 is carbocation, carbanion for E1cB whereas E2 involves simultaneous removal of α proton and leaving group.
3. Strong base facilitate all three types of elimination reactions.
4. E1 needs to have good leaving group, E1cB has poor leaving group and E2 just requires leaving group.
5. In E1, β hydrogen is less acidic, in E2 the β hydrogen is acidic whereas in E1cB β hydrogen is more acidic.

Problem 1.20 Point out the structure of starting aldehyde, intermediate alcohol in the box, reaction conditions question marked and explain with the help of mechanism how reactants transform into the final product.

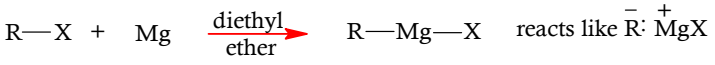
Problem 1.21 Point out how the following compound can be obtained from starting materials. Point out reaction and write simple mechanism for it.





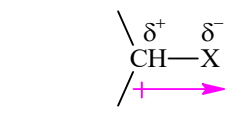
1.17 Organometallic Chemistry

Organic chemistry dealing with compounds containing carbon-metal bond is known as organometallic chemistry. When it comes to mention of organometallics, we encounter Grignard Reagent as starting subject although many reactions such as Wurtz, Corey House synthesis of alkanes, organo-copper and organo-lithium reagents reagent have already been studied in elementary classes. Grignard reagent is symbolized by R-Mg-X, where R is any alkyl group and X is halide. In this reagent, two types of bonding prevail: ionic and covalent. Grignard reagent is made by reacting alkyl halides with magnesium in some inert solvent.

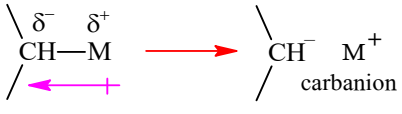


Magnesium, an alkali metal, isn't in +2 oxidation like the one in $MgCl_2$ but its oxidation state resides between +1 and +2 instead. Carbon metal bond is covalent with considerable polarity. We call such bond as polar covalent bonding. Carbon is more electronegative than Mg, hence it acquires partial negative charge that render carbon atom nucleophilic in character. In fact, this carbon metal bond is characteristic of organometallics which differentiates these compounds from other organic compounds where carbon is usually electrophilic as in carboxylic acids or alkyl halides.

The reversal of polarity from electrophilic carbon in ordinary organic compounds to nucleophilic ones in RMgX is tagged as Unpolung which means reversal of polarity. Mg-X bond is fully ionic due to which Mg gets +1 charge.

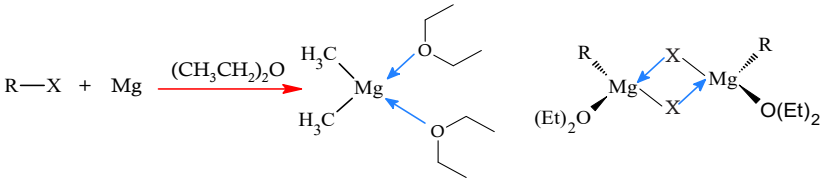


X is any halogen atom which is more electronegative than carbon



M is any metal which is less electronegative than carbon

Structurally, crystalline Grignard reagent can be monomer or dimer, depending upon the nature of solution where it exists. Magnesium (Lewis acid) is electron deficient, it bonds to alkyl group on one hand and halide on the other. Mg acquires +2 oxidation state which is neutralized by coordinating with two ether molecules.

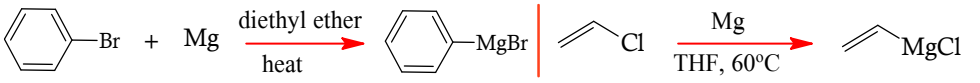


Magnesium coordinates to two ether molecules in addition to two covalent bonds. All four groups are tetrahedrally arranged. In general, dilute ethereal solution of RMgX presents it a monomer but in concentrated solution, the principle species is dimer in which

two magnesium atoms are bridged by two halide atoms. Ether is integral part of RMgX. If ether is evaporated, merely R_2Mg and MgX_2 species are left.

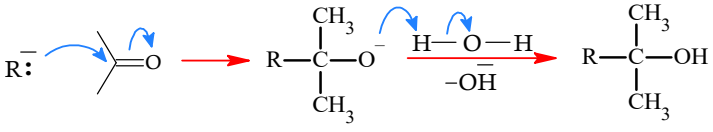
1.171 Synthesis of RMgX

Grignard reagent can be prepared by treating alkyl or aryl halides with magnesium in some inert solvent such as dimethyl ether.

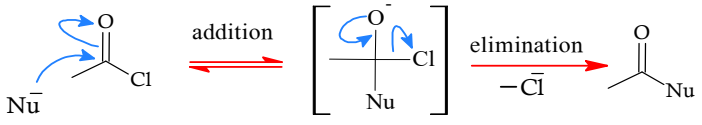


1.172 Reactions

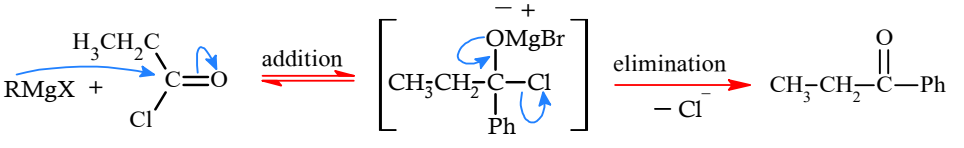
Alkyl group in RMgX is nucleophilic. It reacts with electrophilic part of organic compounds. For instance, RMgX reacts with electrophilic carbon of carbonyl group of aldehyde and ketone yielding primary, secondary or tertiary alcohols that depend upon the nature of substrate.

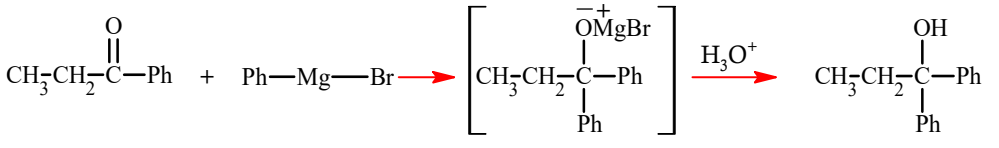


Acid chloride gives different products depending upon the nature of R group in RMgX.

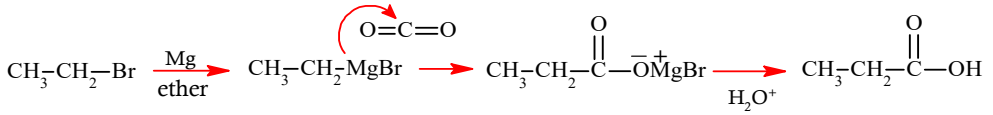


RMgX gives ketone with acid chloride through addition-elimination mechanism. Ketone adds another molecule of RMgX. The product of this step is tertiary alcohol which is obtained through an unstable intermediate product whose hydrolysis gives alcohol. The overall reaction is given below.

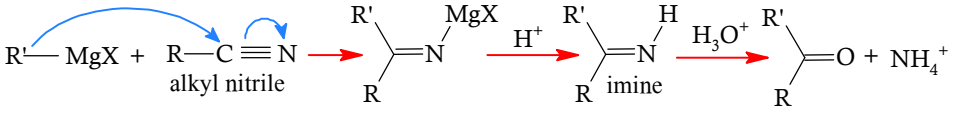




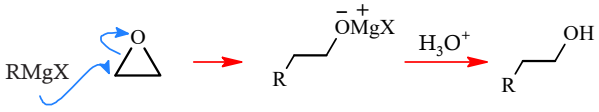
Carbon dioxide gives carboxylic acid with RMgX.



Nitrile gives ketone with RMgX through intermediate formation of imine which is hydrolyzed to ketone.



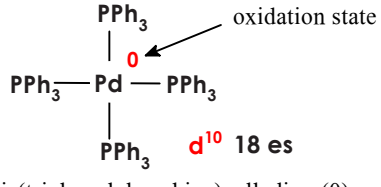
Grignard reagent reacts with cyclic ether to form terminal alcohols through ring opening of epoxides. The alkoxy group of epoxide is poor leaving group yet ring strain makes it good leaving group.



In the ensuing text, oxidation states and bonding pattern will be addressed with reference to palladium and boron so that student could get good grip over analyzing the nature of organometallics compounds. Carbon-palladium bond isn't as much polar as carbon-magnesium bond in RMgX. Higher the polarity of metal carbon bond, higher is its reactivity. For instance, C–M bond in RMgX (M is any metal) is more reactive than such bond in organo-palladium. Remember, higher the electronegative difference, greater will be the polarity of the bond. C–M in organo-lithium is even more polar (reactive) than such bond in RMgX. Electronegativity values (EN) of Li is 1, Mg 1.2, Pd 2.4 and C is 2.5.

1.173 Chemistry of Palladium

An ideal catalyst needs to be inactive and stable in resting state but it should be reactive in solution. For instance, tetrakis (triphenylphosphine) palladium (0) is solid orange powder (heterogeneous catalyst) at room temperature. In solution, it becomes active by losing one or more ligands to make it soluble. This type of catalysis becomes homogeneous which is required in Suzuki coupling reaction.



tetrakis(triphenylphosphine)palladium(0)

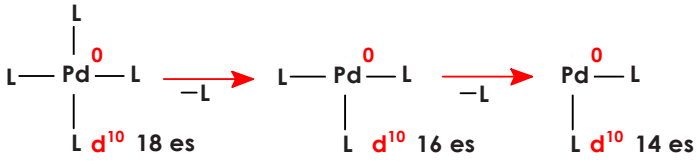
A metal complex is stable when it satisfies 18 electrons rule. A metal in complex carrying 18 electrons noble gas configuration is stable. Ni, Pd and Pt belong to same group which is known as platinum family. This group is extremely significant in catalytic

operations. Their group number is 10 which reflects number of valence electrons in these metals. In fact, the new group number in the *d*-block elements shows the number of electrons in the valence. Pd has d^{10} configuration. It requires 8 more electrons to get 18 electrons noble gas configuration. This requirement is fulfilled by four phosphine ligands with each phosphorus atom has a pair of electron to coordinate with Pd. Coordination to Pd metal doesn't alter its oxidation state.

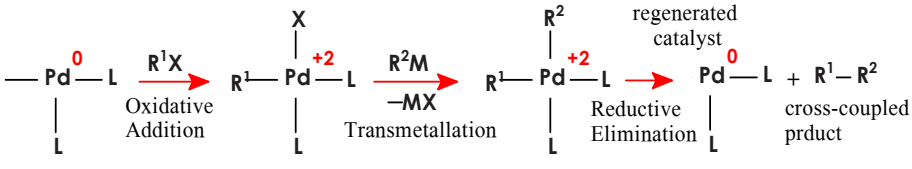
$$^{46}\mathbf{Pd}\ \mathbf{1s^2\ 2s^2\ 2p^6\ 3s^2\ 3p^6\ 4s^2\ 3d^{10}\ 4p^6\ 5s^0\ 4d^{10}}$$

There is exception to 18 electrons rule as well. For instance, Pd (II) also forms stable complex with 16 electrons as in $PdCl_2(MeCN)_2$. This complex contains two chloride (anionic ligands which donate two electrons each) and two acetonitrile (neutral ligands which donate two electrons each) ligands. This complex is reactive as compared to complex of Pd in zero oxidation state. In $Pd(PhP_3)_4$, Pd is in zero oxidation state. Its d^{10} configuration with four neutral phosphine ligands makes the complex a stable 18 electrons system. The catalyst is stable unless it loses one or more ligands to be reactive.

When the complex loses one ligand, it becomes 16 electrons system. For two ligands to lose, it becomes 14 electrons system. Pd is in zero oxidation state in 14 electron system which is required for oxidative-addition. Pd in +2 oxidation state forms stable complexes unlike Pd in +1 state which yields unstable complexes. In fact, Pd chemistry is dominated by these two oxidation states. L stands for ligand which means triphenylphosphine ligands in our case.

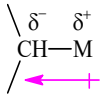


Remember, R^1X (halide) adds to Pd (0) and organometallic reagent (R^2M) to Pd (II) complex. Oxidative-addition is fast step of the mechanism unlike slow transmetallation step. In transmetallation, the organic nucleophile (R^2) from organometallic reagent transfers to Pd(II) complex, which now holds two organic groups (R^1R^2) that ultimately cross-coupled in reductive-elimination step leaving Pd(0) regenerated for next cycle.

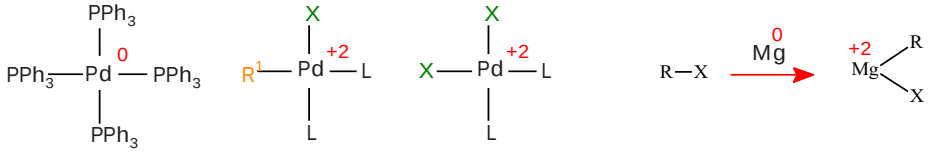


Oxidation States of Palladium

Neutral ligand such as triphenylphosphine (Ph_3P) doesn't alter oxidation state of Pd. Besides Ph_3P, NH_3, CO, RCN, ROR and R_3N are all neutral ligands which don't change the oxidation state of metal in complexes. Other ligands such as halides, hydroxide, hydride, cyanide, alkoxide and alkyl are anionic ligands with -1 charge. They donate two

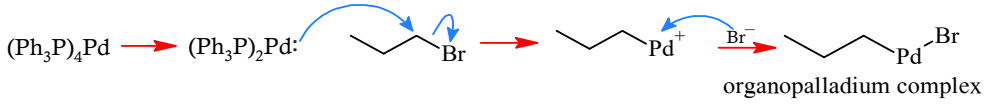


electrons each. Each of such anionic ligands raises oxidation state of metal by +2. For instance, in $(MeCN)_2PdCl_2$, Pd is in +2 oxidation state because two chlorides make a total charge of -2 which is balanced by +2 oxidation state of Pd much like +2 oxidation state of Mg in $MgCl_2$ or $Mg(OH)_2$. In Grignard reagent (RMgX), Mg is in +2 oxidation state because of -1 charge on R group and -1 charge on halide. After oxidative-addition, Pd acquires +2 oxidation state due to halide and alkyl groups.



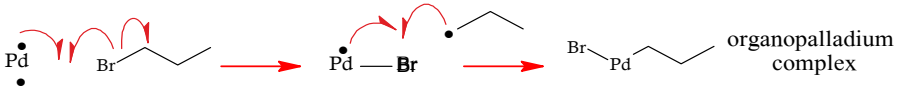
Summary of Mechanism: I have summarized key steps of Suzuki reaction mechanism. Usually, it is difficult for students of organic chemistry to comprehend organometallic chemistry on account of transition metals involvement, I have presented the mechanism to aid them in organic perspective by choosing typical arrow movement associated with organic reaction mechanisms.

S_N2 Route

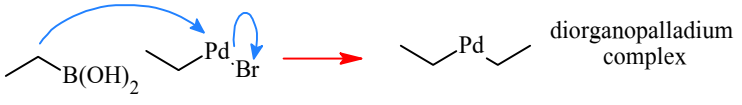


Palladium has two oxidation states: 0 and +2, both of which play pivotal role in its significant chemistry. Transition metals have filled d orbitals and vacant f orbitals. In fact, lone pair of d orbital act as nucleophile required for causing an S_N2 displacement reaction. Pd uses its lone pair of electrons in d subshell to displace halide from R—X in S_N2 fashion yielding a positive charged organo-palladium complex and negative charge halide anion which coordinates with the complex to neutralize it. The halide anion takes it negative charge into the vacant d orbitals of Pd. Consequently, we get Pd in +2 oxidation state where it is coordinated to alkyl group on one hand and halide on the other. There is free radical case as well. Pd acts like free radical by attacking R—X bond which is relatively weak and prone to attack. Halide forms bonds with Pd while leaving carbon free radical which attack the Pd radical form organopalladium complex.

Free Radical Route



In transmetallation step, the carbanion of organometallic reagent attack the Pd in S_N2 fashion expelling halide from the complex that yield diorganopalladium complex.

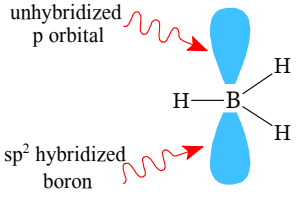


In reductive-elimination step, which is the reverse of oxidative addition, the diorganopalladium complex undergoes homolytic cleavage yielding Pd (0) and two alkyl free radicals which recombine to form a new compound with carbon–carbon connectivity.

Reductive elimination is irreversible unlike the reversible oxidative addition because the former yield a stable C—C bond unlike the latter which involves weak R—X bond of the starting halide. Both complexes of Pd formed are less stable.

1.174 Chemistry of Boron

Boron is electron deficient element which acts as an electrophile or Lewis acid in its reactions. It has six electrons in valence shell, short of two electrons which make it electrophilic in character. Boron makes three s bonds as in BF_3 or BH_3 with sp^2 hybridization. BF_3 exists but BH_3 can't. Instead, BH_3 occurs as dimer B_2H_6 known as diborane.



When boron gets lone pair of electron, it acquires negative charge, the species known as ate complex. For instance, BH_3 is usually used as ate complex of THF in which boron coordinates to THF. EWG makes boron more reactive as in BF_3. Carbon-boron bond is more polar than C-C bond which enables boron to exchange its nucleophilic carbon (if attached) to another electrophile carbon as in RX for establishing C-C cross coupling.

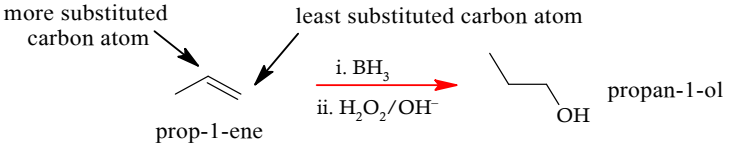
In Suzuki coupling, we use an organoboron species, boronic acid or its ester, which plays crucial role in transmetallation step where boronic acid first couples with organo-palladium complex and then exchanges its alkyl group with the complex to yield new complex of Pd containing two R/Ar groups. In reductive-elimination, the two groups couple regenerating palladium catalyst for repeating new oxidative-addition to C–X bond.

To add water across double bond of alkenes in anti-Markovnikov fashion wasn't possible until H. C. Brown realized that alkylboranes could be formed with anti-Morkovnikov orientation when diboranes were added to alkenes. The consequent alkylboranes could be easily oxidized to alcohols. On account of this new development, Brown was awarded 1979 Nobel Prize for his endeavors revolving around the chemistry of borane. Diborane is difficult to use because it is flammable, explosive and toxic gas. The use of cyclic ethers such as tetrahydrofuran (THF) makes diborane convenient to use because the cyclic ethers form a complex with the reagent.

Hydroboration-Oxidation Reaction (Regioselective & Stereospecific)

Hydroboration-oxidation is hydration reaction of alkenes in which hydroxyl group (–OH) adds to least substituted carbon atom (regioselective) of the double bond in

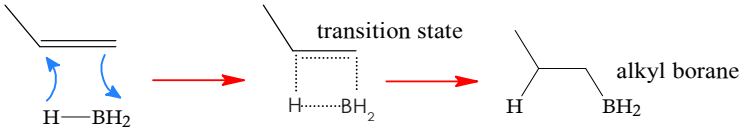
anti-Markovnikov's orientation giving alcohol as product. Consider the following alkene which has transformed into terminal alcohol with application of hydroboration-oxidation reaction.



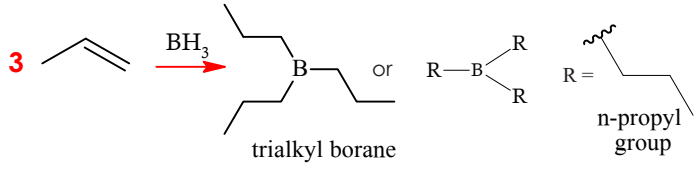
Mechanism

1. Hydroboration

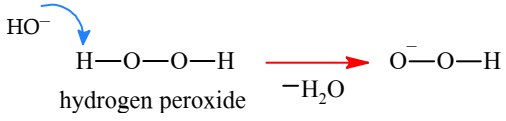
Boron is electron deficient species. It acts as electrophile for addition to the double bond (nucleophilic). For simplicity, we divide BH_3 molecule into H and BH_2 parts as shown below. Hydrogen adds to more substituted carbon of the double bond due to small size and boron part adds to least one for forming a transition state. This type of addition reaction is termed as syn-addition (stereospecific) in which both parts add to the same side of the double bond. We get alkyl borane this way in which the alkyl group from alkene skeleton gets bonded with the BH_3.



Alkyl borane reduces two other molecule of alkene to give trialkyl borane that reacts with peroxide anion for onward reaction.

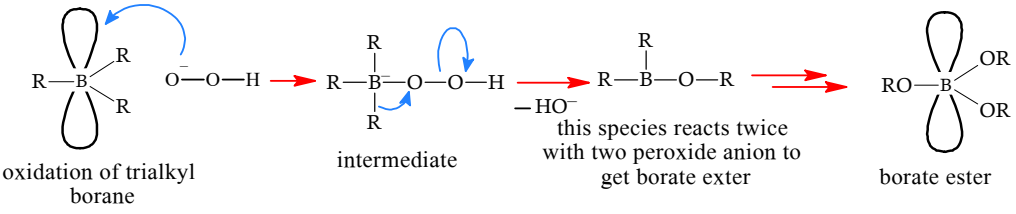


Peroxide anion (nucleophile) forms from H_2O_2 when it is treated with base.

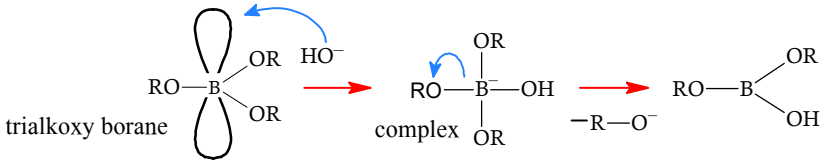


2. Oxidation

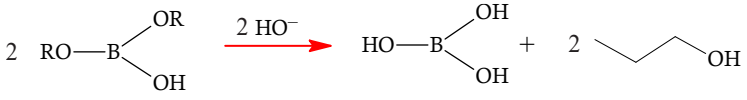
The peroxide anion adds to of trialkyl borane which upon internal rearrangement of alkyl group and subsequent displacement of hydroxide anion from the intermediate. A borate ester is formed upon addition of two more peroxide anions. Remember, the alkyl group migrates with retention of configuration.



Borate ester coordinates with hydroxide anion via boron for giving a complex which eliminate alkoxide anion (propoxide) that takes hydrogen from water to yield first alcohol molecule.



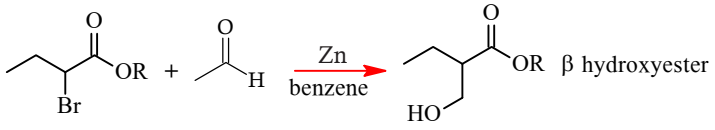
The product of boron in the above reaction adds two more hydroxide to displace second and third alkoxide groups for yielding two more alcohol molecules.



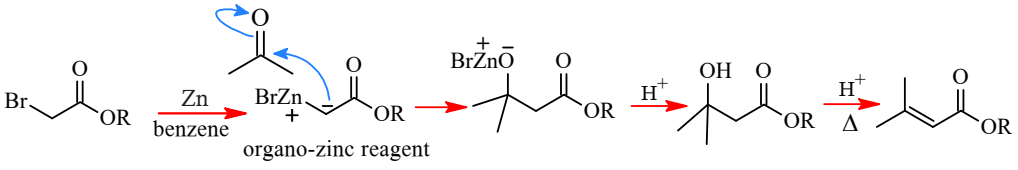
1.175 Organo-Zinc Reagent

Reformatsky Reaction

Reformatsky reaction is important tool in synthetic organic chemistry which combines aldehydes or ketones with a bromoester to form b hydroxyester which can further be hydrolyzed to ab unsaturated esters. The reaction is performed in the presence of zinc metal which is useful for organo-zinc reagent needed for the reaction. In fact, the organo zinc reagent is known as Reformatsky enolate. It is prepared much the same way as do we for synthesis of RMgX. Remember, organo-zinc reagent is less reactive than RMgX since it doesn't add to ester moiety. The reagent is sensitive to steric hindrance, hence it prefers to react with aldehydes and sterically less hindered ketones.



Mechanistically, α haloester reacts with zinc metal in benzene to form organo-zinc reagent. The reagent is an enolate which add to carbonyl compounds for synthesis of b hydroxyester. In final step, hydrolysis coverts the hydroxyester to ab unsaturated ester.

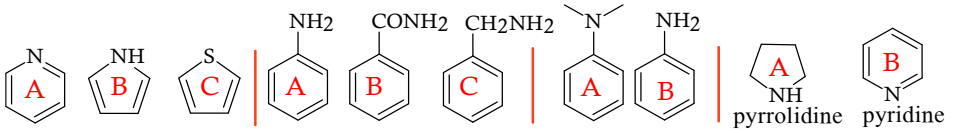


1.18 Exercise

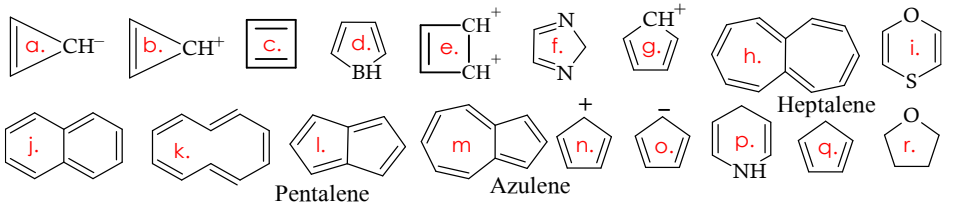
1. Reason the following statements objectively.

a. Does electron withdrawing group on aromatic ring increase acidity of phenol?
b. State difference between resonance and inductive effect? Give examples
c. Why –OH of phenol make it more reactive than benzene although O of –OH group is more electronegative than C of benzene ring to which it attaches.
d. Why o-nitrobenzoic acid is more acidic than its p-isomer?
e. Although halogens are deactivating groups yet they orient incoming electrophiles towards o/p positions, explain.

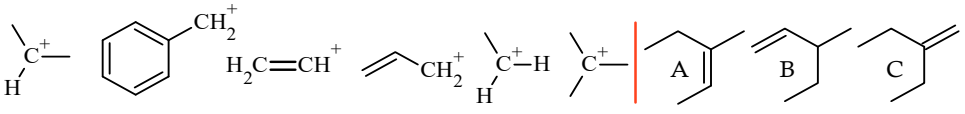
2. Rank the following four sets of compounds in increasing order of basicity and reason your judgement.



3. Point out aromatic, non-aromatic and anti-aromatic



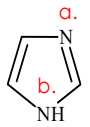
4. Arrange the following carbocations and alkenes in increasing order of stability. State reason for your choice in each of the both cases.



5. Elaborate the following statements briefly!

a. Enlist important conditions for aromaticity.
b. Show with the help of mechanism how acid catalyzed tautomerism take places.
c. Assign pka values of 8.35, 9.99 and 7.14 to ortho nitrophenol, meta nitrophenol and phenol. State reason for your assignment.
d. State some features of organic molecules being influenced by hyperconjugation.
e. Why bond order for delocalized bond is in fraction?
f. Explain orientation effect in aromatic compounds with reference to activating and deactiving groups. State why the former orient towards o/p positions, where the latter orient towards meta positions?
g. State why cyclooctatetraene is non-aromatic although the molecule is 4n electrons which is anti-aromatic number?

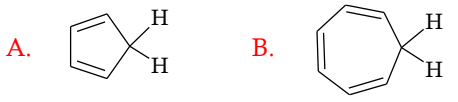
6. Point out which nitrogen is basic, nucleophilic and involves in aromaticity in imidazole? State reason for your assessment.



7. Comment on the following statements and reason your justification!

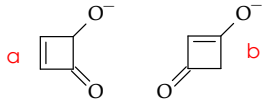
a. Explain why o/p nitrophenol is more acidic than m isomer?
b. Florobenzene is more reactive than other halobenzenes! Comment!
c. We have two trisubstituted carbocations: one with three methyl groups and other with three deuterated methyl groups. Which one would be more stable? Reason!
d. Is ammonia is stronger base than aniline? Comment
e. Alcohols are less acidic than phenols. Comment!
f. How hybridization explain the acidity of terminal alkynes?

8. Prove whether methylene hydrogen are acid or basic in character. State reason for your response.

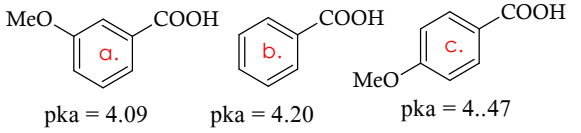


9. Which carbocation is stable? Comment

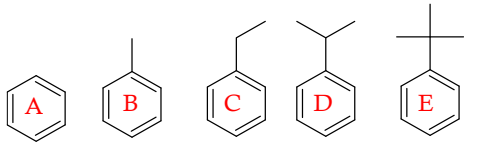
10. Which of the following canonical form is stable? Assign reason.



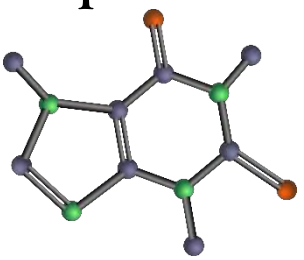
11. Comment on why meta isomer is more acidic?



12. Which one of the following is more reactive, reason?



Naming Organic Compounds



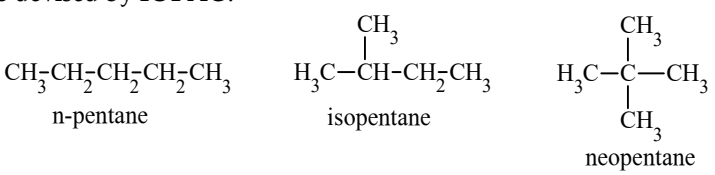
Section 2 Nomenclature

2.1 Introduction

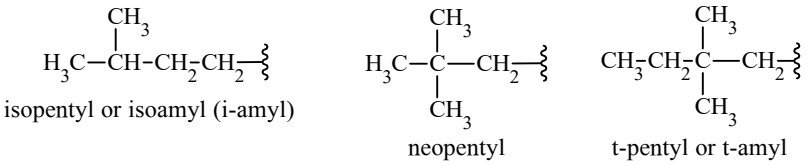
Organic compounds are named both in accordance with common or trivial names and IUPAC names. On account of large number of such compounds, it was decided in its first meeting of International Union of Pure and Applied Chemistry in 1893 to devise rules for naming these compounds. Since then, these rules are globally recognized that help in establishing uniformity of understanding for a particular organic compound across the globe. Before addressing rules for different classes of organic compounds, we first focus on some basics of organic nomenclature.

2.11 Common Names: n, iso and neo Prefixes

Straight chain compounds such as alkanes are easy to name. They are known as n-alkanes. Iso-alkanes have one branch on straight chain. When carbon atom bonds to four other carbon atoms or there are two branches on the same carbon atom, it gives neo-alkanes. All three, n, iso and neo are prefixes of common names. However, on account of large number of isomers, we can't simply rely on common name. For instance, hexane has 5 isomers, octane has 18 and decane has 75 isomers. Instead, we use more systematic nomenclature devised by IUPAC.

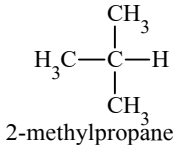


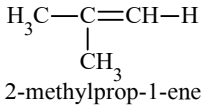
Different alkyl groups (given in section 1) of pentane are given as:

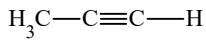


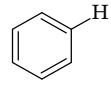
2.12 Alkyl, Alkenyl, Alkynyl and Aryl groups

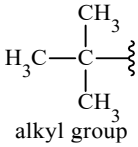
An alkyl group is represented by R which reflects a group obtained after removal of hydrogen or carbon atom from alkane. For example, methyl group is alkyl group which forms after removal of hydrogen atom from methane. Similarly, if hydrogen or carbon is removed from alkenes, the group containing double bond is known as alkenyl group, alkynyl group for alkyne and aryl group for aromatic compounds.

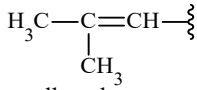

2-methylpropane

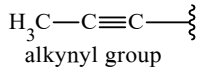

2-methylprop-1-ene

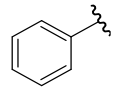

prop-1-yne


benzene


alkyl group


alkenyl group


alkynyl group


aryl group

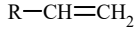
Alkanes, alkenes, alkynes and aromatic compounds fall in the category of hydrocarbons: compounds containing carbon and hydrogen. Replacing hydrogen or making carbon trivalent gives alkyl, alkenyl, alkynyl and aryl groups.

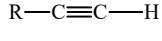
2.13 Functional Groups in Organic Chemistry

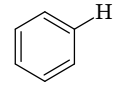
An atom or group of atoms which represents characteristic set of physical and chemical properties that distinguish one class of organic compounds from another is known as functional group. Consider the following hydrocarbons, each with distinct functional group such as single bond in alkane, multiple bonds in alkenes (double bond) and alkynes (triple bond) and benzene ring in aromatic compounds.

Functional Groups of Hydrocarbons


Alkane

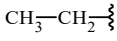

Alkene

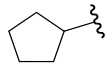

Alkyne

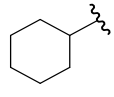

Aromatic

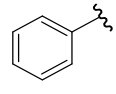
Note: Alkyl group (R) can be acyclic or cyclic


methyl


ethyl


cyclopentyl


cyclohexyl


phenyl

Alkyl Halides and RMgX

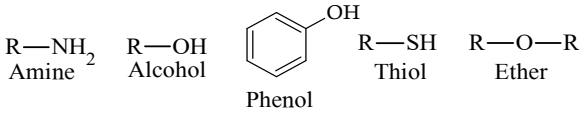
Compounds containing carbon metal bond are termed as organometallic. They are polar and highly reactive in which carbon acts as nucleophile.


Alkyl Halide — Alkyl Magnesium Halid (X = F, Cl, Br, I)

Amines, Alcohols, Phenols, Thiols and Ethers

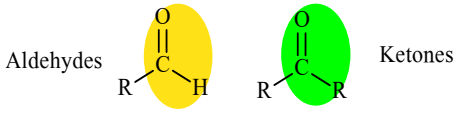
Amine functional group is established by alkyl group bonded to nitrogen. They are widespread in nature and commonly studied under class of natural product known as alkaloids. Alcohols have alkyl group attached to hydroxyl group. When the alkyl group is

substituted by phenyl ones, phenols result. Sulfur analogues of alcohols are termed as thiols. In ethers, an oxygen atom is shared by two alkyl or aryl groups.



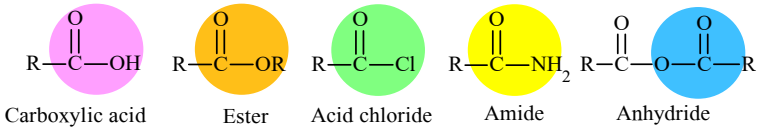
Carbonyl Compounds I (Aldehydes and Ketones)

Aldehydes and ketones represent the first class of carbonyl compounds having formyl (–CHO), the latter has acyl (–COR) functional groups respectively. They are good solvents and play crucial role in synthetic organic chemistry as precursors.



Carbonyl Compounds II (Carboxylic Acids and Derivatives)

Carboxylic acids have carboxyl group. This group can be substituted by other groups or atoms yield new functional groups of esters, anhydrides, amides and acid chlorides as derivatives of carboxylic acids.



2.2 Alkanes

Alkanes are class of organic compounds in which carbon atom is fully saturated. These compounds are least reactive (paraffin) because there is no reactive site for a chemical change unless harsh reaction conditions are applied. We call this class of compounds saturated hydrocarbons because all four valences of carbon atom are fully satisfied. Carbon atoms in alkane are sp^3 hybridized, giving tetrahedral geometry. Methane, known as marsh gas, is the parent member of alkane series.

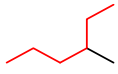
C	IUPAC Name	C	IUPAC Name	C	IUPAC Name
1	Methane	11	Un*decane*	21	Henicosane
2	Ethane	12	Dodecane	22	Docosane
3	Propane	13	Tridecane	23	Tricosane
4	Butane	14	Tetradecane	24	Tetracosane
5	Pentane	15	Pentadecane	30	Tri*acontane*
6	Hexane	16	Hexadecane	31	Hentriacontane
7	Heptane	17	Heptadecane	40	Tetracontane
8	Octane	18	Octadecane	50	Pentacontane
9	Nonane	19	Nonadecane	90	Nonacontane
10	Decane	20	I*cosane*	100	Hectane

Naming alkanes with larger number of carbon atoms	
37	Carbon Alkane: Hepta (7) Tri Acontane (30) Heptatriacontane
69	Carbon Alkane: Non (9) Hex Acontane (60) Nonhexacontane
179	Carbon Alkane: Non (9) Hept (7) Aconta (70) Hectane (100) Nonaheptacontahectane
738	Carbon Alkane: Octatriacontaheptahectane
999	Carbon Alkane: Nonanonacontahectane

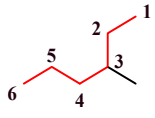
Fig. 2.1 Above tables reflect IUPAC names for alkanes containing different number of carbon atoms. Note correct name for Undecane is Hendecane. We use suffix -ctane for carbons atoms above 100. For example, Dictane is name for 200 alkanes. A 1000 carbon atoms alkane is named as kiliane.

2.21 Rules for Naming Alkanes (One Word Names)

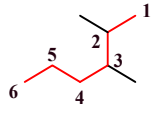
1. Select the longest chain of carbon atoms. The chain will acquire parent name (ending at suffix -ane) based on number of carbon atom in the longest chain. Consider the adjoining structure containing a longest chain of six carbon atoms (hexane) shown in red.



2. Number the parent chain of straight chain alkane from either end. In case, there is branch on parent chain, numbering take places from end that gives lowest number to the first substituent.



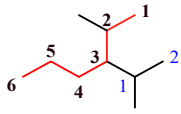
3. For two or more branches on the parent chain, numbering starts from end that gives lowest number to the second or third substituent.



4. Point out position and name of the substituent. Separate numbers by comma and use hyphen for separating name and numbers. If same substituent repeats twice or thrice, use prefixes di, tri and tetra etc. In case there is different substituent, use alphabetical order. For example, ethyl group takes precedence over methyl group.

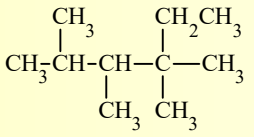
2-methyl, 3-methyl = 2,3-dimethylhexane

5. Prefixes like iso, neo, sec, tert are used in common names but they are so widespread and literature that they are now used as part of IUPAC names. Iso is taken in alphabetical order but not sec or tert. Use one word name for alkanes.

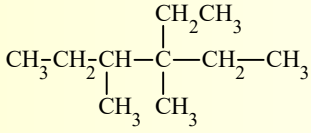


2-methyl-3-(1-methylethyl)hexane
or
3-Isopropyl-2-methylhexane

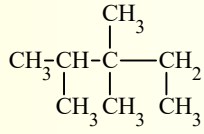
Examples



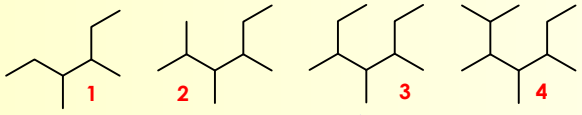
2,3,4,4-tetramethylhexane



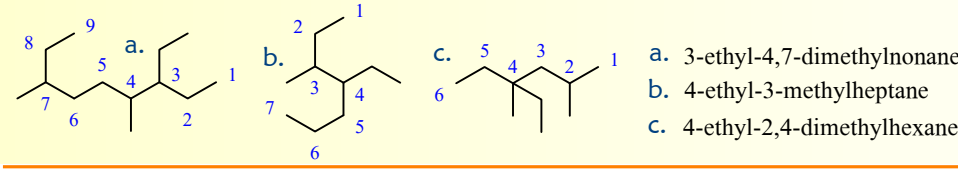
3-ethyl-3,4-dimethylhexane



2,3,3-trimethylpentane



1 3,4-dimethylhexane
2 2,3,4-trimethylhexane
3 3,4,5-trimethylheptane
4 2,3,4,5-tetramethylheptane

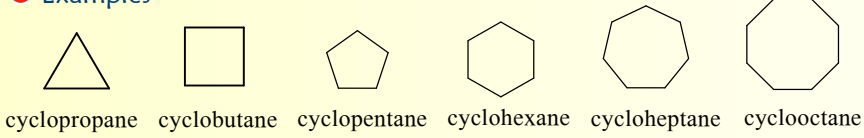


a. 3-ethyl-4,7-dimethylnonane
b. 4-ethyl-3-methylheptane
c. 4-ethyl-2,4-dimethylhexane

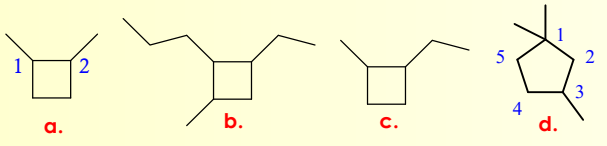
2.22 Naming Cycloalkanes

Cyclic alkane or cyclanes are simple to name in accordance with IUPAC names. These names take cycloalkane prefix. For example, a four member ring is named as cyclobutane. Numbering is done in case there is substituent on the ring. For instance, two methyl substituents on adjacent carbon atoms of four member ring is named as 1, 2-dimethylcyclobutane (see below).

Examples



cyclopropane cyclobutane cyclopentane cyclohexane cycloheptane cyclooctane



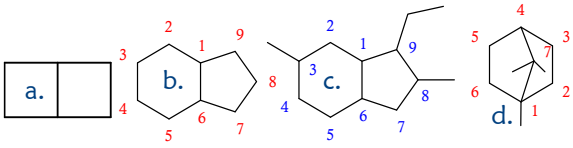
a. 1,2-dimethylcyclobutane
b. 1-ethyl-3-methyl-2-propylcyclobutane
c. 1-ethyl-2-methylcyclobutane
d. 1,1,3-trimethylcyclopentane

2.23 Naming Bridged, Bicyclic and Spiro Alkanes

Bicycloalkanes

Two rings joined by two or more atoms in common are termed as bicyclic compounds. These compounds take "bicyclo" prefix. The root name is based on number of carbon atoms involved in the ring. Bridge head carbon is assigned locant 1 and then numbering is extended to larger ring first and smaller rings later. If substituent is attached, assigned lowest number while moving from larger to smaller ring. The number of carbon

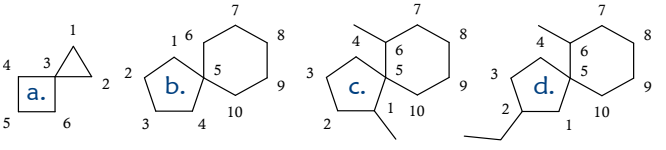
atom besides bridge head carbon are written in square bracket in descending order, separated by dot. Consider the following examples.



a. Bicyclo[2.2.0]hexane
b. Bicyclo[4.3.0]nonane
c. 9-Ethyl-3,8-dimethylbicyclo[4.3.0]nonane]
d. 1,7,7-Trimethylybicyclo[2.2.1]heptane

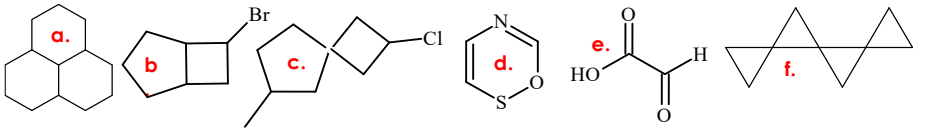
Spiroalkanes

Alkanes containing two rings joined by a common carbon atom are known as spiroalkanes. Such compounds take "spiro" prefix as root name containing total number of carbon atoms present in the ring. Number of atoms in each ring is written in ascending order in square bracket. These numbers are separated by comma. Numbering starts from carbon atom next to spiro carbon. Smaller ring is numbered first.

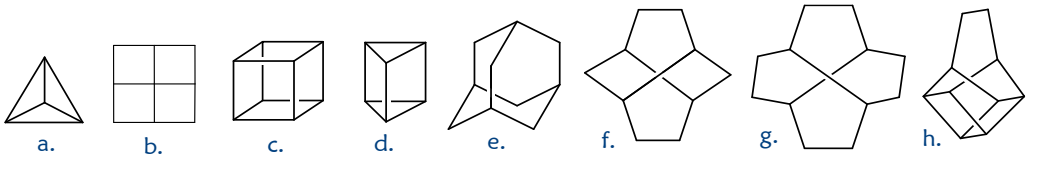


a. Spiro[2,3]hexane
b. Spiro[4,5]decane
c. 1,6-Dimethylspiro[4,5]decane
d. 2-Ethyl-6-methylspiro[4,5]decane

Problem 2.1 Assign IUPAC names to the following molecules



Problem 2.2 Assign IUPAC names to the following molecules whose common names are given below.



a. Tetrahedrane
b. Fenestrane
c. Cubane
d. Prismane
e. Adamantane
f. Twistane
g. Bishomotwistane
e. Basketane

Problem 2.3 What will be the name of alkanes containing 143, 297, 849 and 1675 carbon atoms?

2.3 Alkenes

Alkenes (olefins) are class of organic compounds containing carbon-carbon double bond. Each carbon of the double bond is sp^2 hybridized which makes the geometry of alkenes trigonal planar. Alkenes are prevalent in nature. Ethene (parent member of alkene series) known as ethylene is plant hormone that is responsible for repining of fruits, induces flowering, promotes aging in plants, affect loss of leaves and induces wide variety of other response in plants. Usually, fruit are picked when they are not ripened and treated/gassed with ethylene that affect rapid repining.

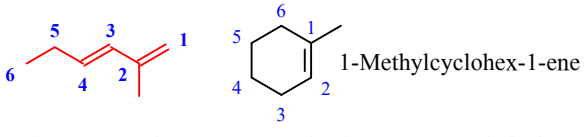
2.31 Rules for Naming Alkenes (One Word Names)

1. Choose longest chain containing double bond. As per revised rules of IUPAC in 1993, instead of naming the adjoining compound as 2-Pentene, put the parent name in front and add suffix -ene at the end after locant number.

2-Pentene: Old format
Pent-2-ene: New format

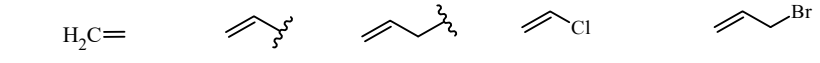
2. Number the chain from end that assigns lowest locant number to double bond. If the double bond is equidistant from both ends, begin numbering from the end that gives lowest locant to the substituent if present.

3. For two or more double bonds, use suffix -diene, triene etc. Cyclic alkenes are named like cycloalkanes, with double bond assigning the lowest number. If substituent present on one of the carbon atom of double bond, assign locant number 1 to the carbon atom.



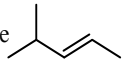
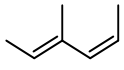
1-Methylcyclohex-1-ene

4. Double bond takes precedence over alkyl group and halogen while assigning numbering to the parent chain.

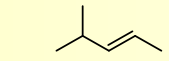


methylene group | vinyl group | allyl group | chloroethene vinyl chloride | 3-bromoprop-1-ene allyl bromide

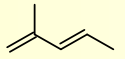
5. For geometrical isomers (cis-trans alkenes), use E (entgegen) for trans alkenes and Z (Zussamann) for cis alkenes. Write position and E or Z prefix in small brackets at the start of the name. Consider the following cases:

(2E)-4-methylpent-2-ene   (2E,4Z)-3-methylhexa-2,4-diene

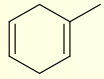
● Examples



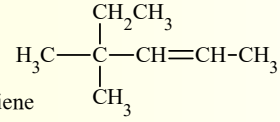
4-Methylpent-2-ene
4-Methyl-2-pentene



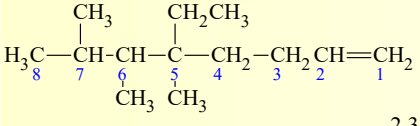
2-Methylpenta-1,3-diene



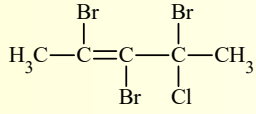
1-Methylcyclohexa-1,4-diene



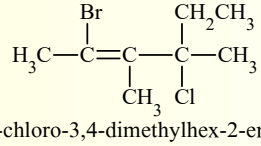
4,4-dimethylhex-2-ene



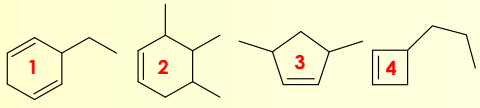
5-ethyl-5,6,7-trimethyloct-1-ene



2,3,4-tribromo-4-chloropent-2-ene



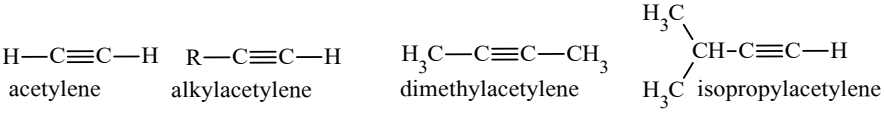
2-bromo-4-chloro-3,4-dimethylhex-2-ene



1 3-ethylcyclohexa-1,4-diene
2 3,4,5-trimethylcyclohex-1-ene
3 3,5-dimethylcyclopent-1-ene
4 3-propylcyclobut-1-ene

2.4 Alkynes

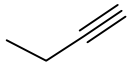
Alkynes are third important class of aliphatic hydrocarbons which contain carbon-carbon triple bond, with each carbon is sp hybridized, thus rendering geometry around triple bond linear. Acetylene is parent member of alkyne series. Alkynes are not common in nature like alkenes. Common names take suffix of acetylene in one word format. For instance, an alkyl group substituted for one of hydrogen of acetylene render the common name as 'alkyl acetylene'. Consider the following examples:



acetylene | alkylacetylene | dimethylacetylene | isopropylacetylene

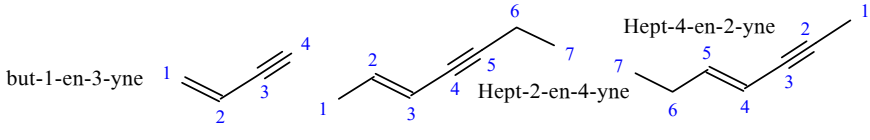
2.41 Rules for Naming Alkynes (One Word Names)

1. Put -yne suffix by replacing -ane of alkane while naming alkynes. For example, propane becomes propyne. All previous rules are same except some minor distinctions.



but-1-yne

2. For a chain containing double and triple bond that take equal numbering, preference will be given to double bond as -ene precedes -yne in alphabetical order. Otherwise, lowest locant number will be assigned to the first multiple bonds.



but-1-en-3-yne | Hept-2-en-4-yne | Hept-4-en-2-yne

3. Alcohols are given preference over alkenes and alkynes. Consider the following priority order while assigning IUPAC names to organic molecules.

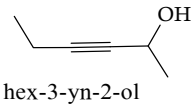
Preference Order

Which functional group will take precedence over other is important to know while naming multifunctional organic compounds. The order of preference is:

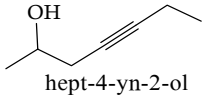
> Carboxylic Acids > Esters > Aldehydes > Ketones > Alcohols > Amines > Alkenes, **Alkynes** > Alkanes > Ethers > Alkyl halides

Order of preference →

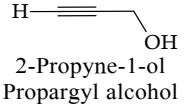
These functional groups have arranged in decreasing order of priority. For instance, amines and alkenes take precedence over alkynes. Consider the following examples with reference to triple bond.



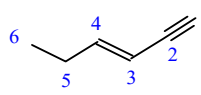
hex-3-yn-2-ol



hept-4-yn-2-ol

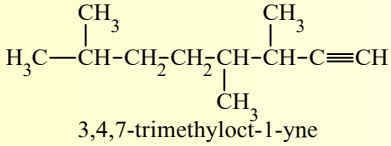


2-Propyne-1-ol
Propargyl alcohol

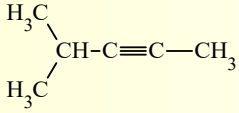


hex-3-en-1-yne
3-hexen-1-yne

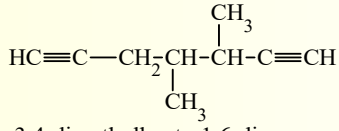
Examples



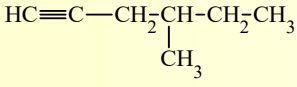
3,4,7-trimethyloct-1-yne



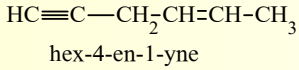
4-methylpent-2-yne



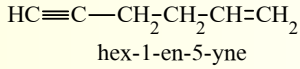
3,4-dimethylhepta-1,6-diyne



4-methylhex-1-yne



hex-4-en-1-yne



hex-1-en-5-yne

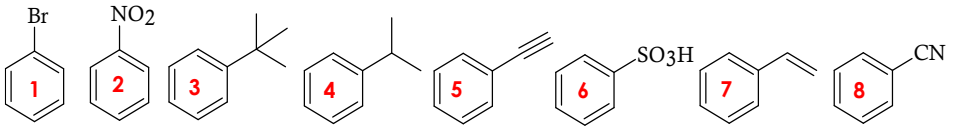
2.5 Aromatic Hydrocarbons

Aromatic compounds are characterized by the presence of benzene ring as fundamental unit. The term 'aroma' connotes 'odor' which is characteristic of this class of compounds. Benzene was discovered by Michael Faraday in 1826. Since then, it took almost 40 years to ascertain its correct structure until August Kekul, German Chemist, pointed out benzene possessed cyclic ring structure. Benzene is colorless and flammable liquid which is obtained from petroleum and coal tar. Benzene offers an important basic unit for many natural and synthetic products. Many drugs are based on benzene rings.

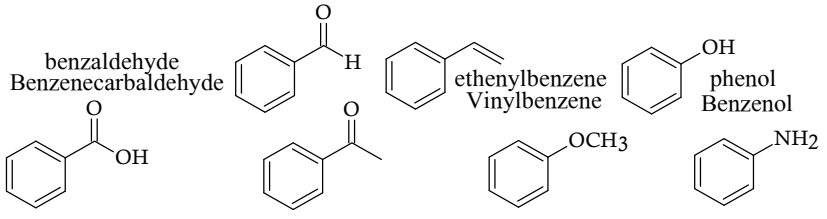
2.51 Rules for Naming Alkynes (One Word Names)

1. Many monosubstituted aromatic compounds are known by common names. These names are so prevalent in literature that they became the part of IUPAC names. These compounds are named with suffix 'benzene' and name of substituent as prefix.

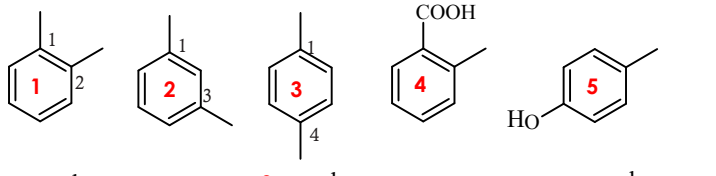
1 Bromobenzene **2** Nitrobenzene **3** t-Butylbenzene **4** isopropylbenzene **5** ethynylbenzene **6** benzenesulfonic acid **7** styrene **8** benzonitrile



2. In the following examples, both common and IUPAC names are given

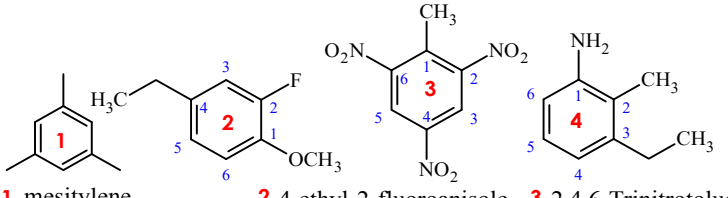


3. Many disubstituted benzene derivatives are either named by their common names or IUPAC names. Locant number 1 is assigned to carbon atom bearing common base name. The carbon to which substituent is attached is known as ipso carbon. Disubstituted compounds are also named by prefixes ortho (1,2 relationship of two substituents), meta (1,3) and para (1,4). Note, o, m and p prefixes are used for disubstituted compounds only.



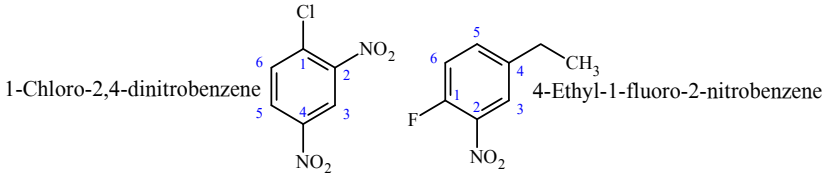
1 o-xylene
1,2-Dimethylbenzene
2 m-xylene
1,3-Dimethylbenzene
3 p-xylene
1,4-Dimethylbenzene
4 o-toluic acid
2-methylbenzoic acid
5 p-cresol
4-methylphenol

4. Some trisubstituted benzene derivatives are also named by their common names. These compounds are named based on their parent chain as root name.



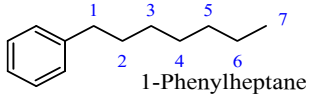
1 mesitylene
1,3,5-trimethylbenzene
2 4-ethyl-2-fluoroanisole
3 2,4,6-Trinitrotoluene
4 3-ethyl-2-methylaniline

5. If simple parent name can't be ascertained, chose benzene instead. Follow all previous rules while assigning IUPAC names. Consider the following examples.

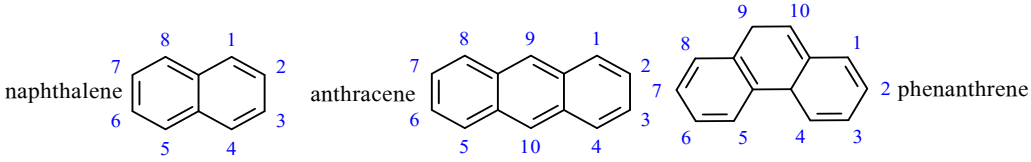


6. For benzene ring attached as substituent, name it as phenyl, benzyl and aryl groups. A group obtained by removal of one hydrogen from benzene ring gives aryl group (-Ar). Phenyl (-Ph) is the simplest aryl group.

7. If the substituent is larger than the benzene ring, say the number of carbon in benzene ring, then benzene ring is treated as substituent itself known as phenyl group. Note, benzene ring as a substituent is named as phenyl group.

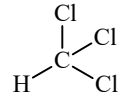


8. Polycyclic aromatic compounds are numbered as follow:

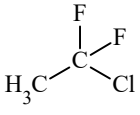


2.6 Alkyl Halides

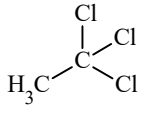
Alky halides (R—Xs, X = F, Cl, Br, I) are compounds containing carbon-halogen bond. These compounds are usually synthetic and perhaps better known as man-made poison because they were used to kill pests. DDT or dichlodiphenytrichloroethane was developed during Second World War to treat malaria and other infectious diseases among soldiers. Later, the compound was used in agriculture sector on widespread scale to kill pest. Soon DDT was discovered as persistent insecticide that threatened environment on account of its non-biodegradable character.



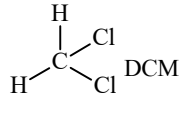
Chloroform



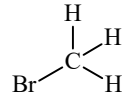
Freon - 22
Refrigerant



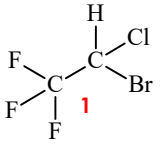
1,1,1-trichloroethane
Cleansing fluid



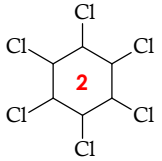
Dichloromethan
Common lab solvent



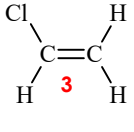
methyl bromide
used to treat termite infestation



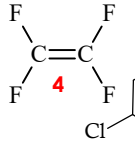
1 Halothane, anesthetic, nonflammable



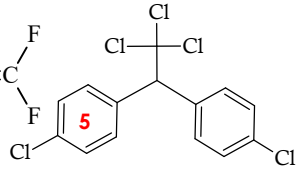
2 Lindane, hexachlorocyclohexane, used in shampoo to treat lices



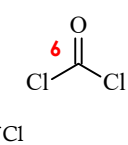
3 Vinyl chloride, monomer of PVC



4 Tetraflouroethylene, monomer of teflon



5 Dichlorodiphenyltrichloroethane, DDT



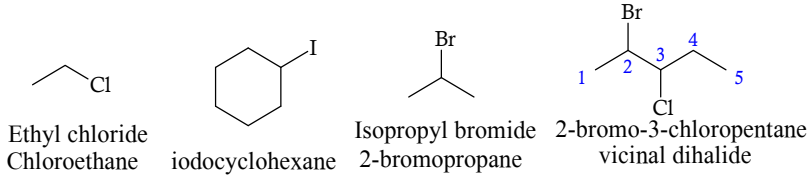
6 Phosogen, extremely toxic

Chlorofluorocarbon (CFCs) is another class of environmentally harmful compounds that were first employed as refrigerants. These compounds have been implicated in depletion of ozone layer. Alkyl halides can be divided into three classes: aliphatic, vinylic and arylic. The chemistry of aliphatic alkyl halides is different from the latter two classes. Alkyl halides containing two halogen atoms are termed as dihalides, which can be vicinal or geminal. When two halogen atoms are present on two adjacent carbon atoms, the dihalide is known as vicinal. When both halogen atoms are present on the same carbon atom, the dihalide is known as geminal.

2.61 Rules for Naming Alkyl Halides

1. Both common and IUPAC names are used for naming alkyl halides. Systematic names follow selection of longest chain containing halogen atom. All rules of alkanes apply while naming alkyl halides. Chloroform is named as 1,1,1-trichloromethane. CHI_3 is Iodoform and $CHBr_3$ is bromoform. IUPAC name for DDT is 1,1,1-Trichloro-2,2-di(4-chlorophenyl)ethane.

2. Sometimes bis, tris or tetrakis are used for di, tri or tetra respectively. In the following example, ethyl chloride (Alkyl halide) is common name where chloroethane (a) is IUPAC. Bromo comes first in alphabetical order among fluro, chloro or iodo prefixes.



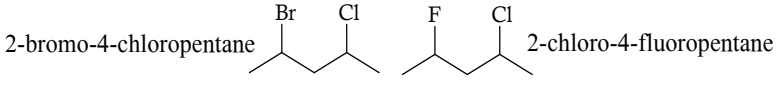
Ethyl chloride
Chloroethane

iodocyclohexane

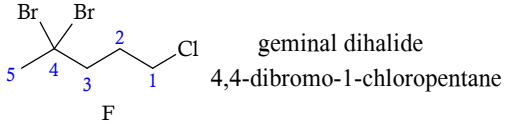
Isopropyl bromide
2-bromopropane

2-bromo-3-chloropentane
vicinal dihalide

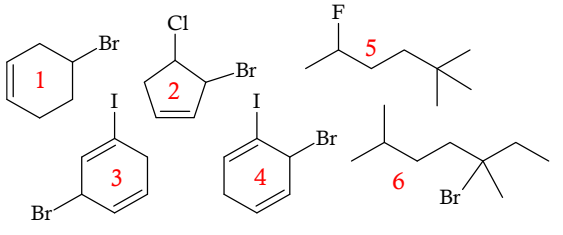
3. When two halogens come on same position, assign numbering that give lowest locant to first substituent of higher atomic number halogen. Consider the following examples:



4. While selecting parent chain, never look at the halogen atom like alcohol or amino group because halogen atom carries least priority, even than alkanes. Focus first substituent for assigning numbering. Double or triple bond carries preference over halogen atom.

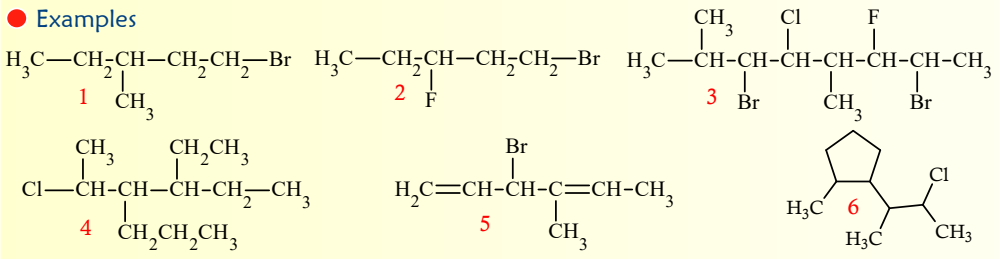


geminal dihalide
4,4-dibromo-1-chloropentane



1 4-bromocyclohex-1-ene
2 3-bromo-4-chlorocyclopent-1-ene
3 3-bromo-1-iodocyclohexa-1,4-diene
4 6-bromo-1-iodocyclohexa-1,4-diene
5 5-fluoro-2,2-dimethylhexane
6 5-bromo-2,5-dimethylheptane

● Examples



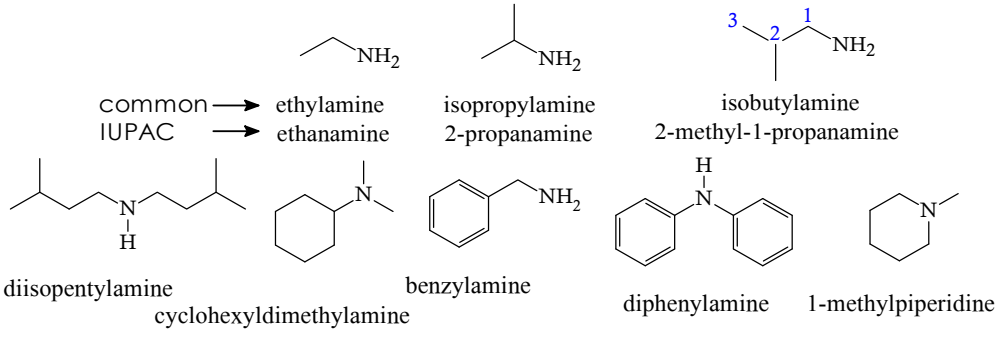
1 1-bromo-3-methylpentane
2 1-bromo-3-fluoropentane
3 2,6-dibromo-5-chloro-3-fluoro-4,7-dimethyloctane
4 4-(1-chloroethyl)-3-ethylheptane
5 3-bromo-4-methylhexa-1,4-diene
6 1-(3-chlorobutan-2-yl)-2-methylcyclopentane

2.7 Amines

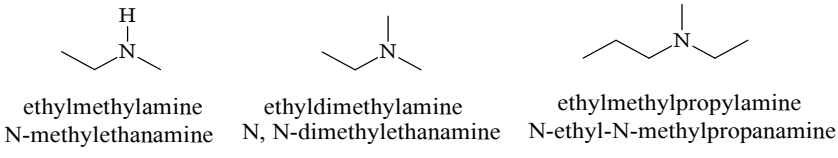
Amine functional group is established by alkyl group bonded to nitrogen. They are widespread in nature and commonly studied under class of natural product known as alkaloids. Alkaloids have characteristic physiological or psychological properties. For example, morphine, cocaine and nicotine are amines. Amines can be aliphatic or aromatic. Aliphatic amines are primary, secondary or tertiary when nitrogen atom bonds to one, two or three alkyl groups respectively. Amines are basic in chemical properties. Some biologically important amines are given below.

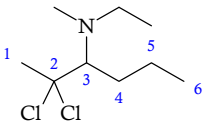
2.71 Rules for Naming Amines

1. Alkylamine is common name, alkanamine is IUPAC one. Note the replacement of alkane 'e' in IUPAC names. Numbering is done from the end close to amino group.

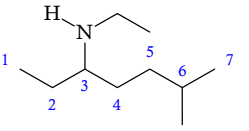


2. Secondary and tertiary amines are named by using N for alkyl group attached to nitrogen atom. Alphabetical order follows as N-ethyl-N-methyl. For similar substituents such as methyl or ethyl linked to nitrogen, we use N,N-dimethyl or N,N-diethyl. Consider the following examples.



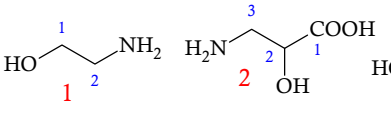


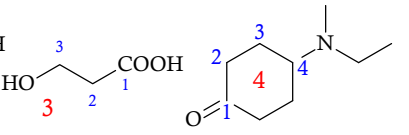
2,2-dichloro-N-ethyl-N-methyl-3-hexanamine



N-ethyl-6-methyl-3-heptanamine

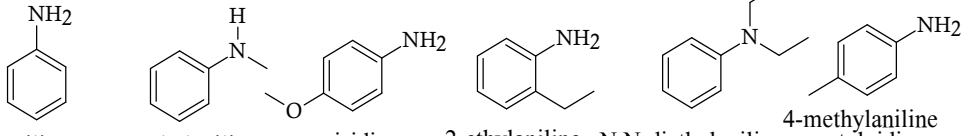
3. Hydroxyl, keto and carboxyl groups have preference over amino group.





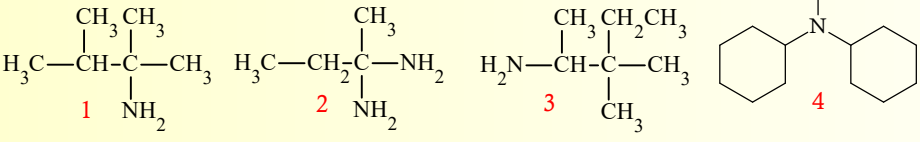
1 2-aminoethan-1-ol
2 3-amino-2-hydroxypropanoic acid
3 3-hydroxypropanoic acid
4 4-[ethyl(methyl)amino]cyclohexan-1-one

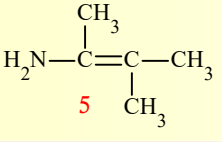
4. Aromatic amines are named as follow:

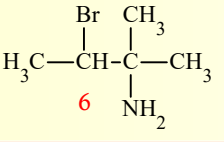


aniline | N-methylaniline | p-anisidine | 2-ethylaniline | N,N-diethylaniline | 4-methylaniline (p-toluidine)

Examples







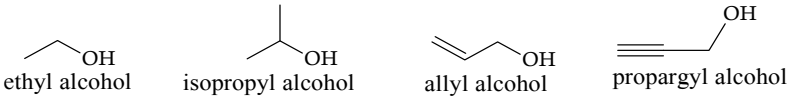
1 2,3-dimethylbutan-2-amine
2 butane-2,2-diamine
3 3,3-dimethylpentan-2-amine
4 N-cyclohexyl-N-methylcyclohexanamine
5 3-methylbut-2-en-2-amine
6 3-bromo-2-methylbutan-2-amine

2.8 Alcohol, Phenol & Ether

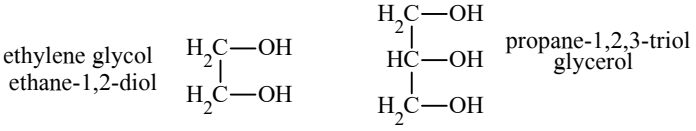
Replacing one of the two hydrogen of water with alkyl group gives alcohol (R—OH). If the replacement is made with phenyl group instead of alkyl group, we get a new class of aromatic compounds known as phenol (Ar—OH). If both hydrogens of water is replaced with alkyl groups we get ethers (R—O—R). Replacement of alcoholic oxygen with sulfur yields another functional group known as thiol (R—SH). All four types are important classes of organic compounds. Alcohols can be primary (1°), secondary (2°) or tertiary (3°) depending upon whether the carbinol carbon (carbon to which hydroxyl group is bonded) is linked to one, two or three other carbon atoms respectively. Methanol (wood alcohol) is the parent member of alcohol series. It is toxic and flammable. Ethanol (grain alcohol) is the next member which is good laboratory solvent and excellent fuel. Isopropyl alcohol (rubbing alcohol) is used as antiseptic agent. Ethylene glycol is important antifreeze and glycerol is useful biological molecule.

2.81 Rules for Naming Alcohols

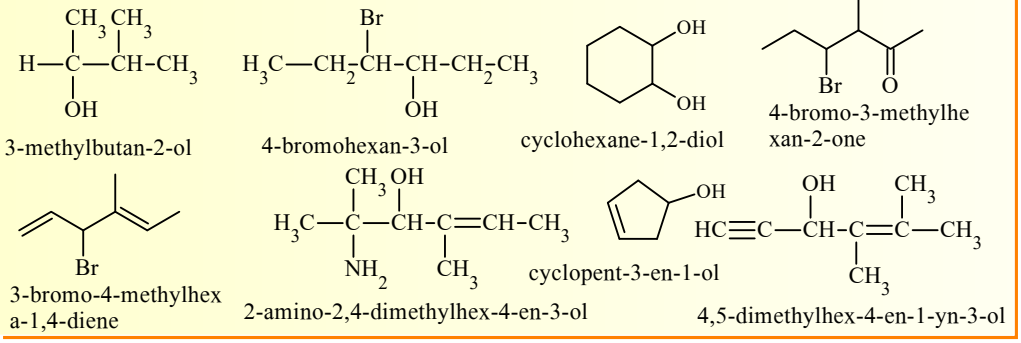
1. Both common and IUPAC names are used for naming alcohols. Common names use alkyl alcohol such as methyl alcohol or ethyl alcohol, whereas IUPAC names require dropping –ane of alkane with –ol such as methanol or ethanol.



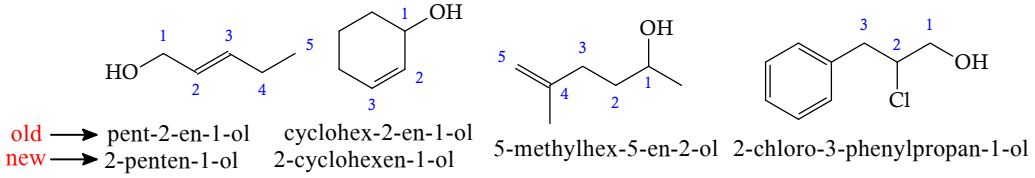
2. Select the longest chain containing hydroxyl group. For two or more —OH groups, we use prefixes di, tri or tetra ols. For example, glycol has two —OH groups, therefore it is named as ethane-1,2-diol. Similarly, glycerol has three such groups. It is named as propane-1,2,3-tiol.



Examples

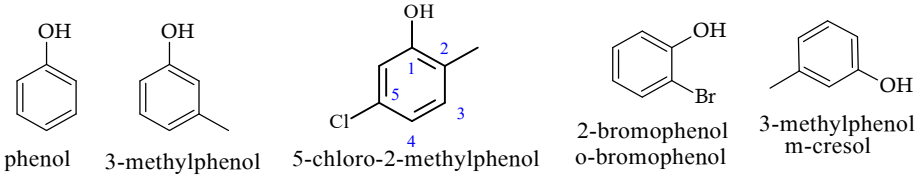


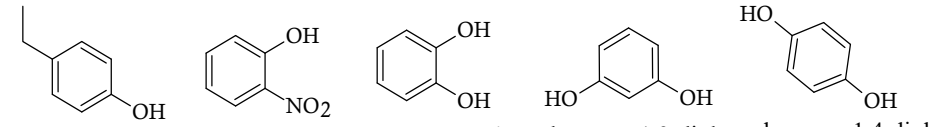
3. Alcohols have preference over double, triple bond and phenyl ring.



2.82 Rules for Naming Phenols

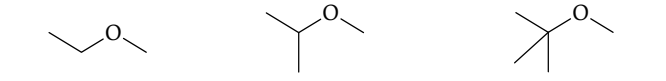
1. Phenols use both simple and IUPAC names. Hydroxyl group on the ring is chosen at position 1. Some common examples are given below:



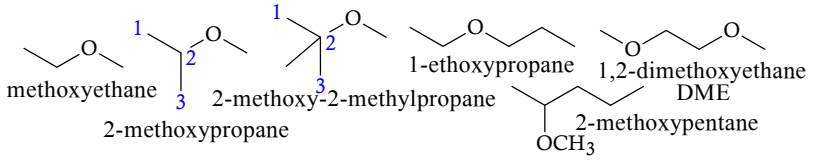


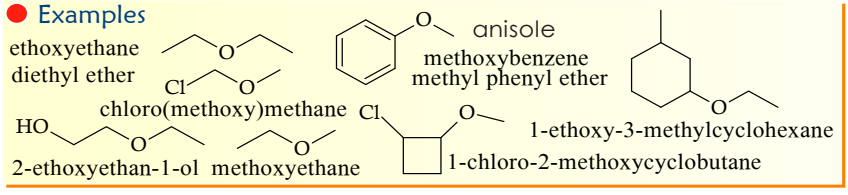
2.83 Rules for Naming Ethers

1. Ethers are assigned both common or trivial names and IUPAC names.



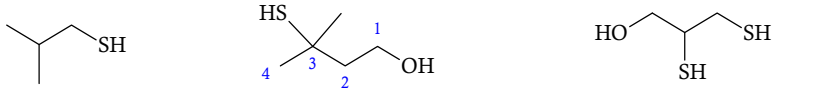
2. IUPAC names involve the longest or complex alkyl group bonded to oxygen as parent name. The other part is named as alkoxy. Hence, ethers are named as alkoxyalkanes (one word names).





2.84 Rules for Naming Thiols

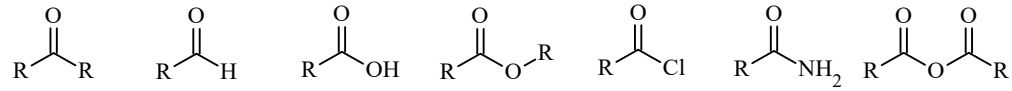
Thiols are most notorious for pungent smell. They are named by using thiol suffix as alkane thiol by retaining the 'e' of alkane. When there is another functional group, —SH group is taken as substituent and is named a mercapto. In fact, the word mercapto (Latin: mercaptans, capturing mercury) derived from drug, mercaptol which is used to treat mercury and lead poisoning.



Drug: dimercaptol

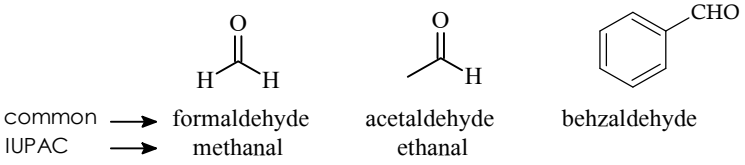
2.9 Aldehydes & Ketones

Formyl group (—CHO) is the functional group of aldehydes where **acyl** group (—COR) is the functional group of ketones. Both aldehydes represent the first class of carbonyl compound.

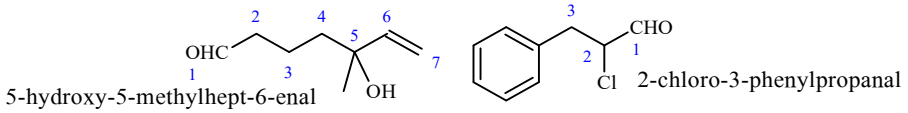


2.91 Rules for Naming Aldehydes & Ketones

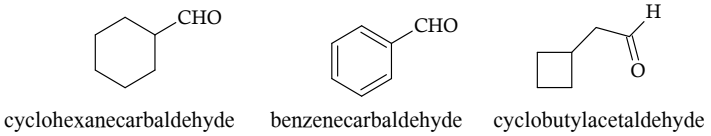
1. Aldehydes are named alkanal by IUPAC nomenclature. Alkane 'e' is dropped. They are also named by common system: formaldehyde, acetaldehyde and benzaldehyde.



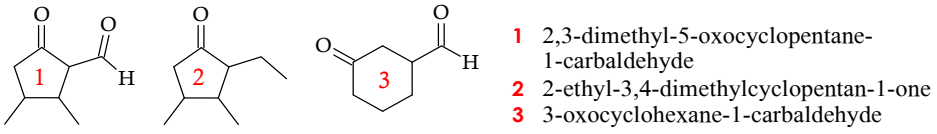
2. Aldehyde carbon is assigned number 1. Aldehyde has preference over alcohol, double and triple bonds.



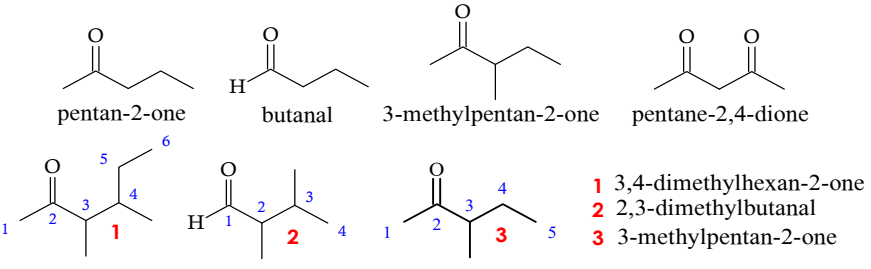
3. A cyclic compound containing —CHO group is named as carbaldehyde.



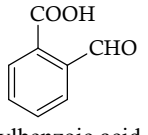
4. Aldehyde has preference over ketone. If both functionalities appear in a molecule, keto group is taken as substituent and is named as oxo.



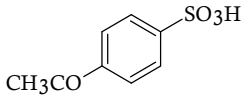
5. Besides common names such as acetone, acetophenone and benzophenone, ketones are named as 'alkanone' by dropping 'e' of alkane according to IUPAC names. Assign least number to the end of chain containing keto group.



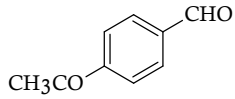
6. When —CHO group is taken as substituent, it is named as methanoyl or formyl. Similarly, —$COCH_3$ group of ketone is named as ethanoyl or acetyl group (Ac).



2-formylbenzoic acid
2-methanoylbenzoic acid

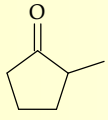


4-acetylbenzene-1-sulfonic acid

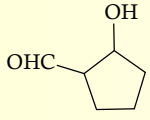


4-acetylbenzaldehyde

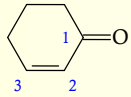
Examples



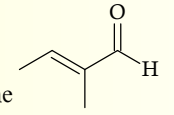
2-methylcyclopentan-1-one



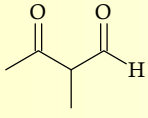
2-hydroxycyclopentane-1-carbaldehyde



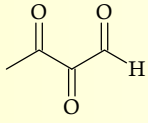
cyclohex-2-en-1-one



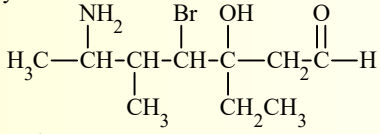
2-methylbut-2-enal



2-methyl-3-oxobutanal



2,3-dioxobutanal



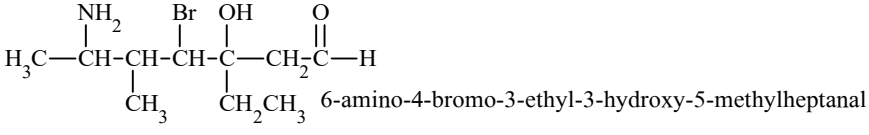
6-amino-4-bromo-3-ethyl-3-hydroxy-5-methylheptanal

2.10 Carboxylic Acids

Carboxyl group (—COOH) functional group of carboxylic acids. When one of hydrogen atom in water is replaced by a carbonyl group (—CO—), the resultant functional group is termed as carboxyl group (—COOH), which represents an important class of organic compounds known by the tag name of carboxylic acids that can either be aliphatic (R—COOH) or aromatic (Ar—COOH) carboxylic acids. An acyl group has alkyl or aryl group linked to carbonyl group (RCO) which is characteristic part of all carbonyl compounds functional groups.

Preference Order: ***Carboxylic acids*** > Anhydrides > Esters > Acid halides > Amides > Nitriles > Aldehydes > Ketones > Alcohols > Thiols > Amines

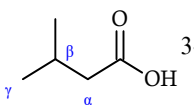
Order of preference



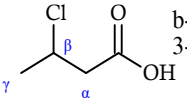
6-amino-4-bromo-3-ethyl-3-hydroxy-5-methylheptanal

2.101 Rules for Naming Carboxylic Acids & Derivatives

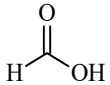
1. Carboxylic acids are named both by common and IUPAC names. Common names include formic acid, acetic acid, oxalic acid and malonic acid etc. Simple acids are known by their common names. Some of the common names are given below.



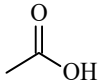
isovaleric acid
3-methylbutanoic acid
b-methylbutyric acid



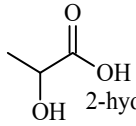
b-chlorobutanoic acid (Common Name)
3-chlorobutanoic acid (IUPAC Name)



formic acid
methanoic acid

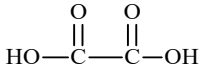


acetic acid
ethanoic acid

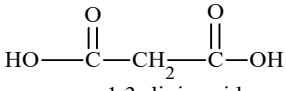


2-hydroxypropanoic acid

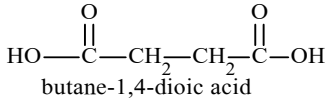
2. IUPAC names involve replacing —ane of alkane with —oic acid. For acids containing two or more carboxyl groups are named a dioic acid, trioic acid etc.



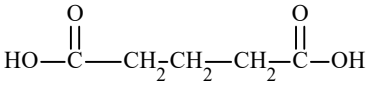
ethane-1,2-dioic acid
oxalic acid



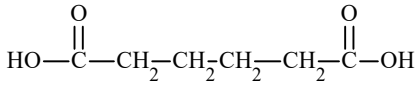
propane-1,3-dioic acid
melonic acid



butane-1,4-dioic acid
succinic acid

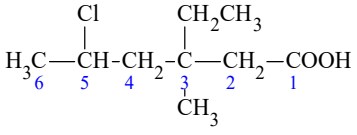


pentane-1,5-dioic acid
glutaric acid

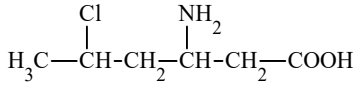


hexane-1,6-dioic acid
adipic acid

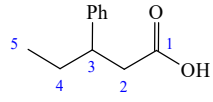
3. Select the longest chain containing carboxyl group. Number the chain from carboxyl group containing end.



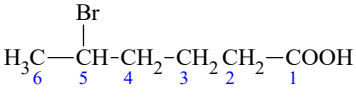
5-chloro-3-ethyl-3-methylhexanoic acid



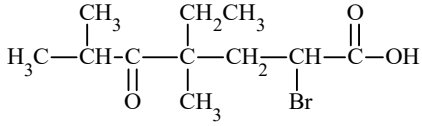
3-amino-5-chlorohexanoic acid



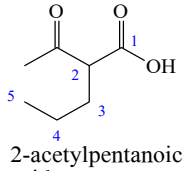
3-phenylpentanoic acid



5-bromohexanoic acid

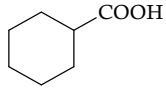


2-bromo-4-ethyl-4,6-dimethyl-5-oxoheptanoi
c acid



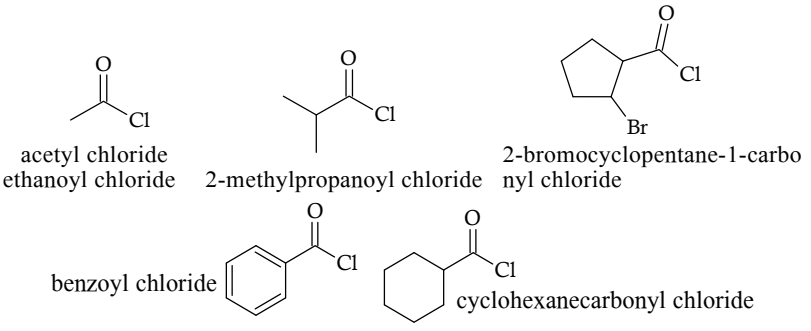
2-acetylpentanoic
acid

4. IUPAC names involve dropping ‘e’ of alkane with —oic acid. For instance, formic acid is named as methanoic acid. If —COOH group is attached as substituent, especially in cycloalkanes, the acid is named by adding suffix ‘carboxylic acid.

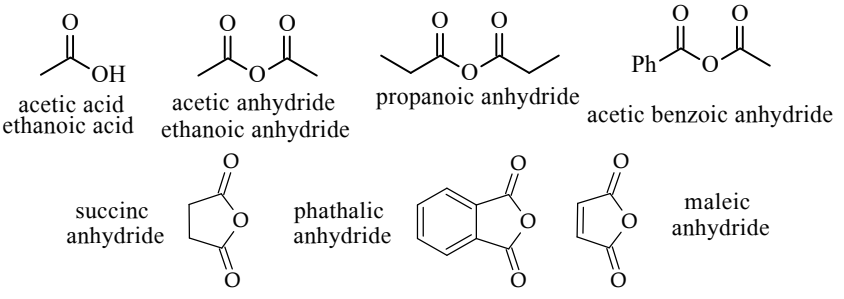


cyclohexanecarboxylic acid

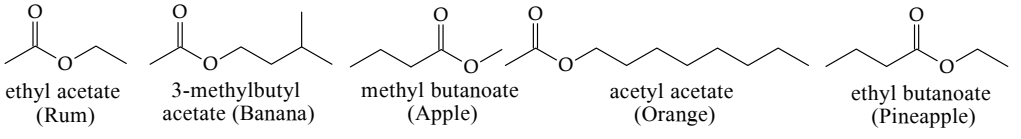
5. **Acid Halides** have acyl (RCO—) functional group. Acid chloride is the common example. Acid halides are named by dropping —ic acid with —yl halide. If acyl group is attached to cycloalkane ring, it is named as —carbonyl chloride.



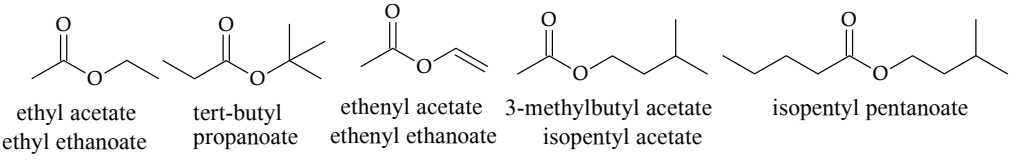
6. **Anhydrides** are named by adding suffix 'anhydride' to the name of carboxylic acid after replacing 'acid' suffix. If common name prefix such as acetic acid is not retained, then IUPAC named is used as prefix. Consider the following example.



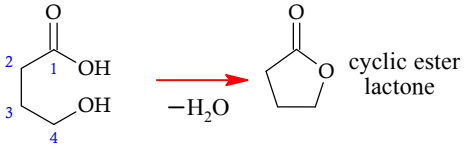
7. **Esters** are sweet flavoring agents which offer important class of food additives. They are named both in common and IUPAC formats. Esters are named by adding suffix —ate.



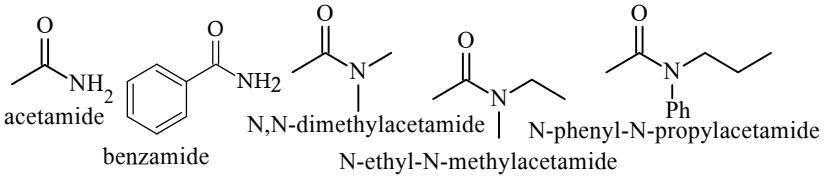
8. Alkyl group attach to oxygen atom of ester is named first. Name of Parent chain ends at —ate and ester acquires the name of alkylalkanoate.



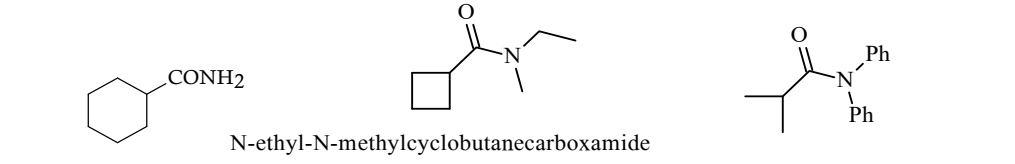
9. Cyclic esters are known as **lactones** which form through dehydration of hydroxy carboxylic acids.



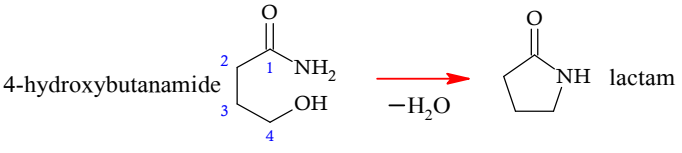
10. **Amides** are named by adding 'amide' suffix in one word format.



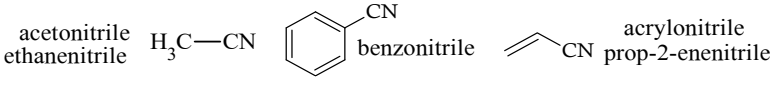
11. For a group —$CONH_2$ attached as substituent to cyclic compounds, we use carboxamide suffix.



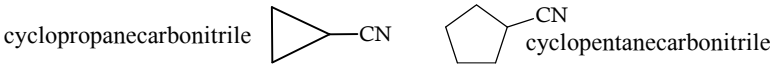
12. Cyclic amides are known as **lactams**.



13. **Nitriles** are named by adding 'nitrile' suffix in one word format.

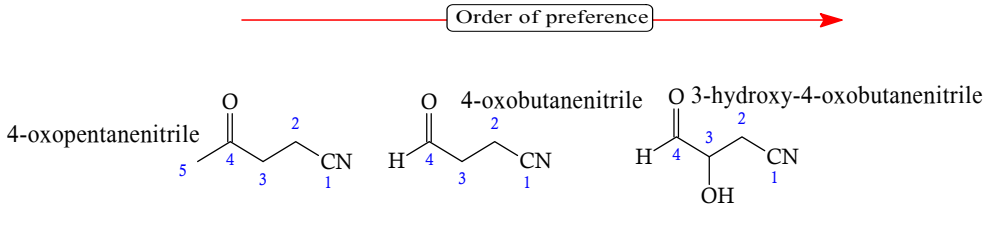


14. For —CN attach to ring, we use cycloalkanecarbonitrile.

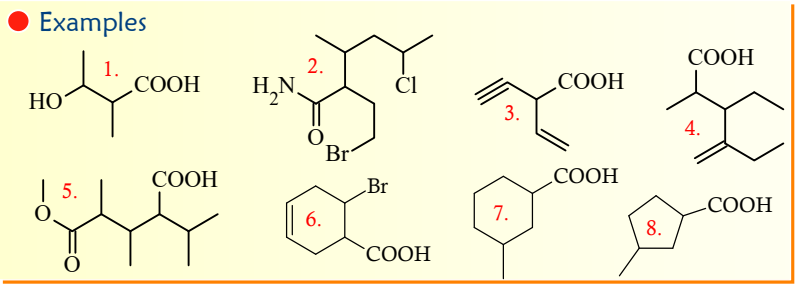


15. Nitriles have preference over alcohols, aldehydes and ketones. Consider the following preference order:

> **Priority Order**: Carboxylic acids > Anhydrides > Esters > Acid halides > Amides > ***Nitriles*** > Aldehydes > Ketones > Alcohols > Thiols > Amines



● Examples



2.11 Heterocyclic Compounds

Heterocyclic compounds are of immense importance in our biological system. Our hereditary units says DNA and RNA are made up of small heterocyclic molecules. Many vitamins are heterocyclic in nature. Vitamin C, ascorbic acid, is useful anti-oxidant which fights free radical to prevent oxidative damage to biological tissues. Ageing in man and other animal is due to free radical interaction with the biological inhibition. In the absence of radical inhibitors such as Vitamin C, the process takes place at swift pace that render the organism aged in short span.

Vitamin C is water soluble antioxidant. The vitamin plays pivotal role in synthesis of collagen which is essential ingredient of connective tissues. Our skin, bones, teeth, bold vessels, cartilage, tendons and ligaments all depend on optimum level of collagen in our body. If the level is altered scurvy results which is a disease of blood vessels deterioration. Symptoms includes hemorrhage, bleeding gums, bruising, lose teeth and tendency of bone to fracture easily. Vitamin C plays significant role in cleansing of arterial plaque that help mitigating cardiovascular diseases. Vitamin C strengthens immune system by boosting the number of white blood cells.

Both trivial or common names and IUPAC names are used to name heterocyclic compounds. The IUPAC system is based on Hanztch-Widmann-Petterson naming system. Before naming such compounds, we need to know certain prefixes, naming based on ring size, preference order and naming bicycle heterocyclic compounds.

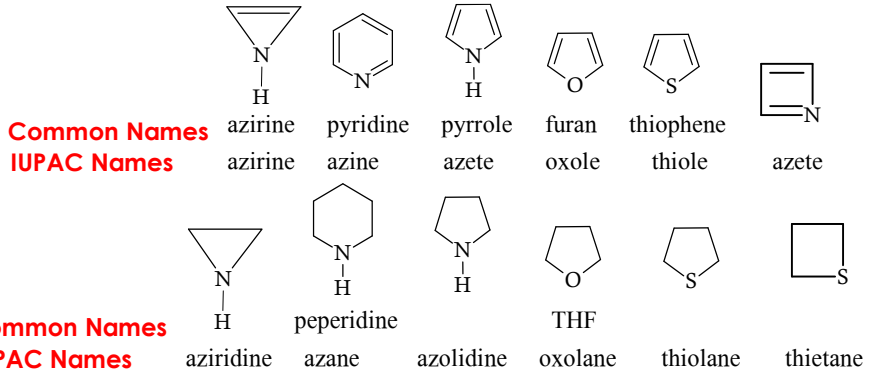
Prefixes: We use specific prefixes for different hetero atoms. A simple table is given below although a detailed one could be reviewed for knowing the prefixes of other elements which are not listed in the table.

Prefixes
Oxa = Oxygen
Aza = Nitrogen
Thia = Sulfur

Prefixes
Bora = Boran
Sila = Silicon
Bisma = Bismuth

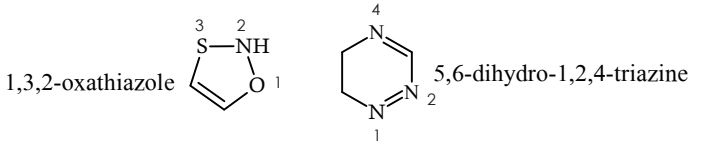
Ring size: Heterocyclic ring can be saturated or unsaturated. In either case, we have different prefixes for naming such compounds. We need to remember two things: ring size and saturation before naming these compounds.

Unsaturated			Saturated		
Ring Size	With N	Without N	Ring Size	With N	Without N
3	irine	irene	3	iridine	irane
4	ete	ete	4	etidine	etane
5	ole	ole	5	olidine	olane
6	ine	ine	6	ane	
7	epine	epin	7	epane	
8	ocine	ocin	8	ocane	



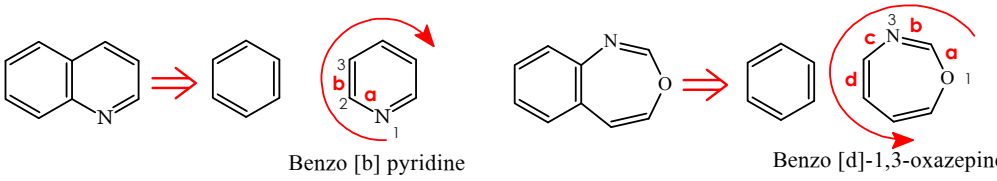
Preference Order

As most heterocyclic compounds contain hetero atoms such as oxygen, sulfur and nitrogen, therefore we need to remember their general preference order, which means when certain heterocyclic compound contain two or more hetero atoms, then we must know which one to be assigned first, second or third priority in numbering. The general preference order is: **O > S > N**



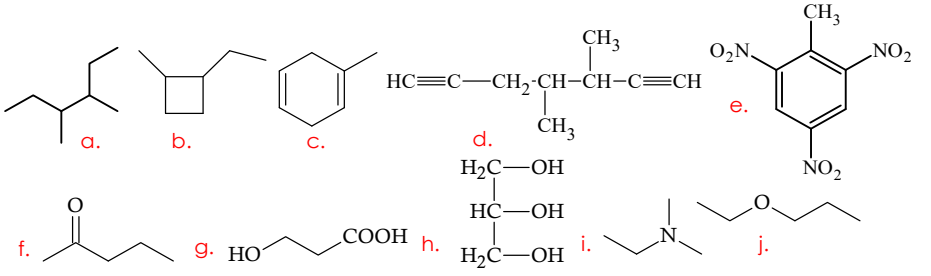
Bicyclic Heterocyclic Compounds

We use prefix 'benzo' for benzene ring in bicyclic heterocyclic compounds. Break the two rings apart and focus heterocyclic one. Start numbering from the hetero atom and move in direction of the benzene ring attached. Note the bonds by small letters so that we could know which bond attaches with another ring. In below example, bond 'b' attaches to benzene ring, so the name of the compound will be Benzo [b} pyridine.



2.12 Exercise

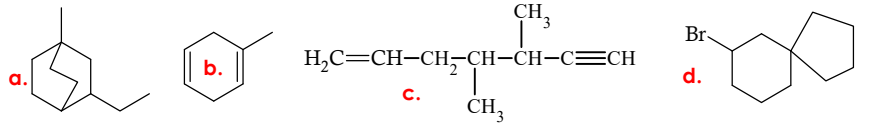
1. Assign IUPAC names to the following functional groups.



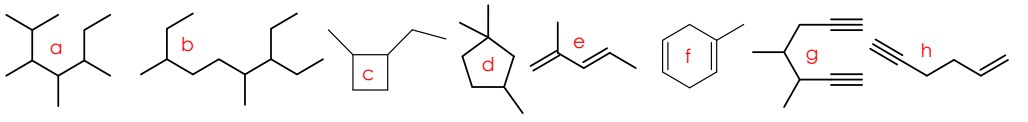
2. Make correct structure of the following IUPAC names.

a. 4-Hepten-2-yne
b. Thiolane
c. 2,4-dihydroxypentane
d. 1-methoxy-2,3-dimethylbutane
e. Cyclohexonic acid
f. Pent-2-en-1-ol
g. 3-methoxypropane
h. 3-(2-methylethyl)hexane

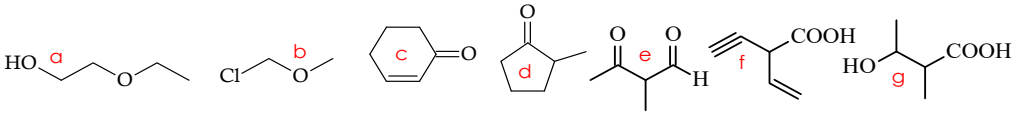
3. Assign systematic names to any three of the following compounds:



4. Point out functional group and name each of the following compound.

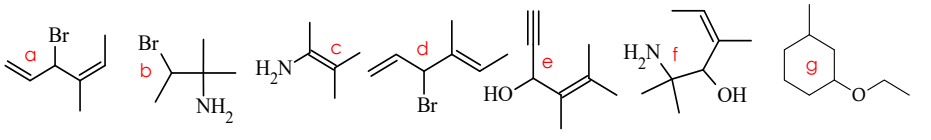


5. Point out functional group and assign systematic names to the following molecules.



6. Give IUPAC names to the pyridine, adipic acid, acetaldehyde, glycol, glycerol, allyl chloride and rubbing alcohols.

7. Assign IUPAC names to the following compounds.



Section 3 Functional Group Chemistry

3.1 Alkanes

3.11 Introduction

Alkanes (paraffin), are class of organic compounds which contain carbon-carbon single bond. They are termed as saturated hydrocarbons because all four valencies of carbon atoms are fully satisfied. They are least reactive of all functional groups. Alkanes don't react under ordinary conditions except when they are subjected to drastic reaction conditions such as combustion or pyrolysis. Methane is the starting member of alkane series.

3.12 Sources of Organic Compounds

Fossil fuel are the chief source of organic compounds. Over a period of million years, the dead remain of plants and animals transformed under anaerobic conditions triggered by varied geological conditions into petroleum. Whatever coal, petroleum or natural gas is available today are the final product of such transformation.

1. Coal

Coal is black mineral of vegetable origin. Anaerobic respiration transforms dead remains of plant and animals into coal. The chief component of coal is carbon. Besides, it also contain limited quantities of oxygen, nitrogen and sulfur. Elemental analysis reflects that empirical formula for bituminous coal is $C_{137}H_{97}O_9NS$ and excellent quality anthracite is $C_{240}H_{90}O_4NS$. Coal is found in different forms which represent the phases of transformation of dead remains of plant and animals.

1. **Peat** is initial stage of conversion of vegetable matter into coal. It is brown in color, very soft and burn with smoke. It contains about 60% of carbon and high percentage of moisture and unchanged vegetable matter.

2. **Lignite** (brown coal) is the next stage of conversion of vegetable matter. It is fairly hard that contains about 67% carbon and a considerable percentage of moisture and unchanged vegetable matter.

3. **Bituminous** (soft coal, source of energy) coal contains about 83% carbon. It is a common variety (most abundant) of coal which is black, hard and strong. Its carbonization or destructive distillation gives coke, coal tar and coke oven gas.

4. **Sub bituminous** coal is next stage of conversion to lignite. It contains about 80% carbon. It is used in power generating stations. This type of coal less efficient source of heat.

5. **Anthracite** represents the final stage of conversion of vegetable matter to coal. It is shining black, hard and crystalline. It contains 85-90% carbon. It also contains some quantities of oxygen, hydrogen and nitrogen. It burns with pale yellow flame which is without smoke and gives a large amount of heat. Therefore it is used as a fuel in boilers and as a domestic fuel.

Destructive Distillation of Coal

When bituminous coal is packed in an iron retort and heated above 500°C in the absence of air, it is decomposed into coke, coke oven gas (coal gas) and coal tar. It is estimated that about 1000 kg of coal gives about 310 m^3 crude coal gas which contains benzole, coal gas, cyanides, and sulfur, 2.2 kg of ammonia as ammoniacal liquor, 50 kg of coal tar, 725 kg of coke and some gas carbon.

1. **Coke** is 100% pure carbon. It is used in steel, as a reducing agent, as a fuel and in the preparation of calcium carbide, graphite, CS_2 and SiC.

2. **Coal gas**: Its major component are hydrogen 50%, methane 35% and CO 8%. It is used as a fuel. At the start of 19^{th} century, coal gas was made by heating coal in the absence of air.

3. **Coal tar**: it contains about 215 different aromatic compounds. When it is subjected to fractional distillation, it gives benzene, toluene, xylenes, naphthalene, phenols, cresols, anthracene etc. The residue of fraction distillation is a thick black liquid called pitch. It is used for metaling of roads.

Coal Gasification/Liquefaction

Water gas is less efficient fuel which is a mixture of CO, CO_2 and H_2. It is formed by reaction of coal with oxygen and steam. A synthesis gas is formed by removing CO_2 from water gas. Synthesis gas is useful precursor for different organic and inorganic compounds such as ammonia, methanol and synthetic natural gas (SNG).

$$N_2(g) + 3\,H_2(g) \longrightarrow 2\,NH_3(g)$$
$$CO(g) + 2\,H_2(g) \longrightarrow CH_3OH(l)$$
$$CO(g) + 3\,H_2(g) \longrightarrow CH_4(g) + H_2O(g)$$
$$2\,CO(g) + 2\,H_2(g) \longrightarrow CH_4(g) + CO_2(g)$$

Synthesis gas could be transformed into liquefied fuels by the application of Fischer-Tropsch process. The process was invented in 1925 by Franz Fischer and Hans Tropsch by developing catalyst that transformed synthesis gas into liquid hydrocarbons.

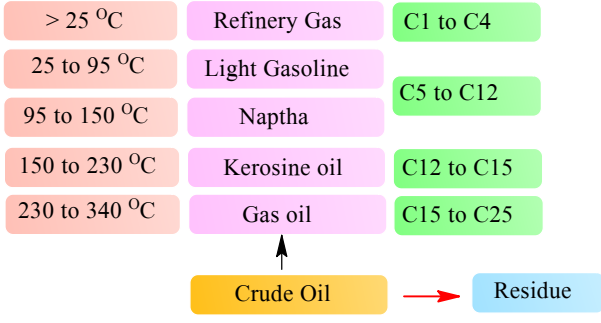
2. Petroleum

Petroleum means rock oil which is dug from earth in the form of thick viscous dark brown crude oil and then subjected to fractional distillation for separating various components containing carbon atoms ranging from 1 to 40. These components carry legion

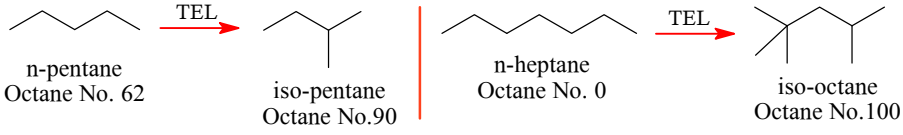
of compounds: alkanes, cyclo-alkanes, alkenes and aromatic hydrocarbons. Petroleum is not only a source of fuel but it serves useful character for manufacturing of drugs, clothes and multiple other products. Naturally, petroleum forms from anaerobic decomposition of fossil fuel.

Fractional Distillation of Petroleum

Subjecting crude oil to fractionating tower and heating the oil at high temperature affect separation based on difference of boiling point. This process is known as fractional distillation. Usually the fraction with lower molar mass having lower boiling point separate at the top of the tower. The bottom is left with thick viscous fluid called residue.



The quality of liquid fuel can be enhanced by refining which involves cracking or reforming. Cracking is breaking down larger molecules into smaller ones either by high temperature (pyrolysis), steam or by employing catalyst (Houndry Process). Reforming improves fuel quality by increasing its capacity to burn efficiently.



The quality of gasoline is gauged by octane number which is tendency of gasoline to burn without knocking. Octane number is usually graded as ratio of heptane and 2, 2, 4-trimethylpentane (iso-octane). Heptane is assigned octane number of zero whereas iso-octane 100. A petrol with octane number 85 means it matches the quality of iso-octane to 85% and heptane to 15%. Generally, branched alkanes and cyclo-alkanes burn efficiently than straight chain alkanes. Short chain alkanes burn more efficiently than long chain. Alkenes burn efficiently as compared to alkanes. Aromatic hydrocarbons burn effectively than both alkenes and alkanes.

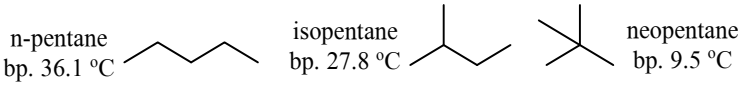
Hydrocarbon	Octane No.	Hydrocarbon	Octane No.
Heptane	0	1-Pentene	84
2-Methylheptane	23	Butane	91
Hexane	25	Cyclohexane	97
2-Methylhexane	44	Iso-octane	100
1-Heptene	60	Benzene	101
Pentane	62	Toluene	112

3. Natural gas

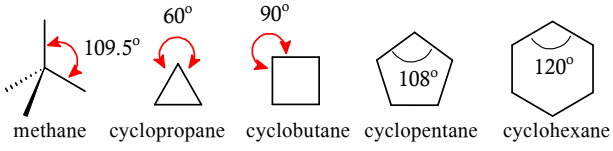
A natural gas is constituted by 70% methane, 15% propane and 10% ethane. It is odorless and colorless. Usually, methane thiol is added to detect leaks. Natural gas is used for heating building and producing electricity. Methane gas is trapped as methane hydrate under the sea bed. Its escape into the atmosphere is global concern because methane is greenhouse gas that could heat up the planet. When methane is compressed, it becomes LPG or liquefied natural gas. Usually, propane and butane fractions constitute LPG. These fractions have replaced Freon. Similarly, CNG or compressed natural gas is compressed format of methane and ethane fraction of natural gas.

3.13 Physical Properties

Alkanes are non-polar. They don't dissolve in water. Petrol or diesel float over water due to their poor solubility and low density. Boiling point for straight chain alkanes increases with every increase in carbon atom. Straight chain alkanes have higher boiling points as compared to branch ones due to larger surface areas for London forces to operate. Alkanes containing 1 to 4 carbon atoms are gases, 5 to 17 carbon atoms are liquid and higher alkanes are solids (waxes).

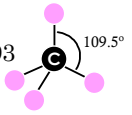


Generally, cycloalkanes have higher boiling points as compared to acyclic ones due to compact structure, tight packing and stronger London dispersion forces.

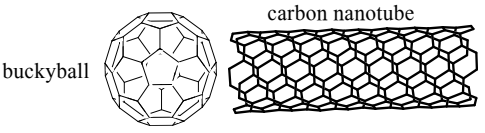


Cyclopropane and cyclobutane are gases, cyclopentane to cycloctane are liquids. Cyclopropane (once used for general anesthesia) is highly strained alkane due to ring and torsional strain. The molecule has bent bonds which make it more reactive than other alkanes. As the ring size increases, strain reduces and ultimately vanishes at cyclohexane due to its stable chair conformation.

In a bid to create new molecules, Richard Smalley of Rice University and Harry W. Kroto of Sussex University, UK, irradiated graphite with laser beam and noticed a compound with C60 formula which resembled soccer ball with 20 six member rings arranged with 12 five member rings. Each five member ring is surrounded by five six member rings. Both scientists shared the 1996 Nobel Prize in Chemistry for their achievement. This exotic compound, a new allotrope of carbon, was most symmetrical with each carbon atom sp^2 hybridized that locate on the vertices of a hexagon. The new molecule was confirmed by spectroscopic and X-ray crystallography experiments. As the molecule was similar to buckyball, it was termed buckminsterfullerene on account of its shape matching with the geodesic dome created by American



engineer and philosopher R. Buckminster Fuller. Since then, all such molecules with carbon contents ranging from 70 to 76 were termed as fullerenes.

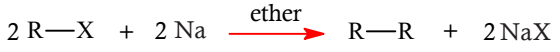


These compounds play significant role in evolution of nanotubes which are multiple times stronger than steel, used in high strength materials, semiconductor devices, molecular sensors, hydrogen storage media and molecular probes. An entirely new discipline of nanotechnology evolved with discovery of nanotubes. Later on, buckyball were used to treat HIV.

3.14 Synthesis

1. Wurtz Reaction

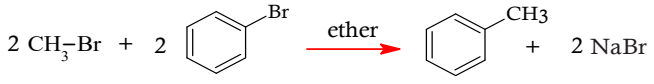
A coupling reaction whereby which two alkyl groups of alkyl halides are coupled in the presence of ether to produce symmetrical alkanes was discovered by French Chemist Charles Adolph Wurtz in 1855.



Mechanism

Wurtz reaction proceed by free radical mechanism which involves the donation of electron by sodium metal to yield alkyl radical and NaX Two alkyl radical couple for alkane synthesis.

This reaction has limitation because with two different alkyl halides we get mixture of products. Moreover, Wurtz reaction proceeds through S_N2 mechanism so it doesn't work with sterically hindered alkyl halides. The reaction is prone to side reaction that involve the formation of alkene in an elimination reaction with secondary or tertiary alkyl halides. A modified version of Wurtz reaction, Wurtz-Fittig reaction, is useful alternative for coupling alkyl with aryl halides. The reaction offer good method for synthesis of toluene and alkyl benzene derivatives.



2. Corey-House Synthesis

A better alternative to Wurtz reaction for few side reactions and good control is Corey-House Synthesis which is coupling reaction that couples alkyl halides with Gilman Reagent (organo-cuperate or lithium dialkylcuperate) for synthesis of higher alkanes. This reaction is also known as Corey-House-Posner-Whitesides Reaction.

$$R_2CuLi + R'—X \longrightarrow R—R' + RCu + LiX$$

Gilman Reagent is made by reaction of alkyl lithium with cuprous halide.

$$R—X + 2\ Li \longrightarrow RLi + LiX$$
$$2\ RLi + CuX \longrightarrow R_2CuLi + LiX$$

This method requires mild reaction conditions for synthesis of unsymmetrical alkanes. The reaction offer selective method for coupling. It works best with primary alkyl halides since the mechanism proceeds through S_N2 reaction.

$$R_2CuLi \longrightarrow R^- + RCu + Li^+$$
$$R^- + R'—X \longrightarrow R—R' + X^-$$

3. Kolbe Electrolysis

This method involves an electrochemical process where a carboxylate anion (sodium or potassium salts of carboxylic acid) is oxidized at anode yielding CO_2 and alkyl radical. The radicals recombine (dimerize) for synthesis of symmetrical alkanes.

$$2\ RCOO^- + 2\ H_2O \longrightarrow R—R + 2\ CO_2 + NaOH + H_2$$

Salts of carboxylic acid could be decarboxylated by heating with soda lime. Elimination of CO_2 yields alkanes.

$$2\ RCO_2Na + NaOH\ (CaO) \longrightarrow R—H + Na_2CO_3$$

Hermann Kolbe was German Chemist who pioneered the evolution of organic chemistry by rejecting "vital force theory" with his synthesis of acetic acid in 1845 from simple inorganic compounds such as CS_2 and chlorine.

4. Reduction of Alkyl Halides

Alkyl halides could be reduced to alkanes by the application of zinc and hydrochloric acid.

$$2\ R—X + Zn + 2\ HCl \longrightarrow 2\ R—H + ZnCl_2$$

This is an example of redox reaction which involves the transfer of electron from metal surface to substrate followed by migration of proton from the acid.

$$Zn \longrightarrow Zn^{+2} + 2e^-$$
$$R—Cl + 2e^- \longrightarrow R^- + Cl^-$$
$$R^- + HCl \longrightarrow R—H + Cl^-$$

Net Reaction: $R—Cl + Zn + HCl \longrightarrow R—H + ZnCl_2$

Lithium aluminum hydride (LAH) reduces primary and secondary alkyl halides to alkanes, sodium borohydride (SBH) reduces tertiary alkyl halides and triphenyl tin

reduces all three classes of alkyl halides for synthesis of alkanes. Moreover, hydrogenolysis of alkyl halide in the presence of palladium-charcoal catalyst also gives alkanes.

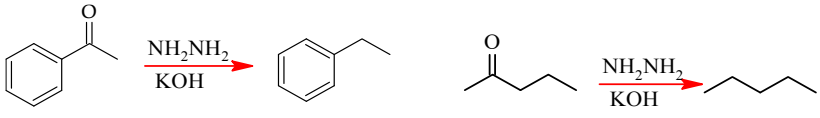
5. Hydrolysis of RMgX

Grignard Reagent is quite reactive. Exposure to water transforms it to alkanes.

$$RMgX + H_2O \longrightarrow R{-}H + Mg(OH)X$$

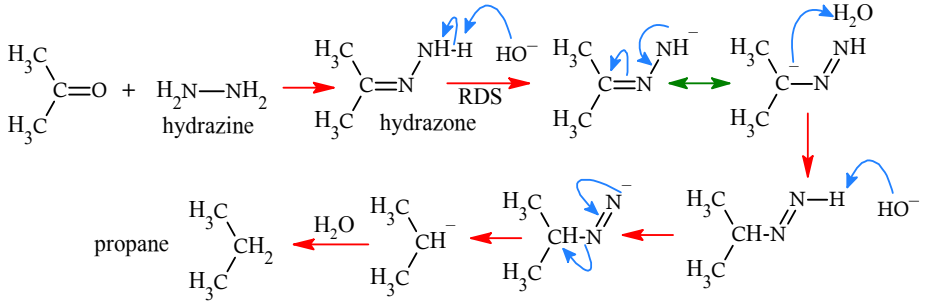
6. Reduction of Carbonyl Group

Different methods such as catalytic hydrogenation, Friedel-Craft acylation, thioacetal reduction, Clemmenson and Wolf-Kishner reduction are used for converting carbonyl group into methylene moiety. Wolf-Kishner reduction require hydrazine as reducing agent in the presence of base, KOH, in high boiling point solvent such as ethylene glycol for reduction of ketones.

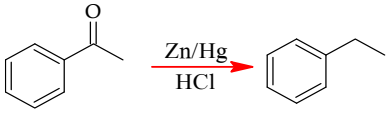


Mechanism

Much like amines add to carbonyl compounds, hydrazine follows similar fashion converting aromatic ketone to hydrazone which contains acidic $-NH_2$ group which is deprotonated in rate limiting step. Consequent rearrangement and protonation leads to final transformation of carbonyl group into methylene moiety.



Another alternative reduces aromatic ketones in the presence of zinc-amalgam catalyzed in strongly acidic medium is known Clemmensen reduction. This method works well with aromatic ketones. Other ketones are not suitable substrates.

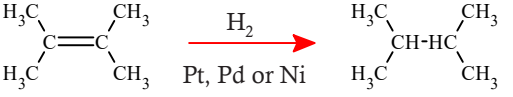


Which reduction is preferable depends upon which reaction condition we are required. For instance, for acid sensitive functional group, Clemmenson reduction is

avoided since it uses strongly acidic medium. Both methods of reduction are effective for making alkanes from carbonyl compounds. However, Clemmenson method is particularly avoided for environmental concerns due to toxic utilization of mercury. Wolf-Kisher reduction gives by-product of nitrogen gas instead of mercury.

7. Reduction of Alkenes

Hydrogen adds to the double bond of alkenes in the presence of transition metal catalyst. This is reduction of alkene whereby which double bond is reduced to single bond. Hydrogenation of alkenes is important industrial process for solidification of vegetable ghee.

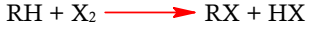


3.15 Reactions

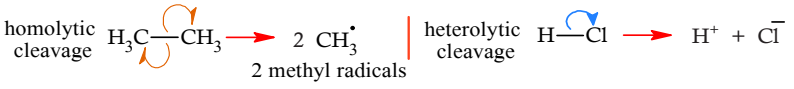
Alkanes are known as paraffin which means little affinity on account of its low reactivity. They don't react unless subject to stringent reaction conditions. These reactions are difficult to control under lab circumstances due to release of excessive energy.

1. Free Radical Substitution Reaction: Halogenation

Reactions in which an atom or a group of atoms replace another atom or a group of atoms are called substitution reactions. When halogen substitute hydrogen of alkanes, the reaction is regarded as halogenations of alkanes which proceeds through free radical mechanism. The reaction takes place in the presence of heat or light.



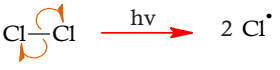
Most widely used halogenation include chlorination and bromination. The reactivity of the halogens decreases in the order $F_2 > Cl_2 > Br_2 > I_2$. Fluorine is an extremely aggressive oxidizing agent, and its reaction with alkanes is strongly exothermic and difficult to control. Direct fluorination of alkanes requires special equipment and techniques, is not a reaction of general applicability. Chlorination of alkanes is less exothermic than fluorination, and bromination less exothermic than chlorination. Iodine is unique among the halogens in that its reaction with alkanes is endothermic and alkyl iodides are never prepared by iodination of alkanes. The most effective wavelength of light is a blue color that is strongly absorbed by chlorine gas. This finding implies that light is absorbed by the chlorine molecule, activating chlorine so that it initiates the reaction with methane. Blue light has about the right energy to split a chlorine molecule into two chlorine atoms, which requires 242 kJ mol (58 kcal/mol).



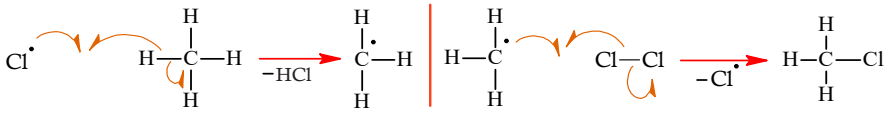
Homolytic cleavage gives rise to formation of radicals where heterolytic cleavage yields ions. When a bond breaks equally, saying each electron becomes the part of each fragment, is said to be homolytic cleavage. The cleavage yields free radicals. Atom or group of atoms carrying unpaired electron with incomplete octet is called free radical which are high reactive species. When a bond breaks unequally, saying both electrons become the part of one fragment, is said to be heterolytic cleavage. The cleavage yields ions.

Mechanism

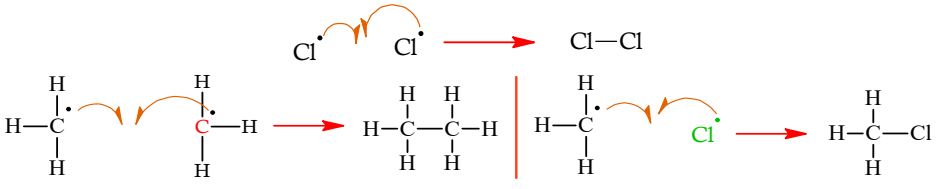
First step, initiation, involves hemolytic cleavage of Cl_2 molecule in the presence of light to give free radicals.



Step 2: This step is regarded as propagation step in which protons from alkane is abstracted by chlorine free radical. Alkyl radicals form during this step.

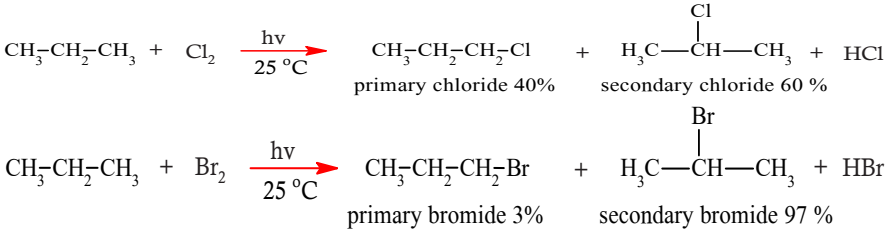


Step 3: The final step is known as termination step which involves radical recombination.

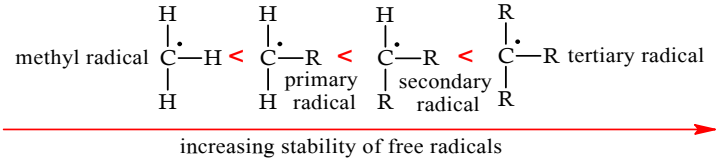


2. Alkanes Reaction with Chlorine and Bromine

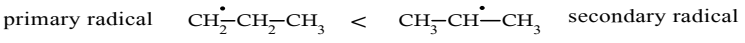
For methane, all hydrogen are equal therefore it doesn't matter which hydrogen atom is abstracted by chlorine radical because all resultant alkyl radicals are same, i.e. methyl radical. However, if alkane different than methane is used for halogenation, products form in different proportions. For example, chlorination and bromination of propane give different products. Consider the following reactions:



For the above reactions, one can conclude bromination is more selective, thus giving greater proportion of secondary bromide than secondary chloride. The question why secondary product prefers over primary could be answered from the stability of free radical. Alky group stabilizes free radical because it donates electrons density to carbon atom bearing radical through hyperconjugation. Consider the stability order of free radical:

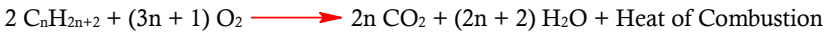


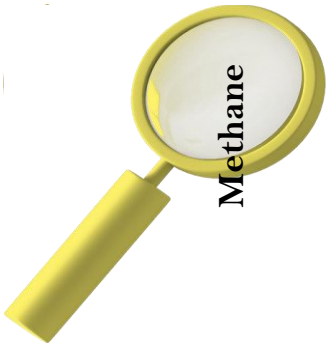
As secondary free radical (secondary propyl radical) is more stable than primary propyl radical, therefore each reaction proceed through a stable free radical generating secondary product in greater proportion instead of primary one.



3. Combustion and Relative Stability of Alkanes

Combustion is a rapid oxidation that takes place at high temperatures, converting alkanes to carbon dioxide and water. Little control over the reaction is possible, except for moderating the temperature and controlling the fuel/air ratio to achieve efficient burning.





Methane is formed in oxygen deficient places (marshes, swamps, sediments of lakes) from decomposition of plant and animal matter. The gas is also produced by bacteria living in termites and digestive tract of plant eating animals. A large cow could produce (belching, flatulence) up to 20 liter of methane per day. Contrary to earth, other planets such as Jupiter, Saturn, Uranus and Neptune have larger proportion of methane in their atmosphere. Gravitational field of earth is weak enough to hold much of hydrogen gas required for synthesis of methane. Methane is potent greenhouse gas, 15 to 30 times more efficient than CO_2 in absorbing heat radiated from earth. Fortunately, methane has lower atmospheric concentration of 2 ppm as compared to CO_2 which is 300 ppm.

Methane is known as natural gas since it is associated with natural deposits of petroleum. It is also found in deposits of coal mines where it is considered dangerous because it forms pockets where air is absent that could potentially cause asphyxiation of miner. When mixed with certain ratio of air, the gas acquires explosive potential. Under lower temperature and high pressure conditions, methane forms hydrate with water. This is known as methane hydrate which is crystalline cages of frozen water holding methane gas in it. The grey ice cube of methane hydrate burns when it is lit by match. Large deposits of methane hydrates are present in sea bed where they are believed to cement the sediments of ocean floor. Tempering with it could cause undersea landslide that could release methane into atmosphere. They are formed by decomposition of plant and animal matter by bacteria.

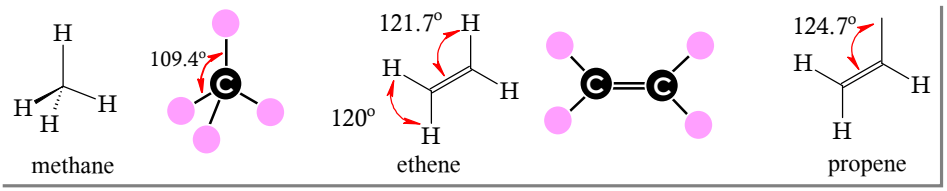
Unsaturated HCs

Properties, Synthesis & Reactions

3.2 Alkenes

3.21 Introduction

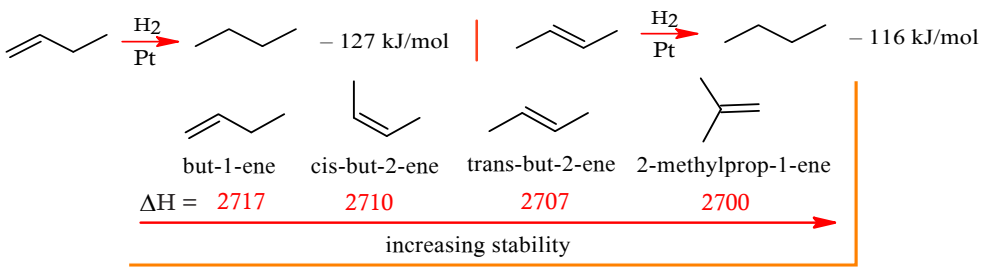
Alkanes (paraffin) are characterized by sp^3 hybridization which involve carbon-carbon single bond. The bond is sigma whose bond strength is 347 kJ/mol. We call alkanes as saturated hydrocarbons. Alkenes (olefins, oil forming) are formed by sp^2 hybridization that adds on π bond to already existing sigma bond. Strength of π bond is 264 kJ/mol which is 347 – 264 = 83 kJ/mol less than sigma bond. Double bond (bond strength is 611 kJ/mol) is shorter than single bond due to sp^2 hybridization. In ethylene, C=C is 1.33 A. In ethane, C–C bond is too longer (1.54 A).



Alkenes are unsaturated hydrocarbons containing carbon-carbon double bond as fundamental functional group. General formulas for alkanes and alkenes are $C_n(H_2O)_n$ and C_nH_{2n} respectively.

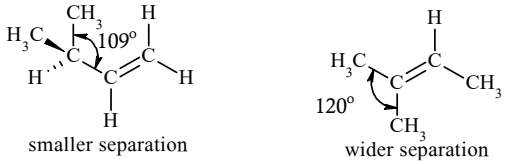
Stability of Alkenes

Heat of hydrogenation is the amount of heat released when one mole of hydrogen is added to π bond. In fact, the heat measures the stability of the π bond. Simple alkenes are less stable and give off more heat unlike substituted ones. For instance, one butene is less stable than 2-butene because the former is mono-substituted where the latter is disubstituted.



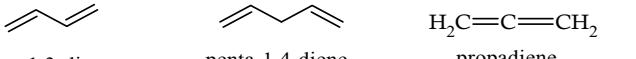
Substitution pattern on double bond renders stability by enabling interaction with pi bond. Generally, alkyl group is electron donating by hyperconjugation effect (no bond resonance) which creates a temporary sp^2 hybridized carbon of alkyl group. This carbon gets an unhybridized p orbital which overlaps with π bond. This resonance of π bond with adjacent alkyl group is stabilizing phenomenon which makes substituted alkenes more stable than unsubstituted counterparts. Steric factor also plays important role in stabilizing

alkenes. In mono-substituted alkenes, alkyl group separates from double bond by normal tetrahedral angle of 109.5°. In tri-substituted, the separation gets the alkyl groups apart by 120° angle.



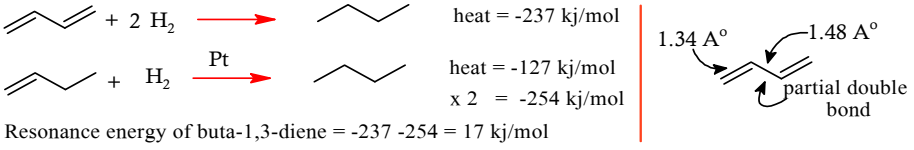
smaller separation wider separation

Conjugation: Conjugated alkenes have two or more double bonds separated by single bonds. Such compounds are stable because double bonds interact with one another and stabilize the system by resonance.



buta-1,3-diene conjugated double bond | penta-1,4-diene isolated double bond | propadiene cummulated double bond

Conjugated alkenes are stabilized by extent of 17 kJ/mol as compared to similar alkenes with isolated double bond. This energy is what we call resonance energy. We can assess the difference by heat of hydrogenation as follow:

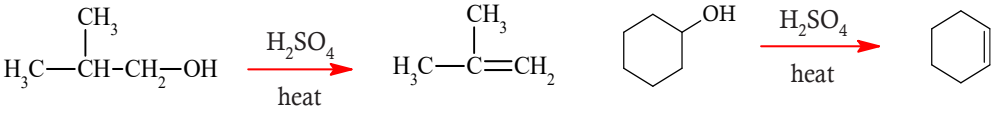


Resonance energy of buta-1,3-diene = -237 -254 = 17 kj/mol

3.22 Synthesis

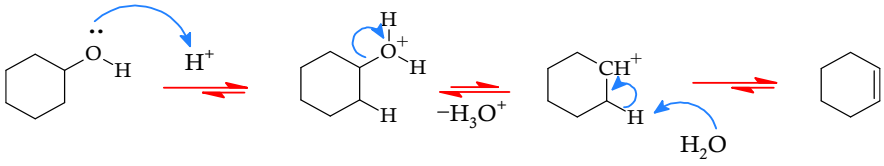
1. Dehydration

Removal of hydrogen and hydroxyl group from adjacent carbon atoms of alcohol is known as dehydration (removal of water). This is excellent method for synthesis of alkenes which is catalyzed by acid such concentrated sulfuric or phosphoric acid.



Mechanism

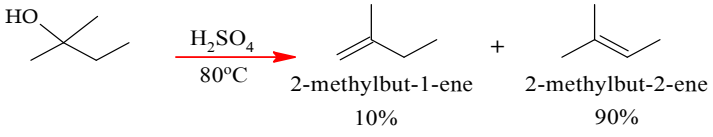
Alcohol is protonated by acid in first step. Removal of water and subsequent formation of carbocation forms in next step.



In third step, base part of acid abstracts proton adjacent to carbocation for yielding substituted alkene in third step. The mechanism is E1 or unimolecular elimination reaction.

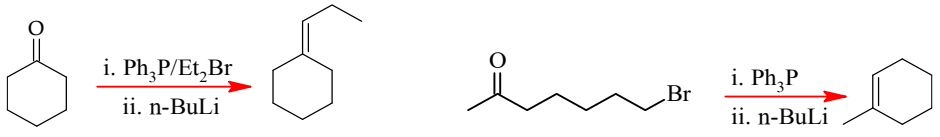
Regioselective Reaction

Regioselectivity (region specific) means chemical changes occurs at specific point within a molecules although many such points are already available. Regioselectivity of alkenes was noted by Alexander M. Zaitsev (pronounced Zait zeff) in 1875 who was Russian chemist from Kazan University. His generalization invented Zaitsev rule which states that in elimination reaction, most substituted alkenes predominant.



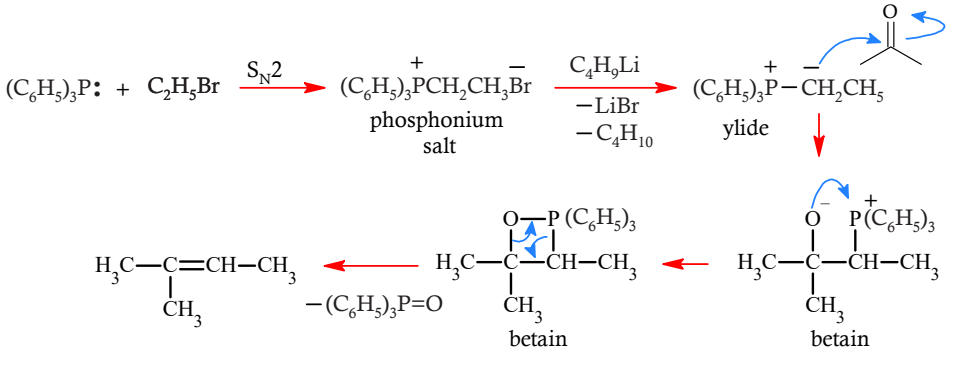
2. Wittig Reaction

A useful reaction for synthesis of alkene involves reaction of aldehydes and ketones with phosphonium ylide. The reaction is commonly known as Wittig reaction which can be both inter and intramolecular.



Mechanism

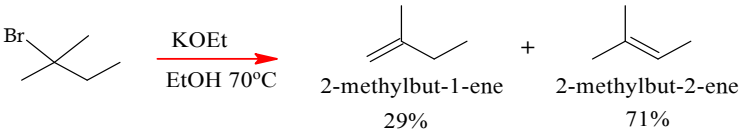
Triphenyl phosphine reacts with alkyl halide to form phosphonium salt. The salt is treated with alkyl lithium to generate ylide which finally reacts with carbonyl compound to establish carboncarbon double bond.



The reaction proceeds through intermediate formation of betain (dipolar ion) that rearranges to oxophosphetane (four member cyclic compound). Finally, the cyclic intermediate break off and yields alkenes.

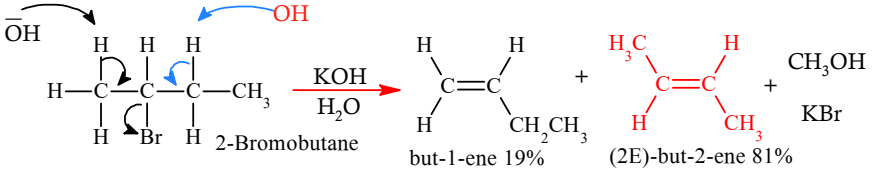
3. Dehydrohalogenation

Removal of hydrogen and halogen from alkyl halides to form alkenes is said to be dehydrohalogenation reaction which proceeds either through E1 or E2 mechanism.



Mechanism

The reaction proceeds by E2 mechanism which means both substrate and base participate in the rate determining step. Hence the reaction is E2 or elimination bimolecular. Base (–OH) abstracts β– proton.



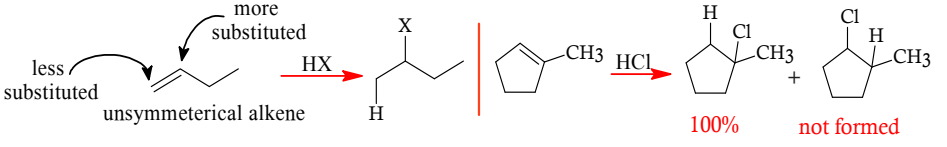
In case where there are two or more β–protons in substrate, base will attack the one which gives the most substituted alkene. In the following example, 2–bromobutane has two different protons adjacent to bromine. The base can attack either, thus yielding two different alkenes. The more substituted alkene is dominant product.

3.23 Reactions

Dehydration of alcohols gives alkenes whose hydration yields alcohols. The reaction is reversible. Hydration is addition reaction which adds hydrogen and hydroxyl groups across the double bond. Forward and reverse reactions go via same mechanistic path in microscopic details. The principle is known as microscopic reversibility. Most alkenes follows addition reactions in Markovnikov fashion. As electrophile initiate the reactions, such reactions are termed as electrophilic addition reactions.

1. Hydrohalogenation

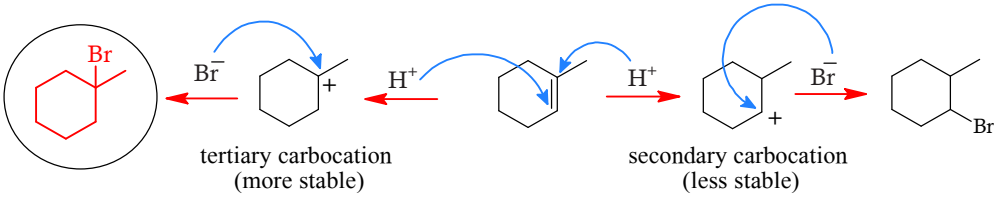
Addition of hydrogen and halide atoms across the double bond is known as hydrohalogenation. Hydrogens adds to least substituted carbon atom of the double bond in Markovnikov fashion in case of un-symmetrical alkenes. We get alkyl halide as product.



Increasing rate of HX addition to alkenes: HF << HCl < HBr < HI

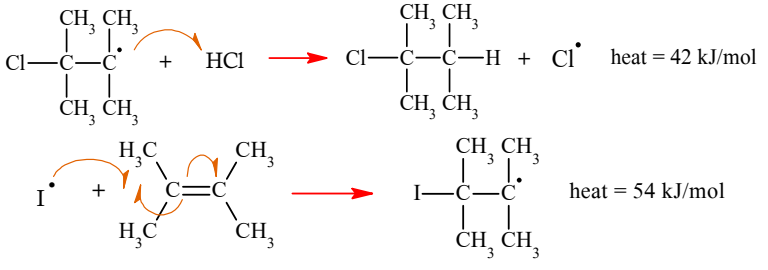
Mechanism

In 1869, Vladimir Markovnikov (pronounced as Mar cov na koff), a Russian chemist, highlighted the orientation of HBr to alkenes by stating that proton adds to the carbon of the double bond which carries more hydrogen atoms in a bid to form stable carbocation. This is what we call Markovnikov rule. In fact, the driving force for Markovnikov addition is the stability of carbocation. Consider the following illustration which entails how stability of carbocation controls Markovnikov orientation.



When peroxide is heated with HBr and add to alkenes, anti-Markovnikov orientation is followed. The reaction mechanism shifts from electrophilic addition to free radical addition reaction. This development was noted by M. S. Kharasch and F. W. Mayo in 1933. Here stability of free radical matters which drives reaction in anti-Markonikov fashion.

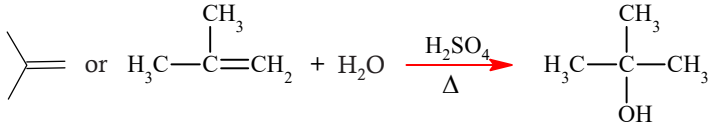
Peroxide triggered anti-Markovnikov reaction occurs only with HBr, not with HCl and HI because the reaction of alkyl radical with HCl is highly endothermic. Similarly, the reaction of iodine radical with alkene is highly endothermic.



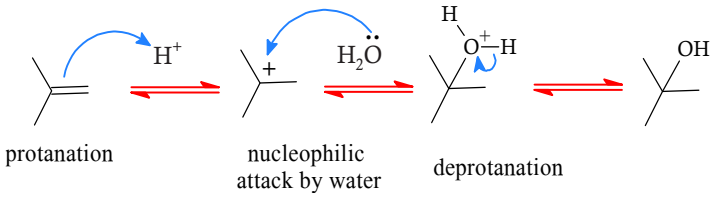
2. Hydration

Acid Catalyzed Addition of Water

Usually, strong acid catalyst is required to execute hydration of alkenes which follows Markovnikov orientation. The reaction yields alcohols.

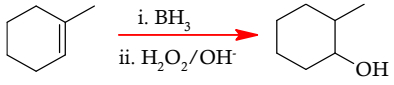


Hydration and dehydration follow principle of microscopic reversibility.



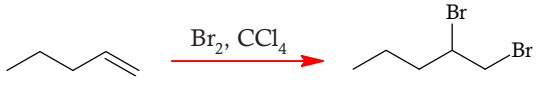
Hydroboration-Oxidation (Anti-Markovnikov)

Hydration of alkenes in the presence of boron compounds offers an interesting examples of regioselectivity and stereospecificity. Hydroboration-oxidation is hydration reaction of alkenes in which hydroxyl group (–OH) adds to least substituted carbon atom (regioselective) of the double bond in anti-Markovnikov's orientation giving alcohol as product. A detailed mechanism has given in section 1.172.



3. Halogenation

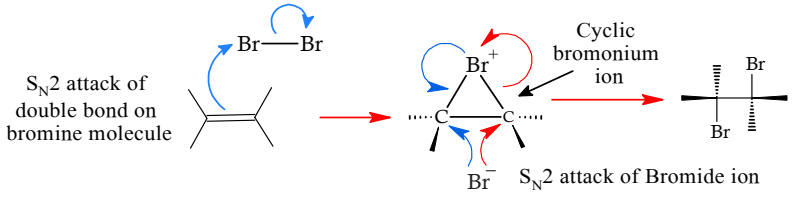
When a deep red color solution of bromine in carbon tetrachloride (CCl_4) adds to alkene, the solution gets rapidly decolorized. This is halogenation reaction of alkene and common test for detection of alkene too.



Halogenation works by treating halogens such as chlorine or bromine in some inert solvent of dichloromethane (DCM), chloroform ($CHCl_3$) or CCl_4 with alkene.

Mechanism

Halogenation proceeds by halonium ion mechanism. Double bond of alkene attacks halogen by displacing halide ion. A cyclic halonium ion emerges which is three member unstable cyclic intermediate which is attacked by halide ion in S_N2 fashion in next step yielding vicinal dihalide (dihalide with two halogen atoms on adjacent carbon atoms). Gem dihalides have two halogen atoms on the same carbon atom.

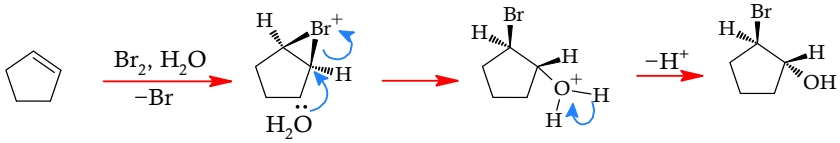


4. Halohydrine

If two adjacent carbon atoms has –X and –OH groups, the compound is termed as halohydrine which is formed by treating aqueous solution of halogen with alkenes.

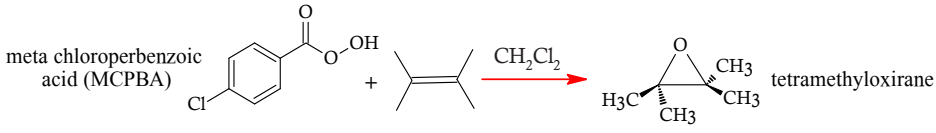
Mechanism

The halonium ion is attacked by water in S_N2 fashion.



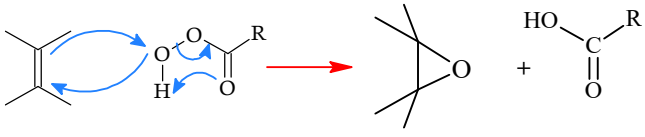
5. Epoxidation

Treating alkenes with peracid such as meta perchlorobenzoic acid (MCPBA) gives epoxides (oxiranes) which are three member heterocyclic compounds. This is oxidation reaction like halogenation. Epoxides are stable and don't decompose unless interact with strongly acidic solution.



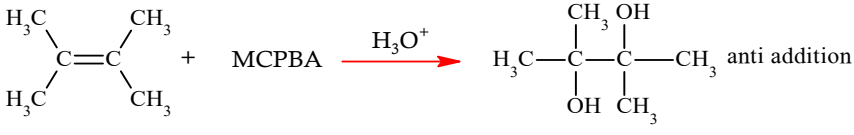
Mechanism

Whether starting alkene or the epoxide, geometry remains same because epoxidation proceeds by concerted single step mechanism that doesn't allow alkene to rotate or change its conformation during the course of reaction.

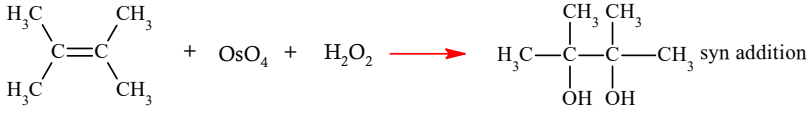


Opening Epoxide (acid catalyzed)

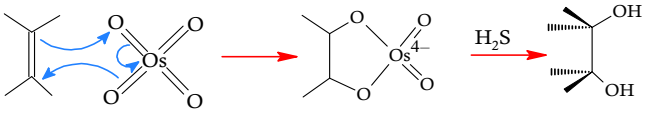
When epoxide is treated with aqueous acid, it gives glycol which is anti-diol (anti glycol) in which two hydroxyl groups are opposite to each other. We call it vicinal dihydroxylation of alkene.



If we want to get syn glycol, we use osmium tetraoxide (osmic acid) or cold dilute solution of potassium permanganate. The former is highly expensive, toxic and volatile. The latter gives low yield but its function can be enhanced.

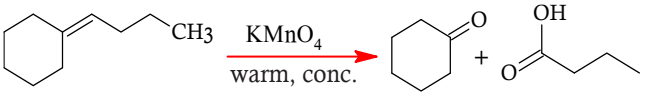


Besides, permanganate offers useful test for alkenes too. A deep purple color vanishes as soon as alkene is added to solution by forming brown precipitate of MnO_2.



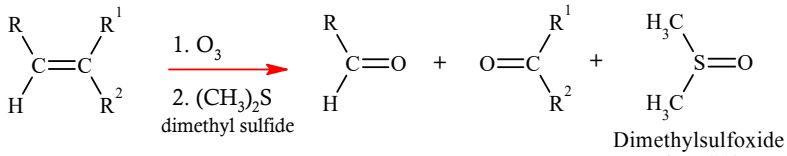
6. Oxidative Cleavage

Syn-diol undergoes oxidative cleavage if alkene is treated with concentrated, warm or too acidic solution of $KMnO_4$. The double bond is broken into two carbonyl groups of aldehyde and ketone. As aldehydes are more reactive, they don't stop at aldehydes stage but further oxidized to carboxylic acids leaving water and carbon dioxide as byproducts.



7. Ozonolysis

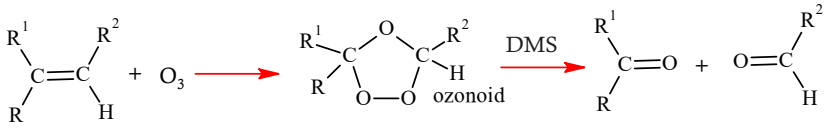
If oxidative cleavage is to be stopped at aldehyde and ketone stage, a milder oxidizing agent of ozone could be harnessed. This could be done by treating alkenes with ozone followed by reduction.



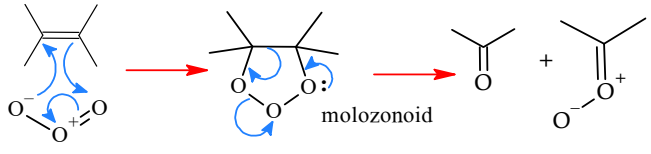
Dimethylsulfoxide (DMSO)

Mechanism

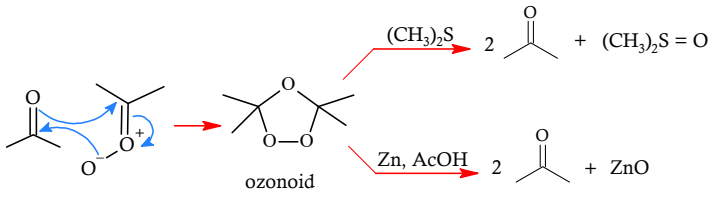
Ozone gives a cyclic compound with alkene which is known as primary ozonoid or molozonoid (takes one mole of ozone). In essence, the reaction proceeds through intermediate formation of ozonoid.



Consider the following mechanistic steps for formation of molozonoid and ozonoid as intermediate for generation of carbonyl compounds.

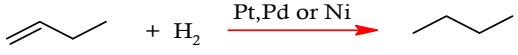


This intermediate is highly unstable because it contains two proxy linkages. It rearranges to ozonoid. Like molozonoid, ozonoid too is unable which can be reduced to aldehyde and ketone by zinc or dimethyl sulfide (DMS).



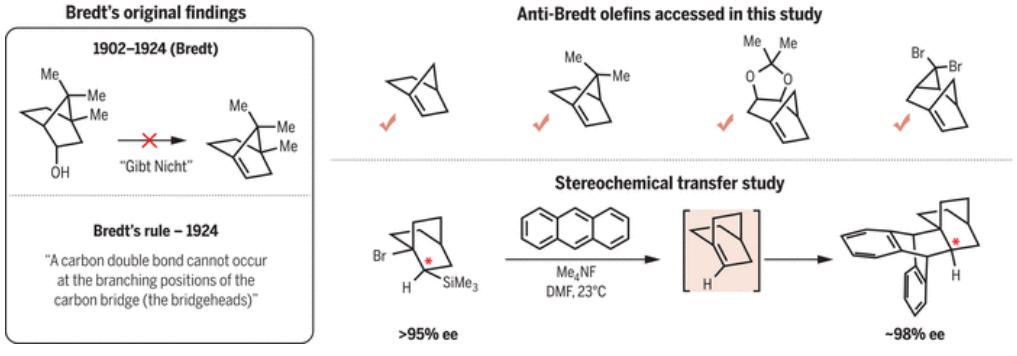
8. Hydrogenation

Hydrogenation of alkenes is a reduction reaction which double bond to single bond in the presences of metal catalyst such platinum, palladium or nickel. The reaction take places at room temperature. Hydrogenation can also be achieved by Wilkison catalyst which is achiral yet it can be made chiral after replacing its triphenylphosphine ligands with chiral analogues. Using chiral catalyst gives chiral product. Such synthesis is termed as asymmetric or enantioselective synthesis which converts optically inactive starting compound into optically active compound. In fact, 2001 Nobel Prize in chemistry was awarded to Royoji Noyori and William Knowles for chirally catalyzed hydrogenation.



Challenging Bredt Rule

Scientists have succeeded to break 100 year old rule by creating olefins which involve the formation of double bond at bridgehead carbon. Prior to the development, Julius Bredt published an observation that alkenes with double bond didn't form stable molecules due to distortion of the normal geometry associated with double bond. He called such molecules with double bond at ring junction as anti-Bredt olefins (ABO). McDermott et al. now published a report in November 2024 on synthesis of such molecules which can be captured in cycloaddition reaction. The team in University of California succeeded to use silicon-fluorine bond formation from a precursor as driving force for synthesis of strained aromatics. The following sketch has taken from the paper published on ABO challenging Bredt's rule.



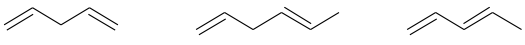
References

1.A solution to the anti-Bredt olefin synthesis problem, volume: 386, Issue: 6721, DOI: (10.1126/science.adq3519)
2.https://www.science.org/doi/10.1126/science.adq3519

3.24 Exercise

1. Markovnikov's addition is followed in electrophilic addition reaction to alkene, however it get reversed with peroxide, reason!

2. Assign enthalpies values of 252, 242 and 225 to the following compounds. Reason your assignment.

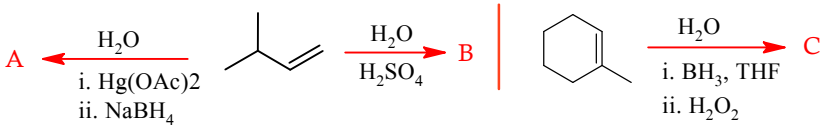


a. b. c.

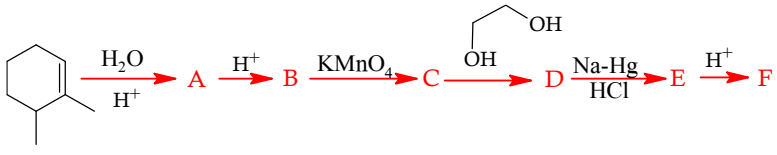
3. Electrophilic addition to alkenes is regioselective. Elaborate the statement with reason and examples.

4. What is the driving force behind Markovnikov and anti-Markovnikov electrophilic addition to alkenes?

5. Write product A, B and C



6. Point out the structure of the compound from A to F.

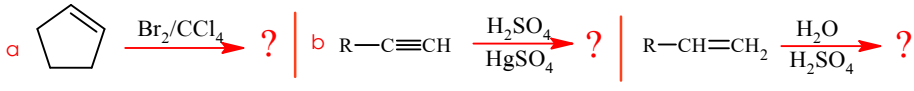


7. How will you transform the following alkene into a terminal alcohol shown below?

8. Predict the products formed when limonene reacts with the following reagents.

a. Excess of HBr
b. Excess of HBr, peroxide
c. Excess of Br_2 in CCl_4
d. Ozone, followed by dimethyl sulfide
e. Warm, conc. $KMnO_4$

9. Write product for any two of the following reaction along with mechanism:



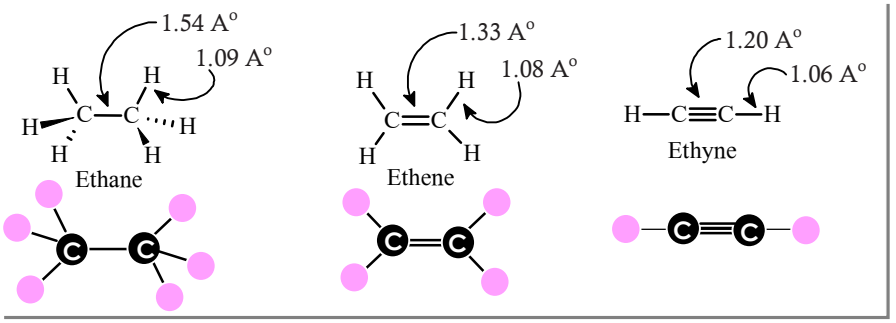
Triple Bond HCs

Properties, Synthesis & Reactions

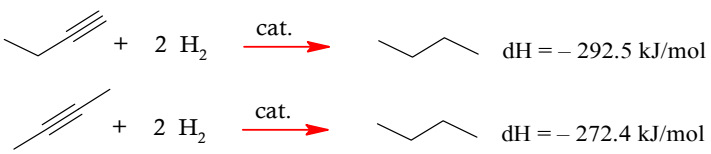
3.3 Alkynes

3.31 Introduction

Alkynes are hydrocarbons with general formula of C_nH_{2n-2} reflecting two hydrogen short of alkenes and four hydrogen short of alkanes. Acetylene is parent member whose oxyacetylene flame (2700 °C) is useful for welding purpose. Alkynes contain C–C triple bond which is governed by sp hybridization. The triple bond is short of double and single bond due to larger (50%) s character. Greater s character means the bonded pair of electrons lies close to the nucleus which shorten bond. In alkynes, the triple bond length is 1.29 A. In alkenes and alkanes, the bond lengths get lengthy to 1.34 A and 1.54 A respectively.

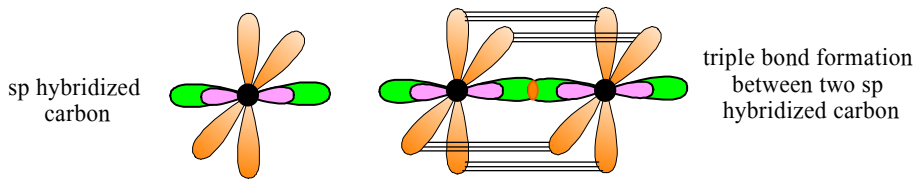


Most of alkynes reactions are similar to that of alkenes except those which involve the acidity of triple bond. Hyperconjugation stabilizes internal alkynes. Terminal alkynes are less stable. For instance, 2-butyne is more stable than 1-butyne by extent of 20 kJ/mol. Heat of hydrogenation offer convenient outlet for comparing relative stability of alkynes.



3.32 Structure

Carbon-carbon triple bond establishes linear geometry. Each carbon atom of the triple bond is sp hybridized. In acetylene, C–H bond angle is 180°. Two pi bonds are formed by lateral overlap of two hybridized p orbitals on each carbon atom.



3.33 Physical Properties

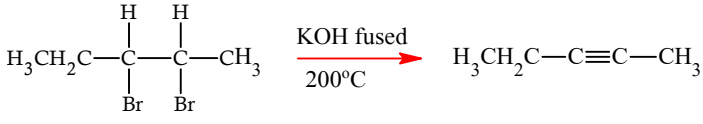
Alkynes are relatively non polar. They don't dissolve in water but show marked solubility in organic solvents such as alcohols, methylene chloride, chloroform and acetone. First three members of alkyne series are gases. Their melting and boiling points are like alkanes and alkenes.

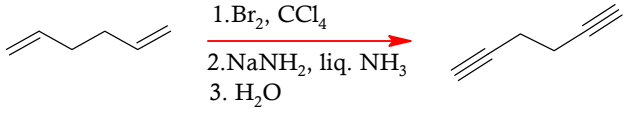
Alkyne	mp °C	bp °C	Density
Acetylene	–82	–84	0.62
Propyne	–101	–23	0.67
But-1-yne	–126	8	0.67
But-2-yne	–32	27	0.69
Pent-1-yne	–90	40	0.70
Pent-2-yne	–101	55	0.71

3.34 Synthesis

1. Dehalogenation of Dihalides

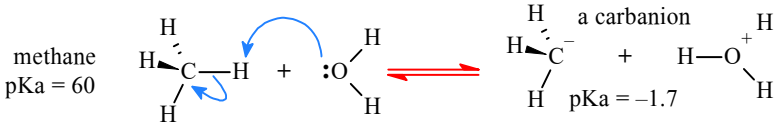
Elimination Reaction: Vicinal dihalides underground two successive elimination reactions with strong base such alcoholic KOH or $NaNH_2$. Alkynes form from the reaction after elimination of two HX molecules. The reaction is dehydrohalogenation in essence.





Reactivity

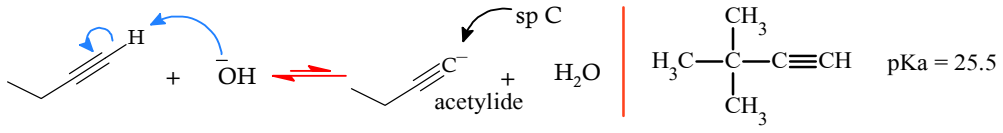
Acidity of terminal alkynes differentiate them from alkenes. Terminal hydrogen of alkynes is acidic in nature. When it ionizes, the conjugate base has negative charge on sp carbon. Such carbanion is relatively stable than corresponding carbanions on sp^2 and sp^3 carbon atoms. This difference makes alkynes more acidic than alkenes and alkanes.



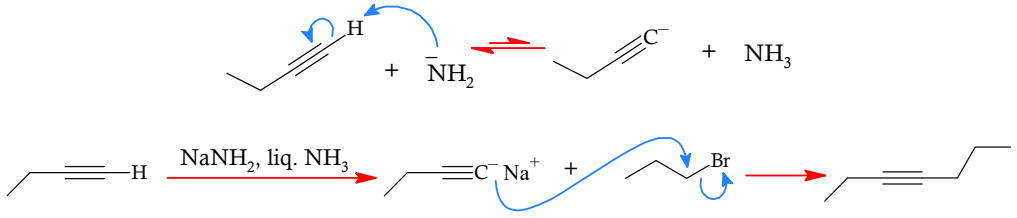
	CH_3CH_3	$CH_2{=}CH_2$	$HC{\equiv}CH$
pKa	62	45	26
	weakest acid		strong acid

Alkynes acidity is less than water and alcohols and both these species are avoided because they protonate acetylide when reactions with terminal alkynes are intended. When

acetylene ionizes, it gives acetylide anion which is strongly nucleophilic. Hydroxide and alkoxide are weak bases to ionize alkynes.

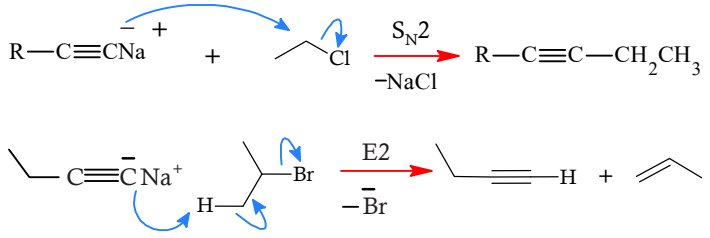


Some strong bases are needed for the purpose. Amide ions is better option to cope with. Usually, sodium amide is taken in liquid ammonia for the purpose to generate amide bases for deprotonating terminal alkynes.



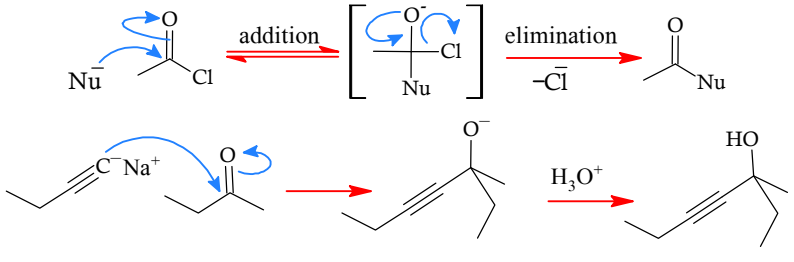
2. Alkylation of acetylide

Substitution Reaction: Acetylide serves as strong nucleophile. It can affect S_N2 reaction if the substrate is primary or less hindered. E2 reaction occurs with hindered ones because acetylide also serves as base as well.



3. Reaction with Carbonyl Compounds

Addition Reaction: Acetylide adds to carbonyl group of aldehydes and ketones. The addition yields an alkoxide which is protonated in separate step to give alcohol. This is an interesting method for synthesis of alcohols with triple bond one bond away from carbinol carbon.



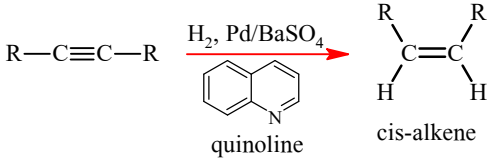
3.35 Reactions

Bond energies of carbon–carbon bonds are given below.

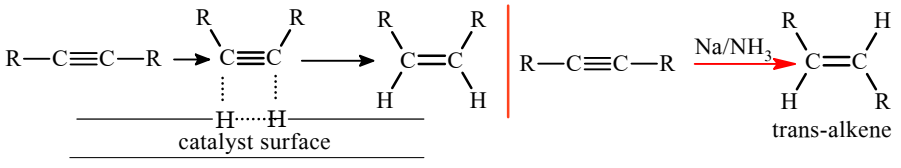
Bond	Tot. Energy	Type of Bond	approx. E
C—C	347	σ bond	247
C═C	611	π bond	264
C≡C	837	another π bond	226

1. Hydrogenation

A double or triple bond can't be reduced unless it is catalyzed with some transition metal such as palladium (Lindlar), platinum (Adam) or nickel (Raney). For instance, despite heating ethene and hydrogen at 200°C can't show any remarkable reaction. The reaction takes place at room temperature if a catalyst is used however. The heat of hydrogenation of alkynes is twice as large as alkenes.



Alkynes add up two moles of hydrogen. Partial hydrogenation gives cis or trans alkenes after addition of just one mole of hydrogen. Cis alkenes are obtained with Lindlar catalyst. Metal (sodium) ammonia reduction gives trans alkenes.

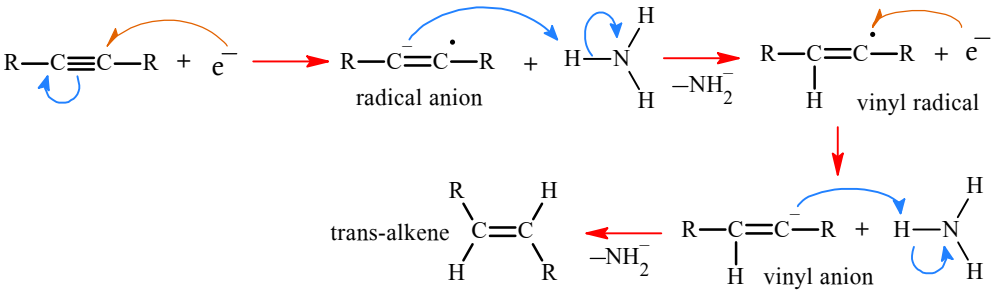


Ammonia (boiling point –33°C) is a gas at room temperature, but it is kept liquid by using dry ice to cool the reaction vessel. As sodium dissolves in liquid ammonia, it gives up electrons, which produce a deep blue color. It is these solvated electrons that actually reduce the alkyne.

$$NH_3 + Na \longrightarrow NH_3 .e^- \text{ (deep blue solution)} + Na^+$$

Mechanism

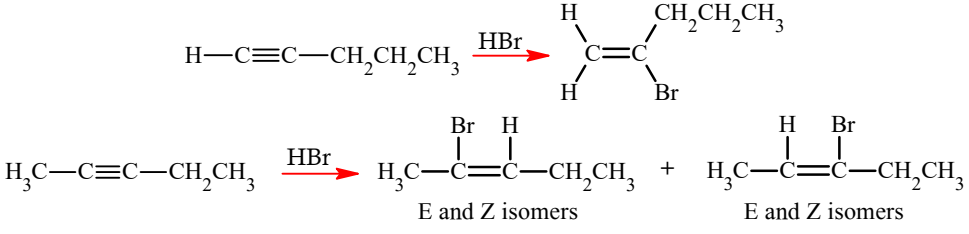
First step involves addition of electron to alkyne which gives rise to formation of radical anion. In next step, the radical anion is protonated to give vinyl radical. In third step, electron adds to vinyl radical giving vinyl anion, which in last step is protonated by ammonia thus yielding the most stable trans alkene.



The anti-stereochemistry of the sodium–ammonia reduction appears to result from the greater stability of the vinyl radical in the trans configuration, where the alkyl groups are farther apart. An electron is added to the trans radical to give a trans vinyl anion, which is quickly protonated to the trans alkene.

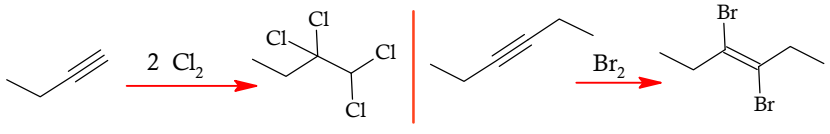
2. Hydrohalogenation

Alkynes can add two moles of hydrogen halide to give geminal dihalide in Markovnikov orientation. For one mole of HX, we get cis or trans alkenes.



3. Halogenation

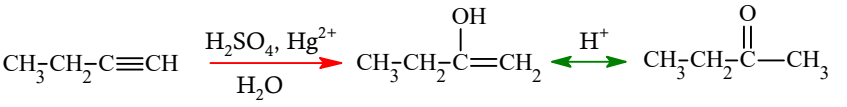
Alkynes give dihaloalkene with one mole of halogen and tetrahalide with two moles of halogens. Halogenation works better with chlorine and bromine because fluorine gives violent reaction and iodine doesn't work well thermodynamically.



4. Hydration

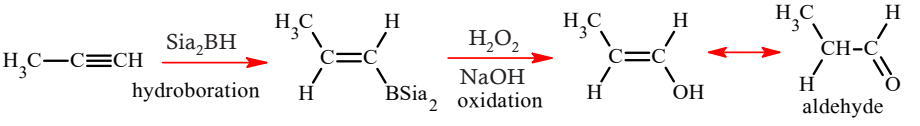
Catalyzed by Acid and Mercuric Salts

An enol (alkene cum alcohol) is obtained when alkynes are exposed to react with water in the presence of sulfuric acid. Enol is relatively unstable and it undergoes keto-enol tautomerism yielding aldehyde or ketone depending upon whether the starting alkynes is terminal (aldehyde) or internal (ketone). This is fine method for synthesis of methyl ketones. Hydration of alkynes follows Markovnikov rule. Hydration is carried out by treating alkyne with water in a mixture of sulfuric acid and mercuric sulfate that serve as catalyst.



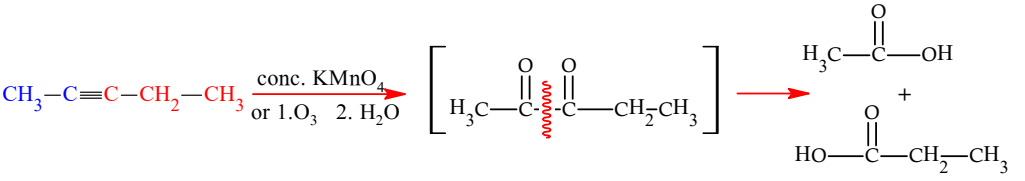
Hydroboration Oxidation

Terminal alkynes give aldehydes whereas internal alkynes give ketones. Hydroboration-oxidation reaction of alkynes proceeds through anti-Markovnikov mechanism which uses diasiamyl borane (used to prevent addition of second addition) and hydrogen peroxide.



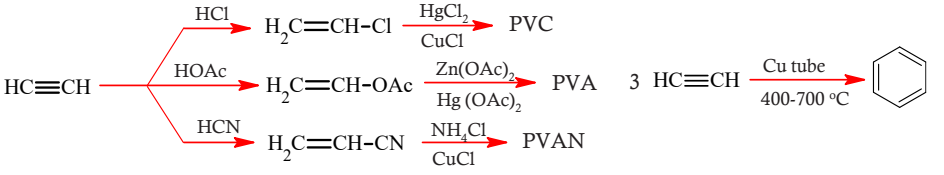
5. Ozonolysis

Classically, ozonolysis was employed for structural determination of alkynes and location of triple bond. When alkynes are exposed to ozonlysis coupled with hydrolysis, triple bond cleaves leaving carboxylic acids as product.



6. Polymerization

Much like alkenes, alkynes also polymerize to yield variety of useful polymer of daily use in our lives. For instance, acetylene gives vinyl chloride with HCl in the presence of mercuric chloride and cuprous chloride. Vinyl chloride polymerize to poly vinyl chloride (PVC). With acetic acid, we get vinyl acetate with acetylene in the presence of zinc acetate and mercuric acetate as catalyst. Vinyl acetate is polymerized to poly vinyl acetate (PVA). When HCN is used, we get vinyl cyanide whose polymerization yields poly vinyl acrylonitrile (PVAN) or Orlon. Moreover, acetylene can be polymerized to benzene when it is passed through copper tube at high temperature. Besides, acetylene molecules polymerize with themselves yielding alkydiynes, alkatriynes and alkapolyynes.



3.34 Confirmation Test

Terminal alkynes can be detected by treating with silver nitrate or cuprous chloride, both in the presence of NH_4OH. Silver nitrate gives white precipitate whereas

cuprous chloride yields red precipitate. On account of acidic nature of terminal alkynes, alkynes form acetylides. Both silver and copper acetylides are highly explosive in dry conditions. Treating them with HNO_3 decomposes them and yield free alkynes.

$$R{-}C{\equiv}C{-}H + Cu_2Cl_2 + 2\,NH_4OH \xrightarrow[-H_2O]{-NH_4Cl} R{-}C{\equiv}C^{-}Cu^{+}$$

red ppt

$$R{-}C{\equiv}C{-}H + 2\,AgNO_3 + 2\,NH_4OH \xrightarrow[-H_2O]{-NH_4NO_3} R{-}C{\equiv}C^{-}Ag^{+}$$

white ppt

3.35 Synthetic Polymer

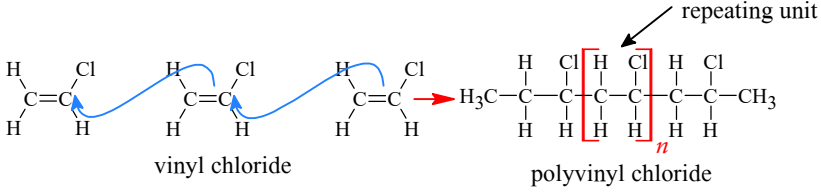
Whether plastic or rubber, pipes or car bumpers, tires or blue water tanks, all are polymers which are significant part of our daily lives. A polymer is a large molecule composed of many smaller repeating units (the monomers) bonded together. Polymer can be biological (biopolymer) such protein, lipids, cellulose and DNA etc. or synthetic such as polyvinyl chloride (PVC), polyethylene and polystyrene etc. First ever polymer was accidently made from polymerization of vinyl chloride in 1838. Polystyrene was discovered in 1839 after styrene was discovered. Today, our lives are impossible without the application of polymers in our clothes, computer, food, drug, automobiles and decorating materials.

Types of Polymer

Synthetic polymers could be divided into addition and condensation polymers.

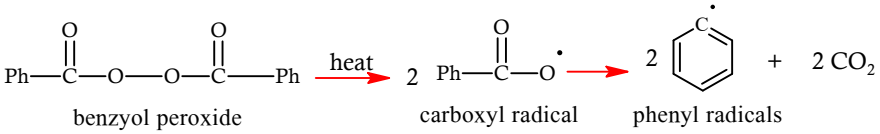
Addition Polymer

PVC or poly vinyl chloride is an example of addition polymer because it forms through successive addition of monomers (usually alkenes) to the growing end of polymer without loss of any molecule. For instance, PVC takes vinyl chloride units. This is an example of chain-growth polymer (addition polymer). Such polymerization proceeds by reactive intermediate of cation, anion or radical.



Polystyrene is another example of addition polymer that forms through free radical polymerization of styrene units. Usually, free radical initiator such as benzoyl peroxide is needed to achieve the polymerization at 100 °C. The peroxide cleaves and

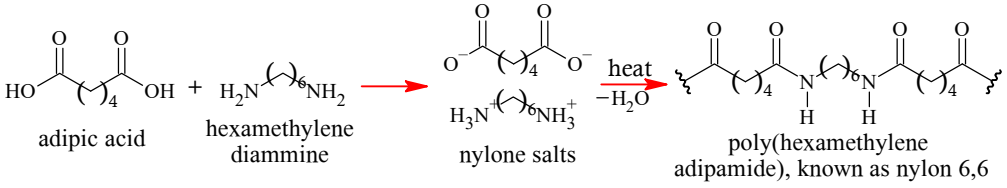
yields phenyl radical which adds to styrene to form as resonance stabilized benzylic radical. This is start of free radical polymerization since the benzylic radical add to another styrene molecules and so on.



Chain growth polymerization can be stopped either by coupling two ends of growing polymer or by addition of some impurities such as oxygen. Free radical chain-growth polymerization is also observed by ethylene and propylene. For instance, LDPE (low density polyethylene) used in polyethylene bags could be obtained at 200 °C and 3000 atm. LDPE is soft, amorphous and flimsy since it is highly branched. LDPE accounts for most of the plastic trash. Contrarily, HDPE (high density polyethylene) is hard, tough and unbranched.

Condensation Polymer

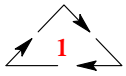
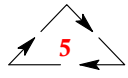
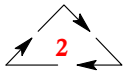
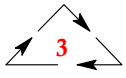
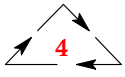
Amides and esters based polymers are formed through condensation reaction where two monomers or polymer chains combine to form a large molecules after loss of small molecule. This sort of polymerization is termed as step-growth or condensation polymerization. Dacron polyester is example of condensation polymerization. Nylon (Perlon) is polyamide polymer used in making strong, flexible ropes and tire cord. It is made from adipic acid and hexamethylenediamine, both are six carbon monomers which also get the name of nylon 6, 6 for the polymer.



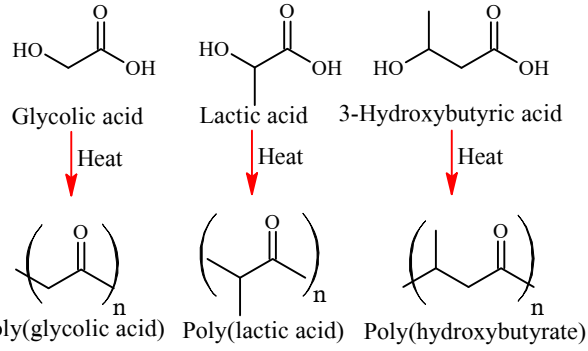
Biodegradable Polymer

Had plastic recycled, it wouldn't be an environmental issue since research has implicated micro plastic in our bodies. In a bid to facilitate recycling, Society of Plastic Industry in 1988 assigned codes to six types of plastics so that they could be aided for recycling which could be done by shredding plastic into pieces, washed, dried and melted for reuse.

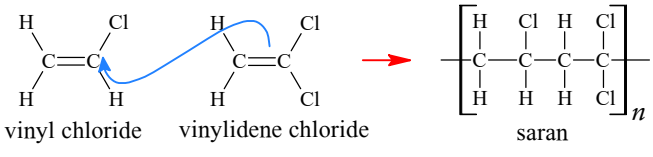
1. Polyethylene terephthalate (PET) used in soft drink bottles
2. High Density Polyethylene (HDPE) used in bottles
3. Polyvinyl chloride (V) used in floor mates
4. Low Density Polyethylene (LDPE) used in grocery bags
5. Polypropylene (PP) used in furniture
6. Polystyrene (PS) used in molded articles

Code	Type	Name	Code	Type	Name
PET		Polyethylene terephthalate *soft drink bottles, vegetable oil bottles*	PP		Polypropylene *straws, diapers, toys*
HDPE		High density polyethylene *milk, water and juice container*	PS		Polystyrene *eggs cartons, disposable utensiles, foam cups*
PVC		Polyvinyl chloride *shampoo bottles and plastic pipers*	others		Multilayer plastic *various flexible items*
LDPE		Low density polyethylene *grocery bags*			

Most polyesters serve as biodegradable polymers because they perish by action of hydrolysis of ester linkage once they are thrown away into the environment. Polyglycolic acid (PGA), polylactic acid (PLA) and polyhydroxybutyrate (PHB) are most common example of biodegradable polymers. A 90/10 copolymer of PGA and PLA is particularly useful in sutures that degraded in 90 days after surgery.



Copolymers are formed by two or more different units. For instance, polymer for wrapping food, Saran, is made from vinyl chloride and vinylidene chloride. ABS polymer is tough, hard, and resilient. It is used in helmets and car bumper is formed by monomers of acrylonitrile, butadiene and styrene.



3.36 Exercise

Attempt the following question briefly!

1. Terminal alkynes are acidic but internal ones are not.

2. Why ozonolysis of alkenes and alkynes gives different products although both are unsaturated hydrocarbons?

3. Are substituted alkynes are stable the same way as do the substituted alkenes? How does hyperconjugation stabilize substituted alkynes? Arrange ethyne, propyne and 2-butyne in increasing order of their stability.

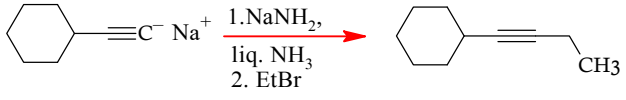
4. Why alkynes undergo electrophilic addition reactions less readily than alkenes?

5. How does the reactivity of triple bond get influenced by adjacent function group? Give examples and justify the statement.

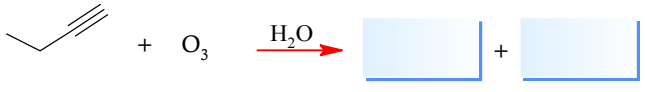
6. Why sigma bond in triple bond is shorter than sigma bond in carbon-carbon double and single bonds?

7. Alkynes are used in organic synthesis for carbon-carbon coupling, comment!

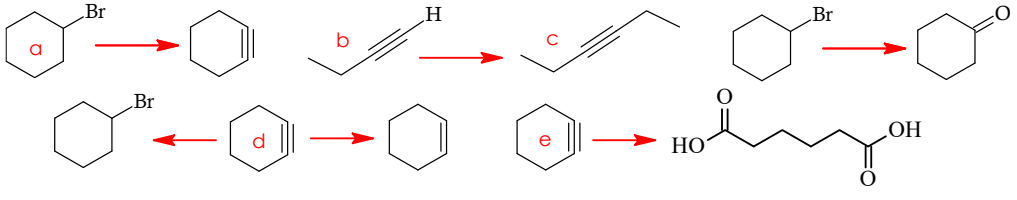
8. Point out mistake in the following reaction



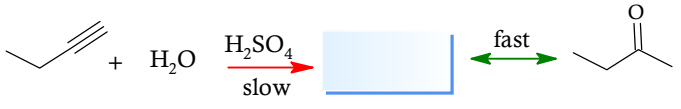
9. Point out product of ozonolysis.



10. Make the following interconversion!



11. Predict the compound in the box and comment on the nature of reaction.



Benzene & Derivative

Properties, Synthesis & Reactions

3.4 Aromatic Hydrocarbons

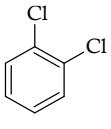
3.41 Introduction

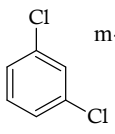
Benzene was discovered in 1826 by Michael Faraday and its modern structure was brought by August Kekule. (German Chemist) in 1866. He proposed a cyclic structure with three double bonds. The structure had issue because it represented two different compound for same molecule. Actually, the structure was considered a cyclohexatriene with stationary double bonds. In fact, single bond would be longer and double bond shorter in Kekule structure. In 1800s, European used named it phenyl which is pronounced as fennil. Benzene is stable and inert. It doesn't react like alkenes or alkynes due to its stability. Benzene doesn't undergo hydrogenation as easily as alkenes or alkynes. Petroleum products and coal tar are sources for benzene. It is colorless and flammable liquid which is added to petrol (2%) and found in smoking. Prolong exposure to benzene is potential source of leukemia which is decrease in RBCs and increase in abnormal WBCs.

3.42 Properties

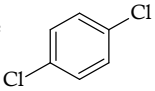
Benzene is less dense than water. Its derivatives are less than water except halogenated ones which are dense than water. Benzene compound normally don't react with water except those containing polar moieties such as phenols and aromatic acids. Benzene and its derivatives are more symmetrical due to their structure than other cyclic and acyclic compounds. This property render benzene and its derivatives better able to pack which enhances melting and boiling points. Similarly, para substituted benzene derivatives have higher melting points than other asymmetrical disubstituted derivatives. Dipole moment plays crucial to ascertain high melting points. Benzene derivatives with higher dipole moment such ortho dichlorobenzene has highest melting point as compared to meta and para derivatives.

o-dichlorobenzene
mp = 181°C
bp = - 17°C





m-dichlorobenzene
mp = 173°C
bp = –25°C

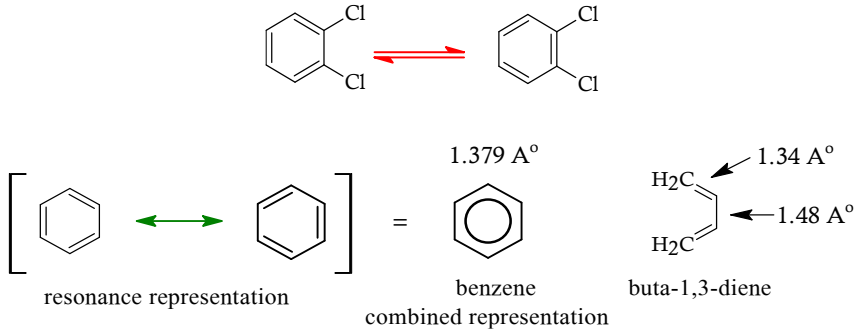


p-dichlorobenzene
mp = 170°C
bp = –54°C

3.43 Structure

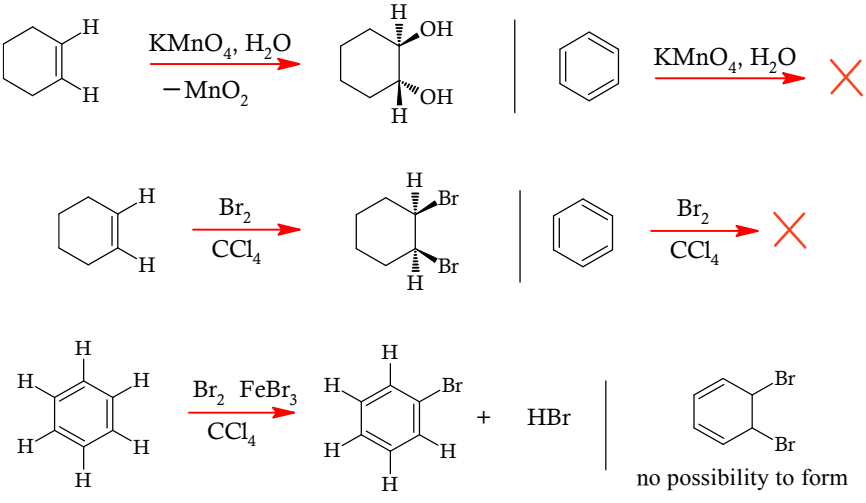
Contrary to Kekul structural elucidation of benzene, spectroscopic studies reveal that all bond in benzene are of same length (1.397 A). Benzene is planar molecule. It is resonance hybrid of two Kekule structures. Bonds in benzene are shorter than normal single bond but longer than normal double bond which is due to delocalisation of pi electrons over ring. In fact, this resonance turns the bond order of benzene in fraction (1.5). Benzene is usually shown as a hexagon with circle inscribe in the mid entailing that there is no single or double bond but a situation somewhat between them. This representation

of benzene is attested by unusual reactions of the compound which are different than normal reactions of alkene, had benzene considered a normal alkene.



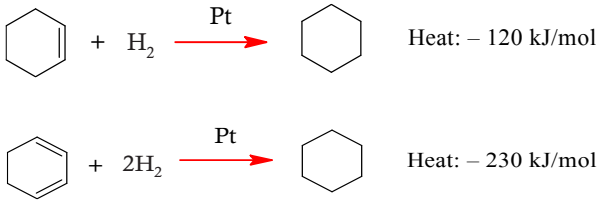
3.44 Unusual Reactions of Benzene

Benzene show different reaction behavior than alkenes due to resonance. An alkene decolorizes $KMnO_4$ or bromine solutions but benzene doesn't. Benzene shows substitution reaction unlike addition reactions of alkenes. Consider the following set of reactions:

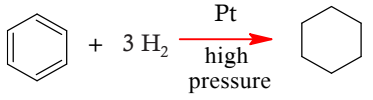


3.45 Unusual Stability of Benzene

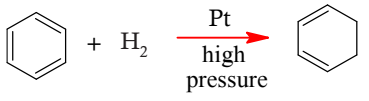
Heat of hydrogenation is compared with other compounds to assess relative stability. Consider the heat for the following compounds:



This reflects the value of 120 for one double bond and 240 for two double bonds. As benzene as three double bonds, therefore its value should 360 instead of actual value of 208 which is short of 152 kJ/mol. This reduced energy of 152 kJ/mol is known as resonance energy which explains the exceptional stability of benzene which release less heat by amount of 152 kJ/mol as compared to other alkenes. This is how benzene undergoes substitution reactions unlike addition reactions of alkenes.



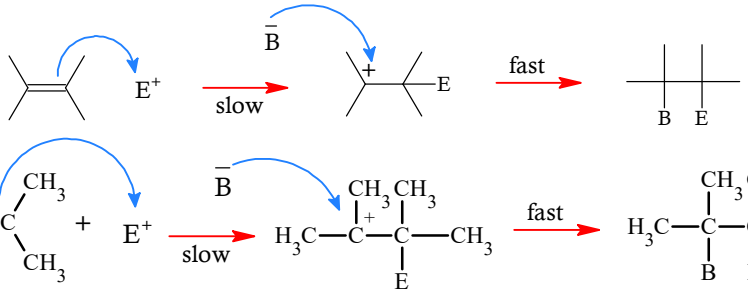
Heat = 208 kJ/mol
3 x cyclohexane = 359 kJ/mol
resonance energy = 151 kj/mol



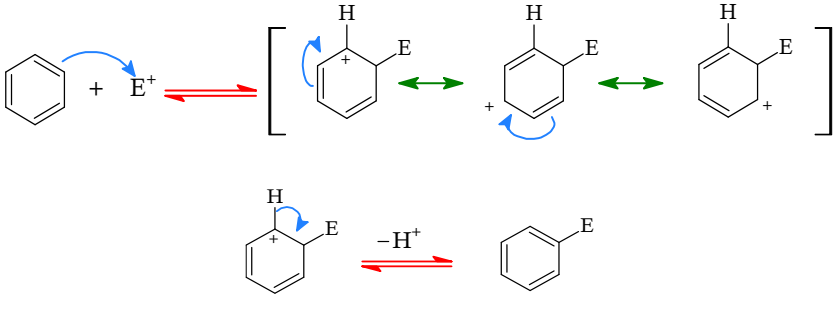
Heat = – 208 kJ/mol
cyclohexa-1,3-diene = 359 kJ/mol
total heat = 24 kJ/mol

3.46 Reactions

Benzene gives substitution reaction which is electrophilic in character because electrophile (E^+) initiates the reaction. More specifically, the type of reaction is known as electrophilic aromatic substitution reaction (EASR). Whether electrophilic addition reaction of alkenes or EASR, positive charge intermediate forms in both cases. Alkenes give carbocation whereas benzene or aromatic compounds arenium ion which is resonance stabilized format of carbocation. Mechanistically, EASR initiates with electrophilic attack on benzene ring for giving arenium ion or sigma complex. We call it sigma because old pi bond diminishes with formation of new sigma bond after electrophilic attack.

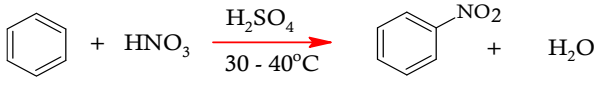


In second step, sigma complex loses proton for restoration of benzene ring.

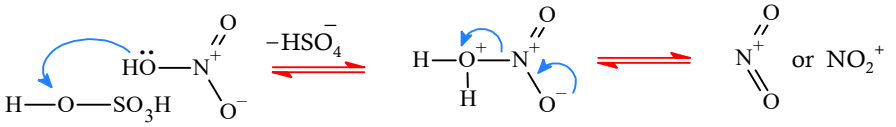


1. Nitration

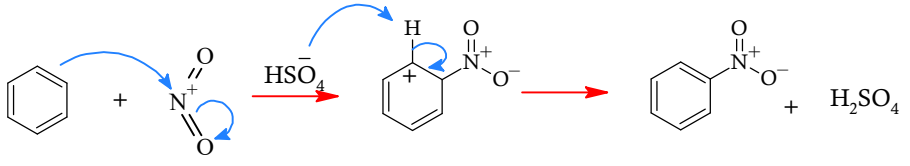
Before executing EASR, electrophile needs to be formed which is positive charge species or neutral with considerable partial positive character. EASR requires electrophiles such as nitornium ion for nitration, alkyl group for alkylation, acyl for acylation and sulphonium ion for suffocation. For nitration, nitrating mixture is used for generation of nitornium ion which attacks benzene ring. The reaction of benzene happens with a solution of nitric acid and sulfuric acid at room temperature. The latter acid acts as catalyst. Introducing nitro group into aromatic compounds offer excellent synthetic outlet because it can easily be reduced to amino group with metals such as zinc, tin or iron in dilute acidic conditions.



Mechanism

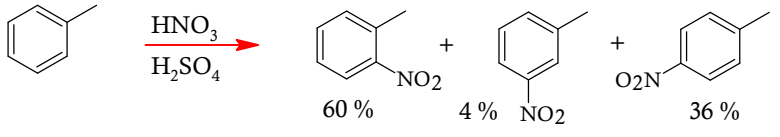


The nitronium ion, with its positively charged nitrogen, then attacks benzene

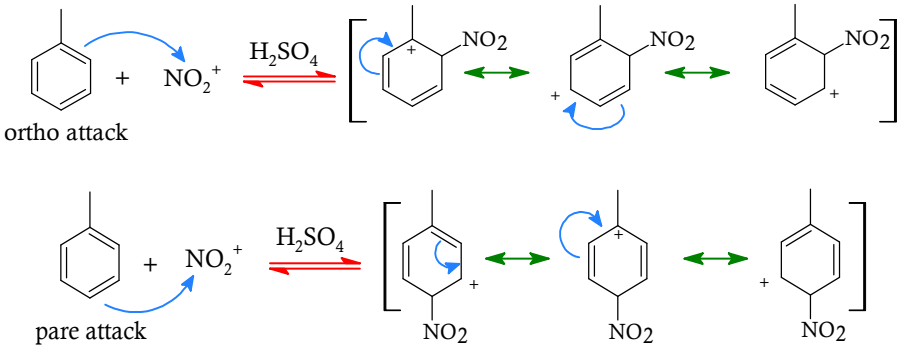


Substituents Effect: Nitration of Toluene

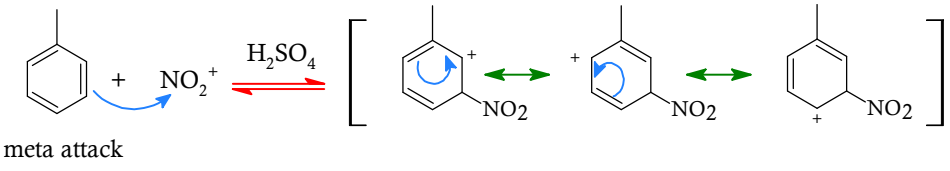
Nitro group is electron withdrawing (EWG) in character. It makes benzene less reactive or deactivate for further reaction. EWGs are also termed as deactivating groups. Methyl group is electron donating (EDG) or activating because it makes benzene ring more reactive. For instance toluene is more reactive than benzene. This can be exemplified by nitration of toluene which is 25 times greater than benzene.



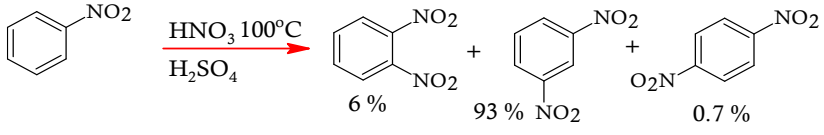
EDGs are ortho and para directors whereas EWGs are meta directors. Consider the nitration of toluene which gives mixture of ortho, para and meta isomers in different proportions.



The question is why o/p isomers form in greater proportion could be answered from the following illustrations.

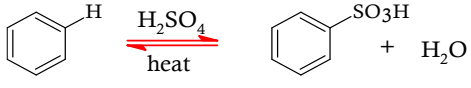


We get a tertiary carbocation for o/p attack which is stabilizing and rate enhancement step unlike meta attack where no such carbocation forms.

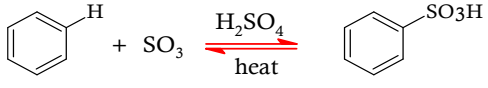


2. Sulphonation

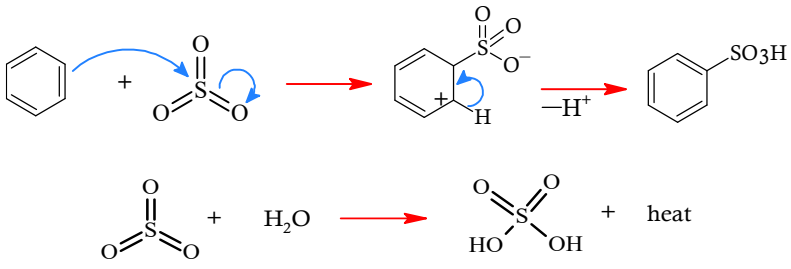
Like nitro group, sulfonic group is EWG too. Usually, fuming sulfuric acid is used for sulfonation of aromatic ring because concentrated sulfuric acid doesn't bring the results. Some 8% of sulfur trioxide is passed through a solution of concentrated sulfuric acid to get fuming sulfuric acid.



Sulfur gets enough electrophilic when it bonds to three electronegative atoms such as oxygen. SO_3 is right candidate for electrophilic attack.

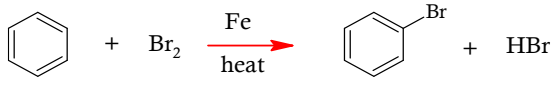


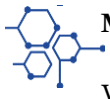
Sulfonation is reversible reaction and benzene sulfonic acid could be easily reversed in dilute sulfuric acid solution. This is desulfonation reaction which is important synthetic tool in organic chemistry for removal of sulfonic acid group.



3. Halogenations

Alkenes add bromine without any trouble because alkenes are more reactive than aromatic compounds. For benzene, bromine isn't reactive enough to stage EASR.

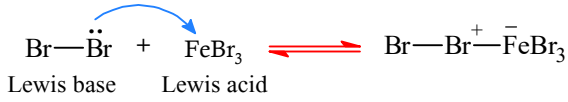




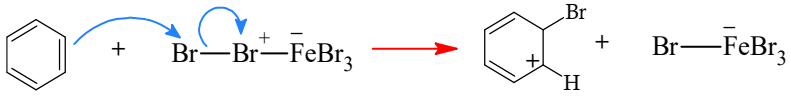
Mechanism

We need strong Lewis acid such as $FeBr_3$ for enhancing electrophilic character of bromine because the acid is electron deficient and it acquire lone pair from bromine. Once this take places, bromine gets enough polarized to react with benzene in an EASR.

Step 1: Activation of Bromine by Lewis Acid



Step 2: Electrophilic attack on benzene by activated bromine

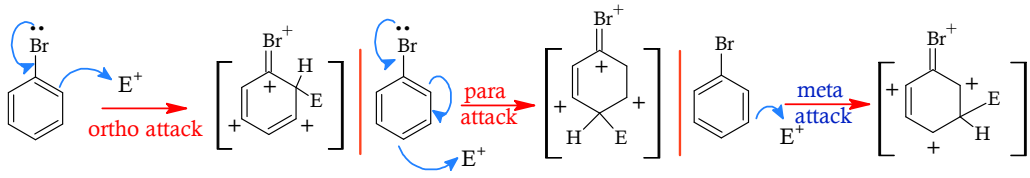


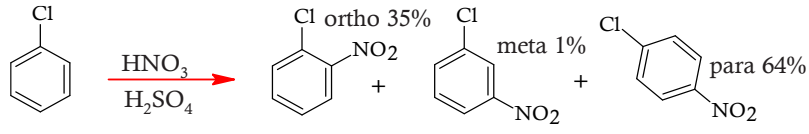
Step 3: Formation of bromobenzene

Orientation of Halogen Group

Halogens are electron withdrawing in character yet they are o/p directors because they exert two effects: resonance effect due to lone pair of electrons present on halogens

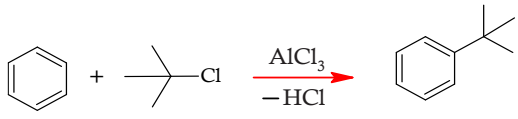
and inductive effect on account of strong electronegativity associated with halogens. Resonance effect makes halogens o/p directors whereas inductive effect causes them to behave as EWGs. Both effects oppose each other. The intermediate of halogenation is known as halonium ion. If halogen attacks at meta position, resonance stabilization by resonance effect of halogen does take place because +ve charge doesn't form where halogen is bonded.





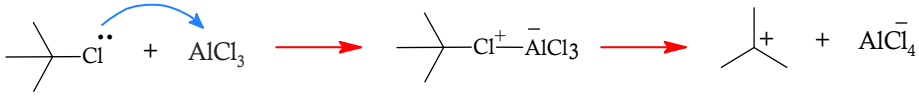
4. Friedel-Craft Alkylation

Connecting carbon with carbon is termed as coupling Reaction which is useful synthetic tool for making millions of different molecules. In modern times, Suzuki Coupling is one such reaction with diverse applications in pharmaceuticals, nanotechnology and photovoltaics. Friedel-Craft reaction is classical format for establishing carbon to carbon connectivity. Treating alkyl halides with Lewis acid forms carbocation which serves as electrophile in Friedel-Craft reaction. The reaction was studied by Charles Friedel, a French alkaloid Chemist, and American James Craft in 1877. The reaction has both alkylation and acylation formats. In acylation, acid halides are used instead for generating acylium ion as electrophile.

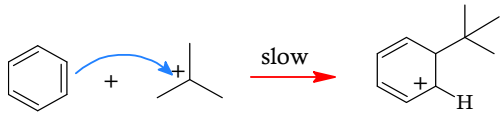


Mechanism

$AlCl_3$ is electrons deficient species. It accepts electron from halogen atom of alkyl halides that gives rise to formation of carbocation.



Step 1: Once the cation is generated, it is attacked by the π electrons of benzene and results in new carbon-carbon bond formation.



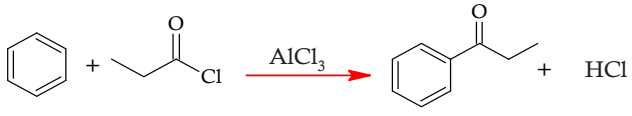
Step 2: Loss of a proton from the cyclohexadienyl cation intermediate yields *tert*-butylbenzene.

Limitations

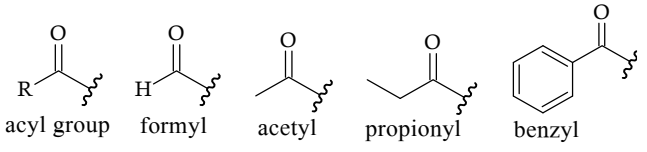
Alkylation brings electron donating group into benzene which makes it further reactive and the reaction doesn't stop at mono alkylation stage. Polyalkylation results. Moreover, alkylation works with benzene and activated benzene derivatives as halobenzene. It doesn't work with strongly deactivated system such as nitrobenzene or benzene sulfonic acid. The electrophile is prone to rearrangement which makes alkylation not a selective tool of synthesis.

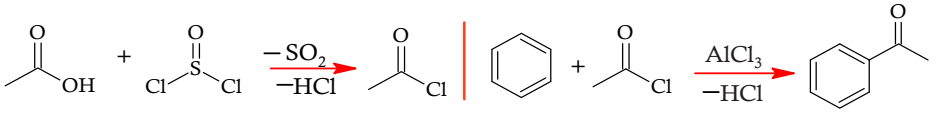
5. Friedel-Craft Acylation

Generally, acid chloride are used in combination with Lewis acid catalyst for acylium ion which acts as electrophile in Friedel-Craft acylation reaction.

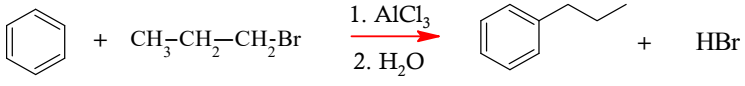


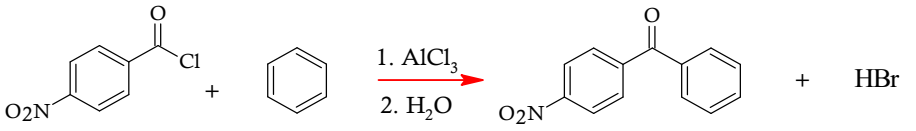
An acyl group is alkyl group bonded to carbonyl group. This reaction is useful for organic synthesis in overcoming the shortcoming of carbocation rearrangement. Once acyl group is incorporated into aromatic ring, it could easily be reduced to simple alkyl group. Furthermore, acyl group deactivates benzene ring and prevent it from further reaction like the drawback of polyalkylation.





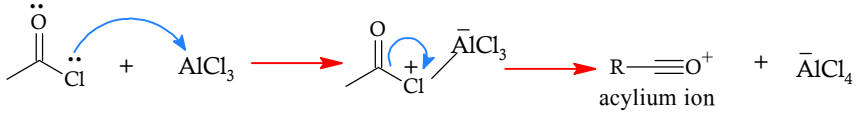
This is excellent method for synthesis of aryl or diaryl ketones.



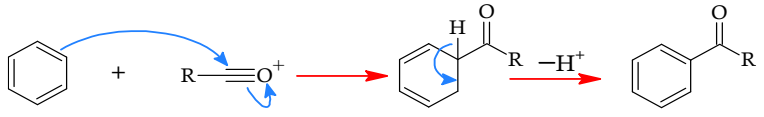


Mechanism

Lewis acid triggers the formation of acylium ion by coordinating with acid chloride. The complex dissociates and yield an electrophile known as acylium ion. The acylium ion is not prone to rearrangement like carbocation.

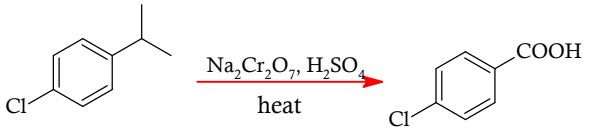


Acylium ion attacks π electrons system of benzene ring. Acyl group is electron withdrawing and it stabilizes benzene ring by making it less reactive and avoids the side-effect of polyalkylation.

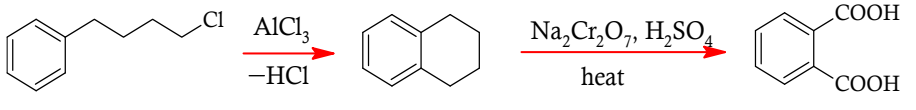


6. Oxidation of Alkyl Benzene

Side chain of benzene ring is oxidized to carboxyl group by the action of strong oxidizing agents such as hot chromic acid or hot potassium permanganate. The reaction has limitation because severe oxidizing conditions oxidizes other functionalities except those which are resistant to oxidation such as –Cl, $–NO_2$, $–SO_3H$ and –COOH.



Aryl halides undergo intramolecular Fridel-Craft alkylation reaction if chain length is suitable and reaction conditions are feasible. Its subsequent oxidation gives benzoic acids or its derivatives.

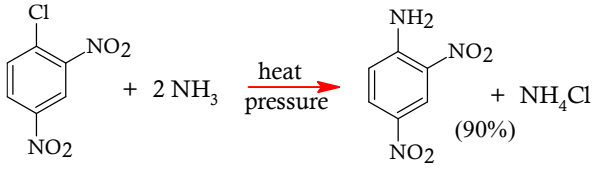


3.47 Nucleophilic Aromatic Substitution Reaction

Nucleophilic substitution on aromatic ring doesn't operate like normal substitution reaction at saturated carbon since electronic cloud, steric hindrance coupled with sp^2 carbon bearing leaving group prevents direct approach of nucleophile to the

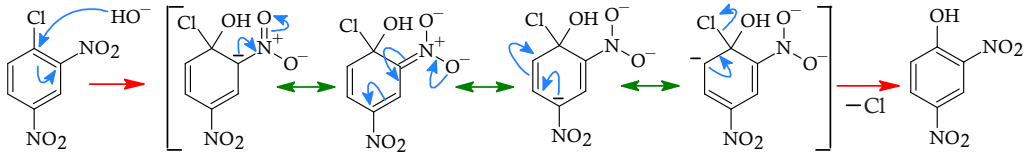
carbon atom bearing leaving group. Contrarily, strong nucleophile either adds up to the benzene ring first and then expel leaving group (addition-elimination) later or a strong base abstracts proton first and subsequent expulsion of leaving group on aromatic ring later (elimination-addition). The type of substitution reaction on aromatic ring is known as nucleophilic aromatic substitution reaction (NASR or S_NAr) which requires strong electron withdrawing group (EWG) at ortho and para positions.

NASR also operates on un-activated aromatic system where no requirement of EWG is needed. Such NASR works by benzyne mechanism. Unlike EASR, NASR requires strong nucleophile for expelling leaving group or strong base for removing proton from benzene ring. In fact, the rate of NASR depends upon the concentration of nucleophile which is involved in rate determining step.



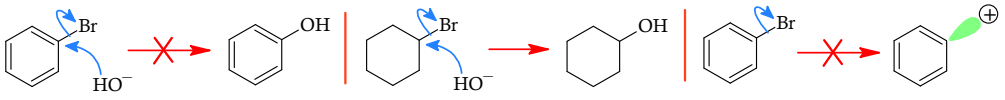
Mechanism

Nucleophile add up to the aromatic system yielding a resonance stabilized intermediate carbanion complex in the first step. The complex is known as Meisenheimer Complex. In second step, the carbanion expels leaving group to give product. The chloride ion takes proton from hydroxyl group. After the reaction completes, the phenoxide ion left is protonated to give back phenol functional group. The reaction proceeds by addition-elimination mechanism.



Solved Problem 3.41: Why aromatic system doesn't observe S_N1 or S_N2 reactions?

Leaving group on aromatic system doesn't ionize like normal S_N1 reaction since the carbocation formed would be highly unstable because the positive charge on aromatic ring wouldn't be resonance stabilized as it locates outside the ring. Aromatic system doesn't observe S_N2 reaction since electronic cloud of benzene ring prevents nucleophile from backside approach. Moreover, ring system strongly hinders nucleophile due to steric hindrance. As a general rule, S_N2 doesn't take place at sp^2 hybridized carbon. In a nutshell, neither S_N1 nor S_N2 reaction takes place on aromatic system. Instead, aromatic system observes electrophilic and nucleophilic substitution reactions such as EASR and SnAr.



S_N2 is not possible at sp^2 carbon

S_N2 take places at saturated carbon

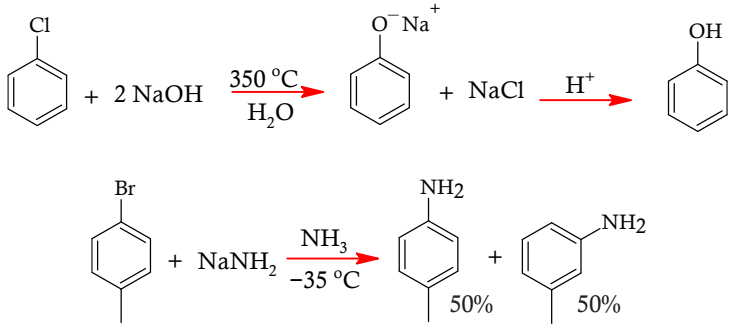
Ionization at sp^2 carbon is not possible since the carbocation isn't resonance stabilized

Solved Problem 3.42: Why electron withdrawing group is required in NASR?

In EASR, sigma complex is resonance stabilized carbocation. In NASR, the intermediate is known as Meisenheimer Complex that is resonance stabilized carbanion. Since carbanions are stabilized by EWG through $-I$ effect, this is NASR requires such groups at o/p position where negative charge deposits.

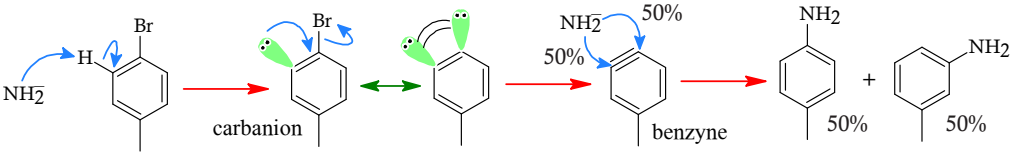
Benzyne Mechanism

Sometimes strong EWG is not required at o/p position to expel leaving group from aromatic ring. For instance Dow process for synthesis of phenol works with chlorobenzene which doesn't possess any EWG. Such reaction which observe NASR without the assistance of EWG proceed by benzyne mechanism which is a sort of elimination-addition reaction. Chlorobenzene also gives aniline with strong base such as sodium amide. This reaction take places at lower temperature in liquid ammonia. The reaction gives equimolar mixture of two isomers. For instance para bromotoluene give 50% m and 50% p-toluidine. This is due to formation of reactive benzyne intermediate.



Mechanism

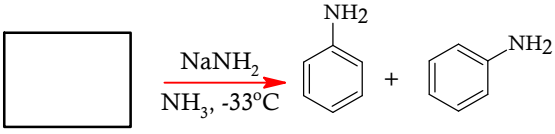
Powerful base abstracts one of benzene proton yielding a carbanion which rearranges to triple bond neutral intermediate after expelling leaving group.



Once the leaving group leaves, an empty sp^2 hybridized orbital is left which interacts with adjacent sp^2 hybridized orbital, giving a strained triple bond. Both orbitals

are oriented at 60°. Consequently, the triple bond formed is bent, weak which is what we call Banana Bond on account of bending orientation. This triple bonded species is known as benzyne which offers equal chance of attack for nucleophile at either carbon of the triple bond.

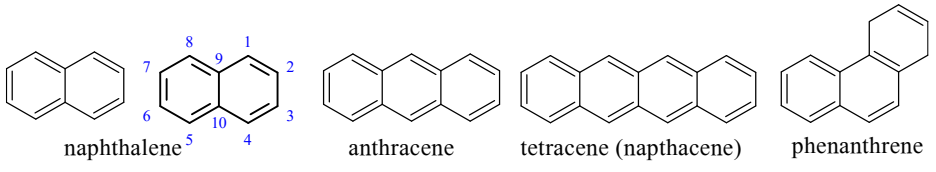
Problem 3.41: Point out starting material for the following reaction



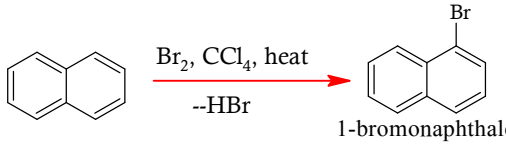
3.48 Polynuclear Aromatic Hydrocarbons

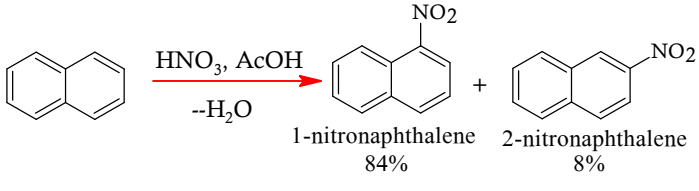
Naphthalene

Naphthalene, most commonly used in moth ball, is represented by formula $C_{10}H_8$ which was determined by Michael Faraday in 1826. This compound is white crystalline solid. It has peculiar odor. Naphthalene along with anthracene, tetracene and phenanthrene are classified as polynuclear aromatic hydrocarbons.



Chemically, naphthalene observes EASR. Most EASR observed on naphthalene are highly selective (regioselective) since most of them take place at position 1.



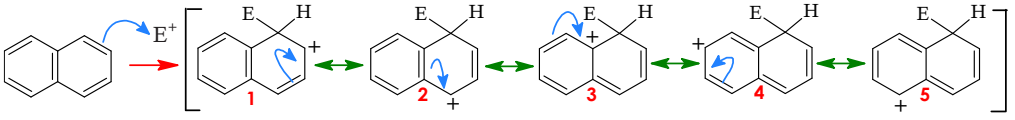


Polynuclear hydrocarbons are more reactive than benzene both in substitution and addition reactions. Theoretically, quantum mechanical calculation reflects that net loss of resonance stabilization energy during first step in EASR decreases progressively from benzene to anthracene which attests the fact that reactivity increases from benzene to anthracene. Naphthalene is more reactive than benzene due to higher resonance energy

which is 255 kJ/mol and 150 kJ/mol for benzene. During reaction of naphthalene, one ring is lost but aromaticity of other ring remains intact with resonance energy of 150 kJ/mol. Benzene loses entire aromaticity upon reaction. Naphthalene sacrifices less energy than benzene to react.

Resonance Energy of Naphthalene = 255 – 150 = 104 kJ/mol

Electrophilic attack on the ring yields five resonance hybrids or canonical forms. Greater the number of such structures, higher will be the reactivity of compound.

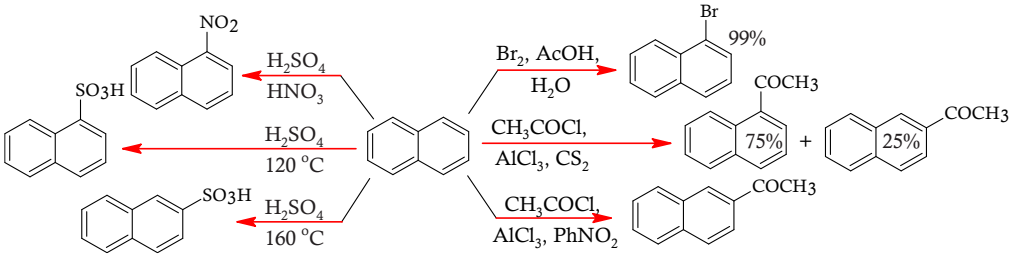


Solved Problem 3.43: Which position is preferable to attack?

The position of attack matters. At position 1, naphthalene yields cation which is stabilized by five canonical forms with two aromatic rings unaffected during resonance stabilization. When electrophile attacks at C2, we are left with only one such aromatic ring intact. Consequently, carbocation emerges from C2 attack is less stable. Since first step is rate determining, attack at C1 is preferable.

Orientation

Presence of group on naphthalene ring influences the direction of up-coming electrophile. Naphthalene is regioselective. For instance, an activating group already present on C1 directs up-coming substituent to C4 and sometime C2. If activating group is present on C2, it directs substituent towards C1.

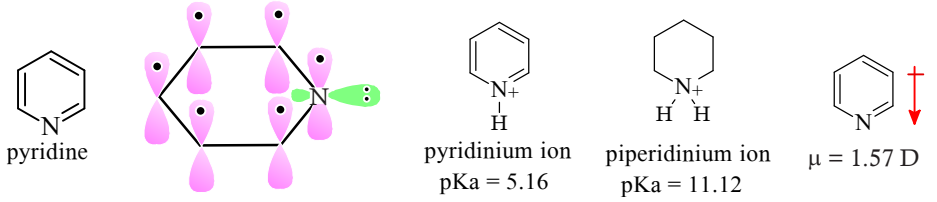


Deactivating group at C1 or C2 directs substituent towards C5 or C8. This isn't an exclusive rule but some exceptions have noted in case of sulfonation. Upon sulfonation, naphthalene gives 1 and 2 products. Product 1 suffer steric hindrance due to hydrogen atom at C8 which makes the product less stable and kinetic which is obtained at lower temperature of 80 °C. Product 2 obtains at 160 °C and it is thermodynamic. Higher temperature transforms product 1 into 2. Solvent plays crucial role in maintaining the direction of up-coming substituent. Naphthalene gives acylated product at C1 and C2 in CS_2 and nitrobenzene respectively.

3.49 Heterocyclic Aromatic Hydrocarbons

Pyridine

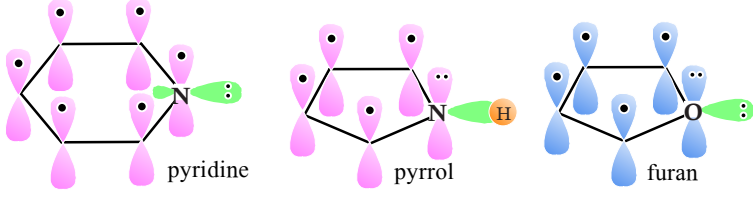
Pyridine is aromatic compound with lone pair of electron on nitrogen atom is laying outside the ring in planar conformation. Since the lone pair isn't involved in resonance, pyridine is basic and it is used in reactions as scavenging agent for trapping fumes of hydrochloric acid.



Pyridinium ion is more acidic than piperidinium ion because in the former case, proton is attacked to sp^2 nitrogen unlike sp^3 N in the latter case. The dipole moment of pyridine is 1.57 D. The electron-withdrawing N is the negative end of the dipole.

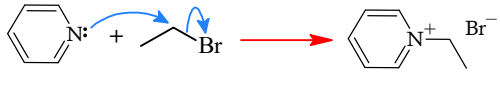
Structural Comparison

In pyridine, pyrrole and furan, the hetero atom is sp^2 hybridized. Nitrogen atom in pyridine shares two of its sp^2 hybridized orbitals for making bonds with two adjacent carbon atoms of ring whereas one sp^2 orbitals remains outside the ring holding a lone pair of electron. Nitrogen in pyrrole uses all three sp^2 hybridized orbitals in making three sigma bonds: two with adjacent carbon atoms of ring and one with hydrogen. Unhybridized orbital holds a lone pair of electrons which is part of aromatic system. Similar is the case with furan, where a lone pair of electron in unhybridized orbital is part of aromatic system whereas one sp^2 hybrid orbital, laying outside ring, holds another lone pair of electron.



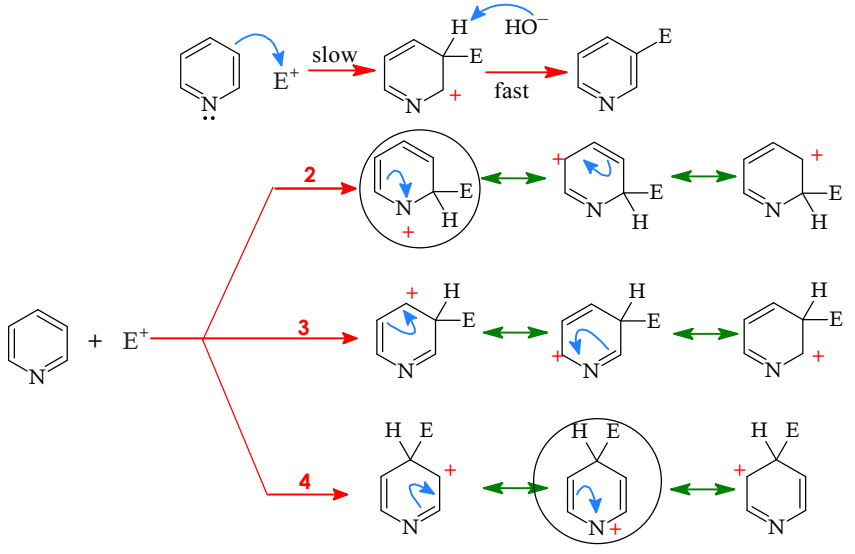
Reactions

Since pyridine carries lone pair of electron on nitrogen atom, it acts as nucleophile and demonstrates characteristic reactions of tertiary amines.



Pyridine exhibits EASR at position 2, 3 and 4. Consider the following canonical forms obtained from attack at these positions. Since we get one least stable form (encircled) from electrophilic attack at position 2 and 4 where nitrogen has incomplete octet and positive charge, therefore, both these position are unlikely to proceed by EASR.

Consequently, EASR preferentially occurs at position 3 since it gives rise to better resonance stabilization of intermediate carbocation.



Solved Problem 3.44: Is pyridine less reactive than benzene?

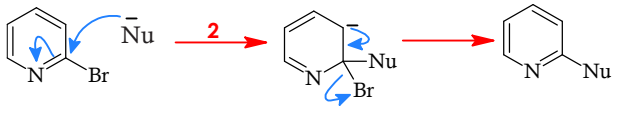
Pyridine is less reactive than benzene because electronegative nitrogen atom destabilize carbocation intermediate more than sigma complex. Pyridine is even less reactive than nitrobenzene. Consider the reactivity order:

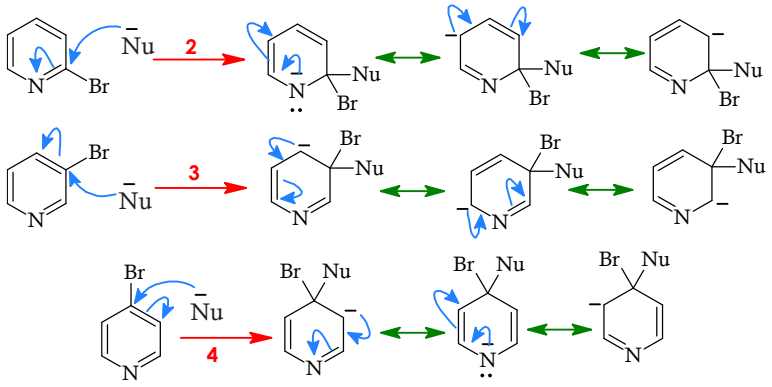
Benzene > Nitrobenzene > Pyridine > 1, 3-dinitrobenzene

This is how pyridine requires vigorous reaction condition for EASR. Yield in such reactions is even low. For instance, bromination, sulfonation and nitration works at higher temperature ranging between 250 to 300 °C or above with low yield of 30, 71 and 22% respectively. A protonated nitrogen of pyridine makes it even further unreactive since it will make carbocation further unstable. Since pyridine is deactivated system, therefore it doesn't demonstrate Friedel-Craft alkylation and acylation reactions.

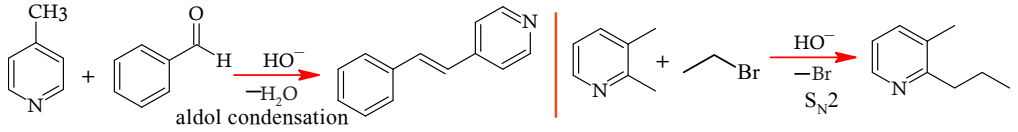
Nucleophilic Aromatic Substitution Reaction

Unlike EASR, pyridine is more reactive than benzene in NASR since nitrogen stabilizes carbanion intermediate. Nucleophile add to the carbon bearing leaving group. This results in formation of resonance stabilized carbanion intermediate. Position 2 and 4 are most preferable because both position involve a canonical form where negative charge resides on nitrogen atom which stabilizes it. Position 3 doesn't yield any such structure.

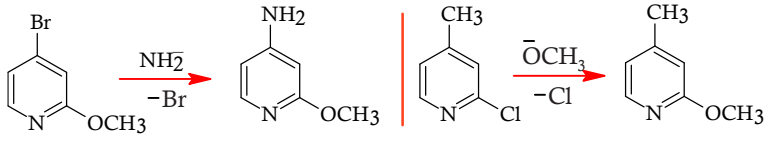




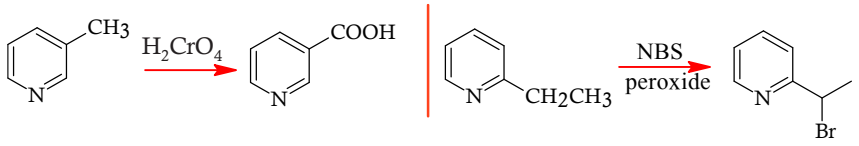
From above resonance stabilization structure, we can justify why methyl hydrogen of 2 or 4 methyl pyridine as much acidic as that of ketone since the negative charge formed after removal of proton delocalize over ring due to electron withdrawing nature of nitrogen.



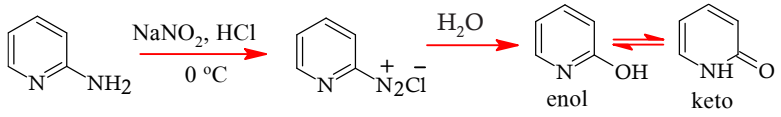
In fact, methyl group could only have acidic protons when it resides on 2 or 4 position. This feature makes methyl pyridine to undergo aldol condensation and S_N2 reaction with primary alkyl halides. In case of two different leaving groups at 2 and 4 positions, nucleophile selectively attacks carbon atom where better leaving group is attached.



Many reactions of benzene are shown by substituted pyridine derivatives.



Amino pyridine derivative can be diazotized. The salt reacts immediately with water yielding hydropyridine which tautomerizes to keto form (α-pyridone) which is more stable than the enol form.

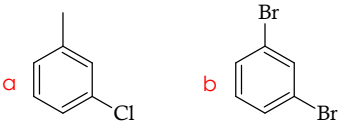


3.50 Exerceise

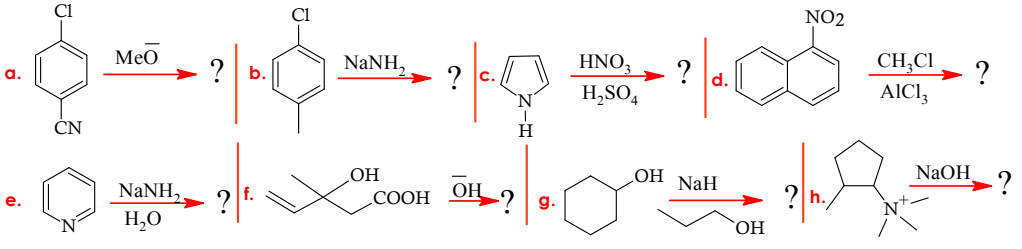
1. Assign Brief reasoning to the following statement.

a. Why both fluorine and hydroxyl groups act as leaving groups in S_NAr and E1cB although it is poor leaving groups.
b. Why florobenzene is less deactivated than other halobenzenes?
c. Why fluoride turns out to be a good choice in nucleophilic aromatic substitution though it is bad leaving group in both S_N1 and S_N2 reactions.
d. Starting with benzene, prepare 3-nitroaniline and 4-bromo-3-cyanotoluene.
e. Why benzene ring resists normal S_N1 and S_N2 reactions?
f. Benzylic and allylic halides undergo S_N2 but vinylic and aryl halides do not?
g. Why halogens are o/p directing although they are deactivating in character.
h. Why flouro compounds are reactive towards ANSR?
i. Pyridine is stronger base than pyrrole but weaker than aliphatic amines, explain.
j. Explain, why pyridinium N-oxide is stronger acid than simple ammonium ion.
k. Is benzye mechanism an example of E1cB mechanism?
l. Why EWG on ortho/para position activate the ring towards NASR?

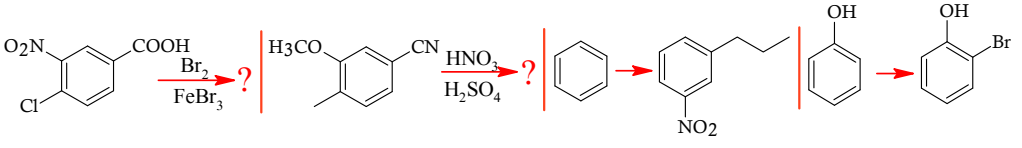
2. Synthesize the following two compounds starting from simple starting materials, toluene for first example and benzene for second one.



3. Write down just products for the following reactions.



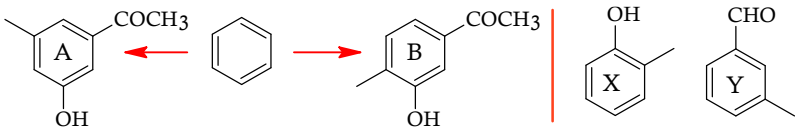
4. Make the following transformation.



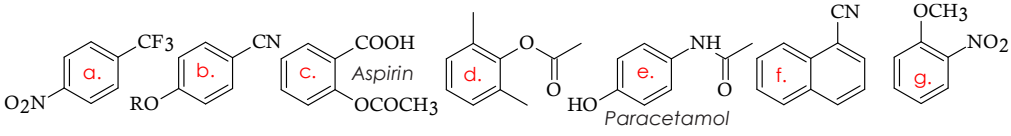
5. Comment on pros and cons Friedel Craft Alkylation and Acylation reactions.

6. In NASR reactions, electron withdrawing groups (EWG) are required at o/p position but no such requirement is needed for benzyne mechanism although the latter also involves nucleophilic substitution on aromatic ring? Reason!

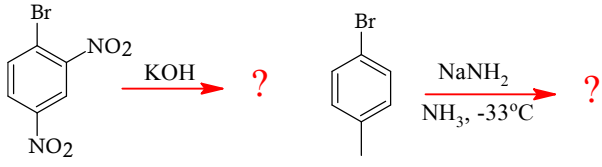
7. Starting from benzene, how will you prepare each of the following, A & B? Specify reaction conditions. Point out two positions for upcoming electrophile on X and Y.



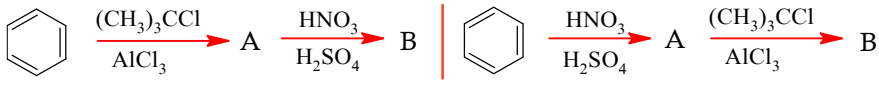
8. Point out relevant position of orientation for upcoming electrophile on each of the following molecule.



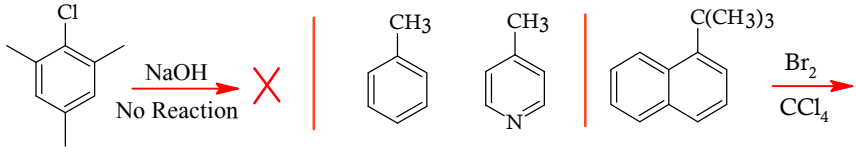
9. Write down product for each the following reactions along with mechanisms and name the reactions.



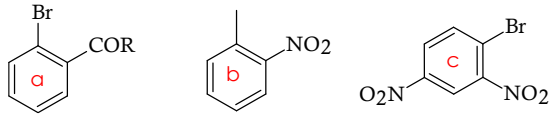
10. Complete reaction whether the product formed in either case is same or different.



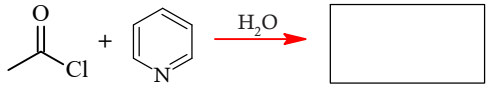
11. Why the following reaction fails to take place? State which methyl protons are acidic and point out product for bromination of naphthalene ring.



12. How benzyne mechanism is different from simple addition elimination mechanism in NASR. Explain why EDG activate benzene ring towards EASR where EWG activate the ring towards NASR. Which of the following compounds is more reactive towards ANSR?



13. Predict the product of the following reaction and reason for your assessment.



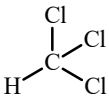
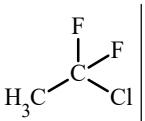
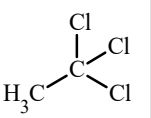
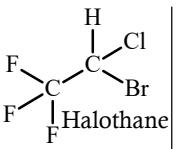
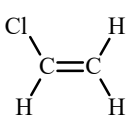
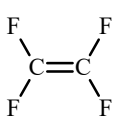
Carbon-Halogen Bond

Properties, Synthesis & Reactions

3.5 Alkyl Halides

3.51 Introduction

Halogens are class of organic compounds containing C—X bond which is quite polar, reactive and unstable as compared to alkane, alkene, alkynes and aromatic hydrocarbons. X is halogen such as F, Cl, Br and I whereas C is carbon atom of alkyl, vinyl or aryl group. The polarity of C—X bond equips RX to demonstrate variety of reactions, common ones are substitution and elimination. When halogen is replaced by some metal, the polarity of the bond changes. Now carbon acquires considerable carbanion character since it is more electronegative than the metal it bonds to. The reversal of polarity (Unpolong) introduces an entire new class of organic compounds knows as organometallic compounds and its chemistry is termed as organometallic chemistry.

					
Chloroform	Freon - 22 Refrigerant	Cleansing fluid	anesthetic nonflammable	vinyl chloride PVC	tetraflouroethylene teflon

3.52 Physical Properties

Melting and boiling points arise from molecular packing and mutual interaction of molecules. Straight chain molecules are more regular and offer larger surface area for greater intermolecular forces (London forces) than branch analogues. The polarity of C—X bond induces dipole moment which influence physical properties of alkyl halides. Electronegativity of halogen makes the bond polar. Alkyl fluorides are more polar than other members as electronegativity of fluorine is larger than other members. The following table compares the values of electronegativity with dipole moment.

$$\text{Electronegativity: } \underset{2.7}{I} < \underset{3}{Br} < \underset{3.2}{Cl} < \underset{4}{F}$$

$$\text{Bond length: } \underset{1.38\,A^{o}}{C{-}F} < \underset{1.78A^{o}}{C{-}Cl} < \underset{1.94A^{o}}{C{-}Br} < \underset{2.14A^{o}}{C{-}I}$$

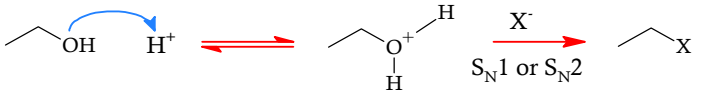
$$\text{Dipole moment: } \underset{1.29D}{C{-}I} < \underset{1.48D}{C{-}Br} < \underset{1.51D}{C{-}F} < \underset{1.56D}{C{-}Cl}$$

Boiling point of n-butane is 0°C, n-butyl fluoride is 33°C, n-butyl chloride is 78°C, n-butyl bromide is 102 °C and n-butyl iodide is 131 °C. Branch chain molecules have lower boiling point because they are spherical, lower surface area and easy to separate. For instance, t-butyl has lower boiling point of 73 °C.

3.53 Synthesis

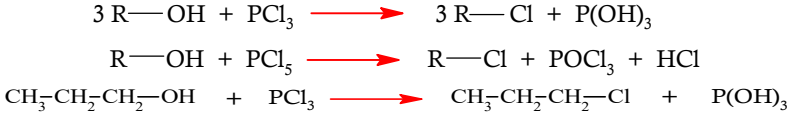
1. Reaction of HX with Alcohols

Hydroxyl group of alcohols is poor leaving group. We will study it later how poor leaving group like OH can be transformed into good leaving group. When alcohols are treated with hydrohalic acid, hydroxyl group get protonated that enables alcohols to react with halide nucleophile. The reaction is nucleophilic displacement S_N2 in nature.

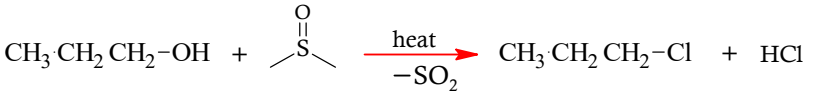


2. Thionyl Chloride and Phosphorus Trihalide

Reacting alcohols with thionyl chloride ($SOCl_2$) or phosphorous trihalide (PX_3) gives alkyl halides. Different PXs can be used to make RXs with alcohols.

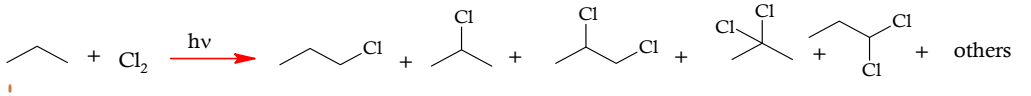


Thionyl chloride is best reagent for making alcohols.



3. Free Radical Halogenation

This reaction has addressed in alkane section. This is not common method for synthesis of alkyl halides as the reaction is not selective which give rises to different by-products.



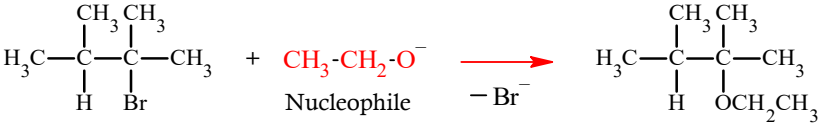
3.54 Reactions

Alkyl halides are reactive on account of its polar C-X bond which makes the carbon electrophilic in character. In the ensuing text, we will focus two common reactions of alkyl halides, the substitution and elimination reactions.

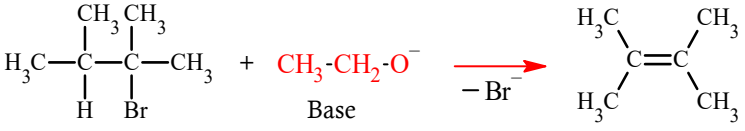
1. Substitution Reactions

Substitution means replacement of one atom or group with another atom or group. For instance, we have seen the replacement OH group from alcohol with halide atom in previous reaction for synthesis of alkyl halide. This is an example of substitution. The

group which leaves is leaving group (LG). The group which comes is known as nucleophile (Nu). Organic reactions involving substitution are termed as substitution reactions. Generally, we encounter two important ionic substitution reactions: the S_N1 and S_N2. We use ionic here because reactions involving the formation of ions are termed as ionic reaction unlike free radical or pericyclic reactions which don't operate through the formation of ions.

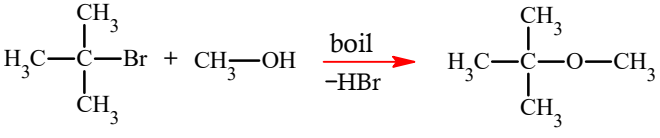


Most common elimination reactions operating by unimolecular and bimolecular mechanism such as E1 and E2 involve base instead of nucleophile for giving alkenes.

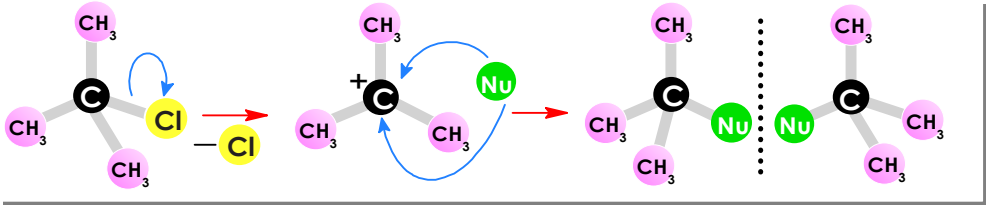


S_N1 Reaction

S stands for 'substitution', N for 'nucleophilic' and 1 for 'unimolecular' or simply acronymed as S_N1. Mostly, alkyl halide (substrate) of tertiary nature where there is possibility for stable carbocation formation works by S_N1 reaction. Besides, benzylic and allylic halides also demonstrate S_N1 reaction since they yield resonance stabilized carbocation.



The following illustration depicts a tertiary butyl chloride which ionizes to a carbocation in S_N1 reaction. The carbocation can be attacked by nucleophile either from above or below the plan yielding R and S isomers in a racemic mixture.

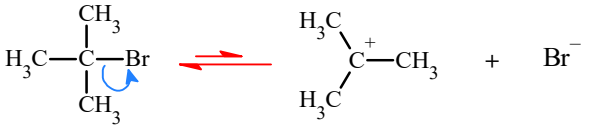


The rate of S_N1 reaction relies on stability of carbocation. As the first step involve only one molecule, we call the reaction unimolecular.

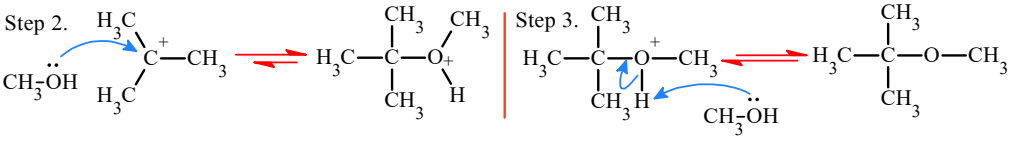
$$S_N1 \text{ rate} = k_r [(CH_3)_3C\text{-Br}]$$

Mechanism

The first step is slow ionization of substrate which gives carbocation that is prone to rearrangement for stabilizing itself. This first step is slow and rate determining. It is highly endothermic with large activation energy.



Second step is fast. The carbocation is attacked by nucleophile either from above or below yielding two different compounds, usually known as enantiomers. There is equal possibility for nucleophile either to attack from above or below the plan. This situation leads to formation of racemic mixture which is equimolar mixture of two enantiomers.



In third step, deprotonation gives neutral product. Consider the following reaction as an example of S_N1 reaction.

Factors Influencing S_N1 Reaction

1. Substrate

We need tertiary substrate for S_N1 because it gives stable tertiary carbocation. The rate of carbocation stability falls in the order of: tertiary > secondary > primary. The substrate can't be only tertiary alkyl halides but any compound having carbocation stabilizing facility could act substrate for S_N1 reaction such as allyl halides.

2. Solvent

Ionization of substrate is rate determining step of S_N1 reaction. Solvent is needed to ionize substrate. A polar solvent aids swift Ionization. The polarity of solvent plays crucial role in enhancing the rate of S_N1 reaction. Solvent can be protic or aprotic. Protic solvent contains potential for hydrogen bonding by possessing groups such as O—H or N—H as in water, alcohols and amine. Protic solvents are better choices for S_N1 reaction because not only they ionize but also stabilize intermediate carbocation.

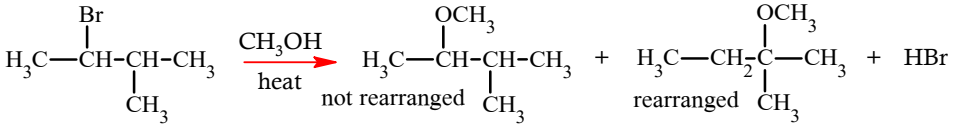
3. Leaving Group

Rate determining step of S_N1 reaction depends whether leaving group leaves with ease or not. A good leaving group should leave easily and it should behave as weak base once it leaves. For instance iodine is good leaving group than chlorine because iodide ion

acts as weak base as compared to chloride. Leaving group should be polarizable as well. A polar leaving group better able to stabilize intermediate carbocation through interaction.

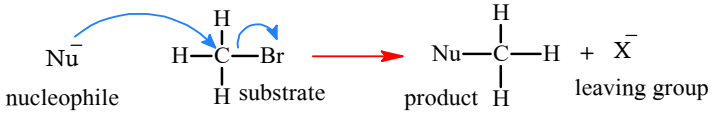
4. Stereochemistry and Rearrangement

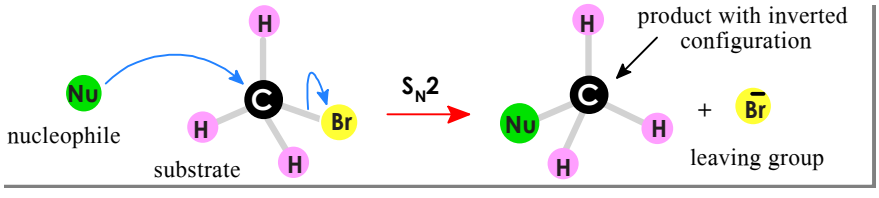
Stereochemically, we get racemic mixture for S_N1 reaction. A reaction is said to be stereospecific if it gives exclusively one product. S_N1 isn't stereospecific reaction. Starting with S enantiomer gives S and R enantiomers as product in equal proportion because nucleophile has equal probability of attacking planar carbocation either from above or below the plan. The proportion isn't exactly 50:50 because the side where leaving group leaves still masked by the leaving group as now it is interaction with the carbocation. It is difficult for nucleophile to reach carbocation from this side. Consequently, inversion product acquire dominant ratio as compared to retention one. The carbocation is prone to rearrangement if there is any possibility to gain stability.



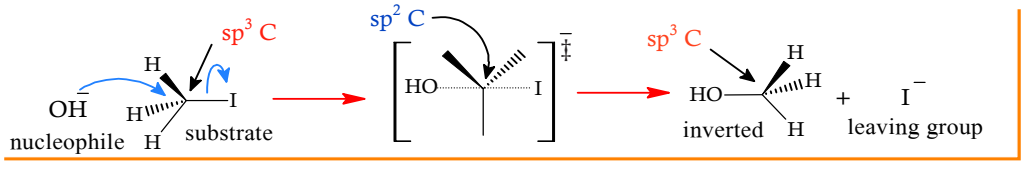
S_N2 Reaction

Unlike S_N1, substitution nucleophile bimolecular S_N2 occurs in single step which involves backside of attack of nucleophile on less hindered carbon atom of substrate, expelling leaving group and giving product with inverted stereochemistry. For instance, if we start with R enantiomer in substrate, we get product with S enantiomer.





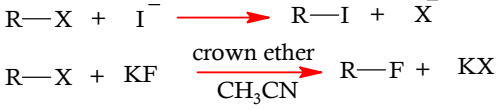
S_N2 reaction is stereospecific because it gives only one enantiomers. S_N2 is concerted reaction because both nucleophile and leaving group simultaneously approach and leaves carbon atom.

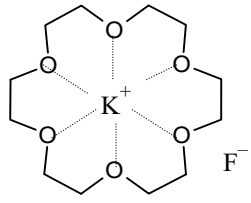


Transition state acquires temporary pentavalent situation. The positive charge carbon is known as carbonium ion unlike carbocation where carbon bearing three bond with positive charge.

Halogen Exchange Reaction

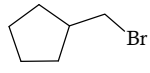
Alkyl fluorides and iodides could be synthesized via S_N2 reaction in a halogen exchange reaction which is useful method for the synthesis. Iodide is good nucleophile. Many alkyl chlorides are transformed into iodide substitutes by reacting with sodium iodide. Alkyl fluorides are difficult to make directly. They are obtained by treating alkyl chlorides or bromides with KF in crown ether, the aprotic solvent which enhances nucleophilicity of fluoride by solvating KF.



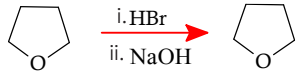


18 – Crown – 6

Problem 3.51 Write expected S_N1 and S_N2 products for the following molecule.



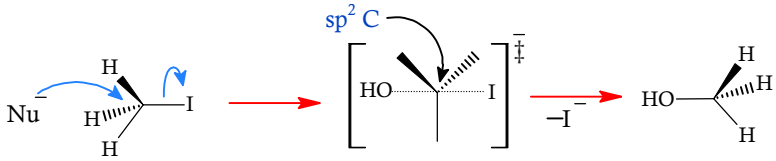
Problem 3.52 Write mechanism for the following transformation.

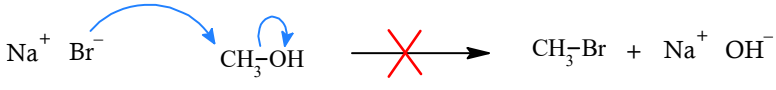


Factors Influencing S_N2 Reaction

1. Substrate

A good substrate for S_N2 is one which is less hindered and carrying good leaving group. The leaving group must be electronegative enough to make carbon electrophilic so that nucleophile could easily approach for expelling leaving group.





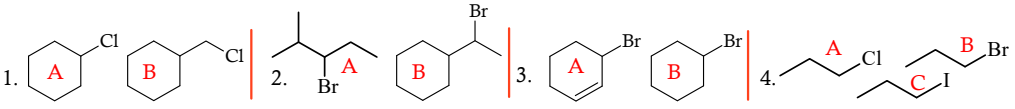
Ions that are strong bases and poor leaving groups:

$$OH^- \qquad O^-\text{—}R \qquad NH_2^-$$

Relative rates for S_N2: CH_3X > 1° > 2° >> 3°

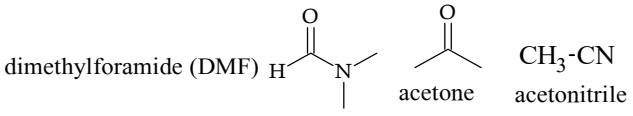
Problem 3.53 Treatment of 4-chloro-1-butanol with NaOH in DMF solvent leads to rapid formation of a compound with the molecular formula C_4H_8O. Propose a structure for this product and suggest a mechanism for its formation.

Problem 3.54 Point out better substrate for S_N2 reaction in each pair given below:

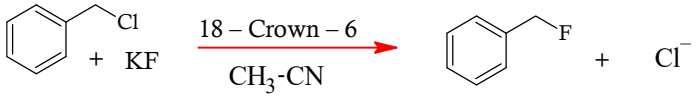


2. Solvent

Protic solvents are good choices for substitution reactions. They are better able to stabilize smaller ions via solvation which is interaction established by hydrogen bonding. For instance, fluoride is poor nucleophile in protic solvent but good one aprotic. Potassium fluoride does solvate well in DMF, crown ether work wonder by solvating potassium while leaving fluoride as free nucleophile.



Generally, less polar solvents are required for S_N2 reaction because they solvate nucleophile. Once nucleophile is solvated, it makes nucleophilic attack difficult because the nucleophile carrying bunch of solvent counter ions. We can say that protic solvent reduces nucleophilicity of anions (nucleophile). Contrary, aprotic solvents such as dimethyl foramide (DMF), acetone and acetonitrile enhance the nucleophilicity.



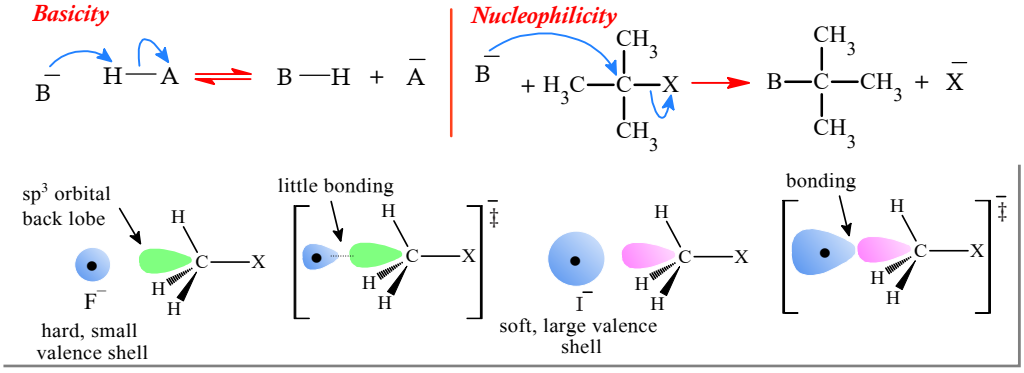
Problem 3.55 Fluoride ion is good nucleophile in aprotic solvent such as DMSO and in gas phase but poor in water. Explain

3. Nucleophile

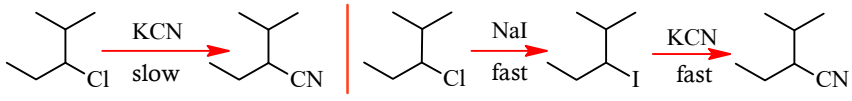
A nucleophile is neutral or negative charge species. Negative charge nucleophiles are generally stronger than neutral ones. For S_N2 reaction, there is need of strong nucleophile. For instance, methoxide anion reacts one million times faster than methanol.

strong nucleophile	moderate nucleophile	weak nucleophiles
$(CH_3CH_2)_2P:$	Br^-	F^-
HS^-	NH_3	H_2O
I^-	CH_3-S-CH_3	CH_3-OH
$(CH_3CH_2)_2\ddot{N}H$	Cl^-	
$-CN$	$CH_3\overset{O}{\overset{\|}{C}}-O^-$	
$(CH_3CH_2)_2N:$		
HO^-		
CH_3-O^-		

Similarly, iodide ion is better nucleophile than fluoride because iodide is larger in size and its negative charge can be easily polarized as it locates away from the influence of nucleus, therefore better able to interact with carbon bearing leaving group. Steric hindrance plays pivotal role in determining the strength of nucleophile. For instance, t-butoxide is weak nucleophile than ethoxide because the bulk of butoxide prevents the nucleophile from access to electrophilic carbon. Undoubtedly, butaoxide is stronger base than ethoxide yet basicity is equilibrium phenomenon which reflects likelihood for abstraction of proton unlike nucleophilicity which reflects tendency for making bond with carbon atom.



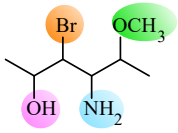
Problem 3.56 State why one case exhibits slow rate of reaction where the other exhibits fast?



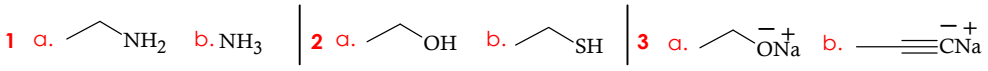
Role of Nucleophile

- Rate of hydrolysis of t-BuBr is not influenced by changing nucleophile from water to hydroxide anion.
- Rate of hydrolysis of methyl bromide increase by 5000 times by changing nucleophile from water to hydroxide anion.
- NH_3 is better nucleophile than water. Iodide is better nucleophile among halides. Alkoxide is weaker nucleophile than sulfide.
- Methoxide is better nucleophile than t-butoxide

Problem 3.57 Rank the following groups in accordance with increasing strength of nucleophile by assigning brief reasoning to your assessment.

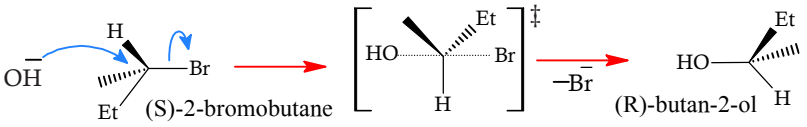


Problem 3.58 Point out better nucleophile



4. Stereochemistry

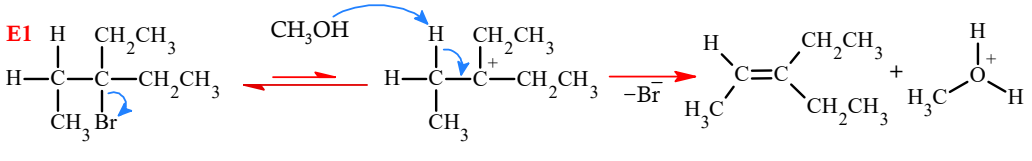
S_N2 reaction is stereospecific. Nucleophile attacks from the backside which leads to inversion of configuration because both leaving group and attacking nucleophile are opposite to each other.

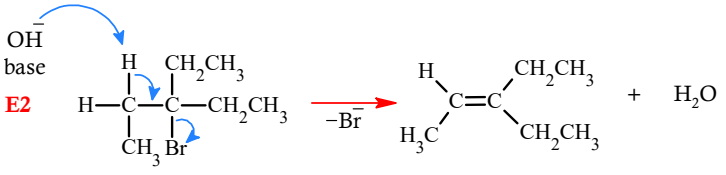


Problem 3.59 A student wanted to synthesize methyl t-butyl ether. He attempted the synthesis by adding sodium methoxide to t-butyl chloride, but he obtained none of the desired product. Show what product is formed in this reaction and give a better synthesis for methyl t-butyl ether.

2. Elimination Reactions

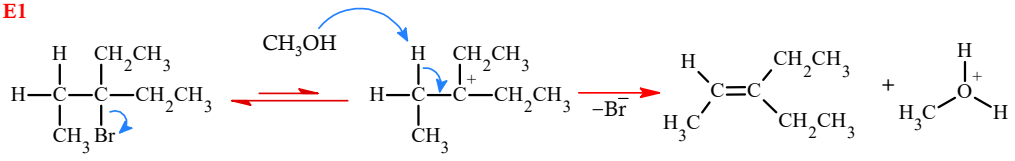
An elimination reaction involves loss of two atoms from adjacent carbon atoms. For instance, loss of hydrogen and halide atoms from two adjacent carbon gives alkenes. This reaction is known as dehydrohalogenation. Elimination reactions have different types. Most common examples proceed by E1 and E2 mechanism. Other types include: alpha elimination, E1cB reaction and pyrolytic elimination reaction.





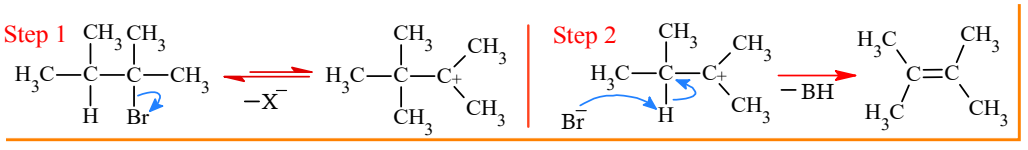
E1 Reaction

Much like S_N1, E1, unimolecular elimination reaction works by ionization of substrate that leads to formation of carbocation. Both reactions share similar first step. The carbocation is prone to rearrangement. In second step, a base comes and abstract proton adjacent to carbocation. This step gives the formation of alkene according to Zaitsev rule which predict the formation of most substituted alkene. Generally, highly substituted alkenes are more stable than lower analogues due to hyperconjugation.



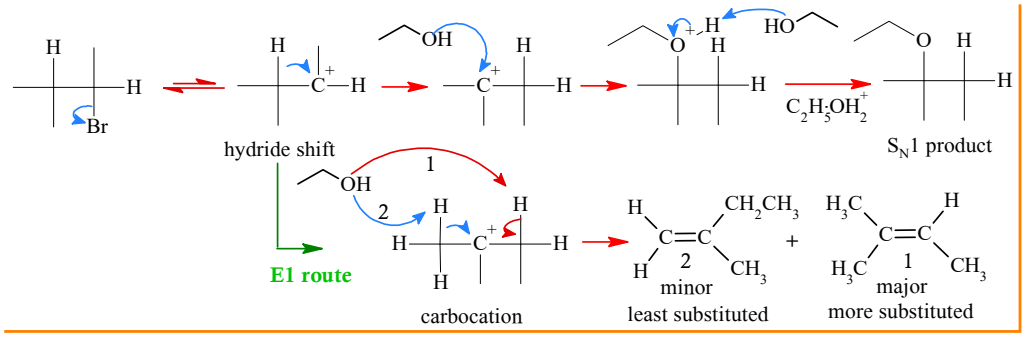
Mechanism

First step proceeds via unimolecular ionization to give a carbocation (rate-limiting) which is deprotonated by weak base (solvent) to give alkene in the second step. The second step is fast. Rate for E1 mechanism is dependent on concentration of substrate alone.



Mechanism: *Rearrangement in Elimination*

First step involves ionization of substrate to carbocation. This is slow step and common for both S_N1 and E1 mechanisms. In second step, a hydride shift forms a more stable carbocation. This is fast step that takes place in both mechanisms.



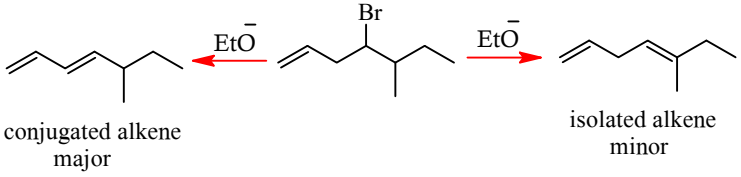
Third step is different for both mechanisms. In S_N1, solvent attack carbocation, where in E1, solvent (base) abstracts protons to give most substituted alkene. ***Zaitsev's Rule (Saytzeff)*** states that in an elimination reactions, most substituted alkene predominates.

$R_2C{=}CR_2$ > $R_2C{=}CHR$ > $RHC{=}CHR$ & $R_2C{=}CH_2$ > $RHC{=}CH_2$

tetrasubstituted trisubstituted disubstituted monsubstituted

Violation of Zaitsev Rule

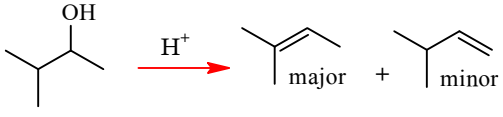
Zaitsev's rule predict the formation of most substituted alkenes in elimination reaction however the rule gets violated when there is chance for formation of conjugated alkenes, presence of bulky base, substrate is quaternary ammonium, sulfonium or phosphonium salts or reaction driven under the influence of Bredt's rule.

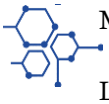


In bicyclic system, double bond resists to form at bridgehead carbon due to restricted and strained conformation of emerging double bond. Latest research (see section 3.23-8) denounces the applicability of Bredt's rule because new molecules have been synthesized molecules with strained double bond at bridgehead carbon of the bicyclic system.

E1 Reaction is Regioselective

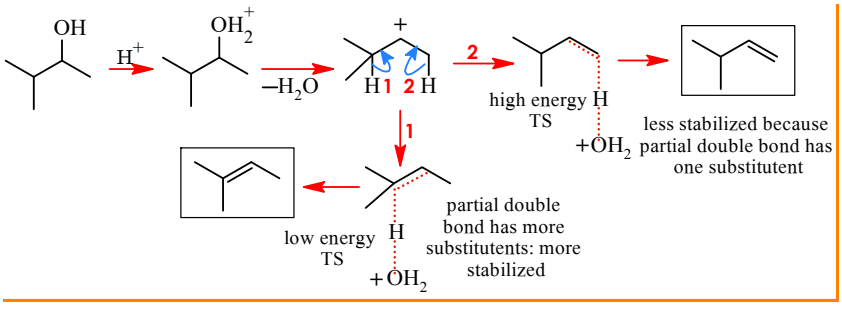
Zaitsev rule predict the formation of substituted alkenes. For E1 reaction, there is possibility we get two or more products yet the one which is most stable predominates with highly substituted double bond. We can say, E1 is regioselective since it gives most substituted alkene. A substituted double bond is stable due to hyperconjugation. More specifically, it is not the stability of double itself which determines the formation of substituted alkenes but the stability of transition state actually ascertain which product to form.





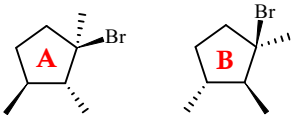
Mechanism

Let's try to explain the formation of most substituted alkene with the help of a mechanism which involves two different transition states and their relative stability. The carbocation formed has two protons, either can be taken by base to give one or the other product.



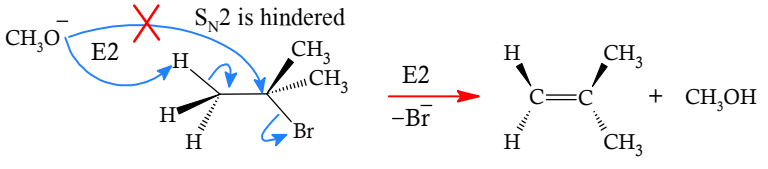
The stability of double bond doesn't tell about why it forms faster. To answer, we need to look at transition state (TS). Only a stable TS will give dominant alkene. A TS which has mono-substituted partial double bond is less stable than the one which has di or tri substituted partial double bond. Less stable means high in energy on reaction profile diagram. Major product for the above reaction has stable transition state since it involves tri substituted partial double bond.

Problem 3.510 State which of the following isomer gives less and which isomer gives more substituted alkenes. Assign reason.

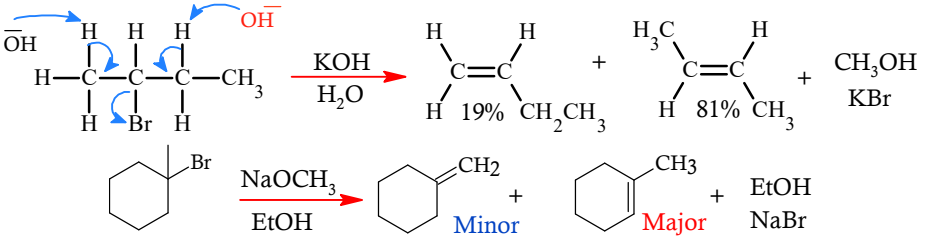


E2 Reaction

Bimolecular elimination reaction or E2 is single step concerted mechanism which require strong base to yield alkene. E2 is S_N2 except base abstracts proton instead of nucleophile attacking carbon as in S_N2. Furthermore, there is no requirement of less hindered substrate for E2 because base approaches less hindered proton instead of hindered carbon atom bearing leaving group. E2 requires tertiary substrate unlike primary for S_N2. The order of E2 reaction: 3° > 2° > 1°. Tertiary alkyl halides are preferred because they yield most substituted alkenes.



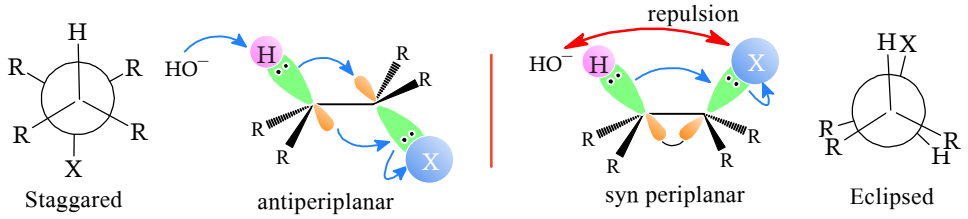
E2 is second order reaction. Concentration of both base and nucleophile matters for affecting the rate of reaction. We get mixture of products in E2 reaction.



Stereochemistry

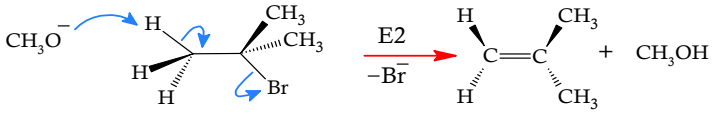
E2 requires anti-periplanar geometry. Both proton and leaving group need to be at 180° for better orbital overlap. When base abstracts proton, the bonding orbital of C—H bond interacts with anti-bonding orbital of C—X bond. This interaction is feasible only when both groups are anti-periplanar. In case of syn periplanar, rate of reaction is greatly declined because smooth overlap of orbital fails to take place. Moreover, approaching base

from the same side of leaving group creates repulsion which decline rate of reaction. Sterically, the molecules with both leaving group and proton on the same side doesn't facilitate E2 reaction to take place.

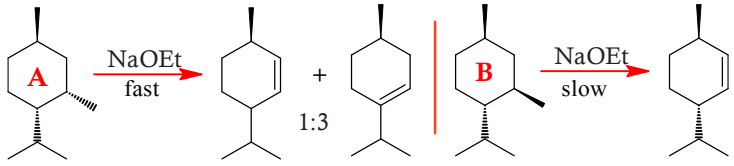


Mechanism

E2 is single step concerted reaction which involves simultaneous abstraction of β proton and removal of halogen atom.



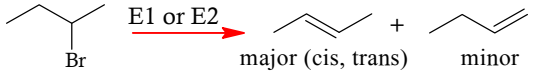
Problem 3.511 Two diasteromers of menthol derivative, A and B, give two different products in an elimination reaction. A gives two products in a very fast reaction, B only one in a slow reaction (250 times slower). Reason the differences!



Problem 3.512 Predict stereochemical products for the following two reactions

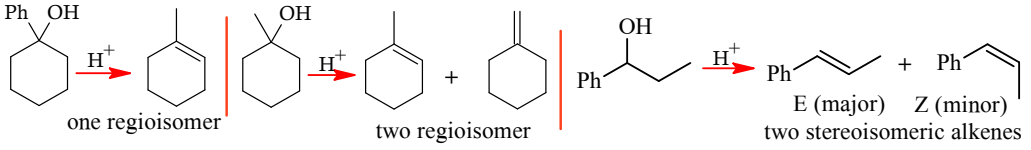
Stereoselectivity, Regioselectivity and Stereospecificity

In most E1 and E2 eliminations with two or more possible products, the product with the most substituted double bond (the most stable product) predominates. This principle is called Zaitsev's rule, and the most highly substituted product is called the Zaitsev product.



There is some stereoselectivity in E1, yet the stereoselectivity is E2 is high since it demands stringent condition of anti-periplanar geometry for transition state. It is important to note that stereoselective reaction gives one predominant product either due to lower

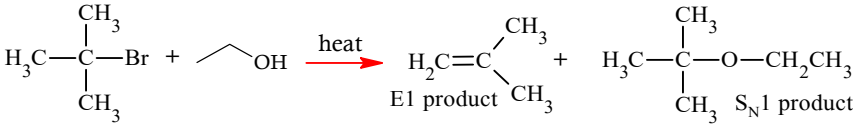
activation energy in transition state (kinetic control) or more stable product formation (thermodynamic control). In stereoselective reaction, the mechanistic pathways has a choice. In stereospecific reaction, only one product is formed due to mechanism of reaction and stereochemistry of starting material. Stereospecific reaction doesn't involve any choice. E2 is stereospecific since it gives different stereoisomers of product for different stereoisomers of reactants. Consider the following examples:



Problem 3.513 Write expected elimination products for A and B along with stereochemistry of emerging alkene.

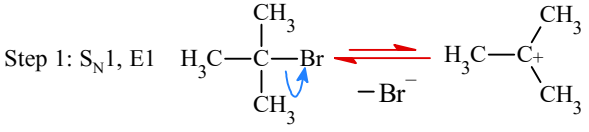
3.55 Analysis of Substition & Elimination Reactions

Both S_N1 and E1 are in competition. Consequently, a mixture of substitution and elimination products form. Consider the following reaction which yields S_N1 and E1 products.

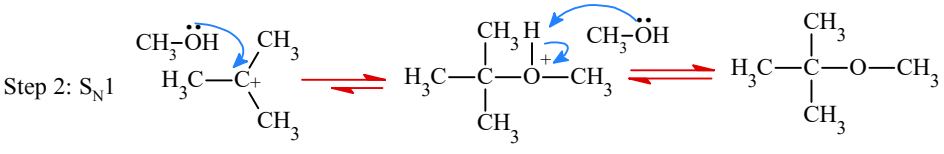


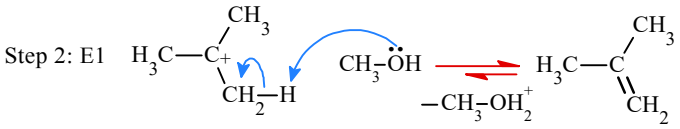
Mechanism

First step for both S_N1 and E1 is same i.e. ionization of substrate to carbocation.



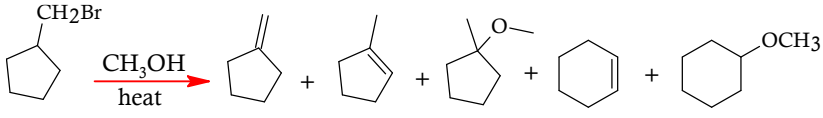
Second step is different for both reactions. In S_N2, nucleophile attacks carbocation giving a substituted product. In E1, base abstracts β proton yielding substituted alkene.





In step 2, the role of solvent decides whether a substitution or elimination reaction to take place. If solvent acts as nucleophile as methanol in above case, substitution product will dominate. If the solvent acts as base, elimination product will dominate. In above case, methanol acts as both nucleophile and base, yielding mixture of substitution and elimination products.

Problem 3.514 Solvolysis of bromomethylcyclopentane in methanol gives a complex product mixture of the following five compounds. Propose mechanisms to account for these products.



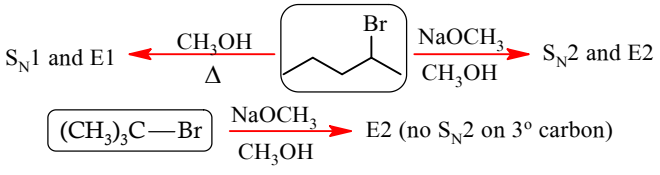
3.56 Rules for Predicting Product

How to decide which type of reaction it is, substitution, elimination or both?

Students often feel overwhelmed to build a strong grip over substitution and elimination reactions because in theory there are too many factors that puzzle them. For instance, nucleophile can be base and base a nucleophile; a solvent can be a nucleophile or ionizing agent. We don't need to memorize everything about such reactions yet there is need to learn some basic facts that could truly build our confidence to solve the problems of such reactions. Remember, such reactions don't involve the formation of single product. Be cautious about minor or major one with relevant stereochemistry. Following rules help us to decide the outcomes of substitution or elimination reactions.

1. Order of reaction is determined by strength of base or nucleophile

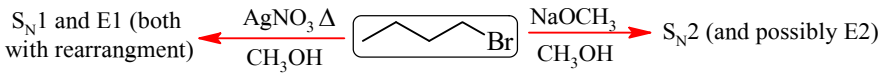
S_N2 or E2 are favored by strong nucleophile or base respectively. A tertiary substrate favors E2 over S_N2. S_N1 or E1 doesn't require strong base or nucleophile. Both are influenced by nature of solvent. Addition of silver salt helps some difficult ionization.



2. Primary halides usually go by S_N2 and occasionally by E2 reactions

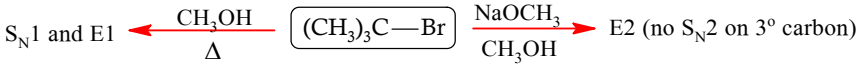
Besides benzylic and allylic halides where carbocation is resonance stabilized, primary substrate rarely observe first order kinetics of S_N1 or E1. Strong nucleophile give

S_N2 with primary substrate. A strong base gives E2 which occurs rarely with primary substrate. High temperature or use of silver salt enable primary substrate to go by first order substitution or elimination which involve rearrangement of carbocation to stable one. Under such circumstances, rearranged S_N1 and E1 products are observed.



3. With strong base, 3° RX go by E2 where with weak base, mixture of S_N1 and E1 products

E2 is observed by tertiary substrate with strong base. In absence of strong base, a mixture of S_N1 and E1 products are observed.

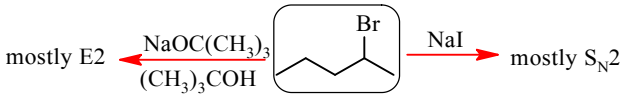


4. Reactions of 2° halides are most difficult to predict

Secondary substrate is difficult to predict whether it undergoes first or second order kinetics. A strong base can give either S_N2 or E2, a weak one coupled with good ionizing solvent give either S_N1 or the E1 reactions. Mixture of products is common.

5. Some nucleophiles and bases favor substitution or elimination

A strong base promote elimination whereas a strong nucleophile gives substitution. Bulky base promotes elimination. Higher temperature also favors elimination. A good nucleophile required for favoring substitution over elimination is one which is conjugate base of a strong acid such as bromide and iodide.



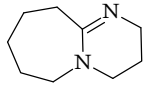
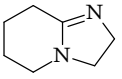
A more simplified format for predicting nature of reaction could be ascertained from the following table. Note that SB stands for strong base, WN for weak nucleophile, WB for weak base and SN for strong nucleophile etc.

RX	SB/WN	SB/SN	WB/SN	WB/WN
1°	E2	E2 S_N2	S_N2	
2°	E2	E2 S_N2	S_N2	
3°	E2	E2	S_N1	S_N1 E1

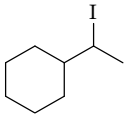
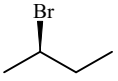
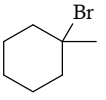
The following table has listed some bases and nucleophiles so that students could find it easy while assessing the nature of base or nucleophile in deciding substitution or elimination reaction. DBU [1,8-diazobicyclo(5.4.0)undec-7-ene] and DBN [1,5-

diazobicyclo(4.3.0)non-5-ene] are strong and bulky bases which favor E2 exclusives for all three categories of alkyl halides.

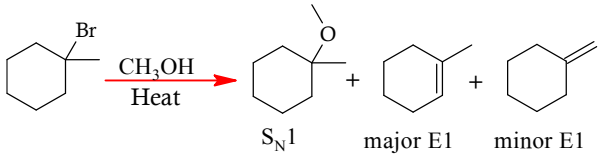
SB/WN	SB/SN	WB/SN	WB/WN
NaH DBN DBU	OH^- MeO^- EtO^-	I^- Cl^- Br^- RS^- HS RSH	H_2O MeOH EtOH

DBU  DBN 

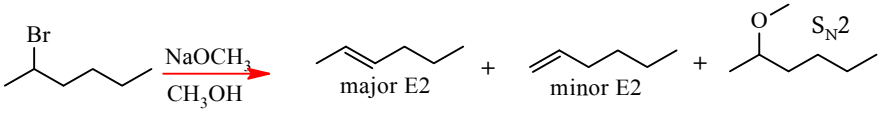
Problem 3.515 Predict major products and reason your assessment.

a.  t-BuOK, H_2O ? b.  NaSH ? c.  H_2O, Heat ?

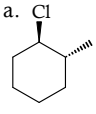
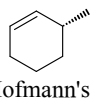
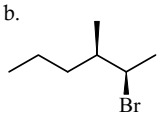
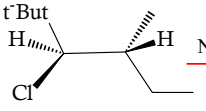
The above table means that for weak nucleophile or weak base such as water, methanol or ethanol, only tertiary alkyl halides react which give mixture of S_N1 and E1 products. For instance, treating 1-bromo-1-methylcyclohexane with methanol yields mixture of substitution and elimination products.



Sodium ethoxide is strong base and strong nucleophile. It can cause both S_N2 and E2 reaction with secondary substrate. E2 gives least (minor) and most substituted alkene (major). Similarly, we get trans alkene (stable) as major product and cis alkene (less stable) as minor product. The following reaction gives trans alkene as the major product. With secondary substrate, minor proportion of S_N2 product is obtained since the reaction doesn't work well with hindered substrate.



Problem 3.516 Predict all possible products for the following reactions. Consider the stereochemistry of the products. Sketch cis or trans product in case of elimination reaction? Also point out major and minor product.

a.  NaOMe, H_2O  Hofmann's b.  NaOH ? c.  NaOH ?

Problem 3.517 Why Hoffman's product is least substituted whereas Saytzeff product is more substituted? Why substituted alkene are stable than less substituted ones.

3.66 Exercise

1. Explain briefly.

a. Thioesters are more reactive than esters.
b. Comment on comparison of alpha and E1cB elimination reactions.
c. Isopropyl ether can be made by two methods. Which method is better?
d. Benzylic & allylic halides undergo S_N2 reaction but vinylic and aryl halides don't?
e. Arrange nucleophiles such as CH_3OH, F^-, NH_3, CH_3COO^-, Cl^- etc. in increasing order of their nucleophilicity.

2. Show with the help of mechanism, what would be the products A and B?

3. Point out nucleophile and electrophile in the following examples:

CH_3OH NH_3 $\bar{C}N$ Ph_3P $C\bar{l}$ $H\bar{S}$ $CH_3C\bar{O}O$ H_2O $\bar{B}r$

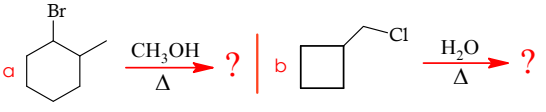
4. Point out the nature of the following molecules as strong/weak base/nucleophile.

NaOMe, H_2O, NaS, DBU, EtOH, RSH, DBN, NaOH, H_2S

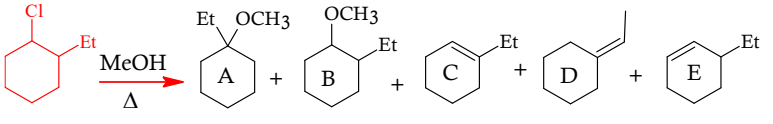
5. Complete the following reactions:

a. $HC \equiv C^{-}{}^{+}Na + CH_3CH_2CH_2CH_2Cl \longrightarrow$
b. $(CH_3)_2CHCH_2Br$ + excess $NH_3 \longrightarrow$
c. $CH_3CH_2CH_2I + NaCN \longrightarrow$
d. 1-chloropentane + NaI $\longrightarrow$
e. 1-chloropentane + KF $\longrightarrow$

6. Draw two substitution products for each of the following two reactions and point out stable one in each case. State why one of the product is more stable than the other?



7. The following reaction gives different products. Show each of these product has formed via relevant reaction mechanism.



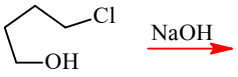
8. A 6th semester student X of session 2021-25 attempts a reaction of potassium cyanide with a substrate containing good leaving group. X performs the reaction in methanol. It took long for X to complete the reaction although X tried to change the substrate from tertiary to primary for effecting swift reaction. Suggest X how can the reaction rate be improved. Also state why X failed to execute smooth reaction.

9. Reason each statement as true or false! Explain your justification.

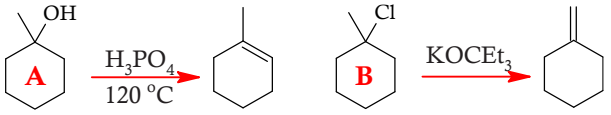
a. In S_N1, usually retention has greater proportion than inversion in the product.
b. DMF is an example of protic solvent.
c. A charge nucleophile gives neutral product in S_N2 reaction.
d. Strong base and crowded substrate favor substitution over elimination.
e. Rise in temperature favors substitution over elimination.
f. Rate determining step is fastest step of a reaction.
g. Nucleophilicity increases from left to right in period, decreases down the group.

10. Account for the following two reactions in which substrate of same functional group reacts under same reaction conditions giving two different products.

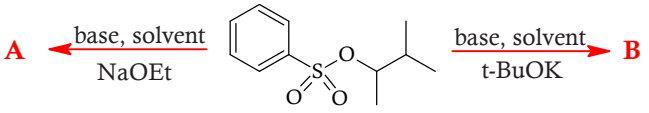
11. Write down product through a mechanism and state the type of reaction with reference to the role of nucleophile, leaving group and solvent?



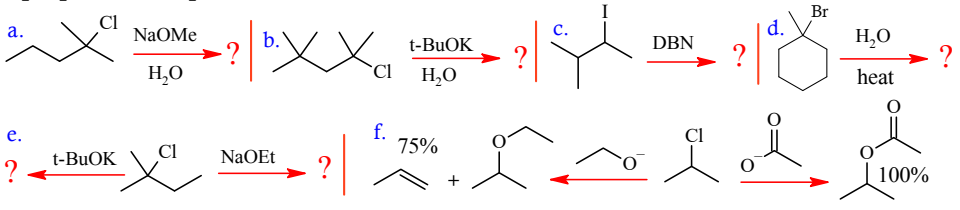
12. Molecule A gives substituted alkene but B yields less substituted one. Viewing reaction conditions, reason your assessment.



13. Predict A and B in the following reaction

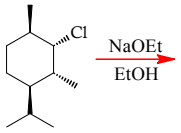


14. Predict the major product from a – d by assigning relevant reasons, explain e briefly by predicting all major and minor products and attribute plausible reason for different proportions of products formed in f.

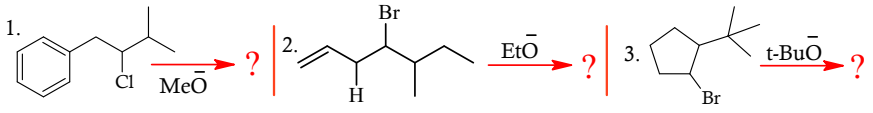


15. Treatment of 4-chloro-1-butanol with NaOH in DMF solvent leads to rapid formation of a compound with the molecular formula C_4H_8O. Propose a structure for this product and suggest a mechanism for its formation.

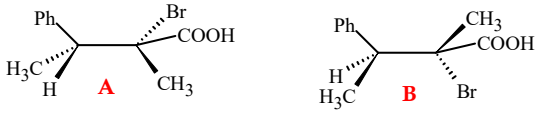
16. Will the following reaction proceed by substitution or elimination? What factors determine the most likely mechanism? Write the expected product and the mechanism by which it forms.



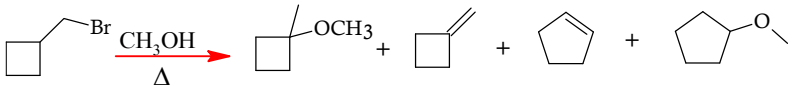
17. Find out major and minor product for the following elimination reactions. Also, state reasons for major and minor product formation.



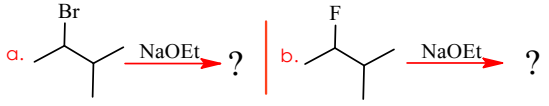
18. Subject the following two molecules to E2 mechanism and point out stereochemistry of consequent geometrical isomers. Show bond rotation on your answer sheet.



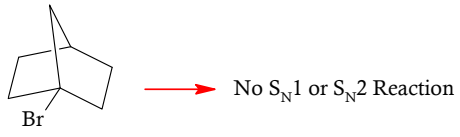
19. When the following compound is heated in methanol, several different products are formed. Propose mechanisms to account for the four products shown.



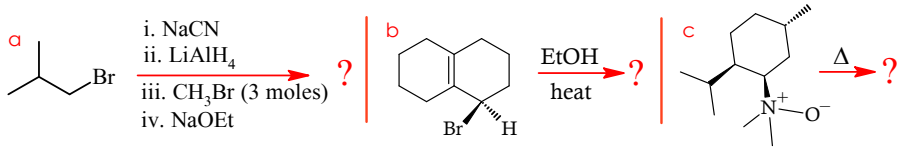
20. State whether the following two elimination reactions give same or different products.



21. When Zaitsev's rule get violated and why the following reaction fails to take place?



22. Complete the following reactions and make cis/trans isomers where needed.

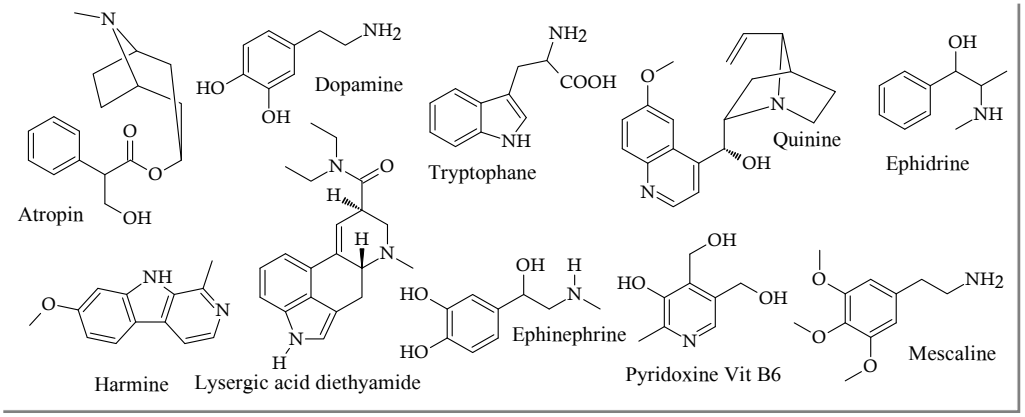


Carbon-Nitrogen Bond
Properties, Synthesis & Reactions

3.6 Amines

3.61 Introduction

Amine are class of organic compounds containing carbon-nitrogen moiety. This is diverse class of compounds which is widely spread in nature. Alkaloids are amine of natural prevalence. Examples such as nicotine, morphine and colchicine are natural amines. Biologically, these compounds serve the paramount role of neurotransmitters, regulators and defensive chemicals.



3.62 Physical Properties

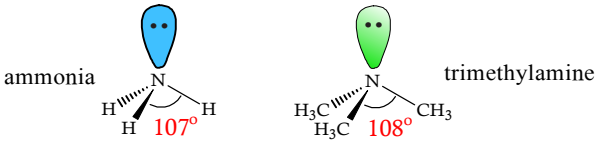
Compound	bp °C
$(CH_3)_3N$:	3
$CH_3—O—CH_2—CH_3$	8
$CH_3—NH—CH_2—CH_3$	37
$CH_3—CH_2—CH_2—NH_2$	48
$CH_3—CH_2—CH_2—OH$	97

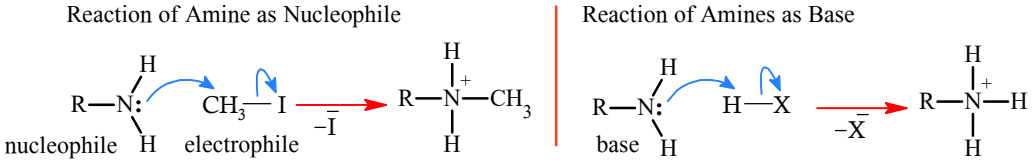
On account of electronegativity of nitrogen, C–N bond is polar whose larger dipole moment makes amines polar molecules. Amines are soluble in water and alcohols due to hydrogen bond formation. Primary and secondary amines participate in hydrogen bonding because they contain N–H bond unlike tertiary amines where no hydrogen bonding is demonstrated due to lack of N–H moiety. However, tertiary amines do form hydrogen bonding with water and alcohols. Amines are less polar than water a d alcohols due higher electronegativity of oxygen than water. These polarity makes amines to boil at lower temperature than water and alcohols.

3.63 Structure & Basicity

Amines are basic due to availability of lone pair of electrons on nitrogen atom. The basicity is further augmented by alkyl group which is electron donating in character. This is how amines are more basic than ammonia. Amines are basic enough to abstract proton from water yielding ammonium and hydroxide ions. Secondary amines are more basic than primary ones. They are even basic than tertiary amines due to steric factor

because in tertiary amines lone pair on nitrogen are camouflaged enough to be adequately solvated by water.

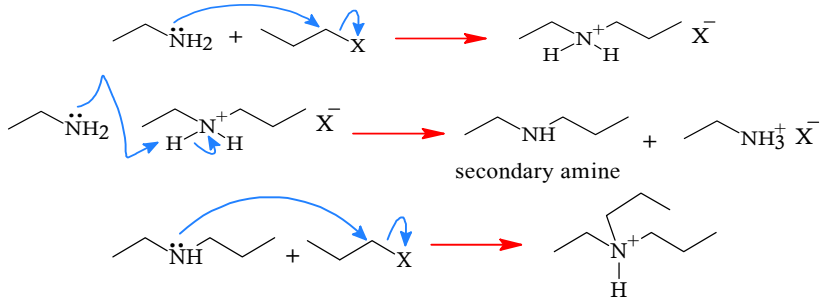




3.64 Synthesis

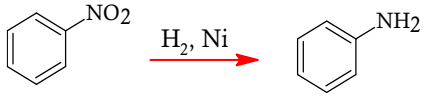
1. Polyalkylation of Ammonia

Amines also serve as nucleophiles. Ammonia is nucleophilic and it reacts with primary and secondary alkyl halides in S_N2 fashion. Reacting with primary alkyl halides, ammonia gives primary amines which are reactive enough to react secondary amines. This reaction has the disadvantage of polyalkylation because we get ammonium salt at the end of reaction.

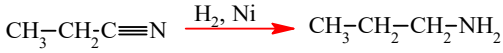


2. Reduction of Nitro Compounds, Nitrile and Amides

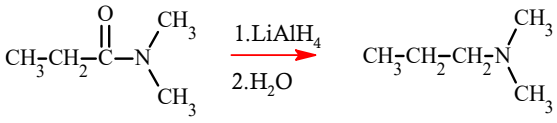
Catalytic hydrogenation reduces both aliphatic and aromatic nitro compounds to corresponding amines. Lithium aluminum hydride (LAH) could be also used for the purpose.



Much like nitro compounds, catalytic hydrogenation also aids in reduction of nitrile to amines.

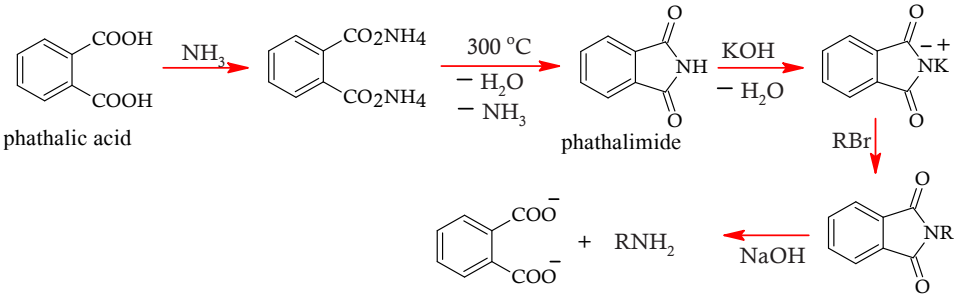


LAH is used in similar fashion like Clemmenson or Wolf Kishner reduction for reducing amides to amines. LAH reduces carbonyl group into methylene one.



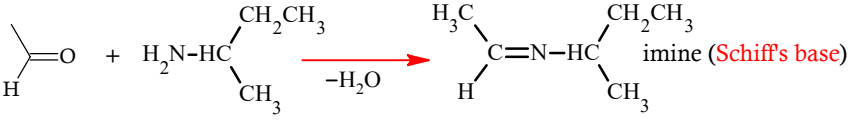
3. Gabriel Synthesis

Gabriel synthesis is protected method for synthesis of primary amines which involves alkylation of protected ammonia. The following sequence of reaction entails the general synthesis of primary amines.

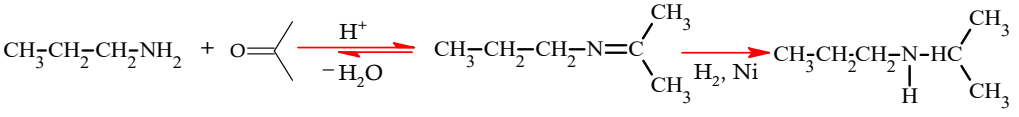


4. Reductive Amination

Amines are nucleophilic. They add to carbonyl group which gives carbinolamine, a compound containing both amine and alcoholic moiety. These compounds are unstable and undergo dehydration yielding imine (basic), a compound containing carbon-nitrogen double bond.

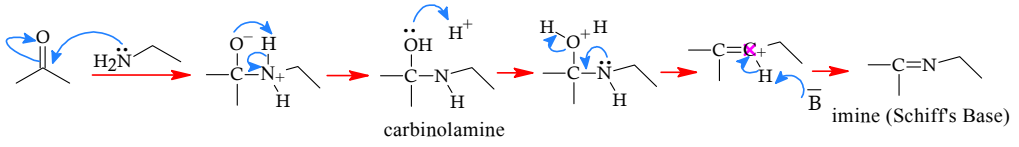


Imines are formed through a condensation reaction. We get N-substituted imine by using primary amine. This compound is known as Schiff Base. Imine is reduced to amine. This is what we call reductive-amination which gives primary, secondary or tertiary amines depending upon the nature of starting material. Imines are nitrogen analogues of aldehydes and ketones.

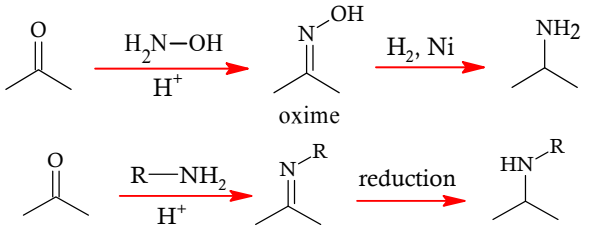


Mechanism

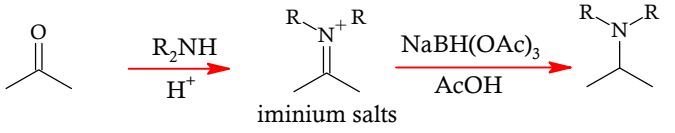
Amines attack carbonyl carbon and give carbinol amine via tetrahedral mechanism. Protonating –OH group of the carbinol amine and subsequent loss of water gives imine or Schiff's base.



When hydroxylamine is added to carbonyl compounds, we get an oxime which is relatively stable as compared to the use of ammonia. Oxime can be reduced to amine using LAH or zinc and HCl combination.

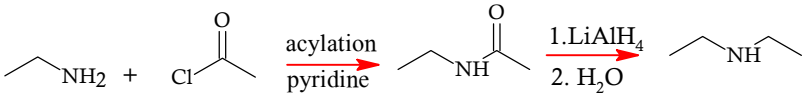


For synthesis of tertiary amines, we condense secondary amines with carbonyl compound. This gives unstable iminium salts which are reduced to tertiary amines.



5. Acylation Reduction

This is another general method for synthesis of primary, secondary and tertiary amines using acid halide. First we get amides, which are reduced to amines using LAH.



3.65 Reactions

Many reactions we studied for synthesis of amines also tell us how amines react. For instance, polyalkylation of amines, reductive-amination, acylation-reduction and reaction with carbonyl compounds reflects the nature of amine reactivity.

1. Salts Formation

Primary amines are stronger bases than ammonia and aromatic amines. They form volatile solid salts with mineral acids or carboxylic acids. These salts are soluble in aqueous medium even if parent amines are insoluble. Salt formation of amines gives characteristic test for detection of amines. Parent amines can be extracted from salts by treating with NaOH. Quaternary ammonium salts don't have proton attaches, they are not affected by base.

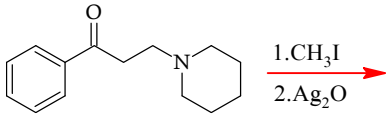
2. Exhaustive Methylation

Polyalkylation of amines is regarded as exhaustive methylation when amine is treated with methyl iodide. In fact, exhaustive methylation served a classical test for

detecting nature of amines. For instance, primary amines take three methyl iodide molecule to give crystalline solids.

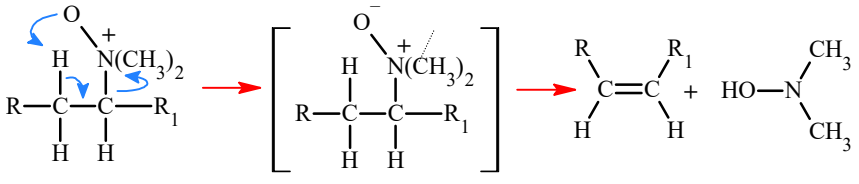
$$R{-}NH_2 + CH_3I \longrightarrow R{-}NH_2^+CH_3I^-$$
$$R{-}NH_2^+CH_3I^- + CH_3I \longrightarrow R{-}NH^+(CH_3)_2I^-$$
$$R{-}NH^+(CH_3)_2I^- + CH_3I \longrightarrow R{-}N^+(CH_3)_3I^-$$

Problem 3.61 Exhaustive methylation was useful method in classical organic synthesis and structural identification for ascertaining the nature of amines. Point out product in the adjoining reaction after subjecting the reactant into exhaustive methylation.

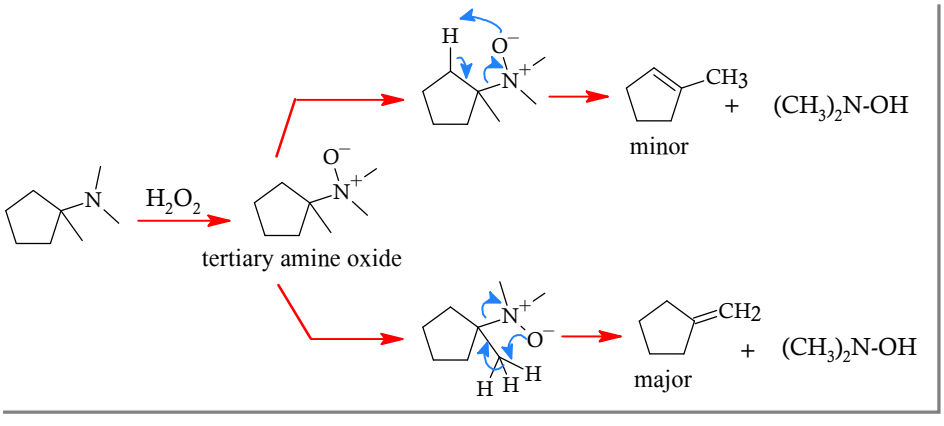


3. Elimination Reaction

Tertiary amines are oxidized to tertiary amine oxide with hydrogen peroxide which can undergo elimination reaction if beta hydrogen is present. Elimination take places upon heating. Such thermal decomposition is termed as Cope elimination. The reaction was developed by Arthur C. Cope of Massachusetts Institute of Technology.

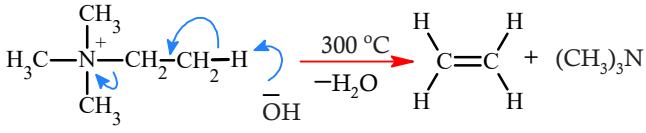


Since both leaving groups leave molecule from the same side, the elimination is termed as syn elimination reaction. The reaction proceeds through single one step (concerted) internal mechanism.



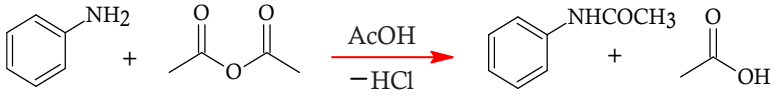
Cope elimination reaction requires milder conditions as compared to Hoffmann elimination reaction which is sort of elimination reaction involving quaternary ammonium salt as substrate. Both type of elimination reactions proceeds by E2 like mechanism. Strong base is required for Hoffmann, however. Cope elimination doesn't require external base.

Hoffmann reaction gives less substituted alkenes (Hoffmann's rule), Cope is governed by Zaitsev's rule which yields more substituted alkenes.



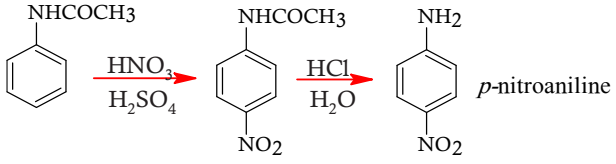
4. Acylation Reaction

Aromatic amines such as aniline can be acylated by treatment with acid chloride or acetic anhydride. Acid chloride is quite reactive and it is difficult to handle in lab, acetic anhydride is usually employed for acylation of amino group. Pyridine is used in the reaction to trap (scavenge) HCl forms during the reaction.



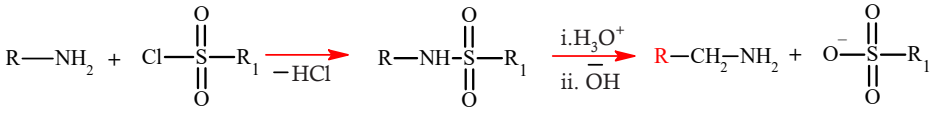
acetanilide

Acetyl group is useful protecting group for amines. For instance, acetanilide could be easily nitrated at para position unlike aniline where acid protonates amino group to generate anilium ion. Its nitration would yield meta isomer since $-NH_3^+$ is electron withdrawing and it directed upcoming electrophile to meta position.



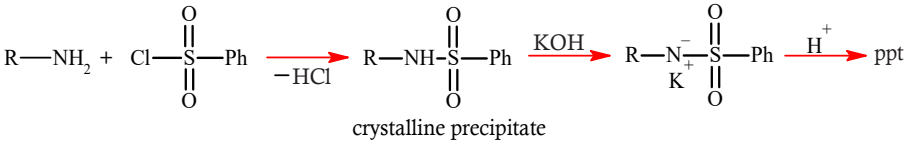
5. Sulfonation

Primary and secondary amines react with sulfenyl chloride (acid chloride of sulfonic acid) to give sulfonic acid and amides (sulfonamide) which serve as sulfa drugs.



sulfonamide

In Hinesburg test, benzyl sulfynyl chloride is used instead for detecting type of amines. The reaction is facilitated in aqueous KOH. We get aromatic sulfonamide which precipitate as crystalline substance which is soluble in KOH. Once the basic solution is acidified, we get the precipitate again.

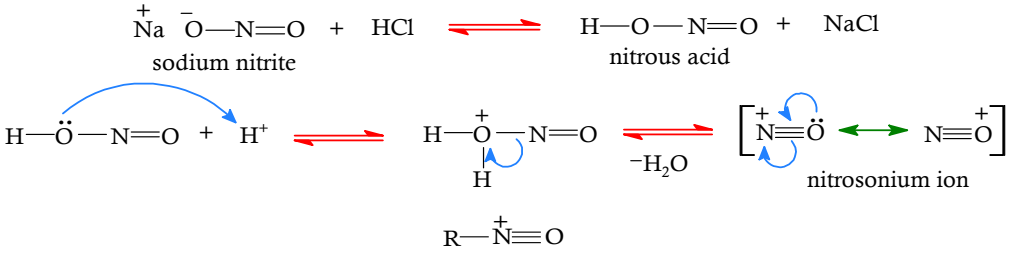


crystalline precipitate

Secondary amines don't give any reaction with KOH since the amine part doesn't have acidic proton. Here, no acidification is required to form precipitate. Tertiary amines don't react with benzyl sulfynyl chloride at all. Acidification of tertiary amines gives clear solution of soluble salts.

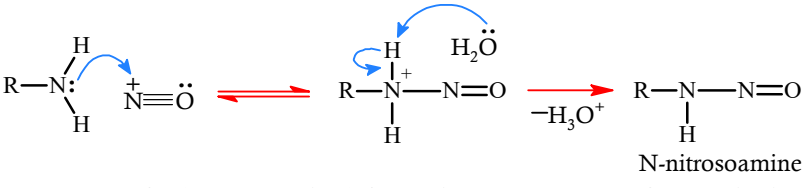
6. Diazonium Salts

Amines could be transformed into variety of functional groups using the significance of diazonium salts which are useful synthetic precursors for making interesting compounds. Most preferably, aromatic amines are employed for diazonium salts due to stability and reliability. An electrophile nitrosonium ion is made by reaction of nitrous acid with HCl. Nitrous acid is weak and it cannot sustain in isolated state but synthesized in situ instead by the reaction of sodium nitrite with HCl. Amines react with nitrosonium ion for yielding diazonium salts which are later transformed into different functional groups using desired chemical conditions. This is what we call diazotization of amines.

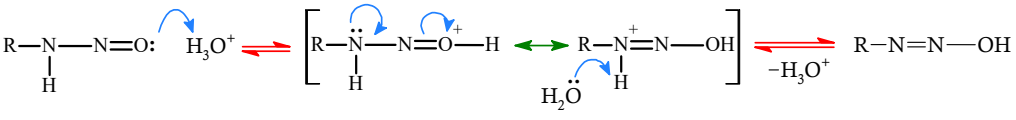


Mechanism

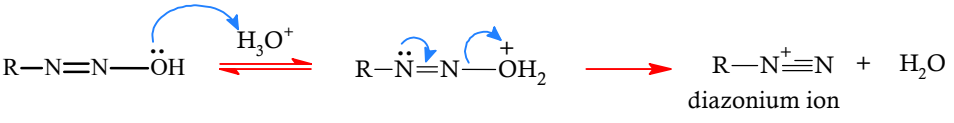
Part 1: Attack on the nitrosonium ion (a strong electrophile), followed by deprotonation, gives an *N*–nitrosoamine.



Part 2: A proton transfer (a tautomerism) from nitrogen to oxygen forms a hydroxyl group and a second bond.



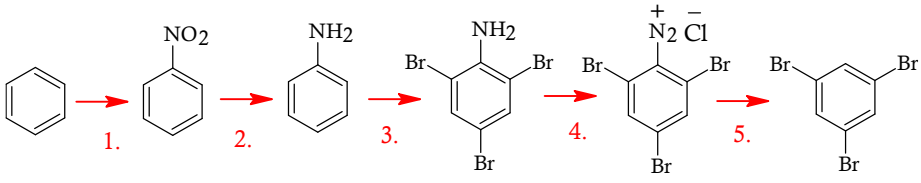
Part 3: Protonation of the OH group, followed by loss of water, gives the diazonium ion.



Alkanediazonium salts are unstable. They decompose to give nitrogen and carbocations.

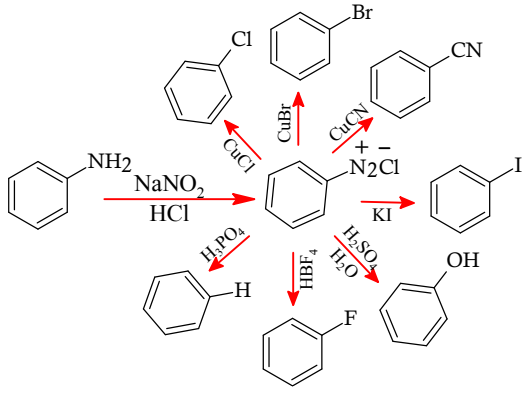
Problem 3.62 Convert aniline into phenol, benzonitrile and bromobenzene.

Problem 3.63 Write down reagent for each step in transforming benzene to 1,3,5-tribromobenzene via diazotization reaction.

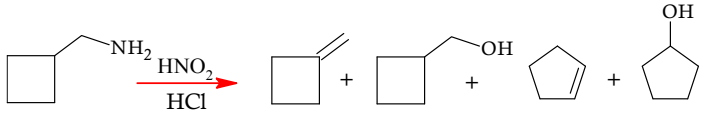


Application of Diazonium Salts

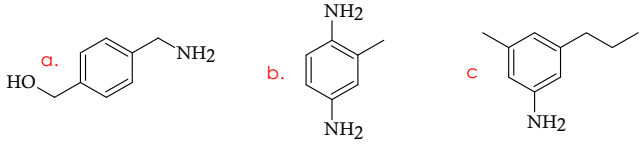
1. Synthesis of phenol
2. Sandmeyer reaction (CuBr, CuCl, CuCN
3. De-amination
4. Synthesis of biaryls (Gamber-Backmann Reaction)
5. Reduction of aryl benzene



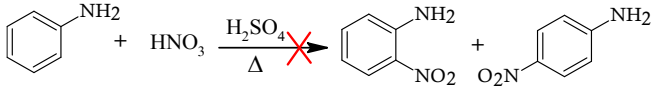
Problem 3.64 Using the application of diazonium salts, make each of the following product through a relevant reaction mechanism.



Problem 3.65 Make the following molecules by taking start from benzene.



Problem 3.66 Explain why the following reaction fails to take place? Suggest plausible alternative to get o/p nitroanilines.



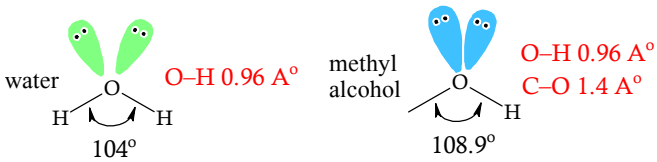
3.7 Alcohols

3.71 Introduction

Alcohols are organic compounds containing hydroxyl group bonded to alkyl group which can be primary, secondary or tertiary. When alkyl group is replaced by phenyl group, we get aromatic alcohol which is known as phenol (carbolic acid). Most common alcohols are methanol (wood alcohol), ethanol (grain alcohol) and isopropyl alcohol (rubbing alcohol). Methanol serves as fuel and solvent, ethanol is used in cosmetic, beverages and pharmaceuticals, and isopropyl alcohol is employed as antiseptic for cleaning injections and minor cuts. The carbon atom to which hydroxyl group of alcohols attaches is known as carbinol carbon.

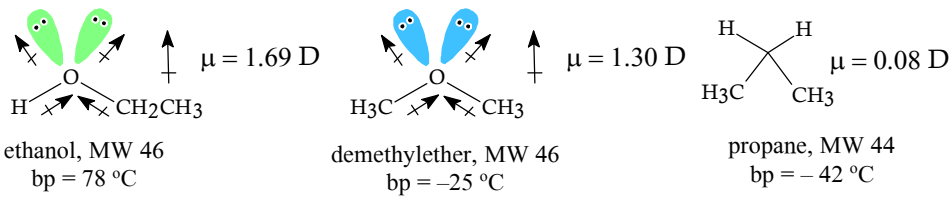
3.72 Structure and Properties

Structurally, alcohols are similar to water but bond angle is wider (108.9°) due to steric repulsion of alkyl group. In water, bond angle is 104.5°. Oxygen atom is sp^3 hybridized in both water and alcohol. It makes tetrahedral geometry with two lone pair on oxygen atom are directed towards the corner of the tetrahedron.



3.73 Properties

Alcohols are polar molecules with alkyl group gives hydrophobic (water hating) and hydroxyl group hydrophilic (water loving) character. They are miscible in water. Alcohols behave like water when it comes to polarity due to presence of hydroxyl group which participates in hydrogen bonding. Consequently, alcohols are highly boiling liquids than corresponding alkanes and ethers of similar molecular weights.



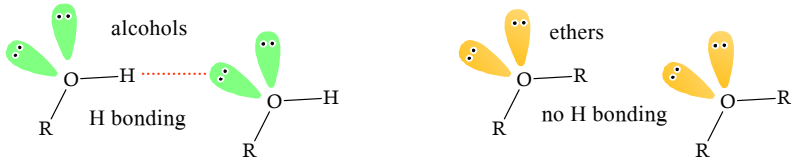
ethanol, MW 46
bp = 78 °C

demethylether, MW 46
bp = –25 °C

propane, MW 44
bp = – 42 °C

Methanol and ethanol are liquids with fruity smell, higher alcohols up to 12 carbon atoms are liquid too. They have fruity smell too. Intermolecular forces such as hydrogen bonding and dipole-dipole interaction render alcohols somewhat different than other compounds. An ordinary hydrogen bond has strength of 21 kJ/mol which is stronger

than other intermolecular forces but weaker than covalent bond which strength ranges from 300 to 500 kJ/mol.



3.74 Acidity of Alcohol and Phenol

Alcohols are weakly acidic. Ionization of hydroxyl group yields proton and alkoxide anion whose stability determines the acidity of alcohols. Methanol is more acidic than ethanol with pKa values of 15.5 and 15.9 respectively. Comparatively, 2-chloroethanol and 2,2,2-trichloroethanol have pKa values of 14.3 and 12.3 respectively. Larger anions aren't solvated adequately as do smaller ones. Solvation renders alkoxide anion stabilized. Methoxide anion is better stabilized than ethoxide which makes methanol a bit more acidic than ethanol. Alcohols are less acidic than phenol (pKa 10) because phenoxide is better stabilized by resonance than alkoxide where no such resonance exists. For instance, phenol is 100 million times acidic than cyclohexanol.

Problem 3.71 Why methanol is more acidic with pka value of 15.5 than ethanol with pka value of 15.9? Ethyl alcohol is more acidic than t-butyl alcohol.

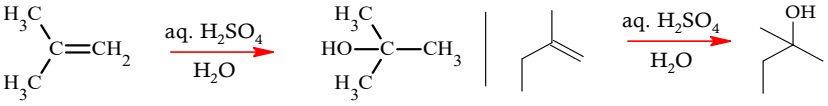
3.75 Metal Alkoxide

Metals are reactive and basic. Alcohols are acidic. When both are reacted, metal alkoxides are formed which are strongly nucleophilic and they serves as excellent nucleophiles in organic synthesis. Metal-alcohol reaction is redox reaction in which metal is oxidized and proton is reduced yielding hydrogen gas which bubbles out of solution. As phenol is more acidic than alcohols, we use aqueous basic conditions of sodium hydroxide or potassium hydroxide for deprotonation of phenols. Primary alcohols such as methanol and ethanol are more reactive than secondary ones. Tertiary alcohols are least reactive and they require more reactive potassium instead of sodium for potassium alkoxide formation. For even less reactive alcohols, sodium hydride in THF is used.

3.76 Synthesis

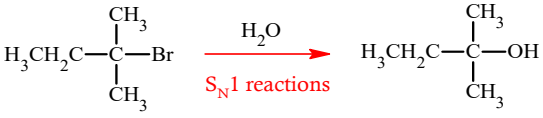
1. Hydration of Alkenes

Hydration reaction is addition of water to the double bond unlike hydrolysis of esters or alkyl halides which involve the cleavage of water molecule. Electrophilic addition of water across the double bond leads to formation of alcohols.



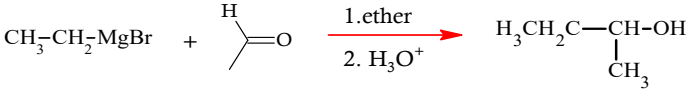
2. Hydrolysis of Alkyl Halides

As noted in S_N1 reaction, treating tertiary alkyl halides with water gives tertiary alcohols.



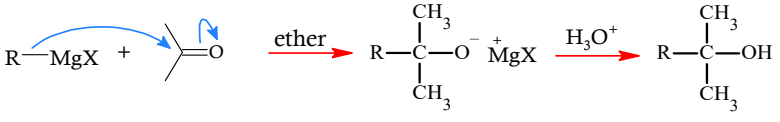
3. Reaction of RMgX with Carbonyl Compounds

Grignard's reagent carries nucleophilic alkyl group which attacks electrophilic carbon of carbonyl group in carbonyl compounds. The reaction gives alcohols with aldehydes and ketones.



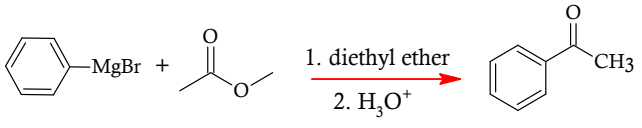
Mechanism

The mechanism for the reaction proceeds through two steps: first step involves addition of alkyl group to carbonyl group which yield tetrahedral intermediate, second step involves hydrolysis of the intermediate to give final product.



4. Reaction of RMGX with Ester and its Derivatives

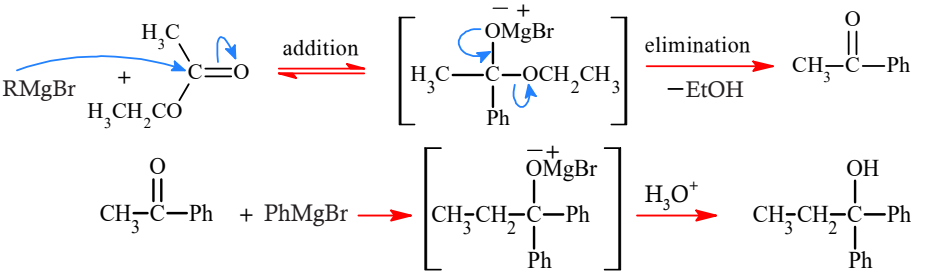
Whether ester or acid chloride, both containing good leaving groups. They take two moles of RMgX to get tertiary alcohols. Esters yields ketones at first stage which are more reactive than starting ester and subsequently react with another mole of RMgX to yield tertiary alcohols.



Mechanism

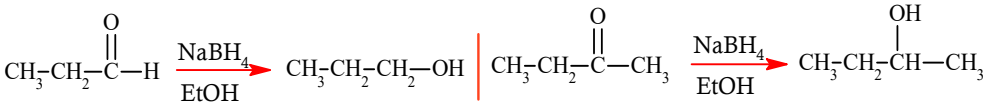
Carbon atom in RMgX is nucleophilic. It adds to electrophilic carbon or carbonyl group in first step leading to formation of tetrahedral intermediate which finally gives

ketones. Remember, ketones are more reactive than ester, therefore they add another molecules of RMgX and alcohols are formed as final product.

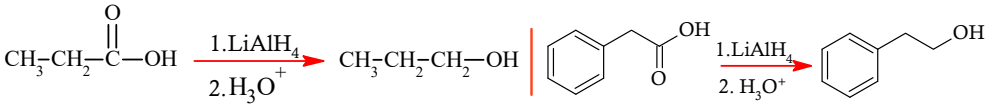


5. Reduction of Aldehyde, Ketone, Acids and Esters

Carbonyl group of aldehyde and ketone can be reduced to alcohols by treating them with suitable reducing agent such as sodium borohydride. LAH reduces carboxylic acids and esters to alcohols. This reaction passes through aldehyde stage which is even more reactive than the starting, therefore it get reduced to final product of alcohols.

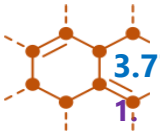


LAH is strong base and it reduces acids to primary alcohols. Initially, aldehydes are formed but reaction can't stop at this stage because aldehydes are more reactive and further reduced to final product.



$LiAlH_4$

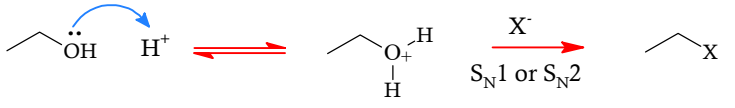
LAH reacts vigorously with water. It can't be used in aqueous medium. LAH is more reactive and less selective. It reduces carboxylic acids, esters, amides, nitriles and nitro compounds. A less reactive and more selective analogue is sodium borohydride (SBH) that can be used in aqueous medium.



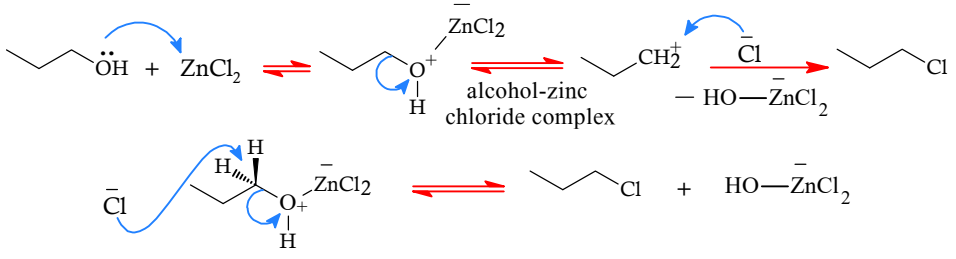
3.77 Reactions

1. Hydrohalic Acid

Alcohols get protonated once they are exposed to HX such HCl, HBr and HI. Hydroxyl group is poor leaving group and it resist expulsion from alcohol no matter how strong nucleophile is used.



Protonation by HX converts OH group into good leaving group which can be expelled by weak nucleophile as well. The protonated alcohol could go through substitution or elimination reaction, depending upon the structure of substrate, base and nucleophile. The carbocation forms is prone to rearrangement. Halide ions are weak bases since they are stable conjugate bases of strong acids. Iodide reacts swiftly than bromide and chloride. For HCl, we use zinc $ZnCl_2$ (catalyst) solution to aid reaction with primary or secondary RXs because chloride is weak nucleophile. This reagent is known as Lucas Reagent which serves useful mixture for testing primary, secondary and tertiary alcohols.



Tertiary alcohols react instantly, secondary alcohols take 1 to 5 minutes whereas primary alcohols are very lazy (take 10 minutes to react) to react with Lucas reagent. The reaction is detected by appearance of cloudiness which becomes evident due to formation of alkyl halides in solution mixture. Alkyl chloride gives poor yield no matter primary or secondary alcohols are used even with Lucas reagent.

Tertiary alcohols are more reactive than the secondary and primary due to following reasons:

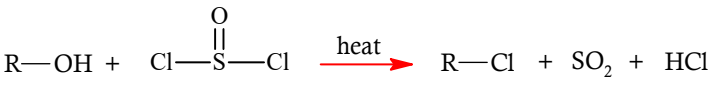
- Stability of carbocation
- Steric hindrance in substitution reactions
- Easy protonation of hydroxyl group
- Reactivity in elimination reaction

Reaction where carbocation intermediate involves, tertiary alcohols have more stabilizing effect on it than other alcohols. Hydroxyl group is poor leaving group, it can easily be protonated due to electron donating tendency of three alkyl groups which further mount electronic density on oxygen atom. Once hydroxyl group is protonated, it can't be expelled in S_N2 reaction due to hindered backside attack. Contrarily, reaction goes by S_N1 which involves carbocation formation. Tertiary alcohols are prone to elimination reaction (E1) since it involves carbocation formation as compared.

2. Thionyl Chloride and PX_3

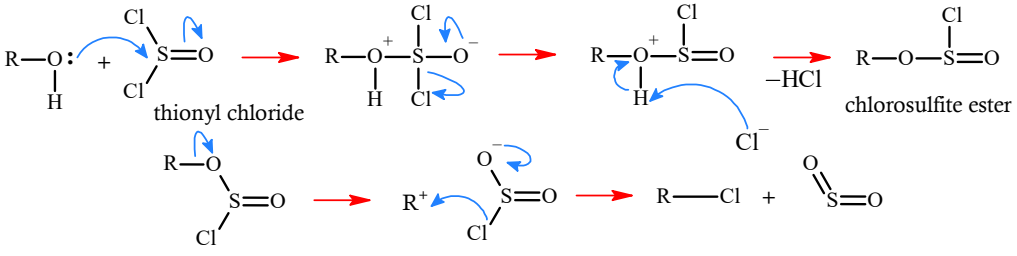
Whether thionyl chloride or phosphorous halides, alcohols react with them yielding alkyl halides. This is sort of substitution reaction in which –OH is substituted by –X.

$$3\ R—OH + PCl_3 \longrightarrow 3\ R—Cl + P(OH)_3$$
$$R—OH + PCl_5 \longrightarrow R—Cl + POCl_3 + HCl$$



Mechanism

S_Ni Mechanism: This is interesting mechanism which proceeds with retention of configuration.

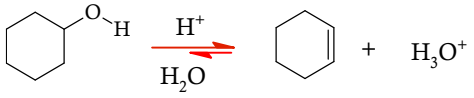


In first step, alcohol attacks sulfur of thionyl chloride giving an unstable tetrahedral intermediate. The intermediate stabilizes itself by eliminating chloride ion which is good leaving group. The product of this step is chlorosulfite ester, whose ionization results in an ion pairs with formation of carbocation. However, the carbocation isn't like the one which forms in S_N1 or E1 mechanism because it is still under partial influence of the possessing molecule. The carbocation is attacked by halide from the same side where old bond breaks, thus giving stereochemistry with retention of ultimate configuration. This special type of reaction is known as S_Ni reaction or substitution nucleophilic internal reaction. This mechanism resembles S_N2 except that the nucleophile is delivered to the carbocation by the leaving group, usually giving retention of configuration as shown in the following example.

Class of alcohol	Chloride	Bromide	Iodide
Primary	$SOCl_2$	PBr_3 or HBr	P/I_2
Secondary	$SOCl_2$	PBr_3	P/I_2
Tertiary	HCl	HBr	HI

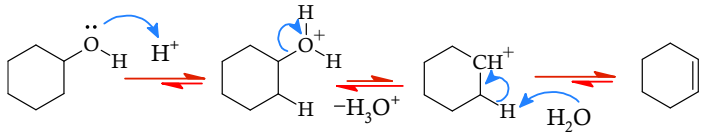
3. Dehydration

Primary, secondary and tertiary alcohols can be dehydrated to alkenes or ether using concentrated H_2SO_4 and varying temperature conditions. Lower temperature favors ether formation. Ethanol gives diethyl ether with Al_2O_3 at 200 °C and ethene at 350 °C.



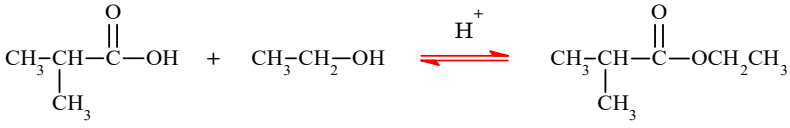
Mechanism

Dehydration reaction proceeds either by E1 mechanism with secondary or tertiary alcohols and E2 with primary ones.



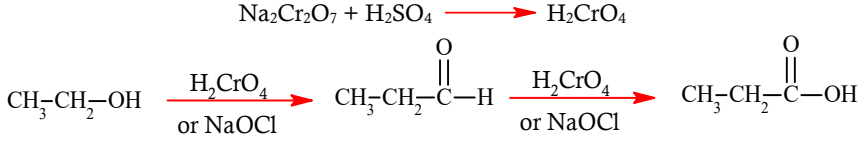
4. Esterification

Alcohol reacts with carboxylic acids in the presence of concentrated H_2SO_4 in an esterification reaction for synthesis of esters. The reaction is most commonly known as Fisher Esterification which is a sort of condensation reaction. The reaction doesn't proceed in basic medium since base deprotonate carboxyl group rendering carbonyl group incapable of reaction. In this reaction, –OH group of acid is replaced with –OR group of alcohol.

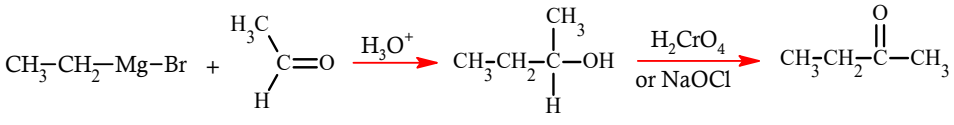


5. Oxidation

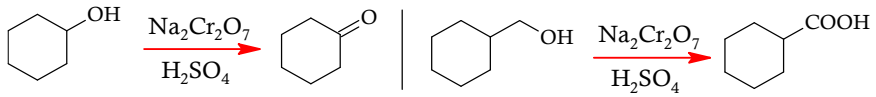
Primary and secondary alcohols are oxidized to ketone and carboxylic acids respectively using variety of oxidizing agents. Tertiary alcohols are resistant to oxidation because carbinol carbon doesn't carry hydrogen to be oxidized. Chromic acid (H_2CrO_4) is traditional oxidizing reagent for turning secondary alcohols into ketones. It is made by treating sodium dichromate with sulfuric acid. The hot oxidizing reagent has orange color. A mixture of chromic acid and H_2SO_4 in aqueous acetone constitutes John's Reagent which is used for oxidation of secondary alcohols. Much like SBH, John's reagent is less reactive and more selective. It doesn't have any influence on double bond.



A cheap alternative is bleach (NaOCl) which also converts secondary alcohols to ketones. Both these reagent gives carboxylic acids with primary alcohols.



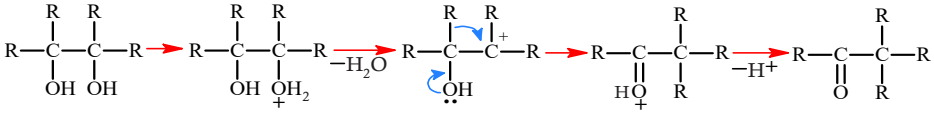
Chromic acid gives useful test for distinguishing primary and secondary alcohols from tertiary ones. When an alcohol, say primary one such as ethanol is added to concentrated solution of potassium dichromate, the orange color of solution vanished and green appears indicating positive test. The oxidation reaction passes through aldehyde stage which is even more reactive than the starting. The reaction can't be stopped at this stage. Selective oxidizing agents such pyridinium chlorochromate (PCC) stops the reaction at aldehyde stage, however.



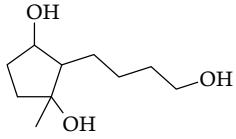
To oxidize	Product	Chromium reagent	Chromium free reagent
Secondary alcohol	Ketone	Chromic acid or PCC	NaOCl, Swern, DMP
Primary alcohol	Aldehyde	PCC	Swern, DMP
Primary alcohol	Carboxylic acid	Chromic acid	NaOCl

Pinacol Rearrangement

1,2-diol is known as pinacol which undergoes acid catalyzed rearrangement reaction yielding aldehydes or ketones. The reaction involves migration of alkyl or aryl group to neighboring carbon along with elimination of water molecule. Pinacol rearrangement reaction is classical example of carbocation rearrangement.

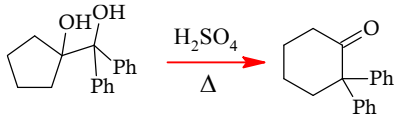


Problem 3.71 Predict the product you expect when the following alcohol is subjected to react with each reagent one by one.



i. Chromic acid
ii. PCC
iii. NaOCl
iv. DMSO & $COCl_2$
v. DMP

Problem 3.72 Point out mechanism for the following transformation.

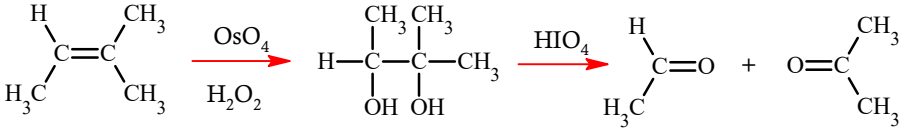


3.78 Iodoform Test

Iodoform test offers an interesting instance of alcohols oxidation. Usually, the carbinol carbon bearing hydrogen atom is prone to oxidation, yielding ketone. A methyl group besides carbinol carbon bearing hydrogen atom is needed for positive iodoform test. For instance, ethanol and 2-propanol. Other alcohols such as 1-propanol and 1-butanol don't fulfill the requirements, hence they give negative iodoform test. The test requires alcohols, 2 M NaOH solution and 10% iodine solution made up in potassium iodide solution. Take alcohol in test tube, put iodine solution almost double the volume of alcohol and then shake. Add dropwise NaOH solution until the dark brown color inside test tube fades away by continuing shaking. Put the test in water bath to facilitate the reaction and note whether a yellow precipitate is formed or we get a clear solution. A yellow precipitate confirms an alcohol capable of oxidizing to methyl ketone such as ethanol or 2-propanol.

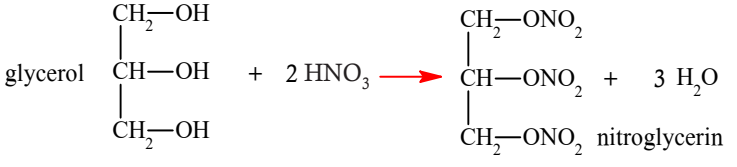
6. Cleavage of 1,2-Diols

Oxidative cleavage of alkenes gives syn diols with OsO_4 or $KMnO_4$. This is said to be dihydroxylation reaction. The diol could be further oxidized to carbonyl compounds such aldehydes, ketones and carboxylic acids using either mild or strong oxidizing agents. Periodic acid (HIO_4) gives aldehydes and ketones.



Nitroglycerine

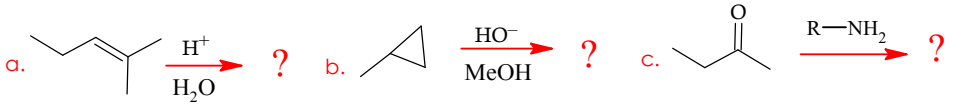
A trihydroxy alcohol is known as glycerol which yields nitroglycerin upon treatment with nitric acid. Nitroglycerin is classical ingredient of dynamite explosives besides significant relevance in medicines (vasodilator, a substance used to increase blood flow). Nitroglycerin is quite shock sensitive in pure state and it explodes by releasing large amount of gases such as N_2, CO_2, H_2O and O_2.



Swern Oxidation

Primary alcohols are selectively oxidized to aldehyde and secondary ones to ketones by DMSO, chloride and hindered base. The reaction is known as Swern Oxidation. Alcohols liberate hydrogen gas with sodium metal and HCl fumes with PCl_5. These reactions are used as identifying test for alcohols.

Problem 3.73 Write product for each of the following reaction.



Problem 3.74 Prepare benzoin acid, benzaldehyde, styrene, phenylacetic acid and phenylacetaldehyde from 2-phenylethanol.

Problem 3.75 Point out the product by treating 1-methylcyclohenol with different reagents such as HBr, H_2SO_4, chromic acid, thionyl chloride, PBr_3 and sodium hydride.

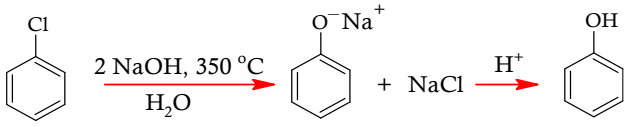
3.8 Phenols

Substituting alkyl group alcohols for phenyl gives phenols which are aromatic alcohols containing alcohol and aromatic functional groups. They are bifunctional organic compounds. Phenol is parent member. It is useful synthetic precursor for synthesis of aspirin. Phenols share many properties with alcohols yet they are remarkably different regarding physical and chemical properties.

3.81 Synthesis

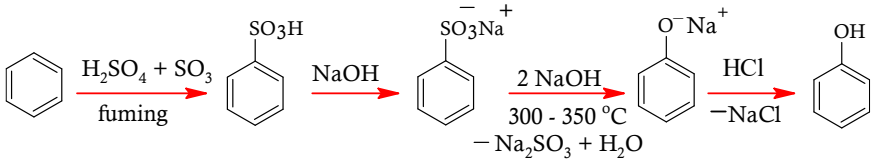
1. Dow Process

Phenol has long been synthesized by Dow Process which involves treatment of chlorobenzene with strong base at elevated temperature. The reaction proceeds through nucleophilic aromatic substitution reaction, more appropriately benzyne mechanism which require leaving group on aromatic ring and strong basic conditions. Sodium hydroxide gives phenol, sodium amide in liquid ammonia gives aniline.



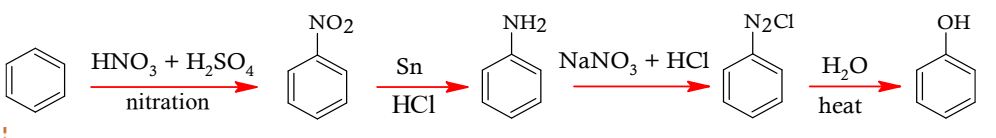
2. Benzene Sulphonic Acid

Benzene sulphonic acid gives sodium benzene sulphonate and sodium phenoxide with sodium hydroxide at high degree of temperature. Treatment with HCl yields phenol.



3. Diazonium Salts

Diazonium salts are important precursors for synthetic purpose which transform aromatic amines into variety of functional group without the requirements of stringent reaction conditions. For instance, preparing phenol at room temperature is excellent application of diazonium salt.

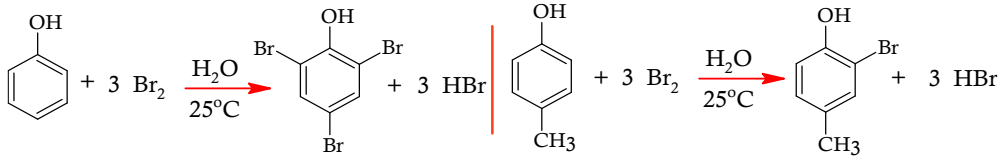


3.82 Reactions

Much like benzene, phenol observes EASR reaction too since it is more reactive than benzene and requires milder conditions for reaction.

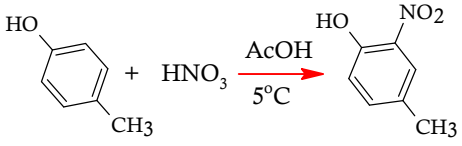
1. Halogenation

On account of its reactivity, phenol undergoes chlorination and bromination without any trouble most preferably at para position but ortho substitution is observed when para is blocked.



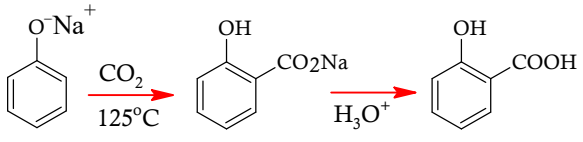
2. Nitration

Phenol doesn't require a mixture of nitric acid and sulfuric acid because phenol is reactive enough to react with simple nitric acid.



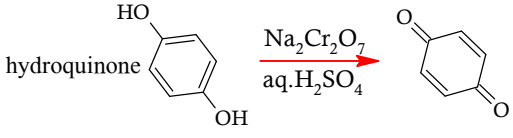
3. Kolbe-Schmidt Reaction

Classically, the reaction has utilized for synthesis of salicylic acid from phenol. Sodium phenoxide is heated with carbon dioxide. The intermediate formed is acidified and salicylic acid is achieved. Salicylic acid is precursor for synthesis of aspirin.



4. Oxidation

Phenol and its derivatives such as hydroquinone are easily oxidized than alcohols by variety of oxidizing agents yielding hydroquinone which are conjugated dicarbonyl compounds.

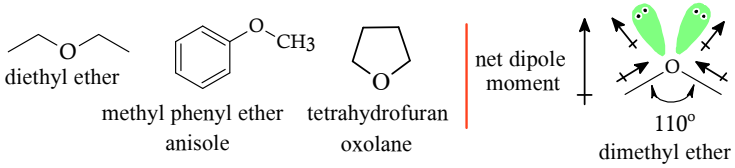


3.9 Ethers

3.91 Introduction

Ethers are inert organic compounds. They are polar and usually used as solvent for reactions and extraction. In the past, ethers were used for causing anesthesia but abandoned later on due to side effects. Substituting hydrogen of alcohol with alkyl group

gives the functional group of ethers which can be acyclic or acyclic ether. Most common cyclic ethers are three member epoxides and five member tetrahydrofuran (THF). Acyclic ethers include dimethyl ether (DME) and diethyl ether.



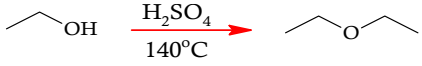
3.92 Properties

Ethers are strongly polar molecules and volatile. They are low boiling point liquids. Lone pair on ether enable it to form hydrogen bond with water and alcohols but they don't form hydrogen bond themselves.

3.93 Synthesis

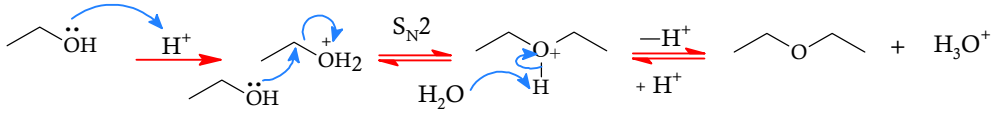
1. Dehydration of Alcohols

Earlier, we have noted alkene synthesis from dehydration of alcohols. This reaction could yield ethers as well if reaction conditions are maintained properly. Dehydration of alcohols yields ethers in bimolecular condensation reaction unlike unimolecular dehydration which gives alkenes. Ethers are obtained in substitution (S_N2) reaction but alkenes are obtained in elimination reaction. Both reactions compete. If reaction condition are controlled, temperature isn't too high and alcohol is primary or secondary, substitution dominates and ethers are obtained. For tertiary alcohols, elimination predominates.



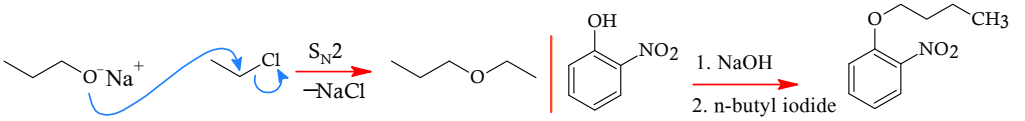
Mechanism

Alcohol is protonated since hydroxyl group is poor leaving group. A protonated alcohol is attacked by neutral alcohol molecule in the second step leading to formation of an intermediate which is finally deprotonated to ether in the third step.



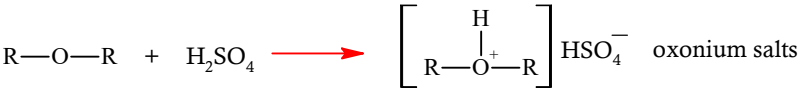
2. Williamson Synthesis

Diethyl ether was prepared in 1850 by British Chemist Alexander Williamson through S_N2 substitution reaction of alkoxide and alkyl halides. The reaction is most effective when the substrate is less hindered, a condition for S_N2 reaction. Steric hindrance of alkoxide doesn't influence rate of reaction. Elimination dominates when substrate is tertiary.



3.94 Reactions

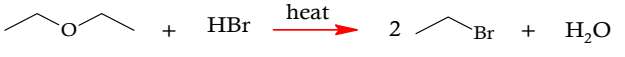
Ethers are less reactive. They don't react with bases but react with acids. Oxonium salts are formed when ethers are made to react with concentrated sulfuric acid.



Ethers don't react like alcohols and other functional groups yet they demonstrate certain reactions under some circumstances. For instance, ethers cleave when they are made to react with HBr or HI upon heating giving alkyl halides.

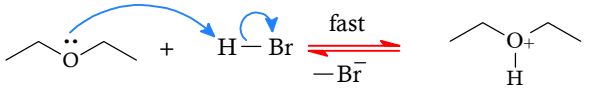
1. Reactions with HX

Unlike alcohols, ethers are not commonly used as synthetic intermediates because they do not undergo many reactions. This underactivity makes ethers attractive as solvents. Even so, ethers do undergo a limited number of characteristic reactions. Ethers are cleaved by heating with HBr or HI to give alkyl bromides or alkyl iodides.

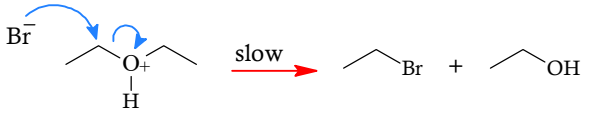


Mechanism

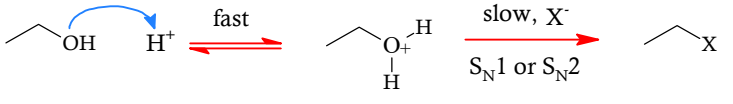
First step involves H^+ transfer to the oxygen of ether to give dialkyloxonium ion.



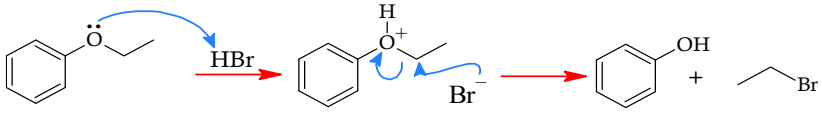
Step 2 proceeds via nucleophilic attack of halide anion on carbon of dialkyloxonium ion which gives RX and ROH.



Step 3 and 4: Both steps do not involve ether at all. They correspond to those in which an alcohol is converted to RX.

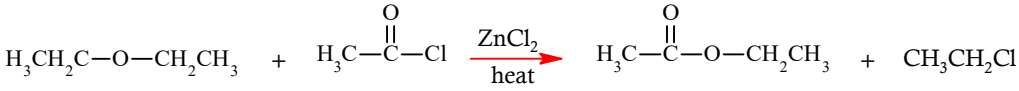


Ethers are unreactive toward most bases, but they can react under acidic conditions. A protonated ether can undergo substitution or elimination with an alcohol serving as a neutral leaving group. Ethers react with concentrated HBr and HI because these reagents are sufficiently acidic to protonate the ether, while bromide and iodide are good nucleophiles for the substitution. Under these conditions, the alcohol leaving group usually reacts further with HX to give another alkyl halide. Phenyl ethers (one of the groups bonded to oxygen is a benzene ring) react with HBr or HI to give alkyl halides and phenols. Phenols do not react further to give halides because the carbon atom of the phenol cannot undergo the S_N2 reaction needed for conversion to the halide.



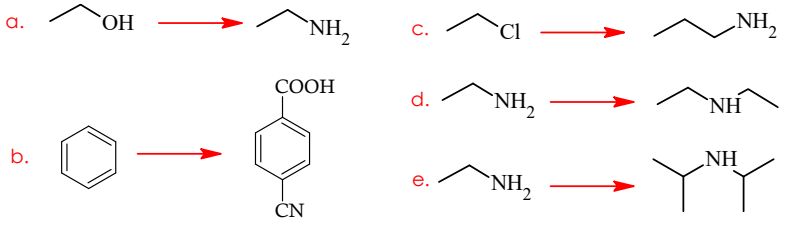
2. Reaction with Acid Chloride

Ethers give ethyl acetate with acid chloride in the presence of zinc chloride.



Problem 3.91 Why carboxylic acids are more acidic than alcohols?

Problem 3.91 Make the following conversions by choosing relevant reaction and reagents.



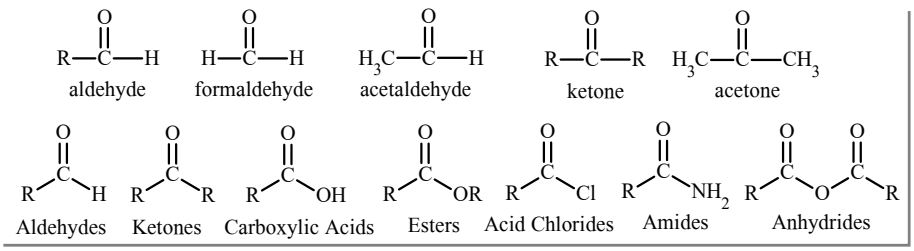
Carbonyl Compounds I

Properties, Synthesis & Reactions

3.10 Aldehydes and Ketones

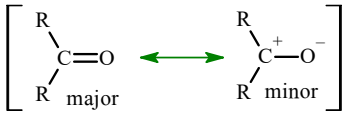
3.101 Introduction

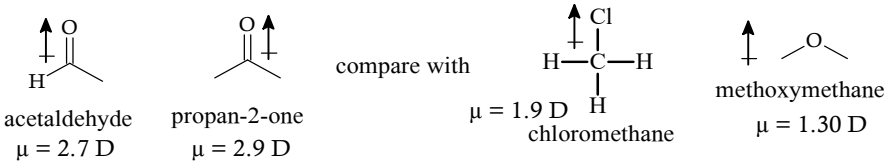
Aldehyde and ketone are first series of carbonyl compounds which are identified by formyl and acyl functional groups. In aldehydes, carbonyl group bonds to alkyl group on one hand and hydrogen on the other. In ketone, the carbonyl group bonds to alkyl groups on both sides. These compounds are widespread in nature. Entire class of terpenoids is based on aldehyde and ketone. Formaldehyde, an irritating gas, is parent member of aldehyde series. It's 40% aqueous solution by volume is known as formalin which is preservative for biological specimen. Benzaldehyde gives almond flavor. Acetone, a nail polish remover, is parent member of ketone. It has sweet odor. It is excellent solvent because it is miscible with both water and non-polar solvent. Acetone has immense significance in industry. Acetone is used to remove water from glassware. This compound is even produced in diabetic patient whose urine gives the smell of acetone. In severe case, acetone can be felt in breath of patient.

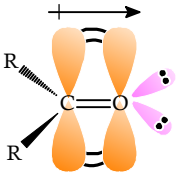


3.102 Structure

Carbonyl group is sp^2 hybridized, having trigonal planner geometry. It has large dipole moment which is directed from carbon to oxygen. Oxygen is more electronegative than carbon, therefore it drags pi electrons of the double bond more toward itself rendering oxygen electron rich and carbon electron deficient. In fact, this polarization is responsible for reactivity of carbonyl group.



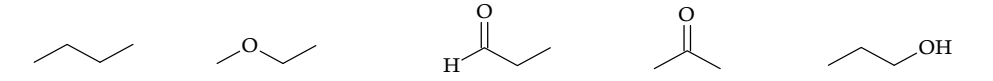




	length	energy
ketone C = O bond	1.23 A°	745 kJ/mol
alkene C = C bond	1.34 A°	611 kJ/mol

3.103 Physical Properties

Carbonyl group of aldehyde and ketone is polar which turns them polar and high boiling compounds as compared to hydrocarbons and ethers of similar molecular weight. Aldehydes and ketones don't have O—H or N—H bonds, therefore they lack participation in hydrogen bonding among their molecules. Lack of hydrogen bonding makes them lower boiling points molecules than alcohols and water. However, presence of lone pair on oxygen atom of carbonyl group make it capable of establishing hydrogen bond with water and alcohols much like ethers. This property renders aldehyde and ketone miscible in water and alcohols. For instance, acetone dissolves water.

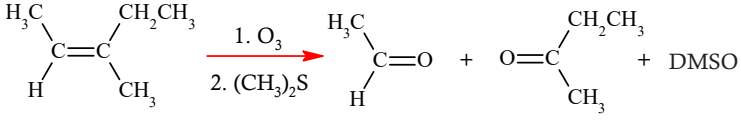


butant bp 0 °C methoxyethane bp 8 °C propanal bp 49 °C acetone bp 56 °C propanol bp 97 °C

3.104 Synthesis

1. Ozonlysis of Alkenes

The cleavage of double bond could be stopped at aldehyde and ketone stage by using milder oxidizing agent of ozone. This could be done by treating alkenes with ozone followed by reduction. This is useful synthetic method for aldehydes and ketones production.

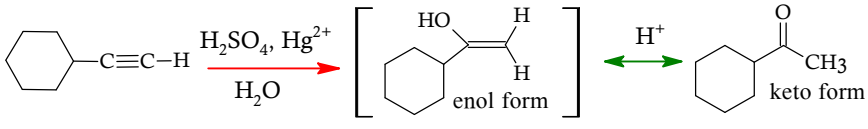


DMSO

Dimethyl sulfoxide is sulfur equivalent of acetone which is odorless liquid and used as solvent. DMSO has polar S = O bond which renders it soluble both in water and less polar organic solvents. DMSO quickly absorbs into skin where it relieves pain and inflammation. Traditionally, it was used as miracle drug for arthritis, sprains, herpes, burns, infections and high blood pressure. Despite all its medical applications, FDA has refused to approve DMSO for medical use.

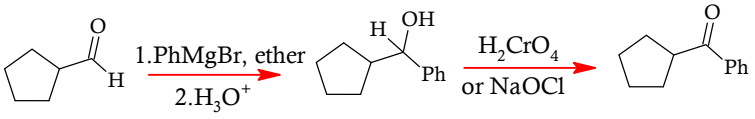
2. Hydration of Alkynes

Alkyne adds up water molecules according to Markovnikov's rule yielding an unstable enol that undergoes keto-enol tautomerism and gives aldehyde or ketone depending upon whether the starting alkyne is terminal or internal one. The reaction is carried out in the presence of mercuric sulfate and sulfuric acid.



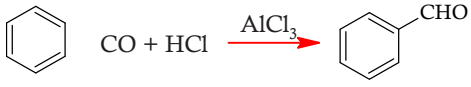
3. Oxidation of Alcohols

Ketones and aldehydes are often made by oxidizing alcohols. When we need to make a carbonyl compound, we can often use a Grignard reagent to synthesize an alcohol with the correct structure and oxidize it to the final product.



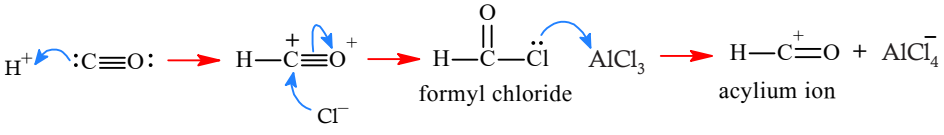
4. Gatterman-Koch Reaction

Formylation of aromatic ring in an electrophilic substitution reaction affected by carbon monoxide in acidic medium is termed as Gattermann-Koch reaction. The reaction is catalyzed by anhydrous $AlCl_3$ or cuprous chloride.



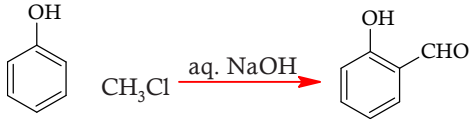
Mechanism

Carbon monoxide is protonated and subsequently attacked by chloride ion to get formyl chloride. Lewis catalyst coordinate with formyl chloride and ultimately gives acylium ion as an electrophile to react with aromatic ring. Rest of the mechanism is similar to Friedel-Craft acylation reaction given in section 3.46-5. Gattermann-Koch reaction doesn't apply to phenol or phenol ethers.



5. Reimer-Tiemann Reaction

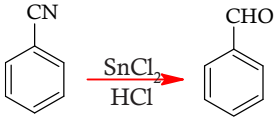
This reaction is useful for ortho formylation of phenolic compounds in a substitution reaction which is affected in basic medium when phenol or phenolic compounds are reacted with chloroform. Undoubtedly, direct formylation of benzene ring is achieved by Gatterman-Koch reaction, Vilsmeier-Haack reaction or Duff reaction, but in case of safety and efficiency Reimer-Tiemann reaction is better alternative in organic synthesis.



6. Stephan Reaction

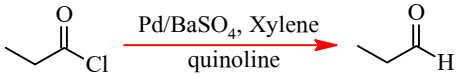
Stephan reaction or Stephan aldehyde synthesis converts nitriles into aldehydes in the presence of HCl and stannous (II) chloride. The reaction is also known as Stephan

Reduction. This reaction transforms –CN group into –CHO (formyl) group. For instance, acetaldehyde is produced from acetonitrile.



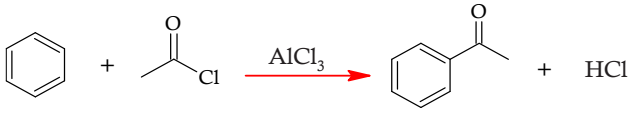
7. Rosenmund Reduction

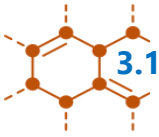
This is hydrogenation reaction which transforms acid halides into aldehydes. The reaction is catalyzed by palladium (Pd) and barium sulfate which is deactivated by quinolone. The reaction is catalytic reduction of acid chloride. BaSO4 is added to reduce the activity of Pd in a bid to halt over reduction. The reaction is further poisoned with quinolone or thiourea so that the aldehyde produced might not be further reduced to alcohols.



8. Friedel-Craft Acylation

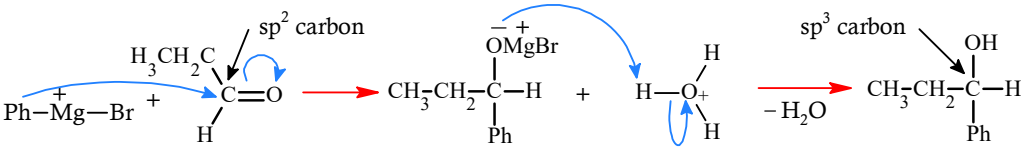
Introducing acyl group into aromatic ring by Friedel-Craft acylation reaction is useful method for synthesis of aromatic ketones. See section 3.46-5 for more details.





3.105 Reactions

A carbonyl group has polar character due to electronegativity of oxygen which makes it a dipole with partial positive charge on carbon atom and partial negative charge on oxygen atom. Carbonyl carbon acquires electrophilic character which enables aldehydes and ketones to react with nucleophile. Consequently, these compounds prefer to react by nucleophilic addition reaction. Consider the following reaction in this regard:



Aldehydes are more reactive than ketones. An alkyl group reduces electrophilic character of carbonyl carbon due to its electron donating potential (electronic effect). In aldehydes, only one such alkyl group is bonded, two in ketones, which makes ketones less reactive. Formaldehyde is more reactive among all aldehydes. Moreover, carbonyl carbon in ketones is sterically hindered. This property also reduces ketones reactivity.

Aldehydes are more reactive than ketone!

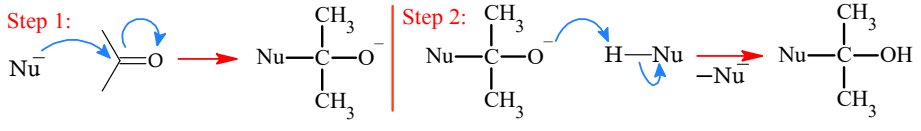
Alky group is electron donating molecular species which generates electronic density through hyperconjugation. An alkyl group linked to carbonyl group has electronic impact, therefore influences the reactivity of the group. For instance, all organic compound which C=O group are said to be carbonyl compounds such as aldehydes, ketones, carboxylic acids and its derivatives. On account of electronegative difference between carbon and oxygen, carbon of the carbonyl group is electrophilic in character. It means that oxygen of the group withdraws electronic density from carbon, thus makes it electron deficient or electrophilic in character. When an alkyl group is bonded to carbonyl carbon, it reduces electrophilic character of C=O group. For instance, aldehydes are more reactive than ketones because the latter have two alkyl group bonded to carbonyl carbon as compared to the former which have one alkyl group bonded to carbonyl group. In other words, two alkyl groups decrease the electrophilic character of the carbonyl carbon more than one alkyl group.

1. Nucleophilic Addition Reactions

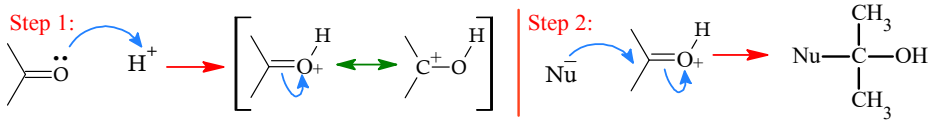
An acid catalyze reaction protonates carbonyl carbon for augmenting the electrophilic character of carbonyl carbon which can be attacked even by weak nucleophile. In base catalyzed reactions, a strong nucleophile such as provided by Grignard reagent is required to affect reaction.

Mechanism

Basic Condition: A strong nucleophile adds to the carbonyl group to form an tetrahedral alkoxide in first step. The alkoxide is protonated by weak acid to yield alcohol in second step.



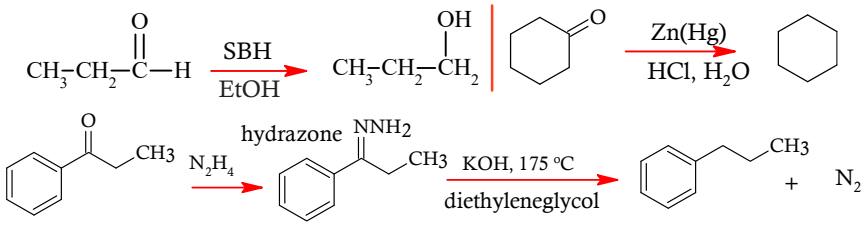
Acidic Condition: First step involves activation of carbonyl group by protonation. In second step, weak nucleophile adds to protonated carbonyl group to give product. Unlike in basic condition, weak nucleophile is required in acidic conditions.



2. Reduction of Aldehydes and Ketones

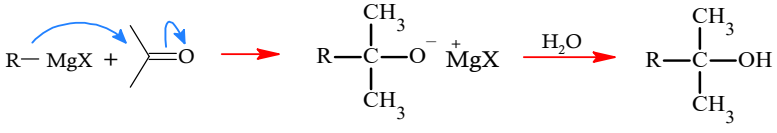
Two reducing agents, $LiAlH_4$ (LAH) and $NaBH_4$ (SBH), have remarkable relevance in organic synthesis. LAH is quite reactive and powerful reducing agent but SBH

is more selective in targeting carbonyl group. An extension of SBH, triacetoxyborohydride, is even less reactive than SBH and selectively reduces formyl group even in the presence of keto group. Besides the utility of LAH and SBH, Clemmenson and Wolfkishner reactions are classical reactions for reducing carbonyl group into methylene moiety. The former requires amalgamated zinc in HCl whereas the latter operates by hydrazine and strong base such KOH in glycolic solution.

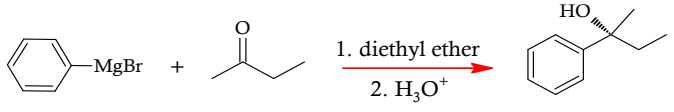


3. Reduction using RMgX

Alkyl or aryl magnesium halide reacts with aldehydes and ketones. Alcohols are the product of the reaction.



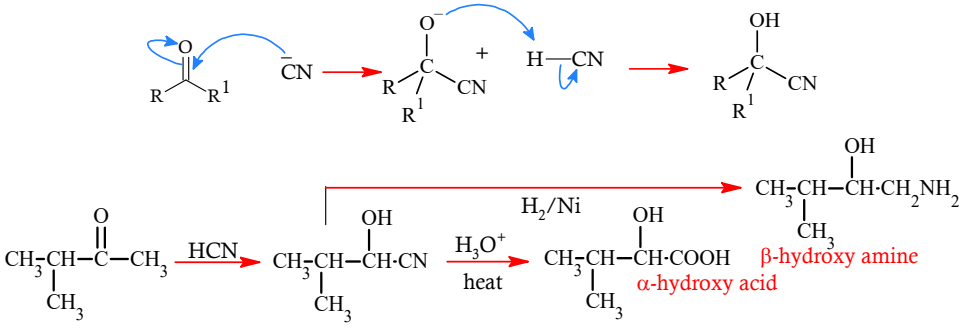
The nature of alcohol depends upon the nature of carbonyl group. The reaction proceeds through intermediate formation of tetrahedral complex. The R group in RMgX could be alkyl or phenyl, both transform carbonyl carbon into a new chiral center.



4. Reduction using HCN

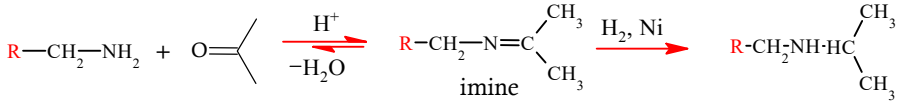
Cyanide is excellent nucleophile which adds to carbonyl group of aldehydes and ketones yielding cyanohydrins which contain hydroxyl group and cyano group on the same carbon atom. The reaction is reduction and it requires hydrogen cyanide (HCN), potassium cyanide (KCN) or sodium cyanide (NaCN) to take places. Since HCN is highly toxic, it is avoided to use. Instead, KCN and NaCN are preferred.

Cyanohydrins are useful synthetic precursor for alpha hydroxy acids and alpha hydroxy amines which are attained through oxidation and reduction respectively.



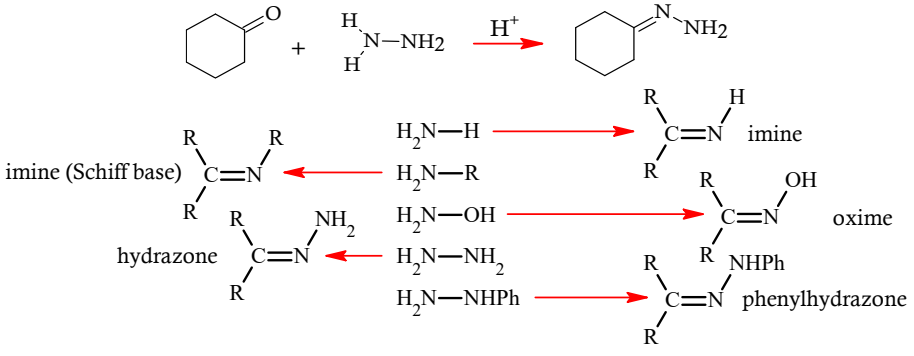
5. Reduction using N Nucleophiles

We have studied reductive amination which involves the reaction of aldehydes or ketones with amines yielding Schiff's base (imine) that can be reduced to higher amines.



6. Reaction with Ammonia and Derivatives

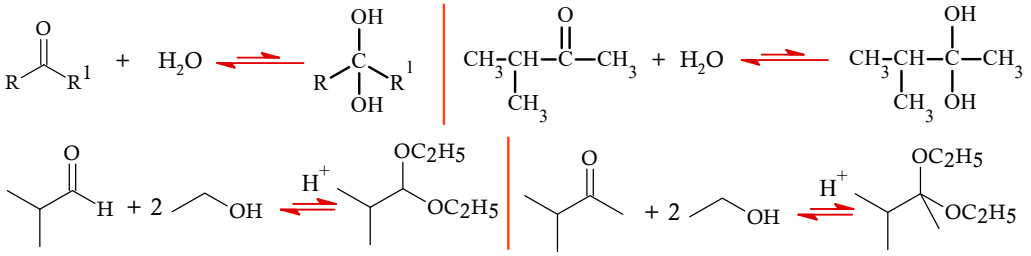
Ammonia and amines condense with aldehydes and ketones. The reaction gives imine. Hydroxyl amines form oximes with this class of carbonyl compounds, hydrazine gives hydrazine and semicarbazide yield semicarbazone. All these reactions proceed through similar mechanism of imine formation.

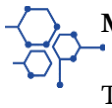


Depending upon the nature of reagent such as ammonia, primary amine, hydroxylamine, hydrazine and phenyl hydrazine, the product obtained with derivatives of hydrazine can be an imine, Schiff's base, an oxime, hydrazone and phenylhydrazone respectively.

7. Reduction using Oxygen Nucleophiles

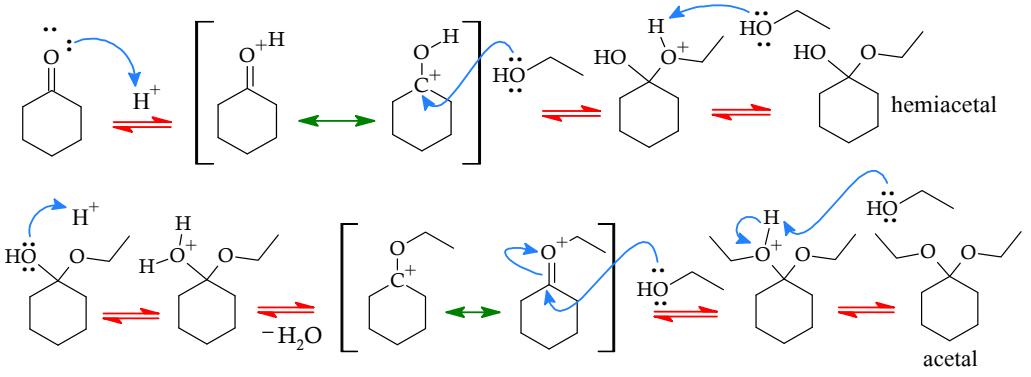
Aldehydes and ketones give hydrates (gem diols) with water. Aldehydes are more reactive and easy to undergo hydration on account of its reactivity. We get acetyl when water is substituted by alcohol. Two molecules of alcohols are taken up by carbonyl group to yield acetyl which are most common compounds in nature such as carbohydrates.





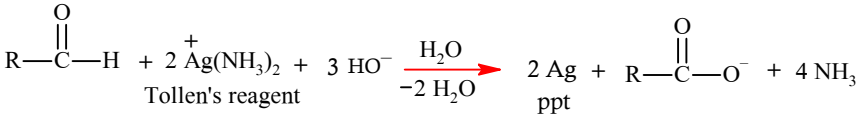
Mechanism for Hemiacetal and Acetal Formation

The reaction proceeds through two main steps: the first step involves acid catalyzed addition of alcohol to ketone. The second half involves S_N1 of the protonated hemiacetal.



8. Oxidation Reactions

Carboxylic acids are achieved from oxidation of aldehydes and ketones. The oxidation could be accomplished by variety of oxidizing agents such as chronic acid, bleach, permanganate or peroxy acids. Aldehydes are easy to oxidize. Even mild oxidizing agents reduce them quite effectively. For instance, in Tollen's test, silver ions oxidize aldehydes to carboxylate anion. Silver gets reduced and form silver mirror on the wall of glassware which is identification test for aldehydes. Ketones give negative test with the reagent.



3.106 Confirmation Test

Aldehydes are confirmed by Benedict reagent which gives red precipitate of Cu_2O when 5 ml of the reagent is mixed unknown aldehyde. Tollen test is also used for confirmation of formyl group. Add NaOH solution to 2 ml of silver nitrate solution. Add dilute NH_3 solution to the mixture dropwise until the precipitate formed is dissolved. Finally, add the unknown organic compound and heat the mixture in water bath.

A Fehling test is used to differentiate aldehydes from ketones. Aldehydes give positive test by forming red precipitate of cupric oxide with the solution. To get the test,

we get two solutions copper sulfate (sol A, deep blue) and alkaline sodium potassium tartrate (sol B, Rochelle salt). Equal volumes are taken from both solutions (actual Fehling reagent, deep blue) in test tube and react with aldehyde or ketone for identification in another test tube. Besides, the test is used to differentiate between reducing and non-reducing sugars. Commonly, the test is used to test sugar in urine. The test can't work with aromatic aldehydes. The test requires basic medium only to work because acidity stabilizes Cu (II) ions and will easily oxidizes aldehydes.

Tollens Test

Dissolve 0.5 g of $AgNO_3$ in 5 ml of distilled water. Add few drops of dil. NaOH solution until brown precipitate of Ag_2O is formed. Slowly add NH_4OH solution until the precipitate dissolve and we get clear solution. This is Tollens reagent which is taken up to 1 to 2 ml in test tube and made reacted with 5 to 10 drops of test compound. Place the test tube in warm water bath (40 to 50 °C) for 5 to 10 minutes. Formation of silver mirror on the inner wall of the test tube is an indication for presence of aldehyde.

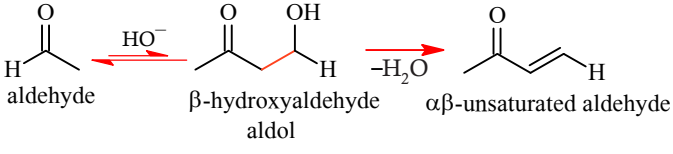
Ketones are identified by iodoform test which gives yellow precipitate. Take 10 ml of acetone, add some crystals of iodine and mix until dissolve. Add NaOH solution dropwise and warm the mixture in water bath until yellow precipitate forms. Alternatively, red wine color is obtained in nitroprusside test for identification of ketones. Add few drops of the reagent into ketone followed by excessive addition of NaOH for confirmation of methyl ketone.

3.107 Condensation Reaction

Organic reactions which involve combination of two or more molecule after release of small molecules such as water, alcohol, oxygen or nitrogen are termed as condensation reactions. Here, we will address two condensation reactions with reference to aldehydes: Aldol and Perkin condensation reactions.

1. Aldol Condensation

Aldol condensation is useful organic reaction which is used for synthesis of complex organic molecules. It has paramount utility in pharmaceuticals and polymer chemistry.

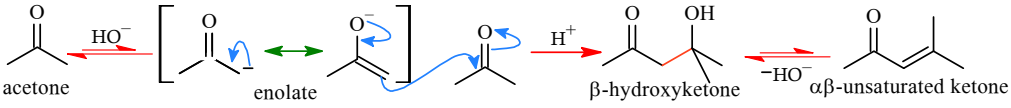


The reaction involves reversible condensation of two aldehydes or two ketones molecules (self condensation) or two molecules of aldehydes and ketones (cross

condensation) for synthesis of β hydroxyl carbonyl (aldol) compounds which are further dehydrated to α, β-unsaturated carbonyl compounds. The reaction can be catalyzed by acid or base. Sometimes, this sort of condensation is observed within molecules. Such reaction is known as intramolecular Aldol condensation.

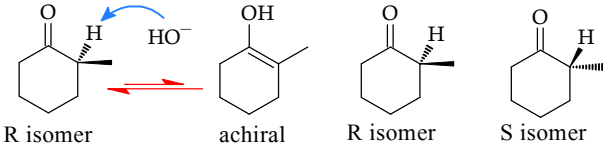
Mechanism

Alpha hydrogen of aldehydes and ketones is acidic. Base abstracts it and conjugate base is formed which is resonance stabilized and termed as enolate since it involves alkene and alcoholic functional groups. Enolate serves as nucleophile and attacks another molecule of aldehyde or ketone leading to formation of β hydroxy aldehyde or β hydroxy ketone. Base catalyzed reaction is nucleophilic addition of enolate to aldehyde or ketone. Hydroxy aldehyde or ketone isn't stable. It dehydrates to α, β-unsaturated aldehydes or ketone. A detailed mechanism for the reaction has given in the first section 1.64-2.



Problem 3.101: Predict the position of hydroxyl group in the following molecule.

Aldehydes and ketones observe keto-enol tautomerism which involves the movement of proton from alpha carbon to carbonyl oxygen result in formation of enol which is resonance stabilized. The proton is said to be enolizable. Aldehydes and ketones carrying enolizable proton on asymmetric alpha carbon effect stereochemistry and alter configuration of molecules. For instance, adding traces amount of acid or base to aldehyde or ketone invert its configuration yielding a racemic mixture (equilibrium mixture of diastereomers).

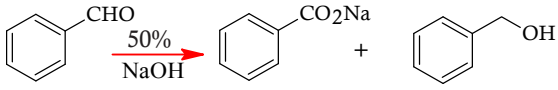


2. Cannizzaro Reaction

Aldol condensation require α hydrogen to take place. Aldehydes such as benzaldehyde, formaldehyde and furfural lack such hydrogen. When such aldehydes are subjected to basic condition, two molecules of the substrate undergo disproportional reaction yielding a molecule of carboxylic acid and primary alcohol. This reaction is known as Cannizzaro reaction.

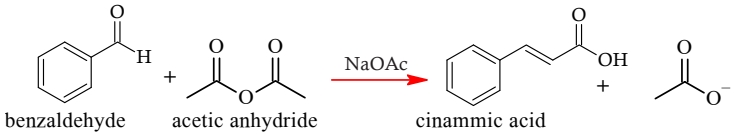
Strong base such as NaOH is required to catalyze the reaction which is first order in base and second order in aldehyde. This is useful reaction in synthesis of natural

products. Cannizzaro reaction is an example of self oxidation-reduction reaction since one molecule of aldehyde gets reduced to alcohol and the other gets oxidized to carboxylic acid. The reaction is disproportionation reaction because one equivalent of aldehyde is needed for reduction and other equivalent is required for oxidation.



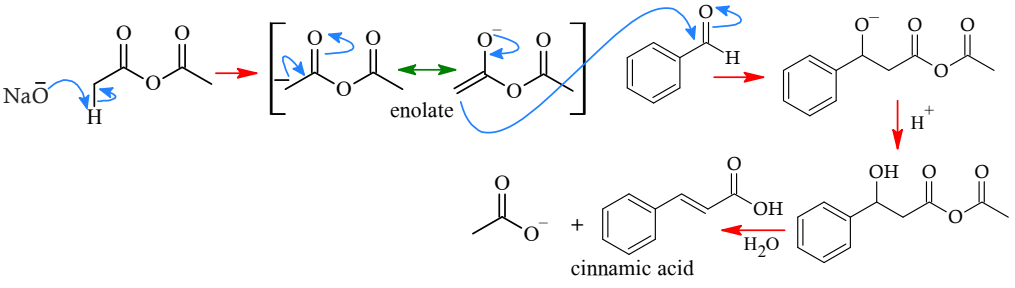
3. Perkin Condensation

Perkin condensation gives α, β–unsaturated aromatic acid (cinnamic acid) by condensation of aromatic aldehydes with acetic anhydride. The reaction is catalyzed by base. This reaction is useful for synthesis of aromatic acids which are used as flavoring agent, perfumes and pharmaceuticals. The reaction follows aldol like mechanism



Mechanism

The mechanism initiate with enolate formation which attacks benzaldehyde. Protonation and subsequent dehydration gives cinnamic acid.

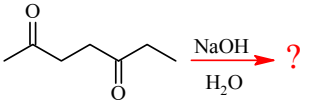


3.108 Exercise

1. Explain the following statement briefly.

a. Ketones give tertiary alcohol but esters give ketones with Grignard reagent although in both cases reaction takes place at carbonyl carbon.
b. Why ketones resist oxidation?
c. Why protonation is needed for activation of carbonyl group for making carbonyl compounds reactive towards nucleophilic addition reaction.
d. Why α hydrogen in carbonyl compounds is acidic?

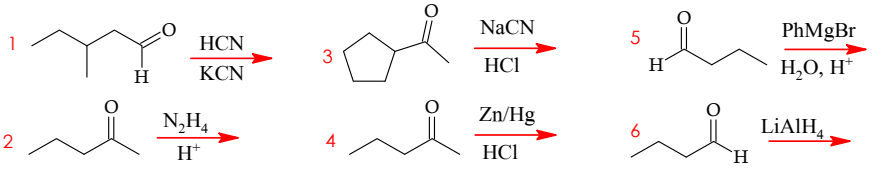
2. Write product for the following reaction and explain the nature of reaction along with mechanism.



3. What product do you expect from a reaction of cyclohexanone with acetaldehyde? The reaction is catalyzed by base? Point out the name of reaction.

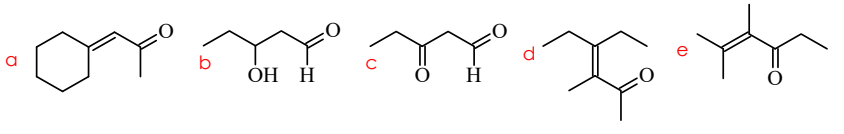
4. Write mechanism for reaction of acetone with ethanol which is catalyzed by acid.

5. Complete the following reactions:

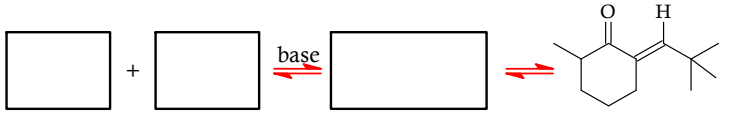


6. A molecule x is oxidized to molecule y which is further oxidized to molecule z. The transformation is known as oxidation reaction. The three compounds gives positive tests with Tollen's reagent, bicarbonate solution and acidified zinc chloride solution separately. Point out the structure of molecule x, y and z and state about how each is identified through a test cited above.

7. Predict starting material for the following aldehydes and ketones and state which reaction is responsible for making these molecules.



8. Fill up the boxes with relevant molecules!



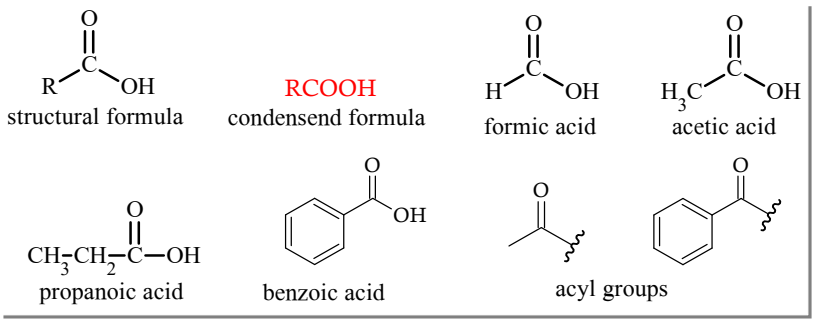
Carbonyl Compounds II

Properties, Synthesis & Reactions

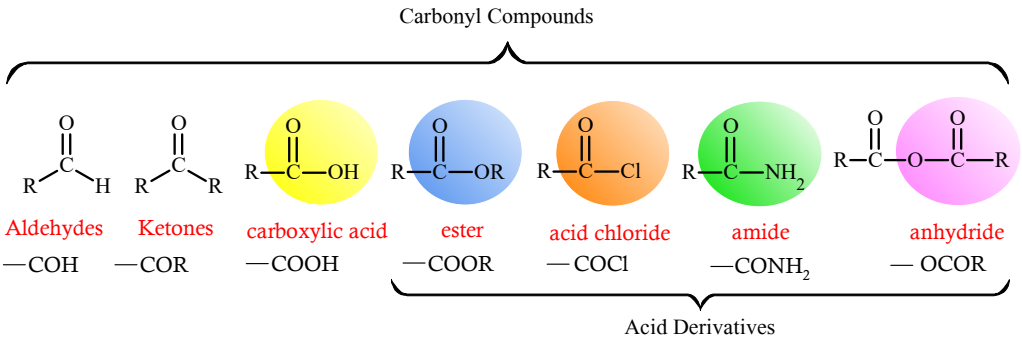
3.11 Carboxylic Acids & Derivatives

3.111 Introduction

A carbonyl group linked to hydroxyl group constitutes carboxyl group which is characteristic functional group of carboxylic acids which could be aliphatic or aromatic in character. Derivatives of carboxylic acids have different functional groups attached to carbonyl group in place of hydroxyl group. Important derivatives of carboxylic acids include: esters, amides, anhydrides and acid chlorides which are obtained by replacing –OH of carboxyl group in each of these compounds with –OR, $–NH_2$, –OCOR and –Cl respectively.

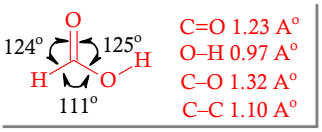


Carboxylic acids, its derivatives, aldehydes and ketones are known as carbonyl compounds because all such compounds have carbonyl group as an integral part of their molecules. Nature presents widespread prevalence of carboxylic acids: both in the form of parent acids and its derivatives.

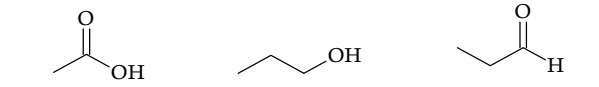


3.112 Structure and Properties

Carbonyl group is planner in orientation. Carbonyl carbon is sp^2 hybridized which renders it trigonal planner in geometry. For example, formic acid has trigonal planner shape. The O–H bond is eclipsed with C=O bond.

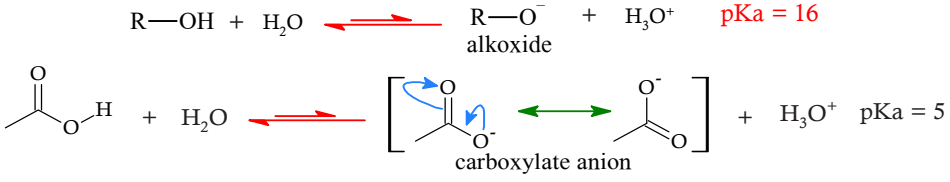


Carboxyl group is polar. It is hydrophilic part of long chain fatty acids. The polar character and hydroxyl group make carboxylic acids to participate in hydrogen bonding not only with itself but also with alcohol, water and amines. Hydrogen bonding makes carboxylic acids high boiling point compounds comparatively to alcohols, ketones or aldehydes of similar molecular weights. For example, acetic acid (MW 60) boils at 118 °C, propan-1-ol (MW 60) boils at 97 °C, and propionaldehyde (MW 58) boils at 49 °C. In fact, hydrogen bonding enhances water solubility of acids.



3.113 Acidity

Acidic strength depends upon the ease with which a molecule donates a proton. Carboxylic acid may dissociate in water to give a proton and a carboxylate ion in aqueous solution.



Carboxylate anion is conjugate base of carboxylic acids. It is resonance stabilized. In fact, resonance makes this anion stable than alkoxide anion of alcohols. Consequently, carboxylic acids are stronger acids than alcohols. For example, acetic acid is 10^{11} times stronger acid than most acidic alcohol. In carboxylate anion, negative charge is delocalized over two oxygen atoms unlike alkoxide where it is localized on just one oxygen atom.

Problem 3.111: Phenol is stronger acid than cyclohexanol but weak than acetic acid. Comment!

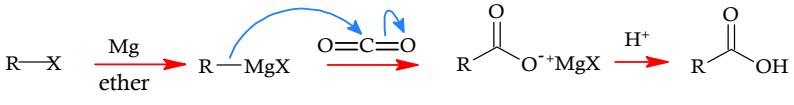
Problem 3.112: HCl is weaker acid than HBr but chloroacetic acid is stronger acid than bromoacetic acid. Comment!

Problem 3.113: Why chloroacetic acid is stronger acid than acetic acid?

3.114 Synthesis

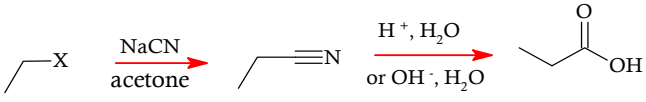
1. Carboxylation of RMgX

Carbon dioxide is electrophilic. Grignard reagent reacts with it and yield carboxylic acid as final product. The reaction proceeds through nucleophilic addition reaction.

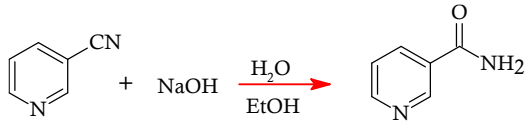


2. Hydrolysis of Nitriles

Grignard reagent is quite reactive. It can't be reacted for synthetic purposes when substrate carrying sensitive functional groups. Hydrolysis of nitriles is useful alternative under such circumstances.



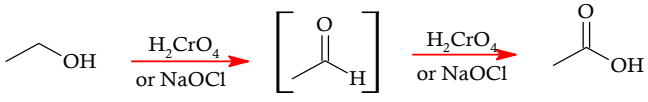
Nitriles are hydrolyzed to amides which could be further transformed to carboxylic acids either by heating with acid or base catalyst. The reaction could be stopped at amide stage by choosing milder reaction conditions.



The mechanism for basic hydrolysis begins with attack by hydroxide on the electrophilic carbon of the cyano group. Protonation gives unstable enol tautomer of an amide. Removal of a proton from oxygen and reprotonation on nitrogen gives the amide.

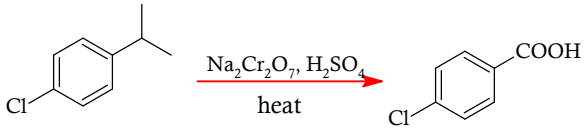
3. Oxidation of Alcohols

Primary alcohols are oxidized to carboxylic acids using variety of oxidizing agents (see detail in section 3.77-5).



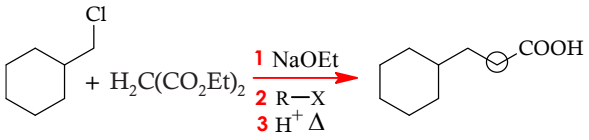
4. Oxidation of Alkyl Benzene

Carboxyl group can be established by oxidation of alkyl group present on aromatic ring. Whether hot chromic acid or potassium permanganate solution, both do the oxidation. This reaction is useful for aromatic compounds containing only alkyl group because presence of other oxidizable moieties such as –Cl, $–NO_2$, $–SO_3H$ and –COOH etc. would also be influenced by oxidation process which would yield undesirable products.

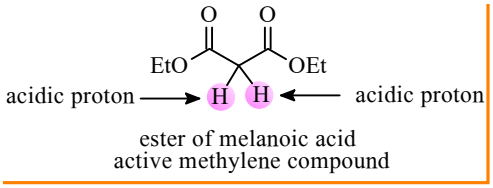


5. Melanoic Ester Synthesis

Alkyl halides can be transformed into carboxylic acids with the application of active methylene reagent i.e. ester of melanoic acid. Notice, this reaction adds one more carbon atom (encircled) to the final carboxylic acid.

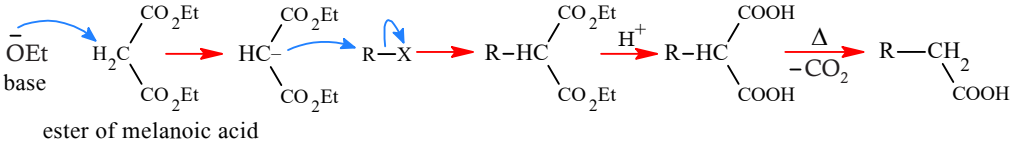


Active methylene compounds are useful reagents in organic synthesis. They have acidic proton which can be removed by base to form a resonance stabilized carbanion. The negative charged species serves as nucleophile that attacks primary alkyl halides in S_N2 fashion yielding alkylated derivative of melanoic ester whose hydrolysis converts the two ester groups into carboxyl groups. Decarboxylation is last step removes one of carboxyl group finally completing the reaction.



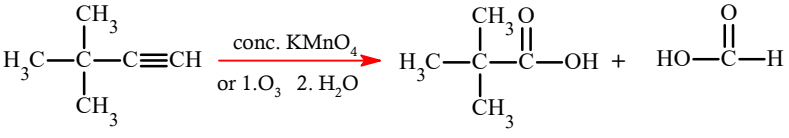
Mechanism

A resonance stabilized enolate is formed in the first step. The reaction is triggered by strong base. In second step, the enolate attacks alkyl halide yielding an alkylated derivative. Hydrolysis and subsequent decarboxylation upon heating give the final acid.



6. Ozonolysis of Alkynes

Triple bond undergoes cleavage upon ozonolysis triggered by ozone and hydrolysis.



3.115 Reactions

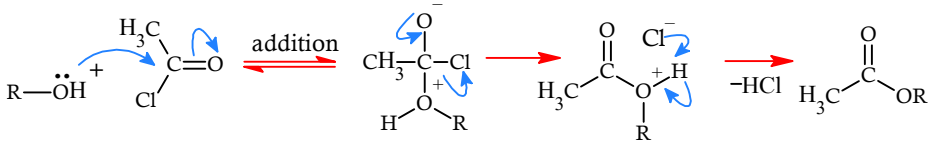
Aldehydes and ketones demonstrate nucleophilic addition reactions but carboxylic acids react by nucleophilic acyl substitution reactions which could be catalyzed either by acid or base. An acyl group is alkyl or aryl group bonded to carbonyl group. For instance, the group left by removal of hydroxyl group from acetic acid is known as acetyl group which is an example of acyl group. Nucleophilic acyl substitution reactions go by tetrahedral intermediate which stabilizes itself by expelling alkoxide group.

1. Acid Chloride to Esters

Scavenging agent such as pyridine is often used with reaction of acid chloride in a bid to trap HCl produce in reaction mixture. Other bases could be used to do away with the task of neutralizing HCl. Alcohol reacts with acid chlorides. The reaction yield esters.

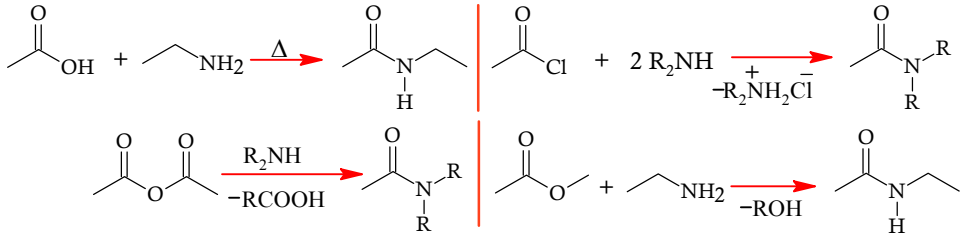
Mechanism

Alcohols are nucleophilic. They add swiftly to electrophilic carbon of acid chloride to give esters. This is excellent industrial method for synthesis of amides.

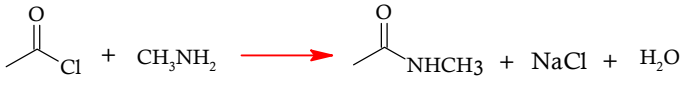


2. Synthesis of Amides

Acids condense with amines yielding amides. The neutralization reaction give ammonium carboxylate salts initially which are transformed to amides upon heating well above 100 °C to drive off steam. Anhydrides could be also used to prepare amides.

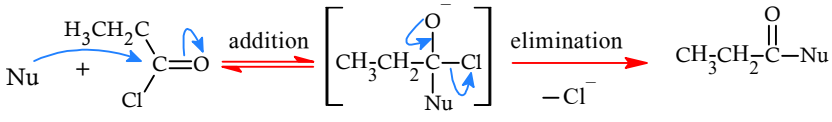


Amides could also be synthesized by reaction of ammonia and amines with acid chlorides. This reaction follows addition-elimination mechanism which is extension of nucleophilic acyl substitution reaction.



3. Thionyl Chlorides

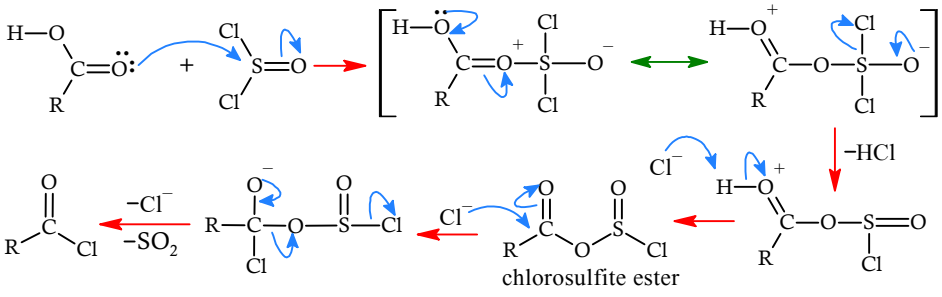
Thionyl chloride and oxalyl chloride (boils at 62 °C) are excellent reagents for transforming carboxylic acids to acid halides because they leave gaseous products which don't contaminate reaction mixture.



Acid halides are the most reactive and activated derivatives of carboxylic acids. Chlorine is excellent leaving group. Its electronegativity makes carbonyl carbon highly electrophilic. For nucleophiles $–OH^–$, $–OR$, $–NH_2^–$, $–Cl^–$, $–CH_3COO^–$, acid chlorides give product of RCOOH, RCOOR, $RCONH_2$, RCOCl and $RCOOCOCH_3$ respectively.

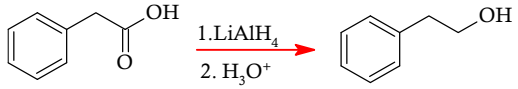
Mechanism

Carbonyl oxygen of acids is nucleophilic. It adds to sulfur of $SOCl_2$ giving tetrahedral intermediate which rearranges and finally gives a reactive chlorosulfite ester. The ester undergoes nucleophilic acyl substitution with chloride ion to give acid chloride.



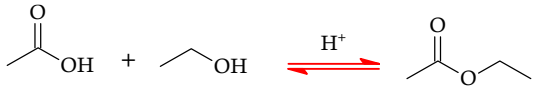
4. Reduction

LAH is strong base and it reduces acids to primary alcohols. Initially, aldehydes are formed but reaction can't stop at this stage because aldehydes are more reactive and further reduced to final product. The reaction transforms carbonyl group into methylene moiety.

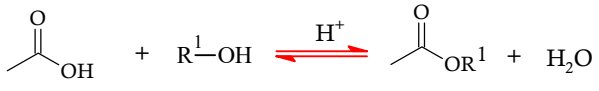


5. Fisher Esterification

The process of ester formation is termed as esterification which involves the reaction of carboxylic acids and alcohols for ester formation through an acid-catalyzed nucleophilic acyl substitution.

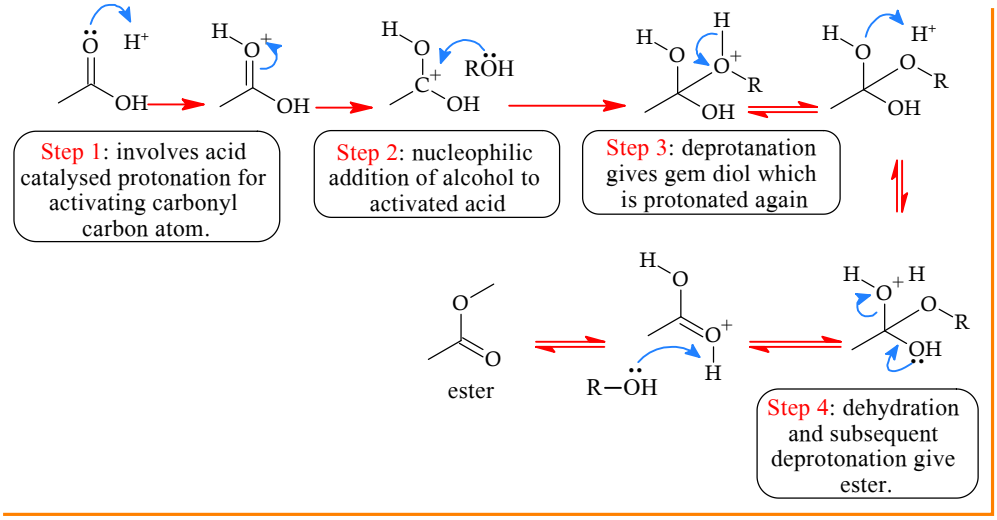


The net reaction is replacement of the acid group by the group of the alcohol. This is an example of nucleophilic acyl substitution reaction which is catalyzed by acid.



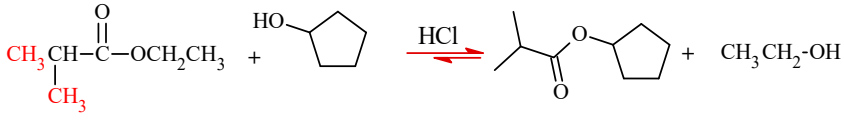
Mechanism

In essence, the mechanism operates through two steps: acid catalyzed addition of alcohol to carbonyl group and acid catalyzed dehydration. In first step, acid catalyzes protonation of carboxylic acid which enhances electrophilic character of carbonyl carbon.



Alcohols are not strong enough nucleophile to add to carbonyl group, therefore it protonation is needed to make carbonyl carbon fully electrophilic. Next step involves addition of alcohol to carbonyl carbon giving tetrahedral intermediate. Deprotonation of the intermediate yields a diol whose subsequent protonation gives another tetrahedral intermediate. Finally, another deprotonation gives esters. Fisher esterification is common method for synthesis of esters. This is an equilibrium reaction which can be shifted to the product side without any difficulty either by using excess of alcohol or by distilling water. Acid chlorides could be used for synthesis of esters by reacting with alcohols but they are more expensive and reactive and could yield side product through dehydration of alcohol

Transesterification is reaction of ester with alcohol in the presence of an acid gives new ester which involves mutual interchange of alkoxy group of alcohol for alkoxy group of ester. The reaction is said to be transesterification reaction which works by similar mechanism of acid catalyzed hydrolysis of ester with exception of alcoholic nucleophile instead of water.

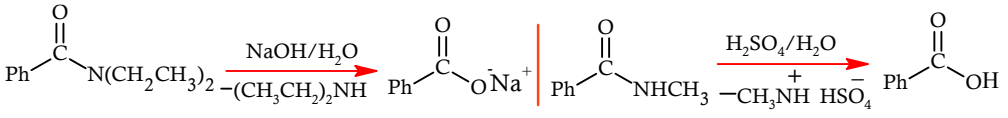


6. Hydrolysis of Acid Derivatives

Either acid or base could trigger the hydrolysis of acid derivatives yielding carboxylic acids as final product.

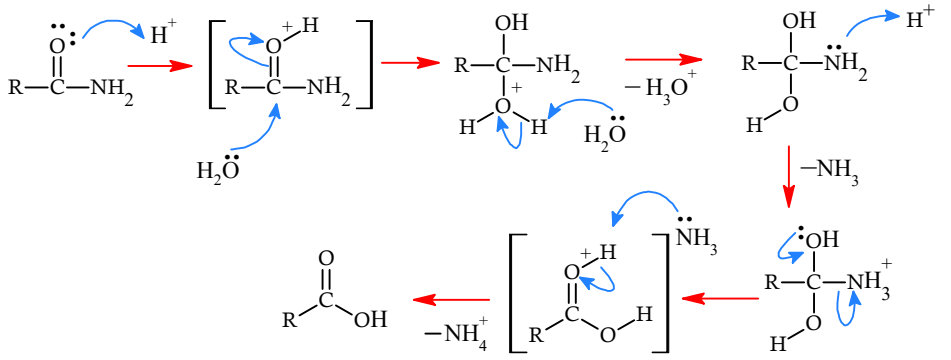
Hydrolysis of Amides

Amides are least reactive and most stable of all acid derivatives. The can be hydrolyzed to carboxylic acids either by acid or base catalysis. This reaction requires harsh conditions than generally required for hydrolysis of esters.



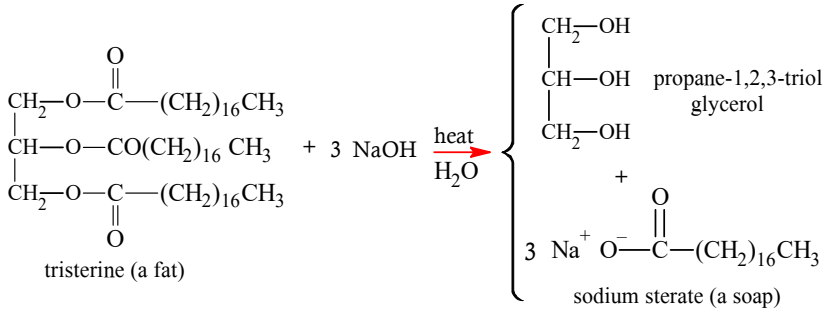
Mechanism

The mechanism is similar to Fisher esterification that proceeds through tetrahedral mechanism. The reaction goes through two steps: first half is acid catalyzed addition of nucleophile, second half requires acid catalyze elimination reaction. In basic hydrolysis, carbonyl group is attacked by base. Internal rearrangement of tetrahedral intermediate and consequent expulsion of amide gives carboxylic acid which is deprotonated and salt of acid and ammonia generated. The mechanism is similar to hydrolysis of ester.

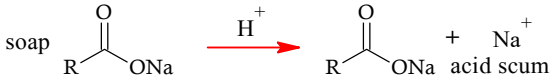


Hydrolysis of Esters

Fisher esterification reaction is reversible. Its equilibrium could be shifted towards the product either by adding more alcohol or removing water through distillation. The reaction could be reversed if water is added which hydrolyze ester back to acid and alcohol.

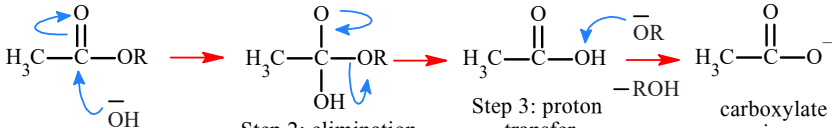


When base is used for catalysis, the hydrolysis of ester is known as saponification (Latin, saponis means soap). Traditionally, saponification was the hydrolysis of ester linkage in fats and oils promoted by base which was discovered some 500 BC. Industrially, animal fats or vegetable oils are used to make soap when they are boiled with strong base such sodium hydroxide. From above reaction, we get sodium salt of long chain fatty acid. Chemically, sodium or potassium salts of long chain fatty acids is termed as soap which gives acid scums when exposed to react with acid.

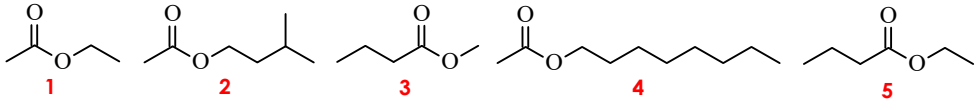


Mechanism

Saponification follows three steps mechanism given as follow:

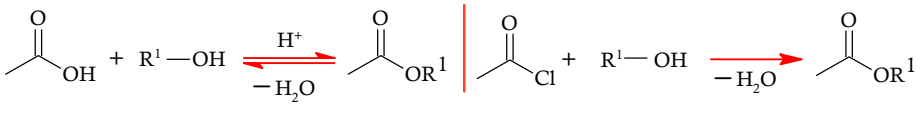


Summary of Esters: Esters are used as flavoring agents. They serve as largest class of food additives. Consider the following esters which are used to add flavor to our food.

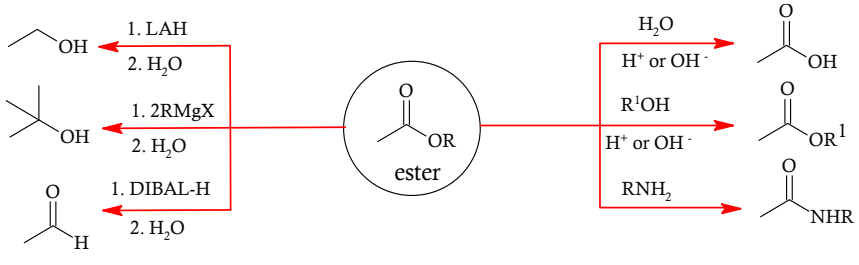


1 ethyl acetate (Rum)
2 3-methylbutyl acetate (Banana)
3 octyl acetate (Orange)
4 methyl butanoate (Apple)
5 ethyl butanoate (Pineapple)

Esters are synthesized by esterification or by treating acid halides with alcohols.

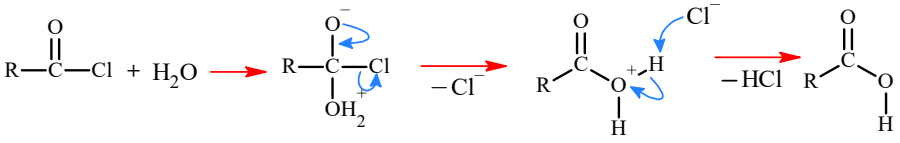


Chemically, esters offers excellent substrate for functional group interconversion. The following set of reactions gives us quick insight into how esters can be transformed into other functional group.



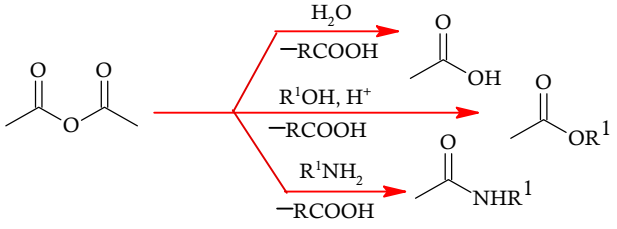
Acid Chlorides and Anhydrides

Whether acid halides or anhydrides, both are quite reactive among all acid derivatives. They are stored in neutral condition such as inert nitrogen to prevent spontaneous hydrolysis by reacting with moisture in air. On account of their reactivity, acid chlorides and anhydrides don't require any acid or base catalysis for hydrolysis.

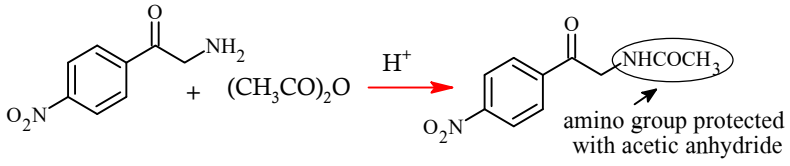


Application of Anhydrides

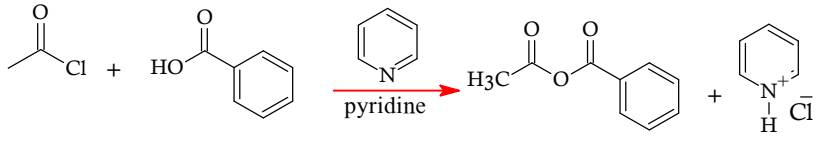
A cyclic diacid with relevant C atoms for cyclization could be transformed into an anhydride which is sometime needed to get bifunctional compound containing ester and amide. This is an example of functional group interconversion (FGI) using cyclic anhydride.



Anhydrides are less reactive and more selective than acid chlorides. This property demands anhydrides to be used as fine acetylation reagent. Acetylation reaction is used for protection of amines.



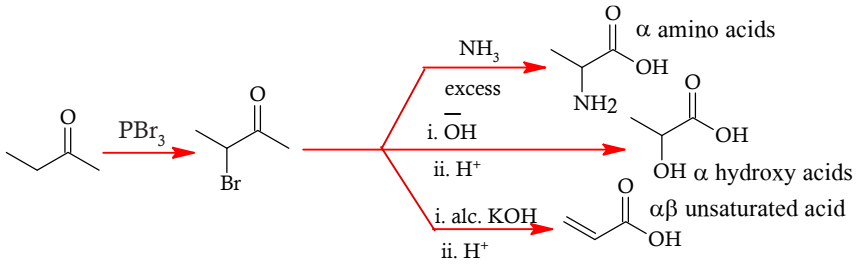
Acetic anhydride is most common among anhydride series which is produced on large scale required for synthesis of drugs, plastics and fibers. It is inexpensive and easy to use and offer better yield than acetyl chloride for acetylation of amines and alcohols. Anhydride are usually made by the reaction of acid chlorides with carboxylic acids.



7. Hell VoIhard Zelinsky Reaction

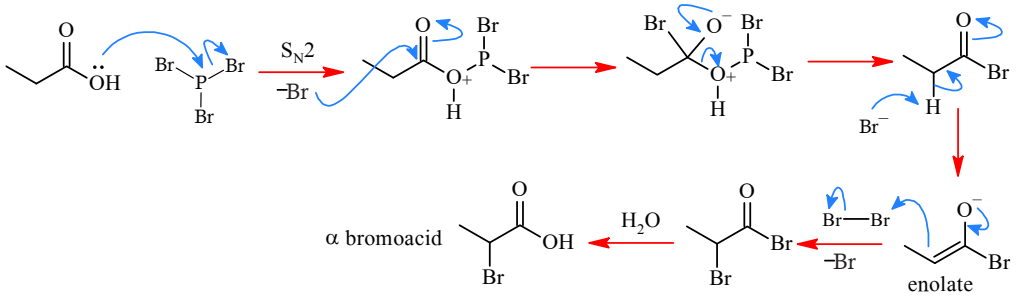
Much like α hydrogen of active methylene compounds are acidic, α hydrogen of carboxylic acids are acidic too. When such hydrogen is substituted by bromine while treating the acid with phosphorous tribromide, the reaction is termed as Hell VoIhard

Zelinsky reaction. Alpha haloacid is useful precursor for synthesis of α amino acids, α hydroxyl acids and αβ-unsaturated carboxylic acids.



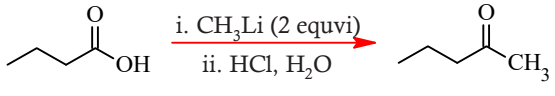
Mechanism

The reaction works through nucleophilic acyl substitution pattern. Red phosphorous (from our match box) reacts with bromine to form PBr_3 which helps removal of hydroxyl group since it is poor leaving group. Once acid bromide is formed, alpha hydrogen is removed by bromide anion giving an enolate. A neutral bromine molecule is attacked by the enolate yielding alpha bromo acid bromide which is finally transformed into alpha bromo acid upon treatment with water.

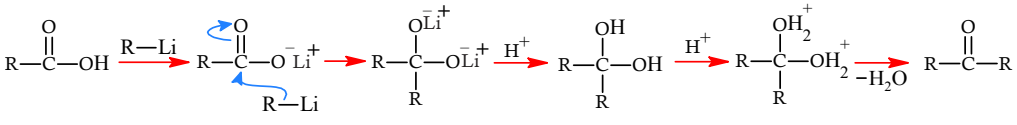


8. Reaction with Alkyl Lithium

Alkyl lithium compounds are highly reactive organometallic reagents which serve as strong base that deprotonates carboxylic acid yielding lithium salt of carboxylic acids.



A second equivalent of RLi add to carbonyl group of the salt giving a dianion which is stable in solution until acid is acid. The dianion is transformed into a hydrate upon acid work up. Protonation and subsequent elimination of water from the hydrate finally gives ketone.



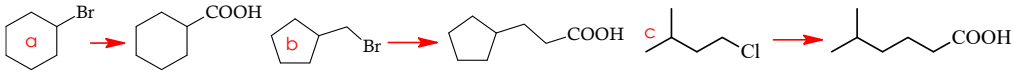
3.116 Exercise

1. Explain the following statement briefly.

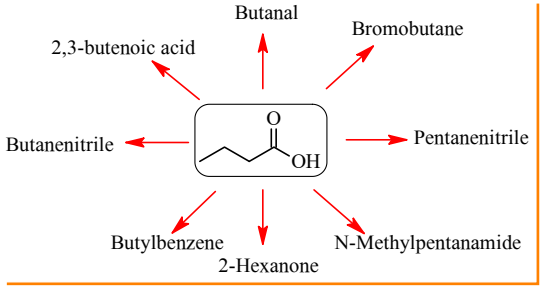
a. Is oxygen of ester removed or retained during hydrolysis of esters?
b. Benzoic acid has higher pKa value as compare to formic acid, reason!
c. Dicarboxylic acids are generally stronger acids than monocarboxylic acids, why?
d. Why Fisher esterification requires acid catalyst though RCOOH is acid itself?
e. Oxalic acid releases its first proton easily, the second can't. Reason!
f. Acid halides are more reactive among all acid derivatives, why?
g. Which one is stronger acid, formic acid or acetic acid?
h. Why methanoic acid is stronger acid than ethanoic acid?
i. Amides are less basic than primary amines, reason.
j. Why acid or base is required for catalyzing the hydrolysis of esters although anhydrides don't require such conditions?

2. Convert butanoic acid into 1-butanol, 1-butene, alpha amino butanoic acid, 1-bromobutane and pentanoic acid.

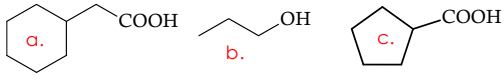
3. Make the following conversion:



4. Make the following functional group interconversion through relevant reaction.

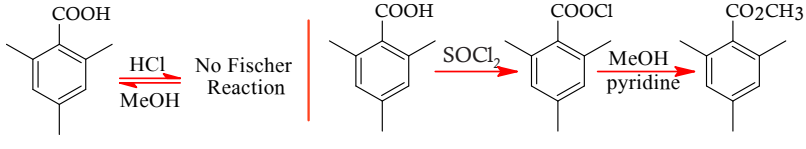


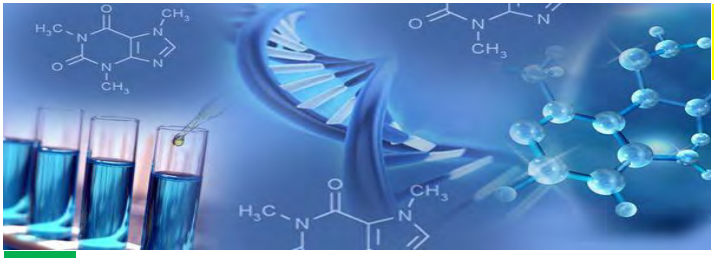
5. Synthesize the following molecules through a relevant reaction mechanism.



6. Carboxylic acids don't undergo addition reactions of aldehydes and ketones, reason why carboxylic acids show different behavior although both are carbonyl compounds.

7. 2,4,6-Trimethyl benzoic acid fails to undergo Fischer esterification. However, converting it to acid halide make it possible to convert to ester. Reason.





Section 4 Biochemistry

4.1 Carbohydrates

The clothes we wear, the book we read and the food we eat are all carbohydrates which represent the most important class of organic compound widely prevalent in nature. Carbohydrate means hydrates of carbon or compounds bearing water molecule per carbon atom. In short, carbohydrates are the compounds of carbon and water. They are represented by general formula of $C_n(H_2O)_n$ where n is the number of carbon atoms and water molecules. Carbohydrates are the most abundant class of organic compounds. They are synthesized by both plants and animals. Plants synthesize them via photosynthesis, animals do so by gluconeogenesis. The following reaction reflects the process of photosynthesis which utilizes light to make glucose from carbon dioxide and water. Glucose is fundamental building block of carbohydrates. Animals extract energy from metabolism of carbohydrate.

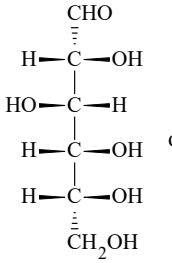
$$6\,CO_2 + 6\,H_2O \xrightarrow{light} 6\,O_2 + \underset{\text{glucose}}{C_6H_{12}O_6} \longrightarrow \text{starch, cellulose} + H_2O$$

Carbohydrates are important biomolecules. They serve as sources of energy and storage compounds besides providing carbon units for synthesis of protein, lipids and nucleic acids. Carbohydrates serve structural basis for DNA and RNA molecules.

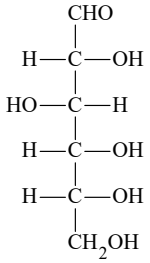
4.11 Classification

Carbohydrates bear multiple hydroxyl groups along with presence of aldehydes or ketone or both functional groups. Technically, they are defined as polyhydroxy aldehydes (aldoses) or polyhydroxy ketones (ketoses) or compound which can easily hydrolyze to them. For instance, glucose is polyhydroxy aldehyde and fructose is polyhydroxy ketone.

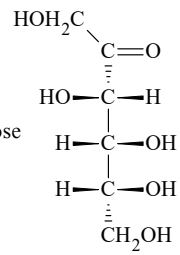
Glucose



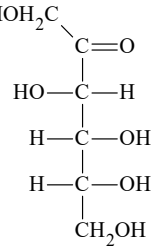
or



Fructose

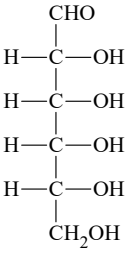


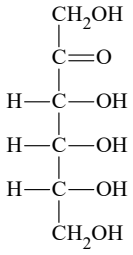
or

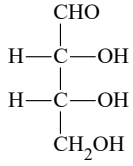


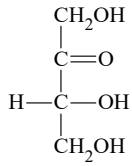
Carbohydrates are classified into three major classes: monosaccharides, disaccharides and polysaccharides. Monosaccharides are simple sugars that can't be further hydrolyzed into simpler units. Glucose and fructose are examples of monosaccharides. Fisher projections are used to represent these molecules.

Sugars have 3 to 7 carbon atoms. A three carbon atom sugar is known as triose, four carbon atoms is tetrose and so one. Aldohexoses and aldopentoses are most common sugars which occur in nature.


aldohexose

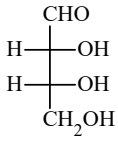

ketohexose

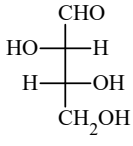

aldotetrose


ketotetrose

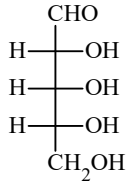
The following table shows the classification of aldehydes and ketones.

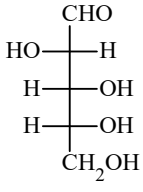
Aldoses

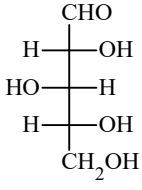

D-Erythrose

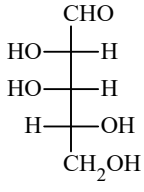

D-Threose

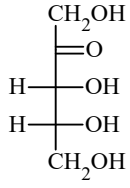
Ketoses

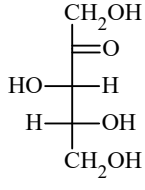

D-Ribose

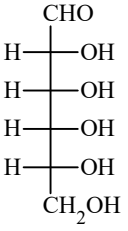

D-Arabinose

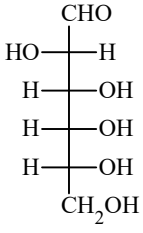

D-Xylose

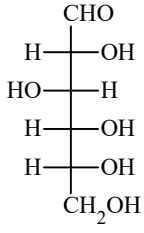

D-Lyxose

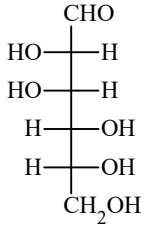

D-Ribulose

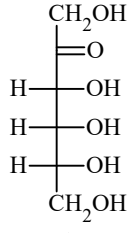

D-Xyloulose

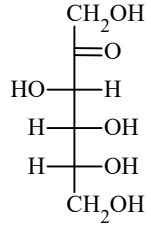

D-Allose

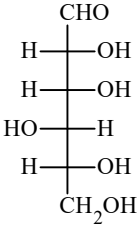

D-Altrose

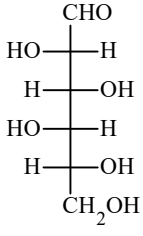

D-Glucose

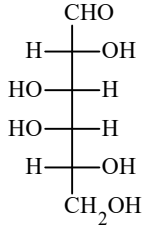

D-Mannose

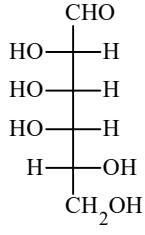

D-Psicose

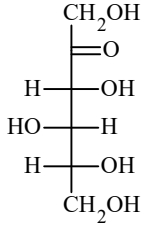

D-Fructose

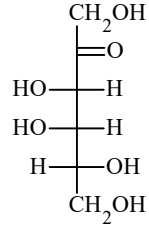

D-Gulose


D-Idose


D-Galsctose


D-Talose


D-Sorbose


D-Tagatose

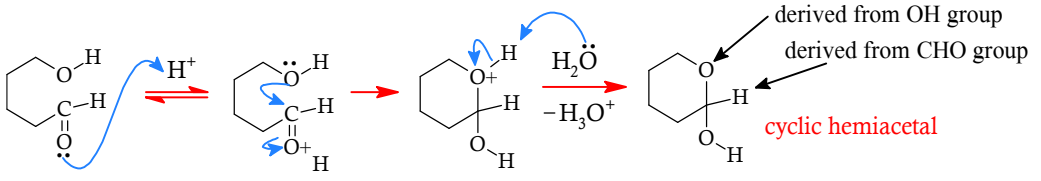
4.12 Cyclic Acetals

Aldehydes or ketones reacts with water to give hydrates. They give hemi-acetals and acetals with alcohols. When aldehyde or ketone adds one molecule of alcohol, it give hemi-acetal. Addition of two alcohol molecules yields acetals. A linear chain (5 or 6 carbon atoms) bearing formyl or keto group on one terminal and hydroxyl group on other gives cyclic hemi-acetals which are relatively more stable as compared to open chain hemi-acetals.

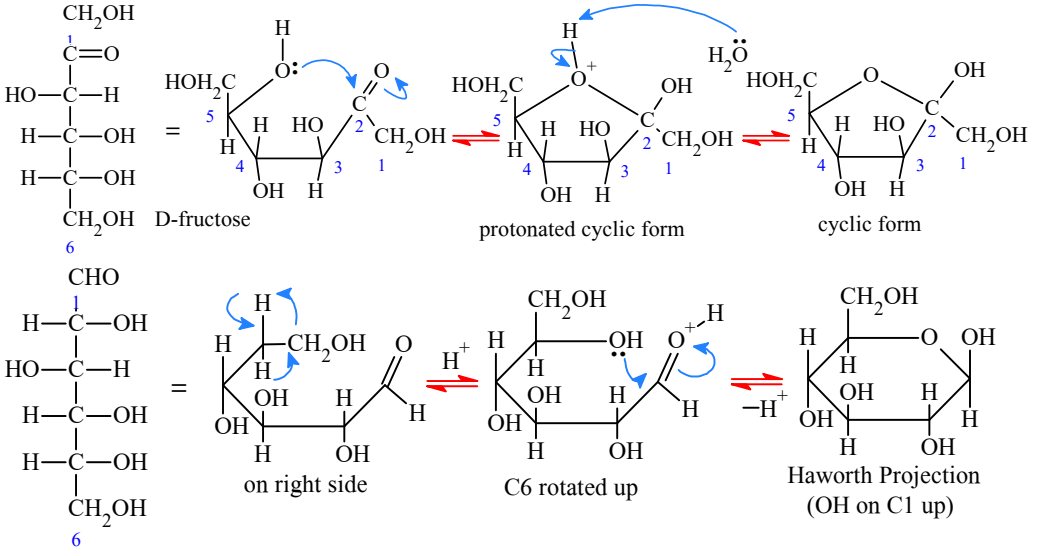
Formation of Cyclic Hemiacetal

Mechanism

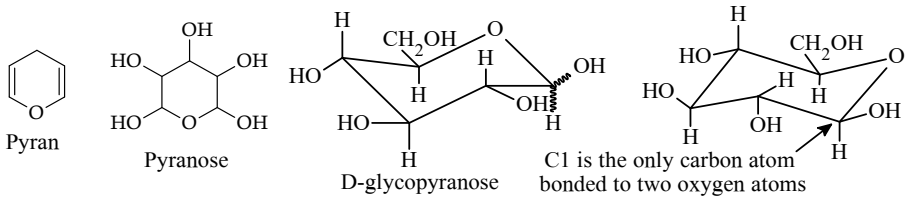
Step 1: Protonation of the carbonyl. ***Step 2:*** The OH group adds as a nucleophile. ***Step 3:*** Deprotonation gives a cyclic hemiacetal.



Aldoses usually exist in cyclic hemi-acetal form in pure crystalline form. In solution state, both open chain and cyclic form exist with equilibrium directed more toward the cyclic acetal form. Haworth projections are used to draw cyclic structures of sugar. Consider 5 and 6 member ring formation for fructose and glucose as follow:



Five (furanose) or six (pyranose) membered cyclic hemi-acetals are named based on furan or pyran respectively. For instance, a six membered cyclic glucose structure is named as glycopyranose and five membered cyclic fructose is named as fructofuranoe.

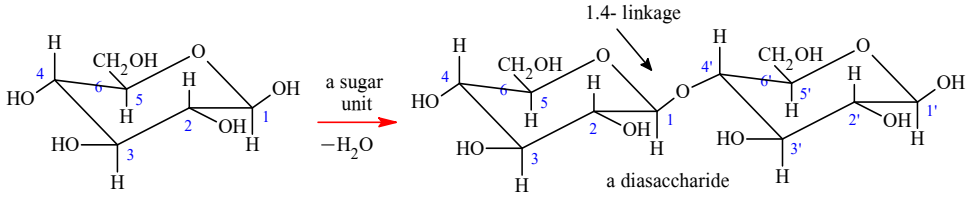


Unlike monosaccharides, disaccharides can be hydrolyzed to monosaccharides units. Dissolving table sugar, sucrose, in water yields glucose and fructose units.

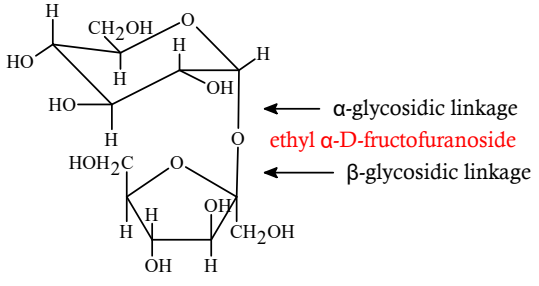
$$1\ \text{Sucrose} + H_3O^+ \longrightarrow 1\ \text{Glucose} + 1\ \text{Fructose}$$

Both mono and disaccharides are sweet in taste and highly soluble in water. The two units of glucose and fructose in sucrose are joined by glyosidic linkage. Hydroxyl group on anomeric carbon of one unit can combine with any hydroxyl group on another sugar unit. An anomeric carbon is one which links to two oxygen atom in cyclic structure of glucose unit. This carbon bears position 1 when we number the cyclic structure.

Disaccharides exhibits different pattern of linkages between two units. This linkage could be 1,1', 1,4' and 1,6'. The digit 1 reflects the anomeric carbon on one unit where the second digit shows the carbon on another unit two which the first unit is bonded through glyosidic linkage. We use prime on the second digit to hint it as second sugar unit.

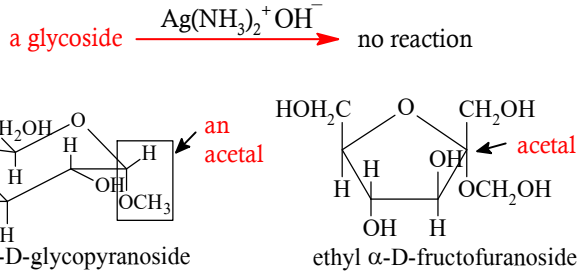


1,1' linkage is observed in sucrose. The glyosidic linkage could be either in alpha (below the plan) or beta (above the plan) position. We call sucrose and α-glycopyranose-β-fructofuranoside because glucose unit is attached via its α position but fructose via its β position.

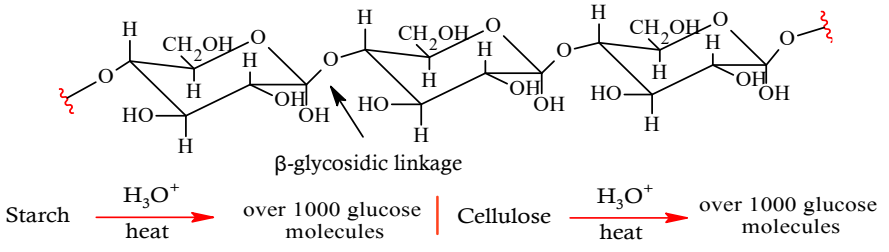


Polysaccharides form third class of carbohydrates which contain multiple monosaccharide units joined by glyosidic linkage. Smaller polysaccharides contain 3 to 10 units are sometimes termed as oligosaccharides. Most common polysaccharides such as starch and cellulose have hundreds and thousands of monosaccharide units. Polysaccharides are natural biopolymers. Since every anomeric carbon on polysaccharide

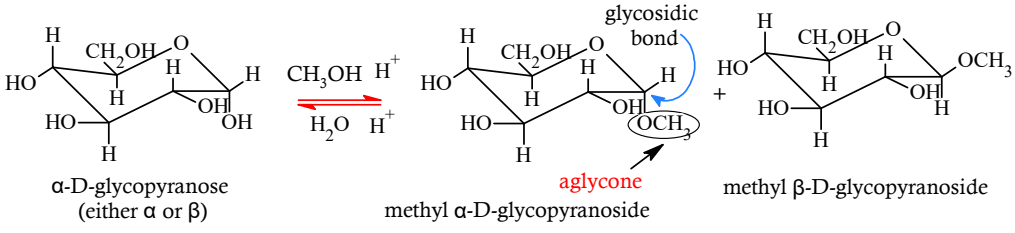
chain is involved in acetal formation, these compounds don't give positive Tollen's test or mutarotate. Tollen's test works with aldehydes containing free formyl or keto group. In acetal or hemi acetals, these group lose identity, therefore they don't give positive Tollen's test. Hemi acetals could give positive test since they are unstable as compared to acetal and they can open to free form in solution. Actually, sugar containing acetal are termed as glycosides whose name ends in suffix –oside. In a nutshell, Tollen's test differentiate between reducing (hemi acetals such as aldoses and ketoses) and non- reducing sugars (glycosides, stable to basic conditions). Reducing sugars muta-rotate but non-reducing ones can't. Consider the examples of non-reducing sugars:



Polysaccharides could be hydrolyzed to multiple glucose units. Cellulose structure has shown below:



An aglycon is group bonded to anomeric carbon atom of a glycoside such as methyl aglycon of methyl glycoside. Glycosides are stable toward basic conditions but they hydrolyze by acidic medium.

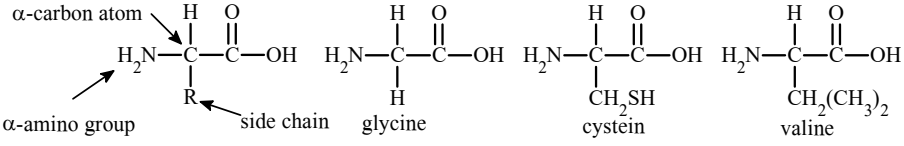


4.2 Proteins

Our biochemical system which run our bodies would not be possible to operate without enzymes which maintain and accelerate important biological process upon which we survive. An enzyme DNA polymerase replicates and repairs DNA. Without it, our cell division won't exist which mean we wouldn't exist. These enzymes are protein in nature which give us insight about the significance of these biomolecules to our lives.

Class of Protein	Example	Function
Structural proteins	Collagen, keratin	Strengthen tendons, skin, hair, nails
Enzymes	DNA polymerase	Replicates and repair DNA
Transport proteins	Hemoglobin, transferrin, HDL, LDL	Transport O_2 to the cells, carries iron from liver to bone marrow
Contractile proteins	Actin, myosin	Cause contraction of muscles, sperm swims due to contractile protein
Protective proteins	Antibodies or immunoglobulins	Complex with foreign proteins
Hormones or messenger proteins	Insulin, glucagon	Regulate glucose metabolism
Toxins	Snake venoms	Incapacitate prey
Storage proteins	Myoglobin	Oxygen storage protein in muscles
Nutrient proteins	Casein, albumin	Milks and eggs

Proteins are polymers. These polymers are made from amino acids which fundamental building blocks of protein. These units are joined by peptide bond. Structurally, amino acid consists of amino group lies alpha to carboxyl group.



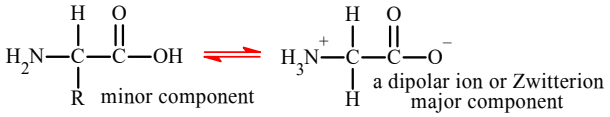
Some amino acids can't be synthesized by our bodies. They are termed as essential amino acids because they are needed for body from external sources such as food or drinks. Arginine, valine and methionine are examples of essential amino acids. Non-essential amino acids are synthesized within our body. Almost half of amino acids can be synthesized within our bodies requires for production of proteins. A complete proteins such as milk, eggs, fish or meat contain all essential amino acids in right proportion.

Diabetes

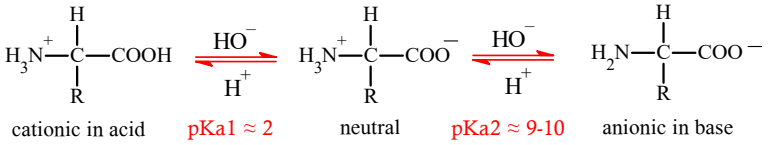
Pakistan has third largest adult population afflicted with diabetes in the world after China and India. Internationals Diabetes Federation records 33 million adult pollution in Pakistan with the chronic disease in 2021. Moreover, 9 million people have not been diagnosed and some 11 million adults have impaired glucose intolerance, a condition known as prediabetes. By 2030, the number is projected to exceed 43 million. Diabetes mellitus (Greek: diabetes means excessive urine, mellitus means sweet) is a chronic non communicable disease like cardiovascular, cancer and respiratory diseases. There are two types of diabetes: type 1 and 2. When body fails to produce sufficient insulin, it is type 1 diabetes. When the body fails to respond to insulin, it is type 2. In Pakistan, type 1 is almost nonexistent. Type 2 is most common which occurs due to lack of exercise, genetics, diet and environmental pollution. If type 2 is not treated, it causes serious disabilities in whole body, especially feet, kidneys, eyes and heart.

Amino acids are dipolar (Zwitterion, German) molecules which is established by loss of proton from –COOH and protonate $–NH_2$ group depending upon the pH of

medium. They are neutral because both acidic and basic groups are present in them. Amino acids are high melting point compounds which are soluble in water more than any other solvent.



Amino acids exist in different forms under different circumstances created by pH variation of medium.



4.3 Enzymes

Enzymes are important biological molecules which play crucial role in operating fundamental biological processes. In essence, enzymes are globular protein which catalyze biological reactions. Enzymes don't disturb equilibrium or do anything to reaction, they just increase the rate of reaction by lowering activation energy. Enzymes are not only effective but also quite specific in their activity. For instance, glucose solution doesn't oxidize by oxygen for months but the same glucose oxidizes inside body within seconds by enzyme. Enzymes are widely prevalent in our biological system. An ordinary cell consists of more than 3000 enzymes. They catalyze just one specific reaction. Urease operates on hydrolysis of area alone. It doesn't do anything to amides.

The chemistry of enzymes is intricate. Some enzymes such as pepsin and trypsin contains poly-peptide (protein part, apoenzyme) chain only. Apoenzymes don't catalyze reaction without its cofactors (organic or inorganic) which are non-protein part of enzymes. The cofactor doesn't function without apoenzyme. Organic cofactors are termed as coenzyme such as heme or vitamin B.

4.31 Factors Affecting Enzyme

Concentration of substrate, temperature and pH of medium affect the rate with which an enzyme operate on particular biological reaction. Increasing the concentration of enzyme increase the rate of reaction. However, different situation, saturation curve, emerges when the concentration of substrate increases but concentration of enzyme is kept constant. Here, the rate doesn't increase but stay the same. The nature of enzyme is influenced by temperature because it changes its conformation and impact enzymatic activity. In an ordinary reaction, temperature increase rate of reaction by increasing the collision frequency. However, the effect doesn't stay the same for enzyme catalyzed reactions. Enzymes work at optimum temperatures (37 °C). Increasing or decreasing the

temperature beyond optimum influences the activity of enzyme that reduces the rate of reaction. Much like temperature, pH of reaction medium also influences the activity of enzyme by changing the conformation. Beyond optimal pH, enzymes could be denatured and rate of reaction declined.

Inhibition

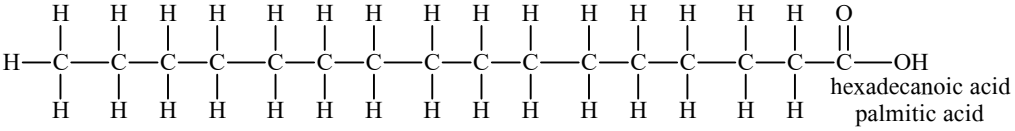
Whatever stop enzymes from normal operation is termed as inhibitor and the process is termed as inhibition which can be reversible or irreversible. Inhibitors could be competitive (resembles features of substrate) or non-competitive. Competitive inhibitor doesn't operated by enzyme. It just block the active site and halts enzymatic action. This is reversible because the interaction is temporary between competitive inhibitor and enzyme. The inhibition could be reduced simply by increasing the concentration of substrate. When inhibitor binds to site other than active site and influences the tertiary structure and activity of enzyme, the inhibition is termed as non-competitive inhibition. Both competitive and non-competitive inhibition are irreversible. An irreversible inhibition involves strong covalent bond between inhibitor and enzyme. This inhibition is permanent that damages enzyme and makes it deactivated. Nerve agents and organophosphate insecticide work by irreversible inhibition of enzyme.

4.4 Lipids

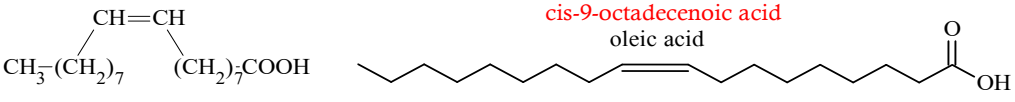
Important bio-molecules such as fats, steroids, oil, waxes, terpenes and prostaglandins are examples of lipid which is important class of biochemistry that serves as energy storage materials, membrane constituents, emulsifying agents, messenger molecules and protective coating materials. Lipids serve source for fat soluble vitamins such as A, D, E and K. They are insoluble or sparingly soluble in water but soluble in organic solvent. In fact, solubility serves basis for classification of lipids: simple (steroids, prostaglandins, terpenes) and complex lipids (fatty acids, glycerides). Simple lipids don't hydrolyze in aqueous acid or basic solution unlike complex ones which yield simple units upon hydrolysis because they are esters called fatty acids.

Hydrolysis of lipids yields derived lipids such as fatty acids, alcohols, glycerides, diglycerides, steroids, terpenes and carotenoids. The latter three represent the most common class of derived lipids. Steroids don't hydrolyze. They are non-saponifiable and don't contain fatty acids. Steroids are widely present in living system, especially animals for driving different physiological processes. Estrane and androstanes are examples of steroids. Natural rubber, carotenoids and menthol represent the class of terpenoids which are widely prevalent in plants (exclusively) and animals. Hydrolysis of fats catalyzed by alkaline solution is known as saponification which gives soap (a mixture of glycerol and fatty acids). Fatty acids are long chain mono carboxylic acids containing 4 to 26 carbon atoms. They could be long chain (12 to 26 carbon atoms), medium (8 to 10 carbon atoms) and short chain fatty acids (4 to 6 carbon atoms). Every fatty acids consists of even carbon atoms because they are synthesized from two carbon acetyl unit. Fatty acids can be saturated (SFAs) or unsaturated (UFAs) whether it has any carbon to carbon double bond or not. Fats possess saturated fatty acids which are solid (animal fat) or unsaturated fatty acids which are liquid (plant fat) at room temperature. They can be further labelled as

mono (MUFAs) or poly (PUFAs) unsaturated fatty acids. A fatty acid such as palmitic acid is represented by molecular formula of $CH_3–(CH_2)_{14}–COOH$. Structurally, palmitic acid is shown as long chain mono carboxylic acid.



Double bond in fatty acids could be either in cis or trans conformation which gives entirely different structure to overall fatty acid.



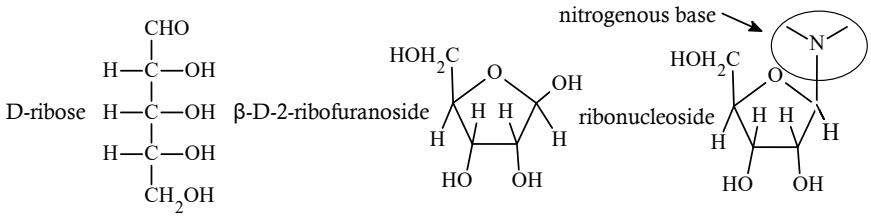
Linoleic acid and linolenic acid are essential fatty acids. They need to be derived from plant sources for diet. Essential fatty acids serve as precursors for different eicosanoids such as prostaglandins and thromboxane which play pivotal function in pain, fever, blood clotting and inflammation. Non-essential fatty acids are synthesized within our biochemical pathways and don't need to be taken via diet. Unsaturated fatty acids have cis double bond which melt them at lower temperature. A cis double bond incorporates bend in the chain which distort the entire conformation. Consequently, packing among molecules is disturbed and oil results. Contrary, saturated fatty acids are linear. They have larger surface area and high melting points. Besides, melting point also depends upon the chain length. In fact, fats and oils are distinguished by physical state at room temperature.

Oil	SFA (%)	MUFA (%)	PUFA (%)
Canola oil	6	58	36
Sunflower oil	11	20	69
Olive oil	14	77	9
Soybean oil	15	24	61
Peanut oil	18	48	34
Coconut oil	92	6	2

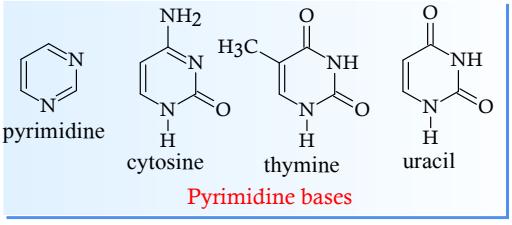
Triglycerides (fats and oils) and phospholipids plants and animal membrane) are most commonly occurring lipids. Triglycerides are made from glycerol backbone bonded to three fatty acids. We call it simple triglycerides if three fatty acids are same and mixed triglyceride is they are different. Besides fatty acids, phospholipids (lecithin, cephalins) contain phosphoric acid and alcohol.

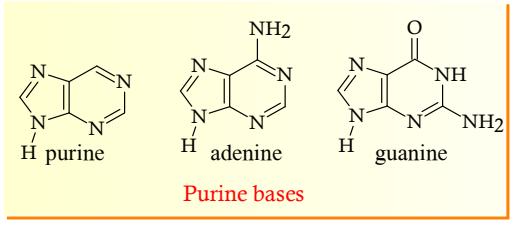
4.5 Nucleic Acids

Our genetic information required for maintaining fundamental architecture and its function are encoded in tiny units which are made by furanoside ring (ribose or deoxy ribose sugar) to which an aglycone of heterocyclic nitrogenous base is attached and a phosphate ester group. These units constitutes giant polymers. DNA and RNA are constituted by four nucleotides monomers.

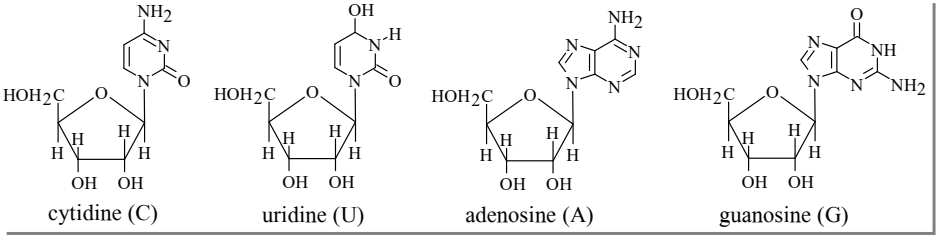


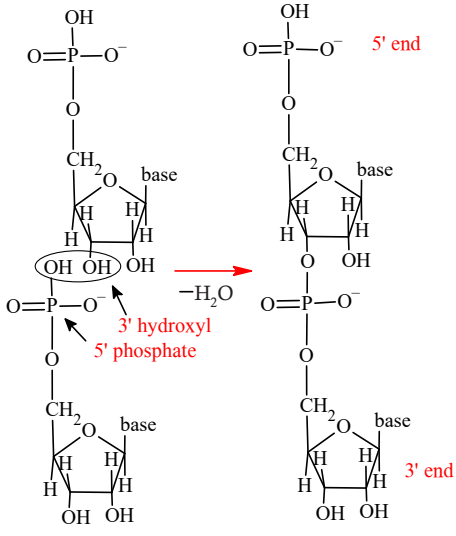
Nitrogenous base of RNA form monocyclic and bicyclic compounds. Monocyclic bases are termed as pyrimidine bases such as cytosine and uracil because they contain pyrimidine nucleus. Bicyclic bases are based on purine nucleus. Adenine and guanine are examples of purine bases.





A ribonucleoside such as cytidine or uridine form when nitrogenous base bonds to ribose sugar. Both rings in ribonucleoside are named separately.

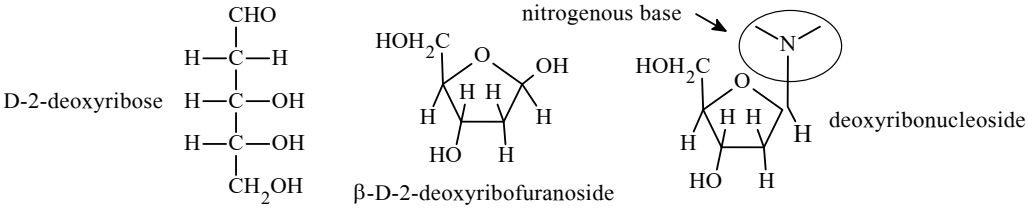




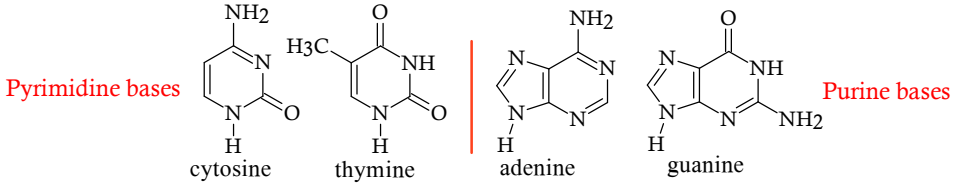
A nucleotide links to two other nucleotides in chain. Each nucleotide attaches to phosphate group of another nucleotide via its carbon atom at position 5 and phosphate

group of another nucleotide via –OH group at position 3 of the ribose sugar. The linkage is termed as phosphate ester linkage between 5' and 3' phosphate groups. An RNA strand has 3' to 5' direction because one end has free 3' terminal and the other has 5' free terminal.

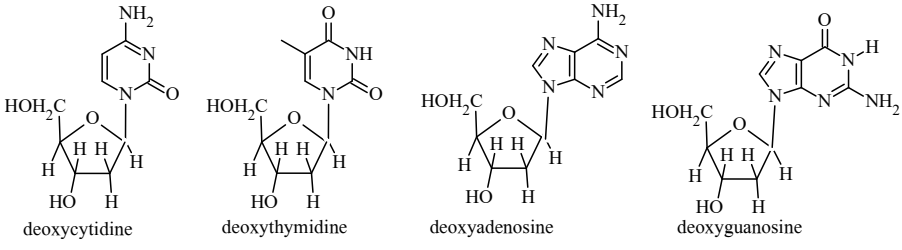
DNA differs from RNA by its –OH group at position 2 which is missing in DNA.



DNA has thiamin nucleotide unlike uracil in RNA. DNA has following four nitrogenous bases.



Consider the nucleoside of DNA



Blood Groups

Human blood is divided into four groups: A, B, AB and O. People with O blood group are universal donor. AB group is universal recipient. For a patient who needs blood transfusion, blood group of donor must match the blood group of recipient. A wrong blood group could be fatal since it causes blood to aggregate and bring death. The following table shows how different blood groups are compatible or not.

	Recipient Blood Type			
Donor Blood Type	A	B	AB	O
A	+	–	+	–
B	–	+	+	–
AB	–	–	+	–
O	+	+	+	+

+ compatible – incompatible

4.6 Minerals

Our body need minerals both in micro and macro level because they are essential for keeping our biochemical system operational. We call a food a balance diet when it contains all essential minerals in optimum quantity. Minerals are atoms or molecules which are required for our body to grow and function. For instance, iron (egg, meat, fish) is needed for hemoglobin. Zinc (meat, fish, grains and vegetables) is essential for synthesis of enzymes, sperm production and sexual maturation beyond a healthy immune system and healing. Healthy bones and teeth, muscle movement, never functioning, blood clotting, blood pressure regulation and healthy immune system are maintained by calcium which is provided by milk, fish and green vegetables. Phosphorous (meat, fish, and eggs) maintains healthy bones and teeth and acid-base balance. Magnesium helps regulate metabolic function which is abundant elements in plant and animal cells. The three elements: Ca, Mg and P account for 98% of minerals by weight required by our body to function properly.

Problem 4.1 Are α and β isomers of glucose are enantiomers? Comment briefly!

Problem 4.2 Comment and explain the following statements whether each is true or false.

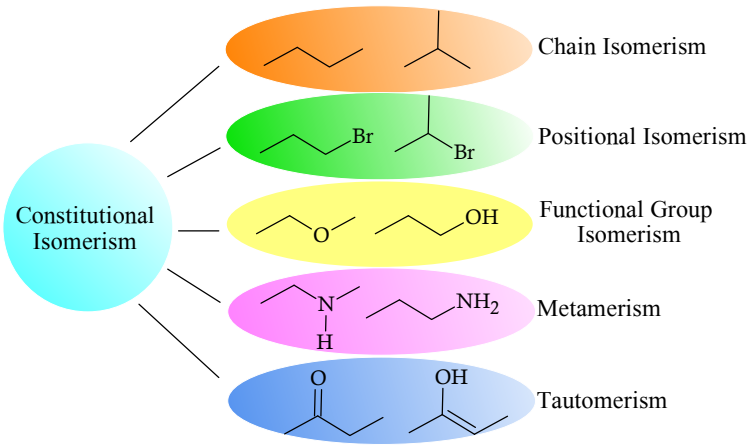
a. Tryptophan is an aromatic amino acid.
b. Lysine is positively charged at pH 7.
c. Asparagine has two amide bonds.
d. Epimers are enantiomers.
e. Isoleucine and leucine are enantiomers.
f. Valine is probably more water-soluble than arginine.
g. α helix and β sheet structures are examples of quaternary protein.
h. Only H bonding is involved in forming the tertiary structure of a protein.
i. Maltose is a monosaccharide.
j. Polysaccharides are a type of carbohydrate.
k. All carbohydrates have an oxygen to hydrogen ratio of 1:2.

3 D View of Organic Molecules

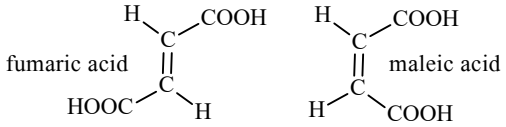
Section 5 Stereochemistry

5.1 Introduction

We discussed constitutional isomers so far whose different types have addressed in previous section. Isomers which differ by connectivity of atoms are known as constitutional isomers such as chain, functional group and positional isomerism.



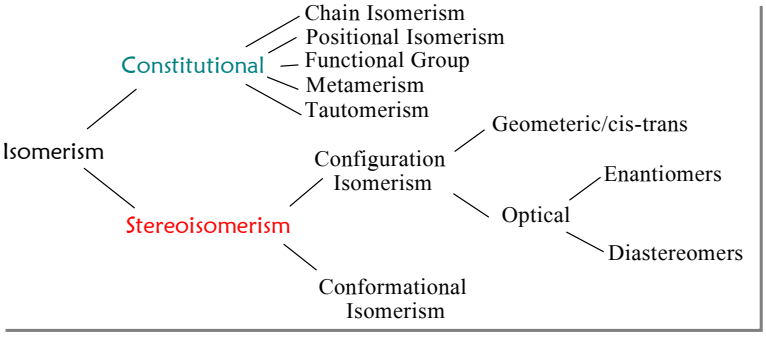
Stereoisomers differ by stereochemistry of atoms or group of atom in three dimensional space. They have different spatial arrangements of atoms. The branch of chemistry which shed light on three dimensional orientation of molecules is known as stereochemistry. This discipline plays crucial role in determining physical, chemical and biological properties of molecules. For instance, fumaric acid and maleic acid are two isomers with same molecular formula and atoms connectivity yet their stereochemistry is different. Fumaric acid is trans isomers whereas maleic acid is cis. Both are geometric stereoisomers. Stereoisomers have different physical and chemical properties. Fumaric acid (mp = 287 °C) is essential metabolite but maleic acid (mp = 138 °C) is toxic.



5.2 Classification

Stereoisomers has two types: conformational and configurational isomerism. Conformers are isomers which are distinguished themselves by rotation of atoms or groups along carbon–carbon single bond. Configurational isomers are divided into geometrical and optical isomers. Configurational isomers differ themselves by configuration of atoms in three dimensional space. They are classified as geometrical and optical isomers. Geometric or cis/trans isomers differs by arrangements of atoms or groups with respect to

double bond. Optical isomers have same physical properties but different behavior toward plan polarized light. When they form mirror image reflections which are not superposable, we call them enantiomers. Diasteromers are neither mirror images nor superposable.

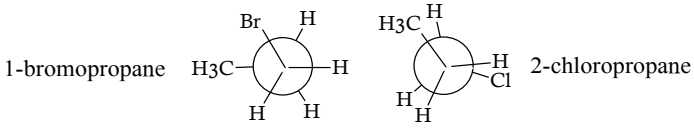


5.21 Conformational Isomerism

When two isomers differ in three dimensional space through rotation along carbon–carbon single bond are known as conformers, the type of isomerism is known as conformational isomerism. For instance, we could have two conformers for ethane: eclipsed and staggered. Conformers are distinguished by its dihedral angle which is angle formed by rotation of one group with respect to other. When dihedral angle is zero, the conformation of ether is eclipsed. When one methyl group of ethane is rotated with respect to other by 60°, the conformer is known staggered. Any other degree of rotation gives skew conformation.

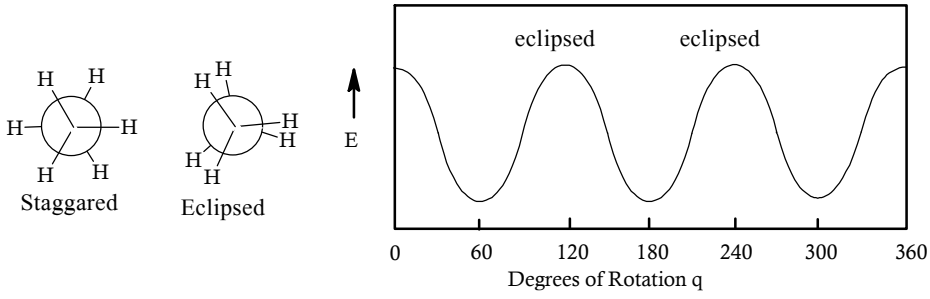
Newman and Sawhorse projections are used to represent conformers. Which isomerism of ethane is stable? In fact, when two hydrogen atoms eclipsed each other, they create steric hindrance which makes the molecule unstable. Staggered conformer is stable because two hydrogen atoms are far apart at 60°. When we move from staggered toward eclipsed conformation, says, from stability towards instability, we encounter a strain which is known as torsional strain. A detailed analysis of energy changes between different conformers is known as conformational analysis.

Consider the Newman projections for ethane and butane. In these projections, rear carbon is shown with circle to which three bonds are attached. The front carbon is shown in the center of the circle with three bonds. Before shedding light on conformational analysis of ethane and butane, let's first consider 1-bromopropane and 2-chloropropane so that we could understand how both molecules could be sketched while using Newman projection.

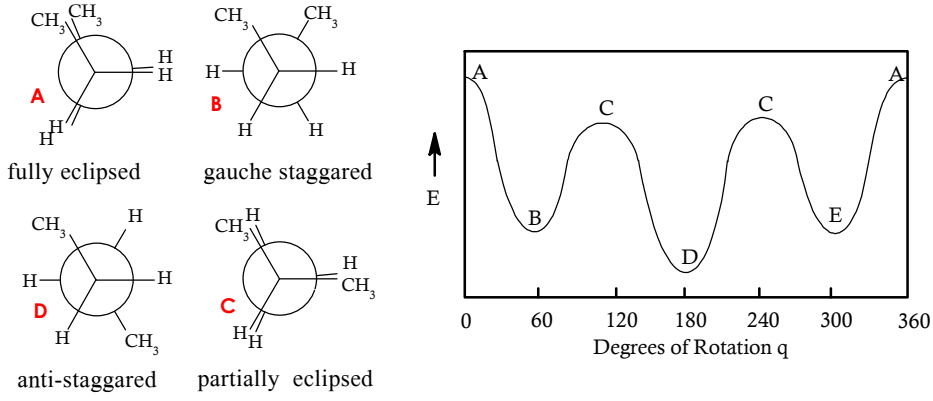


We view the former molecule from the carbon bearing bromine atom. The methylene carbon to which bromine is attached will be shown on the front to which another methylene carbon attached is shown by circle. We attach a methyl group to the

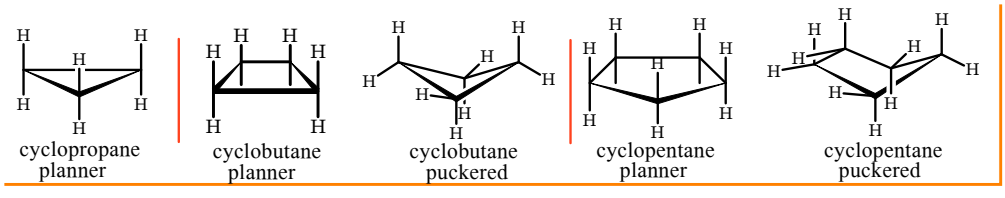
circle for sketching Newman projection of 1-bromopropane. Let's consider ethane and butane molecules now.



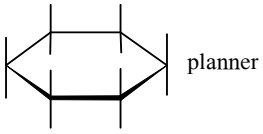
When one hydrogen of ethane is replaced with methyl group to make the molecule a propane, we bring a big group which creates more steric hindrance, hence more torsional energy is required to flip between different conformers.



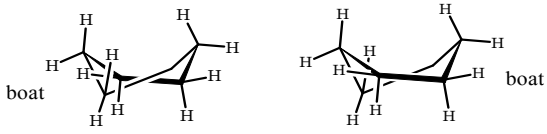
In cyclic alkanes, cyclopropane is more strained because the bonds are bent and unstable. Torsional strain is another factor of instability in cyclopropane because all six hydrogen atoms are eclipsed. In fact, both types of strains make cyclopropane more reactive than other alkanes. Cyclobutane would unstable like cyclopropane if it is planner but it is not so. The molecule relieve some angle strain by slightly distorted geometry which isn't planner. The molecule acquires folded form which also relieve torsional strain as well. Consequently, cyclobutane is more stable than cyclopropane. Cyclopentane acquires puckered envelope to relieve angle and torsional strain.



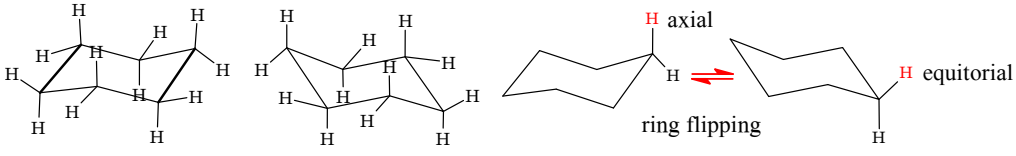
Cyclohexane is more stable than previous cycloalkanes. Had cyclohexane a planner molecule it would be unstable with bond able of 120° and torsional strain due to hydrogen atoms on adjacent methylene groups.



Combustion data reflects that cyclohexane has no strain at all which means all bonds are perfectly tetrahedral with no eclipsing hydrogen atoms. This means that cyclohexane could either have boat, twisted boat or chain conformation. The boat conformation has one shortcoming of two eclipsing hydrogen on two methylene groups. We call them flagpole hydrogens. The boat conformation usually existed in twisted boat conformation to rid of strain because the flagpole interaction is counteracted. The twisted boat conformation is yet unstable than the chair conformation.



Chair conformation has two type of C—H bonding: axial and equatorial. We have twelve hydrogen atoms, two on each methylene group. Six bonds are axial and six are equatorial. Axial bonds are exactly parallel to the axis of molecule. Three bonds are up and three bond on bottom in axial position. Same is the case for six equatorial bonds: three up and three down. This can be understood from the structure of chair conformation of cyclohexane.



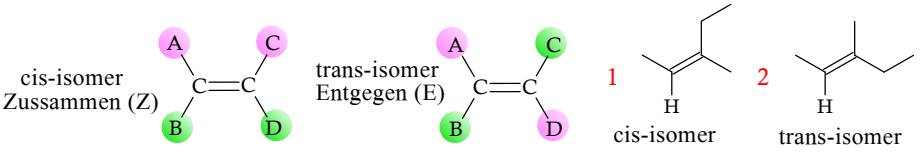
In mono–substituted cyclohexane such methyl cyclohexane, the methyl group could be either in axial or equatorial position. However, axial methyl group would mean more strain than such group in equatorial position where it makes the molecule stable.

5.22 Configurational Isomerism

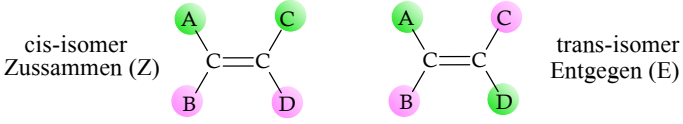
Configurational isomers could be geometrical or optical. Geometrical isomers are different with respect to double bond, hence also termed as cis/trans isomerism. Optical isomerism stems from chirality which make isomers different in their behavior towards plan polarized light.

1. Geometric Isomerism

For geometrical isomerism to prevail, at least two different groups should be attached to each carbon atom of the double bond. Consider the following geometric isomers:



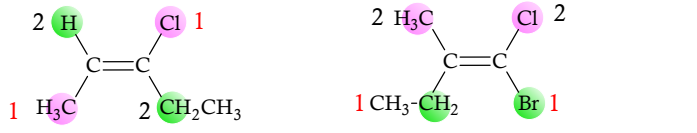
E-Z nomenclature is based on Cahn-Ingold Prelog sequence rules which are applied for naming geometrical isomerism in alkenes. E stands for Entgegen which means **across** or opposite and Z stands for Zussammen, means **together**. In simple words, E reflects trans and Z cis isomers. This system is valid for all cases of geometrical isomers. Following are important points about E-Z nomenclature.



Rules for Naming Geometrical Alkenes

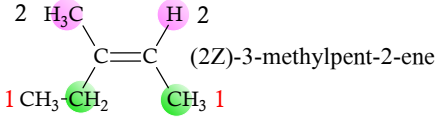
1. Both groups on the double bond are assigned priority order as 1 and 2.

2. Priorities are assigned on the basis of atomic numbers. Atoms with higher atomic numbers are given first priority. For example, if both chlorine and bromine are attached to the one carbon of the double bond, first priority will go to bromine as it has high atomic number than chlorine. See below structure:



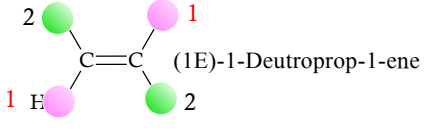
(2E)-3-chloropent-2-ene (1Z)-1-bromo-1-chloro-2-methylbut-1-ene

3. If both groups are same, we will have to look out second atom in each of the group. For example, methyl has hydrogen as second atom, where ethyl has carbon as the second atom. Thus if both groups are present, priority will be assigned to ethyl first.



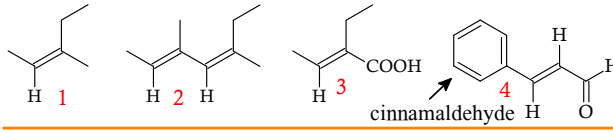
(2Z)-3-methylpent-2-ene

4. In case of isotopes, assigning priorities are based on atomic weight instead of atomic number. For instance, hydrogen (protium) and deuterium are linked to one carbon atom the double bond, deuterium will be assigned first priority as its atomic weight is greater than hydrogen.



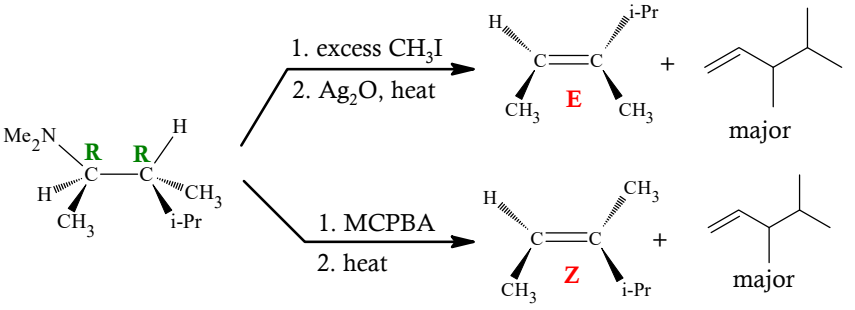
(1E)-1-Deutroprop-1-ene

● Examples

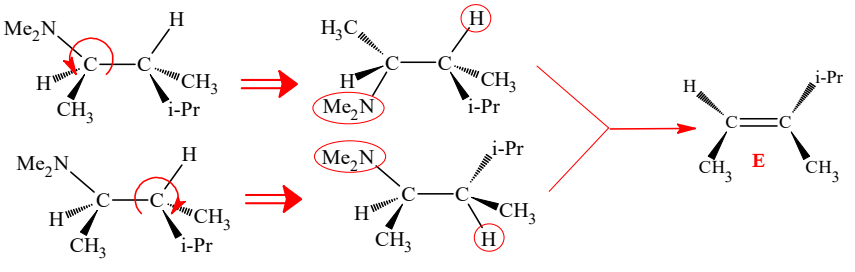


1 (2Z)-3-methylpent-2-ene
2 (2E,4Z)-3,5-dimethylhepta-2,4-diene
3 (2E)-2-ethylbut-2-enoic acid
4 (2E)-3-phenylprop-2-enal

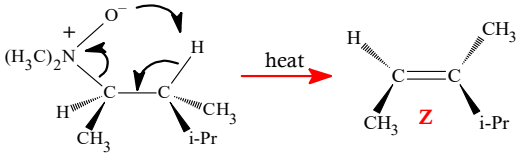
Solved Problem 5.1 The following tertiary amine (R, R isomer) has subjected to different reaction conditions for affecting syn (Cope) and anti-elimination (Hoffmann) reactions.

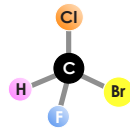


In both types of elimination reactions, the major product is Hoffmann product: one with formation of least substituted double bond formation. Besides, some Zaitsev product is also formed in each case but one such product is of E whereas the other is of Z configuration. Hoffman elimination works by anti-elimination mechanism: leaving group and proton are eliminated in anti-periplanner fashion. In Cope elimination, we get product through syn-elimination because both groups are eliminated from the same direction. Let's use stereochemical sketching to get the desired products with E and Z configurations. For Hoffman elimination, rotate one or another carbon bearing leaving group until it gets anti-periplanner orientations. We have rotated both carbon atoms one by one to get same results.

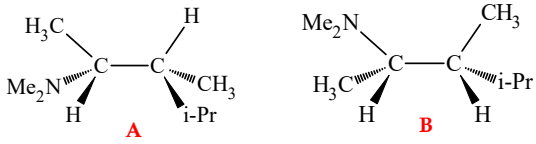


For cope elimination, just simply remove both groups from the same side to get Zaitsev product which gives most substituted product. The major product is Hoffman, however.





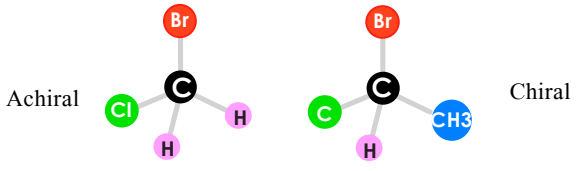
Problem 5.1 Which Zaitsev product would form from each of the following molecule? Sketch each molecule and rotate one or another or both chiral carbon atoms to get desired Zaitsev product in Hoffman elimination reaction.



2. Optical Isomerism

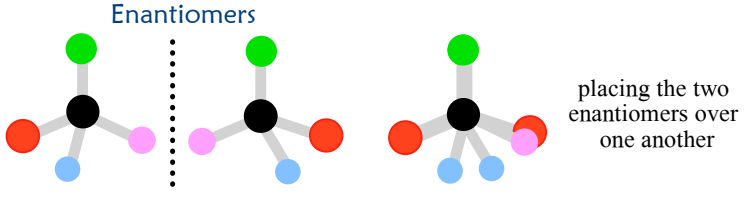
Chirality

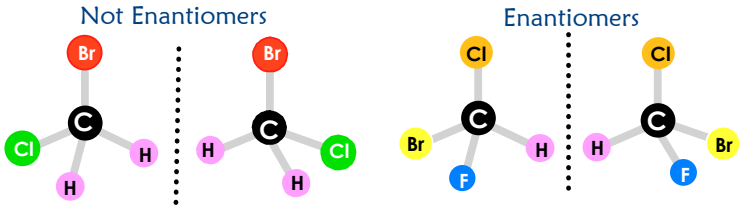
Carbon atom is tetravalent. It uses all its valencies for making four covalent bonds. In most organic compounds, carbon is either bonded to another carbon atom or hydrogen. This types of compounds are known as hydrocarbons such as alkanes, alkenes, alkynes and aromatic compounds. All hydrocarbons are usually achiral. Chiral compounds are those in which carbon atom is bonded to four different groups. The chiral carbon is known as chiral carbon, chiral center or stereogenic center. For instance, carbon atom in 1-Bromo-1-chloroethane is chiral whereas in bromochloromethane is achiral.



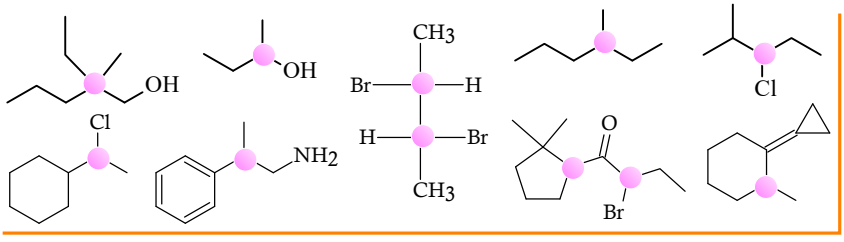
Compounds such as meso ones are still achiral despite the presence of chiral centers. Such compounds have internal imaginary plan that passes and bifurcate the compounds into two halves, each is mirror reflection of other, thus makes the molecule achiral like racemic mixture. Some compounds such as biphenyl and allenes don't have chiral center yet they are chiral.

Chiral compounds are optically active which means they rotate plan polarized light either towards right ride (dextrorotatory) or left (levorotatory) when they are subjected to polarimetry. One is termed D-isomer whereas the other is tagged as L-isomer. Both D/L isomers are known as enantiomer which stereoisomers with same physical properties but different behaviors are towards plan polarized light. R/S nomenclature is used to name enantiomers. Enantiomers are mirror images which are not supposable such as our right hand is not supposable over our left hand.



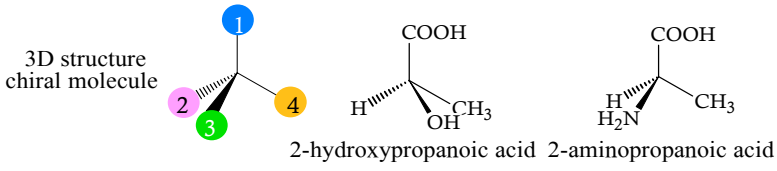


Contrary to enantiomers, stereoisomers which are neither mirror images like enantiomers nor supposable are known as diastereomers. Geometrical isomers are examples of diastereomers such as fumaric and maleic acids. Other diastereomers usually contain two or more chiral centers. In the following molecules, stereocenters (chiral centers or stereogenic center) have marked pink.

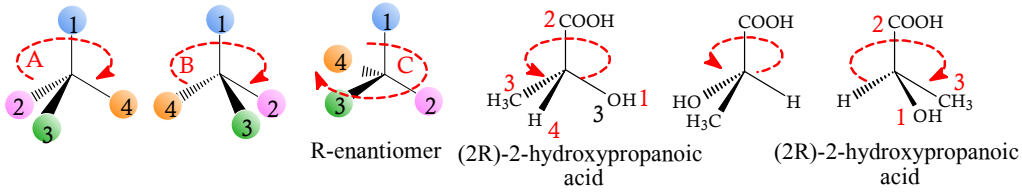


5.3 R/S Nomenclature

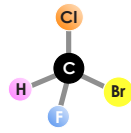
How do we name optical isomers which are represented with three dimensional structures, having wedge, dashed and line bonds? Consider the following molecules:



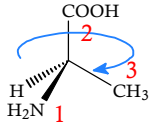
If we are given just the names of chiral molecules, we don't know which isomer they represent. To cope with the issue, R/S nomenclature has devised. R stands for rectus and S for sinister, which mean clockwise and anti-clockwise respectively. Suppose a chiral molecule a steering of a car. When you rotate the steering toward left, assign S to the molecule and vice versa. Put the axial of the steering a low priority group which is always on the rear or away from the observer.



In above example, we rotate structure A in clockwise direction so that we could move lowest priority group 4 to the rear. We get structure B. Again we rotate B in clockwise



fashion so that group 4 goes to the rear. We get structure that can easily tell us whether the molecule is R or S enantiomer. When we start from 1 toward 3 in clockwise direction, the molecule will be R enantiomer. We can arrange above molecule when the lowest priority group is not on the rear which is represented by dashed line. If a molecule has already lowest priority group on the rear, we do not need any rotation. Consider the following example:

(2R)-2-aminopropanoic acid 

Rules for Setting Priority

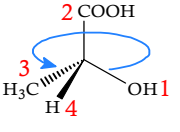
1. Priority of the four groups or atoms attached to chiral center is made on the basis of atomic number. For instance, bromine get first priority over chlorine because of its higher atomic number.

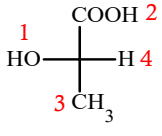
2. We make outward exploration for group attached with similar atom to chiral center. For example, if there is competition between ethyl and isopropyl group, the latter gets first priority because it carbon linked to chiral center is attached to two other carbon atoms unlike ethyl group which is attached to just one carbon atom. This means, for similar atom attached to chiral center, we focus next atom attached to it. This is outward exploration for setting priority order.

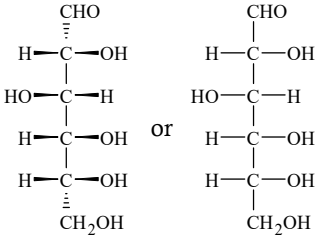
3. For isotopes such as protium and deuterium, atomic weight is given preference. Thus, deuterium will get first priority over protium.

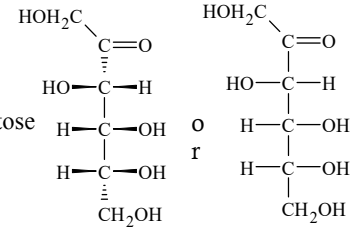
Perspective Drawings

While drawing Fisher projection for a chiral molecule, we generally put a group bonded by dashed line on the bottom in Fisher projection where the group bonded by dashed line is put on the right side of the horizontal line. 180° movement is permissible whereas 90° and 270° are not permissible. Consider the following example:





Glucose 

Fructose 

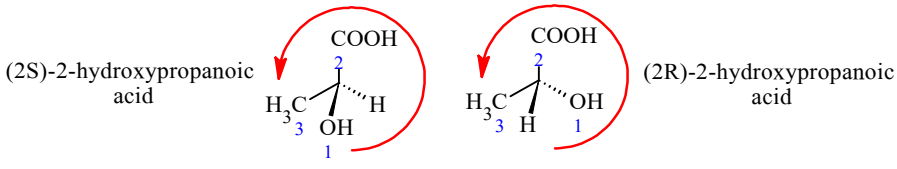
Fisher projections are used to draw the structures of carbohydrates because they offer convenient way for representation of molecules. The shorthand was invented by Emil

Fisher, a carbohydrate chemist, who got Nobel Prize for his proof of glucose structure. Aldoses have formyl group on the top of the structure and it is assigned number 1 and ketoses has keto group on the second carbon from the top and it assigned second number according to these projections.

5.4 Configuration

Configuration means arrangement of atoms in space. An absolute configuration is perfectly known configuration. For instance, when we assign R or S notation to a molecule or chiral atom, we mean absolute configuration because whosoever draws the molecule with R or S nomenclature would sketch same molecule. In fact, absolute configuration tells us exact arrangement of atoms in three dimensional space.

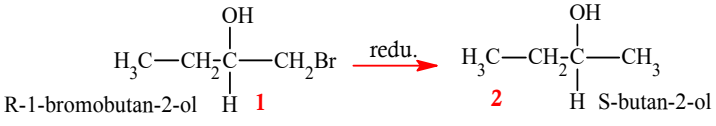
Enantiomers have same physical characteristics but different optical rotation. This doesn't mean that optical rotation tell us about the absolute configuration of molecules. For instance, when lactic acid is converted to its sodium salt, its optical rotation gets changed yet it configuration remains same. If optical rotation (specific rotation) doesn't tell about configuration, then what method is used to ascertain it? In fact, X ray diffraction analysis helps us to know the configuration. Once it is determined, absolute configuration of other molecules such as those linked to lactic acid whose configuration has known by X ray analysis can be established by chemical correlation.



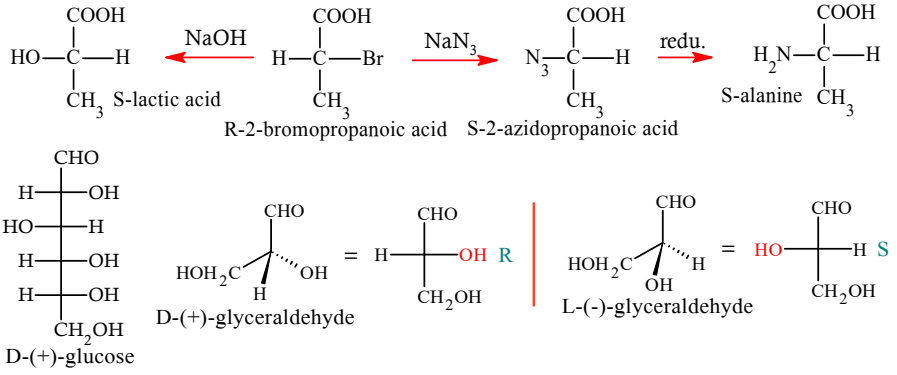
Configuration which is unknown but ascertained by relating it to molecules of known configuration is termed as relative configuration which is experimental in essence. One molecule is converted to another whose configuration is linked to the starting one for knowing the configuration of the final molecule.

5.41 Methods for Determining Configuration

Before the advent of X-ray crystallography back in 1951, chemists often tried to determine the configuration of chiral molecules using classical methods of chemical interconversions. There was no method to ascertain absolute configuration. Chemical correlation was one method to know the configuration of unknown molecules. Consider the following reduction how second highest priority group has converted into third highest priority group, thus giving S isomer.

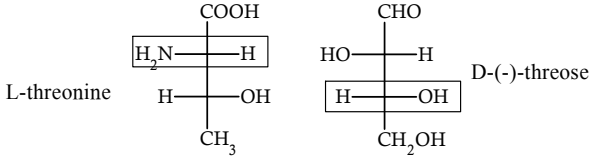


Chemical transformation is another method for ascertaining the configuration of chiral molecules. Consider the following transformation which involves S_N2 reaction.



D/L system or Fischer-Rosanoff Convention was used to assign configuration of sugars and amino acids by relating them to glyceraldehyde. The system was adopted by Emil Fischer back in 1885 for configuration of carbohydrates. He assigned carbohydrates molecules to D or L glyceraldehyde. Naturally occurring glucose has (+) rotation and belongs to D series, hence labelled as D-(+)-glucose. It has four stereogenic centers and 2^4 = 16 possible stereoisomers.

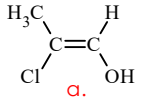
Naturally occurring amino acid, threonine, has same configuration as natural sugar threose. By amino acid convention, it belongs to L series and by sugar convention it belongs to D series.

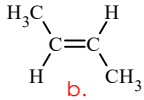


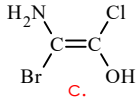
Enzymes are highly stereospecific. They operate on just one enantiomer. If the configuration of enzyme is known, we can find out the configuration of an unknown molecule. This method is known as biochemical correlation. Similarly, chromatographic and spectroscopic methods are also used for latest determination of configuration. Still other methods such as optical rotatory dispersion (ORD), circular dihorism (CD) and asymmetric synthesis are used to find out configuration of unknown molecules. ORD measures specific rotation. Both ORD and CD are used for conformational analysis as well. Infrared and vibrational CD (VCD) are also employed for conformational analysis.

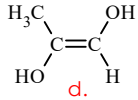
5.5 Exercise

1. Write cis-trans and E-Z names for the following isomers

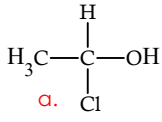

a.

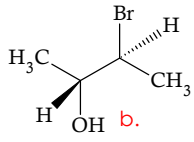

b.


c.


d.

2. Write R/S names for the following molecules


a.

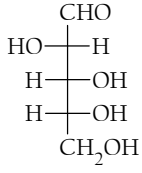

b.

3. Draw cis-trans isomers of cyclohexane derivatives 1,2, 1,3 and 1,4 in both cis and trans configuration. Also state which one is stable and sketch enantiomers and diasteromers which they are possible.

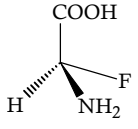
4. Draw Newman and Sawhorse projections for the 2-bromo-2,3-dimethylpentane with reference to E2 elimination. Predict major and minor product.

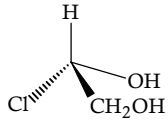
5. An unknown compound is subjected to intramolecular substitution reaction. The product reacts with strong nucleophile in S_N2, whose subjection to E2 gives a compound of unknown stereochemistry. Find out the relative configuration of substrate if the starting material has R configuration?

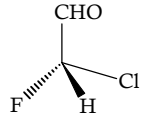
6. Point out the number of chiral centers, number of enantiomers, diastereomers and meso pairs. Assign R/S configuration to each chiral carbon atom.



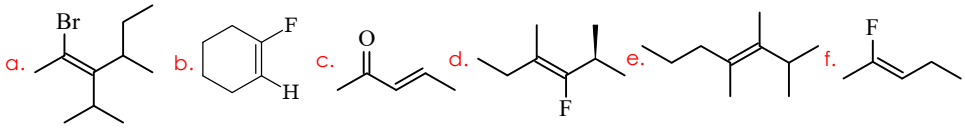
7. Assign R/S configuration to the following molecules







8. Assign E/Z notation to the following molecules



Structural Elucidation Of Organic Molecules

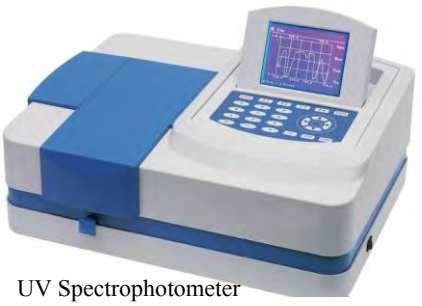
Section 6 Spectroscopy

6.1 Spectroscopy

Spectroscopic technique evolved with advancement in science and technology. Spectrometry turned out the most direct and accurate method for determining atomic and molecular masses. Before the new scientific advancements, combustion analysis turned out to be archaic method for chemical analysis. It has now been replaced by modern analytical techniques such as infrared spectroscopy, ultraviolet spectroscopy, nuclear magnetic resonance spectroscopy and mass spectrometry coupled with atomic emission and atomic absorption spectroscopies. These techniques brought revolution in characterization of matter since it evolved with English physicist Francis William Aston (1877 – 1945) who developed the first mass spectrometer in 1920s. He was awarded Nobel Prize in Chemistry in 1922 for his work. Modern organic chemists use following spectroscopic techniques for characterization of molecules.

1. **Infrared (IR) Spectroscopy** tells us about vibrations of bonds and provides evidence about functional groups.

2. **Ultraviolet (UV) Spectroscopy** gives information about electronic transitions and electronic bonding in sample. It tells us about structure of conjugated system.



UV Spectrophotometer

Fig. 6.1 Modern analytical tools of Fourier Transform Infrared spectrometer (FTIR) and Ultra Violet spectrophotometer.

3. **Mass Spectrometry (MS)** is not a spectroscopic technique because it does not measure absorption or emission of light. A mass spectrometer bombards molecules with electrons and breaks molecules into fragments. Analysis of masses of fragments gives molecular weight, possibly molecular formula, and clues to the structure and functional groups. MS is destructive technique because it destroys less than a milligram of sample.

4. **NMR Spectroscopy** observes chemical environments of atoms in molecules and establishes their structures and functional groups.

These spectroscopic techniques are complementary, and they are powerful when used together. In many cases, an unknown compound cannot be completely identified from one spectrum without additional information, yet the structure can be determined with confidence using two or more different types of spectra.

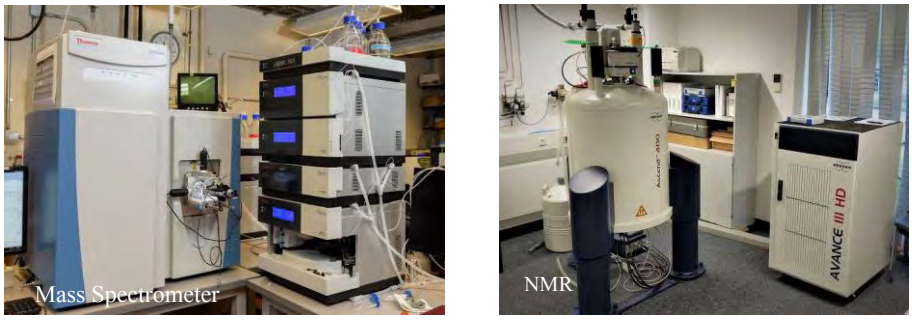
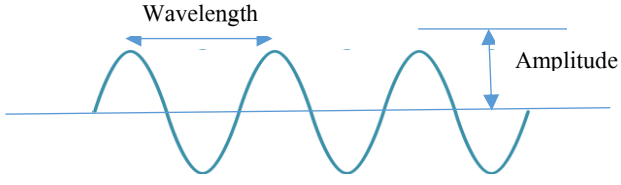


Fig. 6.2 Modern Mass spectrometer and Nuclear Magnetic Resonance Machine.

6.11 Electromagnetic Radiation

Visible light, infrared light, ultraviolet light, microwaves, and radio waves are examples of electromagnetic radiation (emr) which travel as photon. They all travel at the speed of light, about $3x10^{10}$ cm/s but they differ in frequency and wavelength. The frequency of a wave is the number of complete wave cycles that pass a fixed point in a second. Frequency, represented by the Greek letter nu (υ), is usually given in hertz (Hz), meaning cycles per second. The wavelength, represented by the Greek letter lambda (λ), is the distance between any two peaks (crests or troughs) of the wave.



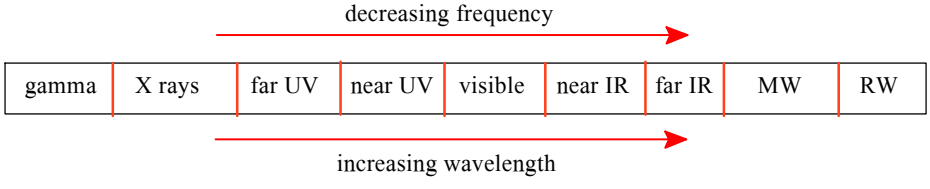
Energy of a photon is proportional to its frequency and inversely proportional to its wavelength.

$$E = h\upsilon = hc/\lambda$$

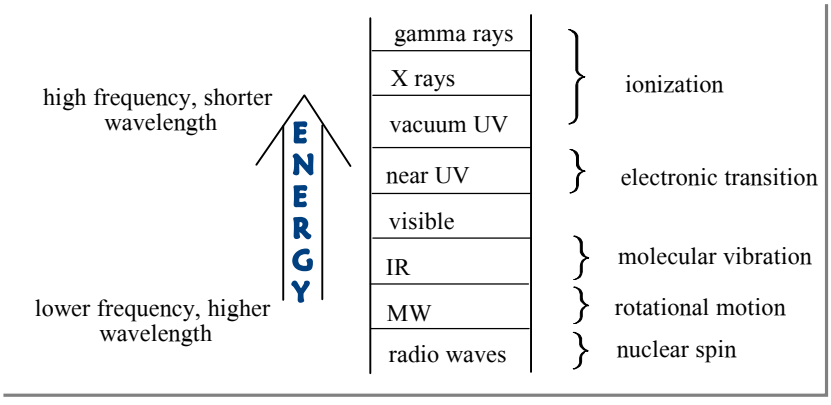
The wavelength and frequency are inversely proportional:

$$\bar{\upsilon}\,\lambda = c$$

$$\lambda = c/\,\bar{\upsilon}$$



The following emr spectrum lists all important radiations with gamma rays on the top and radio waves on bottom. The top show high energy radiation with shortest wavelengths and highest frequency. These radiations cause varied effects when they interact with matter. For instance, gamma and X rays cause ionization, UV electronic excitation and transition, IR molecular vibration and least energetic radio waves induces nuclear spin which is characteristic of nuclear magnetic resonance spectroscopy.



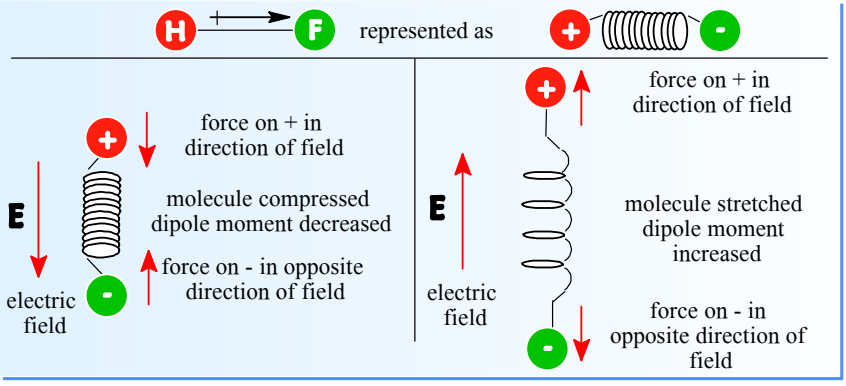
6.2 IR Spectroscopy

6.21 Introduction

Both oxygen (21%) and nitrogen (78%) are naturally abundant gases in our atmosphere but they are not greenhouse gases such as carbon dioxide, methane, water vapors or chlorofluorocarbons (CFCs). Growing concentration of CO_2 is a matter of global concern whose steady elevation in atmosphere has been progressing since industrial revolution. In fact, these greenhouse gases are responsible for global warming.

The question is what makes a gas greenhouse gas or not could be answered by the fact that those gases which have some value of dipole moment are regarded as IR (infrared, Latin infra means below) active whereas those molecules whose net dipole moment is zero are IR inactive. IR falls below visible frequencies that corresponds to wavelength of $8x10^{-5}$ cm to $1x10^{-2}$ cm. An IR spectrometer operates somewhere in the mid of this region: $2.5x10^{-4}$ cm and $25x10^{-4}$ cm which corresponds to 4.6 to 46 kJ/mol. IR active molecules absorb IR radiations that cause vibrational, rotational and translational motion of molecules. These IR active molecules in our atmosphere are regarded as greenhouse gases. Bonds in IR active molecules begin to vibrate when they expose to radiations in IR range.

An emr has both electric and magnetic field components. Its electric field stretches and compresses polar bond. When a molecule with dipole moment which acts like positive and negative charges attach to a spring either interacts with emr, it gets stretched or compressed. When electric field is in direction of polar bond, it gets compressed and dipole moment of the bond gets reduced and vice versa. Once the stretching and compression occur at frequency matching the natural frequency of molecular vibrations, IR gets absorbed.



Symmetrical bond with zero dipole moment doesn't absorb IR. Sometimes, such bonds are made asymmetrical by collision, electric and magnetic interactions or temporary bonding situation. This is where such molecules get IR active. Some bonds such as carbonyl ones (C=O) absorb strongly enough that an overtone appears which is weak peak that occurs at frequency double of fundamental vibration.

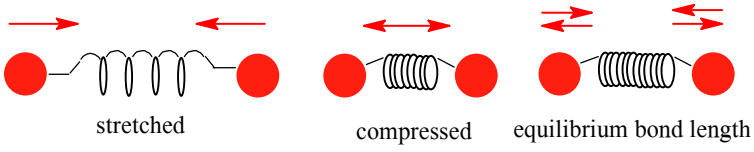
IR spectroscopy deals with this absorptions by different types of bonds in molecules which are recorded in IR spectrum for characterization of organic molecules. IR spectroscopy has largely been successful in assessing the functional groups of organic molecules. This technique is used in conjunction with other spectroscopic techniques such as NMR and MS for holistic assessment of structural identification of different compounds.

IR Active & Inactive Molecules

A symmetrical bond with zero dipole moment doesn't interact with electric field. For example, the triple bond of acetylene has zero dipole moment, and the dipole moment remains zero if the bond is stretched or compressed. Because the vibration produces no change in the dipole moment, there is no absorption of energy. This vibration is said to be IR-inactive, and it produces no absorption in the IR spectrum. The key to an IR-active vibration is that the vibration must change the dipole moment of the molecule.

6.22 Molecular Vibrations

The following illustration signifies vibrational energies of molecules. Atoms with respect to bonds act like linked by a spring. When they are stretched or compressed, force develops which either move the balls towards or away from each other.



Stretching and releasing the balls causes them to vibrate whose frequency of vibration depends upon the masses of the balls. Heavier atoms vibrate slowly than lighter ones. A C–D bond vibrates slowly with lower frequency than C–H bond. The frequency

of vibration decreases with increasing atomic weights. Strong bond are stiff which requires more energy to vibrate (stretch or compress). Consequently, such bonds vibrate more swiftly than weaker ones. For instance, a triple bond vibrates with higher frequencies as compared to double or single bond. An O–H bond is stronger than C–H, hence it vibrates at higher frequencies than C–H bond of alkanes.

Modes of Vibration

Non-linear molecules have 3n – 6 fundamental modes of vibrations. For instance, water with three atoms has 3(3) – 6 = 3 fundamental modes of vibration. Methanol has 12 and ethanol has 21 fundamental mode of vibrations. In IR spectrum, we notice multiple combination and overtones for these mode of vibrations. On account of such diversity, IR spectra of two different compounds don't have least possibility to have similar spectra except enantiomers. All such complex vibrations occurs in the fingerprint region (600 to 1400 cm^{-1}) of IR spectrum.

6.23 IR Spectrum

What does an absorption of 2000 cm^{-1} means? An IR spectrum is usually given in wave number ($\bar{\upsilon}$) which is measured in μm (1 millionth of a meter) or cm. One micron is 10^{-4} cm. A $\bar{\upsilon}$ is the number of cycles (λ) in centimeter. In other words, $\bar{\upsilon}$ is the reciprocal of λ in centimeters.

$$\bar{\upsilon}_{cm^{-1}} = \frac{1}{\lambda_{cm}}$$

As 1 cm = 10,000 μm

$$\bar{\upsilon}_{cm^{-1}} = \frac{10000\ \mu m.cm^{-1}}{\lambda_{\mu m}}$$

A 5 μm absorption means

$$\bar{\upsilon}_{cm^{-1}} = \frac{10000\ \mu m.cm^{-1}}{5_{\mu m}} = 2000\ cm^{-1}$$

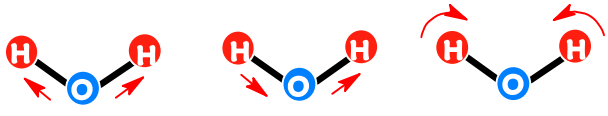
To convert

$$\lambda = \frac{10000\ \mu m.cm^{-1}}{\bar{\upsilon}_{cm^{-1}}} = \frac{10000\ \mu m.cm^{-1}}{2000\ cm^{-1}} = 5\ \mu m$$

This shows that 2000cm-1 corresponds to absorption of IR with λ of 5 μm.

In IR region, absorptions occur due to vibrational modes of bonds. An IR spectrum is plot between energy absorbed by molecule as a function of frequency or wavelength of radiation. Molecules are absorb on account of bending vibrations which include scissoring and twisting vibrations, where bond lengths stay same but bond angle alter. In water, two O–H bond stretch: symmetric (in phase) or anti-symmetric (out of

phase). Besides, H–O–H bond angle encounters bending vibration (scissoring). An IR region of 1600 to 3500 cm^{-1} shows simple stretching which are easy to predict and characterize. Bending vibrations fall in the region of 600 to 1400 cm^{-1} are usually ignored. This is known as fingerprint region which records all bending vibrations: wagging, scissoring, rocking and twisting.



The following table shows different bonds and their absorptions. These values don't need to be memorized because they to mind automatically once different IR spectra are practiced.

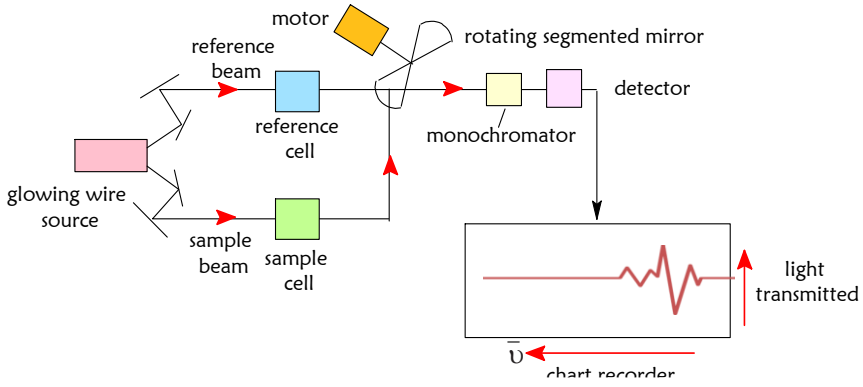
Bond		Bond in kJ	Stretching frequency in cm^{-1}	
		frequency decreases with increasing atomic mass		
C—H	heavier atoms ↓	420	3000	$\bar{\upsilon}$ decreaases ↓
C—D		420	2100	
C—C		350	1200	
		frequency increases with bond energy		
C—C		350	1200	
C=C	stronger bond ↓	611	1660	$\bar{\upsilon}$ increases ↓
C≡C		840	2200	
C—N		305	1200	
C=N	stronger bond ↓	615	1650	$\bar{\upsilon}$ increases ↓
C≡N		891	2200	
C—O	stronger bond ↓	360	1100	$\bar{\upsilon}$ increases ↓
C=O		745	1700	

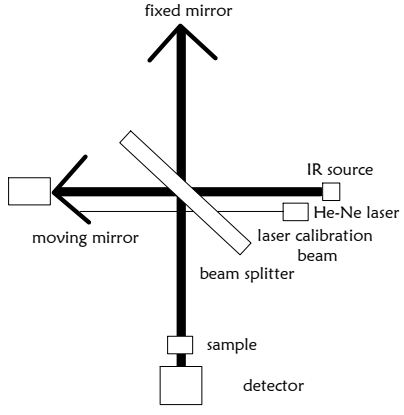
Frequency cm^{-1}	Functional Group		Analysis
3300	alcohol	O—H	always broad
	amine, amide	N—H	may be broad, sharp or broad with spikes
	alkyne	≡C—H	always sharp, usually strong
3000	alkane	C—H	just below 3000 cm^{-1}
	alkene	=C—H	just above 3000 cm^{-1}
	acid	O—H	broad

2200	alkyne	—C≡C—	just below 2200 cm $^{-1}$
	nitrile	C≡N	just above 2200 cm $^{-1}$
1710	carbonyl	C=O	ketones, acid about 1710 cm $^{-1}$ aldehyde about 1725 cm $^{-1}$ esters higher about 1735 cm $^{-1}$ conjugation lower frequency amides lower, about 1735 cm $^{-1}$
1660	alkene	C=C	conjugation lower frequency
	imine	C=N	aromatic C=C about 1600 cm^{-1} stronger than C=C
	amide	C=O	stronger than C=C

6.24 IR Spectrometer

Modern IR spectrometer such as Fourier transform IR is quick and efficient which measures samples either in liquid, solid or gaseous state. A drop of liquid is enough to analyze by placing it between two transparent plates made up of NaCl or KBr disc. Solids are ground with KBr or they can be dissolved in DCM, CCl_4 or CS_2. Gas samples are filled in gas cells which are made of transparent walls.





IR spectrometer uses two beams: sample and reference, which are passed through sample and reference cells. Emerging beams passes through rotator before entering monochromator. The instrument is dispersive because it splits light into different parts and then analyze them individually. This is expensive. It has replaced by FTIR which uses interferometer to measure IR spectrum. FTIR measures all frequencies simultaneously. It requires 1 or 2 seconds to record scan.

6.3 Ultraviolet Spectroscopy

UV (ultra means beyond) spectroscopy is usually neglected although it gives much specialized knowledge than IR or NMR about chain length of a conjugated system. It works by electronic transition because UV is stronger than IR. UV is measured in nanometer and common UV spectrometer operates in the range from 200 to 400 nm which corresponds to 300 to 600 kJ/mol.

Spectral Region	Wavelength λ	Energy kJ/mol
UV	200 - 400 nm	300 - 600
Visible	400 - 800 nm	150 - 300
IR	2.5 - 25 m	4.6 - 46
NMR	0.3 - 5 m	2 - 40 X 10-5

Fig. 6.3 Spectral regions and corresponding energies of electromagnetic radiation used in different spectroscopic techniques.

6.31 UV Light and Electronic Transitions

UV spectroscopy measures electronic transitions between highest occupied molecular orbital (HUMO, π, bonding molecular orbital) and lowest unoccupied molecular orbital (LUMO, π*, anti-bonding molecular orbital). Pi electrons are easy to excite unlike sigma ones (not influenced by UV above 200 nm) which are entangled in strong sigma bond.

Energy difference between HUMO and LUMO determines the absorption of UV light. Generally, conjugated system has low lying vacant orbitals where electronic transition could be facilitated. Energy difference between the two sets of orbitals decrease with increase in conjugation. In ethylene, the transition from HUMO to LUMO is known as π to π* transition which requires UV of 171 nm (686 kJ/mol) of energy. Most spectrometers don't record this rang because it is camouflaged by oxygen in air.

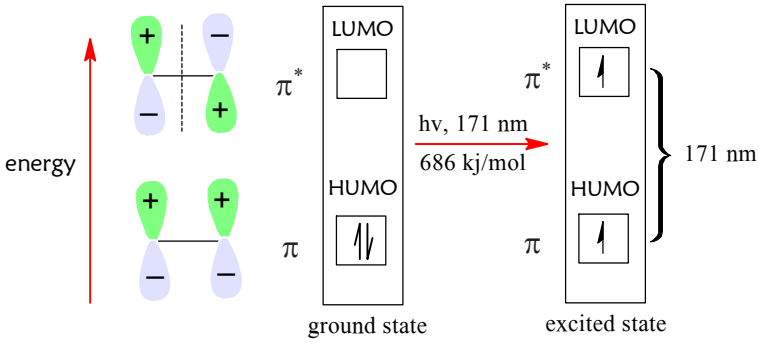
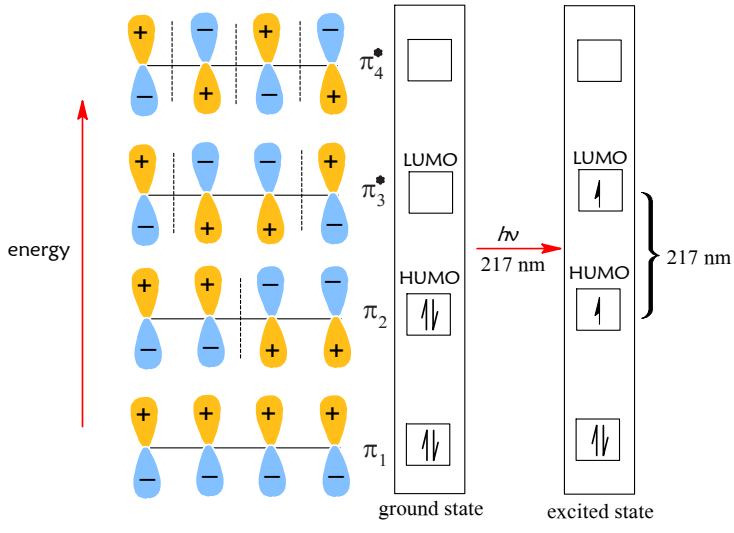


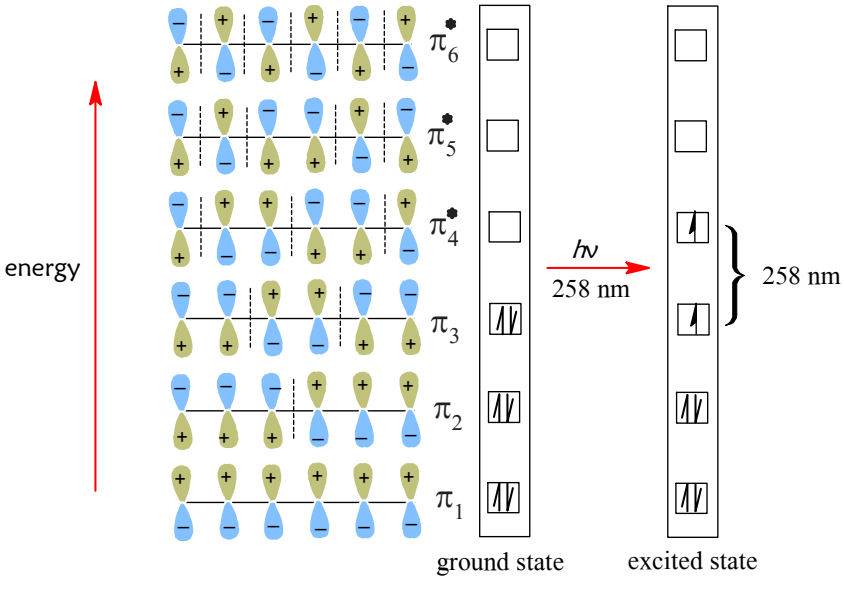
Fig. 6.4 Transition between HUMO and LUMO of butadiene responsible for absorption of light radiation.

In ethylene case, as shown above, compares the MO energies of ethylene with those of butadiene to show that the HOMO and LUMO of butadiene are closer in energy than those of ethylene. The HOMO of butadiene is higher in energy than the HOMO of

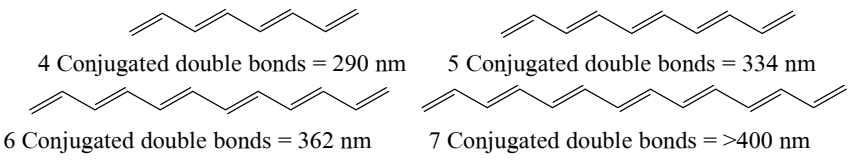
ethylene, and the LUMO of butadiene is lower in energy than the LUMO of ethylene. Both differences reduce the relative energy of the π2 to π3* transition. The resulting absorption is at 217 nm (540 kJ mol, or 129 kcal mol), which can be measured using a standard UV spectrometer. In butadiene, conjugation reduces energy difference to 217 nm which is detectable in UV spectrometer. A UV light of longer wavelength is required to excite electrons from π_2 to π_3* orbitals.



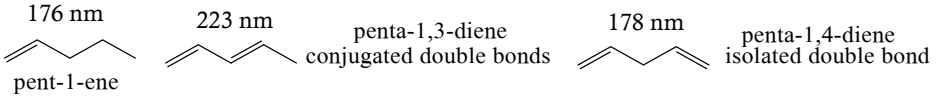
As conjugation increases in hexatriene, therefore energy difference between HUMO (π_3) and LUMO (π_4*) decreases further which requires UV light of 258 nm (452 kJ/mol) to cause electronic transition. Comparatively, the HUMO in hexatriene is slightly higher and the LUMO slightly lower than butadiene.



In a nutshell, higher conjugation causes molecules to absorb at longer wavelengths. The absorption exceeds 400 nm for system containing seven conjugated double bonds.



Isolated double bonds don't contribute to longer wavelengths. Such compounds behave like ordinary alkenes. Consider the following examples:

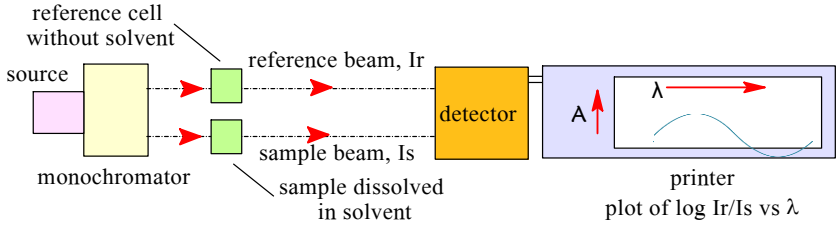


6.32 Ultraviolet Spectrum

Beer-Lambert law serves as basis for functioning of UV spectrometer. The law states that absorbance of sample proportional to concentration of sample and the path length of sample container (cuvette). This law is logarithm of ration of incident light of reference (Ir) and incident light on sample (Is). The value of absorbance is usually above 1 when there is absorption and zero when there is no absorption.

$$\text{Beer's Law: } A = \log (Ir/Is) = \varepsilon cl$$

Molar absorptivity (ε) is constant. Sample is dissolved in some solvent such as ethanol which doesn't absorb above 200 nm. Cuvette are made of quartz which doesn't absorb UV radiation. We use another reference cell which only contain solvent. This is reference cell. A source generates UV light above 200 nm which pass through a monochromator for getting light of one wavelength. The light is split into two beams: one passing through reference cell and another through sample cell. Emerging beam from the cells are focused on detector for signal recording which scan the difference between the two. Molar absorptivity measures how strongly sample absorb lights. UV spectrum gives broad absorption peaks. Usually, maximum value as lambda max is noted for characterization purpose. Sample must be extremely pure, else UV spectrum would be blurred.



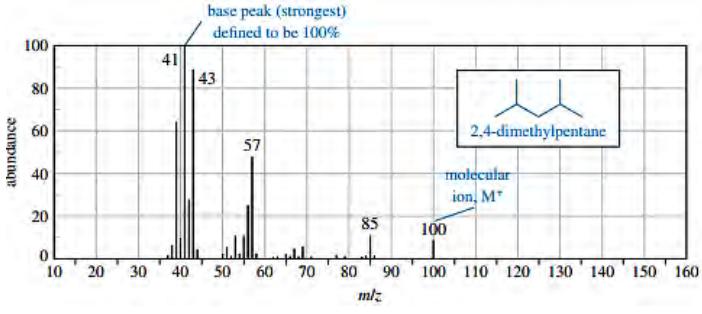
6.4 Mass Spectrometry

Unlike other spectroscopic techniques, mass spectrometry is different because it doesn't use light but beam of electrons for breaking apart sample. MS is destructive because it destroy sample. Structural determination wouldn't have been possible had molecular

weight and molecular formula not known. MS measures both as prerequisite for structural elucidation using high resolution spectrometry (HRMS).

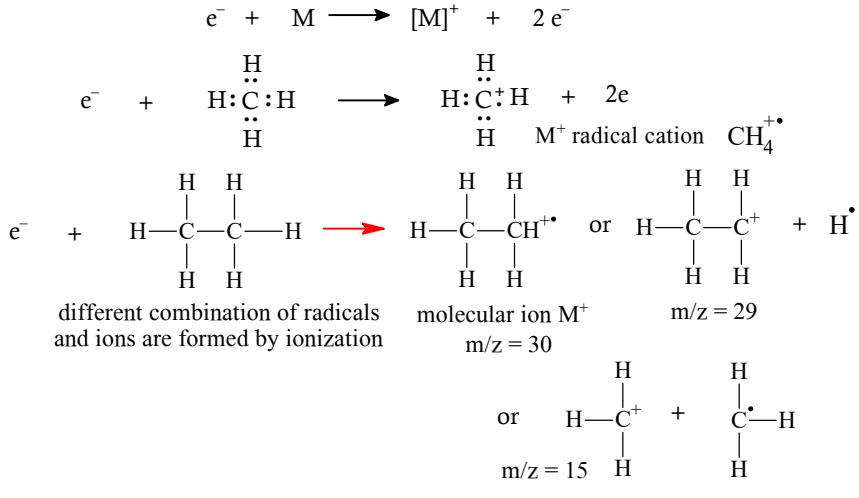
6.41 MS Spectrum

A graphic representation between relative abundance and mass to charge ratio (m/z) is drawn. Relative abundance (in %) tells us the extent of particular fragment in spectrum. A base peak is the strongest of all whose relative abundance is greater than all other peaks. Molecular ion peak (parent peak) reflect the mass of molecule whose structure is to be known.



6.42 How Ions in MS are generated?

A beam of fast moving electrons colloid neutral sample that enable ionization be ejection of electrons. The phenomenon is regarded as electron impact ionization. Consider, a sample M is bombarded with electron. It gives molecular ion peak of M+ which is radical cation after loss of electron.



Besides molecular ion peak, multiple other fragments form too which reflect mixture of cations, anions, radical cation and neutral. Some atoms carrying isotopes give characteristics molecular ion peaks which are easily recognizable from spectrum. For

instance, bromine gives M+ and M+2 peaks of similar height. A peak which differs from parent or molecular ion peak by mass unit of 1 is known as M+1 peak.

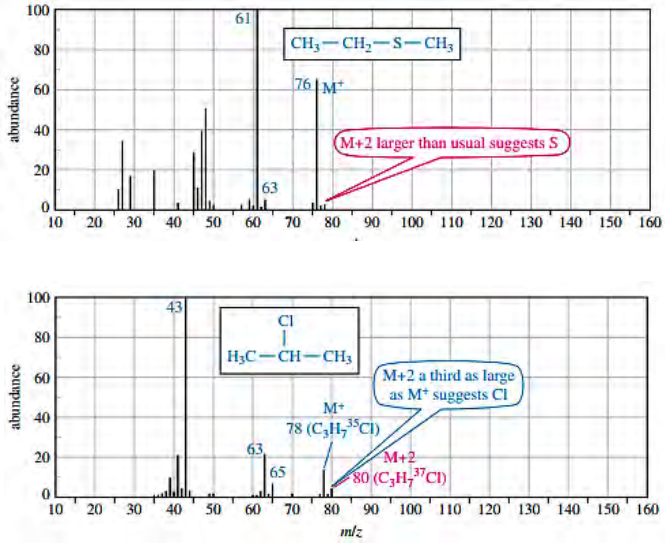
Element	M+		M+1		M+2	
H	^{1}H	100%				
C	^{12}C	98.9%	^{13}C	1.1%		
N	^{14}N	99.6%	^{15}N	0.4%		
O	^{16}O	99.8%			^{18}O	0.2%
S	^{32}S	95%	^{33}S	0.8%	^{34}S	4.2%
Cl	^{35}Cl	75.5%			^{37}Cl	24.7%
Br	^{79}Br	50.5%			^{81}Br	49.5%
I	^{127}I	100%				

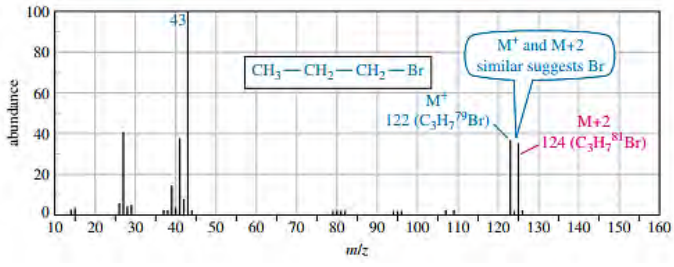
Isotopic Peaks

Elements like S, Cl, Cr, I and N are recognizable from molecular ion peaks. A typical compound with no S, Cl or Br has a small M+1 peak and an even smaller M+2 peak. If a compound contains S, the M+2 peak is larger than M+1 peak about 4%. If ^{37}Cl is present, the M+2 peak is about a third as large as the M^+ peak. For Br, the M+ and M+2 ions have equal abundance. The molecular ion appears as a doublet separated by two mass units. The one mass corresponds to ^{79}Br and the other ^{81}Br.

Recognizable elements in mass spectrum	
Br	M+2 as large as M^+
Cl	M+2 a third as large as M^+
I	I^+ at 127, large gap
N	odd M^+, some even fragments
S	M+2 larger than usual (4% of M^+)

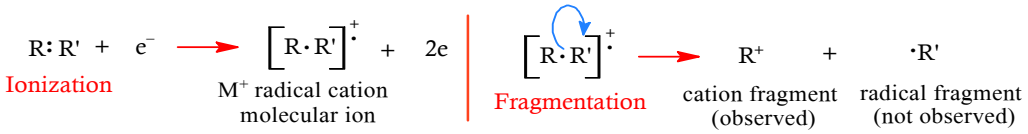
The following spectra show compounds containing sulfur, chlorine and bromine.



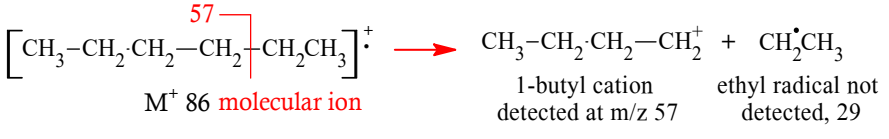


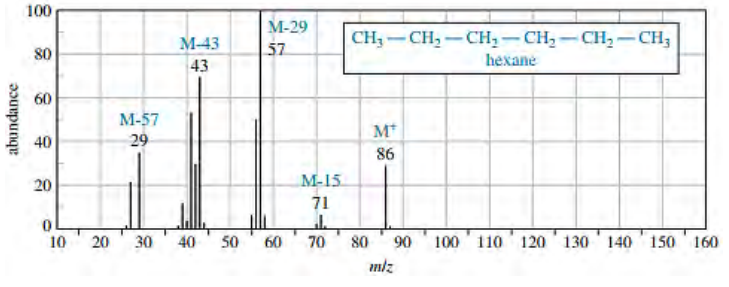
6.43 Fragmentation Pattern

An electron with a typical energy of 70 eV (6740 kJ/mol has far more energy than needed to ionize a molecule. The impact forms the radical cation, and it often breaks a bond to give a cation and a radical. The resulting cation is observed by the mass spectrometer, but the uncharged radical is not accelerated or detected. We can infer the mass of the uncharged radical from the amount of mass lost from the molecular ion to give the observed cation fragment.

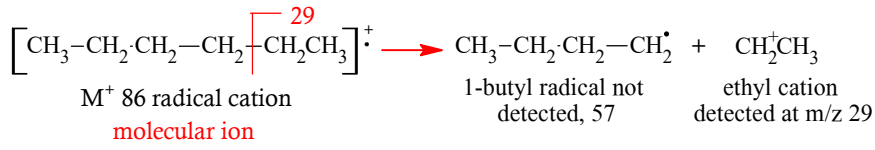


This bond breaking does not occur randomly; it tends to form the most stable fragments. By knowing what stable fragments result from different kinds of compounds, we can recognize structural features and use the mass spectrum to confirm a proposed structure. The mass spectrum of hexane shows several characteristics typical of straight chain alkanes. Like other compounds not containing nitrogen, the molecular ion (M+) has an even numbered mass, and most of the fragments are odd numbered. The base peak (*m/z* 57) corresponds to loss of an ethyl group, giving an ethyl radical and a butyl cation. The neutral ethyl radical is not detected, because it is not charged and is not accelerated or deflected.

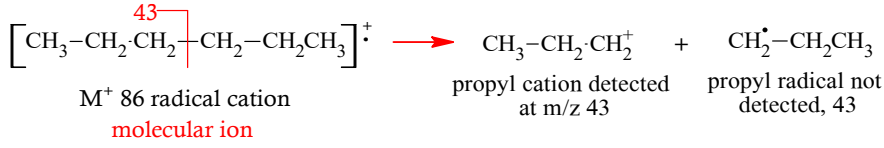




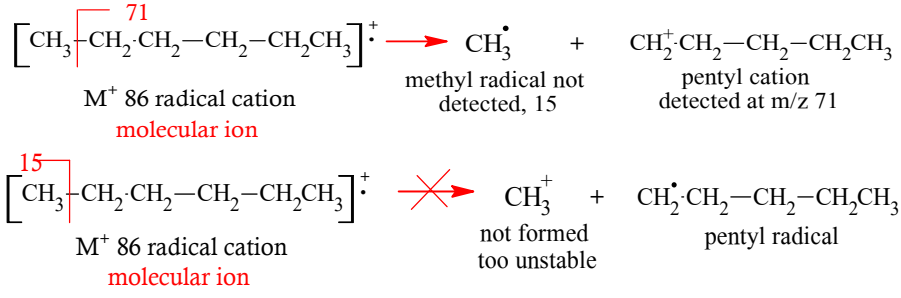
A similar fragmentation gives an ethyl cation and a butyl radical. In this case, the ethyl fragment (*m/z* 29) is detected.



Symmetric cleavage of hexane gives a propyl cation and a propyl radical.



Cleavage to give a pentyl cation (*m/z* 71) and a methyl radical is weak because the methyl radical is less stable than a substituted radical. Cleavage to give a methyl cation (*m/z* 15) and a pentyl radical is not visible because the methyl cation is less stable than a substituted cation. The stability of the cation is apparently more important than the stability of the radical, since a weak peak appears corresponding to loss of a methyl radical, but we see no cleavage to give a methyl cation.



Cation and radical stabilities help to explain the mass spectra of branched alkanes as well. Fragmentation of a branched alkane commonly occurs at a branch carbon atom to give the most highly substituted cation and radical. Fragmentation of 2-methylpentane at the branched carbon atom can give a secondary carbocation in either of two ways:

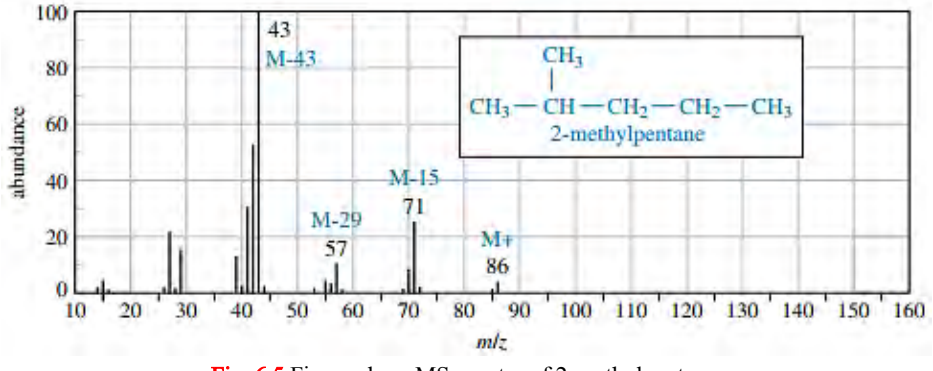
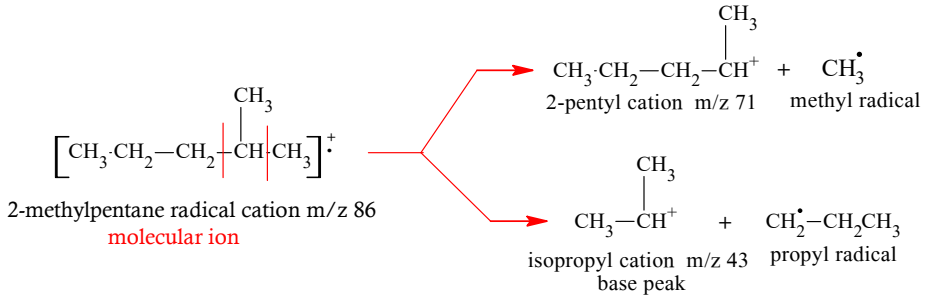
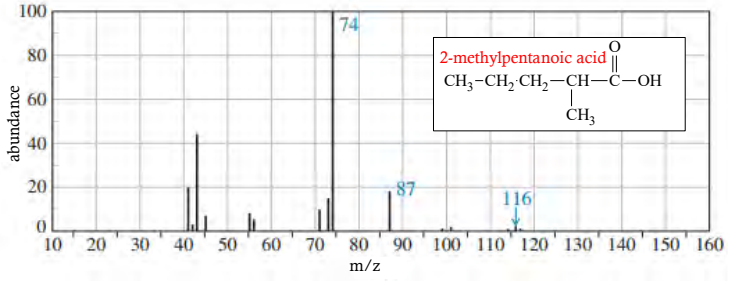


Fig. 6.5 Figure show MS spectra of 2-methylpentane.



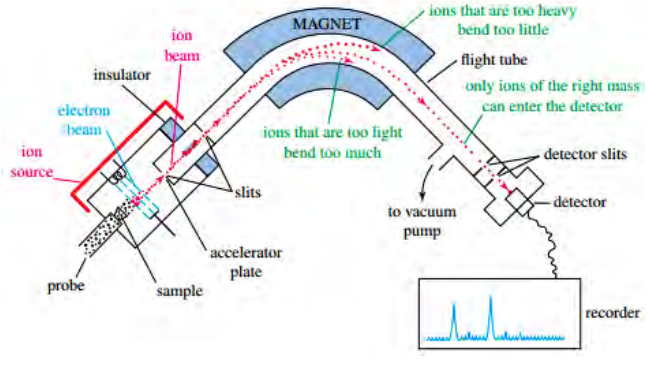
Both fragmentations give secondary cations, but the second gives a primary radical instead of a methyl radical. Therefore, the second fragmentation accounts for the base (largest) peak, while the first accounts for another large peak at *m/z* 71. Other fragmentations (to give primary cations) account for the weaker peaks.

Problem 6.0: Point out fragmentation pattern for the following molecule.



6.44 The Mass Spectrometer

MS irradiates sample with beam of high energy electrons which causes ionization sand subsequent generation of positive ions. With the aid of electric and magnetic field, these ions are pushed and deflected towards detector where they are recorded and ultimately transformed into a spectrum. The spectrum is plot of relative abundance verses m/z value of charge. Smaller ions fall away with larger curvature unlike charges of larger size which fall near and record small curve. Most charges have +1 charge, usually the path of the curve depend upon the mass of ions. The relative abundance depend upon how many ions of particular mass fall on the detector for registering current.



6.5 Nuclear Magnetic Resonance

Both methanol 'wood alcohol' and ethanol 'grain alcohol' are transparent liquids. To differentiate them, we use NMR (nuclear magnetic resonance) technique which senses magnetically active nuclei such as ^{1}H, ^{13}C, ^{14}N, ^{17}O, ^{19}F or ^{31}P in molecules. These nuclei are NMR active. NMR not only detects these nuclei but also extracts useful information about the chemical environment in which these nuclei are present. For instance, methyl and ethyl group of methanol and ethanol can be clearly distinguished with application of NMR which records sample through a spectrum. These nuclei are sensed by NMR. Proton NMR (^{1}H NMR or PNMR) and ^{13}C NMR (CMR) are commonly used because almost every type of organic compound contains hydrogen and carbon atoms. Other nuclei such as ^{12}C or ^{16}O are NMR inactive, which are not detected by NMR. In the ensuing, text we will first focus on ^{1}H NMR and then conclude with ^{13}C NMR spectroscopy. But let's first begin with brief history and development of NMR as an enigmatic analytical tool.

NMR uses giant homogeneous magnet coupled with radio frequency transmitter and computer set up. The magnet is kept cool by filling NMR with liquid nitrogen or helium for better results. Sample is taken in a probe tube for placing unknown compound between the poles of giant magnet to record its spectrum. The spectrum shows different absorption peaks which are usually appear as singlets or multiplets. Radio frequency (RF) is used to enable absorption by sample which appears in form of peaks in NMR spectrum.


Fig. 6.6 A typical NMR instrument

Different atoms in a molecule exhibit different absorption peaks that are distinct for every compound. For instance, ^{1}H NMR of methanol gives two absorption peaks that reflect the compound has two different types of protons: methyl and hydroxyl protons. Ethanol gives three signals: one for methyl, one for methylene (CH_2) and one signal for hydroxyl proton. Two signals split into multiplets, says a triplet (tp) and quartet (qt), whereas one signal stays singlet (s). Both spectra will be discussed in detail later in the ensuing texts. Here, it is enough to point out that methanol and ethanol differ by number of signals they generate: methanol, two and ethanol, three. NMR also counts four protons for methanol and six for ethanol with the aid of integrator. Besides, many other structural differences are made evident by the application of NMR which is paramount spectroscopic technique for structural elucidations.

6.51 History of NMR & and MRI

NMR[1] phenomenon was discovered during 1950s and by 1960s it became available as significant analytical tool for molecular structural characterization. By 1970s, NMR applications got extended to imagining technique known as MRI or magnetic resonance imagining. MRI is in fact NMR, only the nuclear term has substituted by health professionals to ward off any tension of attributing the technique with use of radioactive material. MRI has turned out to be so much pivotal medical tool that entertained Paul C. Lautenberg (left in fig.6.7a) and Peter Mansfield (fig.6.7b) with Nobel Prize in 2003[2] in medicines and physiology for their discoveries that led practical utility of the technique. Lautenberg invented magnetic resonance imagining technique in 1971 and two years later published his theory. An American physician Raymond V. Damadian invented first MRI scanning machine.

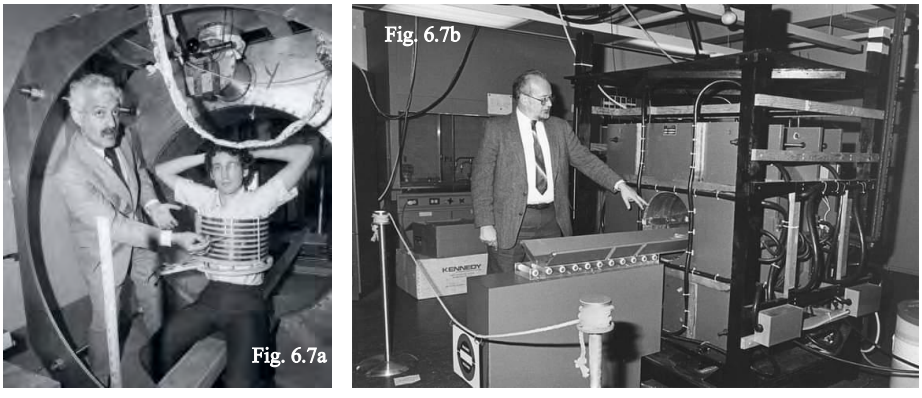


Fig. 6.7 On 3rd July 1977, first MRI test on a live human patient was performed. MRI, identifies atoms by how they behave in a magnetic field, and is an extremely useful non-invasive method for imagining internal bodily structure and diagnosing diseases. MR imaging was invented by Paul C. Lautenberg who developed a mechanism to encode spatial information into an NMR signal using magnetic field gradients in Sept. 1971; and published the theory in March 1973.

Much like PNMR, MRI too comes up with useful information about protons which are present in almost all biological molecules. Phosphorus MRI is also used in diagnostic medicines. MRI helps in detection of tumor formation at early stages. For instance, in 1970, it was reported that relaxation time for water molecules in cancerous cells takes much larger time than healthy tissues. This distinction enabled the detection of cancerous tissues.

Relaxation[3] is de-excitation of excited nuclei to ground state. Remember, excitation of such nuclei is triggered by absorption of RF which is used in NMR technique. MRI also assists in distinguishing white matter from grey one in diagnosis of spinal cord and associated diseases such as multiple sclerosis. MRI is different from X Rays technique because outer hard coating of bones is almost invisible to MRI (visible to X Rays) whereas inside soft and delicate tissues are detectable by MRI (not detected by X Rays).

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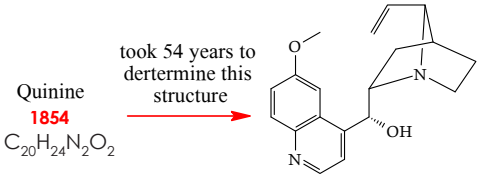
[1] **Felix Bloch** of Stanford and **Edward M. Purcell** of Harvard were awarded Nobel Prize in Physics in 1952 for their discoveries linked to NMR.
[2] https://www.nobelprize.org/prizes/medicine/2003/summary/
[3] Relaxation will be discussed in ^{13}C spectroscopy.

Fig. 6.8 A 300 MHz NMR spectrometer in Gomal University, DIKhan. Dr. Said Badshah is briefing my students about fundamental operations of NMR. I along with my students of GDC Tank visited university on 14 Feb. 2018. Author of the text is standing in front row.

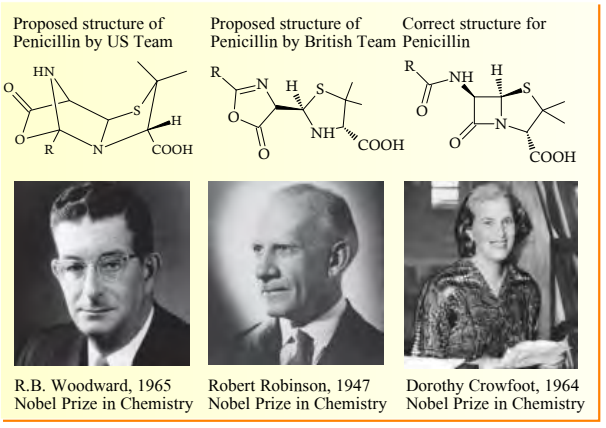
6.52 Significance of Structural Determination

Prior to 1950s when spectroscopic techniques were not discovered or operationally matured, structural determination of molecules was hectic job. Scientists spent years after years to ascertain connectivity of atoms within molecules. Degradation of compounds into fragments and then joining back into parent compound was laborious task to come up with plausible structural elucidation. It took decade for getting correct representation. For instance, quinine took almost 54 years to complete its ultimate structure.



Correct structure of Quinine

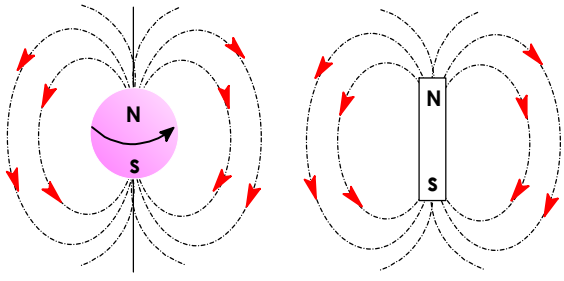
Structure determination is pivotal prerequisite of organic synthesis. Unless a structure for a molecule is ascertained, its synthesis can't be affected. This trouble surfaced with structural identification of penicillin which was discovered by Alexander Fleming in 1928. During World War II when demand for the antibiotics grew alarmingly, natural penicillin from molds was inadequate to cater for wounded soldiers. American and British teams of scientists were set on to find the structure of penicillin before it could be synthesized in lab. Although both groups came up with erroneous presentation of penicillin, yet Dorothy Crowfoot Hodgkin solved the riddle with X-ray crystallography. Light is focused on the sample that enables identification of non-hydrogen connectivity in molecule. It was discovered that penicillin consists of four member ring which was not expected by US and British groups of scientists.



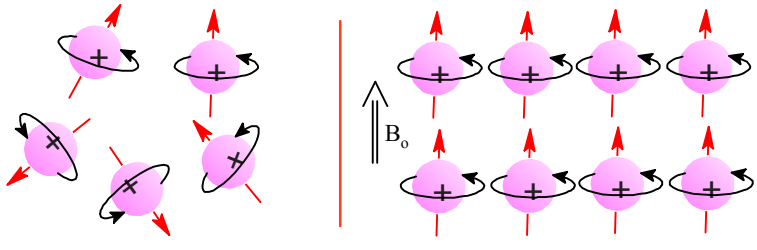
6.6 Proton NMR

6.61 Basic Theory of NMR

Spinning of proton along its axis is natural and intrinsic property which generates magnetic field like a bar magnetic. This magnetic field is known as magnetic moment (μ) which is sensed by NMR to characterize molecules. Strength of magnetic field is expressed in gauss.



Earth's magnetic field is 0.57 gauss. The SI unit of magnetic field is tesla (1T = 10,000 gauss). Spinning of proton is denoted by spin quantum number *I* (s is spin quantum number of electron). *I* is determined experimentally. Number of orientations (*m*) for a proton is addressed by equation[4]: $m = 2I + 1$. For instance, *I* value for proton is 1/2. *I* value for ^{13}C is 1/2 too. Putting this value in the equation gives m = 2 for either ^{1}H or ^{13}C which means proton (hydrogen) or ^{13}C has two spin states: +1/2 (α—alpha spin state) and -1/2 (β—beta spin state). In absence of external magnetic field (B_o), these spin states have random orientations. B_o makes these orientations either align or against the direction of external field (see below).



Solved Problem 6.1: *I* value for chlorine is 3/2 and ^{17}O is 5/2. Their *m* values are **4** (3/2, 1/2, -1/2, -3/2) and **6** (5/2, 3/2, 1/2, -1/2, -3/2, -5/2) respectively.

Analysis: Nuclei with **1/2** spin are NMR active (highlighted in green in table 1).

Those nuclei which have odd protons (atomic number) or odd neutrons (mass number) are NMR active. For example, both ^{1}H and ^{13}C have one proton and 7 neutrons respectively. Nuclei such as deuterium (^{2}H) or ^{4}He are NMR inactive because of mutual

[4] Compare with equation $m = 2nI + 1$ which is used for NMR inactive nuclei such as deuterium. This equation has applied in deuterated solvent section in ^{13}C NMR spectroscopy.

coupling of proton with proton or proton with neutron that renders the vector sum of spin quantum number 1 (deuterium) or zero (helium).

Table 1: NMR Active and Inactive Nuclei

Elements	^{1}H	^{2}H	^{12}C	^{13}C	^{14}N	^{15}N	^{16}O	^{19}F	^{31}P	^{32}S
I (spin)	1/2	1	0	1/2	1	1/2	0	1/2	1/2	0
m = 2I+1	2	3	1	2	3	2	1	2	2	1

In case of deuterium, if the spin of proton and neutron are opposite to each other, say one is parallel and another is anti-parallel, then *I* will be zero. If both are parallel or anti-parallel, then *I* will be 1. Similarly, ^{12}C and ^{16}O are NMR inactive nuclei. Atomic nuclei are usually divided into three groups. Z is atomic number and A is atomic mass in the following table.

Group 1 Z = Even A = Even

^{4}He, ^{12}C, ^{18}O ⟶ P : N = 2 : 2
Potons coupling +1/2 -1/2 = 0
Neutrons coupling +1/2 -1/2 = 0
I = 0

Group 2 Z = Odd A = Even

^{2}D, ^{10}B, ^{14}N ⟶ P : N = 1 : 1
P + N coupling +1/2 +1/2 = 1
I = 1

Group 3 Z = Even or Odd A = Odd

^{1}H, ^{13}C, ^{15}N, ^{17}O ⟶ P : N = 1 : 2
I = 1

In short, if number of particles (p + n) in nucleus are even, they couple or pair up that make resultant nuclear spin number *I* either 1 (*I* = 1,2,3... e.g. ^{2}H, ^{14}N, such nuclei have quadrupole. Their magnetic moment isn't observed by NMR) or zero (^{12}C, ^{16}O, ^{18}O, ^{32}S). Both reflect NMR inactive states. On the other hand, if the number of nuclear particles are odd, *I* value will be integer (1/2) that attests NMR active spin states. Spin *I* = 1/2 is most unified one. Electric and magnetic field surrounding such nuclei are uniform, spherical, homogenous and isotropic in all directions. For nuclei with I > 1/2, electric and magnetic field are unsymmetrical (electric quadrupole) that complicates the behavior of such nuclei in NMR.

Problem 6.1: Calculate spin multiplicity (m) for ^{11}B and ^{17}O with spin quantum number (*I*) of 3/2 and 5/2 respectively.

As stated above, in absence of B_o, nuclear spin states have random orientations. However, when protons are taken under the influence of B_o, the spin states begin to align parallel or anti-parallel with reference to the direction of B_o. Thus, we got two spin states: α and β spin states. α Spin state has lower energy. Consequently, α spin state becomes dominant orientation in external magnetic field.

Difference in energy (ΔE) between the two spin states depends upon the strength of B_o. Higher B_o stretches (widen) gap between the two spin states. The shift of one spin state to another, says transforming α to β state, external energy is required in the form of photon (radio frequency RF).

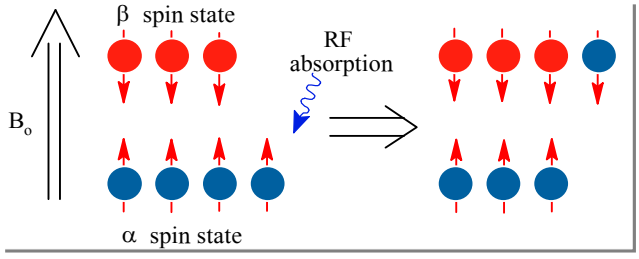


Fig 6.10 Absorption of RF causes nuclei to shift from α spin state to β spin state.

At room temperature, thermal energy is sufficient to populate both energy levels with spinning nuclei. Difference of population (population difference) is essential for NMR phenomenon to happen. If both energy states are equally populated, saturation occurs that resists energy absorption. At saturation level, NMR fails to record any spectrum. Population difference is calculated by Boltzmann's ratio:

$$\frac{N_{upper}}{N_{lower}} = e^{-\Delta E/kT} = e^{h\nu/kT}$$

Energy equation for the difference between the two spin states can be given as:

$$\Delta E = \gamma h B_o / 2\pi$$

ΔE = energy separation between two spin states
γ = magnetogyeric ratio (gyromagnetic ratio)
B_o = external magnetic field
h = Plank's constant

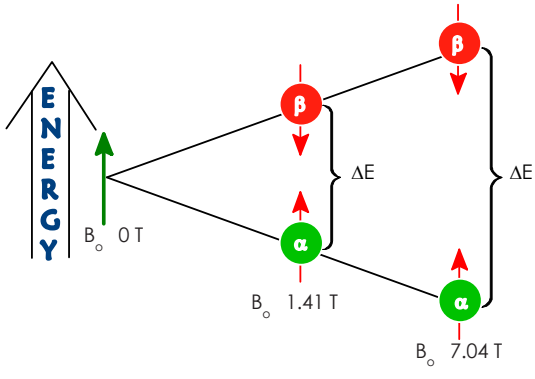


Fig. 6.11 at zero B_o, there is no separation between two spin states of proton. At magnetic strength of 1.41 T, ΔE (2.39×10^{-5} kJ/mol) between two spin states corresponds to resonance frequency (RF) of 60 MHz At 7.04 T, ΔE equals to RF of 300 MHz. This indicates that the energy separation between the two spin states is proportional to strength of B_o. Besides, ΔE is also dependent on γ as well. Remember, spinning frequency remains constant with B_o, only precessional frequency effects.

Magnetogyeric ratio is a constant. It depends upon the magnetic moment of spinning nuclei. Its value for proton is 26,753 sec^{-1} $gauss^{-1}$. Rearranging above equation in energy equation ($E = h\nu$), we get

$$\Delta E = h\nu = \gamma h B_o / 2\pi$$
$$\nu = \gamma B_o / 2\pi$$

ν is resonance (precessional) frequency. To find out ν, we can use above equation. Equation for ν signifies that the resonance frequency for spinning nuclei is directly proportional to strength of external magnetic field and magnetogyeric ratio. Consider γ values for various nuclei:

$$\gamma_{proton} = 26{,}753\ G^{-1}s^{-1}$$
$$\gamma_{carbon\text{-}13} = 67{,}283\ G^{-1}s^{-1}$$
$$\gamma_{flourine\text{-}19} = 251{,}815\ G^{-1}s^{-1}$$
$$\gamma_{phosphorous\text{-}31} = 108{,}394\ G^{-1}s^{-1}$$

In NMR, we rely on radio frequency that enables shifting between spin states. This shifting of α spin state to β with the aid of radio frequency is known as spin flipping (spin inversion) that can be brought up by frequency sweep (B_o is kept constant but frequency varies) or field sweep (B_o varies but frequency is kept constant) modes. Usually, field sweep is preferred for technical purposes.

Problem 6.2: From magnetogyeric ratio given above, calculate ΔE for proton at 2.35 T. Also arrange the above nuclei in decreasing order of sensitivity. If I for ^{31}P is ½, find out number of possible orientation (m) for the ^{31}P nucleus.

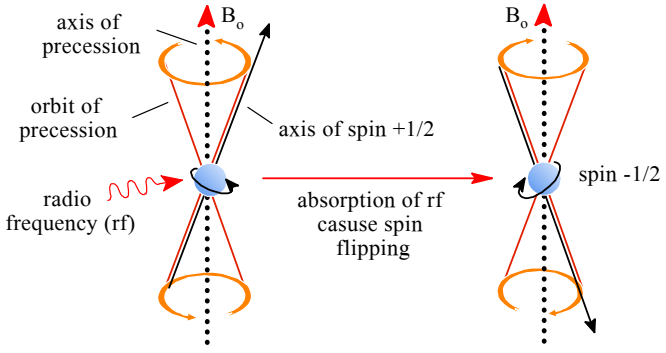
Nuclei are degenerate in absence of B_o. When B_o is set on, these nuclei align with and against the field and begin to precess which is sort of motion much like tumbling spinning top whose spinning axis rotates around the original axis (perpendicular to earth surface). The frequency at which the nuclei precess is known as precessional or Larmour frequency[5]. When radio frequency of NMR device is switched on, precessing nuclei absorb at exactly the same frequency as their precessional frequency. For example, in B_o of 1.41 T, resonance frequency of proton is 60 MHz. At B_o of 2.35 T, the resonance frequency gets to 100 MHz. The ratio is same as the ratio of B_o strength.

$$\frac{2.35\ T}{1.41\ T} = 1.666 \qquad \frac{100\ MHz}{60\ MHz} = 1.666$$

Thus, shift in Hz for a given proton from TMS is 5/3 times longer in 100 MHz than 60 MHz. This sort of measurement is perplexing. To cope with, delta scale of

[5] Angular precessional frequency is a function of $w = \gamma B_o$ with units Rad/s. To get the frequency in linear format, $\nu = w/2\pi$ which is $p_{recession} = \gamma B_o/2\pi$. Precessional frequency is independent of m so all spin orientations of a given nucleus processes at same frequency in a fixed magnetic field. Spin flipping doesn't change precessional frequency. For resonance to occur, radio frequency must be equal to the precessional frequency of a nucleus.

measurement or chemical shift has introduced which will be discussed in the next segment whose value is always same by measuring resonance either in 60 or 100 MHz NMR machine.



Thus, the phenomenon of spin flipping that take places with the assistance of right combination of external magnetic field and radio frequency is known as resonance[6]. In fact, the phrase of nuclear magnetic resonance emerges from this phenomenon which harnesses magnetic moment of nucleus to resonate for structural characterization of organic molecules.

Problem 6.3: What frequency is needed for a proton to be in resonance in NMR of B_o 1.41 T? Also find out energy difference ΔE between the two spin states.

Problem 6.4: What is resonance frequency and ΔE for a proton precessing in B_o of 23,500 G?

Solved Problem 6.2: Why positions of absorption are usually taken in frequency units rather magnetic field units?

Analysis Normally, PNMR spectrum is recorded in field sweep operation. The positions of absorption are better given in frequency which can be measured more precisely than the difference in magnetic field units since 1 G = 4260 Hz.

6.62 Shielding and Deshielding

Besides external magnetic field (B_o), an internal or induced magnetic field is possessed by circulating electrons whose magnetic moment opposes the external field. The phenomenon is known as diamagnetism which shields proton from the external magnetic field. In B_o, circulation of valence electrons is known as local diamagnetic current (LDC[7]), which generates a counter magnetic field that opposes B_o. This effect is known as diamagnetic shielding or diamagnetic anisotropy. LDC in case of aromatic ring is known as ring current. As protons lay in different chemical (electronic) environments, they are

[6] Besides magnetic field, spinning or precessing nuclei are governed by oscillating electric field whose frequency when couples (matches) with the frequency of the oscillating electric field of rf, energy is transferred to the spinning nuclei that flips α spin state to β. This phenomenon is known as **resonance** in NMR parlance.

[7] Circulation of π electron perpendicular to B_o is known as **LDC**. The induce magnetic field generated as a result of LDC is parallel to B_o but perpendicular to LDC.

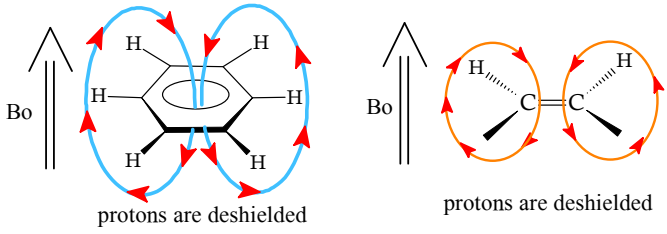
either shielded or deshielded from external magnetic field LDC. Without this phenomenon, NMR would be useless technique because every proton or nuclei would have absorbed same radio frequency that would be unable to distinguish them. The influence of electronic magnetic field (I_{nduced}) could either be aligned with or against external magnetic field. If it aligns, the proton encounters an increase in magnetic field ($E_{ffective}$) i.e. sum of external magnetic field plus the tiny electronic magnetic field. We say the proton is deshielded.

$$\mathbf{B_{eff} = B_o + B_{ind}}$$

On the other hand, when electronic magnetic field aligns against the external magnetic field, the net magnetic field encounters by the proton is decreased by the extent of electronic magnetic field. Here, the proton is said to be shielded.

$$\mathbf{B_{eff} = B_o - B_{ind}}$$

Consider ethylene and aromatic ring in the following figure. Protons in either case are deshielded because they lay in region where induced magnetic field (LDC) reinforces vinylic and aromatic protons.



Hence, net field (B_{eff}) encountered by protons in question is sum of B_o and induced magnetic field. In methanol, –OH proton is deshielded due to inductive effect exerted by electronegative oxygen atom that withdraws electronic density by turning proton naked. Methyl protons are shielded because they are bonded to carbon (less electronegative) instead of oxygen.

6.63 NMR Instrument

An NMR machine consists of a powerful magnet, a radio frequency oscillator and a computer set up. Sample is dissolved in solvent containing no interfering protons such as CCl_4 or $CDCl_3$. Small amount of TMS is added as either internal or external reference depending upon the nature of sample. TMS is not soluble in water. In aqueous solution, it is normally used as external reference. In such case, water soluble salt of DSS (2, 2-dimethyl-2-silapentane-5-sulfonic acid) is preferred as internal reference. Sample is taken in probe tube into the mid of the two poles of giant magnet. Probe tube is cylindrical glass rod which is 5 mm in diameter and 20 cm long.

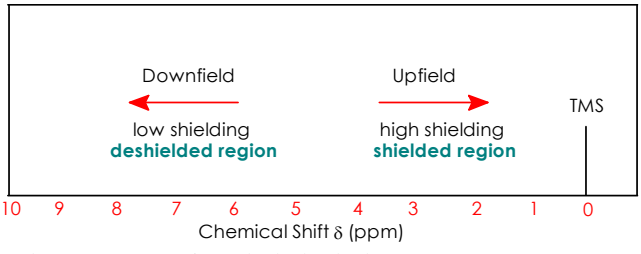
Probe tube is spun at the rate of 20 cycles/s so that every part of the sample encounters uniform magnetic field. For 60 MHz instrument, precessional frequency of proton increases with increase in B_o until it reaches 60 MHz before resonance take places.

Shielded protons precess slowly as compared to deshielded ones. NMR instrument in which magnetic field is continuously varying, scanning from left to right of the spectrum is known as continuous wave or CW-NMR. NMR machine is usually filled with either 80 liter of liquid helium or 40 liter of liquid nitrogen which is needed to cool the magnetic for better operation. Both He and N_2 are cryogens.

6.64 NMR Spectrum

Whether a signal for particular nucleus is less or more intense depends upon the magnetic moment and number of nuclei. For instance, magnetic moment of proton is very high and its relative abundance is very large (99%), therefore both parameters equip proton to exhibit intense signal which is detected very easily. On the other hand, magnetic moment of ^{13}C is low and its relative abundance is quite minimal (1%); therefore, its signal is less intense that needs strong magnetic field for adequate resolution. Magnetic moments of electron (700 times of proton) and free radical are exceedingly very high.

In a typical NMR spectrum, absorption is plotted on y-axis (abscissa) as a function of magnetic field which is taken on x-axis (ordinate). The spectrum can be divided into left and right parts. The left part reflects low field (downfield) values where the right side possesses higher field (up field) values. More shielded protons as methyl ones in case of methanol appears up field (right) whereas deshielded proton such as hydroxyl one in methanol appear downfield (left). Less shielded protons absorb at higher frequencies as compared to more shielded ones.



Consider the spectrum of methyl alcohol on 300 MHz spectrometer.

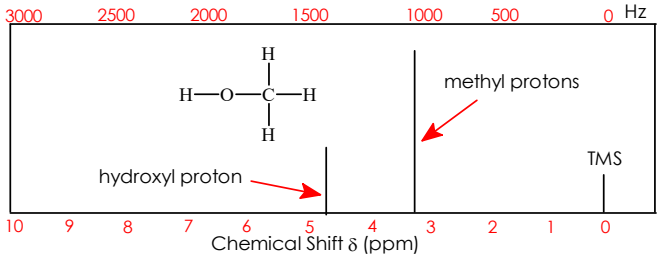


Fig. 6.12 Proton NMR of methanol. Three methyl protons are equivalent because rapid rotation makes them indistinguishable in NMR. Such protons are termed as homotopic.

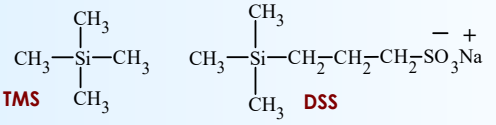
Methyl protons (more shielded) absorb at lower frequency of 1025 Hz, where hydroxyl proton (less shielded) absorbs at higher frequency of 1450 Hz. Protons which are exposed or deshielded are prone to absorb electromagnetic radiation easily. Such protons record absorption at higher chemical shift values.

6.65 Chemical Shift

An NMR sample which contains compound for investigation is taken in tetramethylsilane (TMS) which is not only an excellent compound which dissolves in majority of organic solvents but also serves as reference standard of choice. In TMS, all 12 protons are equivalent. They generate intense signal which appears on the right extreme of NMR spectrum. TMS protons are highly shielded because silicon is less electronegative than carbon. Most other protons are less shielded than ones in TMS. Hence, signals for all such protons appears left to the signal of TMS.

TMS Features

1. TMS is Low boiling liquid (26.5 °C) which enables easy sample recoverl
2. Doesn't participate in H-bonding
3. Insoluble in water but soluble in most organic solvents
4. For biological molecules, DSS is used instead of TMS
5. All 12 protons are highly shielded, their peak appear as sharpe singlet
6. All 12 protons are equivalent, they give just one peak



The difference between absorption peaks of sample protons and reference TMS is known as chemical shift. It is denoted by (delta scale) δ and is measured in part per million (ppm). On shift scale, TMS is assigned 0 value. As absorption take place in frequency value, it can be changed into chemical shift value by dividing the absorption frequency over spectrometer frequency.

Chemical shift in ppm (δ) shift downfield from TMS (Hz)spectrometer frequency (Hz)

Chemical shift value for a proton that absorbs at 70 Hz on 60 MHz spectrometer will be: 70/60 = 1.16 ppm. Chemical shift value remains same on different spectrometers. For example, the shift value will remain 1.16 ppm on 300 MHz NMR as well. However, frequency value varies which can be obtained just my multiplying shift value with NMR strength i.e. 1.16 × 300 = 348 Hz. Chemical shift values remain same no matter an NMR spectrum is taken on 60 MHz or 100 MHz. For instance, at 60 MHz, δ value for proton in $CHBr_3$ is 162 Hz. At 100, δ value for the said proton is 270 Hz.

$$\delta = \frac{162\ \text{Hz}}{60\ \text{MHz}} = 2.7\ \text{ppm} \qquad \delta = \frac{270\ \text{Hz}}{100\ \text{MHz}} = 2.7\ \text{ppm}$$

3. Chemical Shift Values

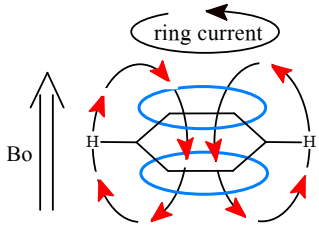
Had all protons absorbed at same value, NMR would be frivolous technique in spectroscopic characterization. Thanks to chemical environment of protons that make them different and distinct in spectroscopic analysis. For instance, the chemical

environments of methyl protons in methanol and alkane are different. This difference makes them distinguishable by recording different chemical shift values.

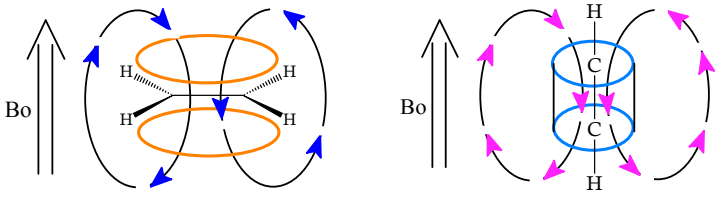
Methyl protons in methanol absorb at δ 3.4 where alkane ones at δ 0.9 (a difference of almost 2.5). In methyl alcohol, presence of electronegative oxygen divests methyl protons of electronic density that render them deshielded. On the other hand, no such electronegative element is present in alkane. When we look at the table that record chemical shift values for different protons, we encounter different results not only for each functional group but for every second molecule within the same functional group because chemical environment of proton is different in every second molecule.

Problem 6.5: Substituting hydrogen with carbon in methyl group cause a downfield shift. For instance, methine, methylene and methyl protons have δ values 1.7, 1.3 and 0.9 respectively. Reason, why this difference occurs? **Hint**: Electronegativity Effect

Consider an example of aromatic protons that absorb at much higher chemical shift value of 7.2. π electronic density of aromatic ring begins to circulate in external magnetic field that generates current known as ring current. This current has induced magnetic field which opposes external magnetic field inside the ring but align outside. As aromatic protons lay outside, they encounter combined effect of ring current and external magnetic field which makes them to absorb at higher shift value of 7.2.



Somewhat similar result is observed for vinylic protons too which are deshielded by double bond the same way aromatic ring does, hence record at higher chemical shift values of 5 to 6.



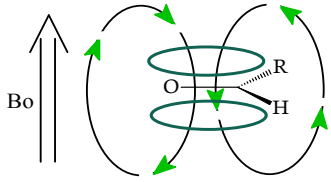
Contrary to these explanations for deshielding effect of multiple bonds, acetylenic proton absorbs at 2.5 which is low as compared to aromatic and alkene system. To explain this difference, triple bond presents a cylindrical electronic density whose circulation and subsequent generation of induced magnetic field opposes external magnetic field at point where acetylenic proton locates. This make them shielded.

Solved Problem 6.3: If two signals appear at 2.1 and 2.3 ppm in 200 MHz, what is frequency difference between them in Hz?
Analysis: At 20 MHz NMR, 1 ppm = 200 Hz. Similarly, at 600 MHz NMR, 1 ppm = 600 Hz.

$$\Delta\delta = 2.3 - 2.1 = 0.2 \text{ ppm}$$
As 1 ppm = 200 Hz on 200 MHz NMR, therefore
$$0.2 \times 200 = 40 \text{ Hz}$$

Note: Resonance frequency changes from NMR to NMR. To avoid this difference, chemical shift or delta scale has introduce.

Aldehyde protons absorbs at 9 to 10, higher than aromatic protons, which is due to the fact that in aldehyde not only circulation of π electron of carbon-oxygen double bond contributes to deshielding effect but also electron withdrawing inductive effect of electronegative oxygen creates much deshielding.



Alcoholic and **N-H bond** of amines absorb at 4.5 and 3.5 respectively in concentrated solution where hydrogen bonding establishes deshielding effect. In dilute solution, where hydrogen bonding diminishes or get attenuated, both values reduce to 2. Signals link to hydrogen bonding are broad because proton exchanges among molecules and encounters varied chemical environment that lead it to absorb over variety of frequencies. Hence, such protons create broad signals. Consider the spectrum of ordinary ethanol which gives singlet for hydroxyl proton (c).

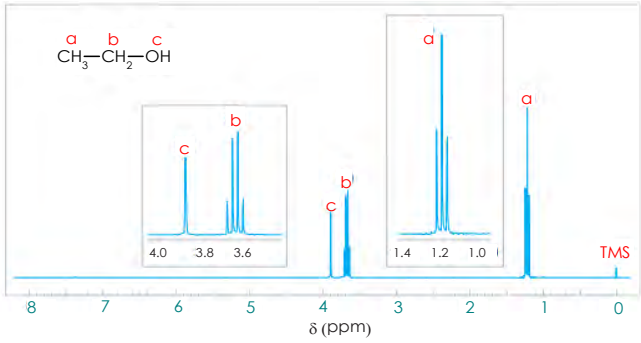


Fig. 6.13 PNMR spectrum of ordinary ethanol. Signals have resolved in boxes for better view.

In ultrapure ethanol, hydroxyl proton splits into a triplet by adjoining methylene group. This means that lack of hydrogen bonding or exchanging capacity of hydroxyl proton in pure form enables —OH proton to couple with —CH_2— protons. Carboxylic acid proton absorbs at 11 to 12. The higher chemical shift values are usually shown offset

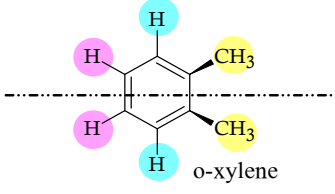
on NMR spectrum. The signal is broad as acids exist in dimeric form. Moreover, the combine effect of deshielding created by negative inductive effect of oxygen and circulation of π electrons subject acid proton to much lower field values. The following table records chemical shift values for protons of different functional groups.

Table 2: Chemical Shift Values for Proton

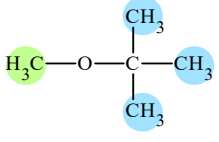
Type of Proton	δ (ppm)	Type of Proton	δ (ppm)
1° alkyl	0.8 - 1.2	RBr	3.4 - 3.6
2° alkyl	1.2 - 1.5	RCl	3.6 - 3.8
3° alkyl	1.4 - 1.8	vinylic	4.6 - 5.0
allylic	1.6 - 1.9	aromatic	6.0 - 8.5
ketone	2.1 - 2.6	aldehyde	2.1 - 2.6
benzylic	2.2 - 2.5	benzylic	9.5 - 10.5
alkyne	2.5 - 3.1	alcohol -OH	0.5 - 6.0
alkyl iodide	3.1 - 3.3	amino	1.0 - 5.0
ether	3.3 - 3.9	phenolic	4.5 - 7.7
alcohol	3.3 - 4.0	carboxylic acid	10 - 13

6.66 Number of Signal & Peak Area

NMR signals depend upon the type of different proton present in a molecule. As stated earlier, all 12 protons in TMS are chemically equivalent, say they are present in same chemical environment, therefore, they generate only one signal. Sometimes fewer signals are obtained than the number of different types of protons present in a molecule. For instance o-xylene has three different types of protons (highlighted in different colors). Six methyl protons are equivalent by symmetry operation. However, ^{1}H NMR spectrum of o-xylene give only two signals: one for two sets of aromatic protons and one for three methyl protons. Actually, the four aromatic protons gives two signals but they are so close that appear one signal. Such protons are termed as accidentally equivalent protons.

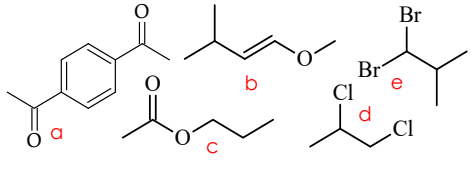


o-xylene



2-methoxy-2-methylpropane
t-butyl ether

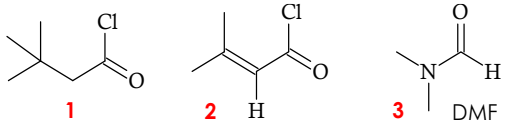
Problem 6.6: Find out number of proton signals in the following molecules.



For methyl t-butyl ether, we have two types of protons. All 9 protons of t-butyl group are chemically equivalent and generate only one peak. Methyl protons are

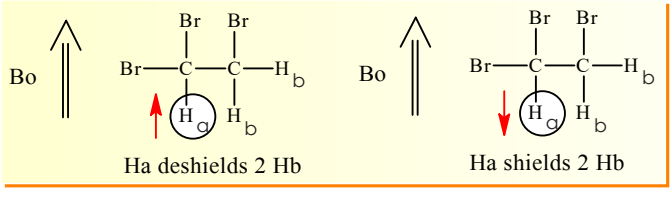
equivalent themselves. However, the area occupied by each type of peak is different: t-butyl group has 9 protons; therefore, peak area is broad as 9 protons are contributing unlike methyl group which has just three protons. NMR spectrometer calculates peaks area with help of integrator.

Problem 6.7: Based on number of proton signals, distinguish following three compounds from one another with application of NMR spectroscopy.



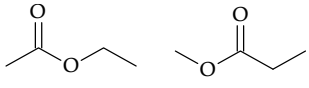
6.67 Splitting of NMR Signals

Not all NMR signals are singlets! Some signals split and divide into many signals or multiplets. This splitting of signal into multiplets is known as spin-spin splitting which gives useful information about the number of protons located on the adjacent carbon atom. Splitting pattern emerges from protons which are close enough (separated by three bonds[8]) that their magnetic field influences each other. Such protons are said to be magnetically coupled. Consider an example of 1, 1, 2-tribromoethane which has two types of proton that will give rise to two signals. However, the two signals are split into a doublet (db, two peaks) and a triplet (tp, three peaks).



To explain the splitting pattern, we consider proton H_a. It has two orientations: one aligns with and another aligns against the external magnetic field. Consequently, proton H_a either shields (when align against external magnetic field) or deshields (when align with external magnetic field) protons b. In other words, in some molecules, proton H_a shield and in some other molecules it deshields protons H_b. The ratio for shielding and deshielding is 50:50. As a result, protons H_b encounter shielding and deshielding effect due to proton H_a. This gives two peaks for proton H_b, a doublet which appear of equal height. Similarly, for two protons H_b, we have four different arrangements or permutations: when both shield, when deshielded and one oppose the other, hence, neither shielding nor deshielding occurs. These three different effects divide signal for proton into a triplet.

Problem 6.8: Using PNMR, how will you distinguish between the following two compounds?



[8] Protons separated by more than three bonds don't record observable splitting pattern.

We use N+1 rule to find out the multiplicity of a signal. N is the number of adjacent protons. For proton H_a, we have two proton b (N =2), hence 2 + 1 = 3 which means a triplet for proton a. Pascal triangle is used to assess relative areas under such peaks.

Table 3: Pascal's Triangle

Coupling protons	Multiplets	Peak Area
1	doublet	1:1
2	triplet	1:2:1
3	quartet	1:3:3:1
4	quintet	1:4:6:4:1
5	sextet	1:5:10:10:5:1
6	septet	1:6:15:20:15:6:1

For a doublet, the ratio from the triangle is 1:1, for a triplet, it is 1:3:1 which means the middle peak of triplet is twice as large as the other two. For an ordinary ethyl group as in ethyl bromide, methylene protons split into a quartet (qt, four peaks) with ratio 1:2:2:1 and methyl protons into a triplet with ratio 1:2:1. See the following fig.

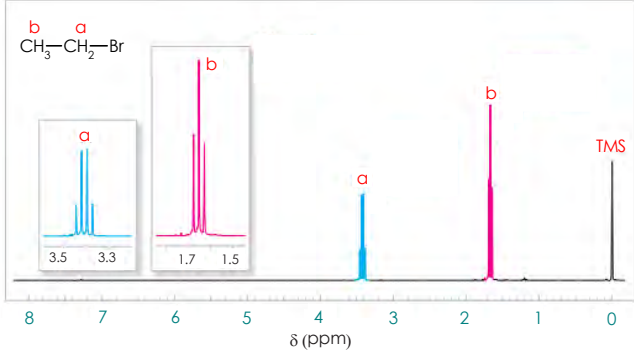
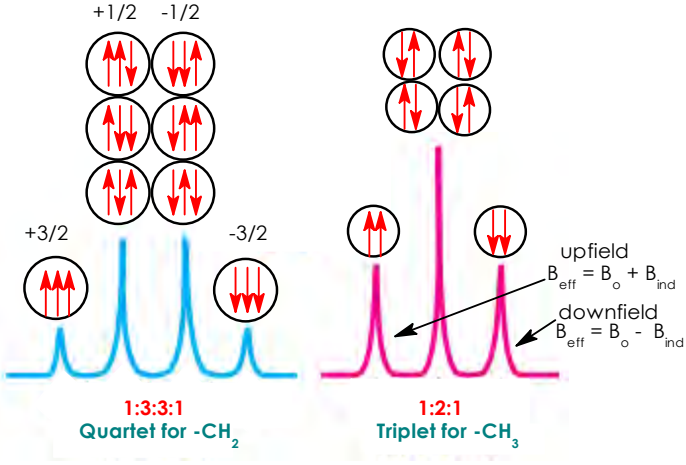


Fig. 6.14 Proton NMR spectrum of bromoethane. Signals have resolved in boxes



Central two peaks of quartet are more intense than the other two because ±1/2 spin arrangements are more probable than 3/2 spin state. Consider the following spectrum of nitropropane which has three set of homotopic[9] protons. Methyl protons split into a

[9] Homotopic protons will be addressed in stereochemical equivalence section 11.

triplet by methyl protons. Methylene protons on C2 split into a septet by both methyl and methylene protons (on C1 bearing —NO_2). C1 protons split into a triplet by adjacent methylene group. All these splitting occur in accordance with N+1 rule.

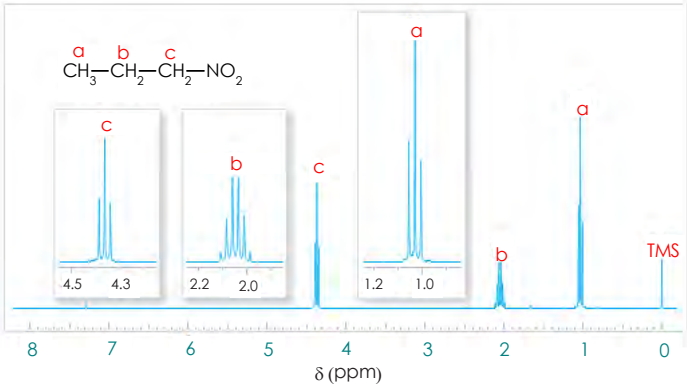
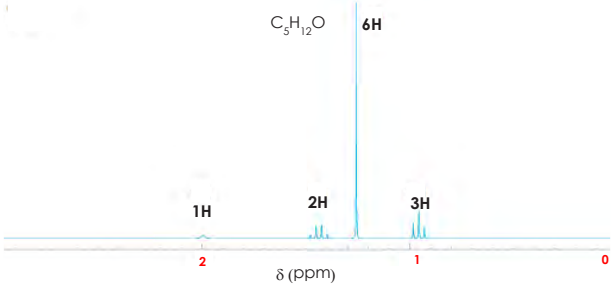


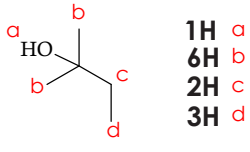
Fig. 6.15 Proton NMR spectrum of nitropropane. Signals have resolved in boxes

Most coupling between protons occurs when they separate by three bonds, say when they are vicinal to each other. Long range couplings do not occur. Protons which are attached to the same carbon atom (geminal) do not couple because they are chemically equivalent. In fact, chemically equivalent protons are not distinguished by NMR unless they are non-equivalent. Chemically non-equivalent protons couple each other.

Solved Problem 6.4: A compound with molecular formula $C_5H_{12}O$ gives the following proton NMR spectrum. Deduce structure for the spectrum.

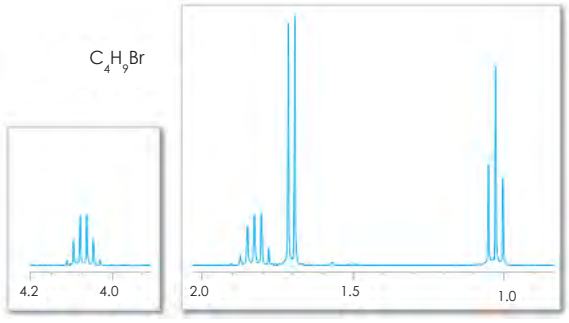


Analysis: From the spectrum, we can clearly deduce presence of ethyl group whose methylene protons split into a quartet and methyl protons into a triplet, both signals are present in the spectrum at δ values of 1.3 and 0.9 respectively. Integration for six protons gives a singlet at δ 1.2 which means all six protons are equivalent.



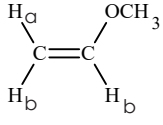
We are left with only one proton and oxygen. The proton gives singlet at δ2.0 which can be hydroxyl group, whose proton gives broad signal. The proposed structure for the molecule is:

Problem 6.9: Sketch the structure for the following resolved spectrum with a molecular formula of C_4H_9Br.



6.68 Coupling Constant

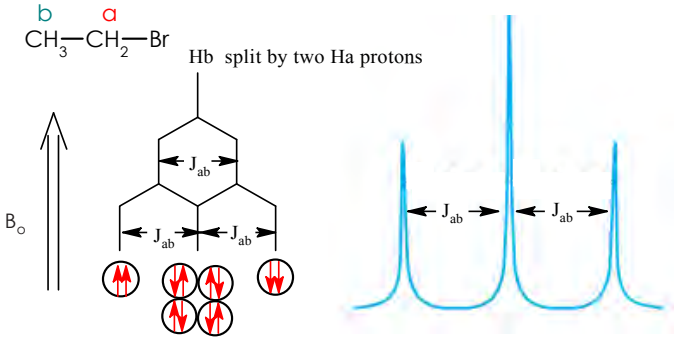
Coupling constant (measured in hertz) is denoted by J is the distance between the peaks of a multiplets which depends upon the coupling tendency of adjacent protons irrespective of magnetic field strength. The value of J measures how strongly a nucleus is influenced by the spin states of its neighbors. As an application, J values are used to predict whether an olefin is cis or trans. The value of J is same for a group of protons that split one another. The magnitude of J depends on the number of bonds between coupling atoms or nuclei. In fact, J^1 (one bond coupling) is large than J^2 (two bonds coupling), which is in turn larger than J^3. Coupling constant for trans nuclei is usually large which means coupling occurs through bonds. Had it operated through space, J value for cis nuclei would have been larger because they are near to each other. Reason for larger J value for trans configuration is due to perfect alignment of orbitals that enhance better communication.



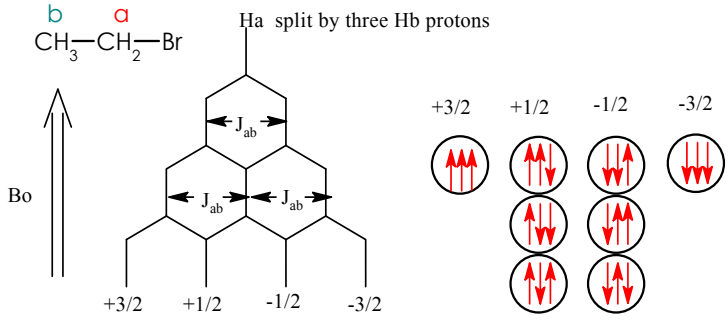
J_{cis} = 10 Hz

J_{trans} = 17 Hz

An NMR, no matter 60 MHz or 300 MHz, records same coupling constant value. This entails that J values are independent of instrumental parameters. However, they depend upon the stereochemistry of molecules. J is useful indicator which helps in distinguishing isomers and stereomers. Consider the following splitting tree diagram for a triplet of methyl protons H_b by methylene protons H_a in bromoethane.

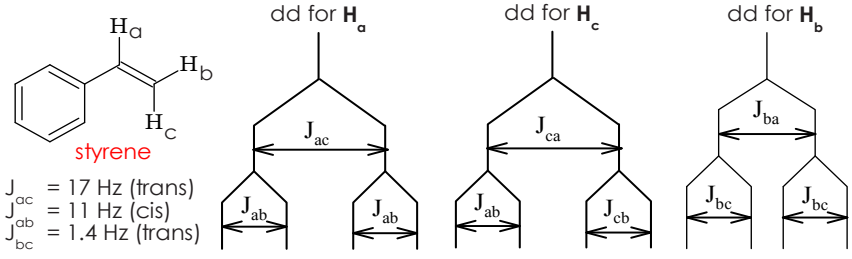


Splitting tree diagram for quartet of methylene protons H_a in CH_3Br is given as:



6.69 Complex Splitting

Sometimes splitting pattern of protons is not uniform. This happens when protons that couple are non-equivalent. Take an example of three vinylic protons in styrene. Proton H_a is split by H_b and H_c in complex manner. For instance, proton H_a is split by H_c (trans coupling) into a doublet with J_{ac} = 17 Hz. H_a is split by H_b into a doublet with J_{ab} = 11 Hz.



For proton H_a, we get a signal which splits into a doublet of doublet (dd) with different coupling constants. This can be visualized by splitting tree diagram with first splitting into a doublet hinting H_a coupling to H_c with larger J values. This doublet further splits into another doublet with smaller J = 11. Similarly, proton H_b couple to H_a with larger J = 17 Hz and H_c (geminal coupling) with smaller J = 1.4 Hz. This is another dd (pronounced as doublet of doublet) in styrene spectrum. Consider another example of vinyl acetate:

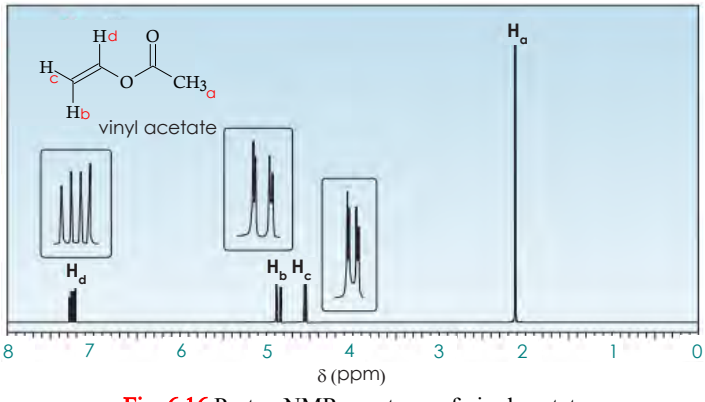
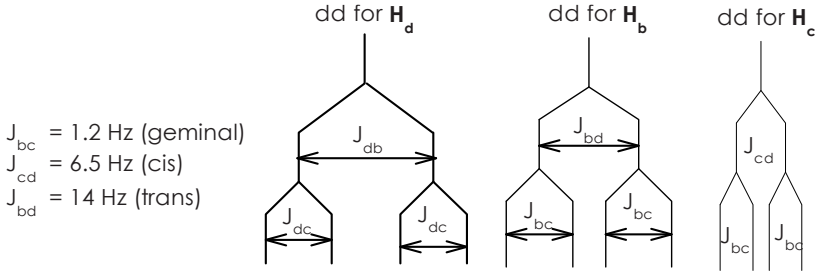


Fig. 6.16 Proton NMR spectrum of vinyl acetate

Splitting tree diagram for vinyl acetate is give below:



Consider splitting tree diagram for H_a in the following molecule which splits into three signals of 24 lines by three different types of protons. The overall signal is a triplet of doublet of quartet (tdq) for which multiplicity is 2H, 1H and 3H i.e. (2+1)×(1+1)×(3+1) = 24. In other words, the signal is divided into 24 lines. Read the signal from below as a triplet (three lines) of doublet (two lines) of quartet (four lines).

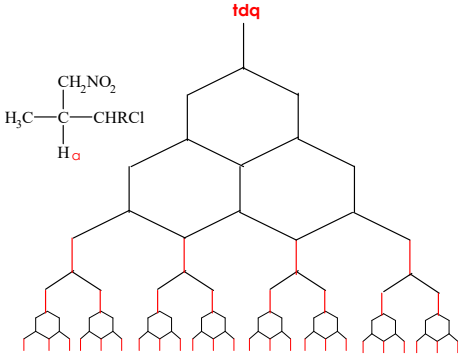


Fig. 6.17 Splitting tree diagram for a signal tdq. Read from below a triplet of doublet of quartet which has shown in red lines.

Following are some splitting tree diagrams for different types of signals.

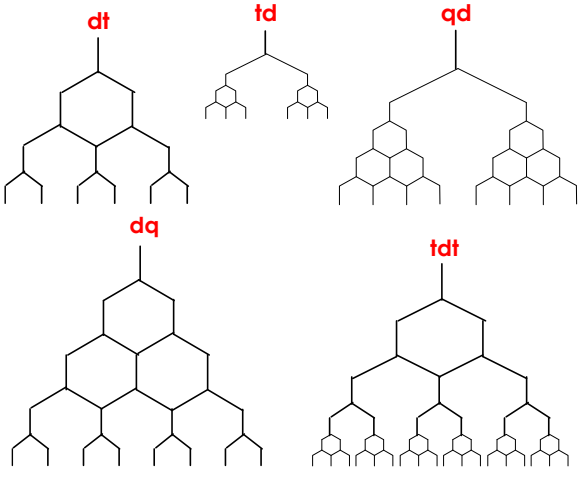
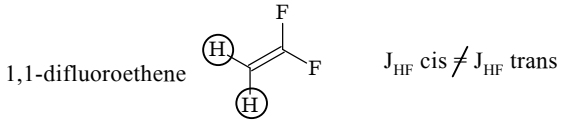


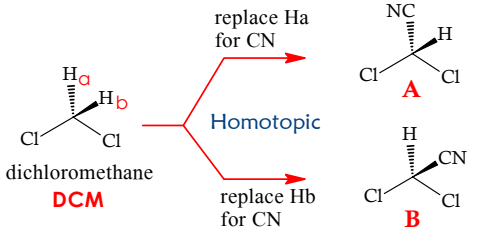
Fig. 6.18 Splitting tree diagrams for doublet of triple (dt), triplet of doublet (td), qd, dq and tdt.

6.610 Stereochemical Equivalence

NMR fails to detect protons which are chemically equivalent: protons which give same molecule no matter they are substituted with different ligands or tested through symmetry operation. For instance, all three methyl protons of acetic acid are chemically equivalent (CE) because rapid rotation renders them indistinguishable, hence equivalent. Such protons or ligands are known as homotopic which are not detected by NMR. Three protons of methyl group in ethanol are also homotopic. CE nuclei are magnetically equivalent (ME). Thus, all ME nuclei are CE but all CE nuclei are not ME. For instance, in the following example, neither fluorine nor hydrogen atoms are ME. For nuclei to be ME, they must not only be CE but also have equal coupling constants to all other nuclei in molecule.

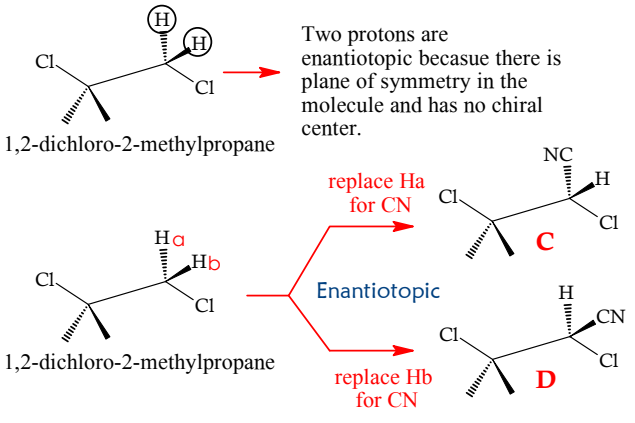


However, protons which are not related to each other symmetrically or if their substitution or tagging gives different molecules such as enantiomers or diasteromers, they are regarded as chemically non-equivalent or heterotopic.



A and B are same molecules

Enantiotopic protons are distinguishable by NMR in chiral media only. Normally, they are not distinguished by NMR. Diastereotopic protons are distinguishable by NMR in either chiral or achiral media. All enantiotopic nuclei are symmetrically equivalent but not all symmetrically equivalent nuclei are enantiotopic.



C and D are enantiomers

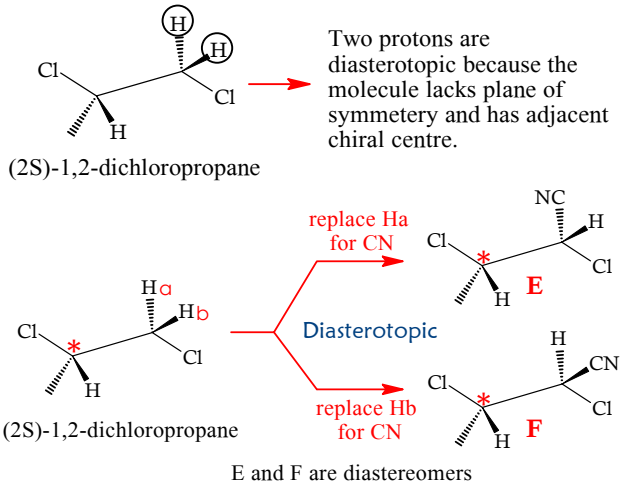
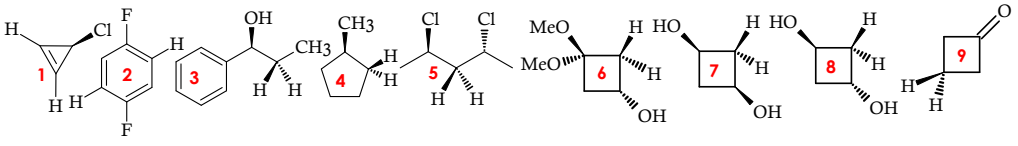


Fig.6.19 Double arrows showing tagging or substitution of the two hydrogen atoms in question to see whether they are enantiotopic or diastereotopic by looking at the outcome of tagging as C and D or E or F. As C and D are enantiomers (mirror images), the two protons in 1, 2-dichloro-2-methylpropane are enantiotopic.

Two vinylic protons of ally bromide are diasterotopic because their substitution with same ligand one by one gives different molecules, say diasteromers. Both protons are distinguishable by NMR. Such protons split each other. They give different chemical shift values. Two protons adjacent to hydroxyl group in cyclobutanol are also diastereotopic. They are distinguished by NMR.

Diastereoisomerism is also exhibited by saturated acyclic system as well. For instance, two protons on C1 in 1, 2-dichloropropane are diastereotopic. These protons not only split each other but also split by adjacent proton too. Thus, C1 protons are split into a doublet by adjacent proton on chiral C2. Proton on C2 is split into a complex multiplet. For diasteromerism to occur, methylene protons next to chiral center are usually diasterotopic. Consider the following examples. You can point out whether a particular set of protons are homotopic, enantiotopic or diastereotopic by tagging operation.

Solved Problem 6.5: Find out whether the two protons in each case are homotopic, enantiotopic or diastereotopic.



Analysis: One can point out whether the two protons are homotopic, enantiotopic or diastereotopic by tagging operation as substituting them with —CN in case of previous examples in which each proton has replaced with same ligand turn by turn and then compare the two products of the tagging for judging whether they are same, enantiomers or diastereomers. If same, the two protons are taken as homotopic and so on.

1 Enantiotopic	4 Diastereotopic	7 Diastereotopic
2 Homotopic	5 Homotopic	8 Homotopic
3 Diastereotopic	6 Enantiotopic	9 Homotopic

Protons which are homotopic or enantiotopic are not distinguishable by NMR. Such protons don't split each other or adjacent ones. Two different nuclei such as protons in propyne or cyclopentanone which are not related to each other by any symmetry operation but precess at exactly same frequency are termed as accidentally equivalent. Both propyne and cyclopentanone give only one signal. Consider the spectrum of methoxyacetonitrile below:

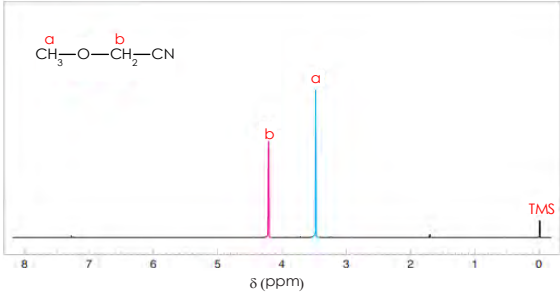


Fig.6.20 Proton NMR of methoxyacetonitrile

Methylene protons are enantiotopic, hence they are not split. Rapid interchanging protons as in methyl group of acetic acid or chair conformation of cyclohexane can be distinguished by NMR when their fast movement or rotation is frozen. For instance, axial and equatorial protons are swiftly interchanging at room temperature. They can't be distinguished by NMR because ring flipping makes them virtually indistinguishable (homotopic). However, ring flipping can be ceased at - 89 °C which means that the two protons are now diasterotopic and distinguishable by NMR. Two separate signals will be generated at this temperature.

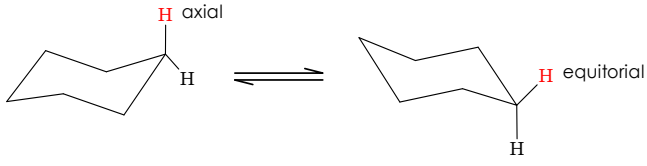


Fig.6.21 At room temperature, swift flipping of cyclohexane ring makes the two hydrogen atoms virtually indistinguishable. Cooling down the system to low temperature freezes flipping which locks interchange between equatorial and axial positions. Here, NMR detects the two hydrogen atoms because they are diastereotopic now, unlike homotopic at room temperature.

Protons of -OH, -NH -COOH or -$CONH_2$ groups are rapidly exchanging in solution. Such protons generate on unsplit signal. If ethanol is taken in ultra-pure form, when there is no exchange of hydroxyl proton, it is split by methylene group and generates a multiplet with a J of about 5 Hz. However, when acidic or basic impurity is introduced into the sample of ethanol, it triggers proton exchange that generates one sharp average signal without any splitting. If the exchange is slow, splitting occurs. A broadened signal is obtained for moderately slow exchange of proton.

6.7 ^{13}C Spectroscopy

Carbon atom to which protons are not bonded such as carbonyl carbon of ketones or internal alkynes remain invisible in PNMR. ^{13}C NMR (CMR) makes it possible to detect such carbons with distinct shift values. ^{13}C signals are less intense as compared to HNMR. This due to the fact that ^{13}C isotope is less abundant, say only 1% unlike 99% of ^{1}H. Secondly, magnetogyeric ratio of ^{13}C is 1/4th of proton which means that resonance frequency for ^{13}C nuclei is 1/4th of proton. Consequently, signals are very weak and less intense that ultimately vanish in noise. These signals require good resolution for adequate translation.

Earlier CW NMR averaged hundred spectra to account for spectroscopic results because ^{13}C is less sensitive than PNMR and usually signals were lost in noise. To cope with the problem, multiple scans were run and then averaged to generate results. Absorption of RF to cause a nucleus to precess at its resonance frequency yield complex signals. The precessing nuclei lose energy they absorbed from pulse. The decaying signal is known as free induction decay (FID) or transient which contains all useful information needed to sketch a spectrum.

^{13}C signals are more deshielded as compared to proton because carbon nuclei are linked immediately to electronegative (electron withdrawing) ligands. In fact, chemical shift values for ^{13}C nuclei are 15 to 20 times larger than proton because ligands that cause shielding or deshielding are one bond closer to carbon as compared to proton. Consider ^{1}H NMR and proton decoupled ^{13}C NMR spectra of methyl acetate:

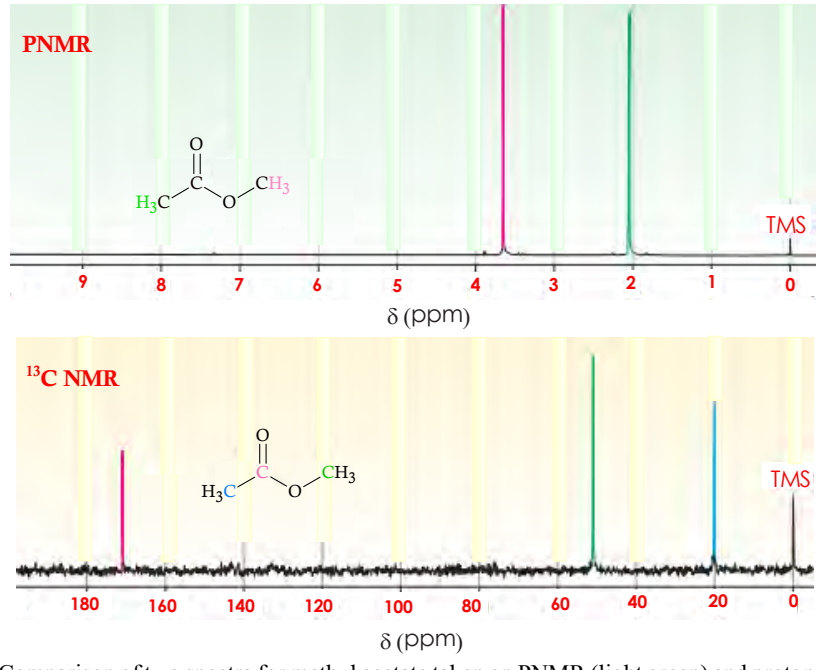
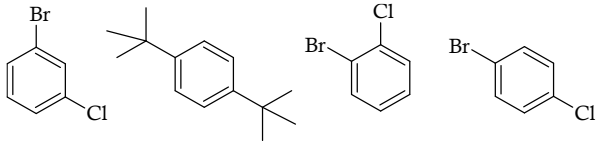


Fig. 6.22 Comparison of two spectra for methyl acetate taken on PNMR (light green) and proton decoupled ^{13}C NMR (light brown).As the molecule has two types of protons, so we get two signals in PNMR. There are three types of carbons in the molecule, so we get three signals in ^{13}C NMR.

Chloroform-d is common solvent for recording ^{13}C spectrum. It appears as equally size triplet signal in spectrum. Deuterated solvents[10] such as chloroform, which is an excellent internal reference for ^{13}C instead of TMS.

Problem 6.11: Predict number of ^{13}C signals in given compounds



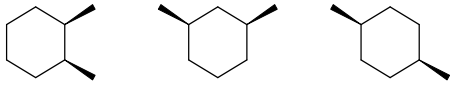
Many features of ^{13}C spectroscopy are same like PNMR. However, there are few differences such as demand for resonance frequency and peak areas. As magnetogyeric ratio for ^{13}C is 1/4th of proton, therefore it requires low RF transmitter whose strength is 1/4th of transmitter required for proton. For instance, a spectrometer with 70,459 gauss magnet requires 300 MHz transmitter for proton but 75.6 MHz for ^{13}C. Approximate chemical shift values for ^{13}C are given in the following table.

Table 4: Chemical Shift Values for 13C

Type of Carbon	Approx.. δ (ppm)	Type of Carbon	Approx.. δ (ppm)
1° alkyl	0.- 40	aryl	100 - 170
2° alkyl	10 - 50	alkyne	60 - 90
3° alkyl	15 - 50	RX/amines	10 - 65
aldehyde/ketone	182 - 215	akene	100 - 170
acids/esters	160 - 185	alcohol/ether	50 - 90

In ^{13}C spectrum, peaks areas are not exact reflection of number of carbon nuclei like proton spectrum. In ^{13}C spectrum, strong peak emerges from the carbon atom bearing two or three proton than those bearing no proton at all. However, latest ^{13}C NMR uses decoupling techniques which equalize the absorption of different carbon atoms. This render peaks integrals proportional to relative number of carbon atoms.

Problem 6.12: Distinguish among the following compounds using ^{13}C NMR.



[10] Usually, deuterated solvents are used for taking ^{13}C NMR whose resonance signals appears as **locked** or **reference signals** in spectrum. **Chloroform-d** is commonly used solvent whose identity is made by appearance of three peaks of uniform intensity (ratio 1:1:1). Recall, we used $m = 2I + 1$ equation in basic theory of NMR for NMR active nuclei to find spin multiplicity (m) or number of possible spin orientations for a nucleus. This equation does not hold for deuterated or NMR inactive nuclei such as deuterium. We use $m = 2nI + 1$ instead, where n is number of such NMR inactive nuclei intended for splitting ^{13}C and I is spin state.

For deuterium, m = 2(1)(1) + 1, we get three, which means one deuterium atom splits ^{13}C into a **triplet** or it has three spin states of +1, 1 and –1. For **DMSO**, we get a septet for each ^{13}C. As 3 deuterium atoms are bonded to each carbon of the DMSO except carbonyl one, therefore, m = 2(3)(1) + 1 = 7. Both groups are same as DMSO is symmetrical molecule and for such molecules we get spectrum of only half of molecule. DMSO is good solvent for carboxylic acids and organic molecules which are unable to dissolve in $CDCl_3$. Deuterated acetone (Acetone-d) gives septet too like DMSO. Its carbonyl carbon appears as singlet. **Acetone-d_5** with one —CHD_2 gives a quintet. Similarly, **acetone-d_4** with —CH_2D gives a triplet like $CDCl_3$.

Splitting pattern in ^{13}C emerging from ^{13}C -^{13}C coupling is quite different from proton coupling because the probability of ^{13}C nuclei to adjacent ^{13}C is very low as ^{13}C makes only 1% of the sample carbon nuclei. This is how such splitting is ignored. However, ^{13}C — H coupling is common and it gives rises to splitting phenomenon in ^{13}C spectrum. Extensive C-H bonds make the splitting complicated. To do away with this, proton spin decoupling technique is employed that reduces carbon signals to single peaks devoid of splitting phenomenon. This technique yield simple ^{13}C spectra. However, some important information is lost while getting such spectra.

To counter the loophole, off resonance decoupled is utilized which simplify ^{13}C spectra by retaining some important splitting pattern in accordance with N+1 rule. For instance, methine carbon is split into a doublet, methylene into a triplet and methyl into a quartet. The utility of this technique is recognized by appearance of TMS as quartet at o chemical shift values. Usually, ^{13}C spectrum is run twice: first, broadband decoupled spectrum which records number of non-equivalent carbon atoms and their chemical shift values, second, off resonance decoupled spectrum is run to get number of protons attached to carbon atoms from spin multiplicities of ^{13}C. This is how we get two trace of ^{13}C spectrum.

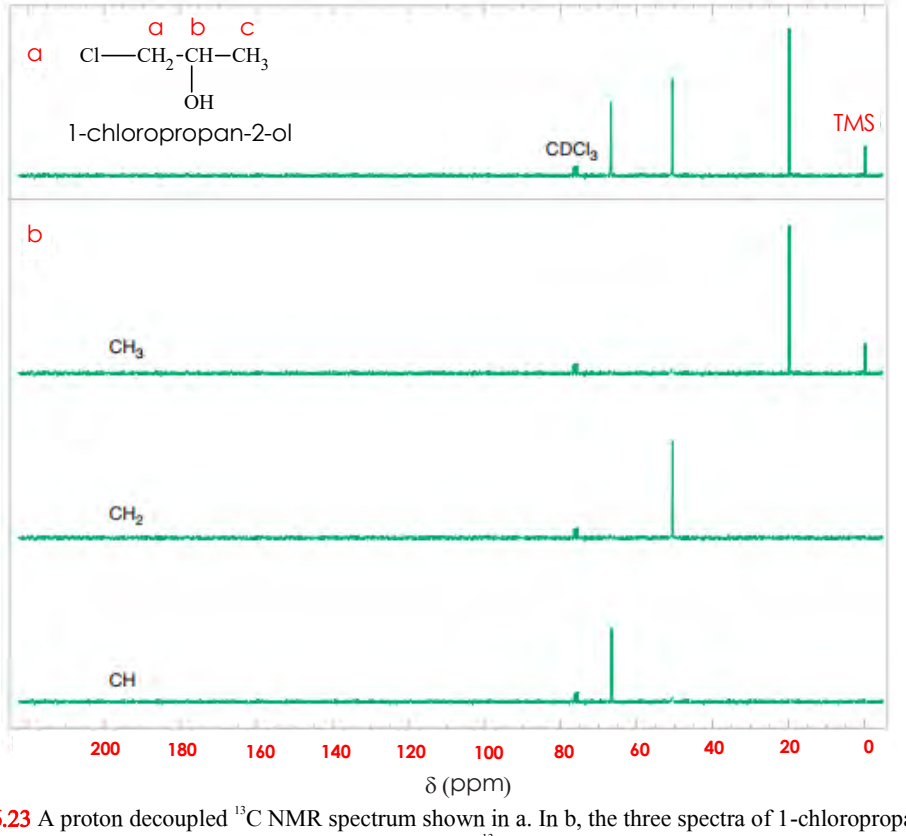


Fig. 6.23 A proton decoupled ^{13}C NMR spectrum shown in a. In b, the three spectra of 1-chloropropan-2-ol reflect DEPT ^{13}C NMR.

Consider three different types of carbon in the spectrum of 1-chloropropan-2-ol. Electronegative atom withdraws electronic density from carbon atom. It makes carbon

atom deshielded that appears farther downfield (left) in ^{13}C spectrum. For instance, hydroxyl oxygen is more electronegative than chlorine, so C_b or C_2 gets more deshielded than C_a and C_c. C_b appears downfield. The following spectrum gives three δ values for 1-chloropropan-2-ol: 20, 51 and 67. We assign δ 67 to more deshielded C_b carbon. Carbon atom to which chlorine is attached is deshielded more than methyl carbon so it gets the value of 51. CH_3 carbon appears with shift value of 20. Besides these three peaks, a single peak which appears as triplet is characteristic of chloroform-d. All ^{13}C spectra containing $CDCl_3$ as a solvent give this peak which appears at 77.

A more advance technique that runs three scans for ^{13}C spectrum is known as DEPT ^{13}C NMR or distortionless enhanced polarization transfer which gives better sensitivity and avoids overlapping multiplets because all peaks are singlets. The three scans involve: a decoupled scan for getting a singlet, a DEPT 90 scan in which only methine carbon appear and a DEPT 135 scan which gives peaks for methyl and methine carbon besides a negative peak for methylene carbon as well. Carbon which is not bonded to any proton does not appear in DEPT 135 scan. DEPT ^{13}C spectra are very simple to elucidate which gives useful information about how many hydrogen atoms are bonded to carbon atom besides yielding chemical shift values contained in broadband proton-decoupled ^{13}C spectrum. Methyl methacrylate is asymmetrical molecule, as shown in the following spectrum, has five different types of carbon atoms which mean the molecule generates five signals at chemical shift values of 167.3, 51.5, 136.9, 124.7 and 18.3. Referring to ^{13}C chemical shifts values listed in the table 2, signal at 167.3 accounts for ester carbonyl carbon.

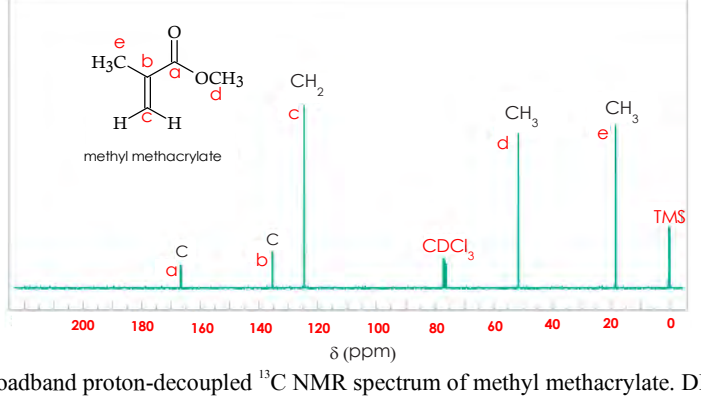


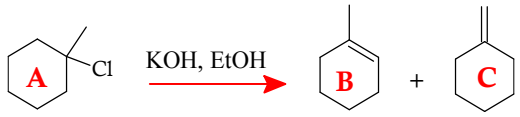
Fig. 6.24 A broadband proton-decoupled ^{13}C NMR spectrum of methyl methacrylate. DEPT ^{13}C NMR information is given above peaks.

Methyl carbon attach to oxygen gives shift value of 51.5. The two signals at 136 and 124 refer to two alkenes carbons and methyl group attached to C_2 comes up with 18.3. Using DEPT ^{13}C information, we can clearly distinguish between alkene carbons. For instance, signal at 124 in fig.15 attests C_3 to which two hydrogen atoms are bonded. Similarly, alkene carbon with no hydrogen atom bonded is of course C_2.

6.71 Significance of ^{13}C & ^{1}H NMR in Structure Determination

^{13}C NMR comes up significant features for structural determination. The spectroscopy not only aids in identifying different types of carbon atoms present in an

unknown molecule but also presents vivid depiction regarding electronic environment of each type of carbon. ^{13}C NMR spectroscopy excels in structural information that can't be even retrieved by MS or IR spectroscopy. For instance, as an evidence to attest the validity of Zaitsev's rule for E2 elimination reaction, 1-Chloro-1-methylcyclohexane (A) could either give 1-methlycyclohexene (B) or methylenecyclohexane (C). If we look at the structure of each type of molecules, methylcyclohexene is unsymmetrical; it has **7** types of carbon atoms (5 sp^3 C + 2 sp^2 C).



Methylenecyclohexene is symmetrical molecule with fewer signals i.e. **5** (3 sp^3 C + 2 sp^2 C). The actual product forms as a result of the E2 reaction is clearly B which is rectified by the following spectrum.

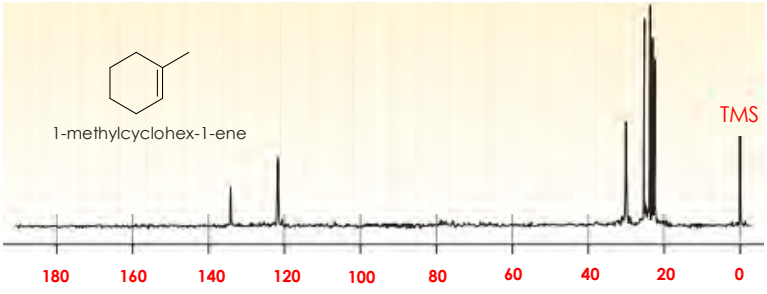
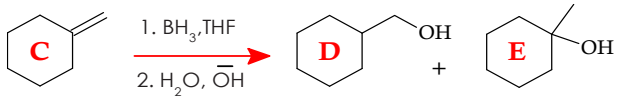
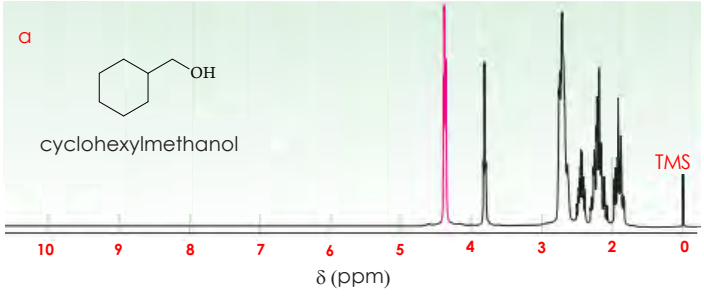


Fig. 6.25 ^{13}C NMR spectrum for methylcyclohexene

In above example, if C is subjected to hydration, it could yield either cycohexylmethanol (D) or 1-methylcyclohexanol (E). If we look at both molecules, the distinguishing feature is presence or absence of methyl group.



Spectrum for the product shows a two protons peak at 3.4 which indicates that a CH_2 group is attached to electronegative atom. Similarly, the spectrum shows no three proton heightened peak near 1, which means the molecule lacks CH_3 group. Both features in the spectrum are enough to prove the product is D. See the spectrum below:



Also compare spectrum 'a' with the following spectrum 'b':

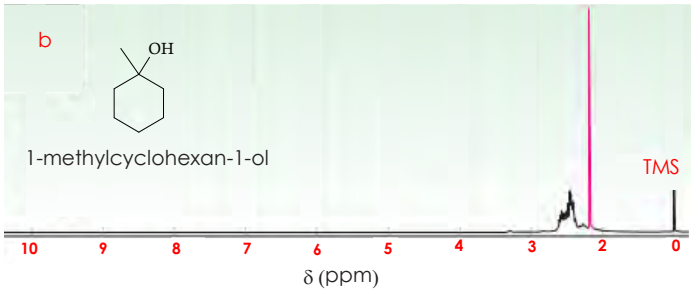
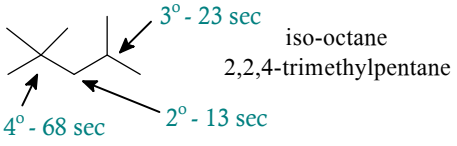


Fig. 6.26 Comparison of Proton NMR spectrum for two different alcohols a and b

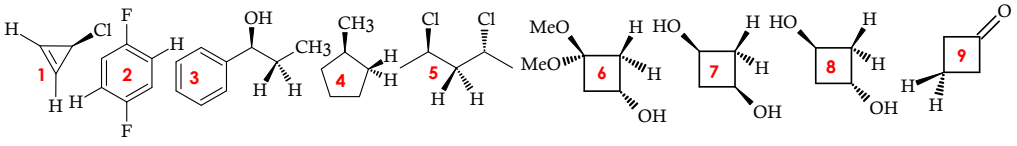
6.72 Relaxation

The process of retiring excited nuclei from β spin state to α one in a bid to establish Boltzmann's equilibrium with release of an FID signal is known as relaxation. FID is free induction decay which is processed into an NMR signal. Relaxation is either spin lattice relaxation (longitudinal) or spin-spin relaxation (transverse). Both types are governed by relaxation time. Spin lattice relaxation (SLR) occurs in direction of B_o. It loses energy to the surrounding lattice as thermal energy. T_1 (time for spin lattice relaxation) is not important for HNMR because its relaxation time is very low. However, relaxation time is significant in ^{13}C NMR. Spin-spin relaxation (SSR) occurs in plane perpendicular to the direction of B_o. It doesn't change the energy of the system.

The principle contributor of both types of relation is dipole-dipole interaction. The spin of excited nuclei interacts (either inter or intra-molecular) with nearby atoms (hydrogen), which induces nuclear spin transition. The mechanism is affected if hydrogen is located nearby. For carbon atom, relaxation is faster if hydrogen is directly bonded as in case of methine, methylene or methyl group. Quaternary carbon atom has longer relaxation time because there is no attached hydrogen. In isooctane we have four different types of carbons as shown below. Relaxation time for quaternary carbon is longer than every other carbon. Its relaxation time is 68 sec.



Problem 6.10: Show how many ^{1}HNMR and ^{13}C NMR signals will be generated by each of these examples from 1 to 9.



6.8 Exercise

1. Critically analyze each of th following problems and conclude relevant answer!

a. A compound with the molecular formula shown below exhibits a ^{1}H NMR spectrum with only one signal. Deduce the structure in each case.

a. C_5H_{10} **b**. $C_5H_8Cl_4$ **c**. $C_{12}H_{18}$

b. When 1-methylcyclohexene is treated with HCl, a Markovnikov addition is observed. How would you use ^{1}H NMR spectroscopy to determine that the major product is indeed the Markovnikov product?

c. Three signals: 50, 110 and 200 Hz were obtained for a sample run on 100 MHz NMR. Calculate chemical shifts for these signals in δ. Find out the position of these signals in Hz when the sample is run on 300 MHz NMR. Also find out their shift values as well.

d. A 500 MHz NMR operates at 11.7 T for a proton. Find out resonance frequency for ^{13}C on this NMR. If radio frequency for ^{13}C is 200 MHz, calculate strength of magnetic field.

e. Find out resonance frequency for ^{1}H, ^{19}F and ^{31}P to bring them into resonance in B_o of 1 T, 4.70 T and 7.05 T.

f. Distinguish TMS and DCM with the help of ^{1}H and ^{13}C NMR.

g. Two signals were observed for two set of protons at 3.721 and 3.735 on 300 MHz NMR. Find out separation between the two signals in Hz?

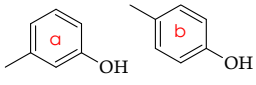
h. Using H NMR, what would be the structure of molecule for given data below:

a. $C_5H_{10}O$	**b. $C_sH_{12}O$**	**c. $C_4H_{10}O$**
δ 1.09 (6H, doublet)	δ 0.91 (3H, triplet)	δ 0.90 (6H, doublet)
δ 2.12 (3H, singlet)	δ 1.19 (6H, singlet)	δ 1.76 (1H, multiplet)
δ 2.58 (1H, septet)	δ 1.50 (2H, quartet)	δ 3.38 (2H, doublet)
	δ 2.24 (1H, singlet)	δ 3.92 (1H, singlet)

2. Propose the structure of a compound consistent with the following δ values:

a. $C_5H_{10}O$, broadband-decoupled ^{13}C NMR: 7.1, 34.6, and 210.5
b. $C_6H_{10}O$, broadband-decoupled ^{13}C NMR: 70.8, 115.2, and 134.8

3. Using ^{13}C NMR, distinguish the following two compounds from each other.

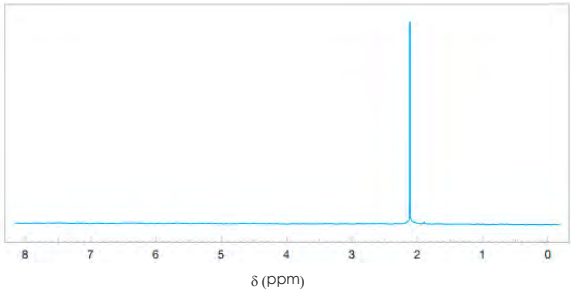


4. Determine the structure of an alcohol with the molecular formula $C_4H_{10}O$ that exhibits the following signals in its ^{13}C NMR spectra:

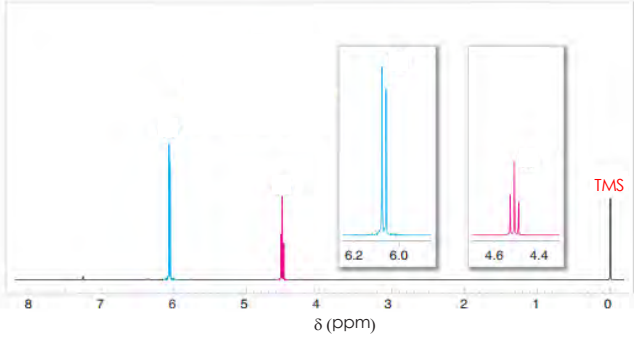
a. Broadband decoupled: 69.3 δ, 32.1 δ, 22.8 δ, and 10.0 δ
b. DEPT-90: 69.3 δ

c. DEPT-135: +ve signals at 69.3 δ, 22.8 δ, and 10.0 δ; –ve signal at 32.1 δ

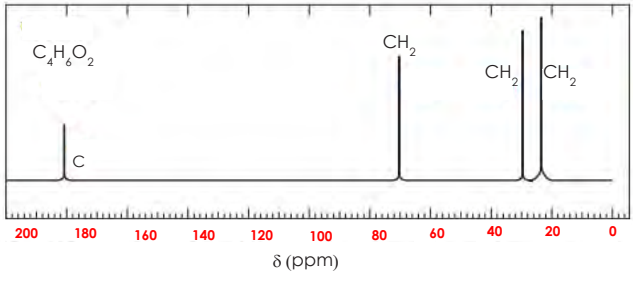
5. What compound with molecular formula $C_3H_6Cl_2$ is consistent with the ^1H NMR spectrum shown in below?



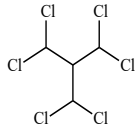
6. If molecular formula for an unknown compound is $C_3H_3Cl_5$, predict the structure of the compound and also assign peaks in accordance with the following spectrum.



7. A student in lab was trying to synthesize 4-hydroxybutanoic acid but obtained a different product of molecular formula $C_4H_6O_2$ instead. Propose the structure and assign the signals to the compound from the following spectrum.



8. Sketch ^{1}HNMR spectrum for the following molecule



Section 7 Synthesis

7.1 Introduction

Organic chemistry offers rich domain of synthesis based on carbon-carbon connectivity. Thanks to applications of organometallic chemistry that has greatly facilitated the art of synthesis. In Friedel-Craft alkylation, we establish the connectivity for making new molecules but the reaction which proceeds through electrophilic aromatic substitution mechanism is prone to certain drawbacks such as low or almost slow rate of reaction on a deactivated system such nitro or cyano-benzene, the problem of poly-alkylation based on activating tendency of alkyl group and the rearrangement of the carbocation that yields different compounds than desired ones. In the past, Wurtz's reaction and Grignard reagent have been used to establish carbon-carbon connectivity but each of such reaction has certain drawbacks. To cope with the problem, carbon-carbon coupling has immensely been explored with astounding results based on organometallic chemistry.

With swift development of science from simple screens made of plasma tubes in classical TVs to modern displays of LED and AMOLED (active matrix organic light emitting diodes), every new moment of research and development hatches up something new, advance and enigmatic. The tale of screen development doesn't stop anywhere because this year Nobel Prize in Chemistry has awarded to three American organic synthetic chemists for development of quantum dots (nanoscale crystals) with spectacular properties ranging from luminance, color variations, sensing, computing and electrical conductivity.

In future, our cellphone would be equipped with more advanced and high resolutions QLED (quantum dot organic light emitting diodes) displays. The use of quantum dots in photovoltaic will open new era of green technology with intent to rivals every predecessor science which contributes to global warming. Science is changing the world swiftly, more amazingly than we ever thought.

Organic synthesis is intriguing field which equates with nature to equip human beings with spectacular organic molecules of stupendous applications in medicines, material chemistry and drug synthesis. Synthesis is challenging field which requires immense energy and resources to come up with novice results. For instance, vitamin B_{12} was isolated in 1956 after it was known that the bio-molecule helps in treatment of pernicious anemia in 1926. The molecule is complex of cobalt. Its structure reflects how complicated it is for organic chemists to synthesize structurally such an enigmatic molecule. Perhaps, this vitamin is the sole known molecule which contains carbon metal bond like ordinary organometallics. Its structure was elucidated by Dorothy Hodgkin in 1956 through her X-ray crystallography studies. She got 1964 Nobel Prize for her amazing work. In 1972, Woodward and Eschenmoser announced the synthesis of this complicated

vitamin which took them 11 years to complete. Almost 100 co-workers took part in the synthesis after executing some 90 reactions for achieving the goal of coming up with synthetic vitamin B_{12}. Classical synthesis was a matter of hectic physical and intellectual expertise. In 1969, Corey established the first total synthesis of prostaglandin PGE_2 which required 21 consecutive steps for getting final product. Later the synthesis was much improved some 20 years later when Noyori reduced the synthesis to just total of 11 steps.

7.2 Chromatography

An analytical tool used to separate analyte (mixture of compounds) into individual components based on distribution ratio between stationary and mobile phases is known as chromatography. An analyte is any compound which is required to be separated from mixture or impurities.

Chromatography has widespread application in medicines, industries, synthesis, food and drinks. Modern chromatography is quite advance and getting digital each day passing unlike classical one where traditional equipment are used for running different chromatographic operations. Historically, Mikhail Semenovich Tsweet, a Russian botanist, in 1903 separated plant pigment into various color bands by applying it to column packed with calcium carbonate over which petroleum ether was passed. He labeled the technique a chromatographic method and the color separation a chromatogram. Here, we will deal two types of chromatography used in our lab: thin layer chromatography and column chromatography. Both are examples of adsorption chromatography. Two stationary phases are commonly used in adsorption chromatography: silica gel or alumina. Both are relatively polar and work by dipole-dipole and dipole-induced-dipole interaction. Silica is both hydrogen bond donor and accepter.

7.21 Thin Layer Chromatography (TLC)

In academic labs, we are usually concerned with TLC and column chromatography which is used to monitor progress of reaction, gauging rate of elution, identification, purification and separation of compounds. Both TLC and CC are examples of solid-liquid chromatography. In TLC, stationery phase (SP) is silica gel (SiO_2) coated on glass, plastic or aluminum foil. Silica is relative polar and it stations polar compounds where non polar ones flow smoothly over it. Besides silica, fluorescent compound such as manganese activated zinc silicate is also used to aid visualization of compound under UV light. It is cautioned not to view UV light directly.

Liquid phase (LP) can be any solvent (eluent) ranging from non-polar such as n-hexane, ether or some other alkanes to polar such as water, ethyl acetate, alcohol or acetone. Besides, a mixture of solvent system such as mixture of ethyl acetate and hexane can be used. Pencil line (spotting line) is drawn 1 cm from the bottom of a chromatogram (TLC plate) where spot is placed with aid of thin bore capillary tube.

A researcher who wants to check the purity of some compound such as benzoic acid can utilize TLC. Impure compound gives many spots. A single spot is an indication of purity of compound. TLC plate is placed in sealed system in some close container as to

avoid evaporation of solvent and affect smooth flow of mobile phase on the surface of SP. TLC is used to check the progress of a reaction where a product is formed or not. Reacting A and B to expect a product C can be done with the help of TLC. For instance, after sometimes, a TLC is done to check the formation of product. Three spots for A, B and reaction mixture (RM) are made on TLC plate. It is placed either in 5% or 10% ethyl acetate system. If a RM shows different spots from A and B, we expect our product to be formed.

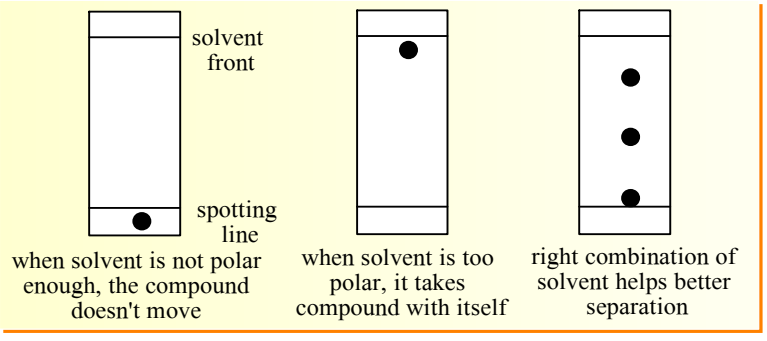
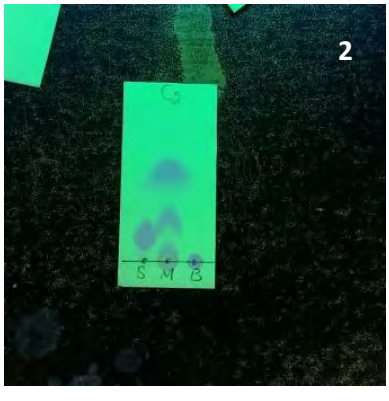


Fig 7.1 Solvent plays pivotal role in distribution of spot on TLC plate. Right combination enables better separation.

Lab Result of TLCs

The following sets of TLCs taken in 5% and 10% (5ml EA: 45ml n-hexane) have developed in ethyl acetate and n-hexane solvent system. We use S for starting (aryl halide), B for boronoic acid and M for reaction mixture on our TLCs. For TLC 2, the M gives two distinct spots showing two different products have formed. Compounds with nitrogen in aromatic system usually give curve spots as evident on the TLC plate. This TLC tells us our reaction is completed.



TLC 4 also gives two spots which give us insight about two different products that have formed in our reaction mixture. Spot 1 is laying on the pencil mark and the spot 2 locates on mid top. A TLC of compound 1 on the right side with single spot tells us just one product in our RM.

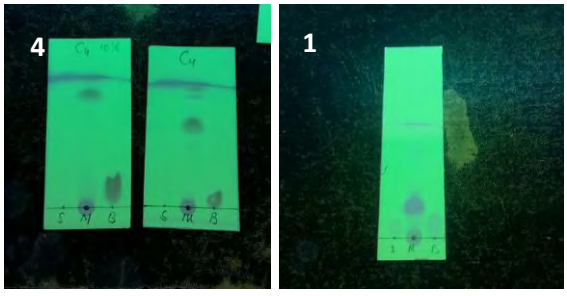


Fig 7.2 Two TLCs for reaction mixtures 4 and 1. For 4, TLC shows two compounds: one lays on pencil spot, the other flows to the top. For 1, the result is cleared: only one spot hinting the formation of just one compound.

TLC assessment of 7 shows three different spots. For 7, our M gives us three different products. TLC 3 on the right side gives complex pattern. It gives a mixture of compounds. Three are distinct. There is evident possibility of impurities in the result. Remember, if the sample on the TLC plate is spotted densely, we get a continuous flow as has shown on the right TLC plate during the analysis of compound 3.

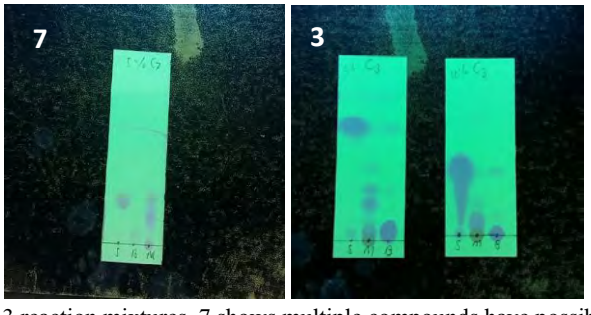


Fig 7.3 TLCs for 7 and 3 reaction mixtures. 7 shows multiple compounds have possibility for impurities as well. Similarly, 3 gives multiple products with rich chance of impurities contamination. 3 has developed both in 5 and 10 % solvent system.

After taking TLCs with positive results, I subjected the reaction mixtures for separation and purification based on column chromatography. Multiple columns have been run to get purified products. We get the following results for 1, 2, 3, 4 and 7. These TLCs have taken to compare our purified product with our reaction mixture M or RM.

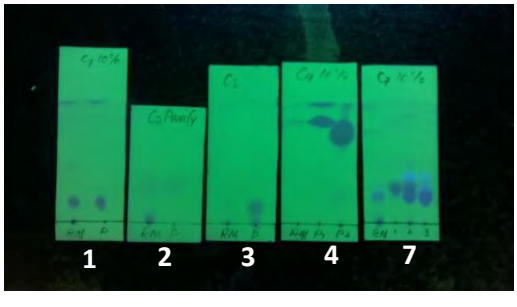


Fig 7.4 All previous compounds rectified by TLCs have separated and purified through column chromatography. Here, final TLCs have taken for five compounds before subjecting them to spectroscopic characterization.

7.23 Column Chromatography (CC)

Column chromatography is useful technique which is employed for extraction, separation and purification of organic molecules. Purification of organic compounds is done with the aid of different physical techniques such as re-crystallization, distillation, liquid-liquid extraction and sublimation but sometimes these techniques are not adequate to separate impurities linked by structural proximities. Here, column chromatography is used to fill the void left by these organic techniques.

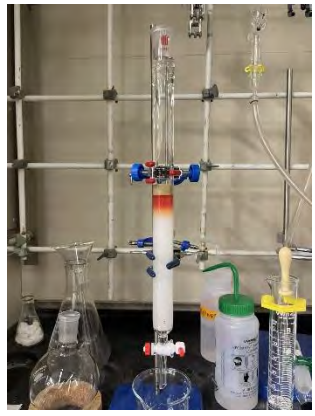


Fig 7.5 A column filled with silica and colored mixture to be separated (orange). The column is filled with solvent which descend down under gravity when knob is opened.

Column chromatography is an example of solid-liquid chromatography in which stationary phase is silica or alumina and mobile phase is liquid which can be solvent (eluent) or mixture of solvents. Elutropic series arranges solvents in increasing order of polarity which starts with least polar (n-pentane) and ending with most polar solvent (acetic acid). The following table shows elutropic series and elution order of different solvent systems.

Elutropic Series	Elution Order
n-pentane	alkanes
petroleum ether	alkenes
cyclohexane	dienes
hexane	aromatic HCs
carbo disulfide	ethers
t-butyl methyl ether	esters
DCM	ketones
THF	aldehydes
dioxane	amines
ethyl acetate	alcohols
2-propanol	phenols
ethanol	acids
methanol	
acetic acid	

Stationary phase is destroyed by water and methanol, hence they are avoided. Hexanes–DCM, hexanes–ethyl acetate and hexanes–toluene are excellent combinations for efficient chromatographic operations in column chromatography where we usually begin with least polar solvent. In fact, least polar organic molecules are the first to elute.

Basic Principle of Column Chromatography: The basic principle associated with column chromatography is the establishment of equilibrium between stationary and mobile phases for smooth elution of mixture of compounds.

Size and Packing of Column: The size of the column can be as thin as pencil used for separation of milligram quantity or barrel used for separation of kilogram quantities (industrial scale). Column can be packed using either dry method or slurry method. In dry

packing, silica gel or alumina is slowly added via funnel to the top of the column containing solvent and slowly allow the adsorbent to settle. In slurry method, silica gel is dissolved in flask containing solvent. Shake and swirl the flask until all bubble removed and excellent suspension obtained. Pour the content directly into the column. Slurry method is best option for even packing. No matter which method is used, evenly packed column is essential for better separation.

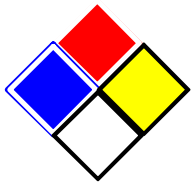
Filling column with silica is known as packing. If not properly filled, cracking appear in the column which disturbs smooth elution of compound across the length of the column. It is necessary to take care in filling the column. A conical flask is taken and filled with certain volume of n-hexane. Fine mesh silica is slowly added and flask is gently swirled to allow smooth mixing. Continue periodic addition until desired amount of the silica is poured into the conical flask. Place the flask for an hour. Cover its mouth to avoid evaporation of solvent. After an hour, mix the content in conical flask by shaking and pour slowly into a column filled with n-hexane with certain volume. Run many turns of n-hexane until no spot appear in elutant.

Slurry of reaction mixture (RM)/impure compound is prepared which is desired to be extracted or purified. It is dissolved in ethyl acetate and then mixed with silica in round bottom flask. To evaporate the solvent, rotary is used. When the flask is completely dried, powder silica is scratched out and collected over a paper which is then poured onto the top of the column to make slurry bed. One or two turns of n hexane is run and then different solvent ratio are run to get adequate separation of different constituents in reaction mixture.

7.3 Health Hazards of Solvents

Handling chemicals is very important to know because almost every second such chemical is associated with certain health hazards. We need to understand National Fire Protection Association (NFPA) hazards before handling the bottle of a chemical. The following illustration gives brief insight into the NFPA symbolism regarding chemical hazards. Students need to be guided before they are asked to work in lab. In certain circumstances, it is difficult for students to cope with the dealing of chemicals. If they are guided and trained about handling of chemicals, they would feel confident about their lab-work.

NFPA Diamond Hazard



National Fire Protection Association lists hazards on 5 point scale in each category with 0 representing minimal and 4 represent severe hazard. Blue diamond shows hazard to health, yellow reflects unstable risk red, flammability hazard, and white, shows special hazard.

To minimize emergency situations, the NFPA symbolism must be told to the students. Once students are alerted and cognizant about the hazards of lab chemicals, they

will minimize the danger of being afflicted by acute and chronic impacts of hazardous chemicals. It is important for instructor to guide students about lab ethics and dealing with chemicals before they are subjected to work inside lab. Only cautious students could maintain better lab management and avoid any untoward situation. The knowledge of chemicals and lab precautions is essential for every student working inside lab.

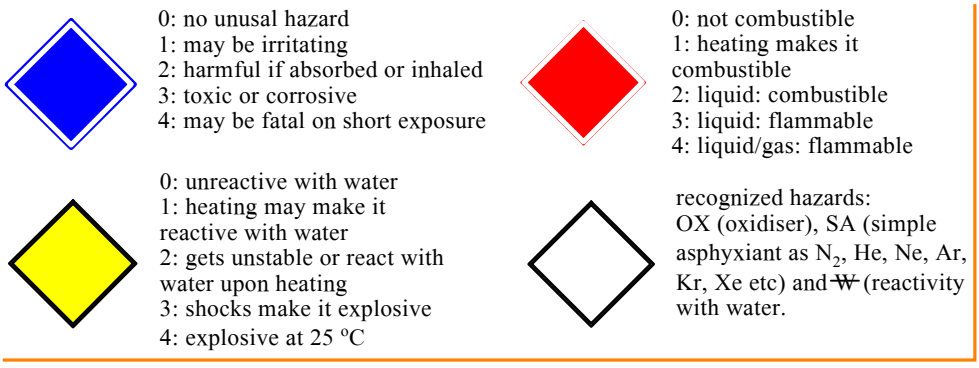


Fig. 7.6 NFPA rating system of chemicals ranges from 0 to 5 with number 4 representing severity.

Before working in lab, knowledge of certain solvents such as n-hexane, ethyl acetate and acetone is essential. In the ensuing text we will focus on these three chemicals because students are mostly concerned with handling of their laboratory work with the aid of these solvent systems. Following symbols are given on chemical bottles. These symbols tell us the nature of the chemical whose knowledge is important to know before we handle any chemical.

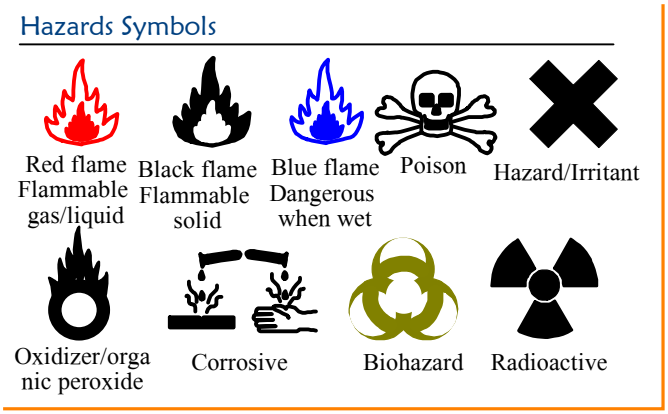
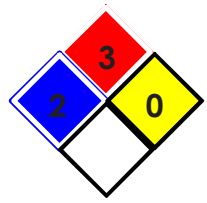


Fig. 7.7 Every chemical bottle is labeled with one or many of these symbols. Although these symbols have been adopted by European Union but they are recognized all around the world.

7.31 N-Hexane

N-hexane is colorless and volatile liquid hydrocarbon with mild disagreeable odor. It occurs both naturally and synthetically. N-hexane is highly flammable and is used as a fraction in petrol to enhance its volatility. The most important use of n-hexane is extraction of oil from plants. Besides as a laboratory solvent and cleaning (degreaser) in printing

industry, n-hexane is also used in shoes, rubber, pharmaceutical and glue industries. N-hexane enters our body through air, water and food. Prolonged exposure could cause various body conditions. Nerve damage is major concern of exposure. Workers in shoe industry who exposed to vapors of n-hexane suffered nervous breakdown known as peripheral neuropathy, the condition where body suffers numbness is arms and feet.



n-hexane

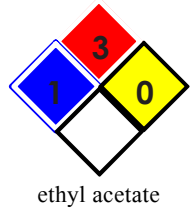
N-hexane itself isn't responsible for nerve damage but its oxidation product, 2, 5-hexadione causes the effect. CNS depression or effects are varying. Public Health of England has recorded general information for safety regarding n-hexane which tells us about how the liquid can be used or treated viewing health impacts of the chemicals.

Inhalation causes incoordination, drowsiness, headache, dizziness and euphoria. Ingestion accelerates stomach disturbance. Once liquid n-hexane is directly inhaled into the lungs, it causes severe lung damage known as pneumonitis. Vomiting results from swallowing the liquid. Irritation, redness, blistering and superficial burns occur from skin contact with n-hexane. Drying and cracking occur in prolong exposure cases. Eyes face pain, tearing and sensitivity to light after exposure to the chemical.

N-hexane is not involved in causing cancer. No study has surfaced yet that could implicate the chemical in agents causing cancer. US Environmental Protection Agency (EPA) and IARC have not listed n-hexane as carcinogen. Instead, EPA has classified the chemical as Group D agent (Barceló, 1993). Teratogenic effects of n-hexane have not been observed in rates exposed to the chemical via inhalation (Barceló, 1993). No study has implicated n-hexane in causing reproductive or developmental effects in human beings. However, testicular damage has observed in male rates that were exposed to n-hexane via inhalation (Barceló, 1993).

7.32 Ethyl Acetate

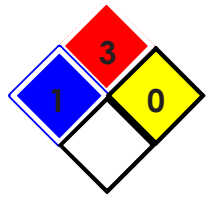
Ethyl acetate (EA) is common chemical for industrial and household utilization. It is colorless liquid (bp 77.1 °C) with agreeable sweet odor. EA is cheap and common laboratory solvent. It is used in perfumes, paints, glues, nail polish removers and artificial flavors. EA is toxic chemical that can damage internal organs. It is highly flammable. Short term exposure to EA causes eyes, skin and throat irritation followed by headache, nausea, vomiting and dizziness. Repeated exposure may cause skin dryness or cracking. Prolong exposure could cause cloudiness of eyes and damages to lungs, heart and kidneys.



ethyl acetate

7.33 Acetone

Acetone or dimethyl ketone is common laboratory solvent which can be either man-made or natural. It is highly flammable colorless liquid with distinct smell and taste. IARC and EPA do not classify acetone as possible carcinogen. However, it can cause



Acetone

moderate to severe eye irritation upon contact. Inhaling acetone is harmful at high concentration that could possibly damage nervous system. Acetone could bring mild irritation to skin. Though the chemical has potential to absorb in skin, yet it doesn't pose serious threat. Ingestion doesn't bring any harmful effect unless it is taken in larger quantity. Skin becomes cracked, red and dry upon long term exposure to acetone (dermatitis). Acetone is not a teratogenic or mutagenic.

7.4 Lab Work in Colleges

Practical lab work is essential for learning science because it offers rich domain to practice theoretical knowledge into practical experimentation. In effort to revive practical lab work at college level, I always yearned to effect as it deserves to be effected for viable scientific encounter with fundamental experimentation at F.Sc. and BS level. Recently, I visited different science departments of my college where I reviewed timetable, noted lab timing, teachers and students participation as per assigned timetable and recorded their commitment to practical lab work. I also took great interest in what is practicing in lab work in comparison to approved curriculum. Whether FSc. or BS, emphasis was laid down on practical utility of experimental work. Teachers and students have asked about their experience and participation in lab work in accordance with official syllabus and recommended academic materials. I reviewed many important aspects of practical in different science departments:

1. Lab work assigned in timetable
2. Recommended syllabus and reading material
3. Accessing students and enquiring them about lab work
4. Maintenance of lab notebook
5. Practical examination and marks distribution
6. Lab time and students engagement
7. Lab attendance
8. Lab equipment and maintenance

Every science department was asked to assess every individual teacher concerned with lab of FSc/BS on following different counts regarding lab work. I developed all these questions in my Science Lab Survey for students to respond.

1. Whether lab is attended as per assigned timetable or not
2. Whether lab attendance is maintained or not
3. Whether lab attended in accordance with the recommended curriculum or not
4. Whether students have given any recommended reading text or not
5. Whether lab performed has monitored throughout by teacher or not
6. Whether lab results concluded or not

7. Whether lab results noted and get checked by teacher or not
8. Whether recommended practical lab syllabus has covered or not
9. Whether lab exam is based on systematic grounds or just focus on viva results
10. Are labs equipped enough to facilitate your practical lab work?
11. Do you feel interest in your science lab work?
12. Are students satisfied with their lab learning like their theory one?

In preliminary visits, I noted shocking absence of students and teachers in their practical lab work. There is general sense of reluctance among teachers and students to participate in lab activities. It felt like they fear practical work. Indeed, anything that is poorly understood is feared or repulsed which is what I noted in my visit regarding practical lab work in our college. Ironically, lab work is not given any priority. Neither recommended curriculum is followed nor lab activities encouraged and appreciated. Almost every teacher claims handsome share of credit hours in their timetable, yet practice on ground is dismal. Even students are examined for nothing regarding their practical examination.

What has come to the notice in few days of work on BS or FSc practical is shocking. Strange anomalies have been surfaced which is if not redressed in time will bury the very meaning of science we have been teaching in our classes. For instance, lab examination has totally been based on viva although every science practical examination is constituted by certain marks distribution such as lab performance, lab attendance, lab notebook and written exam. Students have been found preparing lab notebook a day or two before the final viva. Most alarmingly, whole college free from students by 11.30 am which reflects they are rarely engaged in lab hours despite teachers feel proud of claiming handsome lab credit hours. Recommended curriculum for lab is not followed in letter and spirit and students are not given any recommended syllabus and relevant guiding material to prepare for lab based experimentation. Results and conclusions are hardly gauged and rewarded. Most teachers have been found pretending lack of experimental set up although a minor effort could enable them to arrange for multiple other alternatives within the content of recommended practical lab syllabus.

Despite hundred and thousands of private schools and colleges in DIKhan, hardly anyone facilitates practical performance. Each year, these institutes charge hefty amounts and got bright scores for almost every student yet none performs practical work in science labs. Pre medical and pre engineering disciplines are common in these institutes where science is taught without single practical. One wonders why parents are indifferent to such anomalies. More regretfully, schools and college teachers who are assigned practical duties also fall dumb and blind over taking practical exam without even finding a single lab.

If we distribute 15 practical marks of each FSc. science subject, 4 is awarded to lab demonstration and written exam each, 2 to notebook and 5 to viva. Imagine, lab demonstration is not conducted and written exam and notebook are formalities in inter examinations these days. All marks are awarded based on viva although it carries just 5 marks. BS practical exam is even more regrettable to write on. All 50 marks are awarded

based on mere viva although 20 are assigned for viva, 10 for lab performance, 5 for attendance, 5 for notebook and 10 for written exam. Whether schools or college administration or parents coupled with teachers, all three are responsible for deceiving young generation with high scores without any knowhow regarding their degrees.

One reason why do we hate science is how do we practice it in our academic labs which is evident from how do we treat lab work that is nothing short of fulfilling a formality. Sadly, our practice with science is shameful. Whether theory or science, our students rarely understand any. Theory is essential for practice. Unless theory of science is learned, no scientific practice is enjoyed in our labs. We don't make our science students to think beyond memorization of basic definitions which are questioned for passing exam. Students don't know beyond those definitions because teachers never teach science to think and reason through practicing problems and devising solutions. Imagine the consequences: our scientific productivity is zero where our scientific consumption is 100%.

There is need to arrange a seminar on practical lab work with intent to highlight the significance of science in our labs and its broader applications to a scientifically developed economy. Students and teachers are needed to take on board for magnifying the importance of practical lab work. Teachers should engage students to revive scientific skills in students. Administrative paraphernalia should be evolved with sole intent to sponsor, monitor and support science in lab. Science is not to hate or fear, it is to embrace and utilize for larger benefit of society. Every science department should have fine lab record and efficient monitoring system. Every science lab should be equipped enough to cater for basic science experimentation. To embrace the goal, education department should institute special funds besides annual budget for purchase of lab items. Unless and until lab work is taken on warring footing that equates our theoretical teaching, no science can be respected in its letter and spirit. To respect science, we need to evolve collective efforts for addressing the loopholes that have been burying our scientific work.

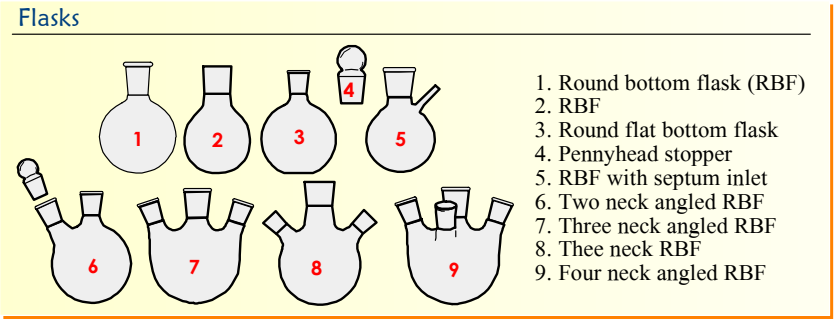
Provincial Higher Education Departments could play effective role once it resolve to administer viable practical lab work. No private school or college should be given NOC unless it invests in science labs. This can be done once provincial boards take interest in science and practical work. Our practical examination must not be a formality but it should be taken on rigorous grounds so that students could be pushed to disengage from taking the task as formality. I hope once these suggestions are taken seriously, Pakistan could be truly a scientific country whose devotion to science can really bring revolution in our scientific productivity.

7.6 Lab Experiments

01. Lassaign Test

Detection of Elements in Organic Compound

An organic compound could be transformed into inorganic salts such as cyanide, sulfide and thiocyanate by treating with sodium metal. A Lassaign extract involves this transformation in essence. A pea size sodium is melted in fusion tube by heating. An unknown organic compound is added to the fusion tube and then heated to red hot. Put the hot fusion tube in 10 ml distilled water contained in China dish. Break the tube to dissolve the mixture in water. Boil the solution for 2 minutes and then filter to get freshly prepared Lassaign extract in a clean test tube.



Detection of Nitrogen

Take few ml of Lassaign extract and treat it with few drops of $FeSO_4$ or $FeCl_3$ solution followed by heating and subsequent cooling. Add few drops of concentrated sulfuric acid after cooling. A Prussian blue (ferric ferrocyanide $Fe_4[Fe(CN)_6]_6$) complex is formed as detection indicator for confirmation of nitrogen in organic compound.

$$FeSO_4 + NaCN \longrightarrow Na_4[Fe(CN)_6] + Na_2SO_4$$

Detection of Sulfur

Treat few ml of Lassaign extract with sodium nitroprusside. A violet or purple color of sodium sulfonitroprusside indicates positive test for confirmation of sulfur.

$$Na + S \longrightarrow Na_2S \text{ (sodium sulfide)}$$
$$Na_2S + Na_2[Fe(CN)_5NO] \longrightarrow Na_4[Fe(CN)_5NOS]$$

Lead acetate gives black precipitate of PbS after acidifying the extract with AcOH for sulfur detection.

$$Na_2S + Pb(CH_3COO^-)_2 \longrightarrow PbS + 2\ AcOH$$

Both sulfur and nitrogen could be detected by thiocyanate test which involves acidification of the extract with HCl followed by addition of two drops of ferric chloride solution. Red color confirms the presence of thiocyanate anion.

Detection of Halogen

To detect halogen in organic compounds such as p-dichlorobenzene, tribromophenol or iodoform, Lassaign extract is first acidified with nitric acid to eliminate interfering anions of cyanide or sulfide ions.

$$NaCN + HNO_3 \longrightarrow NaNO_3 + HCN$$
$$Na_2S + 2\ HNO_3 \longrightarrow 2\ NaNO_3 + H_2S$$

Silver nitrate solution is added. Chlorine give white precipitate of AgCl. Bromine gives pale yellow precipitate of AgBr. Iodine produces yellow precipitate of AgI.

Chromates

If $AgNO_3$ solution is not available, the extract could be treated with lead (II) acetate and potassium chromate. A yellow precipitate of $PbCrO_4$ indicates the presence of chlorine. For bromine and iodine, the extract could be treated with chlorine water to liberate bromine or iodine that could be extracted with chloroform that form orange or violet layer.

An organic compound containing halogen, especially bromine or iodine, could be confirmed by orange or violet color with sodium hypochlorite solution (bleach) that oxidizes halide to halogen. In layer test, halide in organic compound is oxidized to halogen with $KMnO_4$ solution and later extracted with chloroform. Chlorine gives no color change, bromine gives orange red color and iodine yields violet color. Alternatively, Beilstein test could be used to detect halogens in organic compound. The test is less precise, however. A clean copper wire is heated in flame until it ceases to impart any color. Cool the wire and dip in organic compound containing halide. Heat the wire and notice flame color. Green or bluish green flame due to CuX_2 indicate the presence of Cl, Br or I.

02. Recrystallization/Reflux

Procedure 1

Take 1 g of benzoic acid and dissolve in 20 ml of distilled or deionized water. Heat the mixture to the boiling. Gradually add a portion of hot water, continue stirring until whole mixture is dissolved. Remove beaker from heating source and filter the contents. Cool the filtrate at room temperature. Separate the crystals by filtration, dry and weigh the crystals.

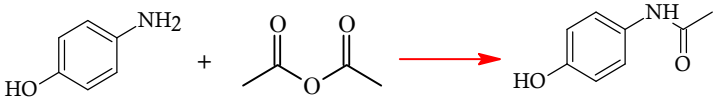
Procedure 2

Add 2.5 g of napthalenein 12 ml ethanol in 50 ml round bottom flask (two neck flask) with magnetic stirrer. Place the flask on magnetic heating plate. Attach condenser to the flask and heat the content until it boils. Add 1 ml of ethanol again via pipette. Continue heating until all solid dissolve. Filter the war solution in Erlenmeyer flask. Cover the flask with suitable plug and allow it to cool for 30 min. Filter the crystals, dry and weigh the content.

03. Synthes of Acetaminophen

Procedure 1

Take 1.375 g of p-aminophenol in 100 ml RBF. Add 3.75 ml of distilled water to it. Add 1.5 ml of acetic anhydride dropwise to the mixture. Reflux the sample for 20-25 minutes at 120 °C. Stop the reaction and cool down the reaction mixture in ice bath for few minutes. If required, place the mixture in freezer for 10 to 15 minutes. Crystal of crude acetaminophen will appear. Dry and recrystallize the product.



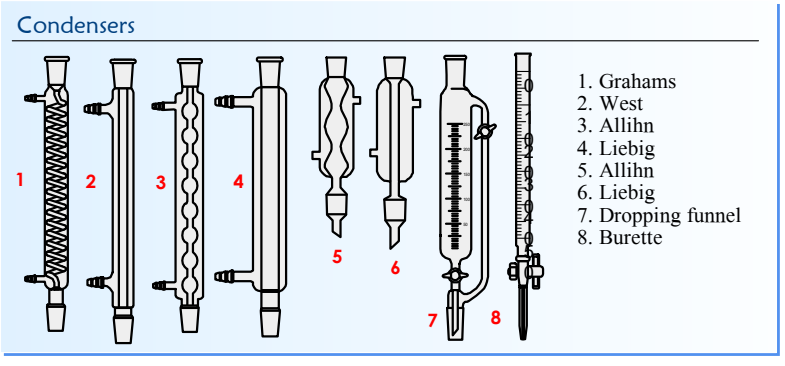
p-aminophenol + acetic anhydride → acetaminophen

Paracetamol (Tylenol)

Procedure 2

Take 3.3 g of p-aminophenol and 9 ml of water in Erlenmeyer flask. Add 3.6 ml of acetic anhydride dropwise and stir reaction mixture constantly. Heat the flask in water bath at 60 °C until complete dissolution of the compound occurs. Continue stirring for 10 more minutes and then cool the solution in an ice bath until the appearance of a slightly pink crystalline product. Filter the crystal.

Recrystallize the crude product in ethanol-water solution (70/30 v/v). Warm the mixture to 60 °C. Add 2 g of animal charcoal to decolorize the product. Filter the solution over water bath and allow it to cool. We get large monoclinic crystals of acetaminophen.



04. Synthesis of N-Phenylacetamide

Synthesis of Acetanilide

Procedure

Take 9 ml (0.1mol) of aniline in 250 ml round bottom flask (RBF). Add 15 ml glacial acetic acid and acetic anhydride each. We can also use acetyl chloride instead with which pyridine is used as scavenging agent. Acetyl chloride is lachrymatory agent. It causes tears. It should be used drop wise. Skin contact should be avoided. Aniline is also toxic. It may absorb in skin.

Establish **reflux** assembly and heat the solution for 10 mins. Let's the reaction mixture in RBF cool down. Pour the crude product (acetanilide) into 50 ml of water contained in beaker. Ice freeze the content. Shake the mixture well, continue stirring with glass rod and then filtrate with the aid of Buchner funnel. After filtration, separate the product and subject it to **recrystallization** in 200 ml water so that pure product is obtained. If color impurities still persist, decolorize it with activated charcoal. Dry the product, weigh it and calculate its yield. Characterize or identify the product through **melting point determination**. ***Note***: the experiment can be done in Erlymner flask by swirling 10 ml of aniline and 12 ml of acetyl chloride.

Study the underline chemicals with reference to their physical and chemical properties coupled with their toxicity and utility. Also note down different marks and labels on their bottles. These techniques are written in bold letters in above text. Study about them and practice them for mastering practical utility.

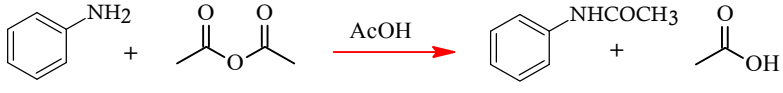
Protection of Amines, Aldehydes, Ketones, Alcohols & Carboxylic Acids
Significance of Protecting Groups in Organic Synthesis

Sometimes we need protecting group to avoid unwanted reaction of particular functional group (FG) while letting other groups to react. A group of atoms that is used to cover or protect FG under consideration from chemical reactivity is known as protecting group. Following are some examples of protecting groups used in organic synthesis.

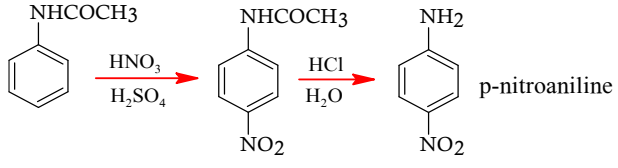
Protecting Groups

1. Acetylation Reaction

Introducing acetyl group into a molecule is known as acetylation reaction. Amino group is basic. To protect it, acetylation reaction is done either with acetic anhydride or acid chloride. Acetanilide (antifebrin) is antipyretic (fever reducing) and analgesic (pain reducing).



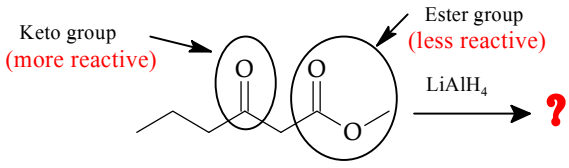
To synthesize paranitroaniline, we need protection of amino group because during nitration step, if it is not protected, amino group will get protonated and the synthesis of the product will be disturbed. An acetylation reaction is done to form acetanilide.



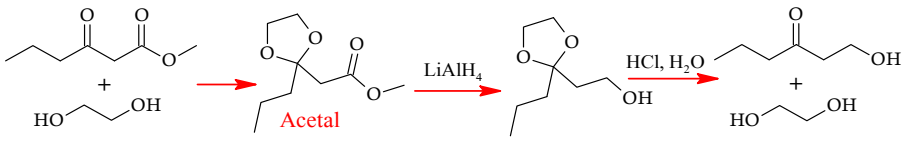
2. Acetal Formation

Aldehydes and ketones are protected through acetal formation. Acetals are gem-diethers in two oxygen atoms are attached to same carbon atom. Usually, a 1, 2-diol such

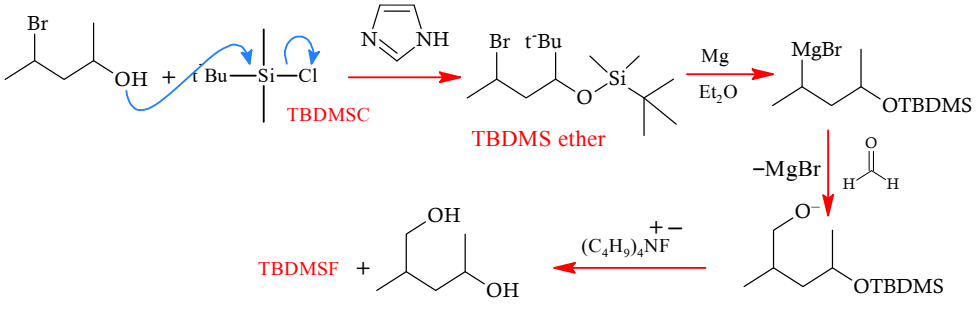
as ethylene glycol or 1, 3-diol are used for acetal formation. If we have organic compound containing both keto and ester FG and we want to make reaction on ester group while preventing keto one, we will protect the reactive group (keto) from unwanted reaction. Acetals are easily removed (deprotection) via simple acid catalyzed hydrolysis.



Acetals are good protecting agents. Like ethers, they do not react with base, oxidizing or reducing agents. Acetal is general term used for both aldehyde and ketone. However, acetal is sometimes used for aldehyde and ketal for ketone.



3. Silyl Ethers

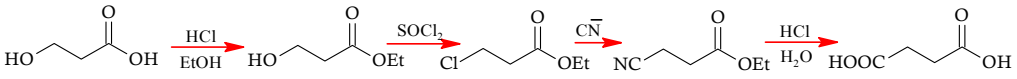


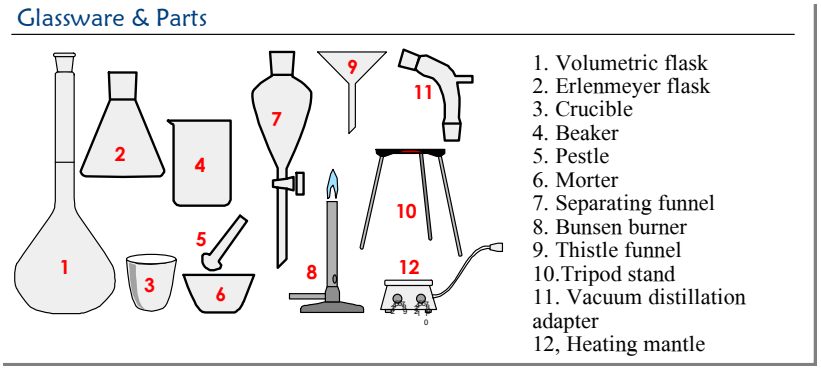
Silyl ether offers best way to protect -OH of alcohols. The reagent used for the protection is t-butyldimethylsilyl chloride represented as TBDMS. The compound its form is TBDMS ether. Although the protecting agent is tertiary in character yet it undergoes bimolecular substitution reaction with alcohol because Si – C bond is longer than C - C. This increase in bond length reduces steric hindrance on the spot of nucleophilic attack, thus facilitating backside attack for making silyl ether.

Imidazole is generally used to trap HCl generated produced during reaction. Once hydroxyl group is protected, Grignard reagent can be synthesized without any trouble posed by presence of -OH acidic proton. Silyl ethers are stable in neutral and basic medium, they can be removed with the aid of t-butylammonium fluoride.

4. Carboxylic Acids

Hydroxyl group of carboxylic acids is protected by converting it into ester.



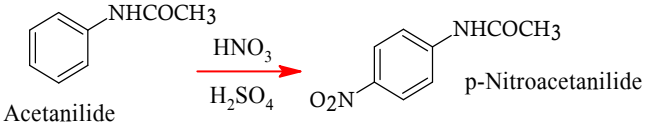


05. Nitration of Acetanilide

Procedure

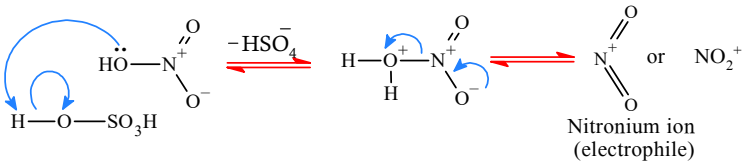
Take 6.3 g of acetanilide and dissolve in 6.5 ml of glacial acetic acid in 250 ml beaker by gentle heating. Add 23 g (125 ml) of conc. H_2SO_4 to mixture.

Take 100 ml beaker. Place 15 ml conc. H_2SO_4 and add 6.75 g (0.05 mol) of acetanilide in small proportion with magnetic stirring. Once all the acetanilide dissolves, place the beaker in ice bath and introduce 6 ml of HNO_3 in 6 ml of conc. H_2SO_4. Maintain the addition gently so that the temperature of the reaction doesn't exceed 35 °C. Remove the beaker from ice bath and allow the reaction mixture to stand at room temperature for about 5 min. Transfer the nitrated acetanilide solution into 600 ml beaker which contains 100 ml water and 30 g of ice. Stir the mixture and get the precipitate of *p*-nitroacetanilide by vacuum filtration in a Buchner funnel. Wash the product with two portions of 50 ml of cold water. Press the product and allow air to pass for drying purpose. Use ethanol to recrystallize for purification. Get the product dried, weigh and determine yield.



Handling Lab Work

Almost all organic reactions need to be done in fume hood because every organic solvent is volatile and it turns into vapor at ordinary temperature leave aside heating at different temperatures. If fume hood isn't available, precautions can be taken by establishing reflux assembly at least to prevent unwanted fumes around us. These fumes can take fire anytime if they are flammable. Never let methanol reaction in open set up while heating. Take great care in your lab work. Never take anything light. Read laboratory manual in a bid to equip you with the art of self-care and collective interest of everyone around you. Be attentive and disciplined in all your academic activities.



06. Hydrolysis of Acetanilide

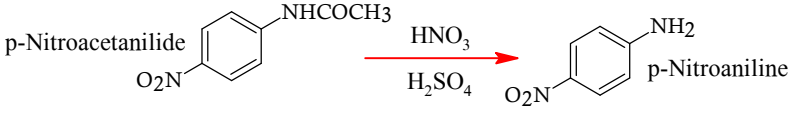
Acid Catalyzed Hydrolysis of p-Nitroacetanilide

Procedure 1

Take wet *p*-nitroacetanilide in 400 ml beaker. Add 100 ml of water and stir the reaction mixture. Shift the reaction mixture to 250 ml RBF. Introduce 35 ml of conc. HCl and arrange a reflux assembly over reaction mixture. Heat to boiling for 35 min. Cool the reaction mixture to room temperature. Pour the reaction mixture into 500 ml beaker that contains 50 - 75 g of crushed ice. *p*-nitroaniline get precipitated after making the reaction mixture basic with ammonia. Filter the reaction mixture with Buchner funnel. Wash the product with small quantity of water. Recrystallize from water. Use activated carbon for decolonization. Dry, weigh and calculate the final yield.

Procedure 2

Alternatively, 2g of p-nitroacetanilide can be treated with 10% H_2SO_4 by an hour reflux followed by pouring the reaction mixture into a cold water where it is acidified by concentrated HCl. Yellow crystals of p-nitroaniline are obtained.



Lab Ethics

Lab activity means your prior understanding of theory, techniques, chemical and physical nature of reagents and solvents, their toxicity, handling and reading bottle labelling. Besides, a cautious student always takes great care in handling lab operations. Lab apron is essential requirement to avoid chemicals contact with your clothes. Wearing gloves and google greatly enhance protection. Avoid prolong exposure to any sort of fumes, smoke or vapors. Never touch chemicals with bare hands or putting any sort of glassware in mouth or smell liquid or solids. Take source of fire away from volatile reagents. Never eat in lab. Avoid placing your bare hands, books or anything you take with yourself on lab slab. Be careful in lab and follow above guidelines.

Procedure 3

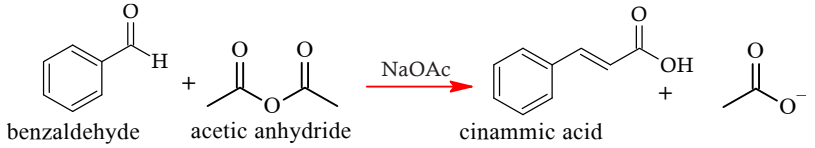
Take 6.3 g of acetanilide and dissolve in 6.5 ml of glacial acetic acid in 250 ml beaker by gentle heating. Add 23 g (125 ml) of conc. H_2SO_4 to mixture.

07. Synthesis of Cinnamic Acid

Perkin Condensation

Procedure

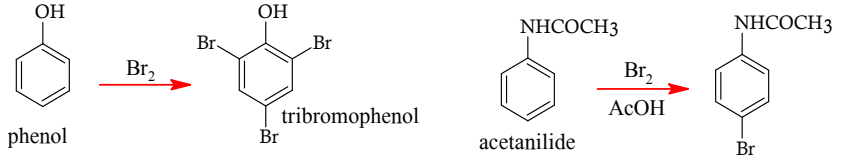
Take 5 g of benzaldehyde and 7.5 g of acetic anhydride and 2.5 g of sodium acetate in 250 ml round bottom flask and set the reflux for three hours. Equip the round bottom flask with drying tube. Allow the reaction mixture to cool at room temperature and add 100 ml of water. Subject the reaction mixture to steam distillation to remove unreacted benzaldehyde. Filter the solution to remove the additional resinous solid. The filtrate is acidified with concentrated HCl by adding it slowly followed by vigorous shaking. Cool the mixture in an ice bath and isolate the resulting solid by vacuum filtration. Recrystallize from water, dry weight and determine the yield. Mechanism for the following reaction has given in section 3.107-2.



08. Bromination of Aromatic Hydrocarbon

Procedure 1

Take 2 g of phenol and 2 ml of bromine. Dissolve phenol in 30 ml of water in a flask. Add 2 ml of liquid bromine in 25 ml of water and stir the reaction flask by shaking. White ppt of tribromphenol forms with disappearance of bromine color. Filter and recrystallize the product from ethanol. Product obtained: mp 91 °C. Yield is 6 g.



Procedure 2

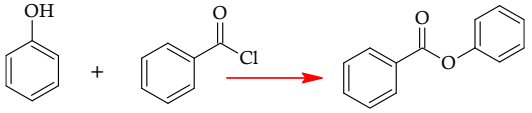
Para-bromoacetanilide: take 7 g, 25 ml glacial acetic acid and 3 ml bromine. Dissolve finely powdered acetanilide in 25 ml of glacial acetic acid in 250 ml flask. Add slowly a solution of 3 ml of bromine in 12.5 ml of glacial acetic acid with constant shaking. Allow the reaction mixture to stand at room temperature for 15 min. Then pour the pale reddish solution into a large excess of water (about 250 ml) where the product will crystallize out. Stir, filter and wash the product with cold water. Drain and recrystallize the product from methylated spirit. Product obtained: colorless, crystalline with mp 167 °C and yield is 8 g.

09. Synthesis of Phenylbenzoate

Procedure

Take 2 g of phenol (or 2.5 ml of liquid phenol) and place in 100 ml Erlymner flask. Add 30 ml of 10% NaOH solution to the flask. Dissolve the mixture by shaking and then

add 4 ml of benzoyl chloride into the solution. Continue shaking for 15 to 20 minutes. Collect the product through filtration. For purification, dissolve the product in ethanol and subject to recrystallization. Calculate yield and determining melting point for determination of compound. Note that phenyl benzoate is irritating and lacrimating agent. Handle carefully. Wash with clean water in case your skin comes in contact with it. Phenol is corrosive. Deal it carefully.

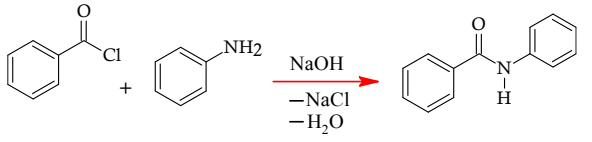


10. Synthesis of Benzanilide

Schotten-Baumann Reaction: Synthesis of benzanilide (Fungicide, Acaricide)

Procedure

Take 2 ml of aniline and 30 ml of 10% NaOH in 250 ml conical flask. Add 3.4 g of benzoyl chloride slowly along with vigorous shaking for 15-20 minutes until the odor of benyol chloride diminishes. Dilute the reaction mixture with cold water. Filter the crude benzanilide. Wash the content with cold water and crystallize from hot solvent. Dry the product and calculate the yield. The Benzoylation of compound with compounds carrying active hydrogen such as phenol, alcohol or aniline with benyol chloride catalyzed by NaOH is known as Schotten-Baumann reaction.



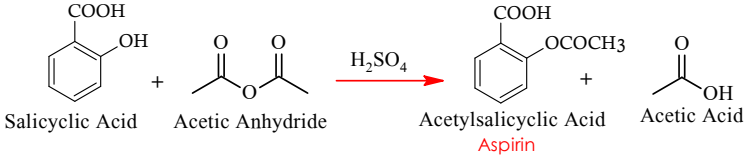
11. Synthesis of Aspirin

Aspirin (MW 180.1g), is acetyl derivative of salicylic acid which is antipyretic (relieve fever), analgesic (relieve pain) and anti-inflammatory in medication. It is closely related to two other drugs, acetaminophen and ibuprofen, all three belong to non-steroidal anti-inflammatory drugs (NSAID) which block the synthesis of prostaglandin and thromboxane from arachidonic acid by binding to the active site of cyclooxygenase enzymes. The latter is implicated in blood clot, therefore many physicians recommend small dose of aspirin to stop platelets aggregation in blood vessels and to prevent heart stroke. Ancient Greek philosopher, Hippocrates, suggested that pain associated with childbirth could be relieved by willow bark which was later known to contain salicylic acid, a compound which irritates stomach, therefore requires its protected form of acetyl salicylic acid. Synthesis of aspirin was achieved by German chemist, Fritz Hoffman of Bayer Chemicals. It reacts with moisture to give salicylic acid and acetic acid. The sample should be discarded if it leaves the smell of acetic acid. Aspirin is white crystalline solid, colorless and odorless.

Procedure

Take 200 ml of conical flask. Add 5g of salicylic acid, 10ml of acetic anhydride and 1 to 2 ml of conc. sulfuric acid. Shake the solution gently. Temperature may rise to 70 to 80 °C. Maintain temperature around 60 to 70 °C by keeping solution in water bath. Continue the process for 15 min. Cool the mixture and pour in 100 ml cold water contained in 500 ml beaker with stirring. Filter with Buchner funnel. Wash the product with cold water. Dry it on filter paper. Recrystallize the crude sample of aspirin from benzene or ethanol to obtain colorless crystals. Don't use hot water as recrystallization solvent because aspirin undergoes partial hydrolysis to salicylic acid and acetic acid in hot solution. The yield for the experiment is 4 g.

Acetylation Reaction



12. Detection of Amines

To demonstrate the application of diazonium salts in lab, we make two reaction mixtures (RM) A and B. We want yellow azo dye to prepare by the application of diazonium salts. RM-A involves the synthesis of diazonium salt whereas RM-B provides a nucleophile to react with diazonium salt. To prepare RM-A, take 50 cm^3 of aniline in beaker placed in cold ice bath. Pour 5 cm^3 of concentrated HCl into beaker. In another beaker placed in ice bath, prepare saturated solution of sodium nitrite. Mix the solution of two beakers followed by vigorous stirring. Consequently we get RM-A of arene diazonium salt.

For RM-B, dissolve some quantity of phenol in sodium hydroxide solution to get sodium phenoxide. Cool the solution and finally add it to RM-A to get yellow azo dye of p-hydroxyazobenzene. An orange red dye is obtained with 2-naphthol whose RM-B could be prepared by taking 0.1g of the said substance and 10% NaOH solution along with 5 ml of water. Nitrous acid is useful reagent for determining whether amine is secondary (yellow precipitate) or tertiary (orange precipitate). Quaternary ammonia salts evolve NH_3 gas with NaOH solution. Aromatic amines gives white precipitate in benzoylation reaction when amine is treated with 10 ml of 10% NaOH solution followed by addition of 1 ml benzoyl chloride. The mixture is shaken vigorously for 10 to 15 minutes to get white precipitate.

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