B. PHARM. SECOND YEAR, (3rd Sem.)
PHARMACEUTICAL ORGANIC CHEMISTRY-II

ANSWER BOOK

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SECTION A

Q. 1. (a) What is aromaticity?

Answer:

AROMATICITY

- An aromatic compound should have the following specific characteristic-

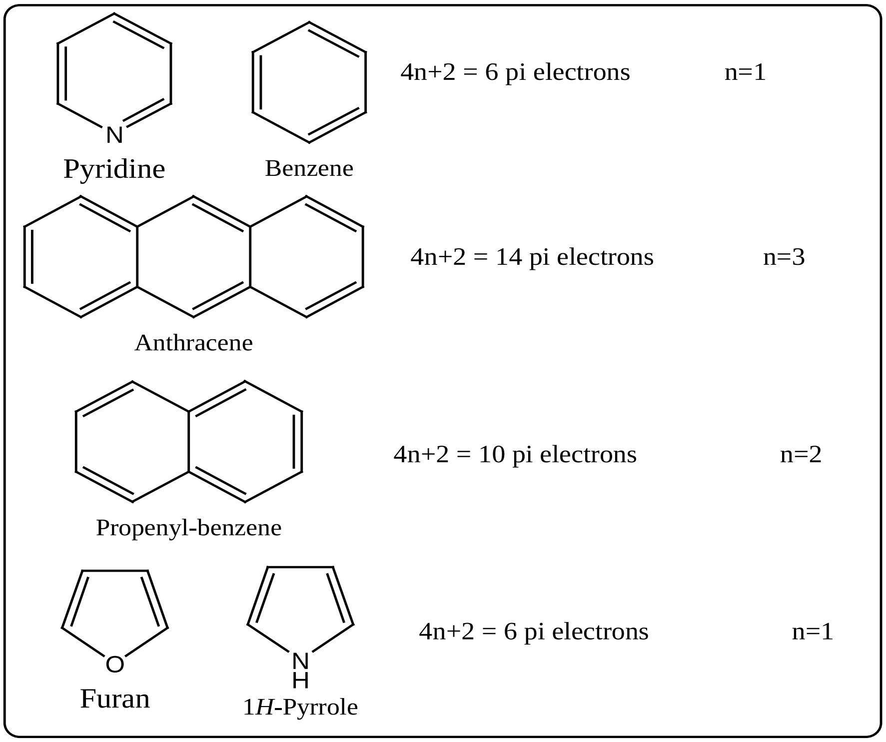
1. **A** delocalised conjugated π-system, most commonly an arrangement of alternating single and double bonds.
2. **Coplanar** structure.
3. Contributing atom arranged in one or more rings.
4. A number of π-delocalised electrons equal to 4n+2, where n=0, 1, 2, 3 and so on. (**Huckels Rule)**

Q. 1(b). Write Huckel's rule.

Answer:

HUCKEL RULE OR (4n+2) RULE

- The cyclic arrangement of p-orbitals in an aromatic compounds must contain **(4n+2) π electrons**, where n= (0, 1, 2, 3, 4…..etc.). Means aromatic compound have 2, 6, 10, 14….π electrons.
- Examples-

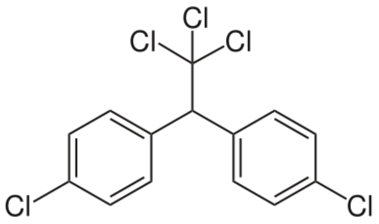


Q. 1(c) Give the structure and uses of DDT and cresol.

Answer:

DDT (Dichlorodiphenyltrichloroethane)

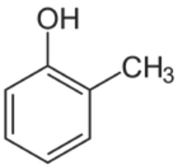
Structure:



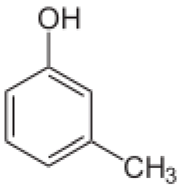
Uses:

- DDT was extensively used in agriculture, In insects, DDT opens sodium ion channels in neurons, causing them to fire spontaneously, which leads to spasms and eventual death the insect.
- DDT has been used in various formulations in multiple forms, including solutions in xylene or petroleum distillates, emulsifiable concentrates, water-wettable powders, granules, aerosols, smoke candles and charges for vaporizers and lotions.

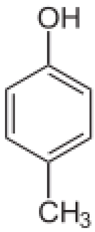
Structure of Cresol



ortho-cresol



meta-cresol



para-cresol

Uses:

- Mixed cresols are used as disinfectants, preservatives, and wood preservatives.
- ***O-Cresol*** is used as a solvent, disinfectant, and chemical intermediate.
- ***m-Cresol*** is used to produce certain herbicides, as a precursor to the **pyrethroid insecticides**, to produce antioxidants and to manufacture the explosive, 2,4,6-nitro-m-cresol.
- ***p*-Cresol** is used largely in the formulation of antioxidants and in the fragrance and dye industries.

Uses for various Drugs Synthesis:

- o-Cresol used for synthesis of Carvacrol.
- *m*-Cresol used for synthesis of Toliprolol, Tolamolol etc.
- *p*-Cresol is consumed mainly in the production of antioxidants, e.g., **Butylated HydroxyToluene** (BHT)
- Most recently, cresols have been used to create a breakthrough in manufacturing carbon nanotubes at scale that are separated and not twisted, without additional chemicals that change the surface properties of the nanotubes.

Q1 (d). Write qualitative test for phenol.

Answer: Qualitative test for phenol

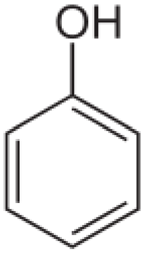
- **Ferric Chloride Test** - Compounds with a phenol group will form a blue, violet, purple, green, or red-brown color upon addition of aqueous ferric chloride. This reaction can be used as a test for phenol groups.

$$3\ ArOH + FeCl_3 \xrightarrow[pyridine]{} \underset{\text{colored complex}}{Fe(OAr)_3}$$

Q1 (e). Write the synthesis and uses carbolic acid.

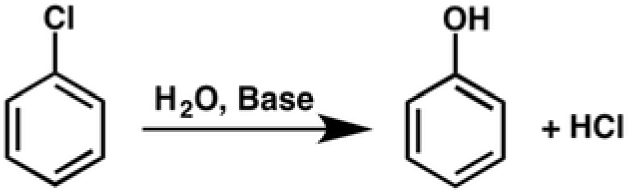
Synthesis and uses carbolic acid (Phenol)

Structure

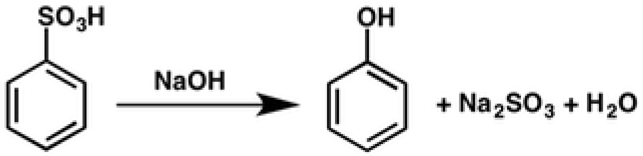


Preparation:

1. **Dow's process**: This method involves the hydrolysis of chlorobenzene in the presence of a base to make phenol with hydrochloric acid as the by-product.



2. **Synthesis of phenol from Benzene sulfonic acid:**



Uses of Carbolic acid (Phenol)

- Approximately two-third of the total phenol produced worldwide is used to prepare reagents used in plastic manufacturing industries.

- The polymerization reaction of phenol with formaldehyde is used to commercially prepare phenolic resins.

- Phenol is also used in the study and extraction of bio-molecules. Molecular biology finds application of phenol in the extraction of nucleic acids from tissue samples for further investigations.

- Phenol is also used in cosmetic industry in the manufacturing of sunscreens, skin lightening creams and hair coloring solutions.

- Phenol is also a versatile precursor to a large collection of drugs, most notably aspirin but also many herbicides and pharmaceutical drugs.

Q1(f). What are fats and oils? How fates are differing with oil.

Answer:

- **Fat:** Fats are oily substances that occur in the animal body, under the skin or around organs. They are mainly composed of saturated fatty acids. Therefore, they are solid at room temperature.

- **Oil:** Oils are viscous liquids which occur in fruits or seeds of plants. Since oils are mainly composed of unsaturated fatty acids, they exist as liquids at room temperature. Unsaturated fats lower the levels of cholesterol in the blood.

- Therefore, unsaturated fats lower the risk of heart diseases. Rapeseed oil, sunflower oil, olive oil, soybean oil, corn oil, and palm oil are examples of oils.

- The main difference between fats and oils is that fats are composed of high amounts of saturated fatty acids which will take a solid form at room temperature whereas oils are composed of mainly unsaturated fatty acids which will take a liquid form at room temperature.

Q1(g). Define saponification value.

Answer:

- **Definition:** The saponification value is the number of mg of potassium hydroxide required to saponify 1 gram of oil/fat.

$$\text{Saponification Value} = \frac{56.1\,(B-S)N}{W}$$

Where,

B = Volume in ml of standard hydrochloric acid required for the blank.
S = Volume in ml of standard hydrochloric acid required for the sample
N = Normality of the standard hydrochloric acid and
W = Weight in gm of the oil/fat taken for the test.

Q1(h). Give the structure and uses of Saccharin and resorcinol.

Answer:

- Saccharin was discovered at Johns Hopkins University in 1879 in the course of research on coal-tar derivatives and is the oldest artificial sweetener.

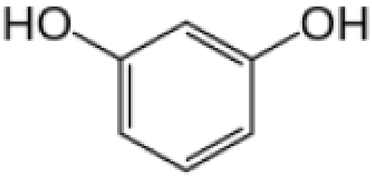
Structure

Saccharin

Uses:

- Its earliest applications were not in weight control, but as a replacement for sugar in the diet of diabetics before insulin became widely available.
- It is used as artificial sweetener in toothpaste, candy, chew gum etc.
- It also used as sweetening agent in various pharmaceutical dosage form.

Structure of Resorcinol



USES OF RESORCINOL

Medicinal Uses

- It is an antiseptic and disinfectant, and is used 5 to 10% in ointments in the treatment of chronic skin diseases such as psoriasis, hidradenitis suppurativa, and eczema.
- It has also been employed in the treatment of gastric ulcers in doses of 125 to 250 mg in pills, and is said to be analgesic and hemostatic (stops bleeding) in its action.
- A 2% solution used to treat external vaginal itching and irritation.

- **Resorcinol** is a skin protectant and topical analgesic.

Chemical Uses

- It is used in the production of diazo dyes and plasticizers and as a UV absorber in resins.
- Resorcinol is an analytical reagent for the qualitative determination of ketoses (Seliwanoff's test).
- Resorcinol reacts with formaldehyde to form a thermoset resin which can form the basis of an **aerogel** (frozen smoke)

Q. 1(i). Benzene undergo ESR not undergoes electrophilic addition reaction like alkenes. Why?

Answer:

- Benzene is a planar molecule having delocalized electrons above and below the plane of ring. Hence, it is electron-rich.
- As a result, it is highly attractive to electron deficient species i.e., electrophiles. Therefore, it undergoes electrophilic substitution reactions very easily.

. **Q1(j) What is differentiate between fats and oils.**

Answer:

Difference between Fats and Oils	
Fats	**Oils**
Solid at room temperature	Liquid at room temperature
Saturated and trans are its types	Unsaturated fats like monounsaturated and polyunsaturated are its types
Mostly derived from animal	Mostly derived from plants
Increases cholesterol levels	Improves cholesterol levels
Mainly comes from animal food but also through vegetable oil by process called hydrogenation	Mainly comes from plants or fish
Example: Butter, beef fat	Example:Vegetable oil, fish oil

Contains 9 cal/gm	Contains 9 cal/gm

SECTION-B

- **Q2(a) Give the chemical proof in favor of present benzene structure.**

STRUCTURE OF BENZENE

- The structure of benzene has been divided on the basis of the following point-

1. **Molecular formula (C_6H_6)**: Elemental analysis indicate that benzene contain six carbon and six hydrogen atoms.
2. **Presence of three double bonds**: Benzene show the unsaturated reaction.
   - Benzene adds on six hydrogen atom catalytically to form cyclohexane (**C_6H_{12}**).
   - Benzene adds on halogen, to form hexahalocyclohexane (**$C_6H_6X_6$**).
   - Benzene form Triozonide (**$C_6H_6(O_3)_3$**).

   This reaction suggest the presence of double bonds
3. **Benzene cannot have open chain structure:**

   The following point suggest that benzene ring cannot have open chain structure-

   a) Alkaline permagnate has no action on benzene in cold but on prolong it decompose to CO_2 & H_2O.
   b) In the presence of sunlight, benzene undergo substitution when treated with halogen.
   c) Halogen acid do not add on to benzene.
   d)
4. **Evidence of cyclic structure:**
   - Benzene give a mono substituted product when treated with halogen.

$$C_6H_6 + Br_2 \xrightarrow{FeBr_3} C_6H_5Br + HBr$$

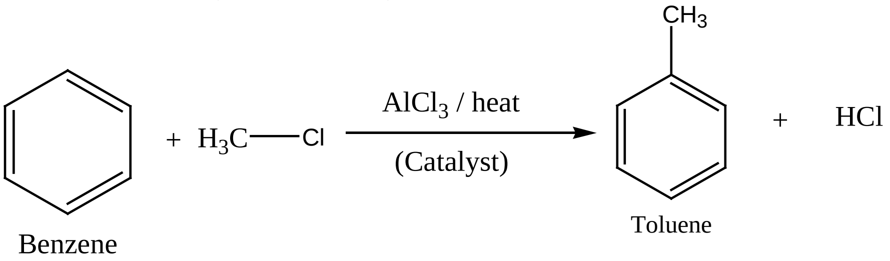
Bromo benzene suggest that all the six hydrogen atoms in benzene are equivalent. It means benzene is having a cyclic structure.

Q.2(b) Give the Friedelcraft Acylation and alkylation reaction with mechanism and its limitation.

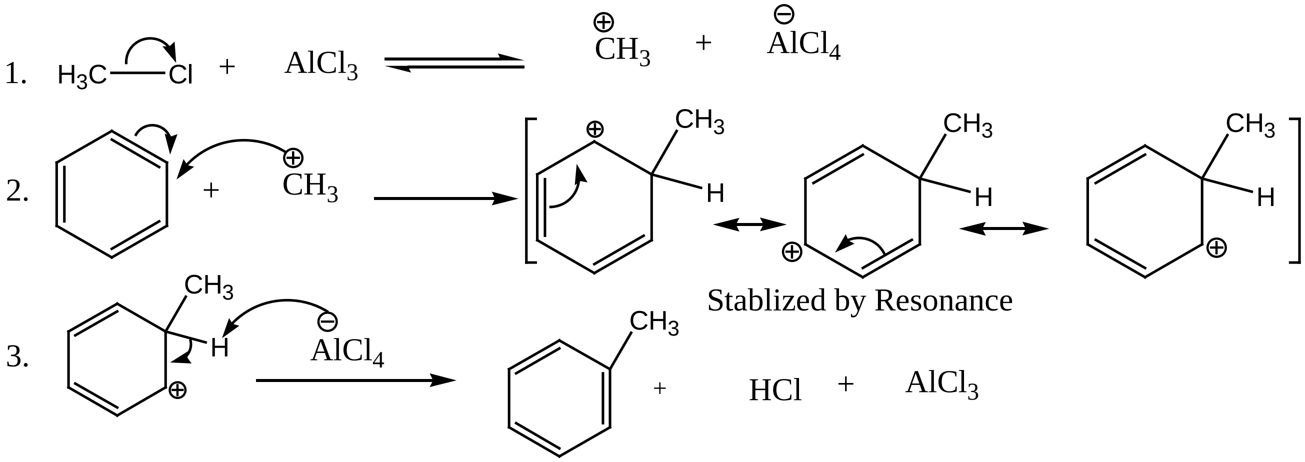
Answer:

1. **Friedel-Craft Reaction (Alkylation and Acylation):**

- The reaction of an alkyl halide or acyl halide with benzene in the presence of a Lewis acid, generally $AlCl_3$ is known as Friedel craft reaction.
- **Alkylation:** The alkylation of benzene, at least with primary alkyl halide.
- Halide are the reagent most frequent use in alkylation and aluminum halides as usually use as catalyst.

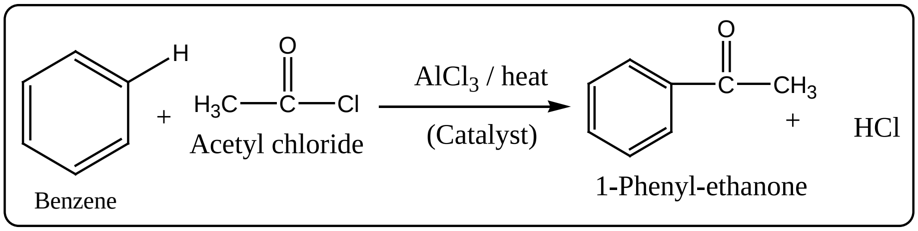


Mechanism:



2. **Acylation (Introduction of CH_3CO- group):**

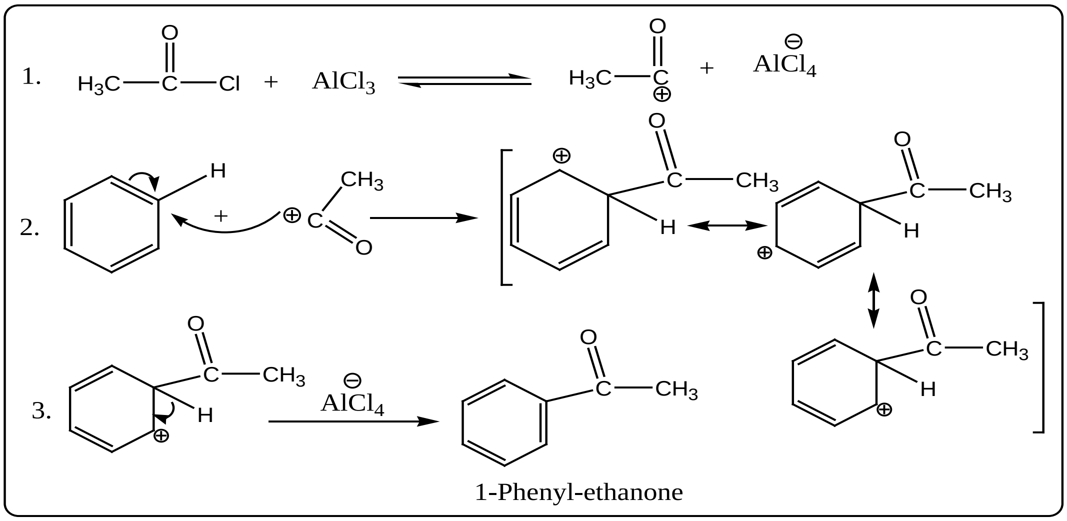
- The acylation of aromatic compound take place in the presence of excess amount of Lewis acid because the product of the reaction is ketene which form complex with Lewis acid.
- **Reaction:**



Acylation process differ from the alkylation in the following points-

- Acylation is usually carried out in a solvent commonly CS_2 or Nitrobenzene or benzene.
- Acylation requires more catalyst than alkylation because catalyst is removed by Ketone.
- It give generally mono-substituted product because it very difficult to introduced second acyl group.

Mechanism:



Limitation of Friedel craft reaction:

The three key limitations of Friedel-Crafts alkylation are:

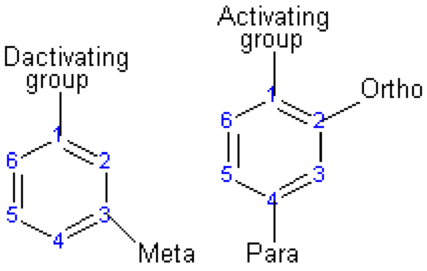
1. Carbocation Rearrangement - Only certain alkylbenzenes can be made due to the tendency of cations to rearrange.
2. **Compound Limitations** - Friedel-Crafts fails when used with compounds such as nitrobenzene and other strong deactivating systems.
3. **Polyalkylation** - Products of Friedel-Crafts are even more reactive than starting material. Alkyl groups produced in Friedel-Crafts Alkylation are electron-donating substituents meaning that the products are more susceptible to electrophilic attack than what we began with. For synthetic purposes, this is a big dissapointment.

4. Aromatic compound whose reactivity is comparable with or greater than that of benzene give this reaction.
5. Compound having –NH_2, -NHR, -NR_2 and –OH group also do not give this reaction.

Q2C (a). Why it is said that deactivating groups are *meta*- directing.

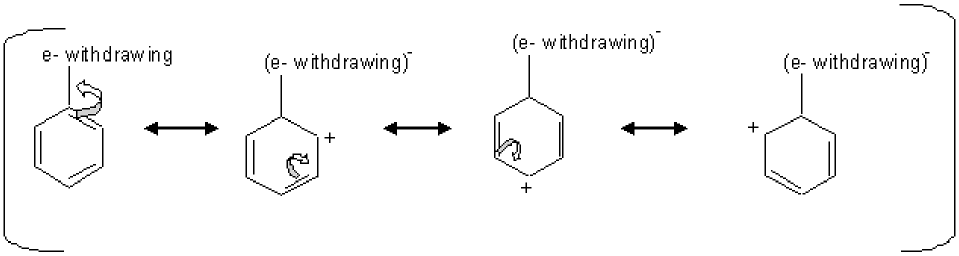
- Substituted rings are divided into two groups based on the type of the substituent that the ring carries:

- **Activated rings**: the substituents on the ring are groups that donate electrons.
- **Deactivated rings**: the substituents on the ring are groups that withdraw electrons.
- Examples of activating groups in the relative order from the most activating group to the least activating:
    - -NH_2, -NR_2 > -OH, -OR> -NHCOR> -CH_3 and other alkyl groups
- Examples of deactivating groups in the relative order from the most deactivating to the least deactivating:
    - -NO_2, -CF_3> -COR, -CN, -CO_2R, -SO_3H > Halogens



Deactivating group (meta directors)

- The deactivating groups deactivate the ring by the inductive effect in the presence of an electronegative atom that withdraws the electrons away from the ring.



- From the above mechanism it is clear that when there is an electron withdraw from the ring, that leaves the carbons at the ortho, para positions with a positive charge which is unfavorable for the electrophile, so the electrophile attacks the carbon at the meta positions.

- Halogens are an exception of the deactivating group that directs the ortho or para substitution.
- The halogens deactivate the ring by inductive effect not by the resonance even though they have an unpaired pair of electrons.
- The unpaired pair of electrons gets donated to the ring, but the inductive effect pulls away the s-electrons from the ring by the electronegativity of the halogens.
- Rancidity of oil

Q. 2C (b). Nitration of benzene with mechanism.

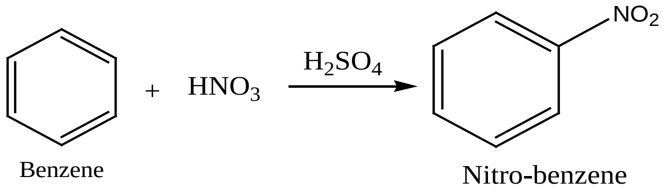
NITRATION OF BENZENE:

- Aromatic compounds can be nitrated using a wide variety of nitrating agents. For less reactive aromatic systems, a mixture of concentrated nitric acid and sulphuric acid is used.

- For reactive systems nitration can be carried out with nitric acid alone, or in water or acetic acid or acetic anhydride.

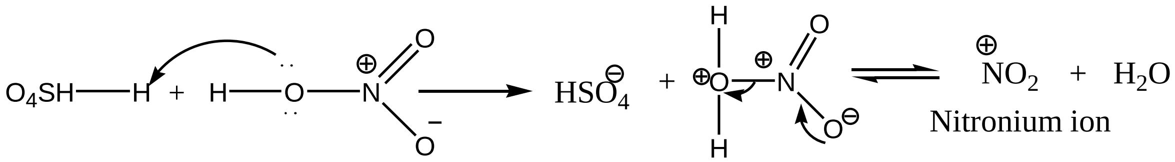
- Nitration of benzene, H_2SO_4 work as a catalyst. Sulphonic acid protonates nitric acid.

Reaction:

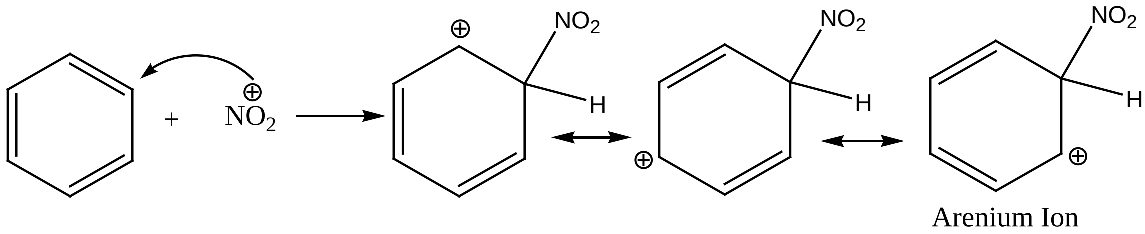


Mechanism of Reaction:

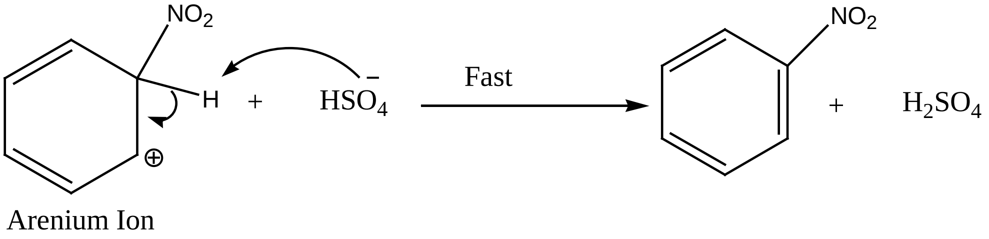
STEP-I



STEP-II: Electrophile nitronium ion react with benzene ring to form σ-complex or arenium ion.



Step-III: The arenium ion losses a proton to a Lewis Base (HSO_4^-).



Application:

- In manufacturing of explosive tri-nitro toluene (TNT), Nitro glycerin etc.
- Aromatic nitro compound are about the only precursor to aromatic amine because nitro group are generally easy to reduce to amine.

Q2C (c). Rancidity of oil.

Answer: Rancidity of oil

- Rancidity is associated with characteristic off-flavour and odour of the oil. There are two major causes of rancidity.
- One occurs when oil reacts with oxygen and is called oxidative rancidity.
- The other cause of rancidity is by a combination of enzymes and moisture.
- Enzymes such as lipases liberates fatty acids from the triglyceride to form diand/or monoglycerides and free fatty acids and such liberation of free fatty acids is called hydrolysis.
- Rancidity caused by hydrolysis is called hydrolytic rancidity. Oxidation is concerned mainly with the unsaturated fatty acids.
- Oxidative rancidity is off special interest as it leads to the development of unfavourable off-flavours that can be detected early on in the development of rancidity more so than in the case of hydrolytic rancidity.

Effects of rancidity on the food use of fats and oils

Flavour deterioration is the most common concern regarding the use of rancid fats and oils but the deterioration of colour and texture attributes as well as nutritional implications such as loss of nutritional value and formation of possible toxic oxidation products are also very important effects.

Rancidity in fats and oils has a characteristic, unpalatable off-flavour and odour in oils.

Secondary oxidation products such as short-chain aldehydes cause the typical off-flavour, which depending on their structure and the amounts formed, lead to odours such as beany, grassy, painty, fishy, tallowy or plain rancidity.

Overcome the rancidity

- Antioxidants retard the onset of oxidation, thereby extending the shelf-life of fats and oils and food products, but cannot prevent it.

  It is the same for synthetic antioxidants such as BHA, BHT, TBHQ and natural antioxidants such as tocopherols.

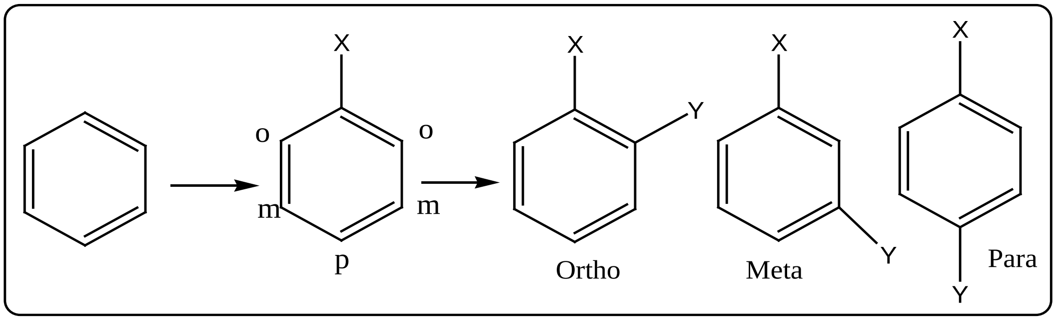
Section c

Q3a (i) Orientation in electrophilic aromatic substitution.

Answer:

ORIENTATION EFFECT (ORIENTATION OF SUBSTITUTION)

- Since six hydrogen atoms of benzene nucleus are identical, when one group (X) is introduced into the benzene ring, only one product is obtained.
- When second substituent (Y) is introduced, three isomers substituted products are possible-



- Nature of the group already present (X) on the benzene nucleus, incoming group (Y), either attached either two –*ortho* or two -*meta* position.
- This effect of the group already present on the nucleus is known as **directive influence of the group** or **orientation effect**.

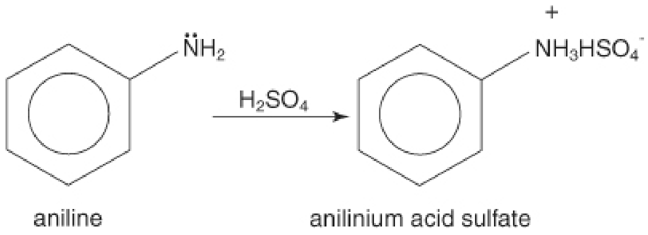
List of Ortho, Para and Meta Directers

Ortho, Para Directers	Meta Directers
$-\bar{O}$	$-CX_3$
$-OH$	$-\overset{O}{\overset{\|}{C}}-NH_2$
$-OCH_3$	$-\overset{O}{\overset{\|}{C}}H$
$-OR$	$-\overset{\oplus}{N}R_3$
$-NHR$	$-\overset{\oplus}{N}(=O)-\bar{O}$
$-NH_2$	$-\overset{O}{\overset{\|}{S}}(=O)-OH$
$-X$	$-C\equiv N$
$-\overset{H}{N}-\overset{O}{\overset{\|}{C}}-CH_3$	$-\overset{O}{\overset{\|}{C}}-Cl$
$-SH$	$-\overset{O}{\overset{\|}{C}}-OH$
$-CH_3$	$-CCl_3$
$-CH_2NH_2$	
$-C_6H_5$	
$-CH_2CN$	
$-CH_2Cl$	

Q. 3a (ii) Reaction of aromatic amines.

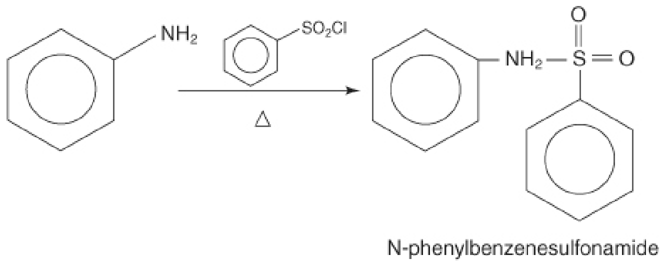
Due to the unshared electron pair, amines can act as both bases and nucleophiles.

1. **Reaction with acids:**
   When reacted with acids, amines donate electrons to form ammonium salts.



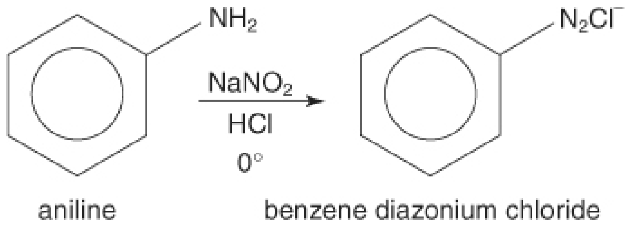
2. Reaction with sulfonyl chlorides

- Aromatic Amines react with sulfonyl chlorides to produce sulfonamides. A typical example is the reaction of benzene sulfonyl chloride with aniline.

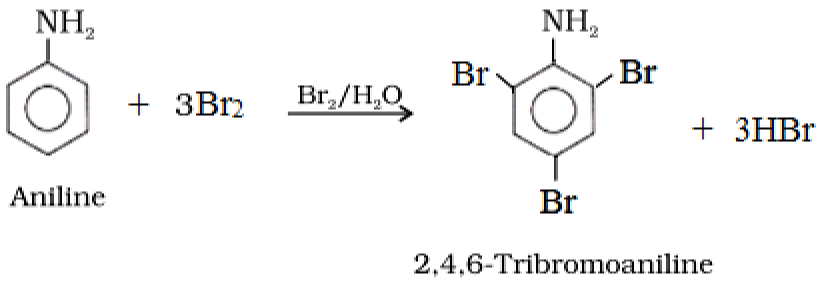


3. Diazotization:

Primary aromatic amines form stable diazonium salts at zero degrees.

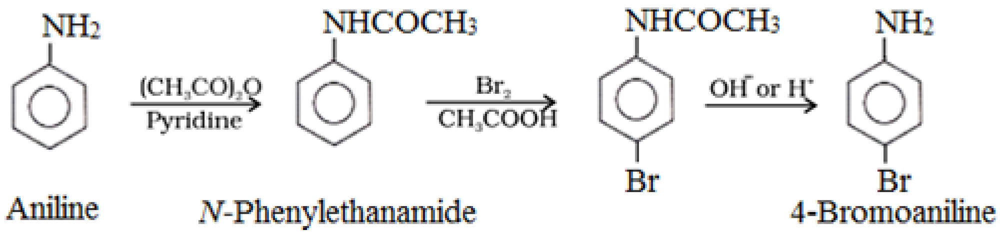


4. Bromination:

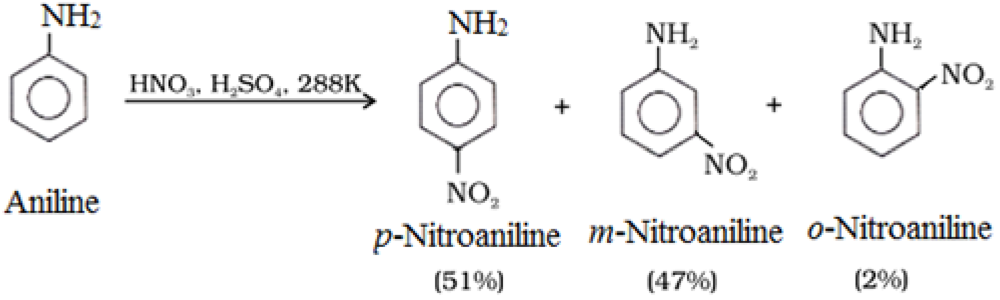


5. Prepare mono-substituted aniline derivative:

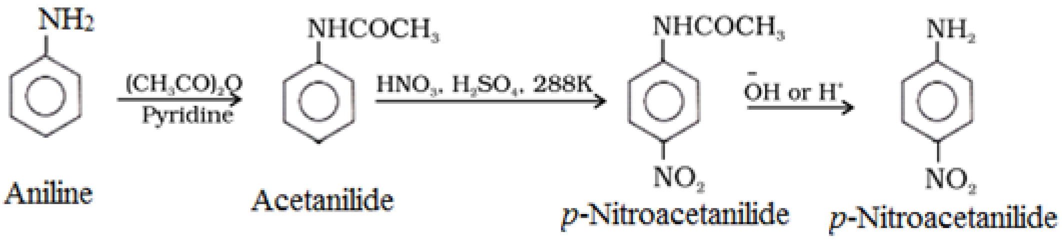
- Carry out the first acetylation of aniline with acetic anhydride to form amide. This is then hydrolyzed. We thus, obtain the monosubstituted amine.



6. Nitration



- To get *p*-nitro derivative as the major product, you have to carry the acetylation of aniline with acetic anhydride. Then, you should carry out the desired substitution of anilide. After this, you must carry out hydrolysis of the substituted anilide to the substituted amine**.**



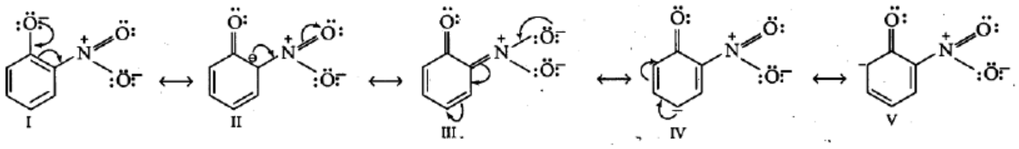
Q.3 a (iii) Acidity of Phenol.

Answer: Effect of Substituent on Acidity of Phenol –

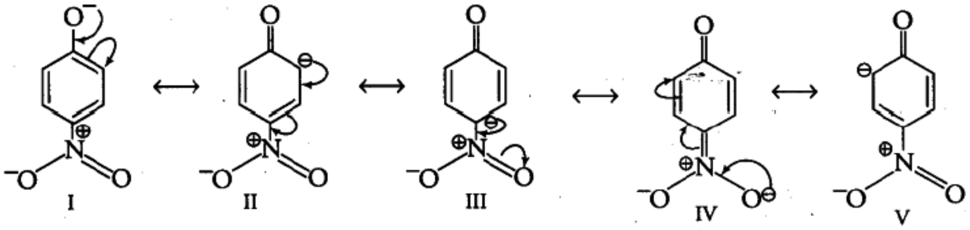
- As the acidic nature of phenol is due to the resonance stabilization of phenate compare to phenol. Therefore the presence of any substituent on aromatic ring which can stabilized the phenoxide ion will tend to increases the acidity of phenol.
- While any substituent which destabilized the phenate ion by increasing the negative charge will decrease the acidic nature of phenol.
- In other words; the presence of electron withdrawing group on benzene ring in phenol increase the acidity of phenol and electron releasing group will decrease the acidity.
- For example; if there is a nitro group substituted on phenol, it will increase the acidic nature of phenol. Hence nitrophenol will be more acidic than phenol as nitro group imparts negative mesomeric effect and negative inductive effect, hence acts as electron withdrawing group.

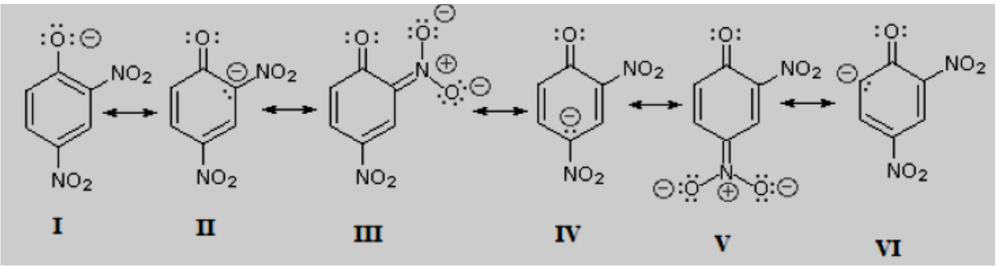
  The position of nitro group on phenol will affect the acidity of phenol.

- A nitro group at -ortho and para-position withdraws electrons from hydroxy group of phenol by stronger –M effect while nitro group at -meta position withdraws electrons by weaker –I effect only, as meta position cannot involve in resonance with hydroxy group.
- Hence o- and p-nitrophenols are more acidic than m-nitrophenol. Similarly as the number of nitro groups increases on phenol, the acidic nature of phenol increases.
- The decreasing order of acidity of nitrophenols is as given below.
    - ***Resonating structures of o-nitrophenoxide ions (o-nitro phenol)***



Resonating structures of p-nitrophenoxide ions (p-nitro phenol)

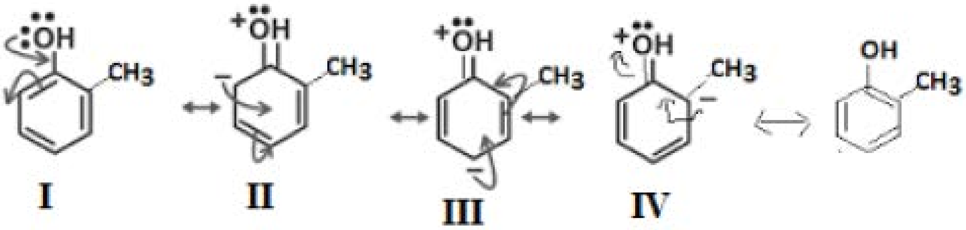




2,**4,6-trinitrophenol > 2,4-dinitrophenol > 4-Nitrophenol > 2-Nitrophenol > Phenol**

- Electron donating groups like amino (-NH2), alkyl (-R) decreases the acidity of phenol.
- For example, cresol or methylphenols are less acidic compare to phenol due to positive inductive effect as well as hyperconjugation of methyl group.

  Resonating structure of o-cresol



- As both of these effects increases the electron density on hydroxy group and results in low acidity of phenols.

- Hyperconjugation can operate only at ortho and para position while inductive effect operates at all the three positions. Therefore o-cresol is least acidic.
- The decreasing order of acidity is as follow-

Phenol > m-cresol > p-Cresol > o-Cresol

Q3a(iv). Drying Oil

Drying oil

- Drying oil is fatty vegetable oil that is capable of chemically reacting with oxygen present in the air and the oil hardens and dries.
- These oils serve as the major component of varnishes, oil paints and other anti-corrosion coatings.
- Drying oils absorb oxygen from the air and are thereby converted into plastic, elastic, resin-like substances.
- Hence, when exposed in a thin layer, as in painting, they form a tough, elastic, waterproof film which adheres tightly to the painted surface and protects it from the weather.
- The two chief drying oils are linseed oil and tung (chinawood) oil, which find wide use in the manufacture of paints, varnishes, artificial rubber, linoleums, and other coverings.

Non-drying oil

- The non-drying oils find a wide variety of industrial uses: they enter into soaps and cleansers, cosmetics, lubricants, leather dressings, and candles.
- They are used in the processes of wool manufacture, especially carding; they are employed in making tin plate and in foundry work. Fats and oils, whether edible or inedible, drying or non-drying, have still other industrial uses.
- They were the primitive illuminants and are still so used in a relatively slight degree. Some of the industrial uses of the fats and oils depend upon their physical properties, others upon their chemical character, to which detailed reference will be made later.
- The drying oils and the non-drying oils is a group of oils which, while they possess the property of absorbing oxygen, do not do so sufficiently to qualify them as drying oils.

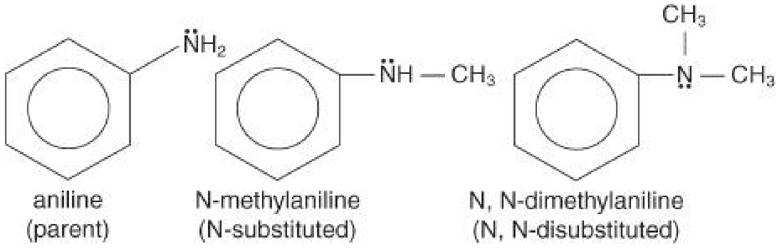
Semi-drying oils

- Semi drying are changed more or less when exposed to the atmosphere, but not as completely as linseed, tung, and certain other drying oils. They are often termed semi-drying oils.
- All gradations are found between completely drying oils and completely non-drying oils. Soy bean oil and corn oil are examples of semi-drying oils.

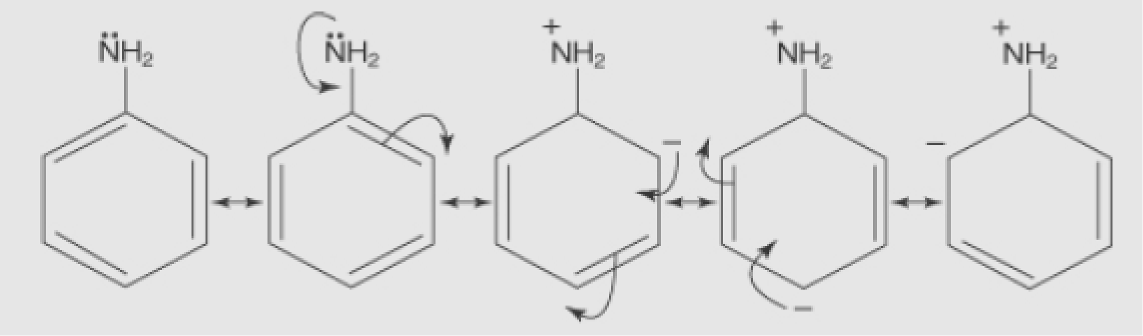
- When exposed to the atmosphere in a thin layer they thicken but do not form a hard, dry film. The film remains sticky and somewhat runny -- tacky is the word often used.
- Under some circumstances appropriate amounts of semi-drying oils are mixed with full-drying oils to make paints of cheaper grades.

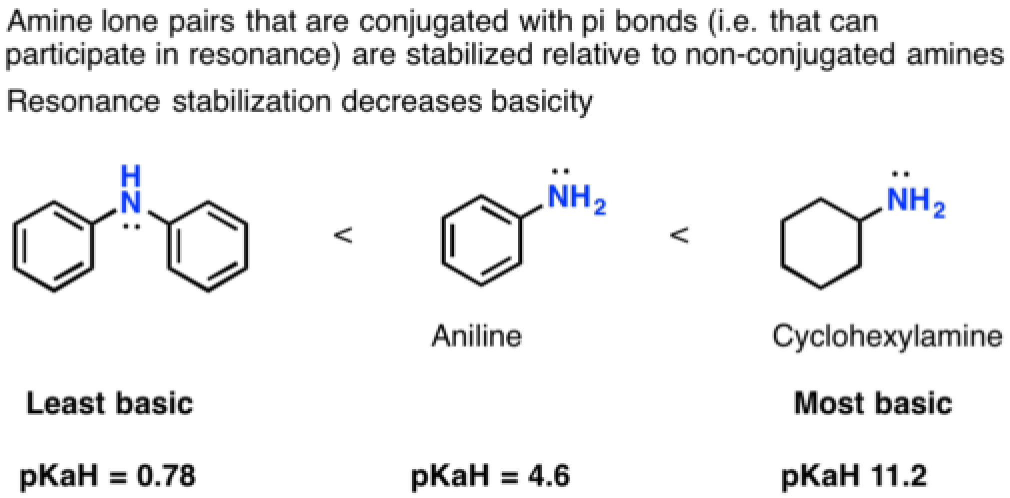
Q3 b(i) Basicity of aromatic amines.

- The lone pair of electrons on the nitrogen atom of amines makes these compounds not only basic, but also good nucleophiles.



- Relative basicity of several nitrogen-containing functional groups: amines, amides, anilines, imines, and nitriles.
- In Aniline (Arylamines), the lone pair on nitrogen (which is free for protonation in a cyclohexylamines) is present in conjugation with the benzene ring, so aniline can't lose electrons as easily show the less basic character.
- The basicity of amines is due to the nitrogen of the amine donating its lone pair of electrons.





Amine lone pairs that are conjugated with pi bonds (i.e. that can participate in resonance) are stabilized relative to non-conjugated amines

Resonance stabilization decreases basicity

-

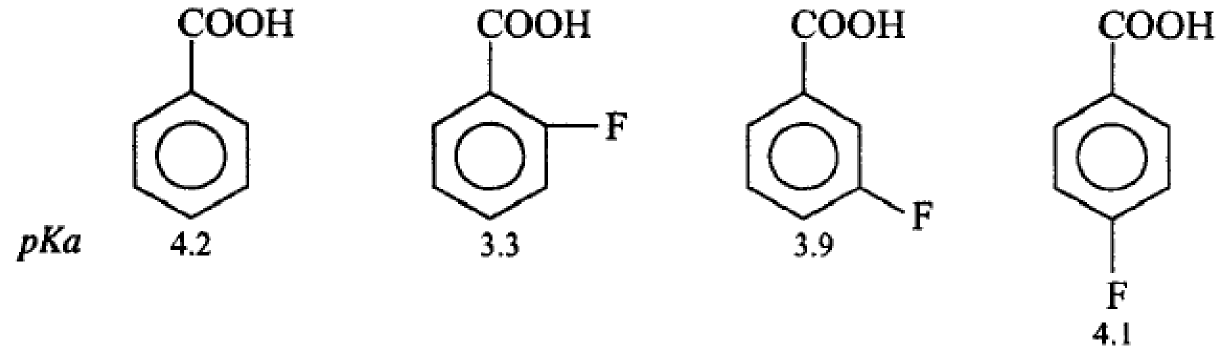
Q3b (ii) Acidity of Aromatic acid

- Acidity of aromatic acids: Aromatic carboxylic acids are stronger acids than aliphatic carboxylic acids.

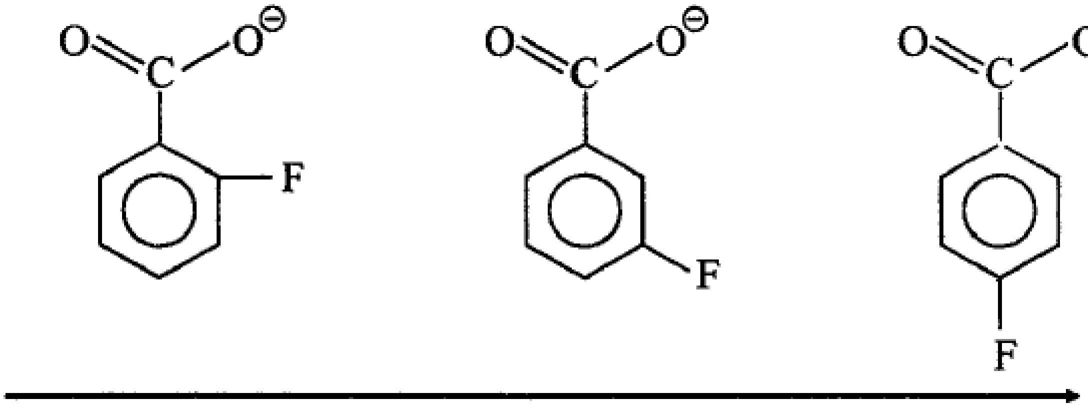
- Benzoic acid, for example, has a *pKa* of 4.2 and is slightl~ stronger acid than acetic acid, *pKa* = 4.8. In benzoic acid, the carboxylic group is bonded to an *sp* -hybridised carbon atom, which is more electronegative than an *sp3* hybridised carbon atom.

- The greater electronegativity of an *sp2* hybridised carbon atom is used to explain the apparent electron-withdrawing inductive effect that the phenyl group demonstrates in stabilising the carboxylate anion.

- Acidity of substituted benzoic acids depends on the nature and position of the substitutent. For example, all the fluorobenzoic acids are more acidic than benzoic acid itself.



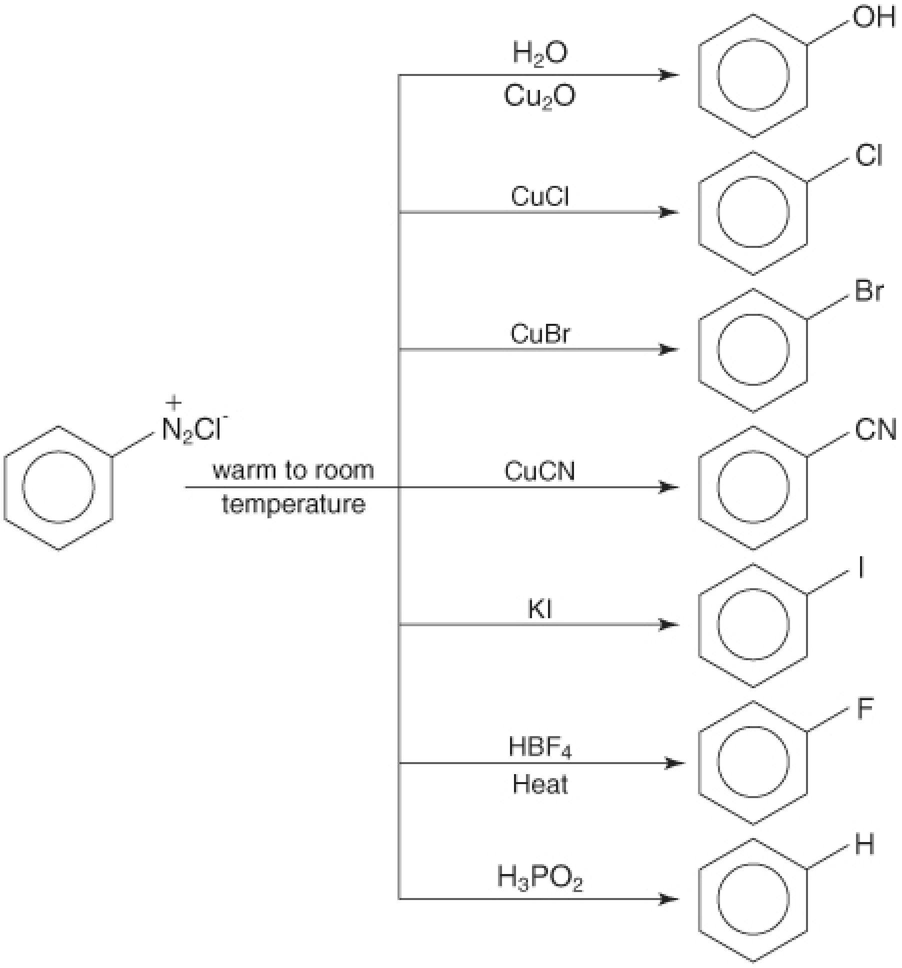
- o-Fluorobenzoic acid, in which the fluorine atom is nearest to the carboxylic group, is the strongest acid of the four, p-fluorobenzoic acid, in which the fluorine atom is farthest from the carboxylic group, is only slightly more acid than benzoic acid.



(i) Increase in the distance between $CO\overset{\ominus}{O}$ and F
(ii) Decrease in –I effect of F
(iii) Decrease in stability
(iv) Decrease in acidity of the conjugate acid

Q3b (iii) Synthetic application of aryl diazonium salts.

Diazonium salts of aromatic amines are very useful as intermediates to other compounds. Because aromatic diazonium salts are only stable at very low temperatures (zero degrees and below), warming these salts initiates decomposition into highly reactive cations. These cations can react with any anion present in solution to form a variety of compounds.



$\overset{+}{N}_2Cl^-$
warm to room temperature
H_2O
Cu_2O
OH
CuCl
Cl
CuBr
Br
CuCN
CN
KI
I
HBF_4
Heat
F
H_3PO_2
H