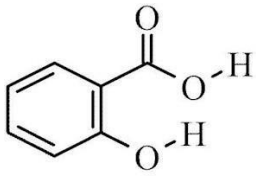
UNIT- II: AROMATIC ACIDS

Aromatic acids are a type of aromatic compound. Included in that class are substances containing an aromatic ringand an organic acid functional group. There are several categories of aromatic acids including:

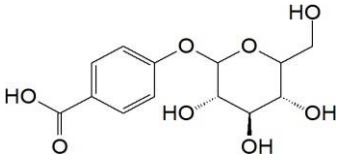
(i) ***Phenolic acids:*** substances containing an aromatic ring and an organic carboxylic acid function (C_6-C_1 skeleton).

(ii) ***Aromatic amino acids*** (e.g. Phenylalanine, Tryptophan)

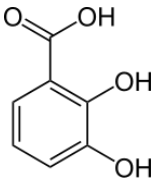
Phenolic acids	***Monohydroxybenzoic acids***	*Aglycones*	Salicylic acid
		Glycosides	*p*-Hydroxybenzoic acid glucoside
	Dihydroxybenzoic acids	2,3-Dihydroxybenzoic acid (Hypogallic acid); Gentisic acid	
	Trihydroxybenzoic acids	Gallic acid	
	Other phenolic acids	Vanillin; Ellagic acid	
Hydroxycinnamic acids	Caffeic acid; Cinnamic acid		
Aromatic amino acids	Phenylalanine; tryptophan		



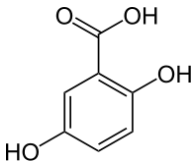
Salicylic acid



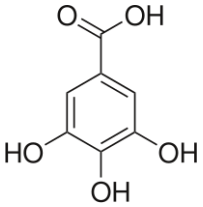
p-Hydroxybenzoic acid glucoside



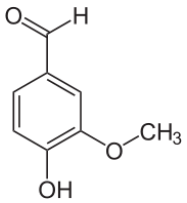
2,3-Dihydroxybenzoic acid (Hypogallic acid)



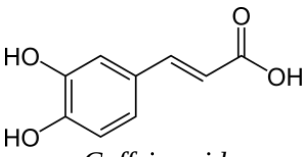
Gentisic acid



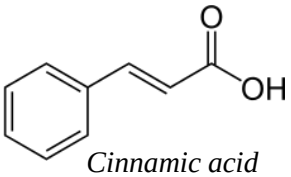
Gallic acid



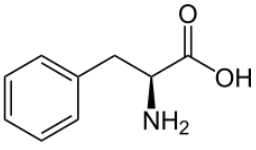
Vanillin



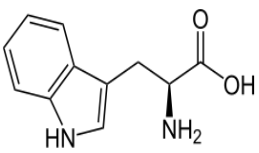
Caffeic acid



Cinnamic acid



Phenylalanine

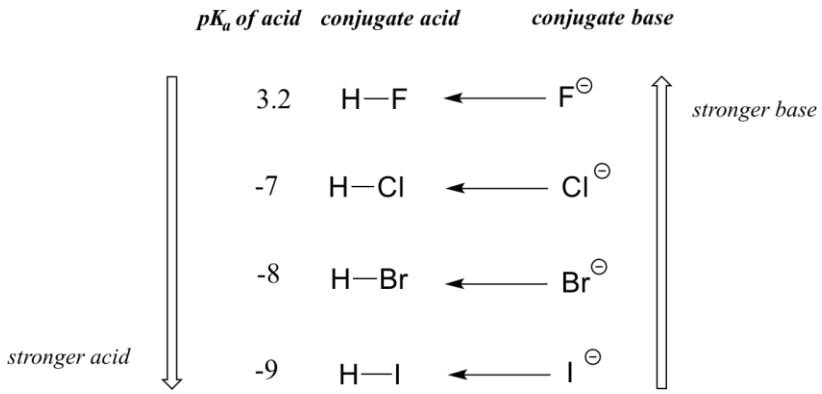


Tryptophan

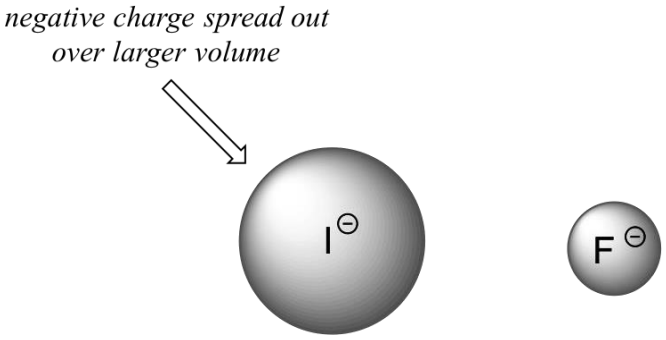
❖ How Substituents Affect the Strength of an Acid

A: Periodic trends

- First, we will focus on individual atoms, and think about trends associated with the position of an element on the periodic table.
- When moving vertically within a given column of the periodic table, we again observe a clear periodic trend in acidity. This is best illustrated with the halo acids and halides: basicity, like electronegativity, increases as we move up the column. Conversely, acidity in the haloacids increases as we move down the column.



- In order to make sense of this trend, we will once again consider the stability of the conjugate bases. Because fluorine is the most electronegative halogen element, we might expect fluoride to also be the least basic halogen ion. But in fact, it is the least stable, and the most basic! It turns out that when moving vertically in the periodic table, the size of the atom trumps its electronegativity with regard to basicity. The atomic radius of iodine is approximately twice that of fluorine, so in an iodide ion, the negative charge is spread out over a significantly larger volume:



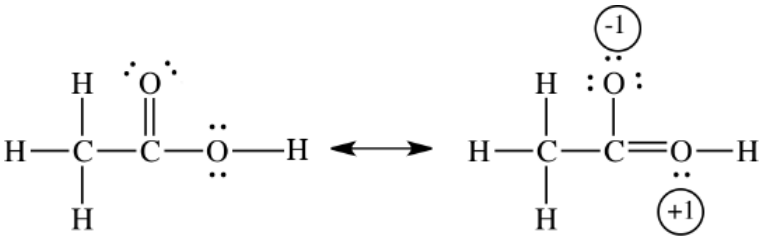
B: Resonance effects

- A huge stabilizing factor for a conjugate base is if the negative charge can be delocalized through resonance.
  - ✓ Consider the acidity of **methanol** and **acetic acid**.

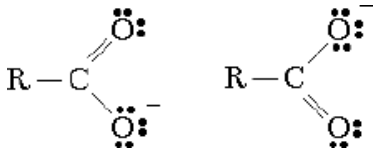
$$CH_3OH + H_2O \rightleftharpoons CH_3O^- + H_3O^+;\ pK_a = 15$$

$$CH_3COOH + H_2O \rightleftharpoons CH_3COO^- + H_3O^+;\ pK_a = 5$$

- In methoxide ion, the negative charge is localized (concentrated) on the oxygen atom.
- Resonance stabilizes both acetic acid and acetate ion,
- In acetic acid, the stabilization is small because the resonance contribution involves separation of charge.



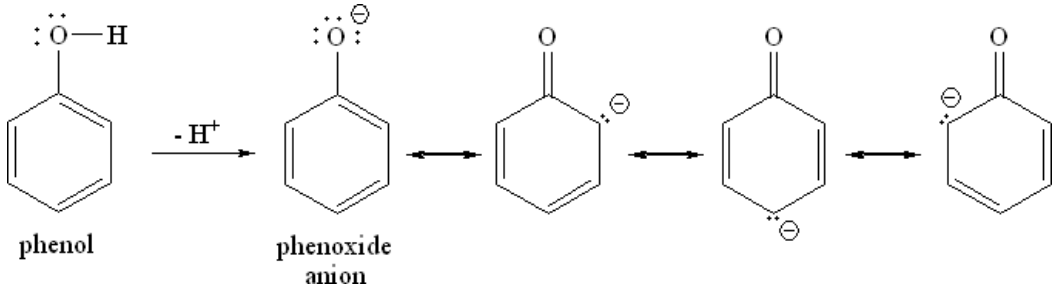
- In acetate ion, there is no separation of charge.



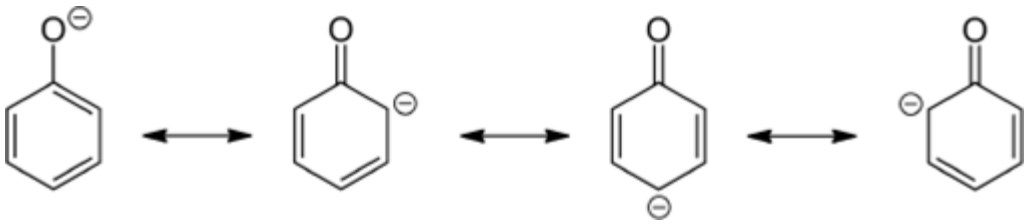
- Instead, the negative charge is delocalized (spread out) over three atoms. This delocalization produces a lower-energy state.
- If the products of a reaction are more stable than the reactants, the position of equilibrium will lie to the right.
- So, the resonance stabilization of acetate ion makes acetic acid more acidic than methanol.
  - ✓ Similarly resonance makes **phenol** more acidic than **ethanol**.
- There is no resonance stabilization in the ethoxide ion.

$$CH_3CH_2OH + H_2O \rightleftharpoons CH_3CH_2O^- + H_3O^+; pK_a = 17$$

- Resonance stabilizes both phenol and phenoxide ion by delocalization of electrons into the ring.
- However, this localization in phenol involves separation of charge and makes the oxygen atom positive.



- The same delocalization in phenoxide ion provides much more stabilization because there is no charge separation.



- The position of equilibrium lies to the right. $pK_a = 10$
- Thus, phenol is 10^7 times as acidic as ethanol because resonance stabilizes the phenoxide ion.

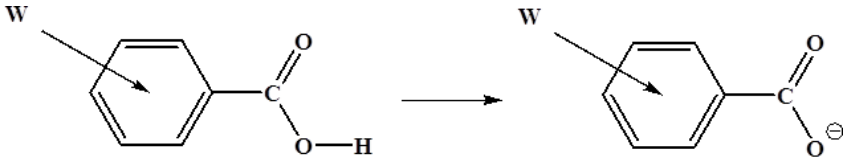
C:Inductive effects

- The inductive effect plays a vital role in deciding the acidity and basicity of a molecule.
- Groups having **+I effect** attached to a molecule increases the overall electron density on the molecule and the molecule is able to donate electrons, making it basic.
- Similarly, groups having **-I effect** attached to a molecule decreases the overall electron density on the molecule making it electron deficient which results in its acidity.
- As the number of **-I groups** attached to a molecule increases, its **acidity increases**; as the number of **+I groups** on a molecule increases, its **basicity increases**.

❖ Acidity of Substituted Benzoic Acids

1. Electron-withdrawing groups

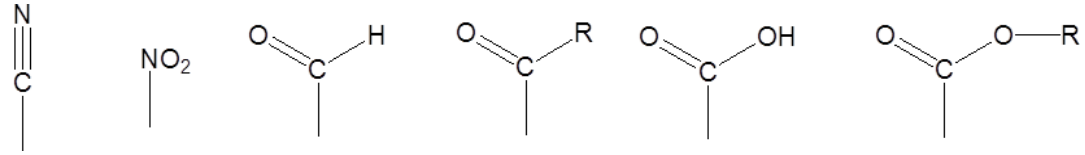
- The conjugate base of benzoic acid is stabilized by **electron-withdrawing groups**. This makes the acid more acidic.



W is an Electron-Withdrawing Group

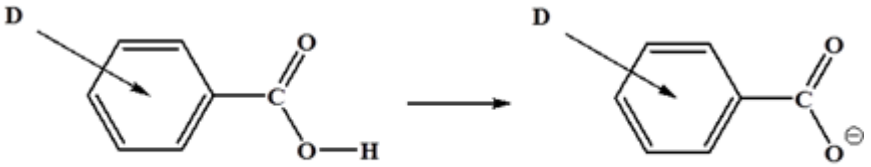
The carboxylate anion is destabilized

- **Electron-withdrawing groups** deactivate the benzene ring to electrophilic attack and make benzoic acids more acidic.



2. Electron-donating groups

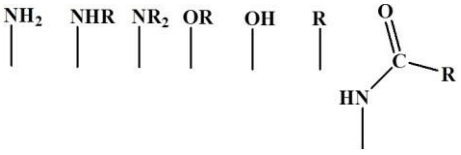
- The conjugate base of benzoic acid is destabilized by **electron-donating groups**. This makes the acid less acidic



D is Electron-Donating Group

The carboxylate anion is destabilized

- **Electron-donating groups** activate the benzene ring to electrophilic attack and make benzoic acids less acidic.

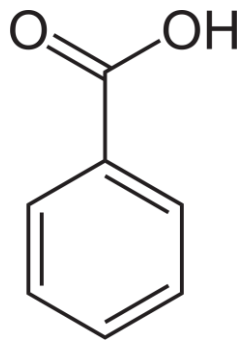


Dissociation Constants of *p*-Substitu		Benzoic Acid
X	**pKa**	
—$N(CH_3)_2$	6.03	Weaker acid
—$NHCH_3$	5.04	
—OH	4.57	
—OCH_3	4.50	
—$C(CH_3)_3$	4.38	
—H	4.20	
—Cl	4.00	
—Br	3.96	
—CHO	3.77	
—CN	3.55	
—NO_2	3.43	Stronger acid

➢ Hydroxyl group: electron-donating or electron releasing group.

- It is behaves differently for different systems.
  - **For aliphatic systems with no conjugation**, it behaves as an electron withdrawing group due to -I effect.
  - **For aliphatic systems with conjugation**, it behaves as an electron withdrawing group by -I effect and an electron donating group by mesomeric effect.
  - **For aromatic systems**,
    - When it is in ***ortho* position**, it behaves as an **electron withdrawing group** by **-I effect** and an electron donating group due to **mesomeric effect**.
    - When it is in ***meta* position**, it behaves as an **electron withdrawing group** by **-I effect**. Since the distance has increased as compared to ortho, its effect decreases.
    - When it is in ***para* position**, it behaves as an electron donating group by **mesomeric effect**. Since the distance has increased further, the electron withdrawing nature by **-I effect is negligible**.

Benzoic acid



Preferred IUPAC name	Benzoic acid
Systematic IUPAC name	Benzenecarboxylic acid
Other names	Carboxybenzene, Dracylic acid, Phenylmethanoic acid
Chemical formula	$C_7H_6O_2$
Molar mass	122.123 g·mol^{-1}
Appearance	Colorless crystalline solid
Density	1.2659 g/cm^3 (15 °C)
Melting point	122 °C
Solubility in water	Insoluble [1.7 g/L (0 °C); 2.7 g/L (18 °C); 3.44 g/L (25 °C); 5.51 g/L (40 °C); 21.45 g/L (75 °C); 56.31 g/L (100 °C)]
Solubility	soluble in acetone, benzene, CCl4, CHCl3, alcohol, ethyl ether, hexane, phenyls, liquid ammonia, acetates

Uses

- Benzoic acid used as precursor to plasticizers.
- Benzoic acid and its salts are used as food preservatives.
- Benzoic acid is a constituent of ***Whitfield's ointment*** which is used for the treatment of fungal skin diseases such as tinea, ringworm, and athlete's foot. As the principal component of gum benzoin, benzoic acid is also a major ingredient in both tincture of benzoin and Friar's balsam.
- Use as topical antiseptics and inhalant decongestants.
- Benzoic acid is a precursor to benzoyl chloride, $C_6H_5C(O)Cl$ by treatment with thionyl chloride, phosgene or one of the chlorides of phosphorus. Benzoyl chloride is an important starting material for several benzoic acid derivatives like benzyl benzoate, which is used in artificial flavours and insect repellents.

➢ Why benzoic acid more soluble in an aqueous alkaline solution than neutral or acid solution?

- Benzoic acid is first and foremost a weak acid and thus dissociates partially in water:

$$C_6H_5COOH + H_2O \rightleftharpoons C_6H_5COO^- + H_3O^+$$

- From this equation and the structure of benzoic acid, we can concluded three things:

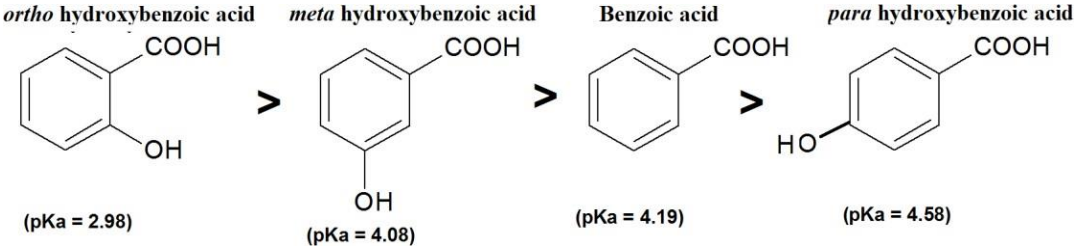
Reason 1:

- In a neutral solution, benzoic acid is slightly soluble in water. It is nearly insoluble in cold water but highly soluble in hot water.
- This is because even though water can form hydrogen bonds with the carboxylate functional group, the bulk of the benzoic acid is still the large benzene ring, which can only form ***Van der Waals*** **forces of attraction** with water (significantly weaker than hydrogen bonding). Also, even though benzoic acid can dissociate in water, as it is a weak acid, it can only dissociate partially, which is insufficient to dissolve benzoic acid. Thus, benzoic acid is insoluble in cold water.
- However, as temperature increases, more energy is present to overcome the hydrogen bonding between water molecules to form weaker Van der Waals forces of attraction between benzoic acid and water. Also, more energy is present to drive the dissociation of benzoic acid forward, as it is endothermic, thus benzoic acid becomes more soluble in hot water.

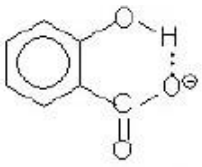
Reason 2: In ***alkaline medium***, benzoic acid becomes soluble. The abundant **OH^- ions** will react fully with benzoic acid in acid-base reaction to form water and benzoate ion, which now is soluble in water due to strong ion-dipole forces of attraction.

Reason 3: In acidic medium, benzoic acid becomes insoluble. The increase in concentration of **H^+ ions** will shift the position of equilibrium of dissociation of benzoic acid to the left, causing benzoic acid to be hardly soluble in acidic medium.

➢ Why *ortho* hydroxy benzoic acid more acidic than *para* hydroxybenzoic acid?



- Because ***ortho*** **hydroxy benzoic acid** is **more acidic** because in the ***ortho*** **isomer**, strong hydrogen bridge will be formed between the **phenolic -OH-** and the **carboxylate ion** and this will tend to stabilize the conjugate **crboxylate base** hence increasing the acidity.



The OH in salicylic acid (the ortho-derivative) will stabilize the anion due to hydrogen bonding.

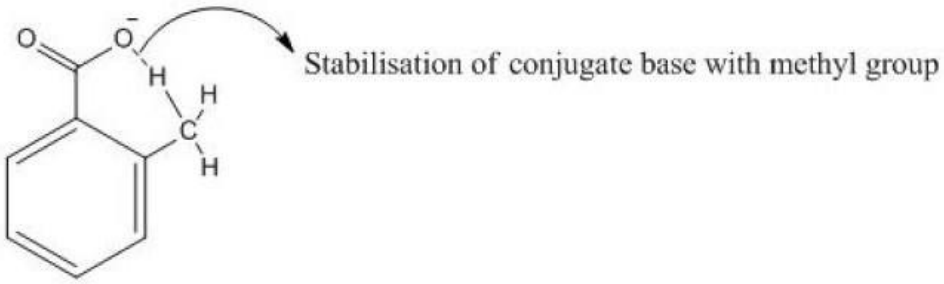
- For the ***para*** **isomer**, the **mesomeric effect** makes the compound **less acidic** in comparison with **benzoic acid**.
- For the ***meta*** **isomer** a minor inductive effect operates, but no resonance effect, which makes it **slightly more acidic**.

➢ Why is *o*-methyl benzoic acid more acidic than *p*-methyl benzoic acid?

- This is a special effect shown by benzene and its derivatives, but is not necessarily a steric effect. Nearly all ***ortho***-substituted **benzoic acids** are stronger than the benzoic acid.
- Benzoic acid is a resonance hybrid, and so the carboxyl group is coplanar with the ring. Any ***ortho***- substituent tends to prevent this **coplanarity**. Thus, resonance is diminished resulting in increased acidic strength.

➢ Why ortho methyl benzoic acid is more acidic than para fluoro benzoic acid.

- In the case of O-methyl benzoic acid, the methyl group attached to the benzene ring is stabilized the conjugate base formed. But in case of Para fluoro benzoic acid, there is no such stabilization is not seen.
- Therefore, ortho methyl benzoic acid is more acidic than para fluoro benzoic acid.



o-Methyl benzoic acid

➢ What is ortho effect of Benzoic acid?

- Due to ortho effect, in most cases, –***ortho***-isomer of Benzoic acid is strongest Acid as compared to Simple benzoic acid or ***meta*** & ***para***-isomers & ***ortho***- isomer.
- Because in case of ***ortho***-substituted benzoic acids, due to steric inhibition, the **-COOH** group goes out of plane and hence decrease in resonance stabilisation of acid as compared to anion make it better acid.
- Acidic Character order:

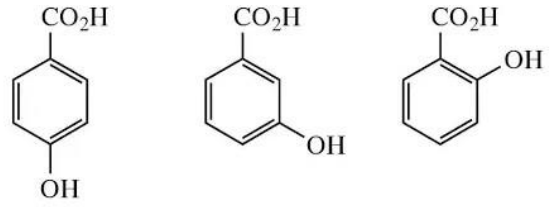
romobenzoic acid [3.1] > *m*-BromoBenzoic acid [3.93] > *p*-BromoBenzoic acid [4.1] > Benzoic acid [4.17]

hloroBenzoic acid [2.89] > *m*-ChloroBenzoic acid [3.82]> *p*-ChloroBenzoic acid [3.98]> Benzoic acid [4.17]

o-FluoroBenzoic acid [3.27] > *m*-FluoroBenzoic acid [3.87]> *p*-FluoroBenzoic acid [4.14]> Benzoic acid [4.17]

o-Toluic acid [3.89] > Benzoic acid [4.17]> *m*-Toluic acid [4.28] > *p*-Toluic acid [4.35]

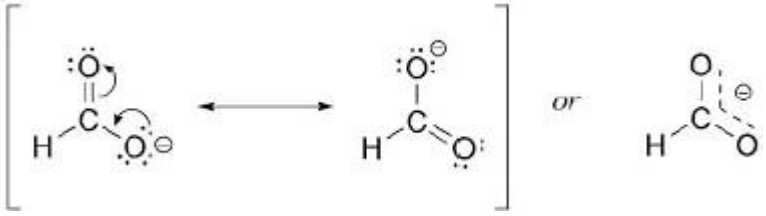
(**Note**- pKa values are given in brackets; less pKa means more acidic)



pK_a (CO_2H) 4.6 pK_a (CO_2H) 4.1 pK_a (CO_2H) 3.0

➢ Why is benzoic acid stronger than acetic acid but weaker than formic acid?

- Acidity of carboxylic acid depends on the type of substituent attached to it.
- An electron withdrawing group increases the acidity while an electron donating group decreases the acidity. The carboxylate ion obtained due to loss of proton should be stable. More the stability, more is the acidity.
- The electron withdrawing group i.e. phenyl will increase the stability of the anion as it will attract electrons towards itself. Whereas, an electron donating group i.e. methyl will reduce the stability as it will donate electrons to the ion.
- In case of **formic acid**, there is no group attached. However it is even more stable than benzoic acid because the negative charge is present only over the oxygen atoms, thereby increasing their electronegativity and making it comparatively easier to lose a proton.



- Hence, order of acidity: $CH_3COOH < C_6H_5COOH < HCOOH$

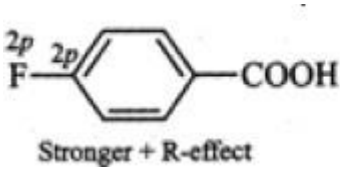
  Formic acid pKa = 3.751

  Benzoic acid pKa = 4.204

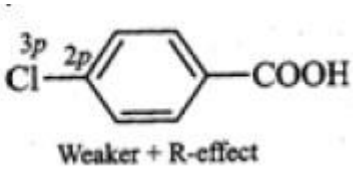
  Acetic acid pKa = 4.756

➢ Why *para* fluoro benzoic acid is is less acidic than *para* chloro benzoic acid?

- Since halogens are more electronegative than carbon and also possess lone pairs of electrons, therefore, they exert both **–I** and **+R**- effects.
- Now in **F**, the lone pairs of electrons are present in **2p-orbitals** but in they are present in **3p-orbitals**. Since **2p-orbitals** of **F** and **C** are of almost equal size, therefore, the **+R-effect** is more pronounced in ***p*-fluorobenzoic** acid than in ***p*-chlorobenzoic acid.**
- Thus, in ***p*-fluorobenzoic acid**, **+R-effect** outweighs (greater) than the **-I -effect** but **is *p*-chlorobenzoic acid**, it is the **-I -effect** which outweighs than the **+R-effect**.
- Consequently, ***p*-fluorobenzoic acid** is a weaker acid than ***p*-chlorobenzoic acid**.



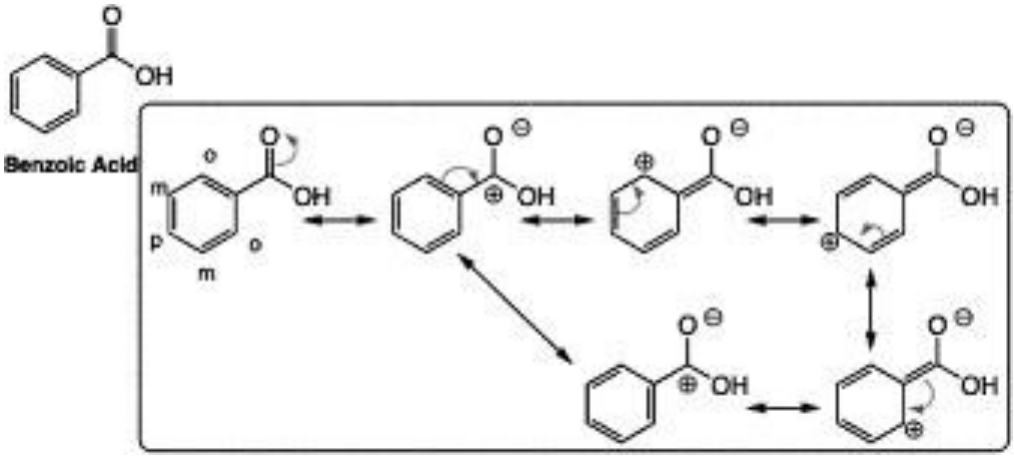
***p*-fluorobenzoic acid**

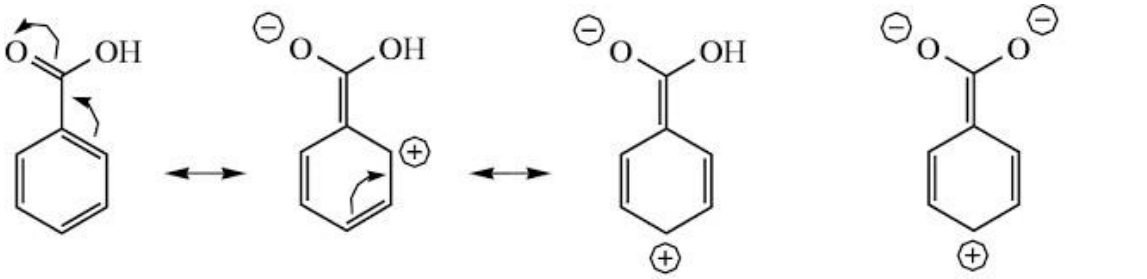


***p*-chlorobenzoic acid**

➢ What are the resonance structures of benzoic acid?

- The benzoic acid shows resonance. It is more acidic than aliphatic acid because the carboxylate ion is stabilised by resonance.
- The resonating structures are as follows:



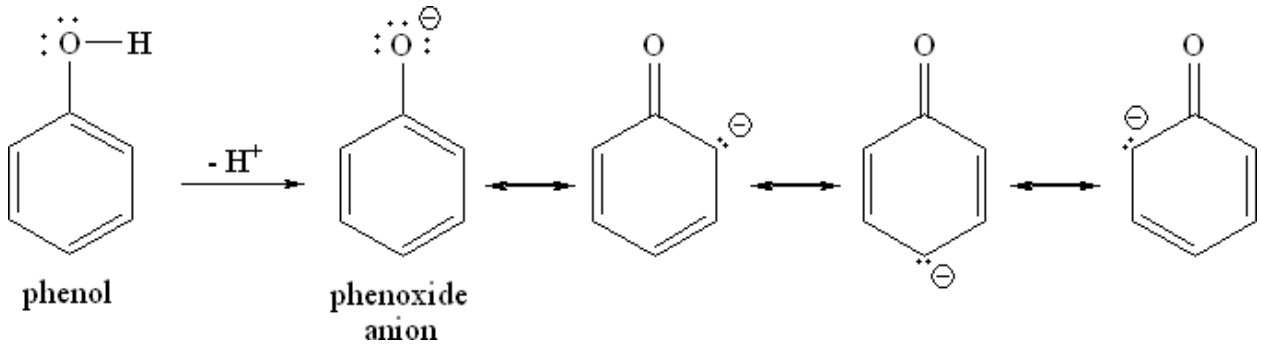


resonance favours non-ionized benzoic acid

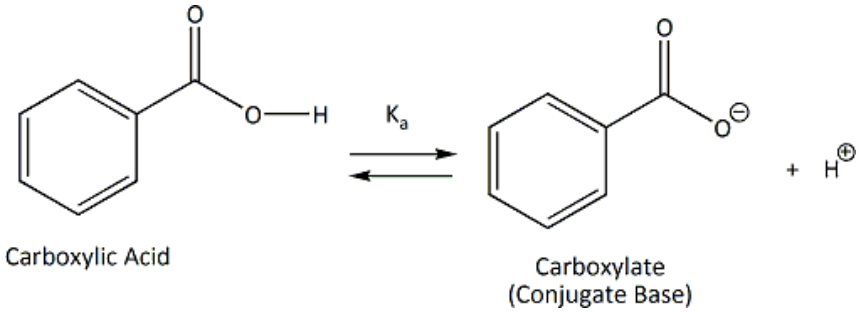
resonance unfavourable in anion

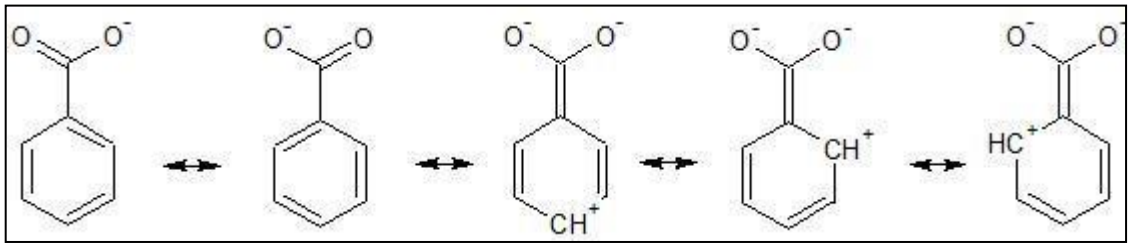
➢ Which is more acidic, phenol or benzoic acid?

- In fact, all carboxylic acids are more acidic than phenols. The pKa of all carboxylic acids is of the order 3–7 whereas the pKa of all phenols is of the order 7-10. Lesser the pKa greater is the acidity.
- When **phenol** dissociates, the negative charge is spread throughout the benzene ring by resonance. This stabilises the phenoxide ion somewhat.



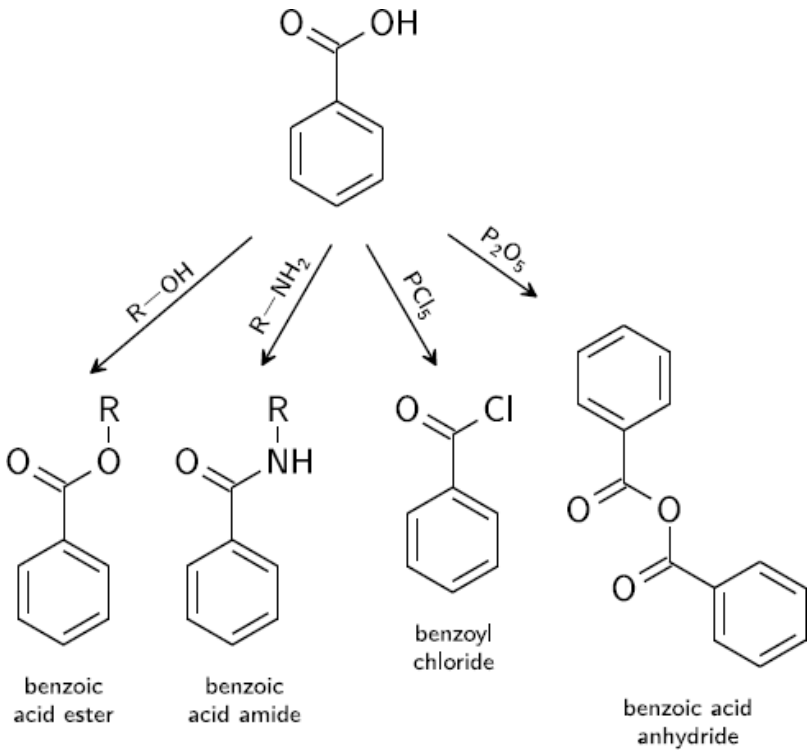
- When **benzoic acid** dissociates, the negative charge is spread over the two oxygens of the carboxylate group. While this is a smaller area and smaller number of atoms over which the charge is spread, the important fact is that it involves an extra oxygen. Since oxygen is a more electronegative than carbon, it's much better at accepting a negative charge. Thus a carboxylate group is more stable than a phenoxide, making benzoic acid comparatively more acidic.



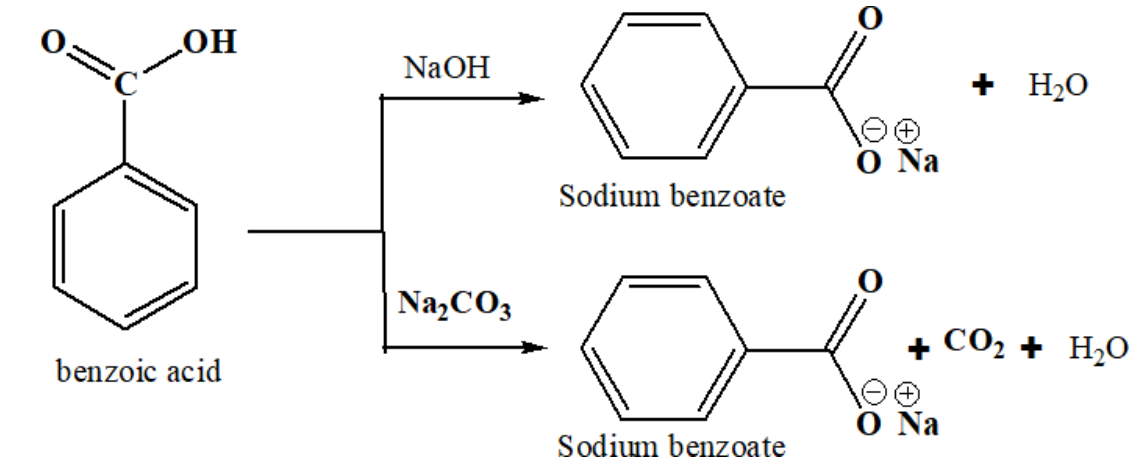


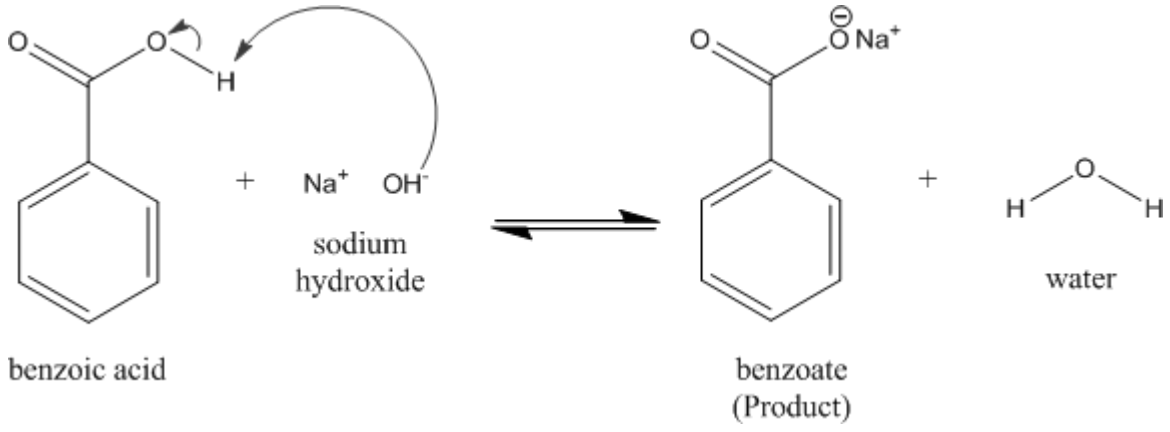
❖ Reactions of Benzoic Acid

- **Reaction of –COOH group**



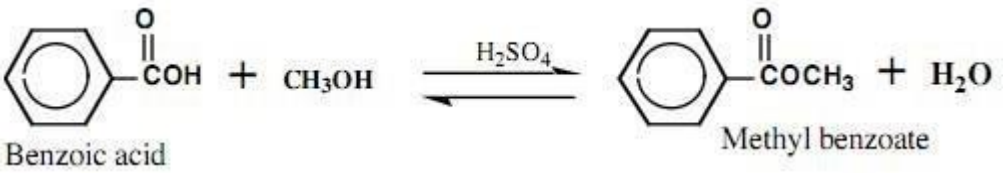
1. Salt formation: Benzoic acid reacts with sodium hydroxide or sodium carbonate to form sodium benzoate.





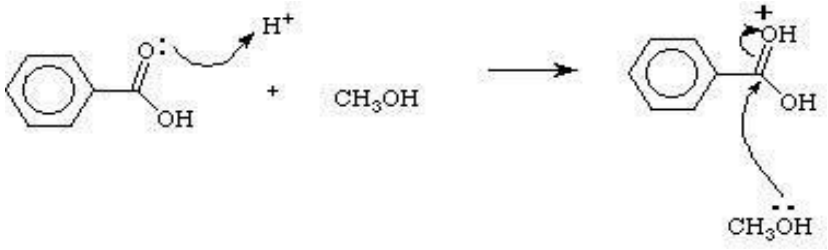
2. Esterification of benzoic acid:

- The acid-catalyzed reaction between a carboxylic acid and an alcohol to give an ester and water.
- The alcohol is usually used as the solvent, and therefore present in excess.
- The acid must be strong; sulfuric acid, phosphoric acid, or p-toluenesulfonic acid are often used for this purpose.



- ***The esterification mechanism***

Step 1: The dissociation of sulphuric acid will produce hydrogen ion which can be used to protonates the carbonyl group in benzoic acid. The carbonyl group is protonated reversibly and caused the positive charge of carbonyl group to be increased. Thus this increases the reactivity of carbonyl group towards nucleophile. The C-O double bond is broken in order to stabilize the OH^+ group to form hydroxyl group in the benzoic acid molecule. The methanol acts as a nucleophile attacks the benzoic acid.

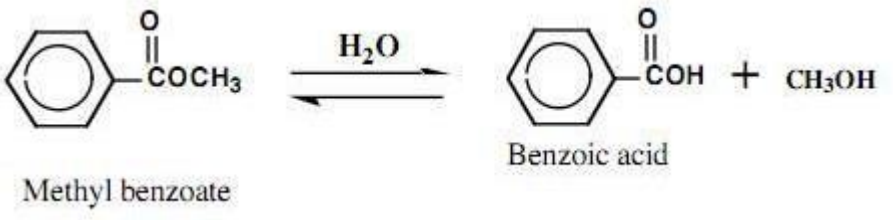


Step 2: The methanol successful attacked the carbonyl group to form a new C-O bond to the carboxyl group in the benzoic acid to form a tetrahedral intermediate. This is called nucleophilic addition. The oxygen atom in the carboxyl group in benzoic acid is more electronegative due to its lone pair electron. The lone pair electron in the particular electron attracts the hydrogen atom from the methanol to form oxonium ion. Now, the oxygen atom in the methanol becomes unstable and hence the C-H bond will tend to be broken down. The electron between the C-H bond will delocalised to the oxygen atom of the methanol. The formation of oxonium ion in the carboxyl group in benzoic acid tends to be released from the intermediate to form water. Eventually, another hydroxyl group will donate the lone pair electron to the attached oxygen atom to form a more stable intermediate.

Step 3: The hydrogen atom in the ester intermediate will be attacked the acid in diagram 3 and the acid catalyze is regenerated. Thus, finally the methyl benzoate is formed.

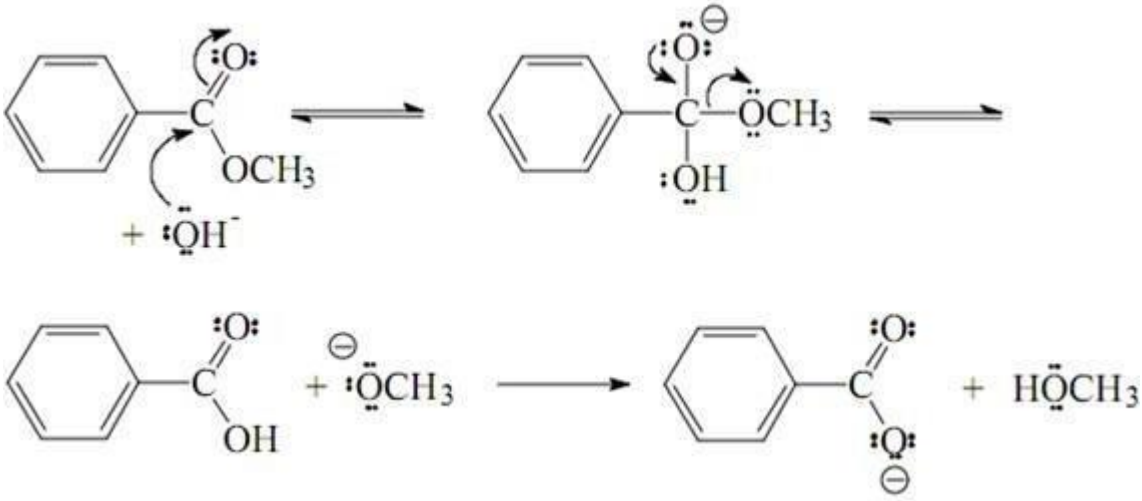
- **Note By:**

- During esterification, the hydrolysis process start to begin once the ester is being produced. The water produced in esterification is used back in the hydrolysis to hydrolyze the ester to form the carboxylic acid and alcohol. The process is a continuous reversible process until the equilibrium is reached. The hydrolysis process would be the following equation:

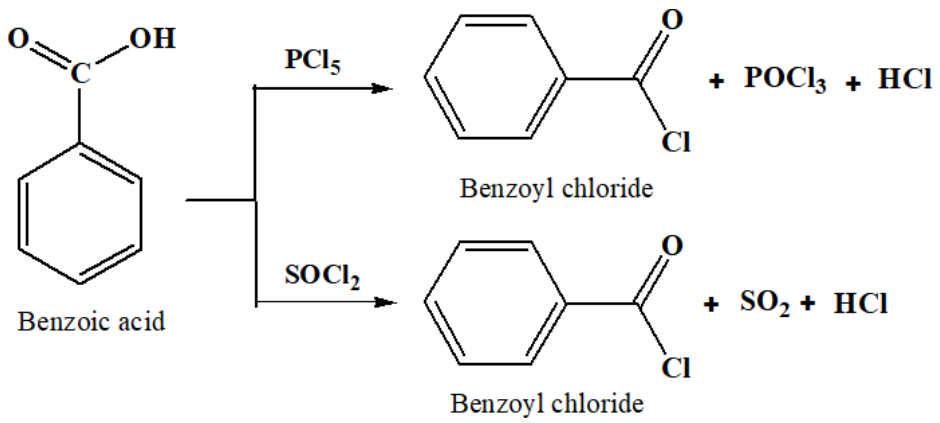


Methyl benzoate Benzoic acid

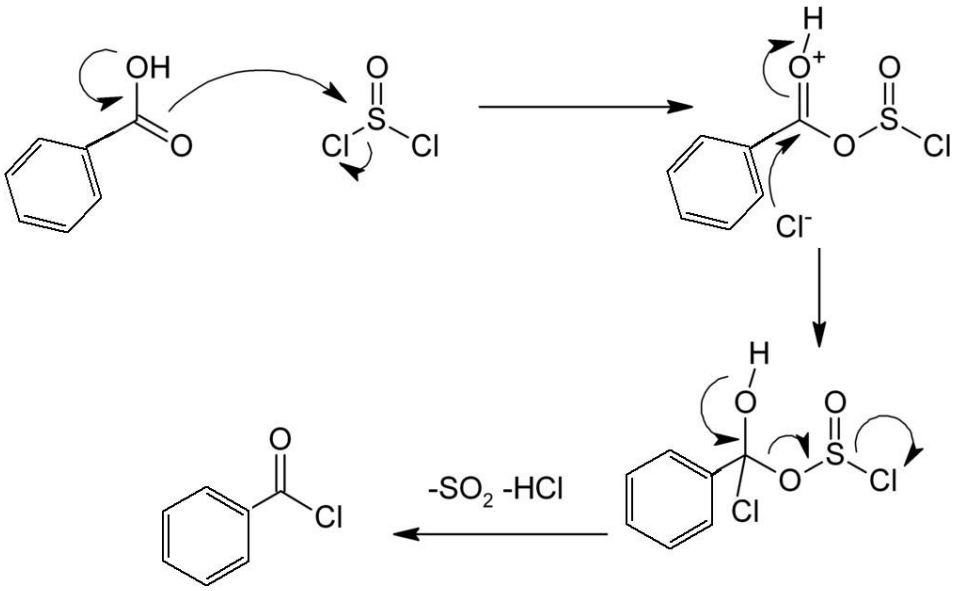
- The hydrolysis process must under acidic or basic condition in order to break down the stable ester molecule. To avoid the hydrolysis process, the water could be removed from the mixture. According to Le Chatelier's principle, the equilibrium position will shift to the product side if water is being removed. Another method to increase yield of ester is by adding more alcohol into the mixture. Hence, more ester could be generated when the amount of alcohol increased which shift the equilibrium to product side.



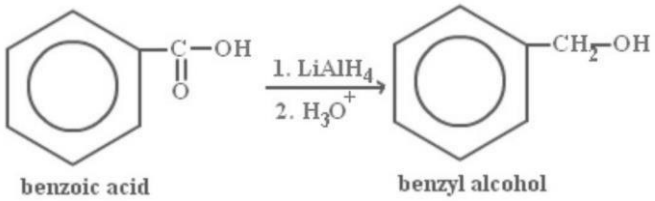
3. Acyl halide formation: Benzoic acid reacts with phosphorus pentachloride or thionyl chloride to form benzoyl chloride.



- ***The Acyl halide formation reaction mechanism***



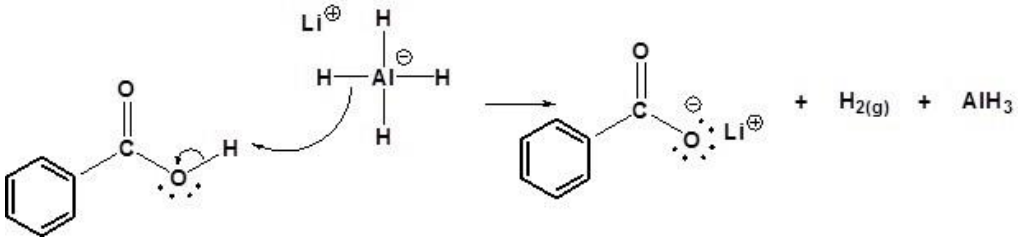
4. Reduction of Benzoic acid to Benzoyl alcohol: Benzoic acid undergoes reduction with lithium aluminium hydride to give benzyl alcohol.



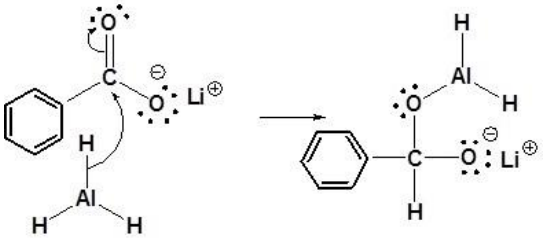
benzoic acid benzyl alcohol

- ***Reduction of Benzoic acid to Benzoyl alcohol reaction mechanism***

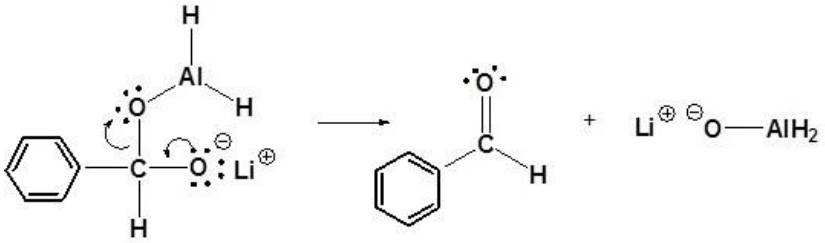
Step I: Deprotonation



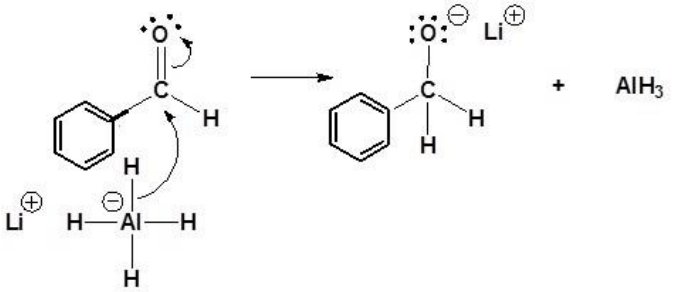
Step II: Nucleopilic attack by the hydride anion



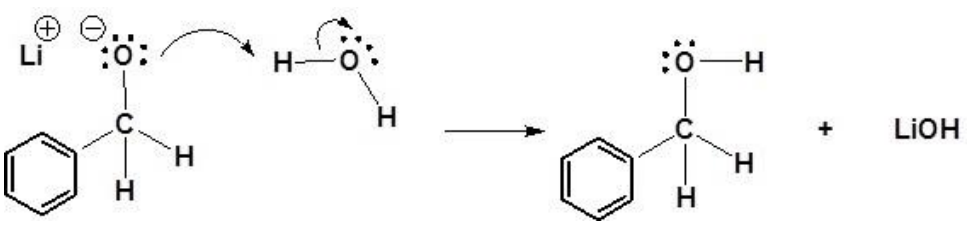
Step III: Leaving group removal



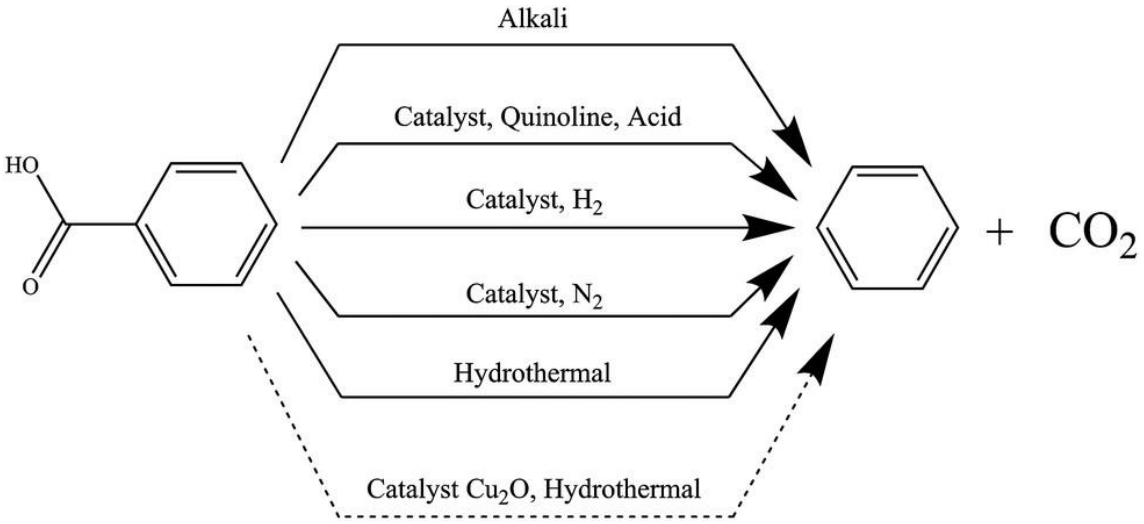
Step IV: Nucleopilic attack by the hydride anion



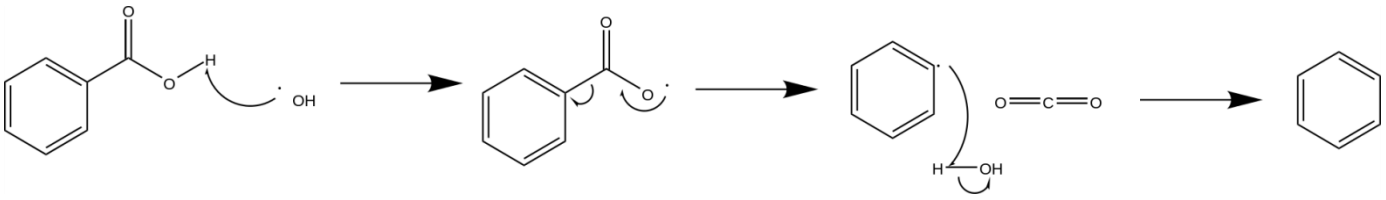
Step V: The alkoxide is protonated

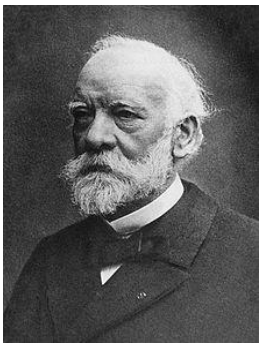


5. Decarboxylation of Benzoic acid:



- The proposed mechanism begins with hydrogen abstraction by the hydroxyl radical, which itself is produced by the Cu^{2+}-catalysed reduction of dioxygen by ascorbic acid:



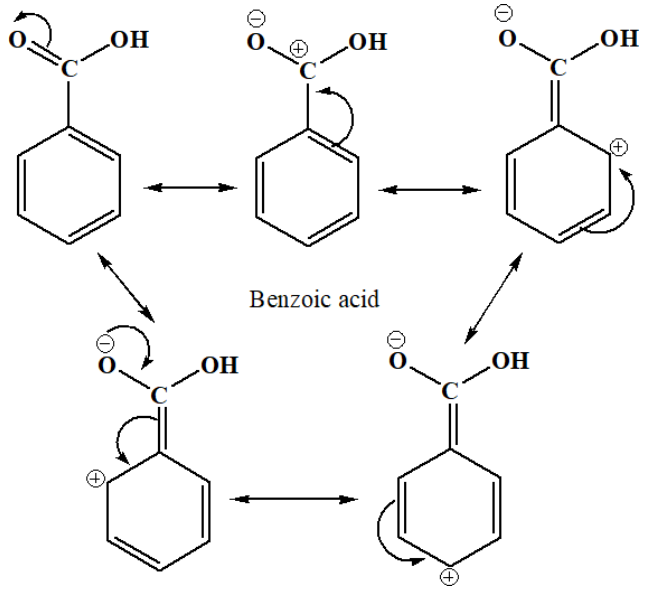


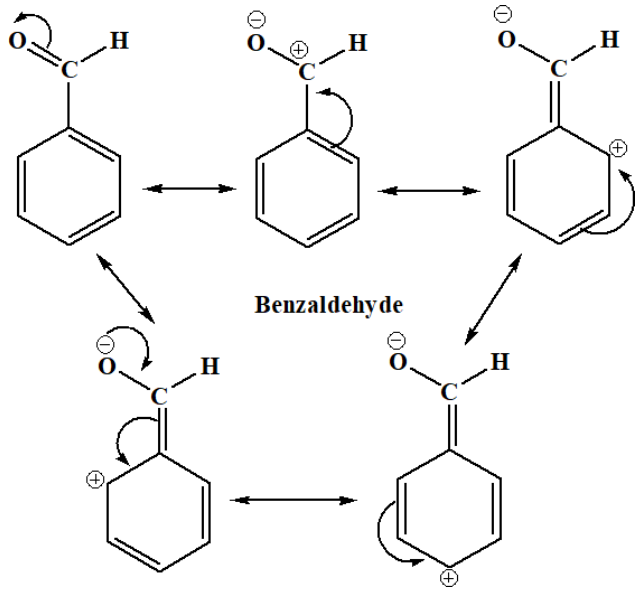
- ***Sir Charles Friedel*** (12 March 1832 – 20 April 1899) was a French chemist and mineralogist.
- Developed the Friedel-Crafts alkylation and acylation reactions with James Crafts in 1877, and attempted to make synthetic diamonds.
- He was a student of *Sir Louis Pasteur* at the Sorbonne. In 1876, he became a professor of chemistry and mineralogy at the Sorbonne.
- **Awards**: Davy Medal (1880)

- ***Sir James Mason Crafts*** (March 8, 1839 – June 20, 1917) was an American chemist, mostly known for developing the Friedel-Crafts alkylation and acylation reactions with Charles Friedel in 1876.
- ***Sir James Crafts*** was born in Boston, Massachusetts and graduated from Harvard University in 1858. Although he never received his Ph.D., he studied chemistry in Germany at the Academy of Mines (1859) of Freiberg, and served as an assistant to Robert Bunsen at Heidelberg, and then with Wurtz in Paris (1861).
- Crafts returned to the United States in 1865. In 1868, he was appointed as the first professor of chemistry at the newly founded Cornell University in Ithaca, New York, where he remained until 1870.
- Craft's investigations were largely in the field of organic chemistry, but his name is connected also with many interesting achievements in physics and in physical chemistry. He invented a new hydrogen thermometer; measured the densities of iodine at very high temperatures; demonstrated an interesting regularity in the variation of the boiling points of chemically allied substances with the external pressure; prepared a number of new compounds of the element silicon, which are interesting because of their chemical resemblance to the corresponding compounds of carbon; and also prepared new compounds of arsenic.

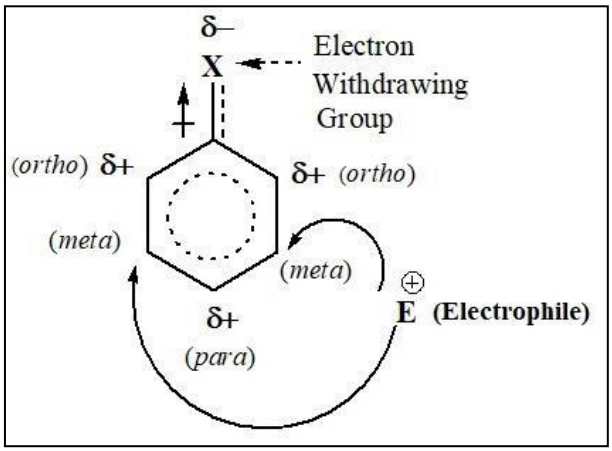
➢ Why benzoic acid and benzaldehyde are *meta* directing group?

- In the case of Benzoic acid, since the **-COOH group** is an **electron withdrawing group**, because of resonance (**-M effect**), the carbon atoms at the ***ortho*** and ***para*** positions get a **positive charge**. Thus, the incoming **electrophile** is directed towards the ***meta*** positions.
- Similarly, **-CHO group** of benzaldehyde is an **electron withdrawing group**. It **<u>deactivated</u>** the aromatic ring by <u>decreasing the electron densiy at the ***ortho*** and ***para*** positions</u>. Thus, the electrophiles attack the ***meta*** position.





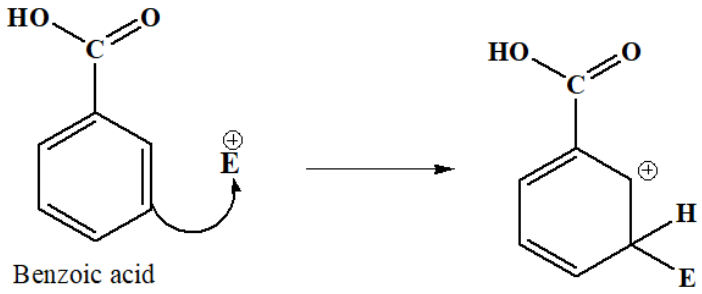
- Groups with double and triple bonds, such as -COOH/-CHO groups, are ***meta* directing**.
- Through resonance, they remove electrons from the **π system**.
- This removes electron density from the ***ortho*** and ***para*** carbons.
- The ***meta* carbons** have higher electron density, so they are more attractive to an attacking electrophile.
- So group like –COOH/-CHO are ***meta*** directing groups.



➢ Benzoic acid *meta* directing electrophilic substitution reaction general mechanism:

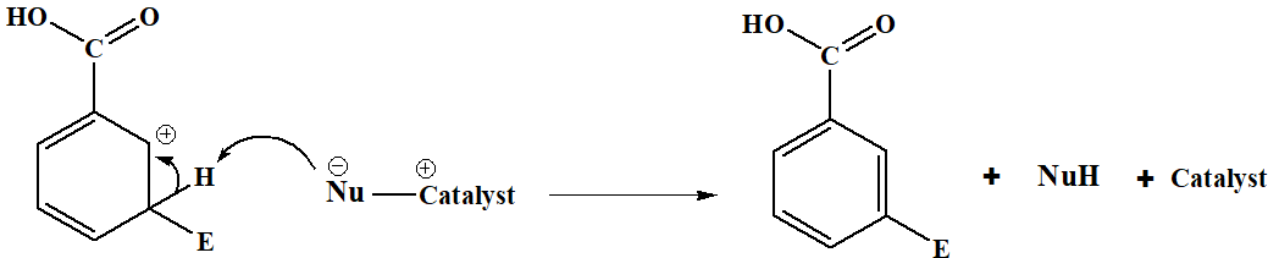
Step I: Electrophile generate

Step II: The electrophile attacks the pie electron system



Benzoic acid

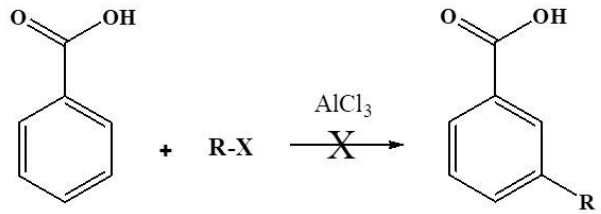
Step III: The aromaticity is restored by the loss of a proton



➢ Why Benzoic acid will not undergo Friedel-Craft Reaction?

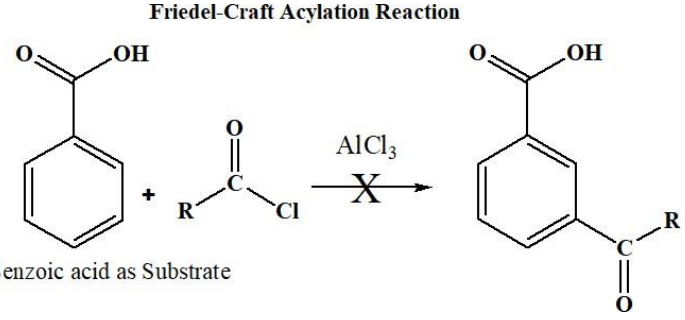
- Because **-COOH** group present in **aromatic carboxylic acids** is an **electron withdrawing group** causing **deactivation** of benzene ring.
- This results in the bonding of anhydrous $AlCl_3$ (Strong Lewis acid) with carboxyl group. Hence, electrophilic substitution i.e., Friedel-Crafts reaction does not occur in aromatic carboxylic acids.
- Friedel-Craft Reaction prefers electron donating or ring activating groups in the substrate.
- Groups or substitutions attached to the benzene ring that favors **Friedel-Craft Acylation Reaction** are- **alkyl**, **alkoxy**, **halogen**, **acetamido** groups.
- Meta directing groups usually do not undergo Friedel-Craft Reaction.

Friedel-Craft Alkylation Reaction



Benzoic acid as Substrate

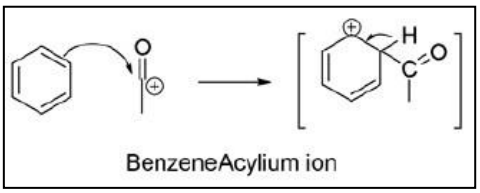
Friedel-Craft Acylation Reaction

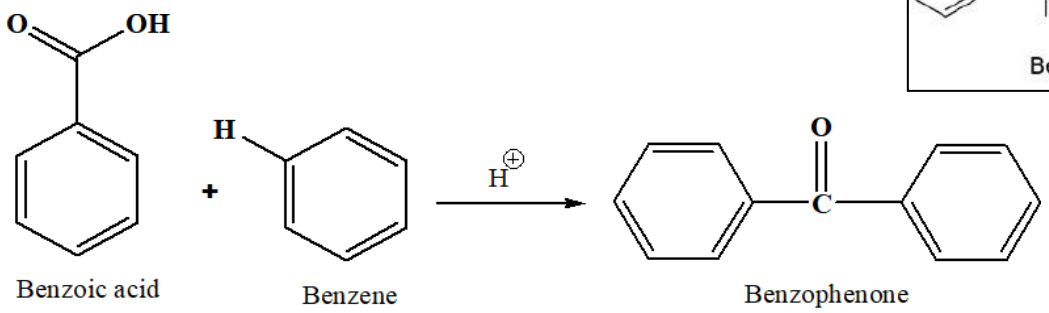


Benzoic acid as Substrate

➢ When Benzoic acid is the reagent (source of the electrophile) for Friedel-Craft Acylation Reaction

- Benzoic acid in the presence of strong acid like PPA (polyphosphoric acid), H_2SO_4 (sulfuric acid), TFA (trifluoroacetic acid), generate acylium ion (Ph-C≡O^+) that is resonance stabilized and therefore will undergo Friedel-Craft Acylation reaction.



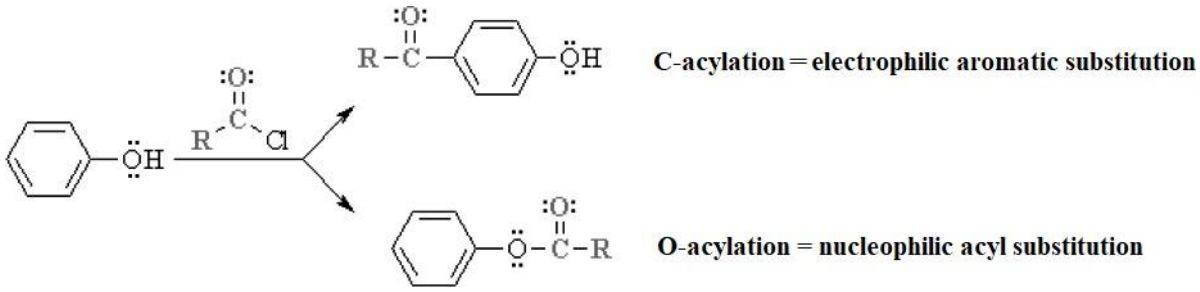


[H^+ example **PPA** (polyphosphoric acid), **H_2SO_4** (sulfuric acid), **TFA** (trifluoroacetic acid)]

Benzoic acid as the electrophile source / reagent

➢ Why Phenol does not undergo Friedel craft reaction?

- Phenol reacts to a very less extent during Friedel-Crafts reaction.
- The reason being that the **oxygen atom** of **phenol** has **lone pair of electrons** which **coordinate** with **Lewis acid**.
- In fact most substituents with lone pair would give poor yield.
- The two pathways involved in the reaction with phenol reduce the overall yield:



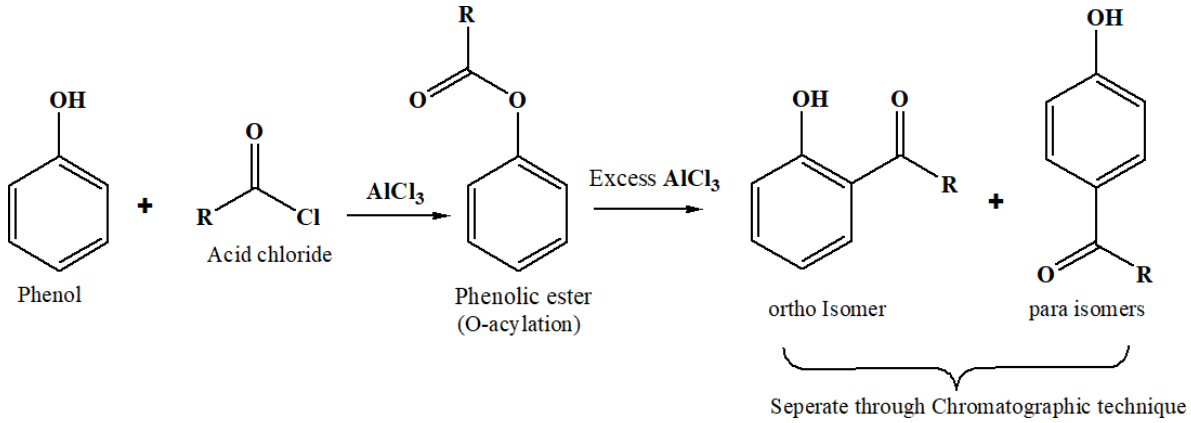
- Phenols are examples of **bidentate nucleophiles**, meaning that they can react at *two* positions:
  - on the aromatic ring giving an aryl ketone via **C-acylation**, a Friedel-Crafts reaction or,
  - on the phenolic oxygen giving an ester via **O-acylation,** an esterification
- Reagents :

  C-acylation : acylating agent (acyl chloride or anhydride) and $AlCl_3$

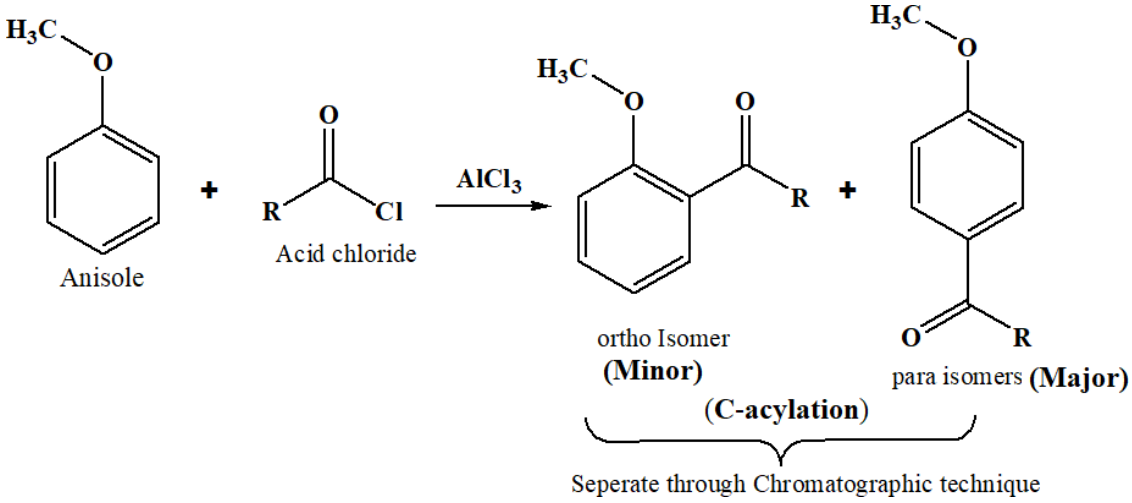
  O-acylation : acylating agent (acyl chloride or anhydride)
- The product of **C-acylation** is more stable and predominates under conditions of **thermodynamic control** (i.e. when $AlCl_3$ is present).
- The product of **O-acylation** forms faster and predominates under conditions of **kinetic control**
- **O-acylation** can be promoted by either:

- acid catalysis via protonation of the acylating agent, increasing its' electrophilicity or
- base catalysis via deprotonation of the phenol, increasing its' nucleophilicity.

- It is also known that aryl esters readily rearrange to aryl ketones in the presence of $AlCl_3$, a reaction known as the **Fries rearrangement.** (*The O-acylated product after isolation is treated with an excess of $AlCl_3$, a reaction known as **Fries rearrangement** to obtain **ortho & para hydroxy acetophenone**. The ortho and the para isomer can be later separated by chromatographic techniques*).

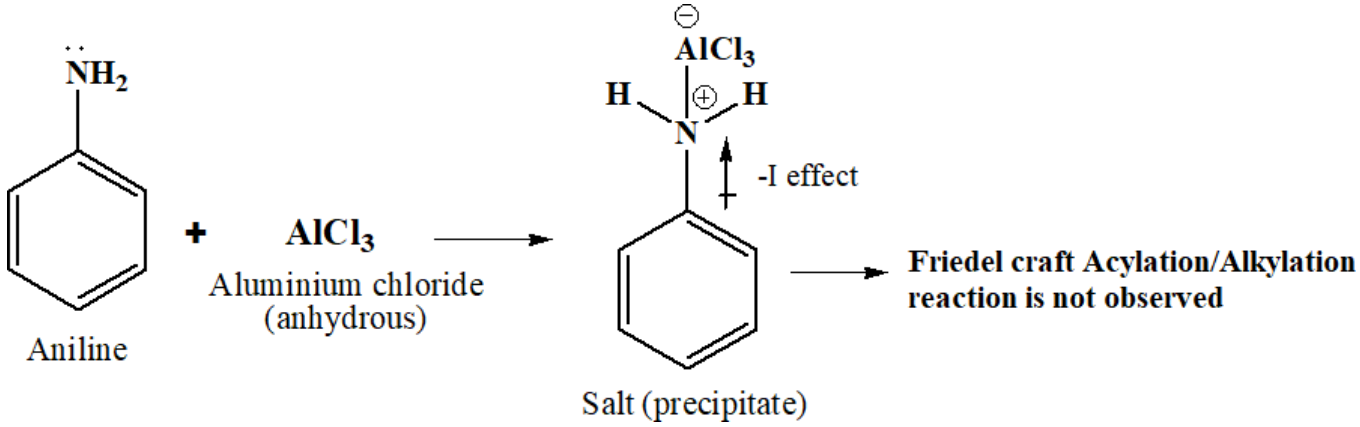


- But if the oxygen of the phenol is substituted, (example, **Anisole**) it then prefers to undergoes acylation reaction at the carbon of the benzene ring (**C-acylation**). The para isomer would be the major product.



➢ Why Aniline does not undergo Friedel craft reaction?

- Aniline do not undergo Friedel crafts reactions because $AlCl_3$ which is used as a Lewis acid and a catalyst in Friedel crafts reactions being electron deficient acts as Lewis base and attacks on the lone pair of nitrogen present in aniline to form an insoluble complex which precipitates out and the reaction does not takes place.
- Under the Friedel Craft Reaction condition, the aniline (Lewis base) binds to the electrophile **$AlCl_3$** (Lewis acid) to give a coordination complex (salt). [**Acid + Base = Salt**]
- The positive charge on the **nitrogen** is **electron withdrawing**, and it pulls the electron density of the ring by **negative inductive effect** (**-I effect**).
- It therefore, **deactivates the ring** for further **acylation/alkylation reactions**. The complex precipitates out of the reaction mixture and the reaction is not observed.



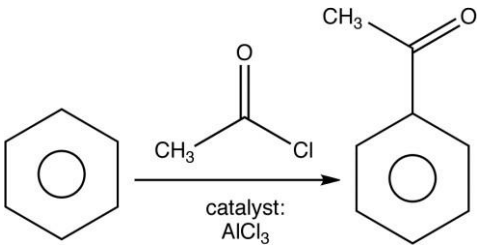
Note By:

✓ Friedel–Crafts acylation

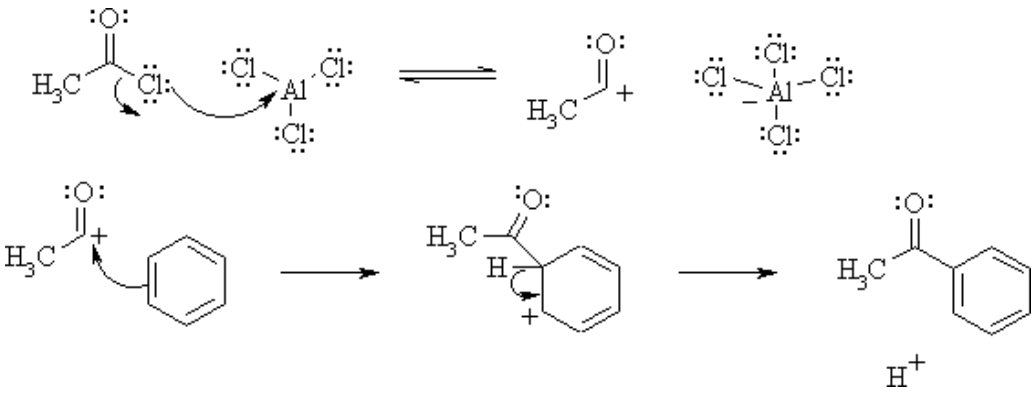
- The Friedel–Crafts acylation is the reaction of an **arene** with **acyl chlorides** or **anhydrides** using a **strong Lewis acid catalyst**.
- This reaction proceeds via electrophilic aromatic substitution to form monoacylated products.

Short note: ***Arene*** *is a hydrocarbon with alternating double and single bonds between carbon atoms forming rings. Example: Aromatic hydrocarbon*

- **Reaction**

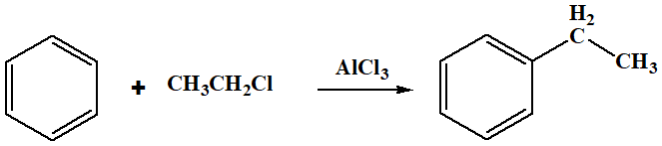


- **Reaction Mechanism:**

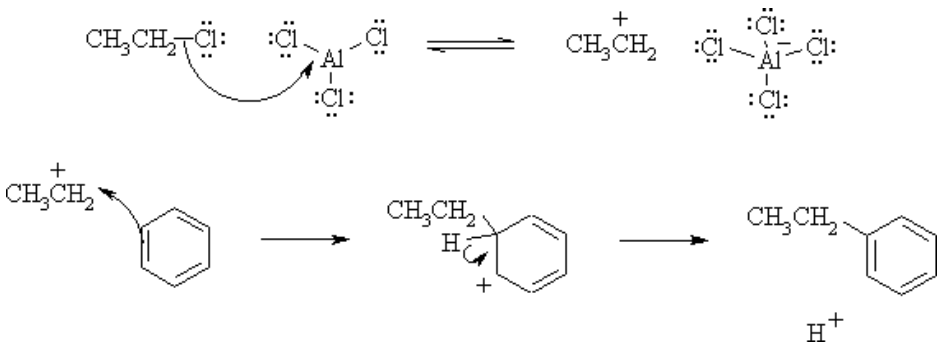


✓ Friedel–Crafts alkylation

- Friedel–Crafts alkylation involves the **alkylation** of an **aromatic ring** with an alkyl halide using a strong **Lewis acid**, such as aluminium chloride, ferric chloride.
- **Reaction:**

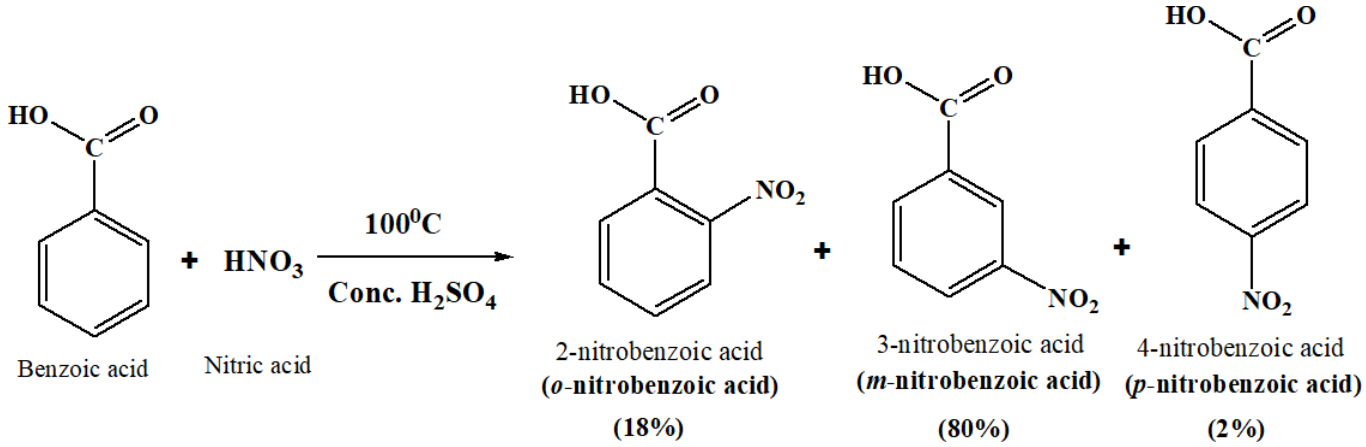


- **Reaction Mechanism:**

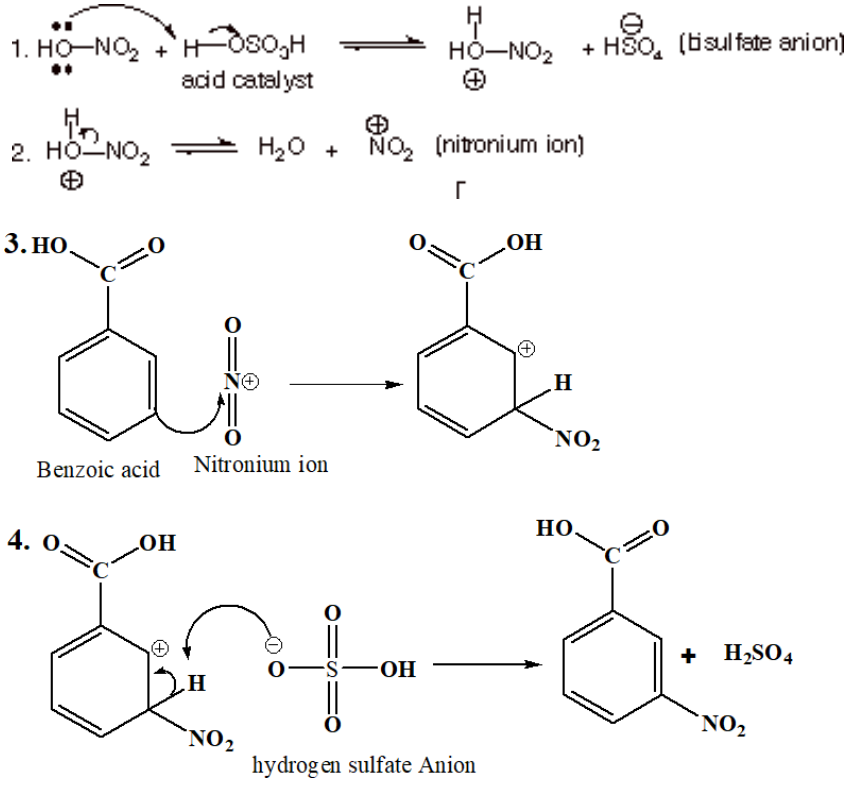


➢ Nitration of benzoic acid

- Nitration of benzoic acid will yield ***meta* nitro benzoic acid** or ***m*-nitrobenzoic acid** as **major products**.
- If a mixture of concentrated sulfuric acid and fuming nitric acid is used, further nitration of the initial product will result in the formation of **3,5-dinitrobenzoic acid** as a secondary product.
- The **carboxyllic acid group** on the benzene is a strong deactivating group. Most deactivating groups are ***meta*-directing**. This is simply because the electron donating effects of activating groups push electron density onto the ortho- and para-positions, while the **electron withdrawing effects** of deactivating groups pull electron density away from the ***ortho*- and *para*-positions**. In both cases, the ***meta*-position** is left almost unaffected, and when electron density is pulled away from the ***ortho*- and *para*-positions**, then the ***meta*-position** becomes the more reactive site.
- **Reaction:**

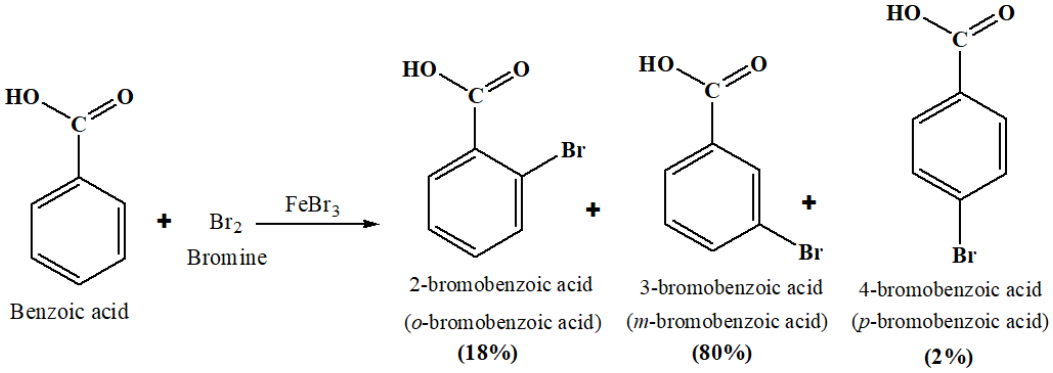


- **Reaction mechanism:**



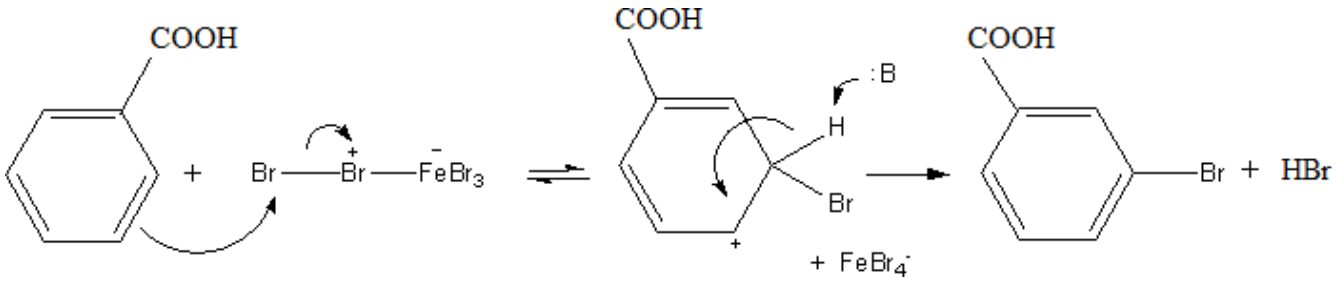
➢ Bromination of benzoic acid

- Carboxyl group in benzoic acid is an electron withdrawing group and therefore, it is ***meta*** directing.
- Similarly bromination of benzoic acid will yield ***meta* bromo benzoic acid** or ***m*-bromo acid** as **major products**.
- **Reaction:**



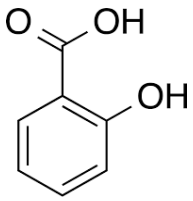
- **Reaction mechanism:**
  - **Step I**

  - **Step II**



❖ Some other important aromatic acids

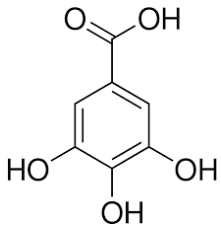
Salicylic Acid



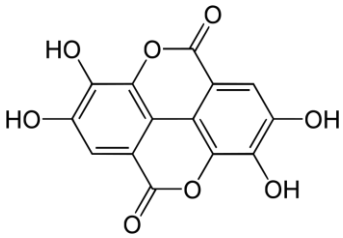
2-Hydroxybenzoic acid

- Salicylic acid is used as a food preservative, a bactericidal and an antiseptic.
- Salicylic acid as a medication is used most commonly to help remove the outer layer of the skin. As such, it is used to treat warts, psoriasis, acne, ringworm, dandruff, and ichthyosis.
- Salicylic acid is a keratolytic

Gallic acid



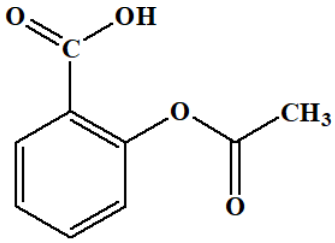
3,4,5-trihydroxybenzoic acid



ellagic acid

- Gallic acid is a **Trihydroxybenzoic acid**, a type of phenolic acid, found in gallnuts, sumac, witch hazel, tea leaves, oak bark, and other plants.
- The gallic acid groups are usually bonded to form dimers such as **ellagic acid**.
- Hydrolyzable tannins break down on hydrolysis to give gallic acid and glucose or ellagic acid and glucose, known as gallotannins and ellagitannins, respectively.
- The gallic acid extracted from grape seeds has been shown to induce apoptosis or cell death in prostate and breast cancer cells. In addition to being toxic towards cancerous cells, gallic acid does not have any negative effects on healthy cells.
- As an antioxidant, gallic acid can defend the body against free radicals and oxidative damage.
- Gallic acid has anti-fungal and anti-viral effects and anti-inflammatory properties.
- Gallic acid can support the heart as well, particularly the hearts of patients suffering from type-1 diabetes. Supplements of galic acid were noted to decrease the chances of developing heart-related conditions among these individuals.
- Regular intake of foods with gallic acid can be good for the brain. Gallic acid can defend the brain's nerves and tissue from deterioration caused by neurodegenerative disease.

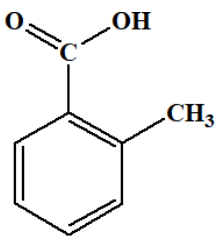
Acetylsalicylic acid (ASA) or Aspirin



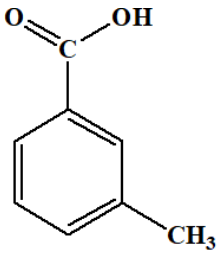
2-acetoxybenzoic acid

- Aspirin is used to reduce fever and relieve mild to moderate pain from conditions such as muscle aches, toothaches, common cold, and headaches. It may also be used to reduce pain and swelling in conditions such as arthritis. Aspirin is known as a salicylate and a nonsteroidal anti-inflammatory drug (NSAID).
- Aspirin to prevent blood clots. This effect reduces the risk of stroke and heart attack.
- Used of aspirin in low doses as a "blood thinner" to prevent blood clots.

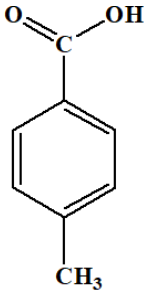
Toluic acid



2-methylbenzoic acid
(*o*-Toluic acid)



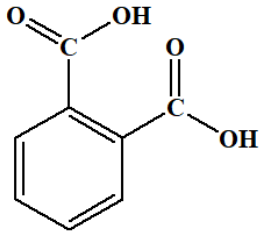
3-methylbenzoic acid
(*m*-Toluic acid)



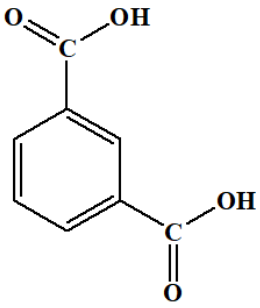
4-methylbenzoic acid
(*p*-Toluic acid)

- Toluic acid has 3 isomers *o*-toluic acid, *p*-toluic acid and *m*-toluic acid.
- *o*-Toluic acid is prepared by oxidation of o-xylene with nitric acid.
- *m*-toluic acid well-known insect repellent.
- *p*-Toluic acid is an intermediate in the conversion of *p*-xylene to terephthalic acid, a commodity chemical used in the manufacture of polyethylene terephthalate.

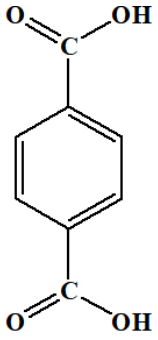
Phthalic acid



phthalic acid
(*ortho*-phthalic acid)



isophthalic acid
(*meta*-phthalic acid)



terephthalic acid
(*para*-phthalic acid)

- Phthalic acid is an aromatic dicarboxylic acid, with formula $C_6H_4(CO_2H)_2$. It is an isomer of isophthalic acid and terephthalic acid.
- It is a dibasic acid, with pKa's of 2.89 and 5.51.
- The monopotassium salt, potassium hydrogen phthalate is a standard acid in analytical chemistry. Typically phthalate esters are prepared from the widely available phthalic anhydride.
- Reduction of phthalic acid with sodium amalgam in the presence of water gives the 1,3-cyclohexadiene derivative.