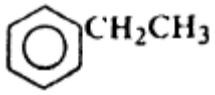
Arenes

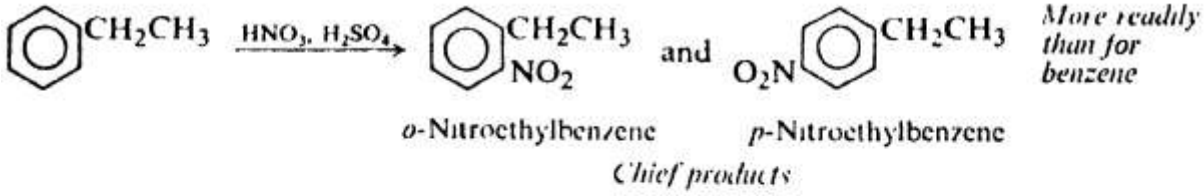
Aliphatic-aromatic hydrocarbons

Many important compounds are not just aliphatic (alkane, alkene, or alkyne) or just aromatic (benzene) but contain both aliphatic and aromatic units; hydrocarbons of this kind are known collectively as **arenes**. Ethylhenzene, for example, contains a benzene ring and an aliphatic side chain.



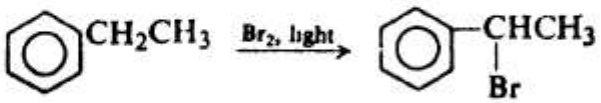
Ethylbenzene

The chemical properties of these mixed aliphatic-aromatic hydrocarbons are expecting it to show two sets of chemical properties. The ring of ethylbenzene should undergo the electrophilic substitution characteristic of benzene, and the side chain should undergo the freeradical substitution characteristic of ethane and the properties of each portion of the molecule should be modified by the presence of the other portion.



o-Nitroethylbenzene *p*-Nitroethylbenzene

Chief products



1-Bromo-1-phenylethane
(α-Phenylethyl bromide)
Only product

The ethyl group should modify the aromatic properties of the ring, and the ring should modify the aliphatic properties of the side chain.Treatment of ethylbenzene with nitric acid and sulfuric acid, for instance, introduces a nitro group into the ring; treatment with bromine in the presence of light introduces a bromine atom into the side chain. But because of the ethyl group, nitration takes place more readily than with benzene itself, and occurs chiefly at the positions ortho and para to the ethyl group; and because of the ring, bromination takes place more readily than with ethane, and occurs exclusively on the carbon nearer the ring. Thus each portion of the molecule affects the reactivity of the other portion and determines the orientation of attack.

In the same way we may have a molecule that is part aromatic and part alkene, or part aromatic and part alkyne. Again each portion of such a molecule shows the properties

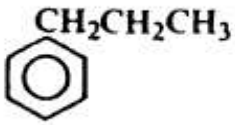
characteristic of its particular structure, although these properties are modified by the other portion of the molecule.

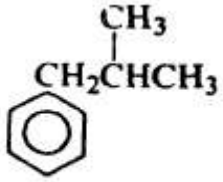
Structure and nomenclature

The simplest of the **alkylbenzenes**, methylbenzene, is given the special name of toluene. Compounds containing longer side chains are named by prefixing the name of the alkyl group to the word -benzene, as, for example, in ethylbenzene, n-propylbenzene, and isobutylbenzene.

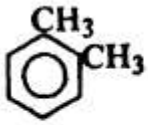

Toluene

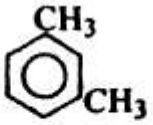

Ethylbenzene


n-Propylbenzene


Isobutylbenzene

The simplest of the dialkylbenzenes, the dimethylbenzenes, are given the special names of xylenes; we have, then, o-xylene, m-xylene, and p-xylene.

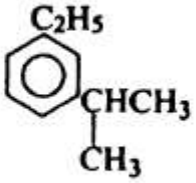

o-Xylene

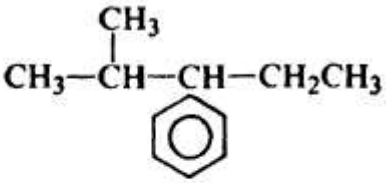

m-Xylene


p-Xylene

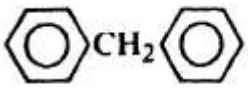
Dialkylbenzenes containing one methyl group are named as derivatives of toluene, while others are named by prefixing the names of both alkyl groups to the word -benzene. A compound containing a very complicated side chain might be named as a phenylalkane (C_6H_5 = phenyl).

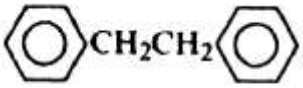

p-Ethyltoluene


m-Ethylisopropylbenzene

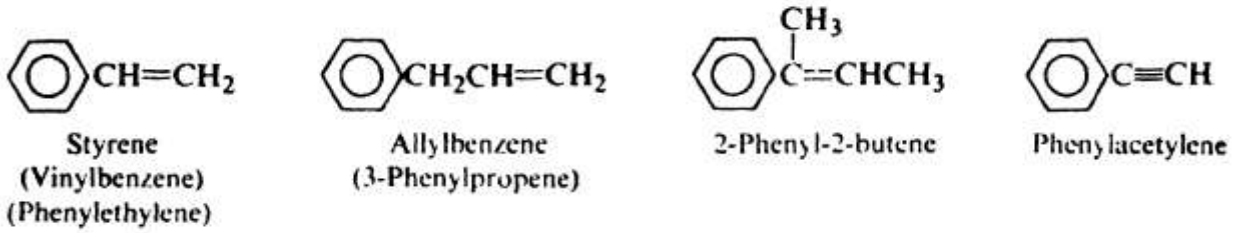

2-Methyl-3-phenylpentane

Compounds containing more than one benzene ring are nearly always named as derivatives of alkanes.


Diphenylmethane


1,2-Diphenylethane

The simplest **alkenylbenzene** has the special name styrene. Others are generally named as substituted alkenes, occasionally as substituted benzenes. **Alkynylbenzenes** are named as substituted alkynes.



Styrene (Vinylbenzene) (Phenylethylene) | Allylbenzene (3-Phenylpropene) | 2-Phenyl-2-butene | Phenylacetylene

Physical properties

As compounds of low polarity, the alkylbenzenes possess physical properties that are essentially the same as those of the hydrocarbons.

- They are insoluble in water, but quite soluble in non-polar solvents like ether, carbon tetrachloride, or ligroin. They are almost always less dense than water.
- Boiling points rise with increasing molecular weight, the boiling point increment being the usual 20-30˚for each carbon atom.
- Since melting points depend not only on molecular weight but also on molecular shape, their relationship to structure is a very complicated one. One important general relationship does exist, however, between melting point and structure of aromatic compounds: among isomeric disubstituted benzenes, the para isomer generally melts considerably higher than the other two.

Industrial source of alkylbenzenes

There are two large reservoirs of organic material, coal and petroleum, and aromatic compounds are obtained from both. **Aromatic compounds are separated as such from coal tar, and are synthesized from the alkanes of petroleum.**

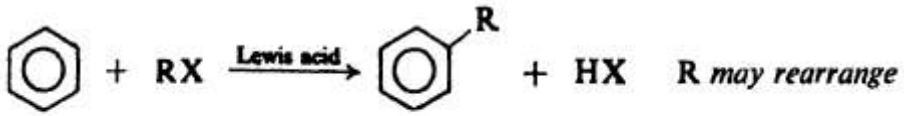
From coal tar by distillation there are obtained a number of aromatic compounds, benzene, toluene, xylenes, phenol, cresols, and naphthalene. Still larger quantities of aromatic hydrocarbons are needed, and these are synthesized from alkanes through the process of catalytic reforming. This can bring about not only dehydrogenation, as in the formation of toluene from methylcyclohexane, but also cyclization and isomerization, as in the formation of toluene from n-heptane or 1,2-dimethylcyclopentane. In an analogous way, benzene is obtained from cyclohexane and methylcyclopentane, as well as from the hydrodealkylation of toluene.

Today, petroleum is the chief source of the enormous quantities of benzene, toluene, and the xylenes required for chemicals and fuels.

Preparation of alkylbenzenes

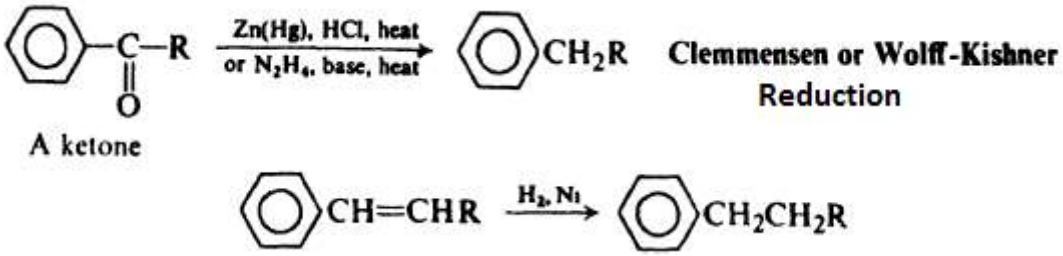
Although a number of the simpler alkylbenzenes are available from industrial sources, the more complicated compounds must be synthesized in one of this ways:

1. **Attachment of alkyl group: Friedel-Crafts alkylation**.



Lewis acid: $AlCl_3$, BF_3, HF, etc.
Ar-X *cannot be used in place of* R-X

2. **Conversion of side chain**.

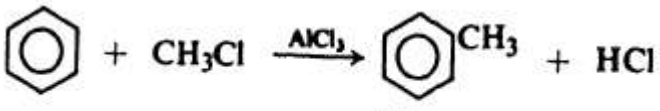


Friedel-Crafts alkylation is extremely useful since it permits the direct attachment of an alkyl group to the aromatic ring.

There are frequently available aromatic compounds containing aliphatic side chains that are not simple alkyl groups. An alkylbenzene can be prepared from one of these compounds by converting the side chain into an alkyl group. The most important side-chain conversion involves reduction of ketones either by amalgamated zinc and HCl (Clemmensen reduction) or by hydrazine and strong base (Wolff-Kishner reduction). This method is important because the necessary ketones are readily available through a modification of the Friedel-Crafts reaction that involves acid chlorides. Unlike alkylation by the Friedel-Crafts reaction, this method does not involve rearrangement

Friedel-Crafts alkylation

If a small amount of anhydrous aluminum chloride is added to a mixture of benzene and methyl chloride, a vigorous reaction occurs, hydrogen chloride gas is evolved, and toluene can be isolated from the reaction mixture.



Toluene

The Friedel-Crafts reaction is an important method for attaching alkyl side chains to aromatic rings.

The alkyl halide may contain an alkyl group more complicated than methyl, and a halogen atom other than chlorine; in some cases alcohols are used or-especially in industry - alkenes. Substituted alkyl halides, like benzyl chloride, $C_6H_5CH_2Cl$, also can be used. Because of the low reactivity of halogen attached to an aromatic ring, aryl halides (Ar X, e.g., bromo- or chlorobenzene) cannot be used in place of alkyl halides.

The aromatic ring to which the side chain becomes attached may be that of benzene itself, certain substituted benzenes (chiefly alkylbenzenes and halobenzenes), or more complicated aromatic ring systems like naphthalene and anthracene.

In place of aluminum chloride, other **Lewis acids** can be used, in particular BF_3 , HF, and phosphoric acid.

The reaction is carried out by simply mixing together the three components; usually the only problems are those of moderating the reaction by cooling and of trapping the hydrogen halide gas. Since the attachment of an alkyl side chain makes the ring more susceptible to further attack, steps must be taken to limit substitution to monoalkylation. As in halogenation of alkanes, this is accomplished by using an excess of the hydrocarbon. In this way an alkyl carbonium ion seeking an aromatic ring is more likely to encounter an unsubstituted ring than a substituted one. Frequently the aromatic compound does double duty, serving as solvent as well as reactant. From polyhalogenated alkanes it is possible to prepare compounds containing more than one aromatic ring:

$$2C_6H_6 + CH_2Cl_2 \xrightarrow{AlCl_3} C_6H_5CH_2C_6H_5 + 2HCl$$

Diphenylmethane

$$2C_6H_6 + ClCH_2CH_2Cl \xrightarrow{AlCl_3} C_6H_5CH_2CH_2C_6H_5 + 2HCl$$

1,2-Diphenylethane

$$3C_6H_6 + CHCl_3 \xrightarrow{AlCl_3} C_6H_5{-}\underset{\displaystyle H}{\overset{\displaystyle C_6H_5}{\overset{|}{\underset{|}{C}}}}{-}C_6H_5 + 3HCl$$

Triphenylmethane

$$3C_6H_6 + CCl_4 \xrightarrow{AlCl_3} C_6H_5{-}\underset{\displaystyle Cl}{\overset{\displaystyle C_6H_5}{\overset{|}{\underset{|}{C}}}}{-}C_6H_5 + 3HCl$$

Triphenylchloromethane

Mechanism of Friedel-Crafts alkylation

There are two mechanisms are possible for Friedel-Crafts alkylation. Both involve electrophilic aromatic substitution, but they differ as to the nature of the electrophile.

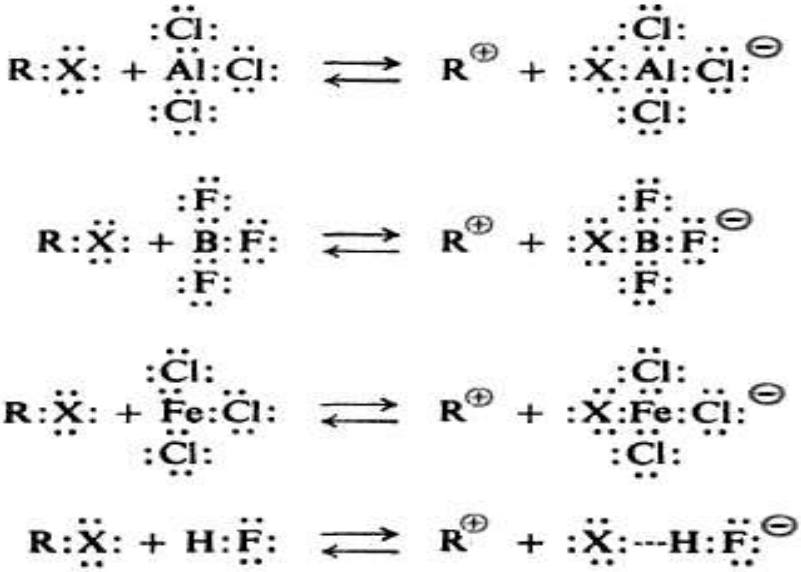
One mechanism for Friedel-Crafts alkylation involves the following steps, in which the

(1) $$RCl + AlCl_3 \rightleftharpoons AlCl_4^- + R^{\oplus}$$

(2) $$R^{\oplus} + C_6H_6 \rightleftharpoons C_6H_5(H)(R)^{\oplus}$$ *Slow*

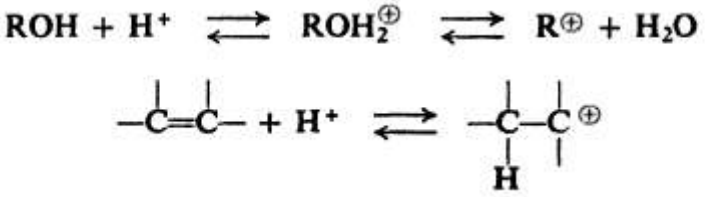
(3) $$C_6H_5(H)(R)^{\oplus} + AlCl_4^- \rightleftharpoons C_6H_5R + HCl + AlCl_3$$ *Fast*

electrophile is an alkyl carbonium ion. The function of the aluminum chloride is to generate this carbonium ion by abstracting the halogen from the alkyl halide. Other Lewis acids can function in the same way and thus take the place of aluminum chloride:



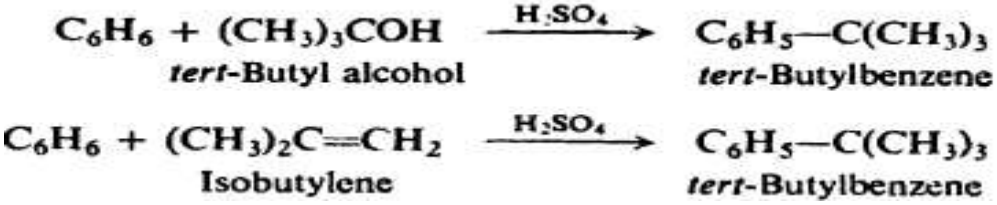
Carbonium ions from alkyl halides

Judging from the mechanism just described, we might expect the benzene ring to be attacked by carbonium ions generated in other ways: by the action of acid on alcohols and on alkenes).

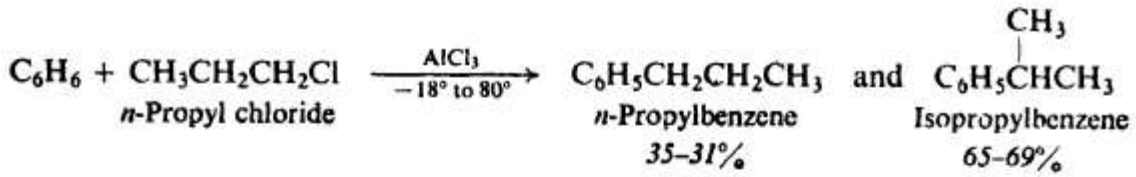


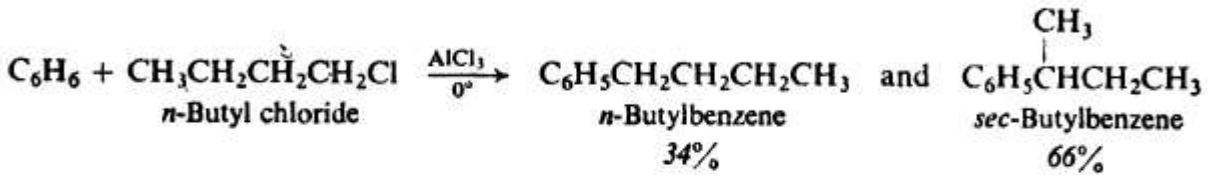
Carbonium ions from alcohols and from alkenes

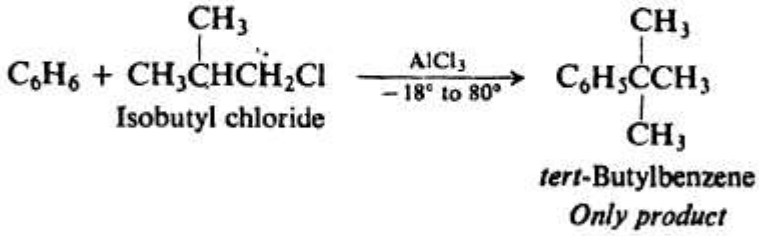
This expectation is correct: alcohols and alkenes, in the presence of acids, alkylate aromatic rings in what we may consider to be a modification of the Friedel-Crafts reaction.

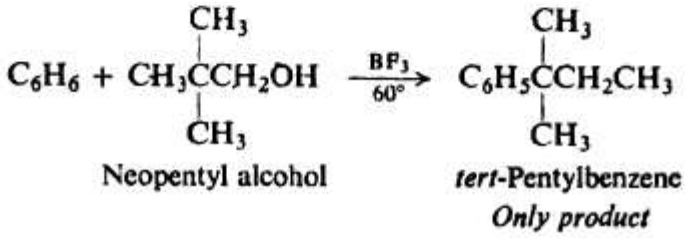


Also judging from the mechanism, we might expect Friedel-Crafts alkylation to be accompanied by the kind of rearrangement that is characteristic of carbonium ion reactions. This expectation, too, is correct. As the 'following examples show, alkylbenzenes containing rearranged alkyl groups are not only formed but are sometimes the sole products. In each case, we see that the particular kind rearrangement corresponds to what we would expect if a less stable of(1˚) carbonium ion were to rearrange by a 1,2-shift to a more stable (2˚ or 3˚) carbonium ion.









A carbonium ion may:

(a) Eliminate a hydrogen ion to form an alkene;

(b) Rearrange to a more stable carbonium ion;

(c) Combine with a negative ion or other basic molecule;

(d) Add to an alkene to form a larger carbonium ion;

(e) Abstract a hydride ion from an alkane;

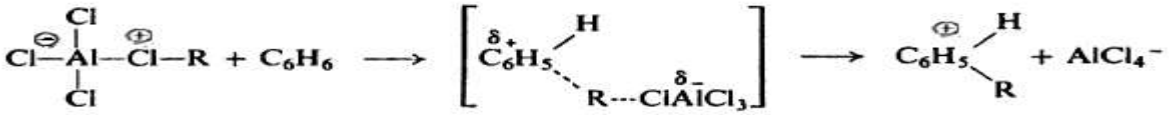
(f) Alkylate an aromatic ring.

A carbonium ion formed by (b) or (d) can subsequently undergoes any of the reactions. In alkylation, as in its other reactions, the carbonium ion gains a pair of electrons to complete the octet of the electron-deficient carbon this time from the π cloud of an aromatic ring.

In some of the examples given above, we see that part of the product is made up of unrearranged alkylbenzenes that because the aromatic ring may tend to seek out the scarce unrearranged ions because of their higher reactivity and in some cases, it is quite possible that some of the carbonium ions react with the aromatic ring before they have time to rearrange; the same low stability that makes primary carbonium ions, for example, prone to rearrangement also makes them highly reactive.

On the other hand, there is additional evidence that there is a second mechanism for Friedel-Crafts alkylation. In this mechanism, the electrophile is not an alkyl carbonium

ion, but an acid-base complex of alkyl halide and Lewis acid, from which the alkyl group is transferred in one step from halogen to the aromatic ring.



Limitations of Friedel-Crafts alkylation

There are three limitations to the use of Friedel-Crafts alkylation:

(a) The danger of polysubstitution ;

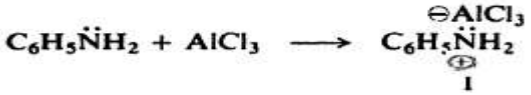
(b) The possibility that the alkyl group will rearrange; and

(c) The fact that aryl halides cannot take the place of alkyl halides.

Besides these, there are several other limitations.

(d) An aromatic ring less reactive than that of the halobenzenes does not undergo the Friedel-Crafts reaction; evidently the carbonium ion, R^+, is a less powerful nucleophile than NO_2 and the other electron-deficient reagents that bring about electrophilic aromatic substitution.

(e) Aromatic rings containing the NH_2, NHR, or NR_2 group do not undergo Friedel-Crafts alkylation, partly because the strongly basic nitrogen ties up the Lewis acid needed for ionization of the alky] halide:

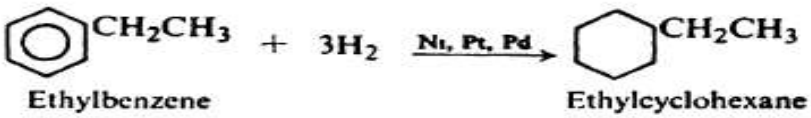


Reactions of alkylbenzenes

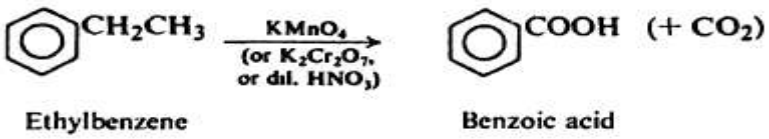
Except for hydrogenation and oxidation, The reactions of the alkylbenzenes are either electrophilic substitution in the aromatic ring or free-radical substitution in the aliphatic side chain.

The experimental conditions determine which portion of the molecule aromatic or aliphatic is attacked, and each portion of the molecule modifies the reactions of the other portion.

1. **Hydrogenation.**

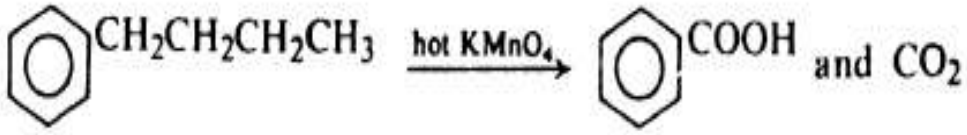


2. **Oxidation**



Although benzene and alkanes are quite unreactive toward the usual oxidizing agents ($KMnO_4$, $K_2Cr_2O_7$, etc.), the benzene ring renders an aliphatic side chain quite

susceptible to oxidation. The side chain is oxidized down to the ring, only a carboxyl group (COOH) remaining to indicate the position of the original side chain. Potassium permanganate is generally used for this purpose, although potassium dichromate or dilute nitric acid also can be used. (Oxidation of a side chain is more difficult, however, than oxidation of an alkene, and requires prolonged treatment with hot KMnO4.)



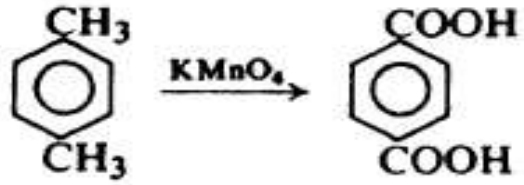
n-Butylbenzene Benzoic acid

This reaction is used for two purposes:

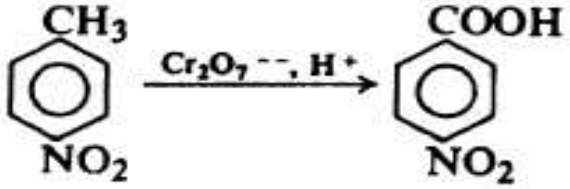
(a) Synthesis of carboxylic acids, and

(b) Identification of alkylbenzenes.

(a) Synthesis of carboxylic acids. One of the most useful methods of preparing an aromatic carboxylic acid involves oxidation of the proper alkylbenzene. For example:



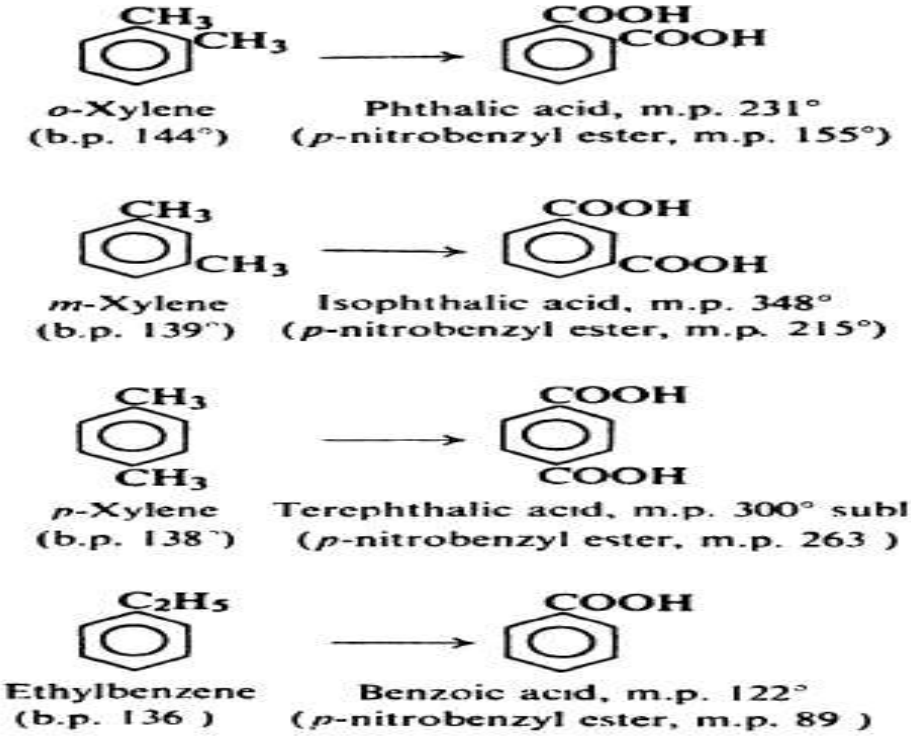
p-Xylene Terephthalic acid
(1,4-Benzenedicarboxylic acid)



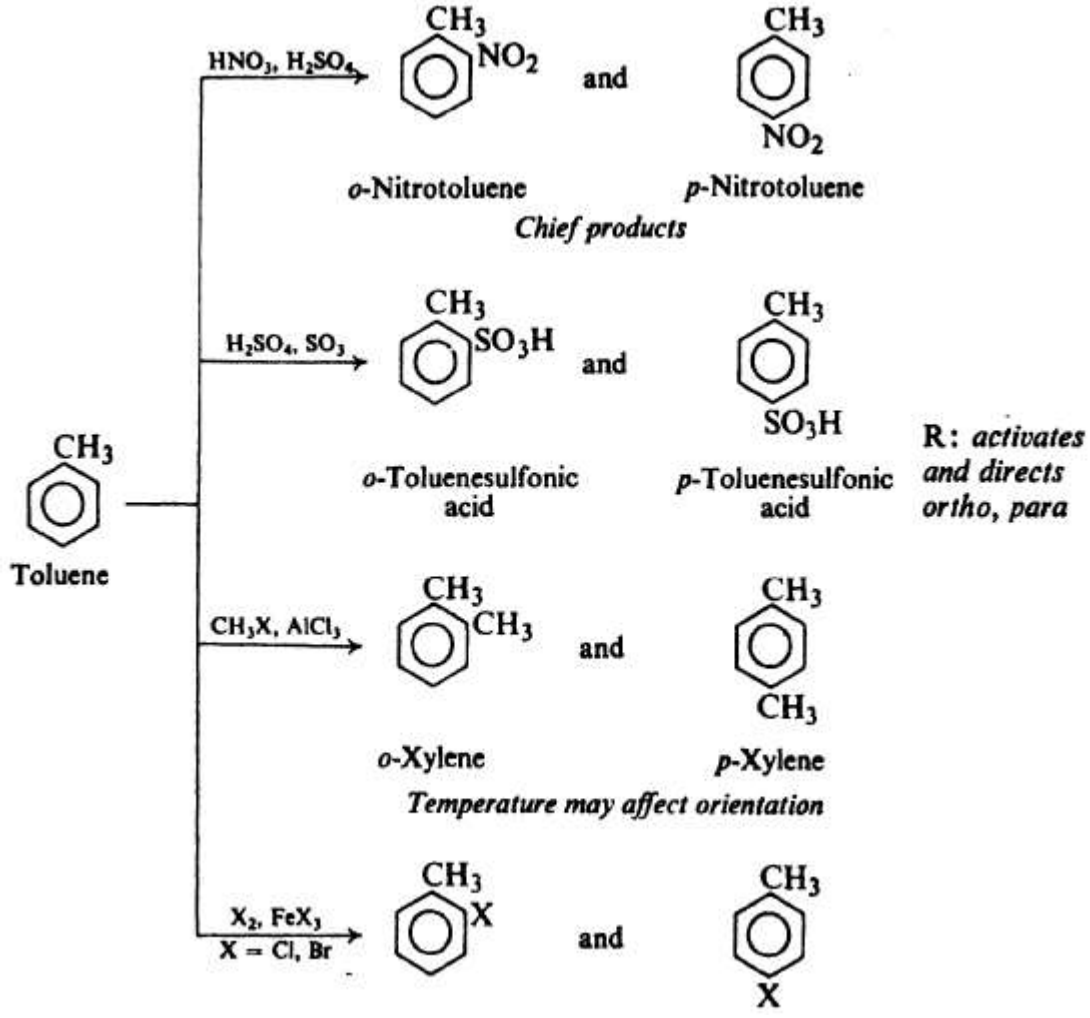
p-Nitrotoluene *p*-Nitrobenzoic acid

(b) Identification of alkylbenzenes. The number and relative positions of side chains can frequently be determined by oxidation to the corresponding acids.

Suppose, for example, that we are trying to identify an unknown liquid of formula C_8H_{10} and boiling point 137-139 that has shown to be an alkylbenzene. Looking in Table of melting point we find that it could be any one of four compounds: o-, m-, or p-xylene, or ethylbenzene. The oxidation of each of these possible hydrocarbons yields a different acid, and these acids can readily be distinguished from each other by their melting points or the melting points of derivatives.

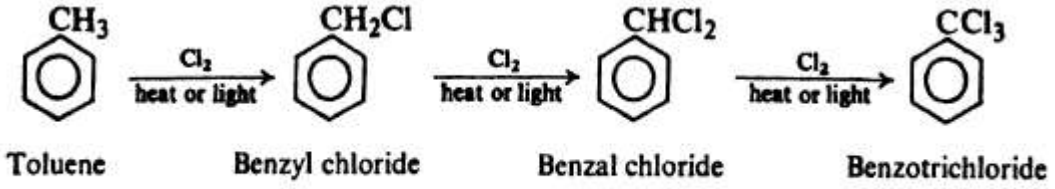


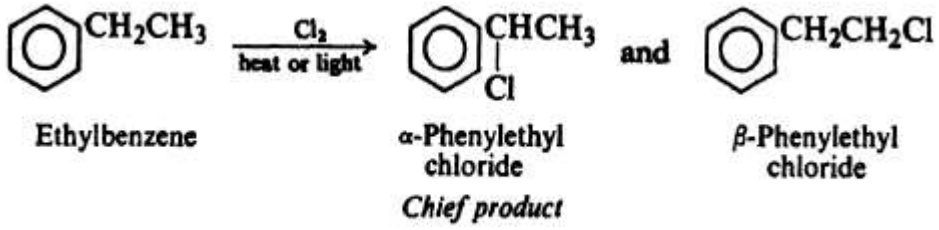
3. **Substitution in the ring. Electrophilic aromatic substitution.**

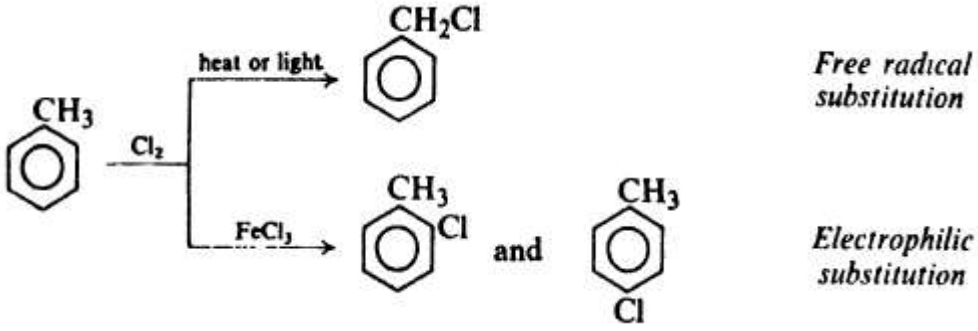


Because of its electron-releasing effect, an alkyl group activates a benzene ring to which it is attached, and directs ortho and para.

4. **Substitution in the side chain. Free-radical halogenation.**



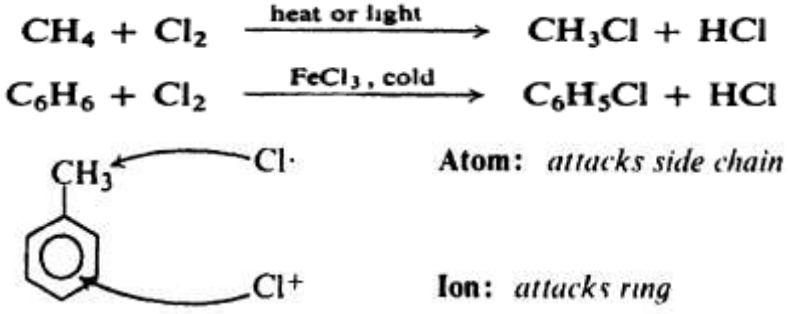




Halogenation of alkylbenzenes: ring vs. side chain

Alkylbenzenes clearly offer two main areas to attack by halogens: the ring and the side chain. We can control the position of attack simply by choosing the proper reaction conditions.

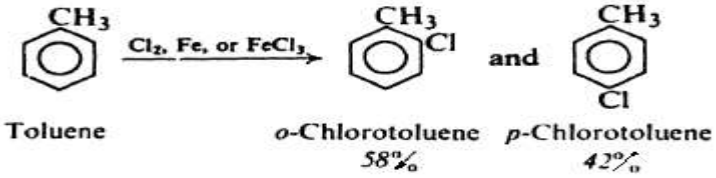
Halogenation of alkanes requires conditions under which halogen atoms are formed, that is, high temperature or light. Halogenation of benzene, on the other hand, involves transfer of positive halogen, which is promoted by acid catalysts like ferric chloride.



We might expect that the position of attack in toluene would be governed by which attacking particle is involved, and therefore by the conditions employed. If chlorine is bubbled into boiling toluene that is exposed to ultraviolet light, substitution occurs

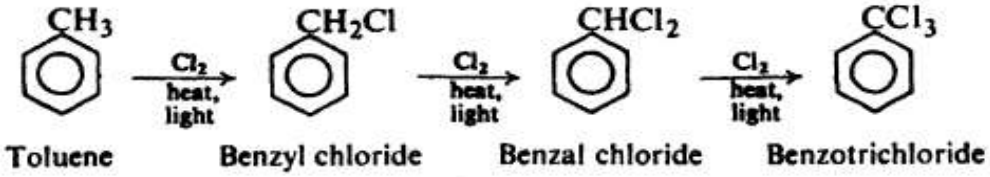
almost exclusively in the side chain; in the absence of light and in the presence of ferric chloride, substitution occurs mostly in the ring.

Like nitration and sulfonation, ring halogenation yields chiefly the o- and p-isomers. Similar results are obtained with other alkylbenzenes, and with bromine as well as chlorine.



Side-chain halogenation, like halogenation of alkanes, may yield polyhalogenated products; even when reaction is limited to monohalogenation, it may yield a mixture of isomers.

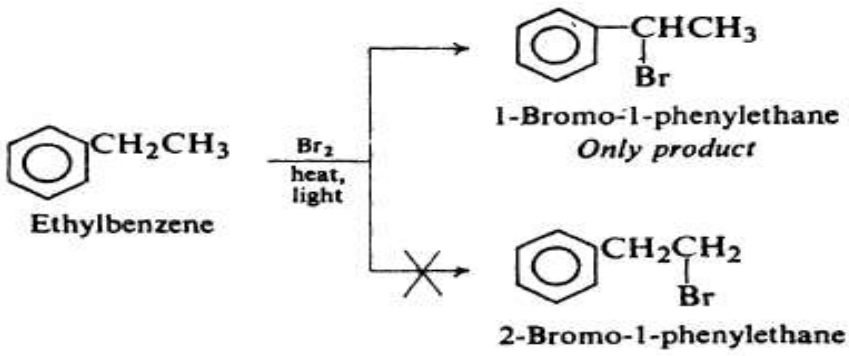
Side-chain chlorination of toluene can yield successively the mono-, di-, and trichloro compounds. These are known as benzyl chloride, benzal chloride, and benzotrichloridem, such compounds are important intermediates in the synthesis of alcohols, aldehydes, and acids.



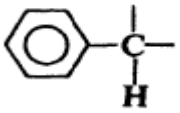
Side-chain halogenation of alkylbenzenes

Chlorination and bromination of side chains differ from one another in orientation and reactivity in one very significant way. Let us look first at bromination, and then at chlorination.

An alkylbenzene with a side chain more complicated than methyl offers more than one position for attack, and so we must consider the likelihood of obtaining a mixture of isomers. Bromination of ethylbenzene, for example, could theoretically yield two products: 1-bromo-l-phenylethane and 2-bromo-l-phenylethane. Despite a probability factor that favors 2-bromo-l –phenylethane by 3:2, the only product found is 1-bromo-l-phenylethane. Evidently abstraction of the hydrogens attached to the carbon next to the aromatic ring is greatly preferred.



Hydrogen atoms attached to carbon joined directly to an aromatic ring are called benzylic hydrogens.



Benzylic hydrogen:
easy to abstract

The relative ease with which benzylic hydrogens are abstracted is shown not only by orientation of bromination but also and in a more exact way by comparison of reactivities of different compounds. Competition experiments show, for example, that at 40˚a benzylic hydrogen of toluene is 3.3 times as reactive toward bromine atoms as the tertiary hydrogen of an alkane -and nearly 100 million times as reactive as hydrogen of methane!

Examination of reactions that involve attack not only by halogen atoms but by other free radicals as well has shown that this is a general rule: benzylic hydrogens are extremely easy to abstract and thus resemble allylic hydrogens.

Ease of abstraction of hydrogen atoms allylic, benzylic > 3° > 2° > 1° > CH_4, vinylic

Side-chain halogenation of alkylbenzenes proceeds by the same mechanism as halogenation of alkanes. Bromination of toluene, for example, would include the following steps:

Toluene — Benzyl radical — Benzyl bromide

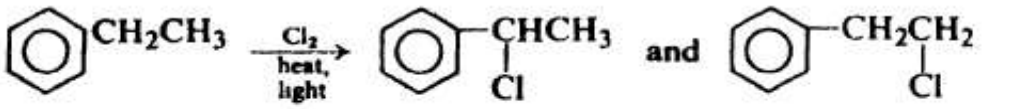
The fact that benzylic hydrogens are unusually easy to abstract means that benzyl radicals are unusually easy to form.

Ease of formation of free radicals allyl, benzyl > 3° > 2° > 1° > CH_3·, vinyl

A benzyl radical contains less energy and is more stable than a tert-bulyl radical.

Stability of free radicals allyl, benzyl > 3° > 2° > 1° > CH_3·, vinyl

Orientation of chlorination shows that chlorine atoms, like bromine atoms, preferentially attack benzylic hydrogen ; but, as we see, the preference is less marked:



Ethylbenzene — 1-Chloro-1-phenylethane *Major product, 91%* — and — 2-Chloro-1-phenylethane 9%

Resonance stabilization of the benzyl radical

The Bond dissociation energies indicate that 19 kcal/mole less energy (104 - 85) is needed to form the benzyl radical from toluene than to form the methyl radical from methane. This is an account for the stability of the benzyl radical

$$\underset{\text{Toluene}}{C_6H_5CH_3} \longrightarrow \underset{\text{Benzyl radical}}{C_6H_5CH_2\cdot} + H\cdot \qquad \Delta H = +85 \text{ kcal}$$

Toluene contains the benzene ring and is therefore a hybrid of the two Kekule structures, I and II:

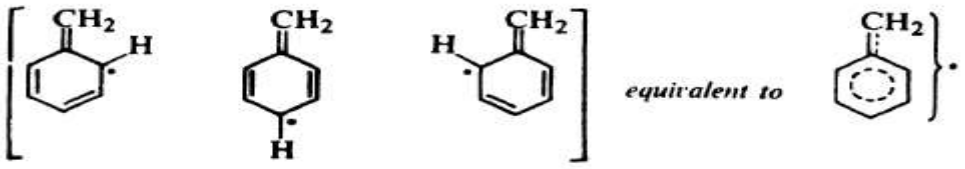
I II

Similarly, the benzyl radical is a hybrid of the two Kekule structures, III and IV:

III IV

This resonance cause's stabilization, that is, lowers the energy content. However, resonance involving Kekule structures presumably stabilizes both molecule and radical to the same extent, and hence does not affect the difference in their energy contents. If there were no other factors involved, then we might reasonably expect the bond dissociation energy for benzylic hydrogen to be about the same as that of methane hydrogen.

Considering further, however, we find that we can draw three additional structures for the radical: V, VI, and VII. In these structures there is a double bond between the side chain and the ring, and the odd electron is located on the carbon atoms ortho and para to the side chain. Drawing these pictures is, of course, our way of indicating that the odd electron is not localized on the side chain but is delocalized, being distributed about the ring.



V VI VII

We cannot draw comparable structures for the toluene molecule.

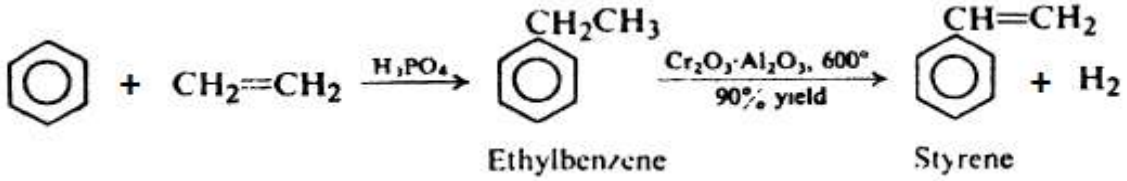
Contribution from the three structures, V-VII, stabilizes the radical in a way that is not possible for the molecule. Resonance thus lowers the energy content of the benzyl radical more than it lowers the energy content of toluene. This extra stabilization of the radical evidently amounts to 19 kcal/mole.

Preparation of alkenylbenzenes: Conjugation with ring

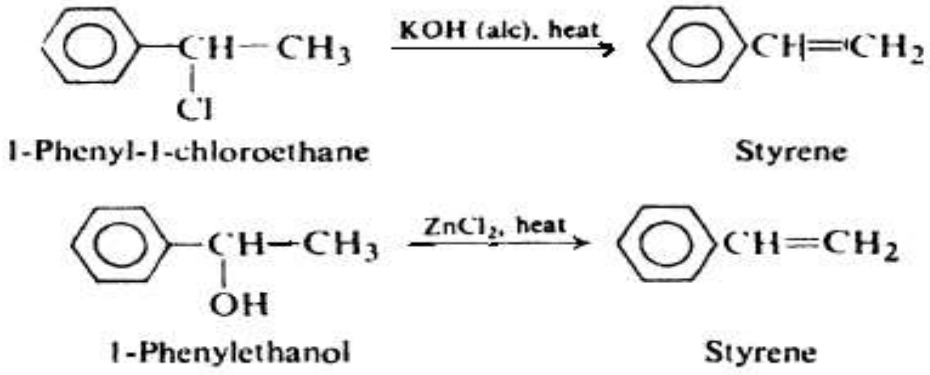
An aromatic hydrocarbon with a side chain containing a double bond can be prepared by essentially the same methods as simple alkenes.

In general, these methods involve elimination of atoms or groups from two adjacent carbons. The presence of the aromatic ring in the molecule may affect the orientation of elimination and the ease with which it takes place.

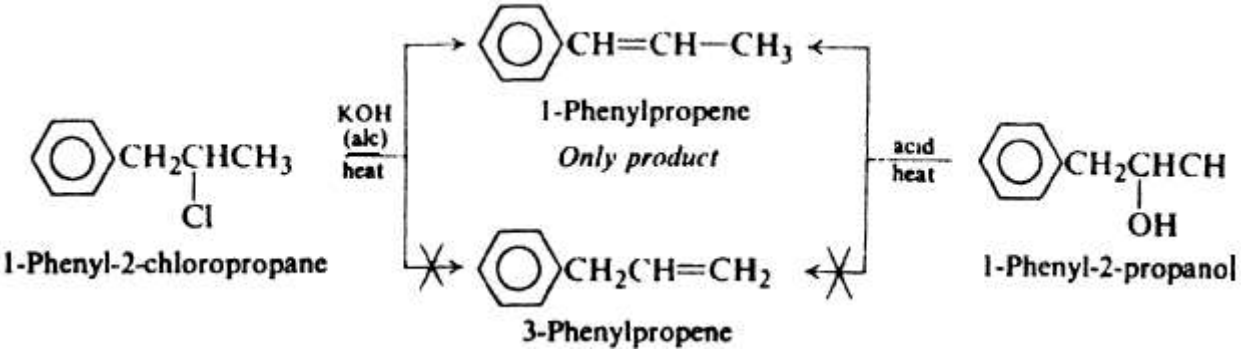
On an industrial scale, the elimination generally involves dehydrogenation. For example, styrene, the most important of these compounds and perhaps the most important synthetic aromatic compound can be prepared by simply heating ethylbenzene to about 600˚ in the presence of a catalyst. The ethylbenzene, in turn, is prepared by a Friedel-Crafts reaction between two simple hydrocarbons, benzene and ethylene.



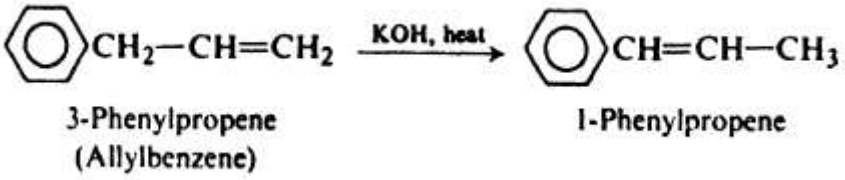
In the laboratory, however, we are most likely to use dehydrohalogenation or dehydration.



Dehydrohalogenation of 1-phenyl-2-chloropropane, or dehydration of 1-phenyl-2-propanol, could yield two products: 1-phenylpropene or 3-phenylpropene. Actually, only the first of these products is obtained. The isomeric alkenes can be formed by elimination, the preferred product is the more stable alkene.

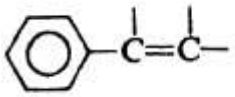


The 1-phenylpropene is much more stable than its isomer is shown by the fact that 3-phenylpropene is rapidly converted into 1-phenylpropene by treatment with hot alkali.



3-Phenylpropene (Allylbenzene) — 1-Phenylpropene

A double bond that is separated from a benzene ring by one single bond is said to be conjugated with the ring. Such conjugation confers unusual stability on a molecule. This stability affects not only orientation of elimination, but, affects the ease with which elimination takes place.



Double bond conjugated with ring:
unusually stable system

Reactions of alkenylbenzenes

Alkenylbenzenes undergo two sets of reactions:

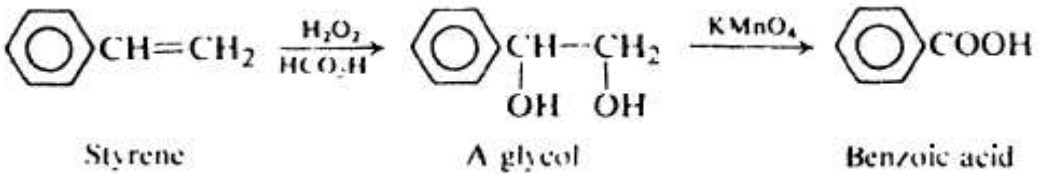
- Substitutionin the ring.
- Addition to the double bond in the side chain.

Since both ring and double bond are good sources of electrons, there may be competition between the two sites for certain electrophilic reagents; it is not surprising that, in general, the double bond shows higher reactivity than the resonance-stabilized benzene ring.

Although both the benzene ring and the carbon carbon double bond can be hydrogenated catalytically, the conditions required for the double bond are much milder; by proper selection of conditions it is quite easy to hydrogenate the side chain without touching the aromatic ring.

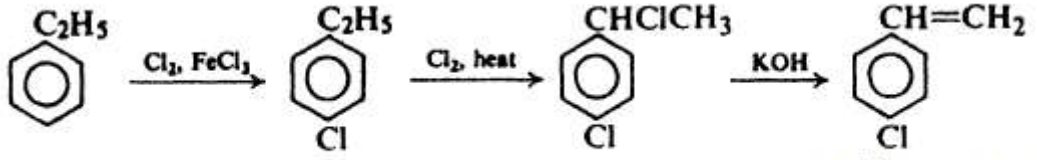
Styrene — Ethylbenzene — Ethylcyclohexane

Mild oxidation of the double bond yields a glycol; more vigorous oxidation cleaves the carbon- carbon double bond and generally gives a carboxylic acid in which the COOH group is attached to the ring.



Styrene — A glycol — Benzoic acid

Both double bond and ring react with halogens by ionic mechanisms that have essentially the same first step: attack on the n cloud by positively charged halogen. Halogen is consumed by the double bond first, and only after the side chain is completely saturated does substitution on the ring occur. Ring-halogenated alkenylbenzenes must be prepared, therefore, by generation of the double bond after halogen is already present on the ring. For example:



p-Chlorostyrene

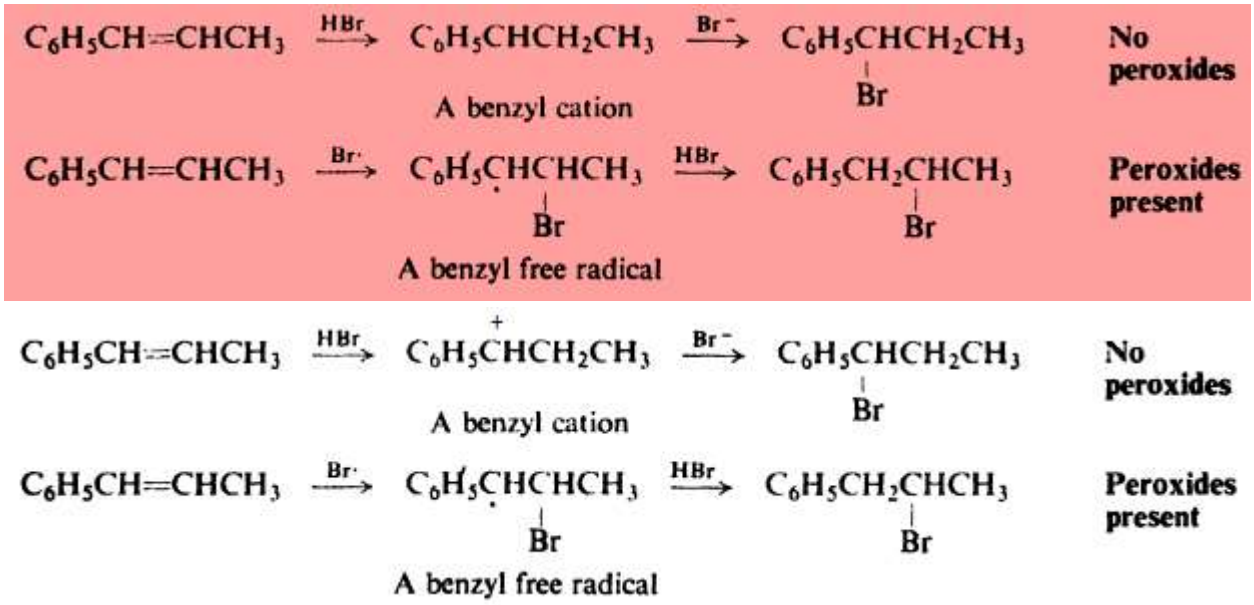
In a similar way, alkenyl benzenes undergo the other addition reactions characteristic of the carbon- carbon double bond.

Addition to conjugated alkenylbenzenes: Orientation, Stability of the benzyl cation

Addition of an unsymmetrical reagent to a double bond may in general yield two different products.

The effect of the benzene ring on orientation can be well illustrated by a single example, addition of HBr to 1-phenylpropene. In the absence of peroxides, bromine becomes attached to the carbon adjacent to the ring; in the presence of peroxides, bromine becomes attached to the carbon once removed from the ring.

According to the mechanisms proposed for these two reactions, these products are formed as follows:

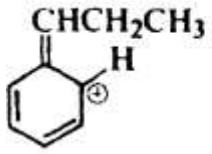


The first step of each of these reactions takes place in the way that yields the benzyl cation or the benzyl free radical rather than the alternative secondary cation or secondary free radical.

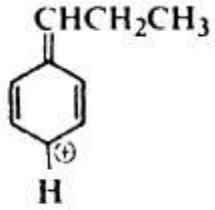
Stability of carbonium ions

$$\underset{3^\circ}{\text{benzyl}} > \underset{2^\circ}{\text{allyl}} > 1^\circ > CH_3^+$$

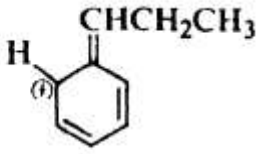
The stability of a benzyl cation relative to the compounds from which it is made is also accounted for by resonance involving the benzene ring. Both the carbonium ion and the compound from which it is made are hybrids of Kekule structures. In addition, the carbonium ion can be represented by three other structures, I, II, and III, in which the positive charge, is located on the ortho and para carbon atoms. Whether we consider this as resonance stabilization or simply as dispersal of charge, contribution from these structures stabilizes the carbonium ion.



I



II



III

Addition to conjugated alkenylbenzenes: reactivity

On the basis of the stability of the particle being formed, we might expect addition to a conjugated alkenylbenzcne, which yields a stable benzyl cation or free radical, to occur faster than addition to a simple alkene. On the other hand, the conjugated alkenylbenzenes are more stable than simple alkenes. On this basis alone, we might expect addition to conjugated alkenylbenzenes to occur more slowly than to simple alkenes.

The situation is exactly analogous for addition to conjugated dienes. Both reactant and transition state are stabilized by resonance; whether reaction is faster or slower than for simple alkenes depends upon which is stabilized more.

Alkynylbenzenes

The preparations and properties of the alkynylbenzenes are just what we might expect from our knowledge of benzene and the alkynes.

Aromaticity

Benzene

All organic compounds divide into two broad classes:

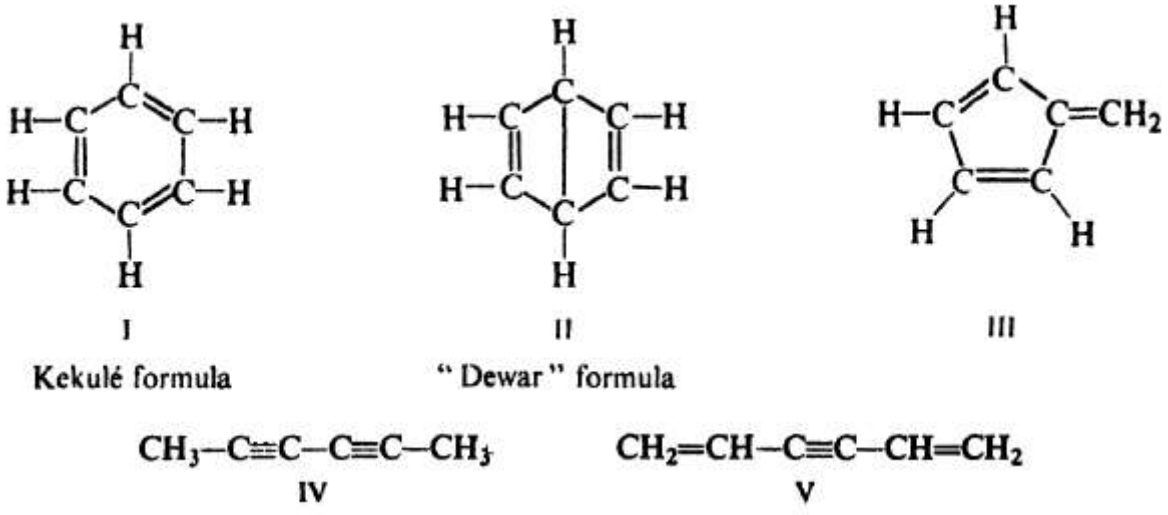
1. **Aliphatic compounds**: Aliphatic compounds are open-chain compounds and those cyclic compounds that resemble the open-chain compounds like alkanes, alkenes, alkynes, and their cyclic analogs.
2. **Aromatic compounds**. Aromatic compounds are benzene and compounds that resemble benzene in chemical behavior. Some compounds that possess aromatic properties have structures that seem to differ considerably from the structure of benzene, however, there is a basic similarity in electronic configuration.

Molecular formula: Isomer number, Kekule structure

Benzene has the molecular formula C_6H_6. From its elemental composition and molecular weight, benzene was known to contain six carbon atoms and six hydrogen atoms. The question was: how are these atoms arranged?

In 1858, August Kekule (of the University of Bonn) had proposed that carbon atoms can join to one another to form chains. Then, in 1865, he offered an answer to the question of benzene: these carbon chains can. Sometimes be closed, to form rings.

Kekule's structure of benzene was one that we would represent today as I.



I — Kekulé formula

II — "Dewar" formula

III

$CH_3-C\equiv C-C\equiv C-CH_3$ IV

$CH_2=CH-C\equiv C-CH=CH_2$ V

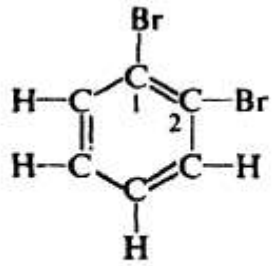
Other structures are, of course, consistent with the formula C_6H_6: for example II- V. Of all these, Kekule's structure was accepted as the most nearly satisfactory according to **isomer number**.

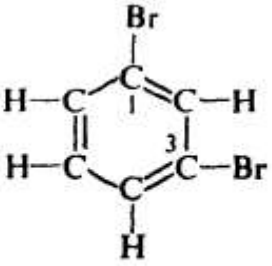
Benzene yields only one monosubstitution product, C_6H_5Y. Only one bromobenzene, C_6H_5Br, is obtained when one hydrogen atom is replaced by bromine; similarly, only one chlorobenzene, C_6H_5Cl, or one nitrobenzene, $C_6H_5NO_2$, etc., has ever been made. This fact places a severe limitation on the structure of benzene: each hydrogen must be exactly equivalent to every other hydrogen, since the replacement of any one of them yields the same product.

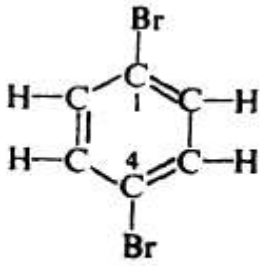
Structure V, for example, must now be rejected, since it would yield two isomeric monobromo derivatives, the 1-bromo and the 2-bromo compounds; all hydrogens are not equivalent in V. Similar reasoning shows us that II and III are likewise unsatisfactory. I and IV, among others, are still possibilities.

Benzene yields three isomeric disubstitution products, $C_6H_4Y_2$ or C_6H_4YZ. Three and only three isomeric dibromobenzenes, $C_6H_4Br_2$, three chloronitrobenzenes, $C_6H_4ClNO_2$, etc., have ever been made. This fact further limits our choice of a structure; for example, IV must now be rejected.

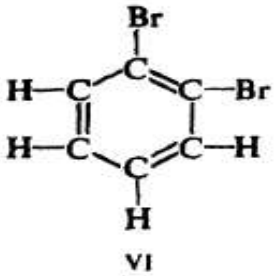
At first glance, structure I seems to be consistent with this new fact; that is, we can expect three isomeric dibromo derivatives, the 1,2- the 1,3-, and the 1,4- dibromo compounds shown:

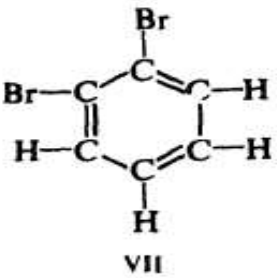

1,2-Dibromobenzene


1,3-Dibromobenzene

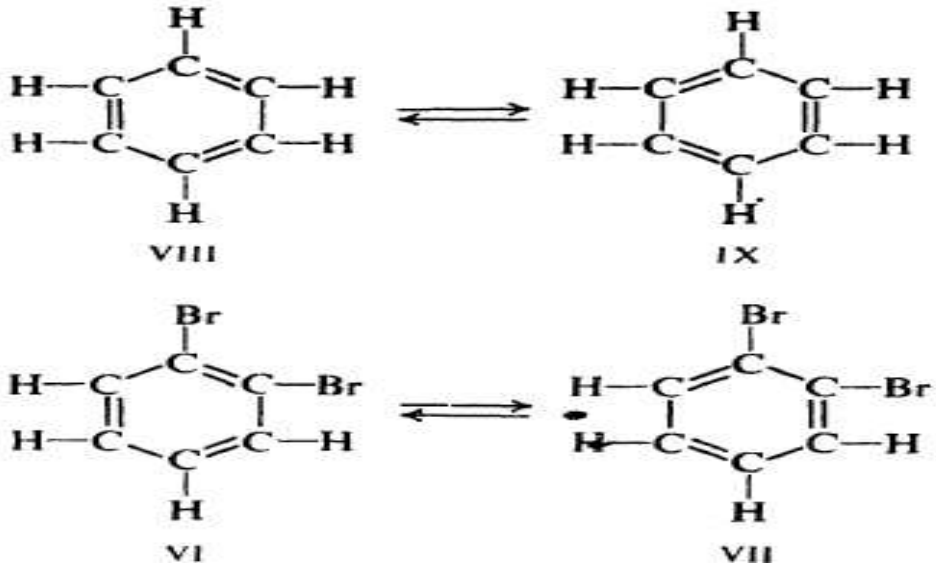

1,4-Dibromobenzene

Closer examination of structure I shows, however, that two 1,2-dibromo isomers (VI and VII), 'differing in the positions of bromine relative to the double bonds, should be possible:


VI


VII

The benzene molecule as a dynamic thing and it's described it in terms of two structures, by Kekul, VIII and IX, between which the benzene molecule alternates. As a consequence, the two 1,2-dibromobenzenes VI and VII would be in rapid equilibrium and hence could not be separated.



Later, when the idea of tautomerism became defined, it was assumed that Kekule's "alternation" essentially amounted to tautomerism. (*Compounds whose structures differ markedly in arrangement of atoms, but which exist in equilibrium, are called tautomers ,like Keto-enol tautomerism).*

Stability of the benzene ring: Reactions of benzene.

Benzene undergoes substitution rather than addition. Kekule's structure of benzene is one that we would call "cyclohexatriene." We would expect this cyclohexatriene, like the very similar compounds, cyclohexadiene and cyclohexene, to undergo readily the addition reactions characteristic of the alkene structure, but this is not the case; under conditions that cause an alkene to undergo rapid addition, benzene reacts either not at all or very slowly.

CYCLOHEXENE vs. BENZENE		
Reagent	**CYCLOHEXENE**	**BENZENE**
$KMnO_4$ (Cold, dilute, aqueous)	**Rapid oxidation**	**No reaction**
Br_2/CCl_4 (In the dark)	**Rapid addition**	**No reaction**
HI	**Rapid addition**	**No reaction**
H_2+Ni	**Rapid hydrogenation at25˚, 20 Ib/in.^{2}**	**Slow hydrogenation at 100-200˚, 1500 Ib/in.^{2}**

In place of addition reactions, benzene readily undergoes a new set of reactions, all involving substitution. The most important are:

REACTIONS OF BENZENE

1. Nitration.

$$C_6H_6 + HONO_2 \xrightarrow{H_2SO_4} C_6H_5NO_2 + H_2O$$
Nitrobenzene

2. Sulfonation.

$$C_6H_6 + HOSO_3H \xrightarrow{SO_3} C_6H_5SO_3H + H_2O$$
Benzenesulfonic acid

3. Halogenation.

$$C_6H_6 + Cl_2 \xrightarrow{Fe} C_6H_5Cl + HCl$$
Chlorobenzene

$$C_6H_6 + Br_2 \xrightarrow{Fe} C_6H_5Br + HBr$$
Bromobenzene

4. Friedel-Crafts alkylation.

$$C_6H_6 + RCl \xrightarrow{AlCl_3} C_6H_5R + HCl$$
An alkylbenzene

5. Friedel-Crafts acylation.

$$C_6H_6 + RCOCl \xrightarrow{AlCl_3} C_6H_5COR + HCl$$
An acyl chloride · A ketone

In each of these reactions an atom or group has been substituted for one of the hydrogen atoms of benzene. The product can itself undergo further substitution of the same kind; the fact that it has retained the characteristic properties of benzene indicates that it has retained the characteristic structure of benzene. It would appear that benzene resists addition, in which the benzene ring system would be destroyed, whereas it readily undergoes substitution, in which the ring system is preserved.

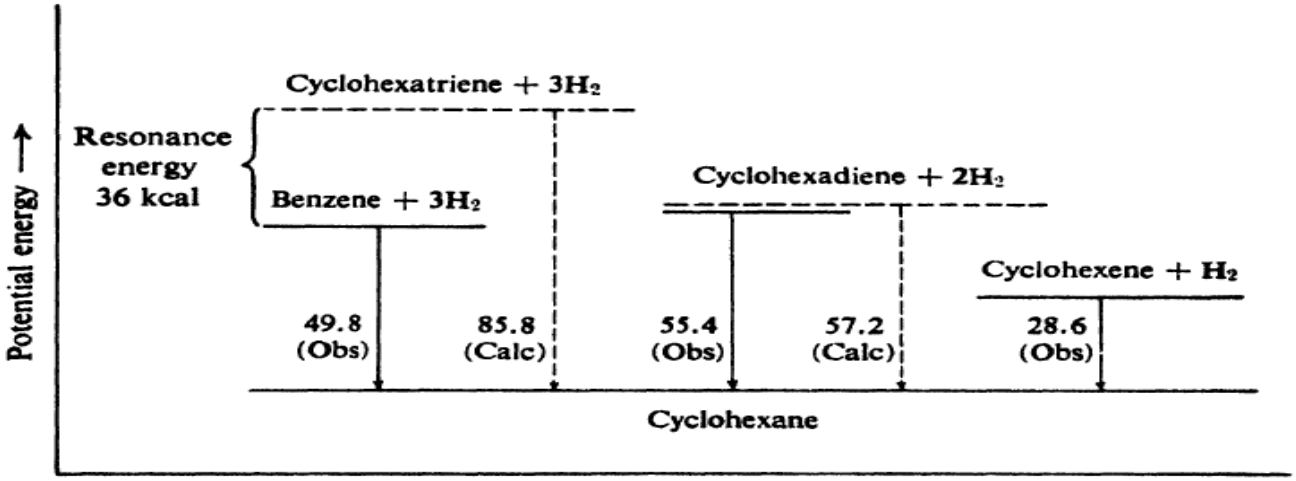
Stability of the benzene ring: Heats of hydrogenation and combustion.

Heats of hydrogenation and combustion of benzene are lower than expected; ***the heat of hydrogenation is the quantity of heat evolved when one mole of an unsaturated compound is hydrogenated.*** In most cases the value is about **28-30 kcal** for each double bond the compound contains.

The cyclohexene has a heat of hydrogenation of 28.6 kcal and cyclohexadiene has one about twice that (55.4 kcal.) We might reasonably expect cyclohexatriene to have a heat of hydrogenation about three times as large as cyclohexene, that is, about 85.8

kcal. Actually, the value for benzene (49.8 kcal) is 36 kcal less than this expected amount.

The fact that benzene evolves 36 kcal less energy than predicted can only mean that benzene contains 36 kcal less energy than predicted; in other words, benzene is more stable by 36 kcal than we would have expected cyclohexatriene to be. The heat of combustion of benzene is also lower than that expected, and by about the same amount.



Heats of hydrogenation and stability: benzene, cyclohexa- diene, and cyclohexene.

Carbon-carbon bond lengths in benzene

All carbon- carbon bonds in benzene are equal and are intermediate in length between single and double bonds.

Carbon-carbon double bonds in a wide variety of compounds are found to be about 1.34 A long.

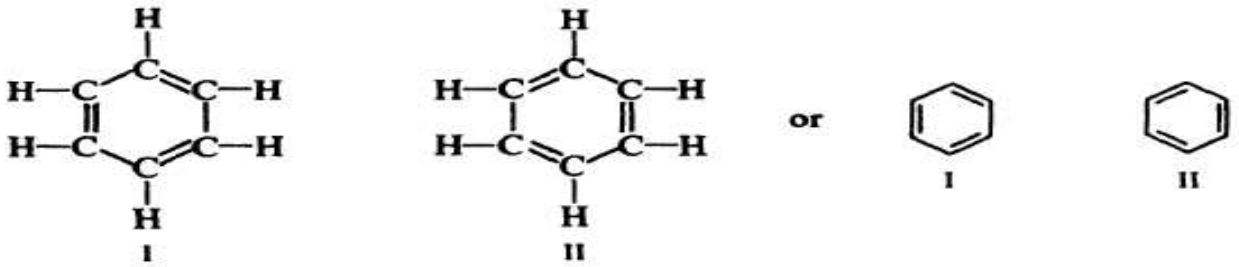
Carbon-carbon single bonds, in which the nuclei are held together by only one pair of electrons, are considerably longer: 1.53 A in ethane, for example, 1.50 A in propylene, 1.48 A in 1,3-butadiene.

If benzene actually possessed three single and three double bonds, as in a Kekule structure, we would expect to find three short bonds (1.34 A) and three long bonds (1.48 A, probably, as in 1,3-butadiene).

Actually, x-ray diffraction studies show that the six carbon-carbon bonds in benzene are equal and have a length of 1.39 A, and are thus intermediate between single and double bonds.

Resonance structure of benzene

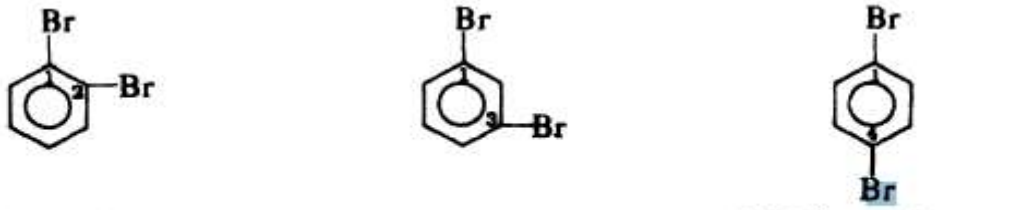
The currently accepted structure did not arise from the discovery of new facts about benzene, but is the result of an extension or modification of the structural theory; this extension is the concept of **resonance**.



The Kekule structures I and II meet the conditions for resonance: structures that differ only in the arrangement of electrons. Benzene is a hybrid of I and II. Since; I and II are exactly equivalent, and hence of exactly the same stability, they make equal contributions to the hybrid. And, also since I and II are exactly equivalent, stabilization due to resonance should be large.

The six bond lengths are identical because the six bonds are identical: they are one-and-a half bonds and their length, 1.39 A, is intermediate between the lengths of single and double bonds.

When it is realized that all carbon-carbon bonds in benzene are equivalent, there is no longer any difficulty in accounting for the number of isomeric disubstitution products. It is clear that there should be just three, in agreement with experiment:



1,2-Dibromobenzene 1,3-Dibromobenzene 1,4-Dibromobenzene

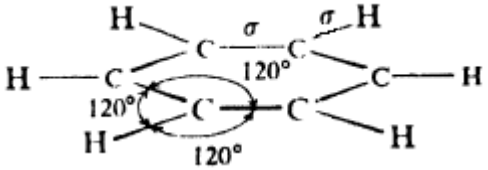
Finally, the "unusual" stability of benzene is not unusual at all: it is what one would expect of a hybrid of equivalent structures. The 36 kcal of energy that Benzene does not contain compared with cyclohexatriene is resonance energy. It is the 36 kcal of resonance energy that is responsible for the new set of properties we call aromatic properties.

Addition reactions convert an alkene into a more stable saturated compound. Hydrogenation of cyclohexene, for example, is accompanied by the evolution of 28.6 kcal; the product lies 28.6 kcal lower than the reactants on the energy scale. But addition would convert benzene into a less stable product by destroying the resonance-stabilized benzene ring system; for example, the first stage of hydrogenation of benzene requires 5.6 kcal to convert benzene into the less stable cyclohexadiene. As a consequence, it is easier for reactions of benzene to take an entirely different course, one in which the ring system is retained: **substitution.**

Orbital picture of benzene

In the benzene each carbon is bonded to three other atoms, it uses sp^2 orbitals (as in ethylene). These lie in the same plane that of the carbon nucleus, and are directed

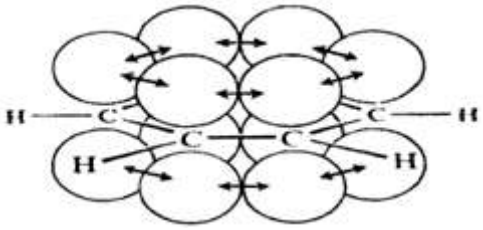
toward the corners of an equilateral triangle. If we arrange the six carbons and six hydrogens of benzene to permit maximum overlap of these orbitals, we obtain the structure shown below.



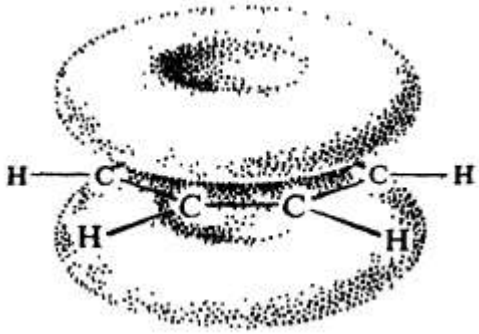
Benzene is a flat molecule, with every carbon and every hydrogen lying in the same plane. It is a very symmetrical molecule, too, with each carbon atom lying at the angle of a regular hexagon; every bond angle is 120

The molecule is not yet complete, however. There are still six electrons to be accounted for. In addition to the three orbitals already used, each carbon atom has a fourth orbital, a p orbital. As we know, this p orbital consists of two equal lobes, one lying above and the other lying below the plane of the other three orbitals, that is, above and below the plane of the ring; it is occupied by a single electron.

As in the case of ethylene, the p orbital of one carbon can overlap the p orbital of an adjacent carbon atom, permitting the electrons to pair and an additional π bond to be formed.



But the overlap here is not limited to a pair of p orbitals as it was in ethylene; the p orbital of any one carbon atom overlaps equally well the p orbitals of both carbon atoms to which it is bonded. The result is two continuous doughnut-shaped electron clouds, one lying above and the other below the plane of the atoms.



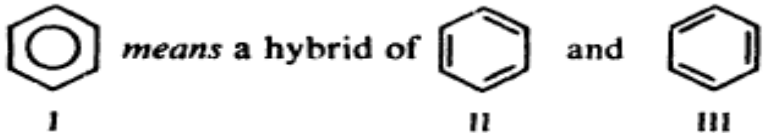
The delocalization of the π electrons and their participation in several bonds, that makes the molecule more stable.

The π electrons are thus particularly available to a reagent that is seeking electrons: the typical reactions of the benzene ring are those in which it serves as a source of electrons for electrophilic (acidic) reagents. Because of the resonance stabilization of

the benzene ring, these reactions lead to substitution, in which the aromatic character of the benzene ring is preserved.

Representation of the benzene ring

For convenience the benzene ring represent by a regular hexagon containing a circle (I); it is understood that a hydrogen atom is attached to each angle of the hexagon unless another atom or group is indicated.



I represent a resonance hybrid of the Kekule structures II and III. The straight lines stand for the σ bonds joining carbon atoms. The circle stands for the cloud of six delocalized π electrons. (From another viewpoint, the straight lines stand for single bonds, and the circle stands for the extra half-bonds.)

Aromatic character: The Huckel (4n + 2) rule

The aromatic compounds as those that resemble benzene. But which properties of benzene must a compound possess before being aromatic? Besides the compounds that contain benzene rings, there are many other substances that are called aromatic; yet some of these superficially bear little resemblance to benzene.

What properties do all aromatic compounds have in common?

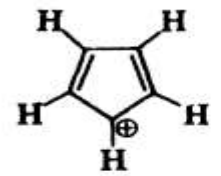
From the experimental standpoint, aromatic compounds are compounds whose molecular formulas would lead us to expect a **high degree of unsaturation, and yet which are resistant to the addition reactions generally characteristic of unsaturated compounds.** Instead of addition reactions, we often find that these aromatic compounds **undergo electrophilic substitution reactions** like those of benzene. Along with this resistance toward addition and they have **an evidence of unusual stability**: **low heats of hydrogenation and low heats of combustion.**

Aromatic compounds are **cyclic generally containing five-, six-, or seven-membered** rings and when examined by physical methods, they are found to **have flat (or nearly fiat) molecules.**

From a theoretical standpoint, to be aromatic a compound must have a molecule that contains **cyclic clouds of delocalized π electrons above and below the plane of the molecule.** Furthermore, the π clouds must contain a total of (4n+2) π electron. That is to say, for the particular degree of stability that characterizes an aromatic compound, delocalization alone is not enough. There must be a particular number of π electrons: 2, or 6, or 10, etc. This requirement, called the 4n + 2 rule or Huckel rule, is based on quantum mechanics, and has to do with the filling up of the various orbitals that make up the π cloud.

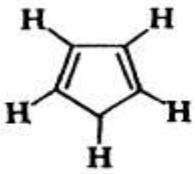
Benzene has six π electrons, the aromatic sextet; six is, of course, a Huckel number, corresponding to n = 1. Besides benzene and its relatives (naphthalene, anthracene,

phenanthrene), a number of heterocyclic compounds are aromatic; these aromatic heterocycles are just the ones that can provide an aromatic sextet.
Or, as further examples, consider these six compounds, for each of which just one contributing structure is shown:



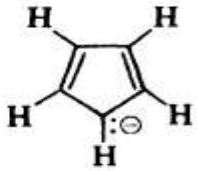
Cyclopentadienyl cation

Four π electrons



Cyclopentadienyl radical

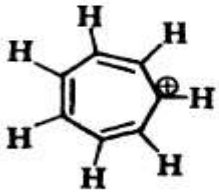
Five π electrons



Cyclopentadienyl anion

Six π electrons

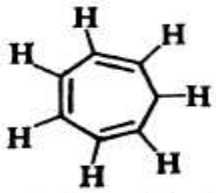
Aromatic



Cycloheptatrienyl cation (Tropylium ion)

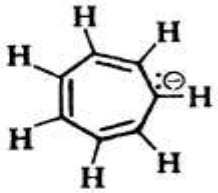
Six π electrons

Aromatic



Cycloheptatrienyl radical

Seven π electrons

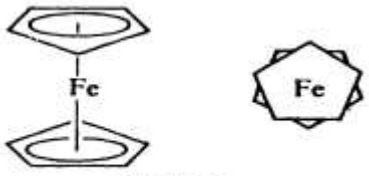


Cycloheptatrienyl anion

Eight π electrons

Each molecule is a hybrid of either five or seven equivalent structures, with the charge or odd electron on each carbon. Yet, of the six compounds, only two give evidence of unusually high stability: the cyclopentadienyl anion and the cycloheptatrienyl cation (tropylium ion).

For a hydrocarbon, cyclopentadiene is an unusually strong acid (Ka = 10^{-15}), indicating that loss of a hydrogen ion gives a particularly stable anion. (It is, for example, a much stronger acid than cycloheptatriene, Ka = 10^{-45}, despite the fact that the latter gives an anion that is stabilized by seven contributing structures.). Dicyclopentadienyl iron (ferrocene), $[(C_5H_5)^-]_2Fe^{++}$, is a stable molecule that has been shown to be a "sandwich" of an iron atom between two flat five-membered rings. All carbon-carbon bonds are 1.4 A long. The rings of ferrocene undergo two typically aromatic substitution reactions: sulfonation and the Friedel-Crafts reaction.

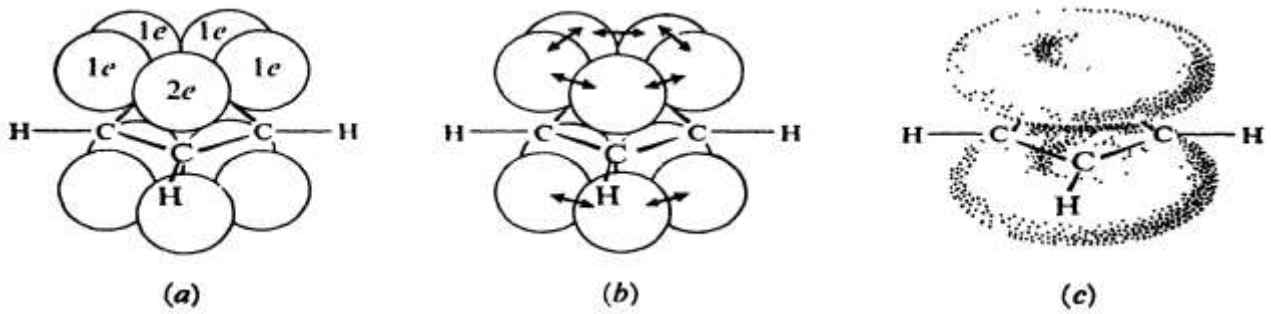


Ferrocene

The cycloheptatrienyl derivatives, on the other hand, it is the cation that is unusual. Tropylium bromide, C_7H_7 Br, melts above 200˚, is soluble in water but insoluble in non-polar solvents, and gives an immediate precipitate of AgBr when treated with- silver

nitrate. This is strange behavior for an organic bromide, strongly suggests, even in the solid, we are dealing with an ionic compound, R^+Br^-, the cation of which is actually a stable carbonium ion.

Consider the electronic configuration of the cyclopentadienyl anion. Each carbon, trigonally hybridized, is held by a σ bond to two other carbons and one hydrogen. The ring is a regular pentagon, whose angles (108˚) are not a bad fit for the 120˚ trigonal angle; any instability due to imperfect overlap (angle strain) is more than made up for by the delocalization that is to follow. Four carbons have one electron each in p orbitals; the fifth carbon (the "one" that lost the proton, but actually, of course, indistinguishable from the others) has two electrons. Overlap of the p orbitals gives rise to π clouds containing a total of six electrons, the aromatic sextet.

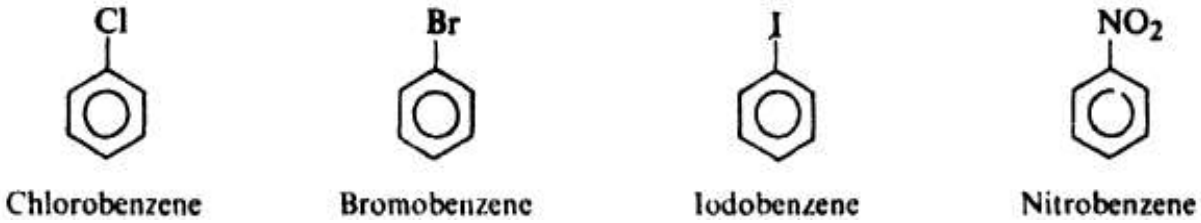


In a similar way, we arrive at the configuration of the tropylium ion. It is a regular heptagon (angles 128.5). Six carbons contribute one p electron each, and the seventh contributes only an empty p orbital. Result: the aromatic sextet.

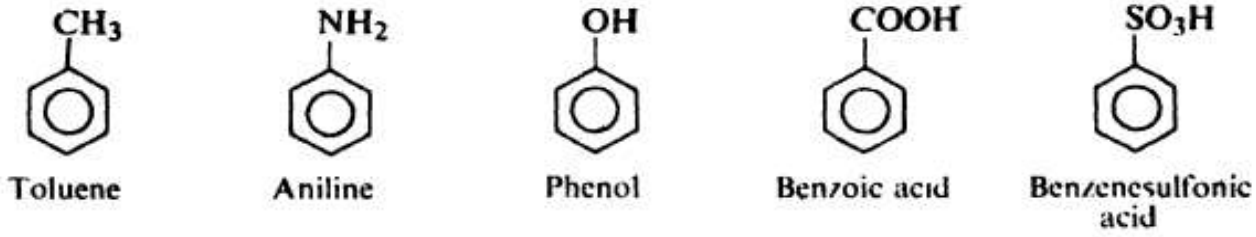
The ions are conveniently represented as:

Nomenclature of benzene derivatives

The nomenclature for many of benzene derivatives simply prefixes the name of the substituent group to the word -benzene, as, for example, in chlorobenzene, bromobenzene, iodobenzene, or nitrobenzene.

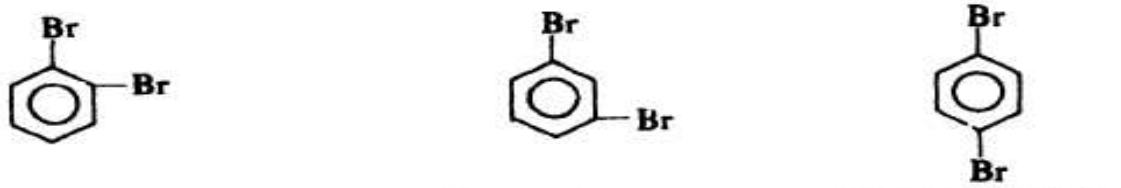


Other derivatives have special names which may show no resemblance to the name of the attached substituent group. For example, methylbenzene is always known as toluene, aminobenzene as aniline, hydroxybenzene as phenol, and so on. The most important of these special compounds are:



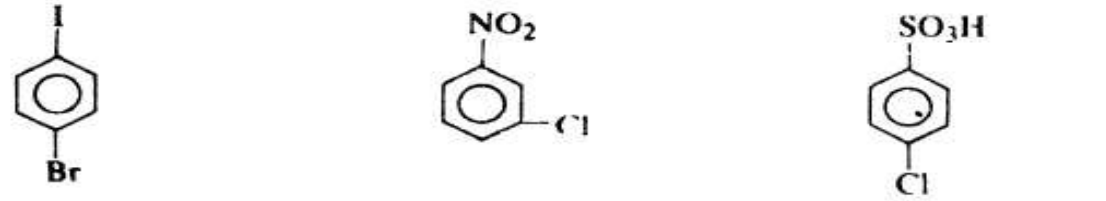
Toluene | Aniline | Phenol | Benzoic acid | Benzenesulfonic acid

If several groups are attached to the benzene ring, we must not only tell what they are, but also indicate their relative positions. The three possible isomers of a disubstituted benzene are differentiated by the use of the names ortho, meta, and para. For example:



o-Dibromobenzene *ortho* | *m*-Dibromobenzene *meta* | *p*-Dibromobenzene *para*

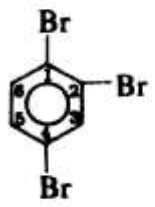
If the two groups are different, and neither is a group that gives a special name to the molecule, we simply name the two groups successively and end the word with -benzene, as, for example, m-chloronitrobenzene, p-bromoiodobenzene, etc. If one of the two groups is the kind that gives a special name to the molecule, then the compound is named as a derivative of that special compound, as, for example, nitrotoluene, bromophenol, etc.



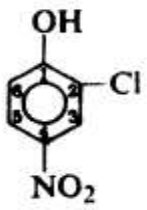
p-Bromoiodobenzene | *m*-Chloronitrobenzene | *p*-Chlorobenzenesulfonic acid

o-Nitrotoluene | *p*-Bromophenol | *m*-Nitrobenzoic acid | *o*-Iodoaniline

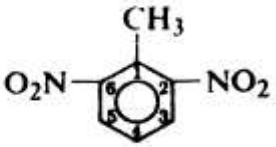
If more than two groups are attached to the benzene ring, numbers are used to indicate their relative positions. For example:



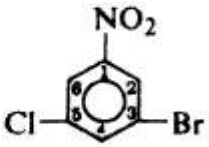
1,2,4-Tribromobenzene



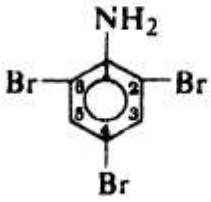
2-Chloro-4-nitrophenol



2,6-Dinitrotoluene



3-Bromo-5-chloronitrobenzene



2,4,6-Tribromoaniline

If all the groups are the same, each is given a number, the sequence being the one that gives the lowest combination of numbers; if the groups are different, then the last-named group is understood to be in position 1 and the other numbers conform to that, as, for example, in 3-bromo-5-chloronilrobenzene.

If one of the groups that gives a special name is present, then the compound is named as having the special group in position 1 ; thus in 2,6-dinitrotoluene the methyl group is considered to be at the 1 -position.

Aromaticity

Electrophilic Aromatic Substitution

The characteristic reaction of benzene is substitution, in which the resonance-stabilized ring system is preserved. Above and below the plane of the benzene ring there is a cloud of π electrons. Because of resonance, these π electrons are more involved in holding together carbon nuclei than are the π electrons of a carbon-carbon double bond. Still, in comparison with σ electrons, these π electrons are loosely held and are available to a reagent that is seeking electrons.

It is not surprising that in its typical reactions the benzene ring serves as a source of electrons, that is, **as a base**. The compounds with which it reacts are deficient in electrons, that is, **are electrophilic reagents or acids**. Just as the typical reactions of the alkenes are electrophilic addition reactions, so the typical reactions of the benzene ring **are electrophilic substitution reactions**.

These reactions are characteristic not only of benzene itself, but of the benzene ring wherever it is found and, indeed, of many aromatic rings, benzenoid and non-benzenoid.

Electrophilic aromatic substitution includes a wide variety of reactions: **nitration, halogenation, sulfonation, and Friedel-Crafts reactions,** undergone by nearly **all aromatic rings;** reactions **like nitrosation and diazo coupling**, undergone only by **rings of high reactivity**; and reactions like **desulfonation, isotopic exchange**, **and many ring closures** which, although apparently unrelated, are found on closer examination to be properly and profitably viewed as reactions of this kind. In synthetic importance electrophilic aromatic substitution is permits the direct introduction of certain substituent groups which can then be converted, by replacement or by transformation, into other substituents, including even additional aromatic rings.

ELECTROPHILIC AROMATIC SUBSTITUTION

Ar = aryl, any aromatic group with attachment directly to ring carbon

1. Nitration.

$$ArH + HONO_2 \xrightarrow{H_2SO_4} \underset{\text{A nitro compound}}{ArNO_2} + H_2O$$

2. Sulfonation.

$$ArH + HOSO_3H \xrightarrow{SO_3} \underset{\text{A sulfonic acid}}{ArSO_3H} + H_2O$$

3. Halogenation.

$$ArH + Cl_2 \xrightarrow{Fe} ArCl + HCl$$
An aryl chloride

$$ArH + Br_2 \xrightarrow{Fe} ArBr + HBr$$
An aryl bromide

4. Friedel-Crafts alkylation.

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

5. Friedel-Crafts acylation.

$$ArH + RCOCl \xrightarrow{AlCl_3} ArCOR + HCl$$
An acyl chloride — A ketone

6. Protonation.

$$ArSO_3H + H^+ \xrightarrow{H_2O} ArH + H_2SO_4$$ *Desulfonation*

$$ArH + D^+ \longrightarrow ArD + H^+$$ *Hydrogen exchange*

7. Thallation.

$$ArH + Tl(OOCCF_3)_3 \xrightarrow{CF_3COOH} ArTl(OOCCF_3)_2 + CF_3COOH$$
Thallium trifluoroacetate — An arylthallium ditrifluoroacetate

8. Nitrosation.

$$ArH + HONO \longrightarrow ArN{=}O + H_2O$$
A nitroso compound

Only for highly reactive ArH

9. Diazo coupling.

$$ArH + Ar'N_2{}^+X^- \longrightarrow ArN{=}NAr' + HX$$
A diazonium salt — An azo compound

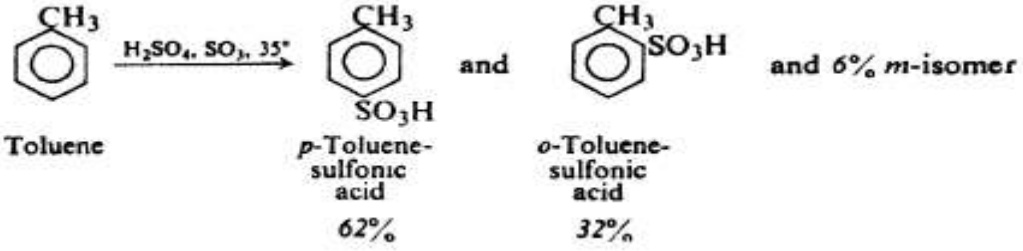
Only for highly reactive ArH

10. Kolbe reaction. Only for phenols.

11. Reimer-Tiemann reaction. Only for phenols.

Effect of substituent groups

Like benzene, toluene undergoes electrophilic aromatic substitution: sulfonation, for example. Although there are three possible monosulfonation products, this reaction actually yields appreciable amounts of only two of them: the o- and p isomers.



Benzene and toluene are insoluble in sulfuric acid, whereas the sulfonic acids are readily soluble; completion of reaction is indicated simply by disappearance of the hydrocarbon layer. When shaken with fuming sulfuric acid at room temperature,

benzene reacts completely within 20 to 30 minutes, whereas toluene is found to react within only a minute or two. Studies of nitration, halogenation, and Friedel-Crafts alkylation of toluene give analogous results. In some way the methyl group makes the ring more reactive than unsubstituted benzene, and directs the attacking reagent to the ortho and para positions of the ring.

On the other hand, nitrobenzene has been found to undergo substitution more slowly than benzene, and to yield chiefly the meta isomer.

Like methyl or nitro, any group attached to a benzene ring affects the reactivity of the ring and determines the orientation of substitution. When an electrophilic reagent attacks an aromatic ring, it is the group already attached to the ring that determines how readily the attack occurs and where it occurs.

A group that makes the ring more reactive than benzene is called an **activating group**.

A group that makes the ring less reactive than benzene is called a **deactivating group**.

A group that causes attack to occur chiefly at positions ortho and para to it is called **an ortho, para director**. A group that causes attack to occur chiefly at positions meta to it is called **a meta director**. The reactivity and orientation of substitution is based on mechanism for electrophilic aromatic substitution.

Determination of orientation

To determine the effect of a group on orientation is, in principle, quite simple: the compound containing this group attached to benzene is allowed to undergo substitution and the product is analyzed for the proportions of the three isomers. Identification of each isomer as ortho, meta, or para generally involves comparison with an authentic sample of that isomer prepared by some other method from a compound whose structure is known.

In this way it has been found that every group can be put into one of two classes: **ortho, para directors or meta directors.** The orientation of nitration in a number of substituted benzenes show that of the five positions open to attack, three (60%) are ortho and para to the substituent group, and two (40%) are meta to the group; if there were no selectivity in the substitution reaction, we would expect the ortho and para isomers to make up 60% of the product, and the meta isomer to make up 40%. We see that seven of the groups direct 96-100% of nitration to the ortho and para positions; the other six direct 72-94% to the meta positions.

ORIENTATION OF NITRATION OF C_6H_5Y

Y	*Ortho*	*Para*	*Ortho* plus *para*	*Meta*
—OH	50–55	45–50	100	trace
—$NHCOCH_3$	19	79	98	2
—CH_3	58	38	96	4
—F	12	88	100	trace
—Cl	30	70	100	trace
—Br	37	62	99	1
—I	38	60	98	2
—NO_2	6.4	0.3	6.7	93.3
—$N(CH_3)_3^+$	0	11	11	89
—CN	—	—	19	81
—COOH	19	1	20	80
—SO_3H	21	7	28	72
—CHO	—	—	28	72

A given group causes the same general kind of orientation predominantly ortho, para or predominantly meta whatever the electrophilic reagent involved.

The actual distribution of isomers may vary, however, from reaction to reaction. For example, compare the distribution of isomers obtained from toluene by sulfonation or bromination with that obtained by nitration.

ORIENTATION OF SUBSTITUTION IN TOLUENE

	Ortho	*Meta*	*Para*
Nitration	58	4	38
Sulfonation	32	6	62
Bromination	33	—	67

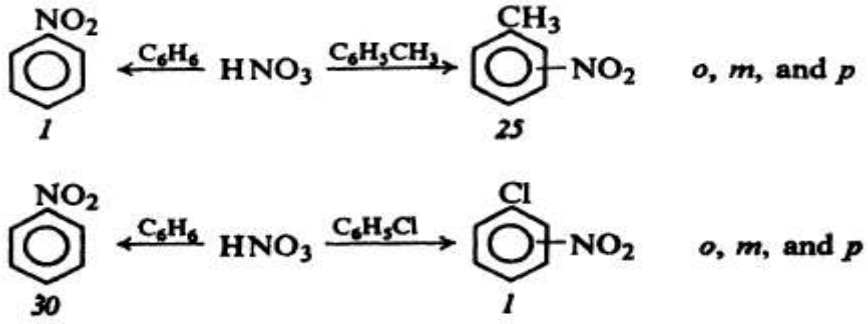
Determination of relative reactivity

A group is classified as activating if the ring it is attached to is more reactive than benzene, and is classified as deactivating if the ring it is attached to is less reactive than benzene. The reactivity's of benzene and substituted benzene are compared in one of the following ways.

- **The time required for reactions to occur under identical conditions** can be measured. Example, toluene is found to react with fuming sulfuric acid in about one-tenth to one-twentieth the time required by benzene. Toluene is more reactive than benzene, and $-CH_3$ is therefore an activating group.
- **The severity of conditions** required for comparable reaction to occur within the same period of time can be observed. For example, benzene is nitrated in less than an hour at 60˚ by a mixture of concentrated sulfuric acid and concentrated nitric acid; comparable nitration of nitrobenzene requires treatment at 90˚ with

fuming nitric acid and concentrated sulfuric acid. Nitrobenzene is evidently less reactive than benzene, and the nitro group, NO_2, is a deactivating group.

- **Quantitative comparison under identical reaction conditions**, ***competitive reactions*** can be carried out, in which the compounds to be compared are allowed to compete for a limited amount of a reagent. For example, if equimolar amounts of benzene and toluene are treated with a small amount of nitric acid (in a solvent like nitromethane or acetic acid, which will dissolve both organic and inorganic reactants), about 25 times as much nitrotoluene as nitrobenzene is obtained, showing that toluene is 25 times as reactive as benzene. On the other hand, a mixture of benzene and chlorobenzene yields a product in which nitrobenzene exceeds the nitrochlorobenzenes by 30: 1, showing that chlorobenzene is only one-thirtieth as reactive as benzene. The chloro group is therefore classified as deactivating, the methyl group as activating.



The activation or deactivation caused by some groups is extremely powerful: aniline, $C_6H_5NH_2$, is roughly one million times as reactive as benzene, and nitrobenzene, $C_6H_5NO_2$, is roughly one-millionth as reactive as benzene.

Classification of substituent groups

All substituent groups fall into one of two glasses:

- Activating and ortho, para directing,
- Deactivating and meta-directing.
- **The halogens are in a class by themselves**, being deactivating but ortho, para directing.

EFFECT OF GROUPS ON ELECTROPHILIC AROMATIC SUBSTITUTION

Activating: *Ortho,para* Directors

Strongly activating
—NH_2 (—NHR, —NR_2)
—OH

Moderately activating
—OCH_3 (—OC_2H_5, etc.)
—$NHCOCH_3$

Weakly activating
—C_6H_5
—CH_3 (—C_2H_5, etc.)

Deactivating: *Meta* Directors
—NO_2
—$N(CH_3)_3^+$
—CN
—COOH (—COOR)
—SO_3H
—CHO, —COR

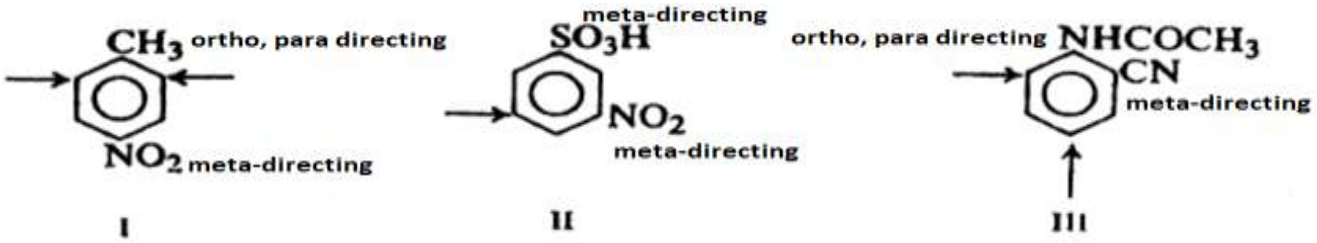
Deactivating: *Ortho,para* Directors
—F, —Cl, —Br, —I

Bromination of nitrobenzene will yield chiefly the *m*-isomer and that the reaction will go more slowly than the bromination of benzene itself; indeed, it will probably require severe conditions to go at all while the nitration of $C_6H_5NHCOCH_3$, (acetanilide) will yield chiefly the 0-and p-isomers and will take place more rapidly than nitration of benzene.

Orientation in di-substituted benzenes

The presence of two substituents on a ring makes the problem of orientation more complicated, but we can frequently make very definite predictions.

First of all, the two substituents may be located so that the directive influence of one **reinforces** that of the other; for example, in I, II, and III the orientation clearly must be that indicated by the arrows.



I II III

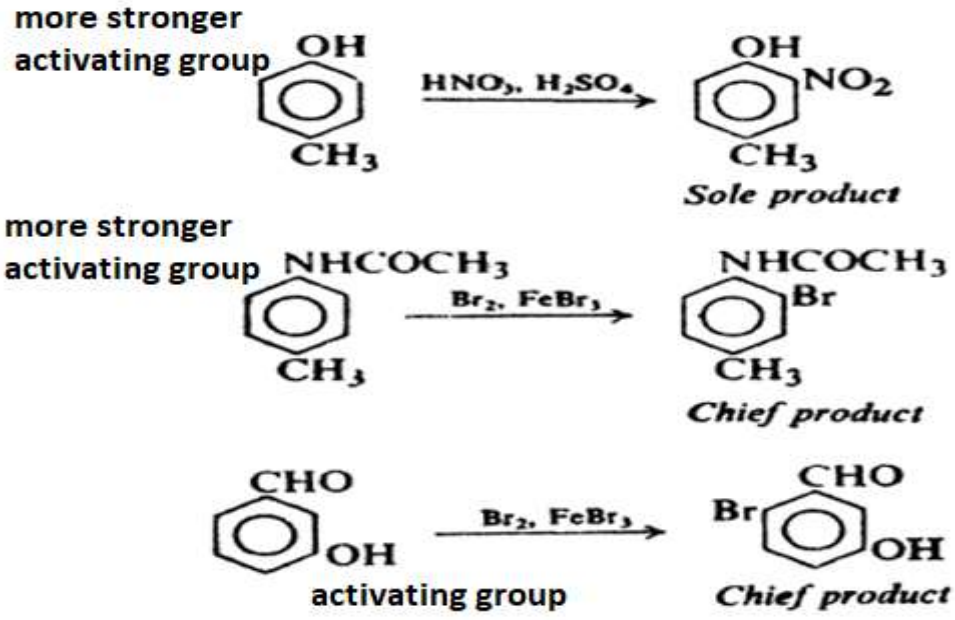
On the other hand, when the directive effect of one group **opposes** that of the other, it may be difficult to predict the major product; in such cases complicated mixtures of several products are often obtained.

Even where there are opposing effects, however, it is still possible in certain cases to make predictions in accordance with the following generalizations.

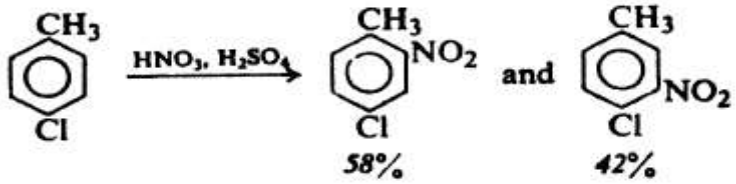
- Strongly activating groups generally win out over deactivating or weakly activating groups. The differences in directive power in the sequence:

$$-NH_2,\ -OH > -OCH_3,\ -NHCOCH_3 > -C_6H_5,\ -CH_3 > \textit{meta}\ \text{directors}$$

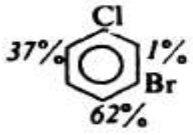
are great enough to be used in planning feasible syntheses. For example:



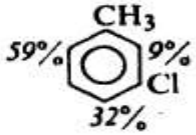
There must be, however, a fairly large difference in the effects of the two groups for clear cut results; otherwise one gets results like these:



- There is often little substitution between two groups that are meta to each other. In many cases it seems as though there just is not enough room between two groups located meta to each other for appreciable substitution to occur there, as illustrated by IV and V:



Nitration
IV

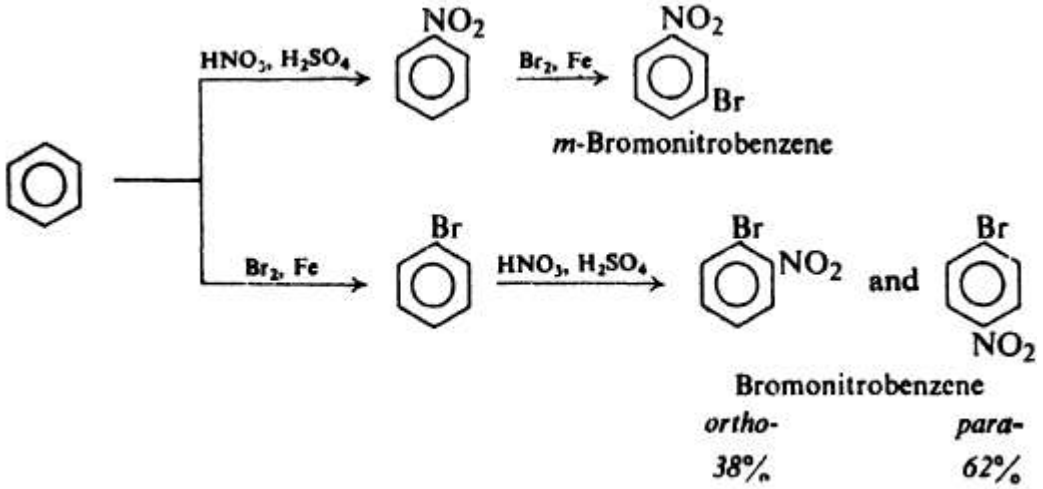


Nitration
V

Orientation and synthesis

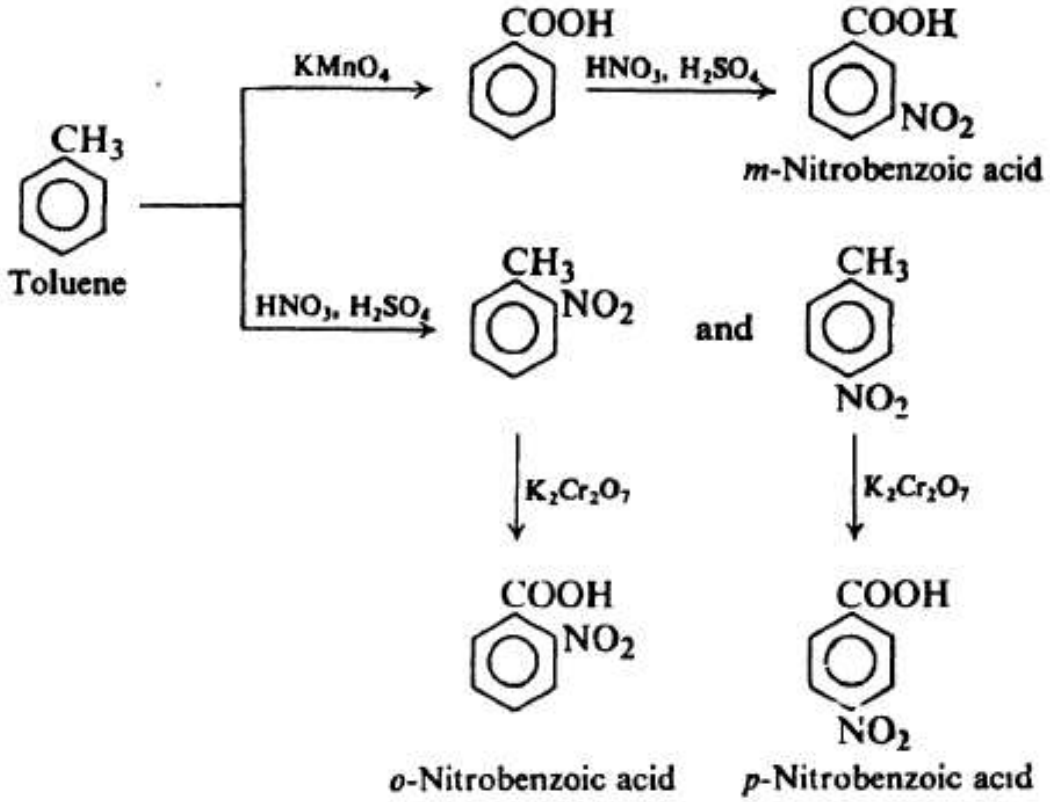
A laboratory synthesis is generally aimed at obtaining a single, pure compound. Whenever possible we should avoid use of a reaction that produces a mixture, since this lowers the yield of the compound we want and causes difficult problems of purification. The knowledge of orientation is important in the synthesis of pure aromatic compounds.

First of all, we must consider the order in which we introduce these various substituents into the ring. In the preparation of the bromonitrobenzenes, for example, it is obvious that if we nitrate first and then brominate, we will obtain the *m*-isomer; whereas if we brominate first and then nitrate, we will obtain a mixture of the o- and p-isomers. The order in which we decide to carry out the two steps, then, depends upon which isomer we want.



Next, if our synthesis involves conversion of one group into another, we must consider the proper time for this conversion. For example, oxidation of a methyl group yields a carboxyl group. In the preparation of nitrobenzoic acids from toluene, the particular product obtained depends upon whether oxidation or nitration is carried out first.

Substitution controlled by an activating group yields a mixture of ortho and para isomers; nevertheless, we must often make use of such reactions, as in the examples just shown. It is usually possible to obtain the pure para isomer from the mixture by fractional crystallization. As the more symmetrical isomer, it is the less soluble, and crystallizes while the solvent still retains the soluble ortho isomer. Some para isomer, of course, remains in solution to contaminate the ortho isomer, which is therefore difficult to purify. As we shall see, special approaches are often used to prepare ortho isomers.



In the special case of nitro compounds, the difference in boiling points is often large enough that both ortho and para isomers can be obtained, pure by fractional distillation. As a result, many aromatic compounds are best prepared not by direct substitution but by conversion of one group into another.

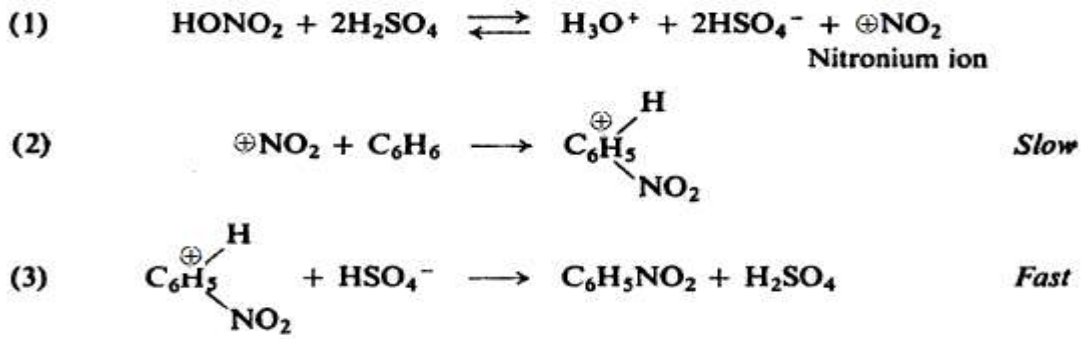
Mechanism of nitration

Benzene reacts with hot, concentrated nitric acid to give nitrobenzene. This sluggish reaction is hazardous because a hot mixture of concentrated nitric acid with any oxidizable material might explode. A safer and more convenient procedure uses a

mixture of nitric acid and sulfuric acid. Sulfuric acid is a catalyst, allowing nitration to take place more rapidly and at lower temperatures.

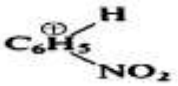
The first step in doing this is to examine the mechanism for the reaction. Let us begin with nitration, using benzene as the aromatic substrate.

The commonly accepted mechanism for nitration with a mixture of nitric and sulfuric acids involves the following sequence of reactions:

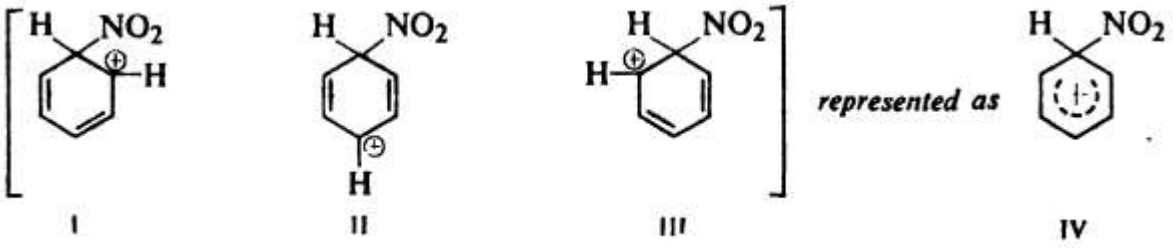


Step (1) generates the nitronium ion, $^+NO_2$, which is the electrophilic particle that actually attacks the benzene ring. This reaction is simply an acid-base equilibrium in which sulfuric acid serves as the acid and the much weaker nitric acid serves as a base. We may consider that the very strong acid, sulfuric acid, causes nitric acid to ionize in the sense, $HO^-\ldots{}^+NO_2$ rather than in the usual way, $H^+ \ldots {}^-ONO_2$ (donate proton to the base HNO_3). The nitronium ion is well known, existing in salts such as nitronium perchlorate, $NO_2^+ClO_4^-$, and nitronium fluoborate, $NO_2^+BF_4^-$.

The solutions of these stable nitronium salts in solvents like nitromethane or acetic acid have been used to nitrate aromatic compounds smoothly and in high yield at room temperature. Needing electrons, the nitronium ion finds them particularly available in the π cloud of the benzene ring, and so in step (2) attaches itself to one of the carbon atoms by a covalent bond. This forms the carbonium ion, often called a benzenonium ion.



This carbonium ion can be representing it by three structures (I, II, and III) that differ from each other only in position of double bonds and positive charge. The actual ion must then be a resonance hybrid of these three structures.



I II III IV

This means, of course, that the positive charge is not localized on one carbon atom, but is distributed over the molecule, being particularly strong on the carbon atoms ortho and para to the carbon bearing the NO_2 group.

The dispersal of the positive charge over the molecule by resonance makes this ion more stable than an ion with a localized positive charge. It is probably because of this stabilization that the carbonium ion forms at all, in view of the stability of the original benzene itself.

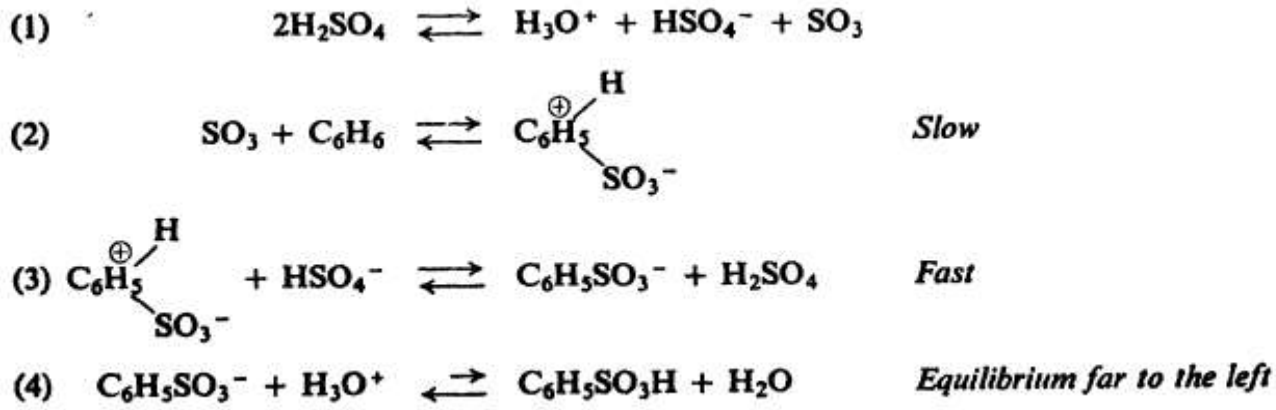
Thus far the reaction is like addition to alkenes: an electrophilic particle, attracted by the π electrons, attaches itself to the molecule to form a carbonium ion. But the fate of this carbonium ion is different from the fate of the ion formed from an alkene. Attachment of a basic group to the benzenonium ion to yield the addition product would destroy the aromatic character of the ring. Instead, the basic ion, HSO_4^- , abstracts a hydrogen ion (step 3) to yield the substitution product, which retains the resonance-stabilized ring. Loss of a hydrogen ion is one of the reactions typical of a carbonium ion; it is the preferred reaction in this case.

As with other carbonium ion reactions, it is the formation of the carbonium ion (step 2) that is the more difficult step; once formed, the carbonium ion rapidly loses a hydrogen ion (step 3) to form the products.

Electrophilic substitution, then, like electrophilic addition, is a stepwise process involving an intermediate carbonium ion. The two reactions differ, however, in the fate of the carbonium ion.

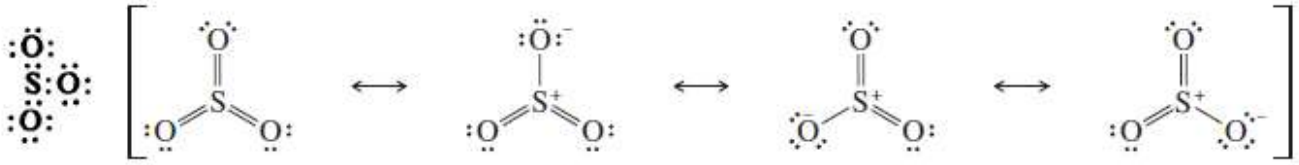
Mechanism of sulfonation

Sulfonation of many aromatic compounds involves the following steps:



Again the first step, which generates the electrophilic sulfur trioxide, is simply an acid-base equilibrium, this time between molecules of sulfuric acid. For sulfonation we commonly use sulfuric acid containing an excess of SO_3; even if this is not done, it appears that SO_3 formed in step (1) can be the electrophile.

"Fuming sulfuric acid" is the common name for a solution of 7% SO_3 in H_2SO_4. Sulfur trioxide is the anhydride of sulfuric acid, meaning that the addition of water to SO_3 gives H_2SO_4. Although it is uncharged, sulfur trioxide is a strong electrophile, with three sulfonyl S=O bonds drawing electron density away from the sulfur atom.



sulfur trioxide, a powerful electrophile

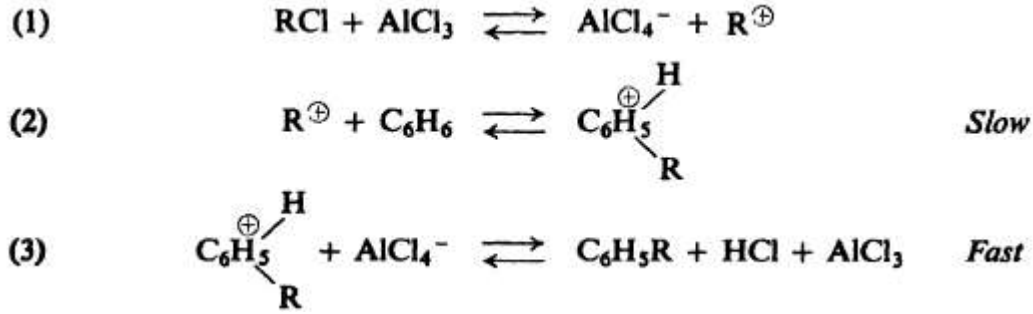
In step (2) the electrophilic reagent, SO_3, attaches itself to the benzene ring to form the intermediate carbonium ion. Although sulfur trioxide is not positively charged, it is electron-deficient, and hence an acid.

Step (3) is the loss of a hydrogen ion to form the resonance-stabilized substitution product, this time the anion of benzenesulfonic acid which, being a strong acid, is highly dissociated (step 4).

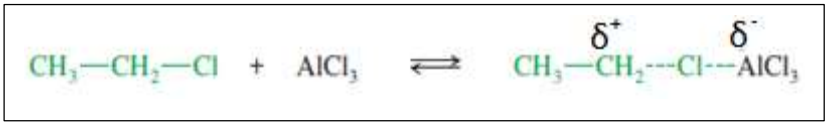
With some aromatic substrates and at certain acidities, the electrophile may be HSO_3^+ or molecules that can readily transfer SO_3 or HSO_3^+ to the aromatic ring.

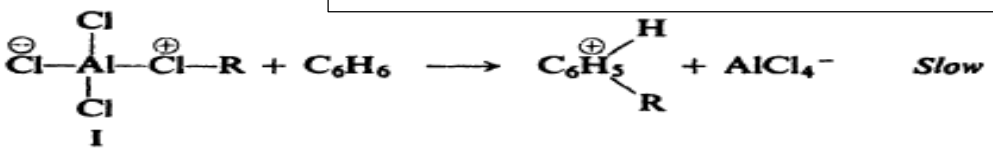
Mechanism of Friedel-Crafts alkylation

In Friedel-Crafts alkylation, the electrophile is typically a carbonium ion. It, too, is formed in an acid-base equilibrium, this time in the Lewis sense (bases donate pairs of electrons and **acids** accept pairs of electrons):



In certain cases, there is no free carbonium ion involved. Instead, the alkyl group is transferred without a pair of electrons directly to the aromatic ring from the polar complex, **I**, between $AlCl_3$ and the alkyl halide. In this complex, the carbon–halogen bond is weakened (as indicated by dashed lines) and there is considerable positive charge on the carbon atom.





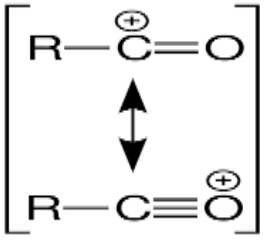
The electrophile is thus either **(a) R^+ or (b) a molecule like I** that can readily transfer R^+ to the aromatic ring. This duality of mechanism is common in electrophilic aromatic substitution. In either case, the Lewis acid R^+ is displaced from RCl by the other Lewis acid, $AlCl_3$.

Friedel–Crafts alkylations are used with a wide variety of primary, secondary, and tertiary alkyl halides. With secondary and tertiary halides, the reacting electrophile is probably the carbonium ion. With primary alkyl halides; the free primary carbonium ion is too unstable. The actual electrophile is likely a complex of aluminum chloride with the alkyl halide, **(I)**.

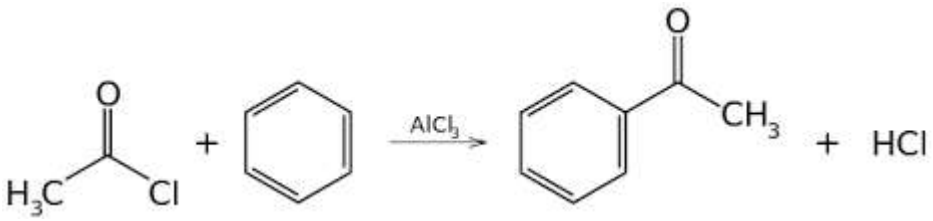
We speak of the Friedel-Crafts reaction as electrophilic substitution and, from the viewpoint of the aromatic ring, it is. But, just as an acid reacts with a base, so an electrophile reacts with a nucleophile (nucleus-lover), a molecule which can provide the electrons that the electrophile seeks. From the opposite point of view, then, this reaction involves nucleophilic attack by the aromatic ring on the alkyl group of complex I. The $AlCl_4^-$ ion is a better leaving group than Cl^- would be; the Lewis acid, $AlCl_3$, serves the same purpose here that a Lowry-Bronsted acid (*Acid: A substance that donates a hydrogen ion (proton donor)*) does in protonation of an alcohol (*the protonation of the alcohol by an acid, followed by loss of water to give a carbocation)*. The Friedel-Crafts reaction involves reactants other than alkyl halides (*several ways of generating carbocations, and most of these can be used for Friedel–Crafts alkylations. Two common methods are protonation of alkenes and treatment of alcohols with BF_3)* and Lewis acids other than aluminium chloride: BF_3, $SnCl_4$, HF, and even H^+.

Mechanism of Friedel–Crafts Acylation

The mechanism of Friedel–Crafts acylation resembles that for alkylation, except that the electrophile is a resonance-stabilized acylium ion. The acylium ion reacts with benzene or an activated benzene derivative via an electrophilic aromatic substitution to form an acylbenzene.

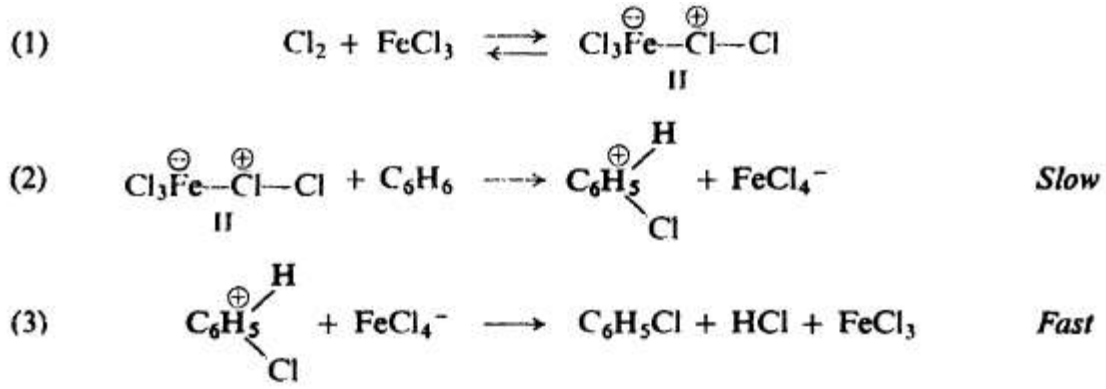


Resonance-stabilized acylium ion



Mechanism of halogenation

Aromatic halogenation, illustrated for chlorination, involves the following steps.



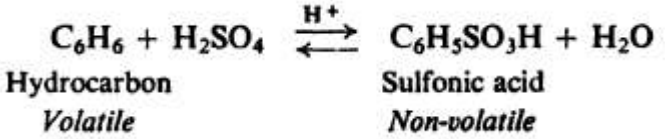
In step (1) chlorine it is not sufficiently electrophilic to react with benzene, and the formation of Cl^+ is difficult. A strong Lewis acid such as $FeCl_3$ catalyzes the reaction by forming a complex with Cl_2 that reacts like Cl^+. Chlorine donates a pair of electrons to $FeCl_3$, forming a stronger electrophile with a weakened Cl—Cl bond and a positive charge on one of the chlorine atoms.

In the key step (2) the chlorine is transferred, without its electrons, directly to the ring. Benzene is not as reactive as alkenes, which react rapidly with halogens at room temperature to give addition products.

Addition of halogens to alkenes, similarly involves attack by positive halogen to form an intermediate carbonium ion. The loosely held π electrons of an alkene make it more reactive, however, and positive halogen is transferred from the halogen molecule itself, Cl_2, with loss of Cl^-. The less reactive benzene molecule needs the assistance of a Lewis acid; reaction occurs with the loss of the better leaving group, $FeCl_4^-$. Indeed, more highly reactive aromatic compounds, i.e., those whose it electrons are more available, do react with halogens in the absence of any added Lewis acid.

Desulfonation: Mechanism of protonation

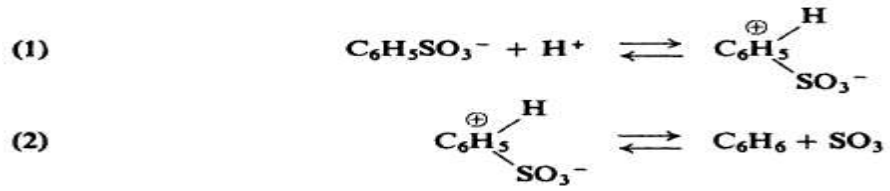
When an aromatic sulfonic acid is heated to 100-175 with aqueous acid, it is converted into sulfuric acid and an aromatic hydrocarbon. This desulfonation is the exact reverse of the sulfonation process by which the sulfonic acid was originally made.



By applying the usual equilibrium principles, we can select conditions that will drive the reaction in the direction we want it to go. To sulfonate we use a large excess of concentrated or fuming sulfuric acid; high concentration of sulfonating agent and low concentration of water shift the equilibrium toward sulfonic acid. To desulfonate we

use dilute acid and often pass superheated steam through the reaction mixture; high concentration of water and removal of the relatively volatile hydrocarbon by steam distillation shift the equilibrium toward hydrocarbon.

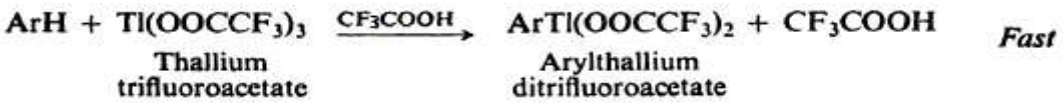
The mechanism of desulfonation must be the exact reverse of the mechanism of sulfonation.



The reaction is simply another example of electrophilic aromatic substitution. The electrophile is the proton, H^+, and the reaction is protonation or, more specifically, protodesulfonation.

Mechanism of thallation

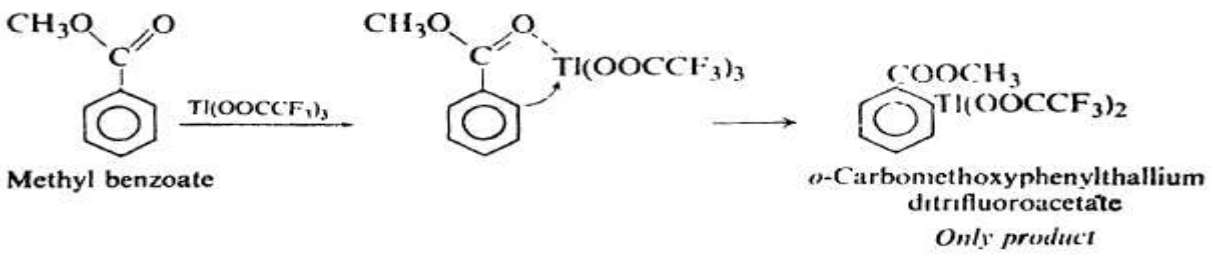
Treatment of aromatic compounds with thallium trifluoroacetate, $Tl(OOCCF_3)_3$, dissolved in trifluoroacetic acid (CF_3COOH) gives rapidly and in high yield arylthallium ditrifluoroacetates, stable crystalline compounds. Reaction is involving electrophilic attack on the aromatic ring by the (Lewis) acidic thallium.



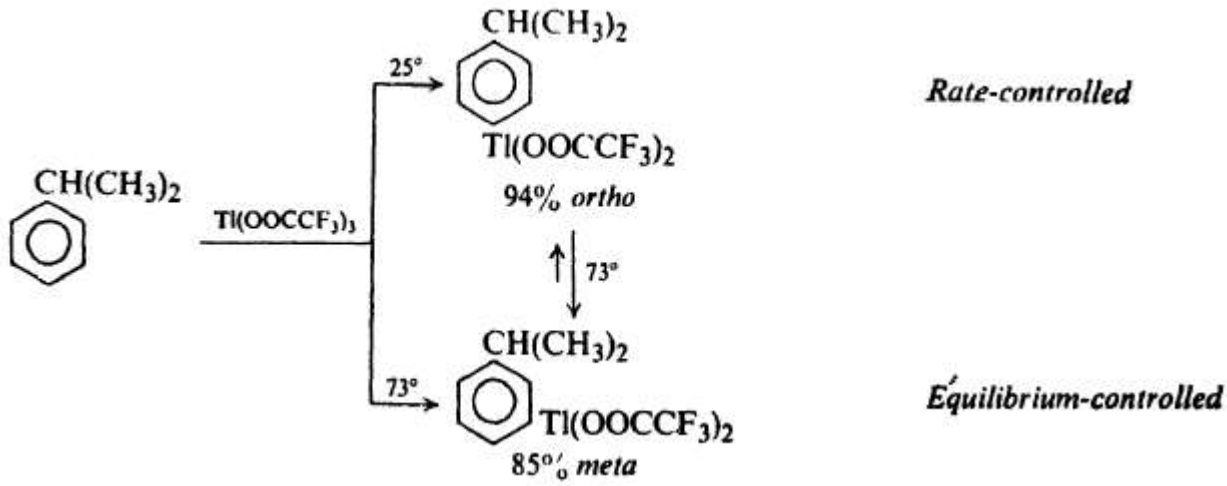
Thallium compounds are very poisonous, and must be handled with extreme care.

Although substituent groups affect the reactivity of the aromatic substrate as expected for electrophilic substitution, orientation is unusual in a number of ways, and it is here that much of the usefulness of thallation lies. Thallation is almost exclusively para to R, Cl, and OCH_3, and this is attributed to the bulk of the electrophile, thallium trifluoroacetate, which seeks out the uncrowded para position.

Thallation is almost exclusively ortho to certain substituents like COOH, $COOCH_3$, and CH_2OCH_3 (even though some of these are normally meta directing), and this is attributed to prior complexing of the electrophile with the substituent; thallium is held at just the right distance for easy intramolecular delivery to the ortho position. For example:



(In $C_6H_5CH_2CH_2COOH$, however, it is evidently held too far from the ring, and must leave the substituent before attacking the ring intermolecularly at the para position.)
Thallation is reversible, and when carried out at a higher temperature (73˚ instead of room temperature) yields the more stable isomer: usually the meta. For example:

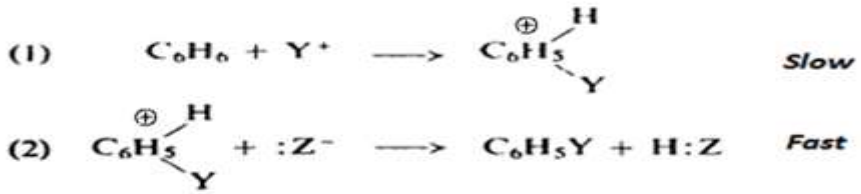


Now, these arylthallium compounds are useful, not in themselves, but as intermediates in the synthesis of a variety of other aromatic compounds. Thallium can be replaced by other atoms or groups which cannot themselves be introduced directly into the aromatic ring or at least not with the same regiospecificity (*being a chemical reaction in which one structural isomer is produced exclusively when other isomers are also theoretically possible*). In this way one can prepare phenols and aryl iodides.
Direct iodination of most aromatic rings does not work very well, but the process of thallation followed by treatment with iodide ion gives aryl iodides in high yields.

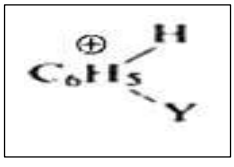
$$ArH + Tl(OOCCF_3)_3 \xrightarrow{CF_3COOH} ArTl(OOCCF_3)_2 \xrightarrow{KI} ArI$$

Mechanism of electrophilic aromatic substitution: a summary

Electrophilic aromatic substitution reactions seem, then, to proceed by a single mechanism, whatever the particular reagent involved. This can be summarized for the reagent YZ as follows:



Two essential steps are involved:
(1) Attack by an electrophilic reagent upon the ring to form a carbonium ion,

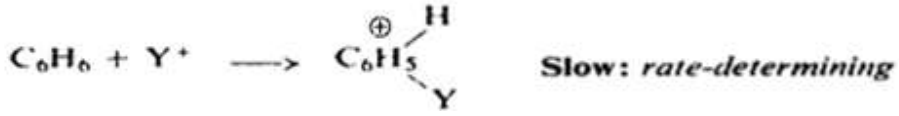


2) Abstraction of a hydrogen ion from this carbonium ion by some base. In each case there is a preliminary acid-base reaction which generates the attacking particle; the actual substitution, however, is contained in these two steps.

Reactivity and orientation

There are certain groups activating the benzene ring and direct substitution to ortho and para positions and that other group deactivate the ring and (except halogens) direct substitution to meta positions. The reactivity and orientation are both matters of relative rates of reaction. Methyl is said to activate the ring because it makes the ring react faster than benzene; it causes ortho, para orientation because it makes the ortho and para positions react faster than the meta positions.

Now, we know that, whatever the specific reagent involved, the rate of electrophilic aromatic substitution is determined by the same slow step -attack of the electrophile on the ring to form a carbonium ion:

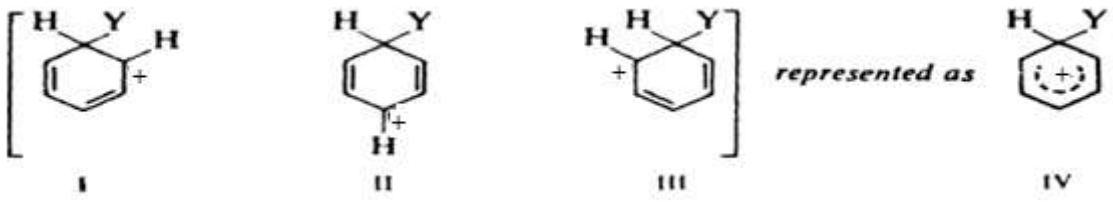


Any differences in rate of substitution must therefore be due to differences in the rate of this step.

For closely related reactions, a difference in rate of formation of carbonium ions is largely determined by a difference in stability of transition states.

The factors that stabilize the ion by dispersing the positive charge should for the same reason stabilize the incipient carbonium ion of the transition state. Here again we expect the more stable carbonium ion to be formed more rapidly.

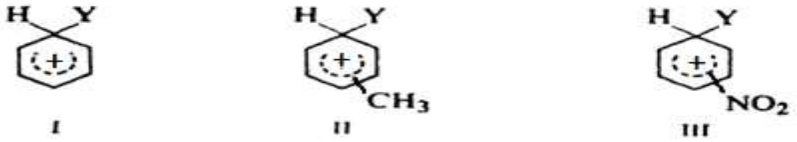
In electrophilic aromatic substitution the intermediate carbonium ion is a hybrid of structures I, II, and III, in which the positive charge is distributed about the ring, being strongest as the positions ortho and para to the carbon atom being attacked.



A group already attached to the benzene ring should affect the stability of the carbonium ion by dispersing or intensifying the positive charge, depending upon its electron-releasing or electron-withdrawing nature. It is evident from the structure of the ion (I-III) that this stabilizing or destabilizing effect should be especially important when the group is attached ortho or para to the carbon being attacked.

Theory of reactivity

To compare rates of substitution in benzene, toluene, and nitrobenzene, we compare the structures of the carbonium ions formed from the three compounds:



I II III

By releasing electrons, the methyl group (II) tends to neutralize the positive charge of the ring and so become more positive itself; this dispersal of the charge stabilizes the carbonium ion. In the same way the inductive effect (*An inductive effect is an electronic effect due to the polarisation of σ bonds within a molecule or ion. This is typically due to an electronegatvity difference between the atoms at either end of the bond.*) stabilizes the developing positive charge in the transition state and thus leads to a faster reaction (Substitution ortho or para to the alkyl group gives a transition state and an intermediate with the positive charge shared by the **tertiary carbon atom**. As a result, alkylbenzenes undergo electrophilic aromatic substitution faster than benzene, and the products are predominantly ortho- and para-substituted. An alkyl group is therefore an activating substituent, and it is **ortho, para-directing.** This effect is called **inductive stabilization** because the alkyl group donates electron density through the sigma bond joining it with the benzene ring.).

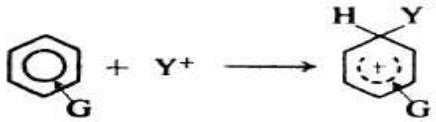
Transition state. *developing positive charge*

Carbonium ion: *full positive charge*

The NO_2 group, on the other hand, has an electron-withdrawing inductive effect (III); this tends to intensify the positive charge, destabilizes the carbonium ion, and thus causes a slower reaction.

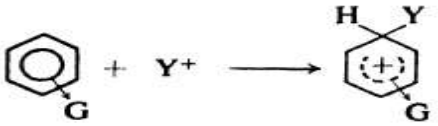
Reactivity in electrophilic aromatic substitution depends, then, upon the tendency of a substituent group to release or withdraw electrons. A group that releases electrons activates the ring; a group that withdraws electrons deactivates the ring.

Electrophilic Aromatic Substitution



G releases electrons, stabilizes carbonium ion, activates

G = $-NH_2$, $-OH$, $-OCH_3$, $-NHCOCH_3$, $-C_6H_5$, $-CH_3$



G withdraws electrons; destabilizes carbonium ion, deactivates

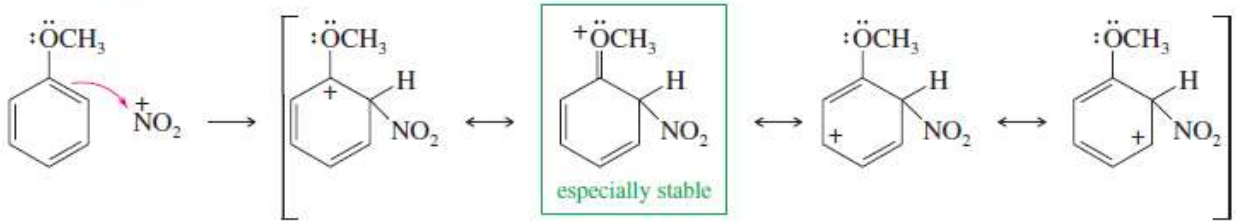
G = $-N(CH_3)_3^+$, $-NO_2$, $-CN$, $-SO_3H$, $-COOH$, $-CHO$, $-COR$

Like CH_3, other alkyl groups release electrons, and like CH_3 they activate the ring. For example, tert-butylbenzene is 16 times as reactive as benzene toward nitration. Electron release by NH_2 and OH, and by their derivatives OCH_3 and $NHCOCH_3$, is due not to their inductive effect but to resonance.

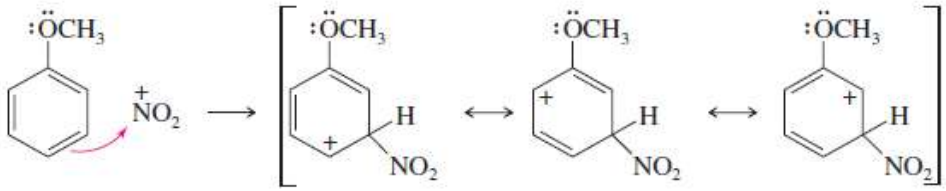
Methoxybenzene undergoes nitration about 10,000 times faster than benzene and about 400 times faster than toluene. This result seems curious because oxygen is a strongly electronegative group, yet it donates electron density to stabilize the transition state and the carbonium ion. The nonbonding electrons of an oxygen atom adjacent to a carbocation stabilize the positive charge through resonance.

The resonance form puts the positive charge on the electronegative oxygen atom, but it has more covalent bonds, and it provides each atom with an octet in its valence shell. This type of stabilization is called **resonance stabilization,** Resonance forms show that the methoxy group effectively stabilizes the carbonium ion if it is ortho or para to the site of substitution, but not if it is meta.

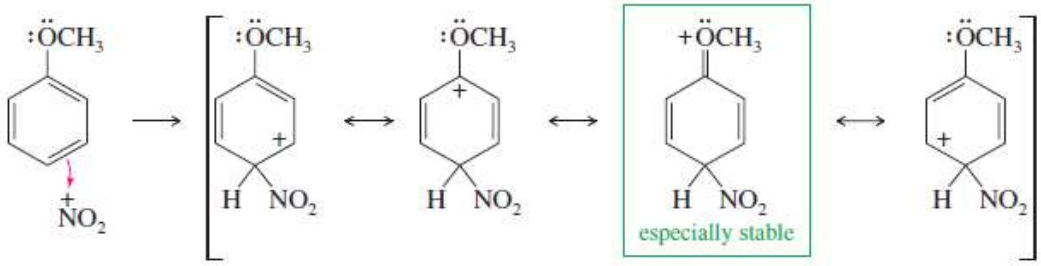
Ortho attack



Meta attack

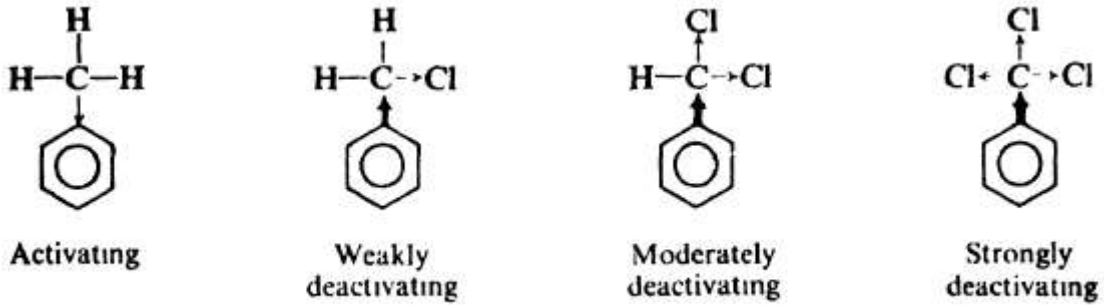


Para attack



In the other deactivating groups (e.g., NO_2, CN, COOH), the atom next to the ring is attached by a multiple bond to oxygen or nitrogen. These electronegative atoms attract the mobile π electrons, making the atom next to the ring electron-deficient; to make up this deficiency, the atom next to the ring withdraws electrons from the ring.

We might expect replacement of hydrogen in CH_3 by halogen to decrease the electron-releasing tendency of the group, and perhaps to convert it into an electron-withdrawing group.



Toward nitration, toluene is 25 times as reactive as benzene; benzyl chloride is only one-third as reactive as benzene. The CH_2Cl group is thus weakly deactivating. Further replacement of hydrogen by halogen to yield the $CHCl_2$ and the CCl_3 group's results in stronger deactivation.

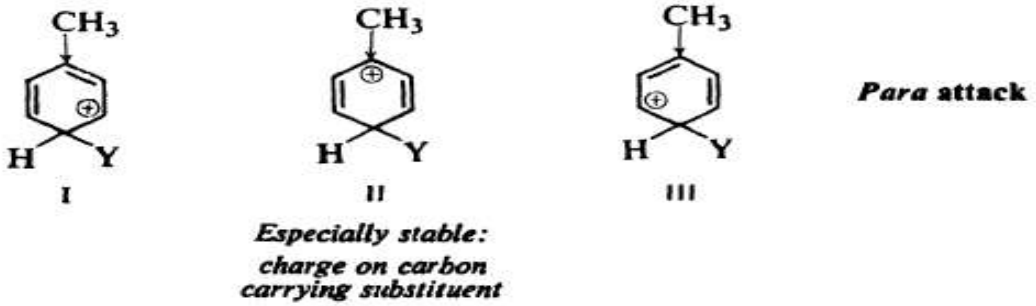
Theory of orientation

An activating group activates all positions of the benzene ring; even the positions meta to it are more reactive than any single position in benzene itself. It directs ortho and para simply because it activates the ortho and para positions much more than it does the meta.

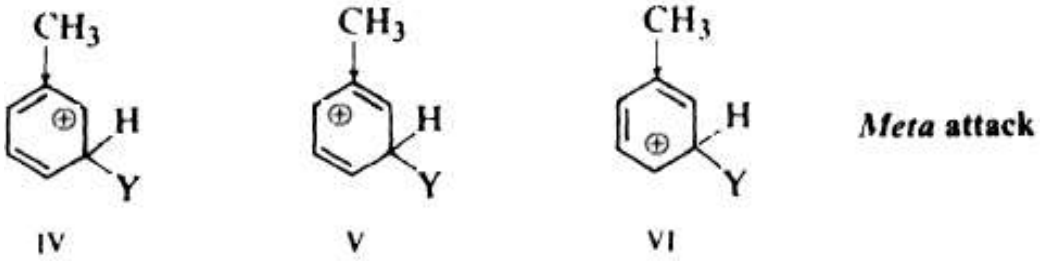
A deactivating group deactivates all positions in the ring, even the positions meta to it. It directs meta simply because it deactivates the ortho and para positions even more than it does the meta.

Thus both ortho, para orientation and meta orientation arise in the same way: the effect of any group whether activating or deactivating is strongest at the ortho and para positions.

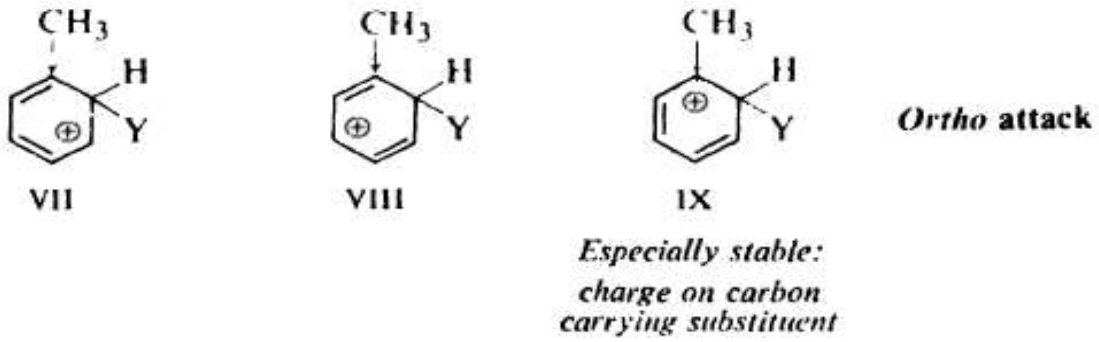
To see if this is what we would expect, let us compare, for example, the carbonium ions formed by attack at the para and meta positions of toluene, a compound that contains an activating group. Each of these is a hybrid of three structures, I-III for para, IV-VI for meta. In one of these six structures, II, the positive charge is located on the carbon atom to which CH_3 is attached. Although CH_3 releases electrons to all positions of the ring, it does so most strongly to the carbon atom nearest it; consequently, structure II is a particularly stable one.



Because of contribution from structure II, the hybrid carbonium ion resulting from

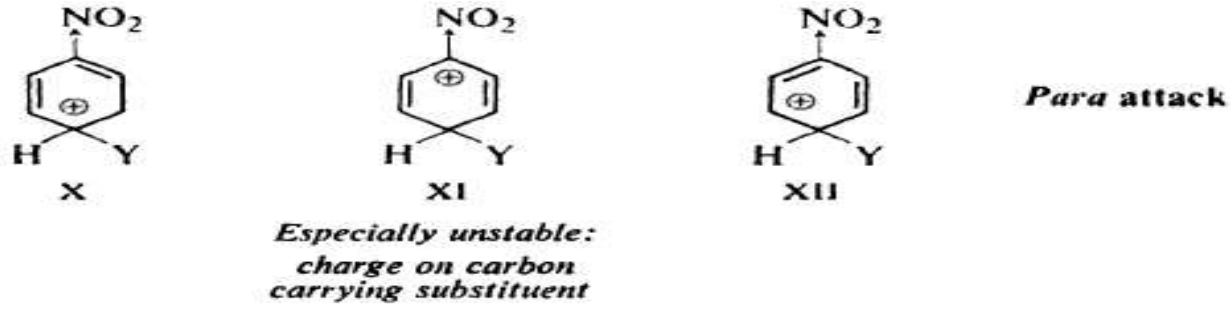


attack at the para position is more stable than the carbonium ion resulting from attack at a meta position. Para substitution, therefore, occurs faster than meta substitution. In the same way, it can be seen that attack at an ortho position (VII-IX) also yields a more stable carbonium ion, through contribution from IX, than attack at a meta position.



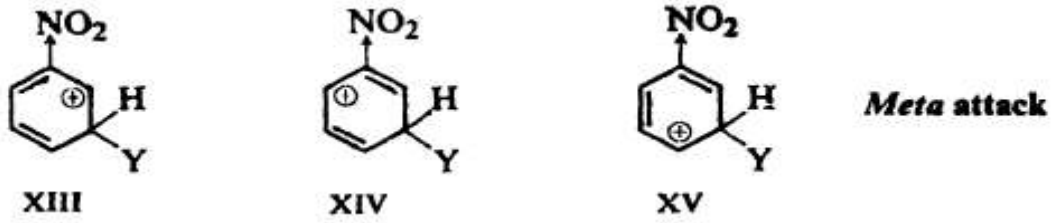
In toluene, ortho, para substitution is thus faster than meta substitution because electron release by CH_3 is more effective during attack at the positions ortho and para to it.

Next, let us compare the carbonium ions formed by attack at the para and meta positions of nitrobenzene, a compound that contains a deactivating group. Each of these is a hybrid of three structures, X-XII for para attack, XIII-XV for meta attack. In one of the six structures, XI, the positive charge is located on the carbon atom to which

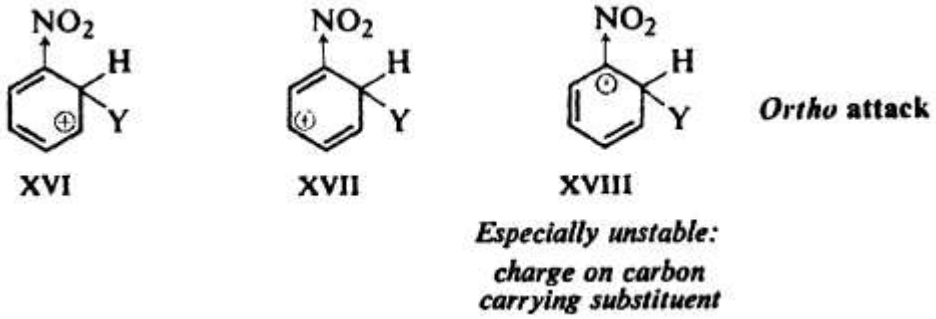


NO_2 is attached. Although NO_2 withdraws electrons from all positions, it does so most from the carbon atom nearest it, and hence this carbon atom, already positive, has little tendency to accommodate the positive charge of the carbonium ion. Structure XI is thus a particularly unstable one and does little to help stabilize the ion resulting from attack at the para position. The ion for para attack is virtually a hybrid of only two structures, X and XII; the positive charge is mainly restricted to only two carbon atoms.

It is less stable than the ion resulting from attack at a meta position, which is a hybrid of three structures, and in which the positive charge is accommodated by three carbon atoms. Para substitution, therefore, occurs more slowly than meta substitution.



In the same way it can be seen that attack at an ortho position (XVI-XVIII) yields a less stable carbonium ion, because of the instability of XVIII, than attack at a meta position.



In nitrobenzene, ortho, para substitution is thus slower than meta substitution because electron withdrawal by NO_2 is more effective during attack at the positions ortho and para to it.

Thus we see that both ortho, para orientation by activating groups and meta orientation by deactivating groups follow logically from the structure of the intermediate carbonium ion. The charge of the carbonium ion is strongest at the positions ortho and para to the point of attack, and hence a group attached to one of these positions can exert the strongest effect, whether activating or deactivating.

The unusual behavior of the halogens, which direct ortho and para although deactivating, results from a combination of two opposing factors, inductive effect and resonance effect.

Electron release via resonance

The substituent group affects both reactivity and orientation in electrophilic aromatic substitution by its tendency to release or withdraw electrons. So far, we have considered electron release and electron withdrawal only as inductive effects, that is, as effects due to the electronegativity of the group concerned.

But certain groups (NH_2 and OH, and their derivatives) act as **powerful activators** toward electrophilic aromatic substitution, even though they contain electronegative atoms and can be shown in other ways to **have electron-withdrawing inductive effects**. If our approach to the problem is correct, these groups must **release electrons**

in some other way than through their inductive effects; they are believed to do this by a **resonance effect**.

Although electronegative, the nitrogen of the NH_2 group is basic and tends to share its last pair of electrons and acquire a positive charge. Just as ammonia accepts a hydrogen ion to form the ammonium (NH_4^+) ion, so organic compounds related to ammonia accept hydrogen ions to form substituted ammonium ions.

$$\ddot{N}H_3 + H^+ \longrightarrow NH_4^+ \qquad R\ddot{N}H_2 + H^+ \longrightarrow RNH_3^+$$

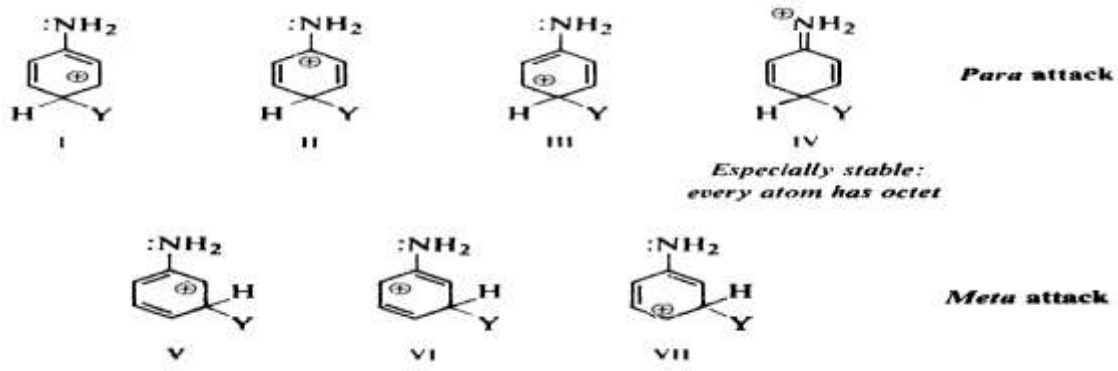
$$R_2\ddot{N}H + H^+ \longrightarrow R_2NH_2^+ \qquad R_3\ddot{N} + H^+ \longrightarrow R_3NH^+$$

The OH group shows similar but weaker basicity; example oxonium ions, ROH_2^+.

$$H_2\ddot{O} + H^+ \longrightarrow H_3O^+ \qquad R\ddot{O}H + H^+ \longrightarrow ROH_2^+$$

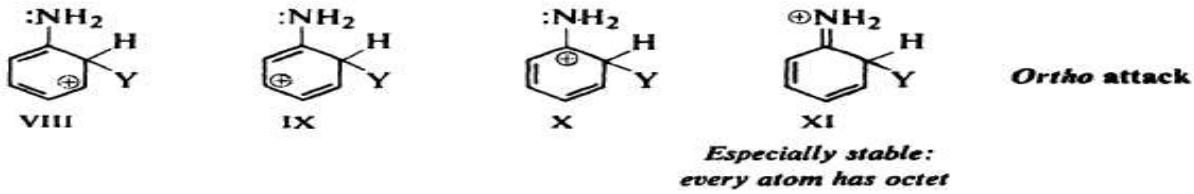
The effects of NH_2 and OH on electrophilic aromatic substitution can be accounted for by assuming that nitrogen and oxygen can share more than a pair of electrons with the ring and can accommodate a positive charge.

The carbonium ion formed by attack para to the NH_2 group of aniline, for example, is considered to be a hybrid not only of structures I, II, and III, with positive charges located on carbons of the ring, but also of structure IV in which the positive charge is carried by nitrogen. Structure IV is especially stable, since in it every atom (except hydrogen, of course) has a complete octet of electrons. This carbonium ion is much more stable than the one obtained by attack on benzene itself, or the one obtained (V-VI1) from attack meta to the NH_2 group of aniline; in neither of these cases is a structure like IV possible.



Here it is not a matter of which atom, nitrogen or carbon, can better accommodate a positive charge; it is a matter of which atom has a complete octet of electrons.

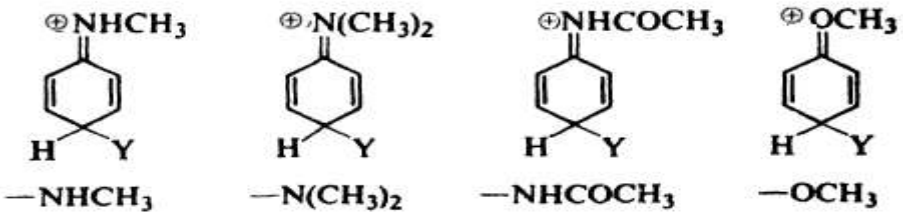
Examination of the corresponding structures (VIII-XI) shows that ortho attack is much like para attack:



Thus substitution in aniline occurs faster than substitution in benzene, and occurs predominantly at the positions ortho and para to NH_2.

In the same way activation and ortho, para orientation by the OH group is accounted for by contribution of structures like XII and XIII, in which every atom has a complete octet of electrons:

The similar effects of the derivatives of NH_2 and OH are accounted for by similar structures (shown only for para attack):

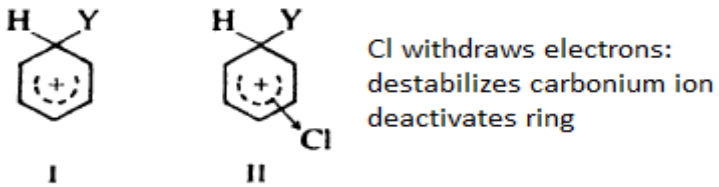


Effect of halogen on electrophilic aromatic substitution

Halogens are unusual in their effect on electrophilic aromatic substitution: they are deactivating yet ortho and para-directing. Deactivation is characteristic of electron withdrawal, whereas ortho, para orientation is characteristic of electron release. Can halogen both withdraw and release electrons? The answer is yes.

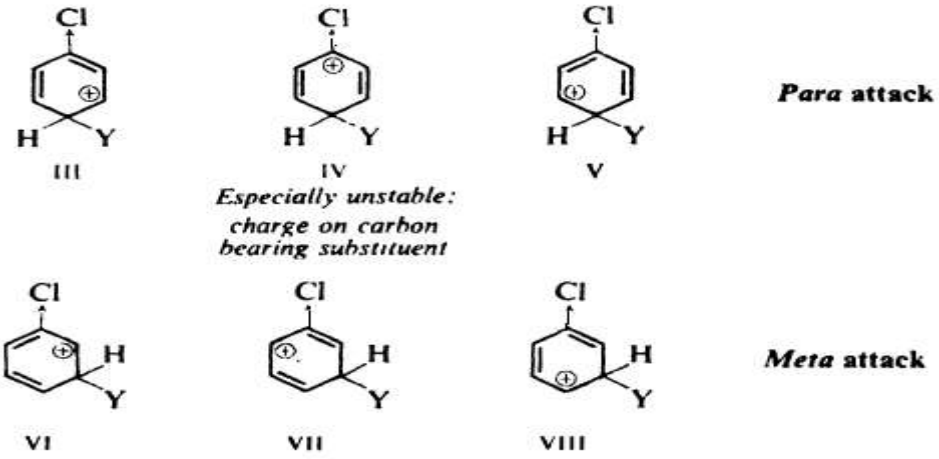
Halogen withdraws electrons through its inductive effect, and releases electrons through its resonance effect. So, presumably, can the NH_2 and OH groups, but there the much stronger resonance effect greatly outweighs the other. For halogen, the two effects are more evenly balanced, and we observe the operation of both.

Let us first consider reactivity. Electrophilic attack on benzene yields carbonium ion I, attack on chlorobenzene yields carbonium ion II.



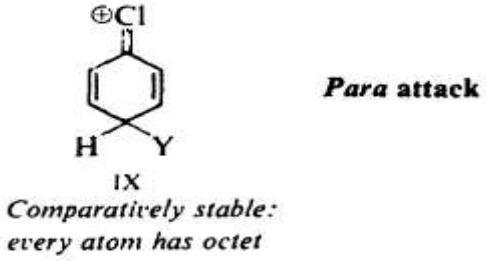
The electron withdrawing inductive effect of chlorine intensifies the positive charge in carbonium ion II, makes the ion less stable, and causes a slower reaction.

Next, to understand orientation, let us compare the structures of the carbonium ions formed by attack at the para and meta positions of chlorobenzene. Each of these is a hybrid of three structures, Ill-V for para, VI-VIII for meta.



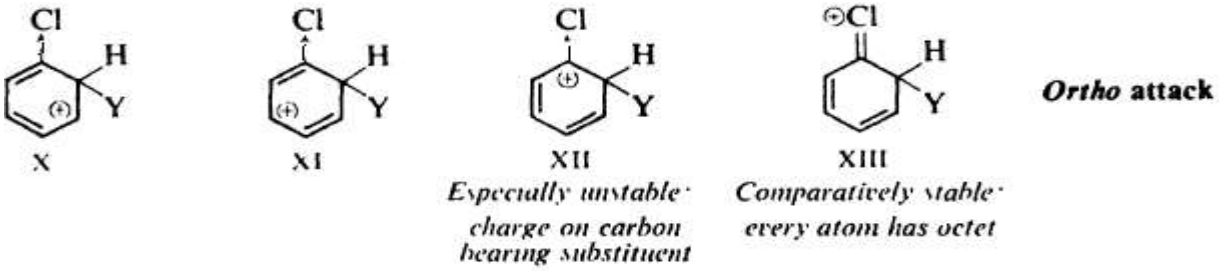
In one of these six structures, IV, the positive charge is located on the carbon atom to which chlorine is attached. Through its inductive effect chlorine withdraws electrons most from the carbon to which it is joined, and thus makes structure IV especially unstable. As before, we expect IV to make little contribution to the hybrid, which should therefore be less stable than the hybrid ion resulting from attack at the meta positions. If only the inductive effect were involved, then, we would expect not only deactivation but also meta orientation.

But the existence of halonium ions (is any ion containing a halogen atom carrying a positive charge) has shown us that halogen can share more than a pair of electrons and can accommodate a positive charge. If we apply that idea to the present problem, what do we find? The ion resulting from para attack is a hybrid not only of structures III-V, but also of structure IX, in which chlorine bears a positive charge and is joined to the ring by a double bond. This structure should be comparatively stable, since in it every atom (except hydrogen, of course) has a complete octet of electrons. (Structure IX is exactly analogous to those proposed to account for activation and ortho, para direction by NH_2 and OH.) No such structure is possible for the ion resulting from meta attack. To the extent that structure IX contributes to the hybrid, it makes the ion resulting from para attack more stable than the ion resulting from meta attack.



Although we could not have predicted the relative importance of the two factors the instability of IV and the stabilization by IX the result indicates that the contribution from IX is the more important.

In the same way it can be seen that attack at an ortho position also yields an ion (X-XIII) that can be stabilized by accommodation of the positive charge by chlorine.



Through its inductive effect halogen tends to withdraw electrons and thus to destabilize the intermediate carbonium ion. This effect is felt for attack at all positions, but particularly for attack at the positions ortho and para to the halogen.

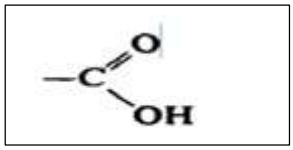
Through its resonance effect halogen tends to release electrons and thus to stabilize the intermediate carbonium ion. This electron release is effective only for attack at the positions ortho and para to the halogen.

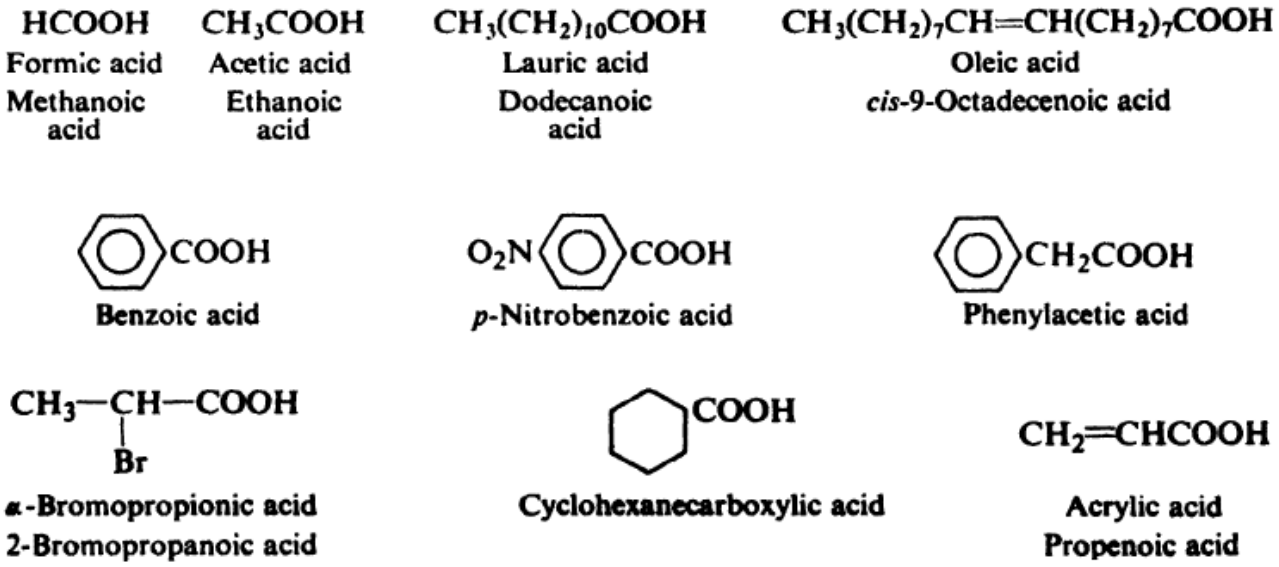
The inductive effect is stronger than the resonance effect and causes net electron withdrawal and hence deactivation for attack at all positions. The resonance effect tends to oppose the inductive effect for attack at the ortho and para positions, and hence makes the deactivation less for ortho, para attack than for meta.

Reactivity is thus controlled by the stronger inductive effect, and orientation is controlled by the resonance effect, which, although weaker, seems to be more selective.

Carboxylic Acids

The organic compounds that show appreciable acidity are the carboxylic acids. These compounds contain the carboxyl group attached to either an alkyl group (R-COOH) or an aryl group (Ar-COOH). For example:





Whether the group is aliphatic or aromatic, saturated or unsaturated, substituted or unsubstituted, the properties of the carboxyl group are essentially the same.

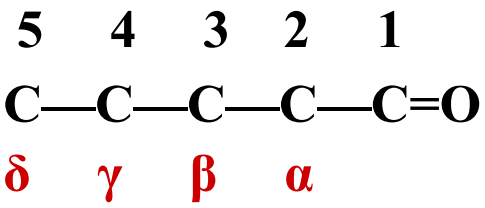
Nomenclature

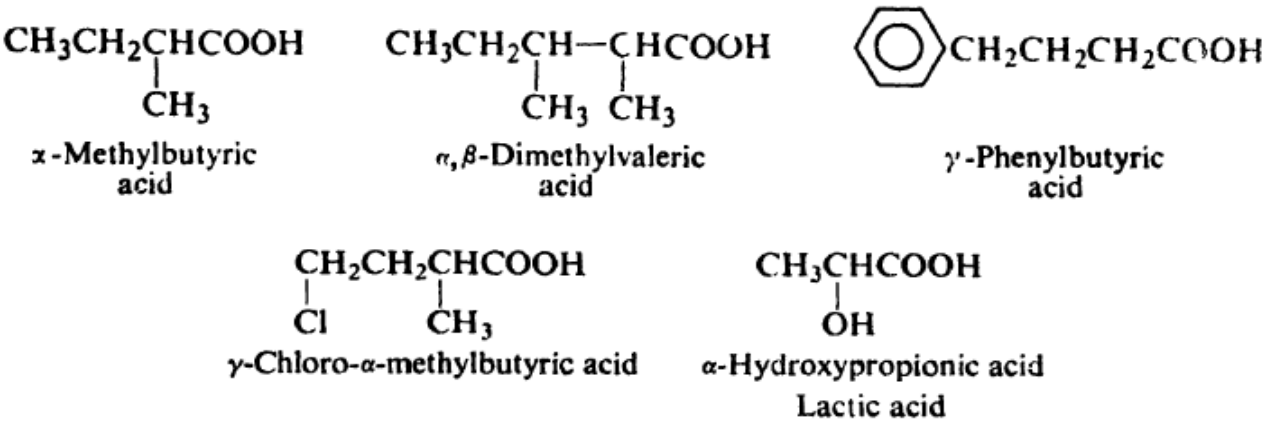
The aliphatic carboxylic acids have been known for a long time, and as a result have common names that refer to their sources rather than to their chemical structures. The common names of the more important acids are

Chemical structure	**Chemical names**	**Common names**
H-CO_2H	Formic acid	*L. formica*, ant
CH_3-CO_2H	Acetic acid	*L. acetum*, vinegar
CH_3-CH_2-CO_2H	Propionic acid	*G. "first salt"*
CH_3-CH_2-CH_2-CO_2H	Butyric acid	*L. butyrum*, butter
CH_3-CH_2-CH_2 -CH_2-CH_2-CO_2H	Caproic acid	*L.* caper, goat

Formic acid, for example, adds the sting to the bite of an ant (Latin: formica, ant); butyric acid gives rancid butter its typical smell (Latin: butyrum, butter); and caproic, caprylic, and capric acids are all found in goat fat (Latin: caper, goat).

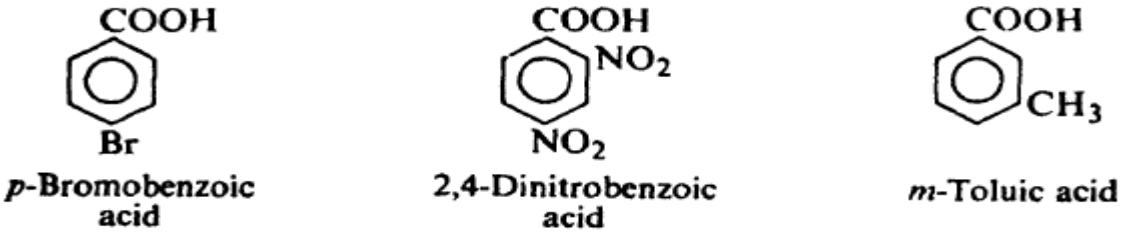
Branched-chain acids and substituted acids are named as derivatives of the straight-chain acids. To indicate the position of attachment, the Greek letters, **α-, β-, γ-,δ -,** etc., are used; the **α** -carbon is the one bearing the carboxyl group,





Generally the parent acid is taken as the one of longest carbon chain, although some compounds are named as derivatives of acetic acid.

Aromatic acids, ArCOOH, are usually named as derivatives of the parent acid, benzoic acid, C_6H_5COOH. The methylbenzoic acids are given the special name of toluic acids.

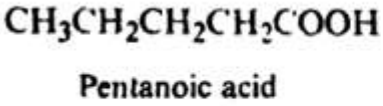


The IUPAC (International Union of Pure and Applied Chemistry) names follow the usual pattern. The longest chain carrying the carboxyl group is considered the parent structure, and is named by replacing the **-e** of the corresponding alkane with **-oic acid**. For example:

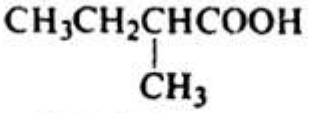
HCOOH **methanoic acid**

CH_3CO_2H **ethanoic acid**

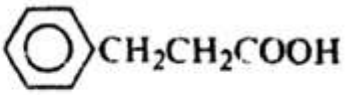
$CH_3CH_2CO_2H$ **propanoic acid**



Pentanoic acid



2-Methylbutanoic acid



3-Phenylpropanoic acid

The position of a substituent is indicated as usual by a number.

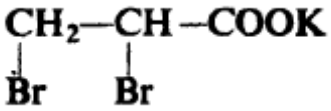
C—C—C—C—OOH Used in IUPAC names

4 3 2 1

The carboxyl carbon is always considered as **C- I**, and hence **C-2** corresponds to **α** of the common names, **C-3** to **β**, and so on. (Caution: Do not mix Greek letters with IUPAC names, or Arabic numerals with common names.)

The name of a salt of a carboxylic acid consists of the name of the cation (sodium, potassium, ammonium, etc.) followed by the name of the acid with the ending **-ic acid** changed to **-ate**. For example:

CH_3CO_2Na	**Sodium acetate** **Sodium ethanoate**
$CH_3CH_2CH_2CO_2NH_4$	**Ammonium butyrate** **Ammonium butanoate**
$(CH_3CH_2COO)_2Mg$	**Magnesium propionate** **Magnesium propanoate**



Potassium α,β-dibromopropionate
(Potassium 2,3-dibromopropanoate)

Sodium benzoate

Physical properties

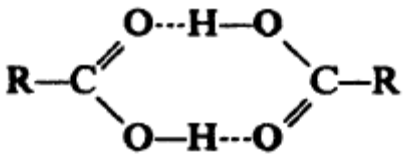
As we would expect from their structure,

- Carboxylic acid molecules are polar compounds.
- Like alcohol molecules can form hydrogen bonds with each other and with other kinds of molecules.

The aliphatic acids therefore show very much the same solubility behavior as alcohols: the first four are miscible with water, the five carbon acid is partly soluble, and the higher acids are virtually insoluble. Water solubility arises from hydrogen bonding between the carboxylic acid and water. The simplest aromatic acid, benzoic acid, contains too many carbon atoms to show appreciable solubility in water.

- Carboxylic acids are soluble in less polar solvents like ether, alcohol, benzene, etc.
- The carboxylic acids have a high boiling point even higher than alcohols.

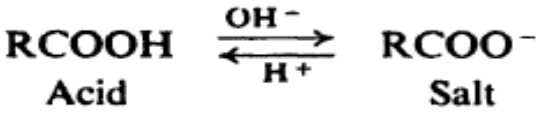
For example, propionic acid (b.p. 141) boils more than twenty degrees higher than the alcohol of comparable molecular weight, n-butylalcohol (b.p. 118). These very high boiling points are due to the fact that a pair of carboxylic acid molecules is held together not by one but by two hydrogen bonds:



- The odors of the lower aliphatic acids progress from the sharp, irritating odors of formic and acetic acids to the distinctly unpleasant odors of butyric, valeric, and caproic acids; the higher acids have little odor because of their low volatility.

Salts of carboxylic acids

Although the carboxylic acids are much weaker than the strong mineral acids (sulfuric, hydrochloric, nitric), but they are more acidic than the very weak organic acids (alcohols, acetylene) and they are much stronger acids than water. Aqueous hydroxides therefore readily convert carboxylic acids into their salts; aqueous mineral acids readily convert the salts back into the carboxylic acids.



The properties of the salts of carboxylic acids

- Salts of carboxylic acid like all salts are crystalline non-volatile solids made up of positive and negative ions.

The strong electrostatic forces holding the ions in the crystal lattice can be overcome only by

- ❖ Heating to a high temperature, or by a
- ❖ Very polar solvent.

The temperature required for melting is so high that before it can be reached carbon-carbon bonds break and the molecule decomposes. A decomposition point is seldom useful for the identification of a compound, since it usually reflects the rate of heating rather than the identity of the compound.

- The alkali metal salts of carboxylic acids (sodium, potassium, and ammonium) are soluble in water but insoluble in non-polar solvents; most of the heavy metal salts (iron, silver, copper, etc.) are insoluble in water.

Thus we see that, except for the acids of four carbons or less, which are soluble both in water and in organic solvents, carboxylic acids and their alkali metal salts show exactly opposite solubility behavior. Because of the ready interconversion of acids and their salts, this difference in solubility behavior may be used in two important ways: for identification and for separation. "A water-insoluble organic compound that dissolves in cold dilute aqueous sodium hydroxide must be either a carboxylic acid or one of the few other kinds of organic compounds more acidic than water; that it is indeed a carboxylic acid can then be shown in other ways.

$$\underset{\substack{\text{Stronger acid}\\ \textit{Insoluble in } H_2O}}{RCOOH} + NaOH \longrightarrow \underset{\substack{\textit{Soluble in } H_2O}}{RCOONa} + \underset{\substack{\text{Weaker acid}}}{H_2O}$$

Instead of sodium hydroxide, we can use aqueous -sodium bicarbonate; even if the unknown is water-soluble, its acidity is shown by the evolution of bubbles of CO_2.

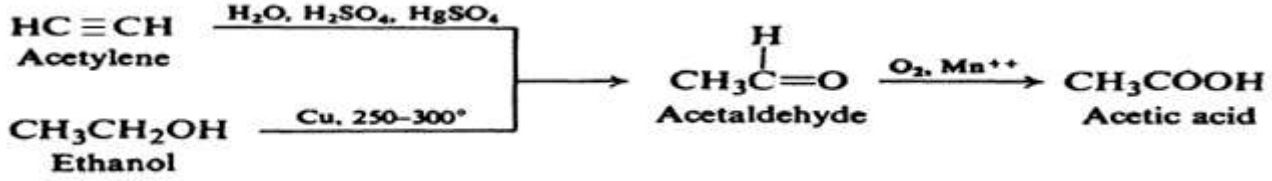
$$\underset{\textit{Insoluble in } H_2O}{RCOOH} + NaHCO_3 \longrightarrow \underset{\textit{Soluble in } H_2O}{RCOONa} + H_2O + CO_2\uparrow$$

We can separate a carboxylic acid from non-acidic compounds by taking advantage of its solubility and their insolubility in aqueous base; once the separation has been accomplished, we can regenerate the acid by acidification of the aqueous solution. If we are dealing with solids, we simply stir the mixture with aqueous base and then filter the solution from insoluble, non-acidic materials; addition of mineral acid to the filtrate precipitates the carboxylic acid, which can be collected on a filter. If we are dealing with liquids, we shake the mixture with aqueous base in a separatory funnel and separate the aqueous layer from the insoluble organic layer; addition of acid to the aqueous layer again liberates the carboxylic acid, which can then be separated from the water. For completeness of separation and ease of handling, we often add a water-insoluble solvent like ether to the acidified mixture. The carboxylic acid is extracted from the water by the ether, in which it is more soluble; the volatile ether is readily removed by distillation from the comparatively high-boiling acid.

For example, the carboxylic acid prepared by oxidation of an alkylbenzene may very well be contaminated with unreacted starting material; the carboxylic acid can be taken into solution by aqueous base, separated from the insoluble hydrocarbon, and regenerated by addition of mineral acid.

Industrial source

Acetic acid, by far the most important of all carboxylic acids, is prepared by air oxidation of acetaldehyde, which is readily available from the hydration of acetylene, or the dehydrogenation (oxidation) of ethanol.

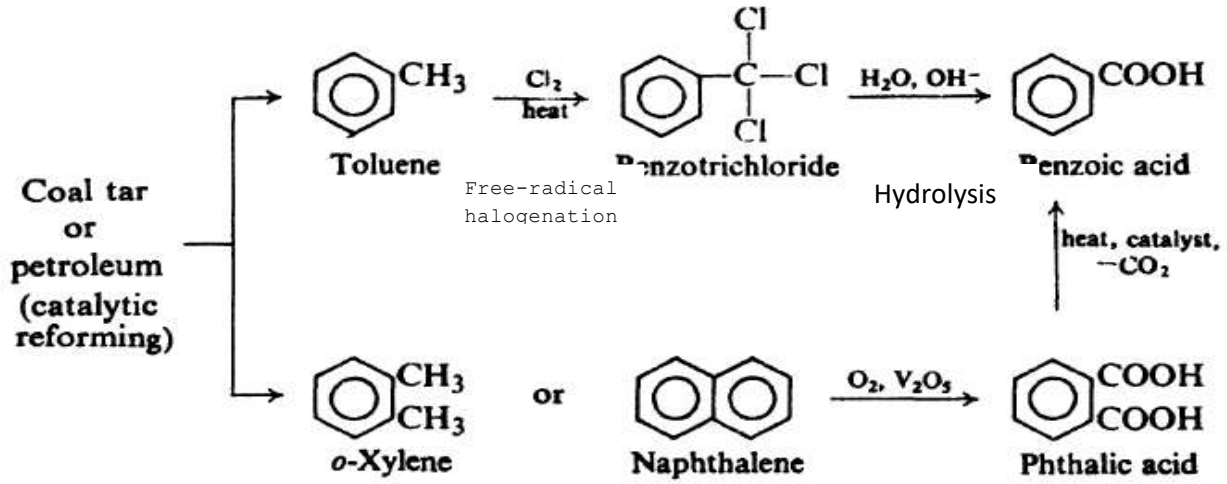


Large amounts of acetic acid are also produced as the dilute aqueous solution known as vinegar. Here, too, the acetic acid is prepared by air oxidation; the compound that is oxidized is ethyl alcohol, and the catalysts are bacterial (Acetobacter) enzymes.

The most important sources of aliphatic carboxylic acids are the animal and vegetable fats. From fats there can be obtained, in purity of over 90%, straight-chain carboxylic acids of even carbon number ranging from six to eighteen carbon atoms. These acids can be converted into the corresponding alcohols (alcohols that converted into other kinds of compounds having the same carbon skeleton), which can then be used, to make a great number of other compounds containing long, straight chain units.

The most important of the aromatic carboxylic acids, benzoic acid and the phthalic acids, are prepared on an industrial scale by an oxidation of alkylbenzenes.

The toluene and xylenes required are readily available from coal tar and, by catalytic reforming of aliphatic hydrocarbons, from petroleum; another precursor of phthalic acid (the ortho isomer) is the aromatic hydrocarbon naphthalene, also found in coal tar. Cheap oxidizing agents like chlorine or even air (in the presence of catalysts) are used.



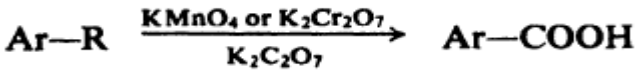
Preparation

The straight-chain aliphatic acids up to C_6, and those of even carbon number up to C_{18}, are commercially available, as are the simple aromatic acids. Other carboxylic acids can be prepared by these methods:

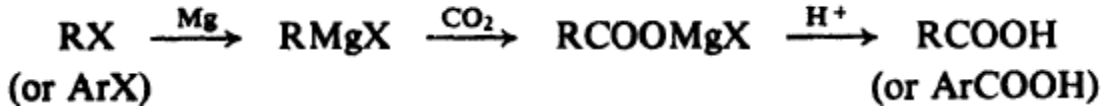
Carboxylic acids, syntheses:

1. **Oxidation of primary alcohols**

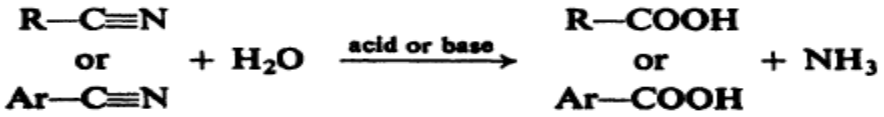
2. **Oxidation of alkylbenzenes.**



3. **Carbonation of Grignard reagents**



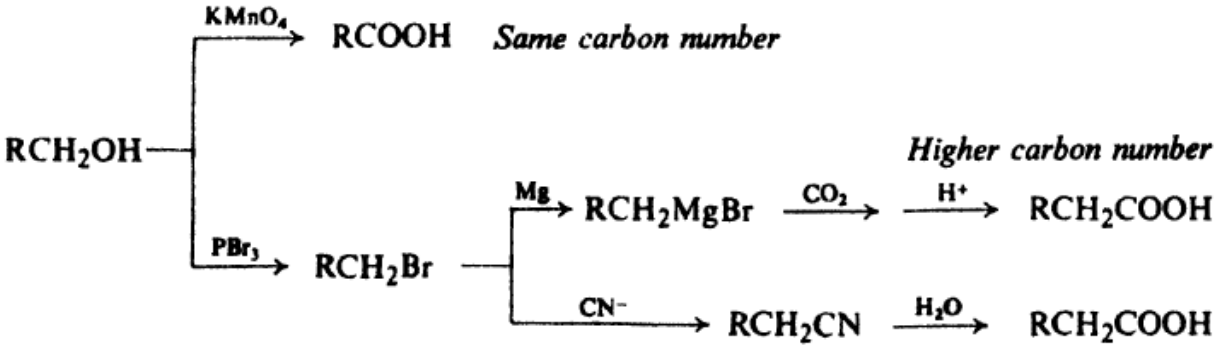
4. **Hydrolysis of nitriles**



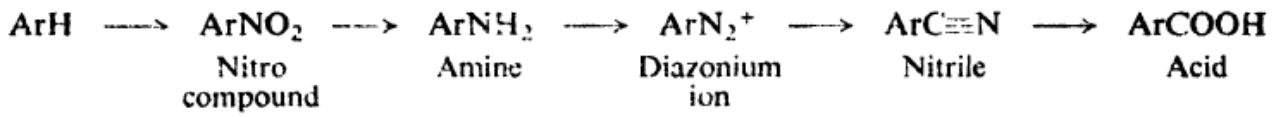
All the methods listed are important; our choice is governed by the availability of starting materials.

Oxidation is the most direct and is generally used when possible, some lower aliphatic acids being made from the available alcohols, and substituted aromatic acids from substituted toluenes.

The Grignard synthesis and the nitrile synthesis have the special advantage of increasing the length of a carbon chain, and thus extending the range of available materials. In the aliphatic series both Grignard reagents and nitriles are prepared from halides, which in turn are usually prepared from alcohols.



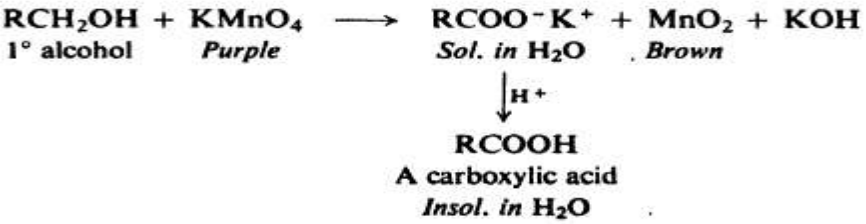
Aromatic nitriles generally cannot be prepared from the unreactive aryl halides. Instead they are made from diazonium salts. Diazonium salts are prepared from aromatic amines, which in turn are prepared from nitro compounds. Thus the carboxyl group eventually occupies the position on the ring where a nitro group was originally introduced by direct nitration.



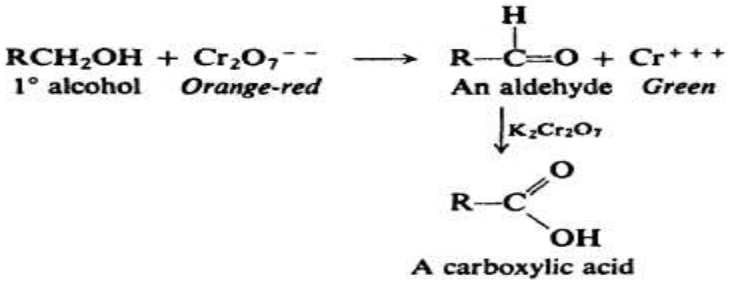
Oxidation of primary alcohols

The compound that is formed by oxidation of an alcohol depends upon the number of hydrogens attached to the carbon bearing the OH group, that is, upon whether the alcohol is primary, secondary, or tertiary to produce aldehydes, ketones, and carboxylic acids

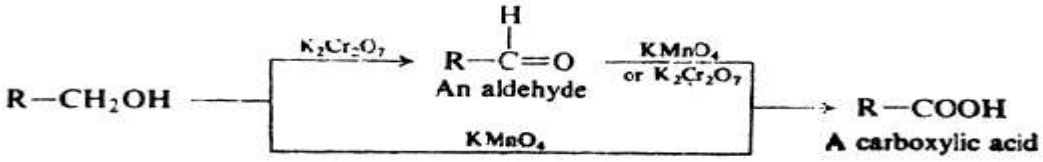
Primary alcohols can be oxidized to carboxylic acids, RCOOH, usually by heating with aqueous $KMnO_4$. When reaction is complete, the aqueous solution of the soluble potassium salt of the carboxylic acid is filtered from MnO_2, and the acid is liberated by the addition of a stronger mineral acid.



Primary alcohols can be oxidized to aldehydes, RCHO, by the use of $K_2Cr_2O_7$, aldehydes are themselves readily oxidized to acids, and the aldehyde must be removed from the reaction mixture by special techniques before it is oxidized further.



The both reaction can be summarized as follow:

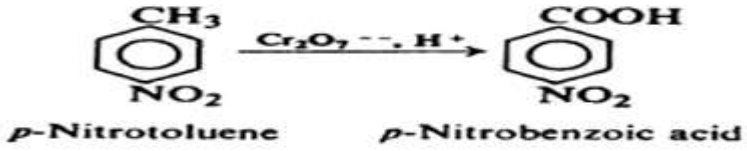


While the oxidation of secondary alcohols (R^1R^2CH-OH) normally terminates at the ketone (R^1R^2C=O) stage. Tertiary alcohols ($R^1R^2R^3C$-OH) are resistant to oxidation.

Oxidation of alkylbenzenes

Although **benzene and alkanes** are quite unreactive toward the usual oxidizing agents ($KMnO_4$, $K_2Cr_2O_7$, etc.), the **benzene ring renders an aliphatic side chain quite susceptible to oxidation.** The side chain is oxidized down to the ring, only a carboxyl group (COOH) remaining to indicate the position of the original side chain. Potassium permanganate is generally used for this purpose, although potassium dichromate or dilute nitric acid also can be used. (Oxidation of a side chain is more difficult, however, than oxidation of an alkene, and **requires prolonged treatment with hot $KMnO_4$.)**

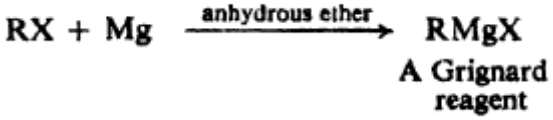
This mothed is consider one of the most useful methods of preparing an aromatic carboxylic acid involves oxidation of the proper alkylbenzene. For example:



Carbonation of Grignard reagents

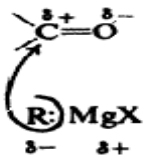
The Grignard reagent, has the formula RMgX, and is prepared by the reaction of metallic magnesium with the appropriate organic halide.

This halide can be alkyl (1, 2, 3), allylic, arylalkyl (e.g., benzyl), or aryl (phenyl or substituted phenyl). The halogen may be Cl, Br or I.

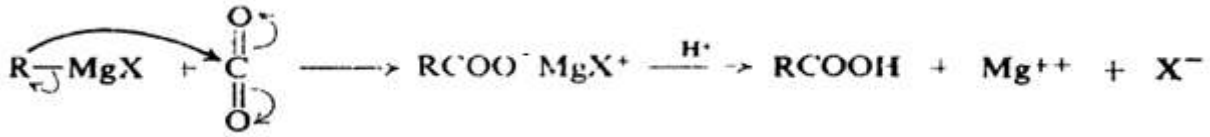


The Grignard synthesis of a carboxylic acid is carried out by bubbling gaseous CO_2 into the ether solution of the Grignard reagent, or by pouring the Grignard reagent on crushed Dry Ice (solid CO_2); in the latter method Dry Ice serves not only as reagent but also as cooling agent.

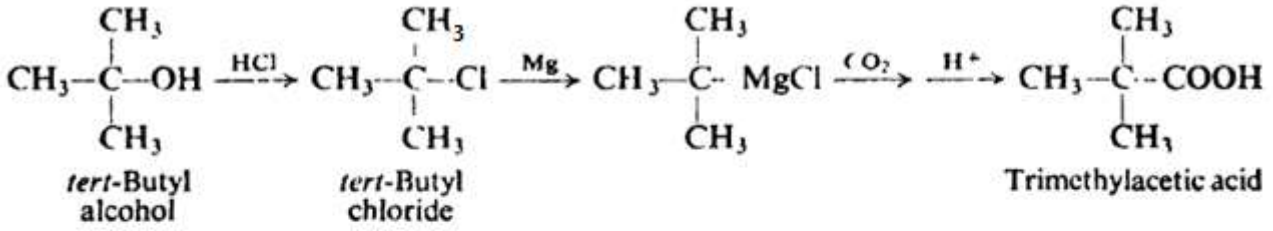
The Grignard reagent adds to the carbon-oxygen double bond (CO_2) just as in the reaction with aldehydes and ketones.

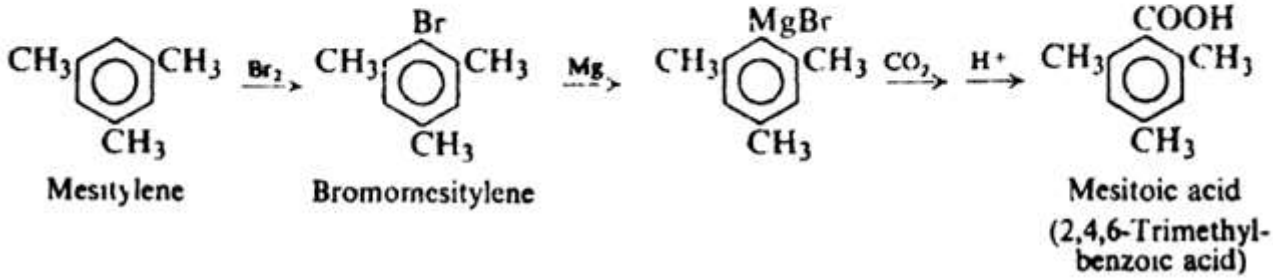


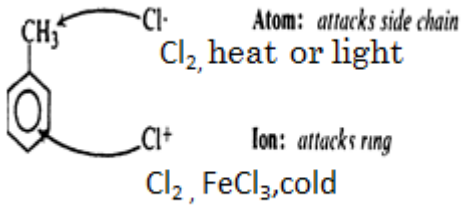
The product is the magnesium salt of the carboxylic acid, from which the free acid is liberated by treatment with mineral acid.



The Grignard reagent can be prepared from primary, secondary, tertiary, or aromatic halides; the method is limited only by the presence of other reactive groups in the molecule. The following syntheses illustrate the application of this method:







The position of attack is control simply by choosing the proper reaction conditions.

The very reactivity of Grignard reagent limits how we may use it. We must keep this reactivity in mind when we plan the experimental conditions of the synthesis, when we select the halide that is to become the Grignard reagent, and when we select the compound with which it is to react.

The Grignard reagent is reacting with water to form an alkane; the stronger acid, water, displaced the extremely weak acid, the alkane, from its salt. In the same way, any compound containing hydrogen attached to electronegative element oxygen, nitrogen, sulfur, or even triply-bonded carbon is acidic enough to decompose a Grignard reagent.

A Grignard reagent reacts rapidly with oxygen and carbon dioxide, and with nearly every organic compound containing a carbon-oxygen or carbon-nitrogen multiple bond.

How does these affect reactions contain a Grignard reagent? First of all, **alkyl halide, other reactant, and the ether** used as solvent must **be dried** and freed of the alcohol

from which each was very probably made; a Grignard reagent will not even form in the presence of water. Our apparatus must be completely dry before we start. We must protect the reaction system from the water vapor, oxygen, and carbon dioxide of the air: water vapor can be kept out by use of calcium chloride tubes, and oxygen and carbon dioxide can be swept out of the system with dry nitrogen. Having done all this we may hope to obtain a good yield of product.

Hydrolysis of nitriles

Aliphatic nitriles are prepared by treatment of alkyl halides with sodium cyanide in a solvent that will dissolve both reactants as dimethyl sulfoxide, reaction occurs rapidly and exothermically at room temperature. The resulting nitrile is then hydrolyzed to the acid by boiling in aqueous alkali or acid.

$$RX + CN^- \longrightarrow RC{\equiv}N + X^-$$

$$RC{\equiv}N + H_2O \xrightarrow{H^+} RCOOH + NH_4^+$$

$$RC{\equiv}N + H_2O \xrightarrow{OH^-} RCOO^- + NH_3$$

The reaction of an alkyl halide with cyanide ion involves nucleophilic substitution.

$$\underset{\text{A nucleophilic reagent}}{R{:}X + {:}Z} \longrightarrow \underset{\text{Leaving group}}{R{:}Z + {:}X^-} \qquad \textbf{Nucleophilic substitution}$$

The fact that HCN is a very weak acid that mean cyanide ion is a strong base; as we might expect, this strongly basic ion can abstract hydrogen ion and thus cause elimination as well as substitution.

$$\underset{n\text{-Butyl bromide}}{CH_3CH_2CH_2CH_2Br} + CN^- \dashrightarrow \underset{\text{Valeronitrile}}{CH_3CH_2CH_2CH_2CN} \qquad 1^\circ \text{ halide: } \textit{substitution}$$

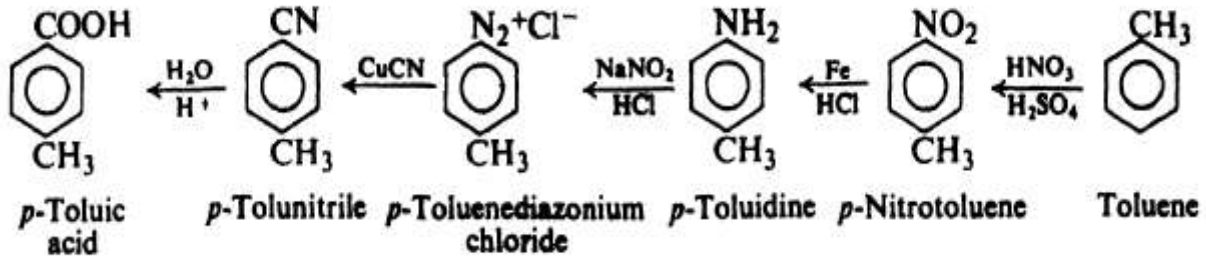
$$\underset{\textit{tert}\text{-Butyl bromide}}{(CH_3)_3CBr} + CN^- \longrightarrow \underset{\text{Isobutylene}}{(CH_3)_2C{=}CH_2} + HCN \qquad 3^\circ \text{ halide: } \textit{elimination}$$

Indeed, with tertiary halides elimination is the principal reaction; even with secondary halides the yield of substitution product is poor. Here again we find a nucleophilic substitution reaction that is of synthetic importance only when primary halides are used.

Aromatic nitriles are made, not from the unreactive aryl halides, but from diazonium salts. Replacement of the diazonium group by CN is carried out by allowing the diazonium salt to react with cuprous cyanide. To prevent loss of cyanide as HCN, the diazonium solution is neutralized with sodium carbonate before being mixed with the cuprous cyanide.

$$ArN_2^+X^- \xrightarrow{CuCN} ArCN + N_2$$

Hydrolysis of nitriles yields carboxylic acids. The synthesis of nitriles from diazonium salts thus provides us with an excellent route from nitro compounds to carboxylic acids. For example:



p-Toluic acid | *p*-Tolunitrile | *p*-Toluenediazonium chloride | *p*-Toluidine | *p*-Nitrotoluene | Toluene

Although nitriles are sometimes named as cyanides or as cyano compounds, they generally take their names from the acids they yield upon hydrolysis. They are named by dropping -**ic acid** from the common name of the acid and adding -**nitrile**; usually for euphony an "**o**" is inserted between the root and the ending (e.g., acetonitrile). In the IUPAC system they are named by adding -**nitrile** to the name of the parent hydrocarbon (e.g., ethanenitrile). For example:

Acetonitrile (Ethanenitrile) | Benzonitrile | *p*-Tolunitrile

Reactions of carboxylic acids

The characteristic chemical behavior of carboxylic acids is, of course, determined by their functional group, carboxyl, COOH. This group is made up of a carbonyl group (C=O) and a hydroxyl group (OH). The OH that actually undergoes nearly every reaction

- Loss of H^+.
- Replacement by another group.

but it does so in a way that is possible only because of the effect of the C=O. The rest of the molecule undergoes reactions characteristic of its structure; it may be aliphatic or aromatic, saturated or unsaturated, and may contain a variety of other functional groups.

REACTIONS OF CARBOXYLIC ACIDS

1. Acidity: Salt formation.

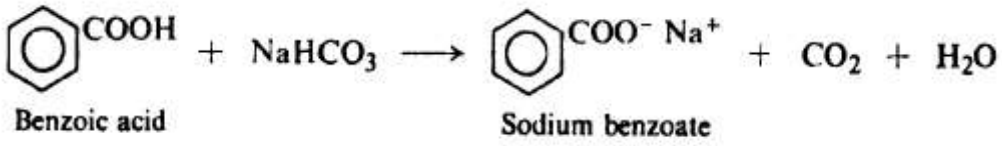
Carboxylic acids are typically weak acids, meaning that they only partially dissociate into H^+ cations and $RCOO^-$ anions in neutral aqueous solution.

$$RCOOH \rightleftharpoons RCOO^- + H^+$$

Their tendency to give up a hydrogen ion is such that in aqueous solution, a measurable equilibrium exists between acid and ions; they are thus much more acidic than most of organic compounds.

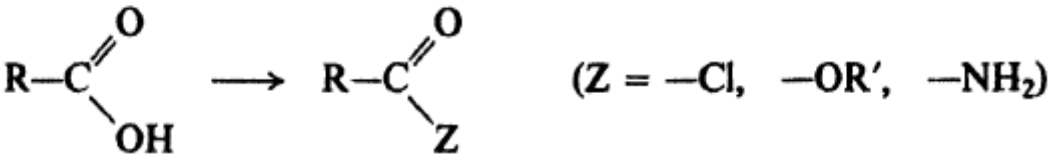
$$\underset{\text{Acetic acid}}{2CH_3COOH} + Zn \longrightarrow \underset{\text{Zinc acetate}}{(CH_3COO^-)_2Zn^{++}} + H_2$$

$$\underset{\text{Lauric acid}}{CH_3(CH_2)_{10}COOH} + NaOH \longrightarrow \underset{\text{Sodium laurate}}{CH_3(CH_2)_{10}COO^-Na^+} + H_2O$$

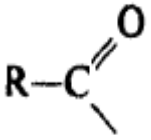


Benzoic acid — Sodium benzoate

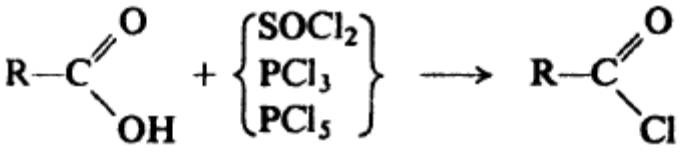
2. Conversion into functional derivatives



The OH of an acid can be replaced by a number of groups Cl, OR', NH_2 to yield compounds known as acid chlorides, esters, and amides. These compounds are called functional derivatives of acids; they all contain the acyl group:

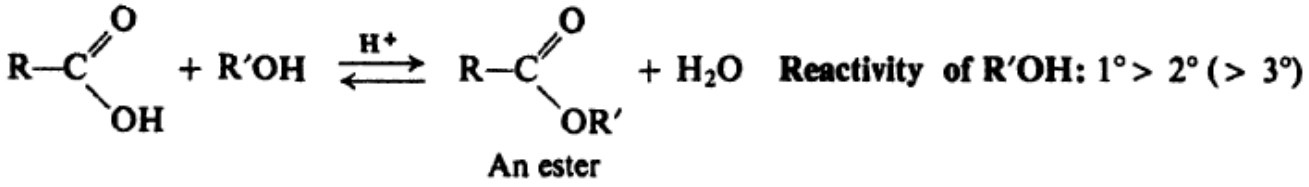


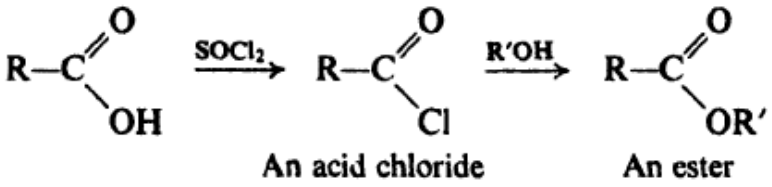
a) Conversion into acid chlorides.



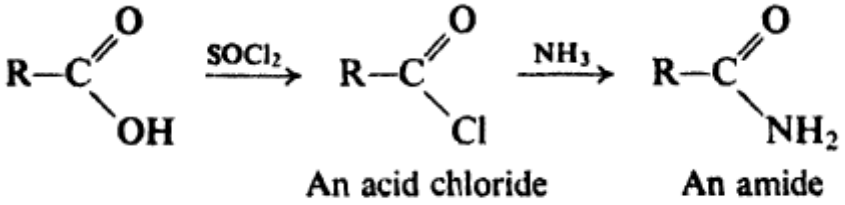
Acid chloride

b) Conversion into esters.

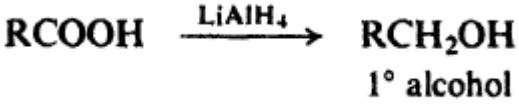




c) Conversion into amides.



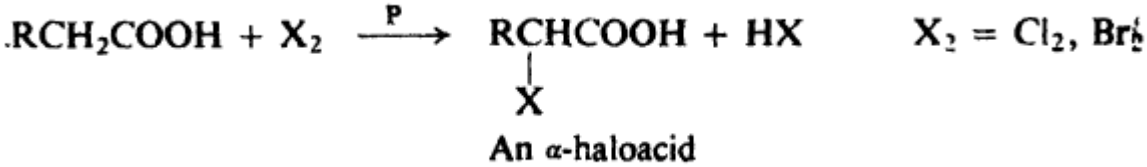
3. Reduction.



One of the few reducing agents capable of reducing an acid directly to an alcohol is lithium aluminum hydride, $LiAlH_4$.

4. Substitution in alkyl or aryl group

a) Alpha-halogenation of aliphatic acids: Hell-Volhard-Zelinsky reaction.

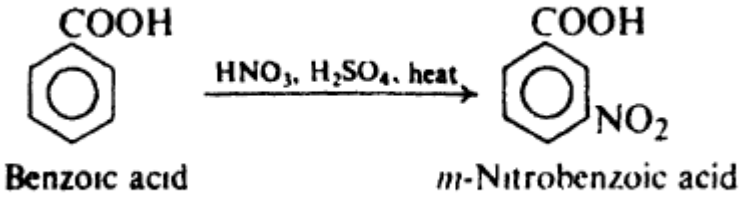


The hydrocarbon portion of an aliphatic acid can undergo the free-radical halogenation characteristic of alkanes, but because of the random nature of the substitution it is seldom used. The presence of a small amount of phosphorus, however, causes halogenation (by an ionic mechanism) to take place exclusively at the alpha position. This reaction is known as the Hell-Volhard-Zelinsky reaction (**The Hell-Volhard-Zelinsky reaction is an organic reaction used to convert a carboxylic acid with an α-hydrogen**

and a halogen, to an α-halo carboxylic acid, using a phosphorous catalyst and water.), and it is of great value in synthesis.

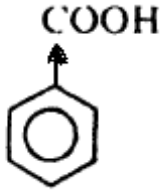
b) Ring substitution in aromatic acids.

-COOH: deactivates, and directs Meta in electrophilic substitution.



Benzoic acid — *m*-Nitrobenzoic acid

An aromatic ring bearing a carboxyl group undergoes the electrophilic aromatic substitution reactions expected of a ring carrying a deactivating, meta directing group. Deactivation is so strong that the Friedel-Crafts reaction does not take place.



-COOH withdraws electron: deactivates, direct meta in electrophilic aromatic substitution

Ionization of carboxylic acids. Acidity constant

In aqueous solution a carboxylic acid exists in equilibrium with the carboxylate anion and the hydrogen ion (actually, of course, the hydronium ion, H_3O^+).

$$RCOOH + H_2O \rightleftharpoons RCOO^- + H_3O^+$$

As for any equilibrium, the concentrations of the components are related by the expression

$$K_a = \frac{[RCOO^-][H_3O^+]}{[RCOOH]}$$

Since the concentration of water, the solvent, remains essentially constant, this term is usually omitted.) The equilibrium constant is called here the **acidity constant**, $\mathbf{K_a}$ (**is a quantitative measure of the strength of an acid in solution** (**a** for acidity)). Every carboxylic acid has its characteristic $\mathbf{K_a}$, which indicates how strong an acid it is. Since the acidity constant is the ratio of ionized to unionized material, the larger the Ka the greater the extent of the ionization (under a given set of conditions) and the stronger the acid. We use the $\mathbf{K_a}$'s, then, to compare in an exact way the strengths of different acids.

$$pK_a = -\log_{10} K_a$$

The larger the value of pK_a, the smaller the extent of dissociation, the weaker the acid. The lower the value of pK_a, the higher the extent of dissociation the stronger the acid.

Carboxylic acids are stronger weak acids. Values of pK_a for most aliphatic and aromatic carboxylic acids fall within the range 4 to 5.

$$CH_3COOH + H_2O \rightleftharpoons CH_3COO^- + H_3O^+$$

$$K_a = \frac{[CH_3COO^-][H_3O^+]}{[CH_3COOH]} = 1.74 \times 10^{-5}$$

$$pK_a = 4.76$$

The greater acidity of carboxylic acids relative to alcohols, both of which contain an OH group, is due to resonance stabilization of the carboxylate anion.

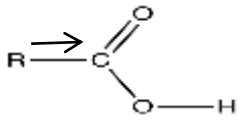
The carboxylate anions are moderately basic, with an appreciable tendency to combine with protons. They react with water to increase the concentration of hydroxide ions, a reaction often referred to as hydrolysis. (Common kind of hydrolysis occurs when a salt of a weak acid or weak base (or both) is dissolved in water. Water spontaneously ionizes into hydroxide anions and hydronium cations. The salt also dissociates into its constituent anions and cations. For example, sodium acetate dissociates in water into sodium and acetate ions. Sodium ions react very little with the hydroxide ions whereas the acetate ions combine with hydronium ions to produce acetic acid. In this case the net result is a relative excess of hydroxide ions, yielding a basic solution.)

$$RCOO^- + H_2O \rightleftharpoons RCOOH + OH^-$$

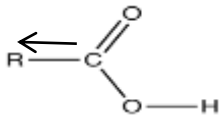
As a result aqueous solutions of carboxylate salts are slightly alkaline. (The basicity of an aqueous solution of a carboxylate salt is due chiefly to the carboxylate anions, not to the comparatively few hydroxide ions they happen to generate.)

Relative acid strength CH_4 (RH) < NH_3 < HC≡CH < ROH < HOH < **RCO_2H**

Certain substituted acids are much stronger or weaker than a typical acid like CH_3COOH. Acid strength is measured according to the ability of acid to lose its proton, as they lose it easily (the proton) the stronger the acid is. The electron donating group makes the loss of proton difficult so the acid is weak while the electron withdrawing group makes the loss of proton easy so the acid is strong.



Electron donating group



Electron withdrawing group

Equilibrium

Most of the chemical reactions have been essentially irreversible; that means, they have been one-way reactions but some other chemical reactions are reversible; that means, the forward and backward reactions can occur at the same time.

In a chemical reaction, chemical equilibrium is the state in which both reactants and products are present in concentrations which have no further tendency to change with time. Usually, this state results when the forward reaction proceeds at the same rate as the reverse reaction. The reaction rates of the forward and backward reactions are

generally not zero, but equal. Thus, there are no net changes in the concentrations of the reactant(s) and product(s). Such a state is known as dynamic equilibrium.
Let us consider the reversible reaction between A and B to form C and D. The yield of

$$A + B \rightleftharpoons C + D$$

C and D does not depend upon how fast A and B react, but rather upon how completely they have reacted when equilibrium is reached. The concentrations of the various components are related by the familiar expression, in which Keq is the equilibrium constant. The larger is [C][D] compared with [A][B], the larger the **Keq.** The value of **Keq** is therefore a measure of the tendency of the reaction to go to completion.

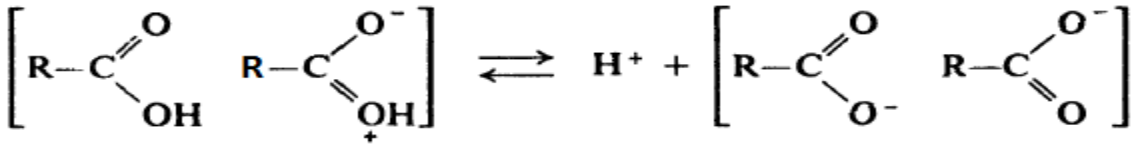
$$K_{eq} = \frac{[C][D]}{[A][B]}$$

Acidity of carboxylic acids

The acidity is determined by the difference in stability between the acid and its anion. There is the fact that carboxylic acids are acids at all. The OH of a carboxylic acid tends to release a hydrogen ion so much more readily than the OH group of an alcohol.
The examination of the structures of the reactants and products in these two cases, show that the alcohol and alkoxide ion are each represented satisfactorily by a single structure.

$$R{-}O{-}H \rightleftharpoons H^+ + R{-}O^-$$

However, we can draw two reasonable structures (I and II) for the carboxylic acid and two reasonable structures (III and IV) for the carboxylate anion. Both acid and anion are resonance hybrids. But the resonance is not equally important in the two cases. The resonance is much more important between the exactly equivalent structures III and IV than between the non-equivalents structures I and II. As a result, although both acid and anion are stabilized by resonance, stabilization is far greater for the anion than for the acid.



Equilibrium is shifted in the direction of increased ionization, and Ka is increased. The resonance is less important for the acid because the contributing structures are of different stability, whereas the equivalent structures for the ion must necessarily be of equal stability. In structure II two atoms of similar electronegativity carry opposite charges; since energy must be supplied to separate opposite charges, II should contain more energy and hence be less stable than I.

The acidity of a carboxylic acid is thus due to powerful resonance stabilization of its anion. This stabilization and the resulting acidity are possible only because of the presence of the carbonyl group.

Structure of carboxylate ions

The carboxylate ion is a hybrid of two structures which, being of equal stability, contribute equally. Carbon is joined to each oxygen by a one-and-one-half bond. The negative charge is evenly distributed over both oxygen atoms.

That the anion is a resonance hybrid is supported by the evidence of bond length. Formic acid, for example, contains a carbon-oxygen double bond and a carbon-oxygen single bond; these bonds have different lengths. Sodium formate, on the other hand, if it is a resonance hybrid, ought to contain two equivalent carbon-oxygen bonds; these bonds have the same length, intermediate between double and single bonds

Formic acid contains one carbon-oxygen bond of 1.36 A (single bond) and another of 1.23 A (double bond); sodium formate contains two equal carbon-oxygen bonds, each 1.27 A long.

Effect of substituents on acidity

The factors that stabilize the anion more than it stabilizes the acid should increase the acidity; while the factors that make the anion less stable should decrease acidity.

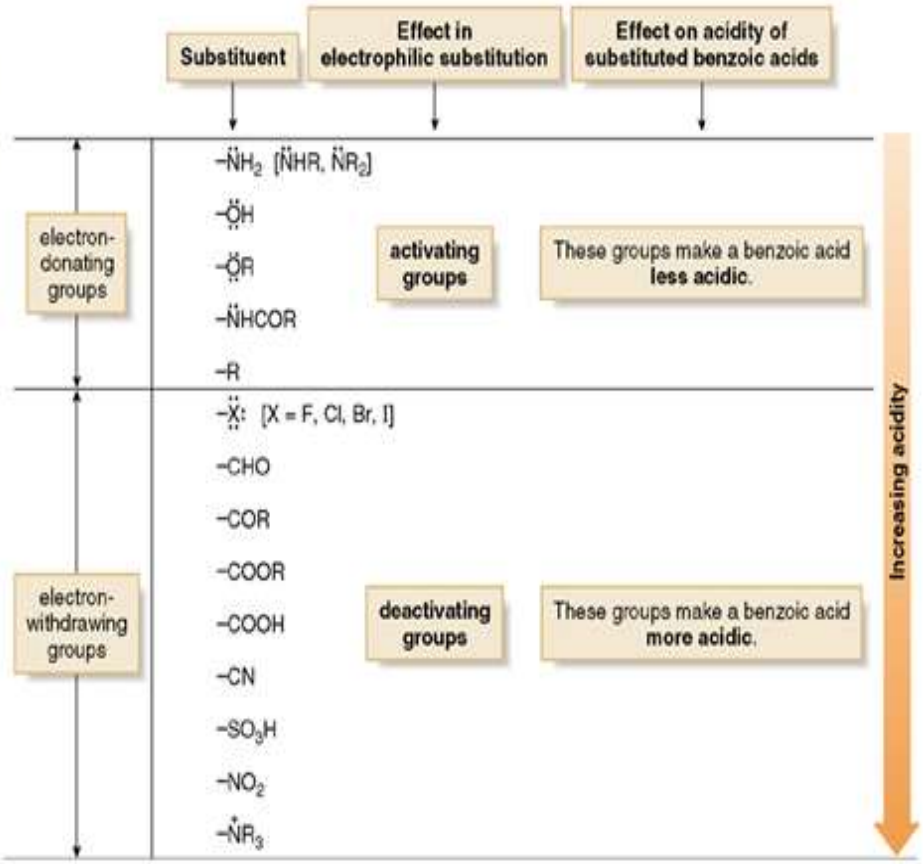
Electron-withdrawing substituents should disperse the negative charge, stabilize the anion, and thus increase acidity. Electron-releasing substituents should intensify the negative charge, destabilize the anion, and thus decrease acidity.

The electron-withdrawing halogens strengthen acids: chloroacetic acid is 100 times as strong as acetic acid, dichloroacetic acid is still stronger, and trichloroacetic acid is more than 10,000 times as strong as the unsubstituted acid. The other halogens exert similar effects. α-Chlorobutyric acid is about as strong as chloroacetic acid. As the chlorine is moved away from the COOH, its effect rapidly dwindles: β-chlorobutyric acid is only six times as strong as butyric acid, and γ-chlorobutyric acid is only twice as strong. It is typical of inductive effects that they decrease rapidly with distance, and are seldom important when acting through more than four atoms.

The substituents I, Br, Cl, F, and NO_2, increase the acidity of the CO_2H group over that of the unsubstituted compound (S = H). In contrast, the substituents CH_3 or CO_2^- decrease the acidity of the CO_2H group compared to the unsubstituted compound.
The aromatic acids are similarly affected by substituents: CH_3, OH, and NH_2 make benzoic acid weaker, and Cl and NO_2 make benzoic acid stronger.
The acid-weakening groups are the ones that activate the ring toward electrophilic substitution (and deactivate toward nucleophilic substitution). The acid-strengthening groups are the ones that deactivate toward electrophilic substitution (and activate toward nucleophilic substitution). Furthermore, the groups that have the largest effects on reactivity whether activating or deactivating have the largest effects on acidity.

How common substituents affect the reactivity of a benzene ring towards electrophiles and the acidity of substituted benzoic acids

- **Groups that donate electron density activate a benzene ring towards electrophilic attack and make a benzoic acid *less* acidic.** Common electron-donating groups are R groups, or groups that have an N or O atom (with a lone pair) bonded to the benzene ring.
- **Groups that withdraw electron density deactivate a benzene ring towards electrophilic attack, and make a benzoic acid *more* acidic.** Common electron-withdrawing groups are the halogens, or groups with an atom Y (with a full or partial positive charge) bonded to the benzene ring.

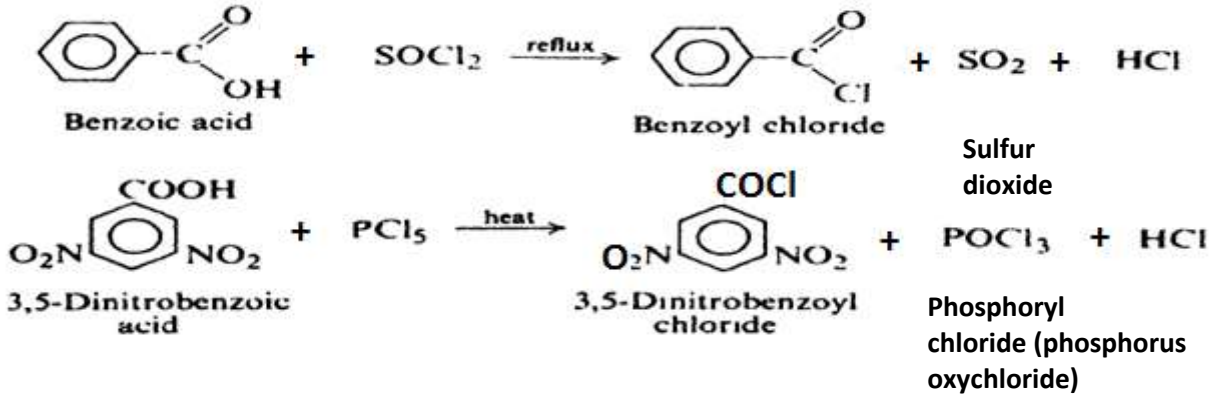


The -OH and -OCH_3 (ortho and para directed) groups display both kinds of effect we have attributed to them from the meta position, an electron-withdrawing acid-

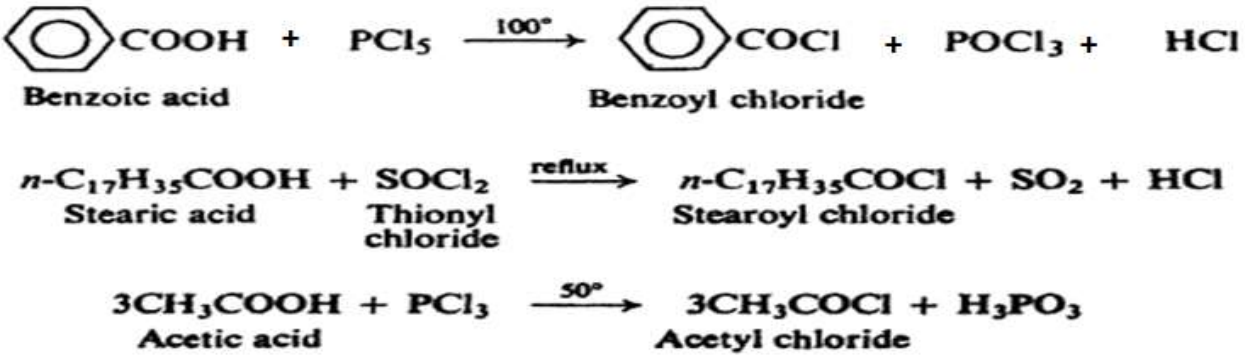
strengthening inductive effect; and from the para position, an electron-releasing acid-weakening resonance effect (which at this position outweighs the inductive effect).
Ortho substituted aromatic acids do not fit into the pattern set by their meta and para isomers, and by aliphatic acids. Nearly all ortho substituents exert an effect of the same kind acid-strengthening whether they are electron-withdrawing or electron-releasing, and the effect is unusually large. This ortho effect undoubtedly has to do with the nearness of the groups involved, but is more than just steric hindrance arising from their bulk.
Thus we see that the same concepts inductive effect and resonance that is found so useful in dealing with the rates of reaction are also 'useful in dealing with equilibria. By using these concepts to estimate the stabilities of anions, we are able to predict the relative strengths of acids.

Conversion into acid chlorides

A carboxylic acid is more often converted into the acid chloride than into any other of its functional derivatives. From the highly reactive acid chloride there can then be obtained many other kinds of compounds, including esters and amides.
An acid chloride is prepared by substitution of Cl for the OH of a carboxylic acid. Three reagents are commonly used for this purpose: thionyl chloride, $SOCl_2$; phosphorus trichloride, PCl_3; and phosphorus pentachloride, PCl_5.

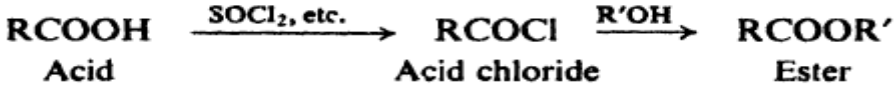


Thionyl chloride is particularly convenient, since the products formed besides the acid chloride are gases and thus easily separated from the acid chloride; any excess of the low-boiling thionyl chloride is easily removed by distillation.
Examples:

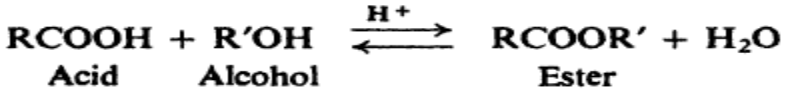


Conversion into esters

Acids are frequently converted into their esters via the acid chlorides:



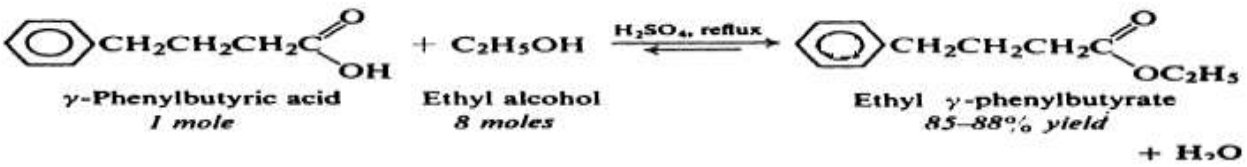
A carboxylic acid is converted directly into an ester when heated with an alcohol in the presence of a little mineral acid, usually concentrated sulfuric acid or dry hydrogen chloride. This reaction is reversible, and generally reaches equilibrium when there are appreciable quantities of both reactants and products present.



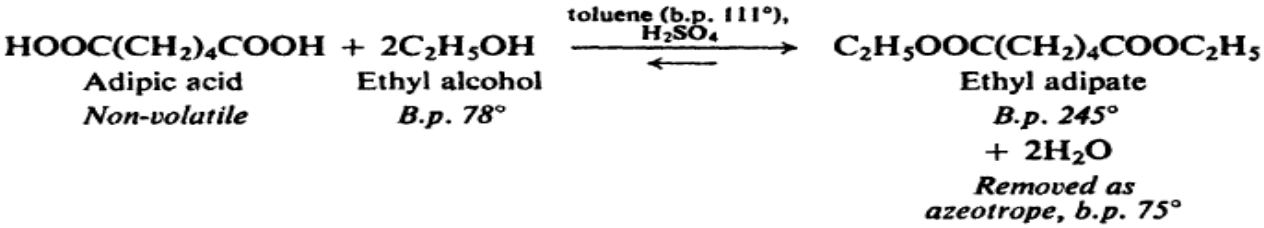
For example, when we allow one mole of acetic acid and one mole of ethyl alcohol to react in the presence of a little sulfuric acid until equilibrium is reached (after several hours), we obtain a mixture of about two-thirds mole each of ester and water, and one-third mole each of acid and alcohol. We obtain this same equilibrium mixture, of course, if we start with one mole of ester and one mole of water, again in the presence of sulfuric acid. The same catalyst, hydrogen ion, that catalyzes the forward reaction, esterification, necessarily catalyzes the reverse reaction, hydrolysis.

This reversibility is a disadvantage in the preparation of an ester directly from an acid; the preference for the acid chloride route is due to the fact that both steps preparation of acid chloride from acid, and preparation of ester from acid chloride are essentially irreversible and go to completion.

Direct esterification, however, has the advantage of being a single-step synthesis; it can often be made useful by application of our knowledge of equilibria. If either the acid or the alcohol is cheap and readily available, it can be used in large excess to shift the equilibrium toward the products and thus to increase the yield of ester. For example, it is worthwhile to use eight moles of cheap ethyl alcohol to convert one mole of valuable γ-phenylbutyric acid more completely into the ester:



Sometimes the equilibrium is shifted by removing one of the products. An elegant way of doing this is illustrated by the preparation of ethyl adipate. The dicarboxylic acid adipic acid, an excess of ethyl alcohol, and toluene are heated with a little sulfuric acid under a distillation column. The lowest boiling component (b.p. 75) of the reaction mixture is an azeotrope of water, ethyl alcohol, and toluene as fast as water is formed it is removed as the azeotrope by distillation. In this way a 95-97% yields of ester.

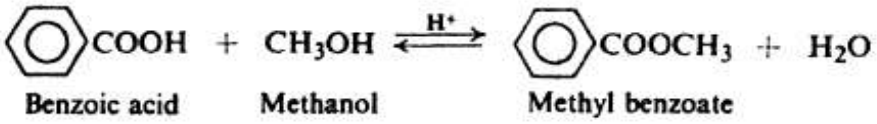


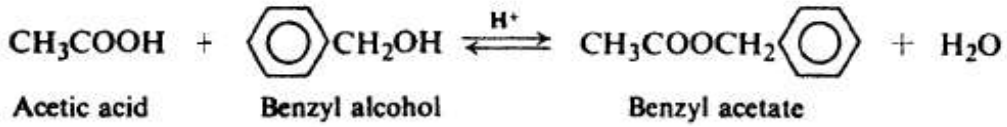
The equilibrium is particularly unfavorable when phenols (ArOH) are used instead of alcohols; yet, if water is removed during the reaction, phenolic esters (RCOOAr) are obtained in high yield.

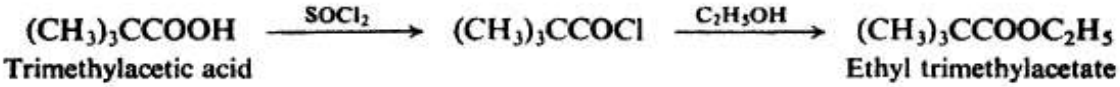
The presence of bulky groups near the site of reaction, whether in the alcohol or in the acid, slows down esterification (as well as its reverse, hydrolysis). This steric hindrance can be so marked that special methods are required to prepare esters of tertiary alcohols or esters of acids like 2,4,6-trimethylbenzoic acid (mesitoic acid).

Reactivity in esterification	$CH_3OH > 1° > 2° (> 3°)$
	$HCOOH > CH_3COOH > RCH_2COOH > R_2CHCOOH > R_3CCOOH$

Examples:



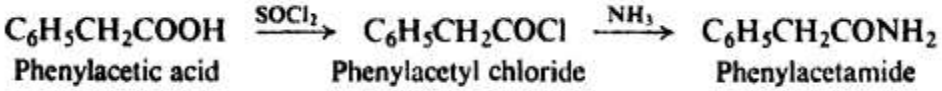




Conversion into amides

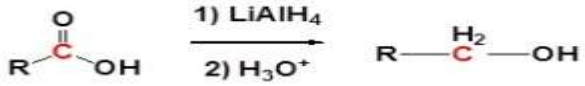
Amides are compounds in which the OH of the carboxylic acid has been replaced by NH_2. These are generally prepared by reaction of ammonia with acid chlorides.

Example:



Reduction of acids to alcohols

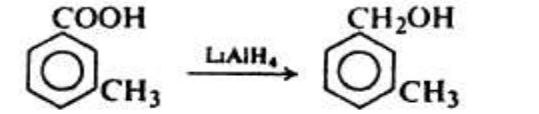
Conversion of alcohols into acids is important because alcohols are more available than acids. This is not always true, long straight-chain acids from fats are more available than are the corresponding alcohols, and here the reverse process becomes important: reduction of acids to alcohols. Lithium aluminum hydride, $LiAlH_4$, is one of the few reagents that can reduce an acid to an alcohol; the initial product is an alkoxide from which the alcohol is liberated by hydrolysis:



$$4RCOOH + 3LiAlH_4 \longrightarrow 4H_2 + 2LiAlO_2 + (RCH_2O)_4AlLi \xrightarrow{H_2O} \underset{1^\circ \text{ alcohol}}{4RCH_2OH}$$

Example:

$$\underset{\text{Trimethylacetic acid}}{4(CH_3)_3CCOOH} + 3LiAlH_4 \xrightarrow{\text{ether}} [(CH_3)_3CCH_2O]_4AlLi + 2LiAlO_2 + 4H_2 \xrightarrow{H^+} \underset{\text{Neopentyl alcohol (2,2-Dimethyl-1-propanol)}}{(CH_3)_3CCH_2OH}$$



m-Toluic acid — *m*-Methylbenzyl alcohol

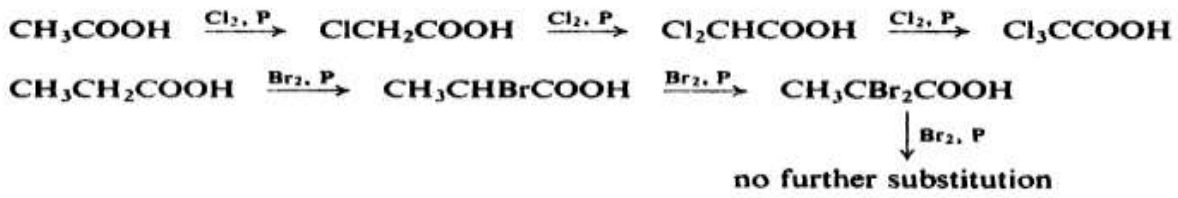
As an alternative to direct reduction, acids are often converted into alcohols by a two-step process: esterification, and reduction of the ester. Esters can be reduced in a number of ways that are adaptable to both laboratory and industry.

$$\underset{\text{Ester}}{RCOOR'} \xrightarrow{\text{reduction}} \underset{1^\circ \text{ alcohol}}{RCH_2OH} + R'OH$$

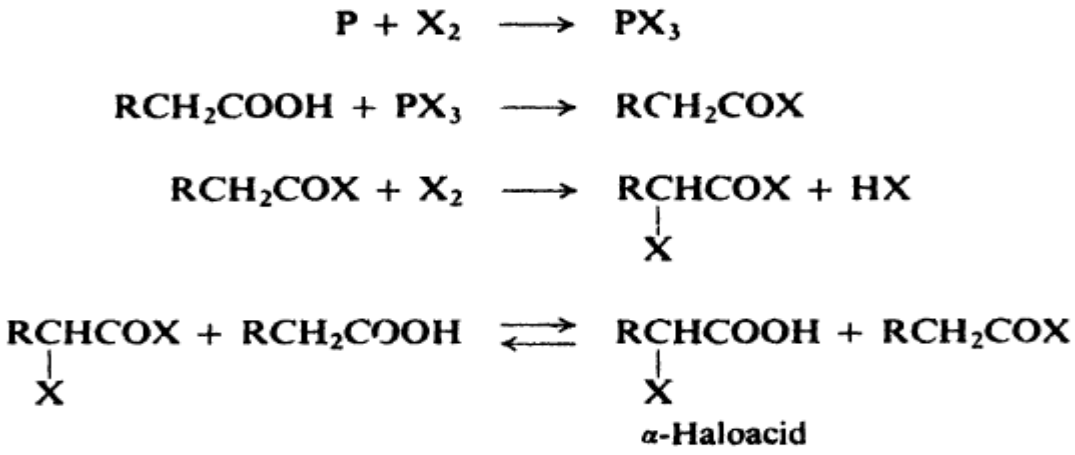
$$\underset{\text{Methyl laurate (Methyl dodecanoate)}}{CH_3(CH_2)_{10}COOCH_3} \xrightarrow[150^\circ,\ 5000\ lb/in.^2]{H_2,\ CuO.CuCr_2O_4} \underset{\text{Lauryl alcohol (1-Dodecanol)}}{CH_3(CH_2)_{10}CH_2OH} + CH_3OH$$

Halogenation of aliphatic acids: Substituted acids

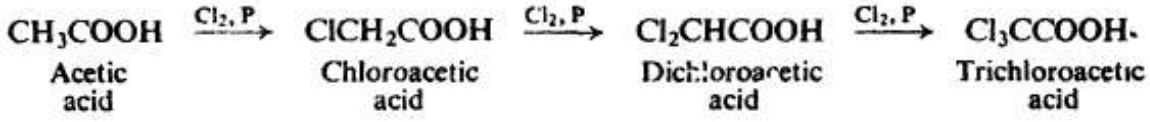
In the presence of a small amount of phosphorus, aliphatic carboxylic acids react smoothly with chlorine or bromine to yield a compound in which α-hydrogen has been replaced by halogen. This is the Hell-Volhard-Zelinsky reaction. Because of its specificity (only alpha halogenation) and the with which it takes place, it is of considerable importance in synthesis.

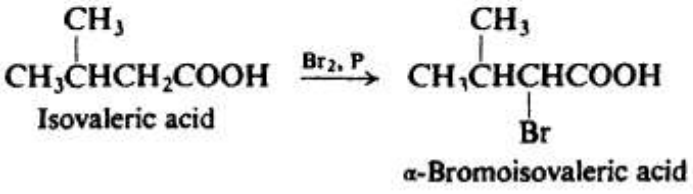


The function of the phosphorus is ultimately to convert a little of the acid into acid halide. In this form each molecule of acid sooner or later undergoes α-halogenation.

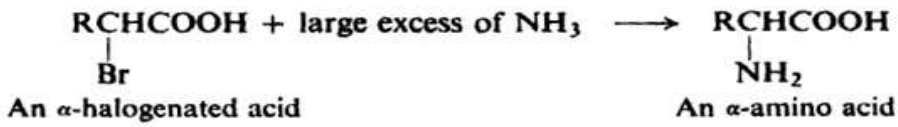


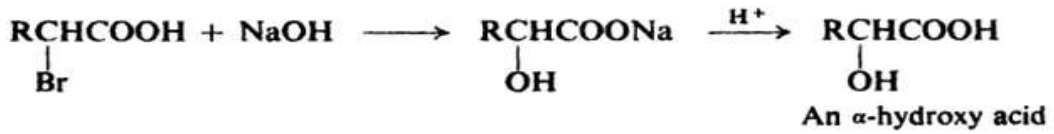
Examples:





The halogen of these halogenated acids undergoes nucleophilic displacement and elimination much as it does in the simpler alkyl halides. Halogenation is therefore the first step in the conversion of a carboxylic acid into many important substituted carboxylic acids:

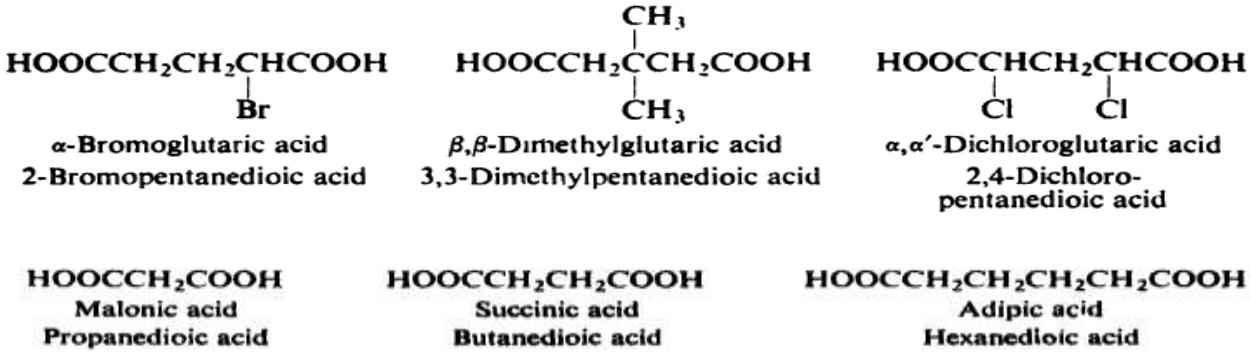




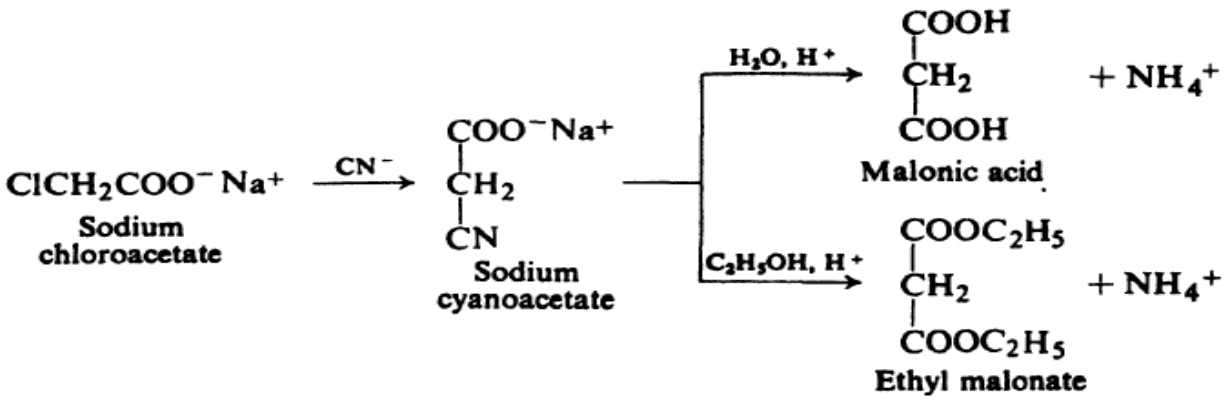
These new substituents can, in turn, undergo their characteristic reactions.

Dicarboxylic acids

If the substituent is a second carboxyl group, we have a dicarboxylic acid. For example:

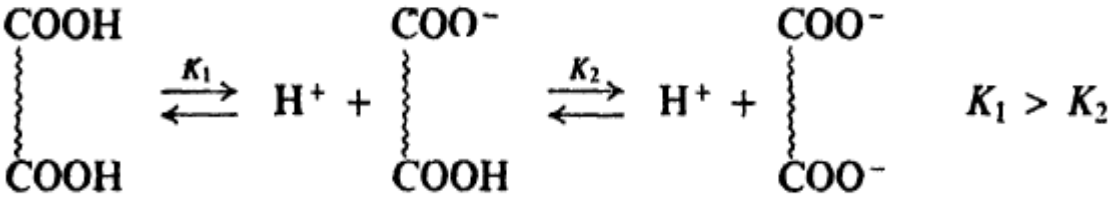


Most dicarboxylic acids are prepared by adaptation of methods used to prepare monocarboxylic acids. Where hydrolysis of a nitrile yields a monocarboxylic acid, hydrolysis of a dinitrile or a cyanocarboxylic acid yields a dicarboxylic acid; where oxidation of a methylbenzene yields a benzoic acid, oxidation of a dimethylbenzene yields a phthalic acid. For example:



In general, dicarboxylic acids show the same chemical behavior as monocarboxylic acids. It is possible to prepare compounds in which only one of the carboxyl groups has been converted into a derivative; it is possible to prepare compounds in which the two carboxyl groups have been converted into different derivatives.

As with other acids containing more than one ionizable hydrogen (H_2SO_4 , H_2CO_3 , H_3PO_4 , etc.), ionization of the second carboxyl group occurs less readily than ionization of the first.



More energy is required to separate a positive hydrogen ion from the doubly charged anion than from the singly charged anion.

Analysis of carboxylic acids: Neutralization equivalent

Carboxylic acids are recognized through their acidity. They dissolve in aqueous sodium hydroxide and in aqueous sodium bicarbonate. The reaction with bicarbonate releases bubbles of carbon dioxide.

Once characterized as a carboxylic acid, an unknown is identified as a particular acid on the usual basis of its physical properties and the physical properties of derivatives. The derivatives commonly used are amides and esters.

Particularly useful both in identification of previously studied acids and in proof of structure of new ones is the **neutralization equivalent NE**: **the equivalent weight of the acid as determined by titration with standard base.** The NE is identical to the equivalent weight of the carboxylic acid. If the acid has only one carboxyl group, the NE and the molecular weight of the acid are identical. If the acid has more than one carboxyl group, the NE equals the molecular weight of the acid divided by the number of carboxyl groups that is the equivalent weight. The NE can be used much like a derivative to identify a specific carboxylic acid.

A weighed sample of the acid is dissolved in water or aqueous alcohol, and the volume of standard base needed to neutralize the solution is measured. **For example**, a 0.224-g sample of an unknown acid (m.p. 139-140) required 13.6 ml of 0.104 N sodium hydroxide solution for neutralization (to a phenolphthalein end point). Since each 1000 ml of an unknown of the base contains 0.104 equivalents, and since the number of equivalents of base required equals the number of equivalents of acid present,

$$\frac{0.224}{Eq} \times 1000 \quad = \quad 0.104 \times 13.6$$

$$Eq = \frac{0.224 \times 1000}{13.6 \times 0.104}$$

1 equivalent of acid =158

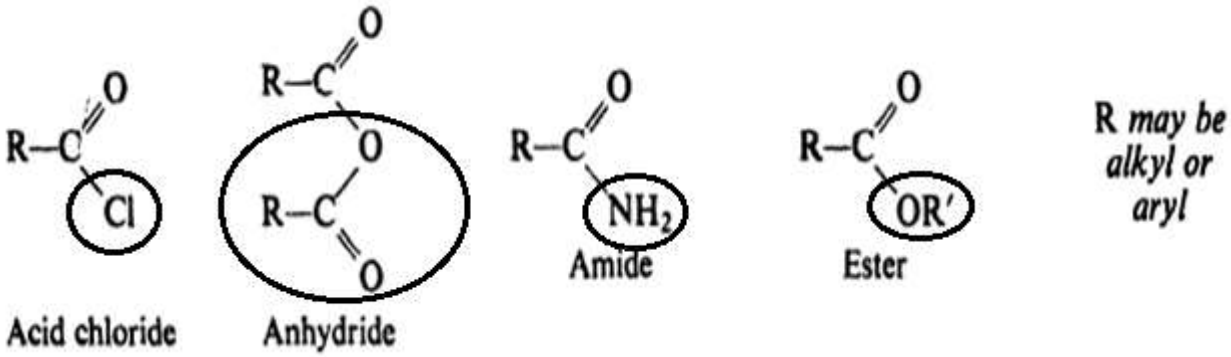
A metal salt of a carboxylic acid is recognized through these facts:

- It leaves a residue when strongly heated (ignition test).
- It decomposes at a fairly high temperature/ instead of melting.
- It is converted into a carboxylic acid upon treatment with dilute mineral acid.

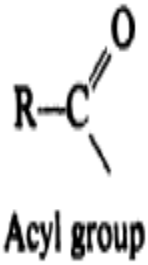
Functional Derivatives of Carboxylic Acids
Nucleophilic Acyl Substitution

Structure

Closely related to the carboxylic acids and to each other, are a number of chemical families known as **functional derivatives of carboxylic acids**: acid chlorides, anhydrides, amides, and esters. These derivatives are compounds in which the OH of a carboxyl group has been replaced by Cl, OOCR, NH_2, or OR' as (chloro, acyloxy, amino and alkoxy)l.



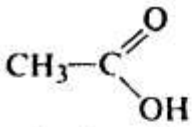
They all contain the acyl group:



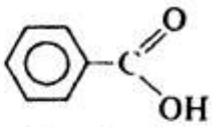
Like the acid to which it is related, an acid derivative may be aliphatic or aromatic, substituted or unsubstituted; whatever the structure of the rest of the molecule, the properties of the functional group remain essentially the same.

Nomenclature

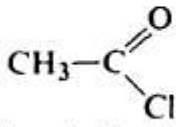
The names of acid derivatives are taken in simple ways from either the common name or the IUPAC name of the corresponding carboxylic acid. For example:



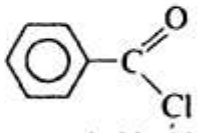
Acetic acid
Ethanoic acid



Benzoic acid

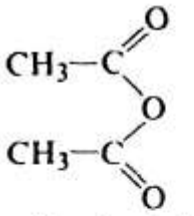


Acetyl chloride
Ethanoyl chloride

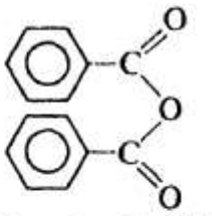


Benzoyl chloride

Change:
-ic acid to *-yl chloride*

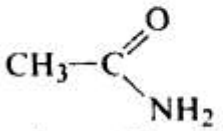


Acetic anhydride
Ethanoic anhydride

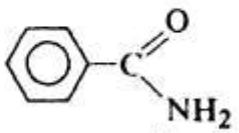


Benzoic anhydride

acid to ***anhydride***

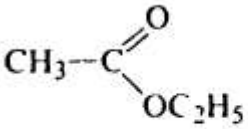


Acetamide
Ethanamide

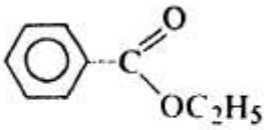


Benzamide

-ic acid of common name
(or *-oic acid* of IUPAC name)
to *- amide*



Ethyl acetate
Ethyl ethanoate

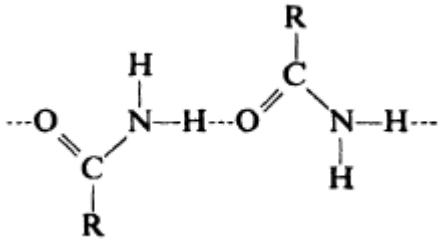


Ethyl benzoate

-ic acid to *-ate*,
preceded by name of
alcohol or phenol group

Physical properties

The presence of the C=O group makes the acid derivatives polar compounds. Acid chlorides, anhydrides and esters have boiling points that are about the same as those of aldehydes or ketones of comparable molecular weight. Amides have quite high boiling points because they are capable of strong intermolecular hydrogen bonding.



Volatile esters have pleasant, rather characteristic odors; they are often used in the preparation of perfumes and artificial flavorings. Acid chlorides have sharp, irritating odors, at least partly due to their ready hydrolysis to HCl and carboxylic acids.

Nucleophilic acyl substitution.

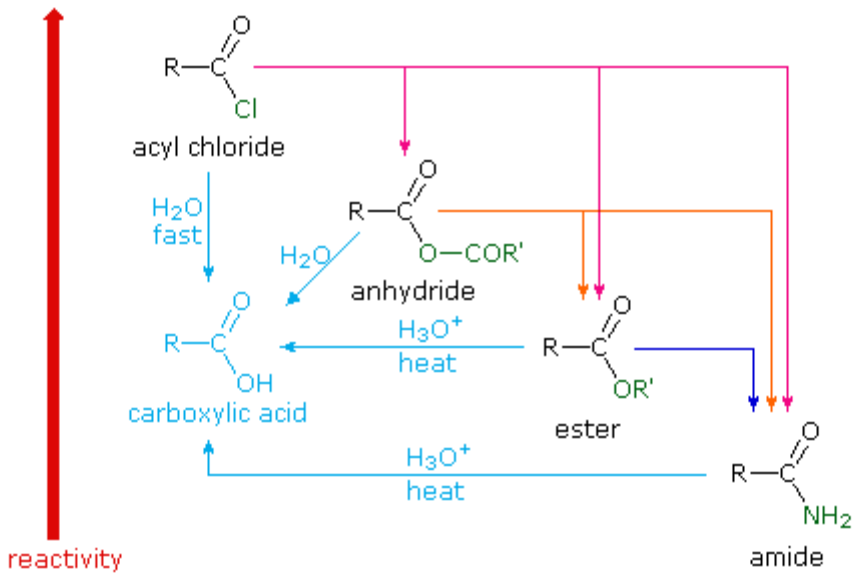
Role of the carbonyl group

Each derivative is nearly always prepared directly or indirectly from the corresponding carboxylic acid, and can be readily converted back into the carboxylic acid by simple hydrolysis. Much of the chemistry of acid derivatives involves their conversion one into another, and into the parent acid. In addition, each derivative has certain characteristic reactions of its own.

Different carboxylic acid derivatives have very different reactivities, acyl chlorides and bromides being the most reactive and amides the least reactive. The change in reactivity is dramatic. In homogeneous solvent systems, reaction of acyl chlorides with water occurs rapidly, and does not require heating or catalysts. Amides, on the other hand, react with water only in the presence of strong acid or base catalysts and external heating.

Reactivity: acyl halides > anhydrides >> esters ≈ acids >> amides

Because of these differences, the conversion of one type of acid derivative into another is generally restricted to those outlined in the following diagram.

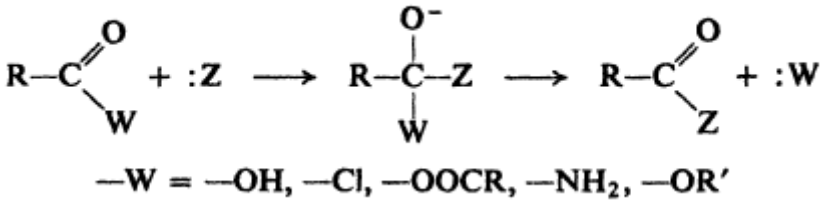


The derivatives of carboxylic acids, like the acids themselves, contain the carbonyl group, C=O. This group is retained in the products of most reactions undergone by these compounds, and does not suffer any permanent changes itself. But by its presence in the molecule it determines the characteristic reactivity of these compounds, and is the key to

the understanding of their chemistry, as in aldehydes and ketones, the carbonyl group performs two functions:

- **It provides a site for nucleophilic attack.**
- **It increases the acidity of hydrogens attached to the alpha carbon.**

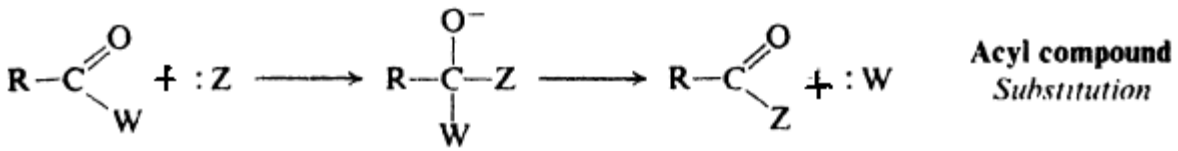
Acyl compounds, carboxylic acids and their derivatives, typically undergo **nucleophilic substitution** in which -OH, -Cl, OOCR, NH_2, or -OR' is replaced by some other basic group. Substitution takes place much more readily than at a saturated carbon atom; indeed, many of these substitutions do not usually take place at all in the absence of the carbonyl group, as, for example, replacement of -NH_2 by -OH.



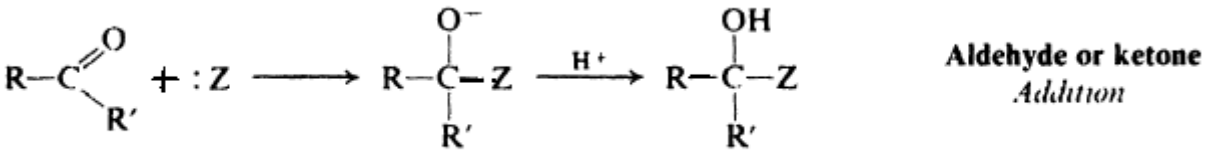
Both electronic and steric factors make the carbonyl group particularly susceptible to nucleophilic attack at the carbonyl carbon:

- The tendency of oxygen to acquire electrons even at the expense of gaining a negative charge.
- The relatively unhindered transition state leading from the trigonal reactant to the tetrahedral intermediate.

These factors make acyl compounds susceptible to nucleophilic attack. In the second step of the reaction for the acyl the tetrahedral intermediate compound ejects the :W group, returning to a trigonal compound, and thus the result is **substitution**. (While in aldehyde and ketone the tetrahedral intermediate gains a proton, and the result is addition).



While



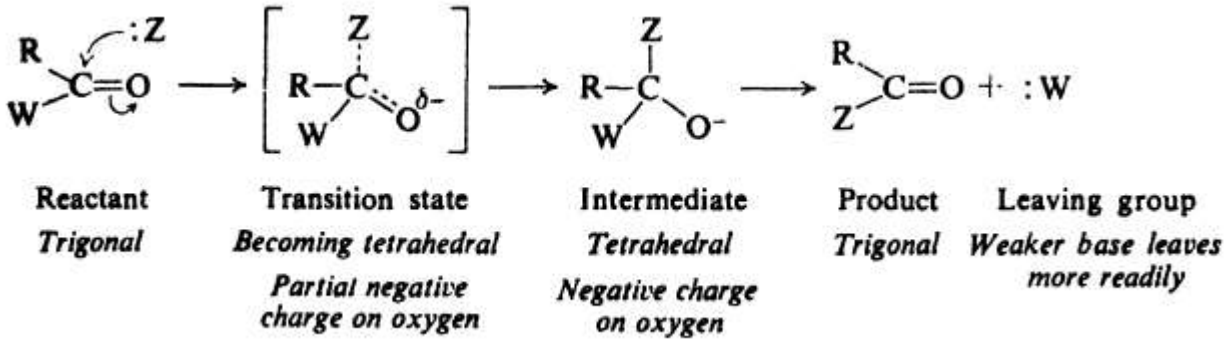
We can see why the two classes of compounds differ as they do. The ease with which :W is lost depends upon **its basicity**: *the weaker the base, the better the leaving group*. For acid chlorides, acid anhydrides, esters, and amides, :W is, respectively: the very weak base Cl^- ; the moderately weak base $RCOO^-$; and the strong bases $R'O^-$ and NH_2^-. But

for an aldehyde or ketone to undergo substitution, the leaving group would have to be hydride ion ($:H^-$) or alkide ion ($:R^-$) which are the strongest bases of all, and so with aldehydes and ketones addition almost always takes place instead.

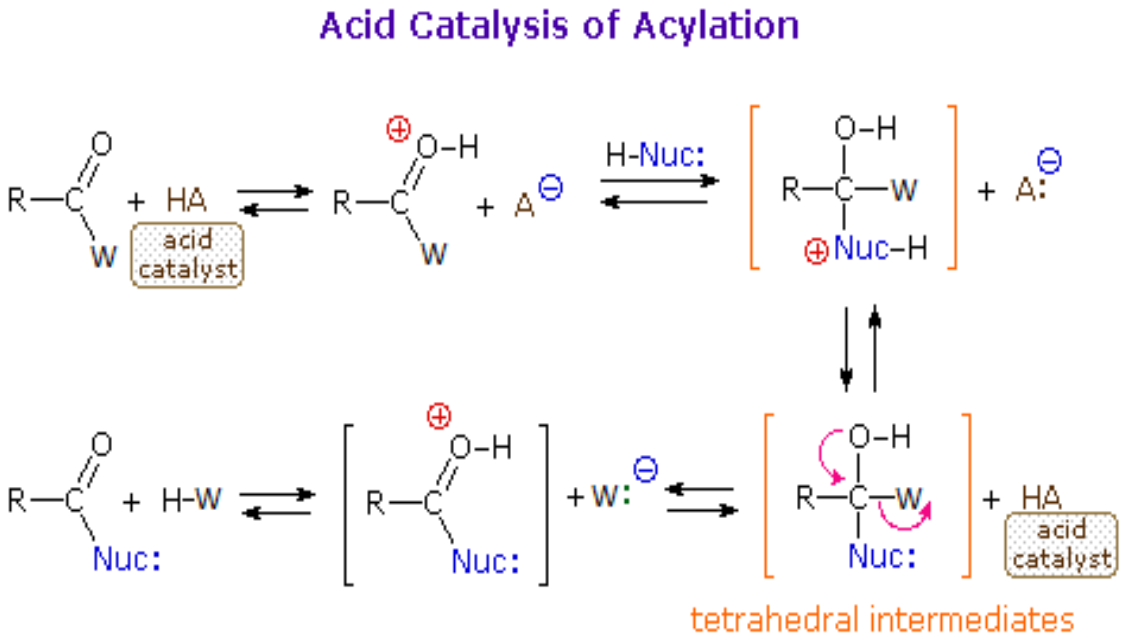
Nucleophilic acyl substitution proceeds by two steps, with the intermediate formation of a tetrahedral compound. Generally, the overall rate is affected by the rate of both steps, but the first step is the more important. The first step, formation of the tetrahedral intermediate, is affected by the same factors as in addition to aldehydes and ketone

- It is favored by electron withdrawal, which stabilizes the developing negative charge; and
- It is hindered by the presence of bulky groups, which become crowded together in the transition state.

The second step depends on the basicity of the leaving group, :W.



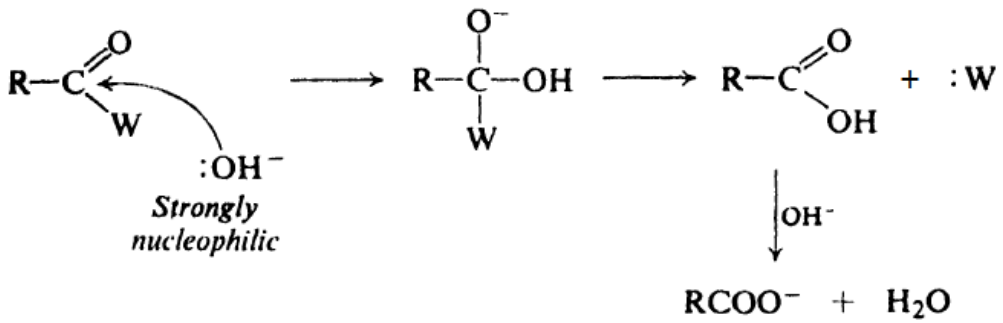
If acid is present, H^+ becomes attached to carbonyl oxygen, thus making the carbonyl group even more susceptible to the nucleophilic attack; oxygen can now acquire the π electrons without having to accept a negative charge.



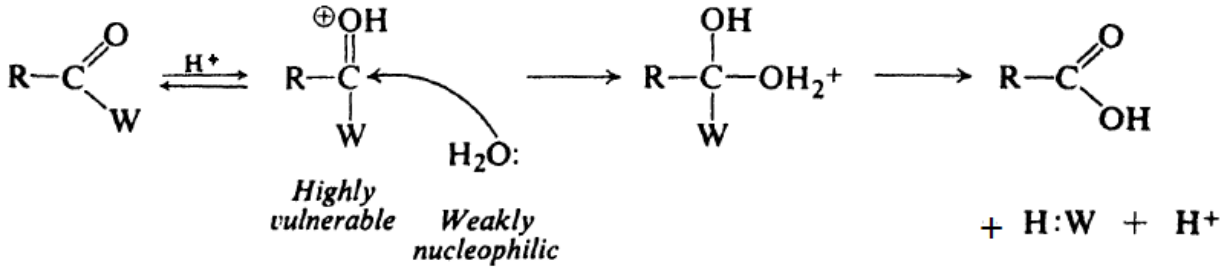
The acid derivatives are hydrolyzed more readily in either alkaline or acidic solution than in neutral solution:

- Alkaline solutions provide hydroxide ion, which acts as a strongly nucleophilic reagent.
- Acid solutions provide hydrogen ion, which attaches itself to carbonyl oxygen and thus renders the molecule vulnerable to attack by the weakly nucleophilic reagent, water.

Alkaline hydrolysis



Acidic hydrolysis

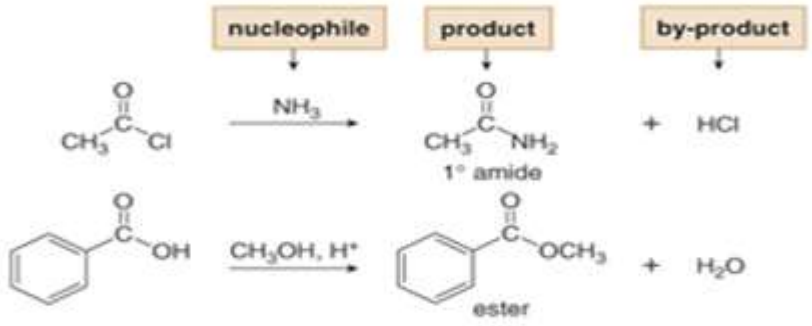


To draw any nucleophilic acyl product:

[1] Find the sp^2 hybridized carbon with the leaving group.

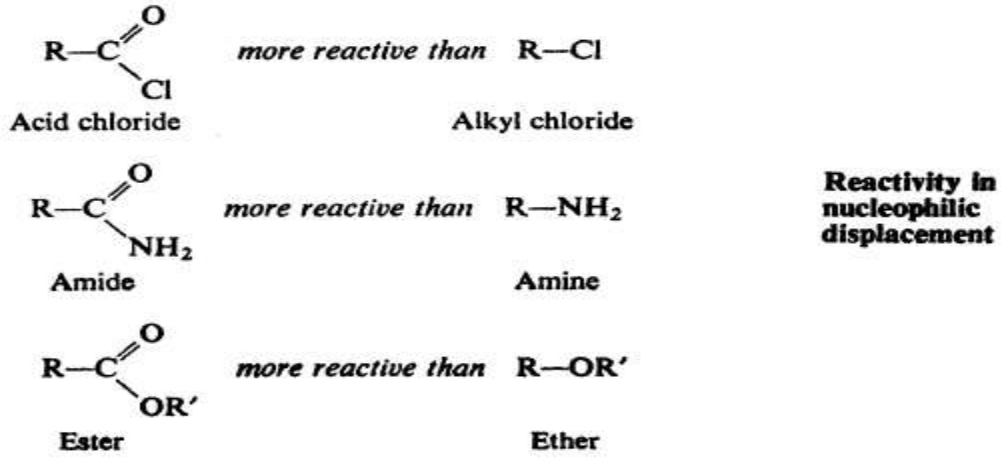
[2] Identify the nucleophile.

[3] Substitute the nucleophile for the leaving group. With a neutral nucleophile, the proton must be lost to obtain a neutral substitution product.

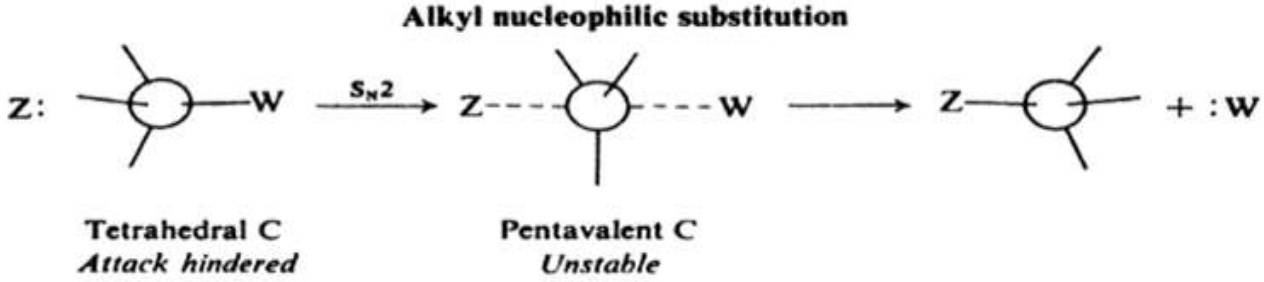


Nucleophilic substitution: alkyl vs. acyl

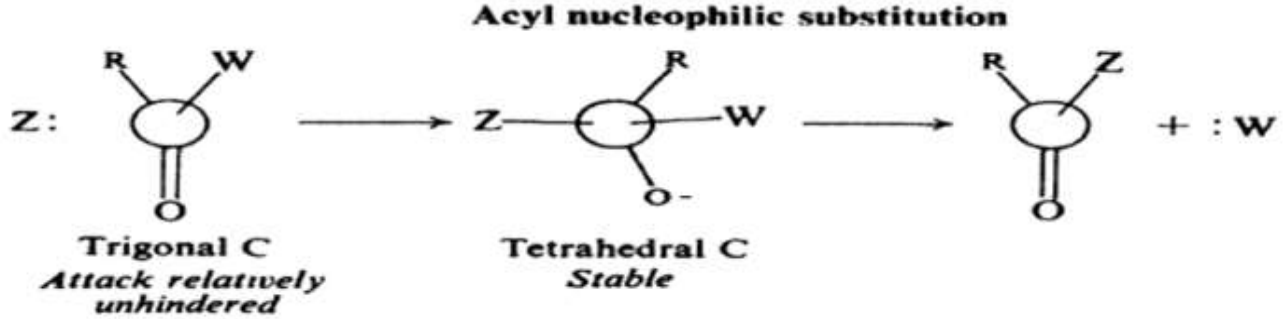
The nucleophilic substitution takes place much more readily at an acyl carbon than at saturated carbon. Thus, toward nucleophilic attack acid chlorides are more reactive than alkyl chlorides, amides are more reactive than amines (RNH_2), and esters are more reactive than ethers.



The carbonyl group makes acyl compounds more reactive than alkyl compounds. Nucleophilic attack (S_N2) on a tetrahedral alkyl carbon involves a badly crowded transition state containing pentavalent carbon; a bond must be partly broken to permit the attachment of the nucleophile:



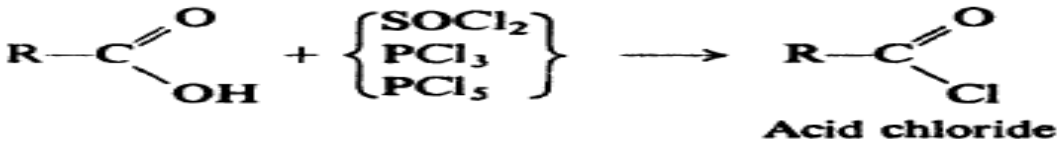
Nucleophilic attack on a flat acyl compound involves a relatively unhindered transition state leading to a tetrahedral intermediate that is actually a compound; since the carbonyl group is unsaturated, attachment of the nucleophile requires breaking only of the weak π bond, and places a negative charge on an atom quite willing to accept it; oxygen.



ACID CHLORIDES

Preparation of acid chlorides

Acid chlorides are prepared from the corresponding acids by reaction with thionyl chloride, phosphorus trichloride, or phosphorus pentachloride.

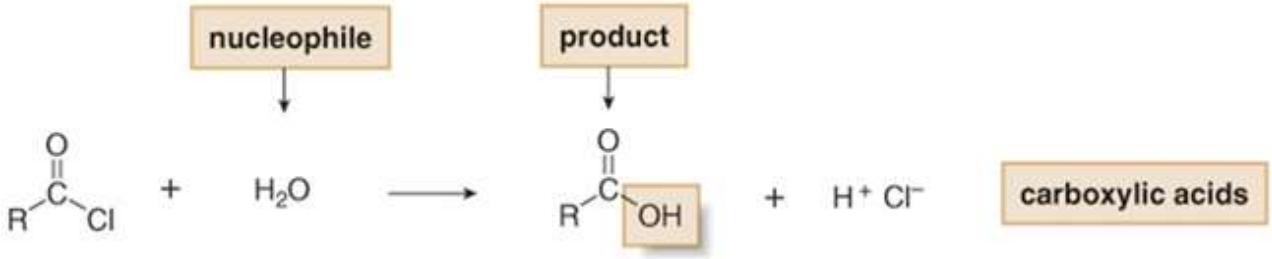


Reactions of acid chlorides

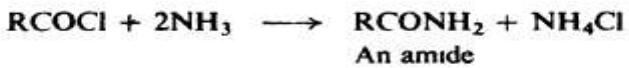
Acid chlorides typically undergo nucleophilic substitution. Chlorine is expelled as chloride ion or hydrogen chloride, and its place is taken by some other basic group. Because of the carbonyl group these reactions take place much more rapidly than the corresponding nucleophilic substitution reactions of the alkyl halides. Acid chlorides are the most reactive of the derivatives of carboxylic acids.

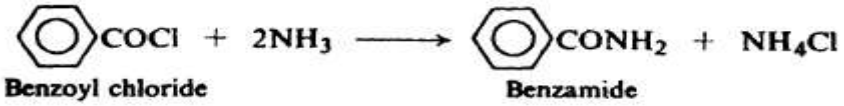
1. **Conversion into acids and derivatives.**

(a) **Conversion into acids: Hydrolysis**.

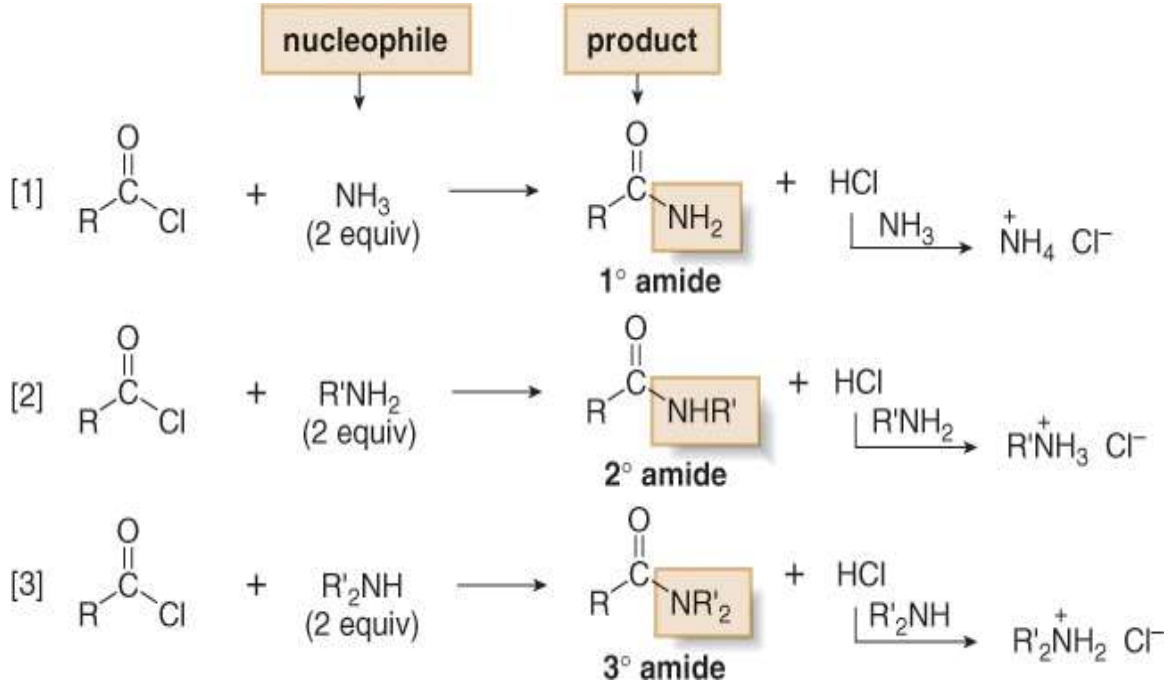


(b) Conversion into amides. Ammonolysis

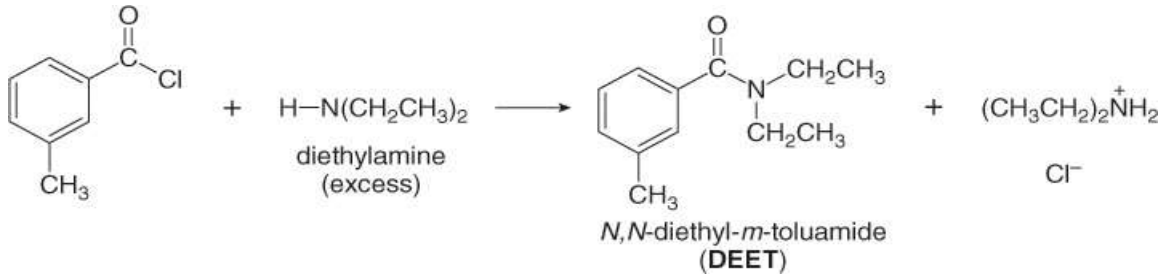




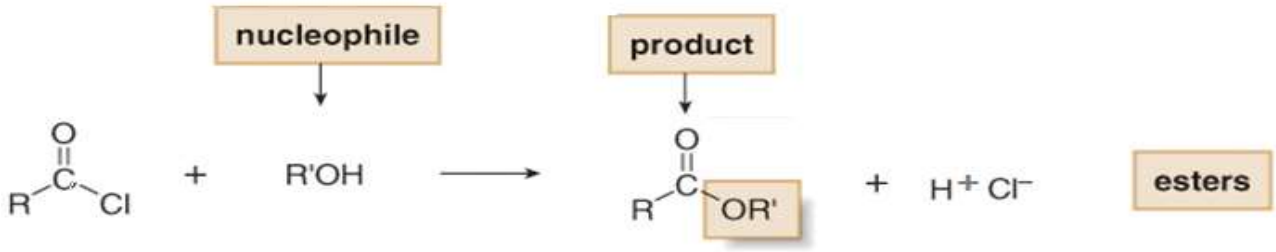
- Acid chlorides also react with ammonia and 1° and 2° amines to form 1°, 2° and 3° amides respectively.
- Two equivalents of NH_3 or amine are used.
- One equivalent acts as the nucleophile to replace Cl, while the other reacts as a base with the HCl by-product to form an ammonium salt.



- As an example, reaction of an acid chloride with diethylamine forms the 3˚ amide *N*,*N*-diethyl-*m*-toluamide, popularly known as DEET.

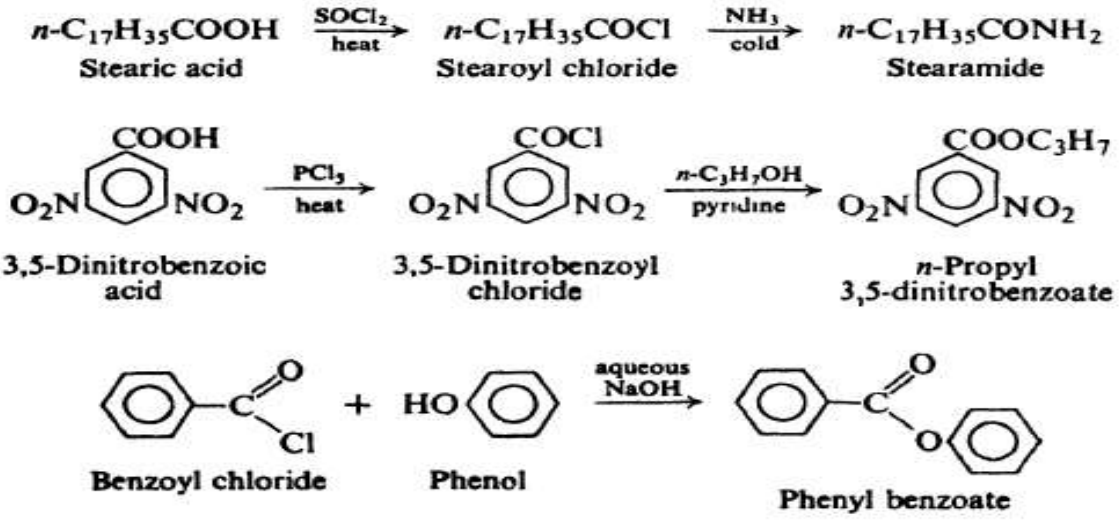


(c) Conversion into esters. Alcoholysis



Conversion of acid chlorides into acid derivatives

Amides and esters are usually prepared from the acid chloride rather than from the acid itself. Both the preparation of the acid chloride and its reactions with ammonia or an alcohol are rapid, essentially irreversible reactions. It is more convenient to carry out these two steps than the single slow, reversible reaction with the acid. For example:



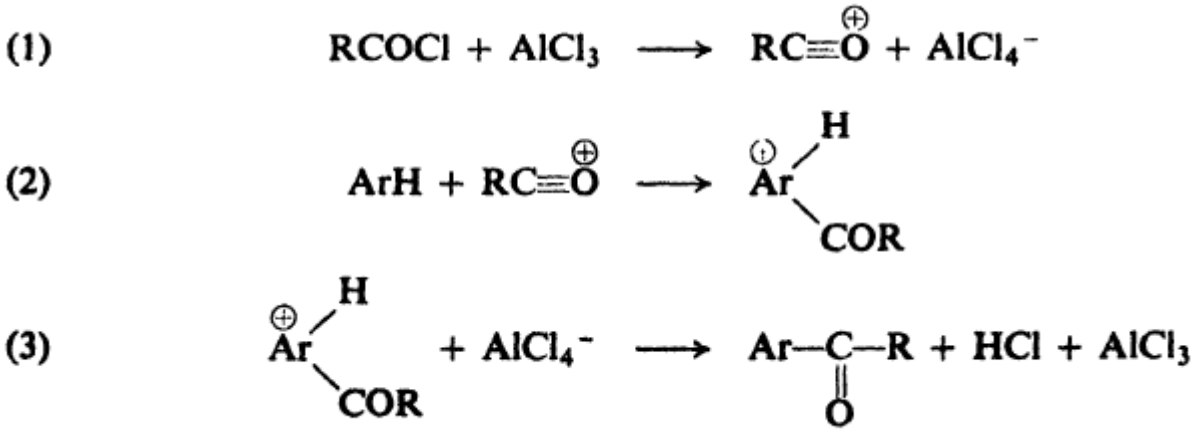
Aromatic acid chlorides (ArCOCl) are considerably less reactive than the aliphatic acid chlorides. With cold water, for example, acetyl chloride reacts almost explosively, whereas Benzoyl chloride reacts only very slowly. The reaction of aromatic acid chlorides with an alcohol or a phenol is often carried out using the special technique called **Schotten-Baumann technique**: the acid chloride is added in portions (followed by vigorous shaking) to a mixture of the hydroxyl compound and a base, usually aqueous sodium hydroxide or pyridine.

The function of the base is not clear; it seems not only to neutralize the hydrogen chloride that would otherwise be liberated, but also to catalyze the reaction.

2. **Formation of ketones. Friedel-Crafts acylation.**

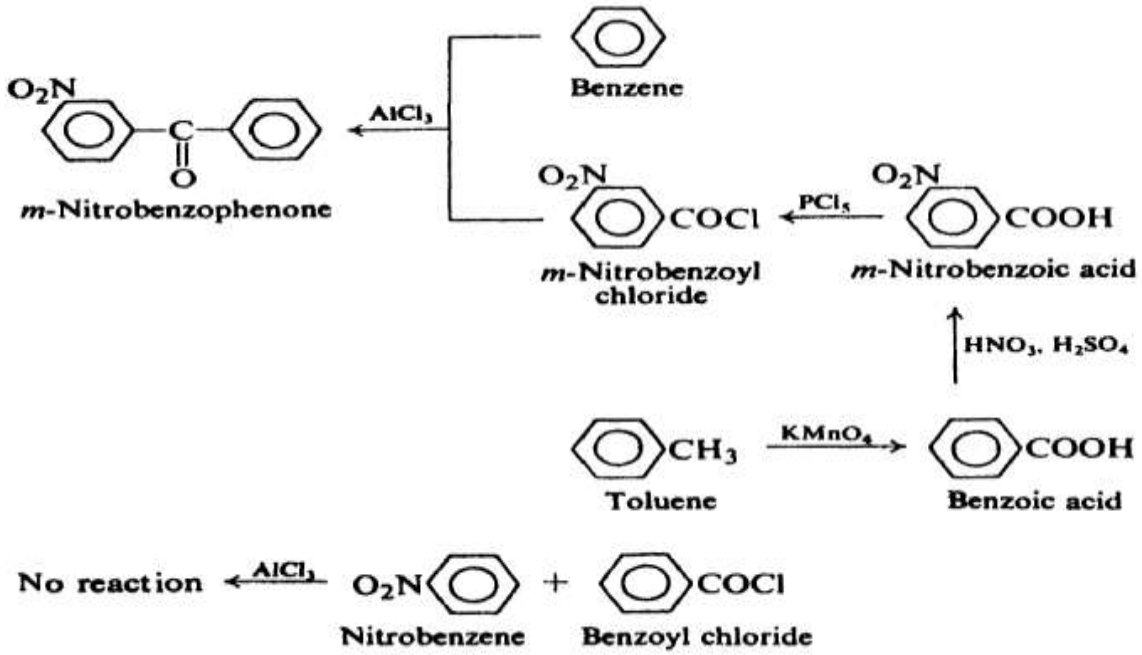
One of the most important modifications of the Friedel-Crafts reaction involves the use of acid chlorides rather than alkyl halides. An acyl group, RC=O , becomes attached to the aromatic ring, thus forming a ketone; the process is called acylation. As usual for the Friedel-Crafts reaction, the aromatic ring undergoing substitution must be catalysis by aluminum chloride or another Lewis acid.

The most likely mechanism for Friedel-Crafts acylation is analogous to the carbonium ion mechanism for Friedel-Crafts alkylation and involves the following steps:



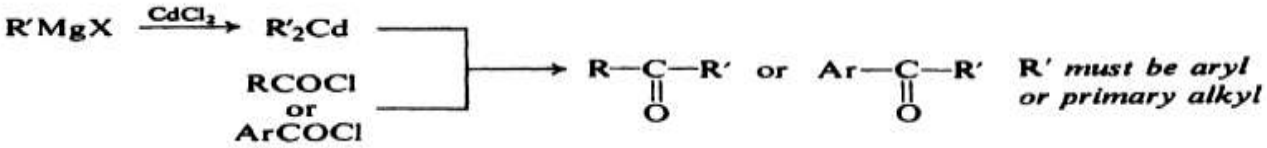
The acylium ion is considerably more stable than ordinary carbonium ions since in it every atom has an octet of electrons.

In planning the synthesis of diaryl ketones, ArCOAr', it is particularly important to select the right combination of ArCOCl and Ar'H. In the preparation of m-nitrobenzophenone, for example, the nitro group can be present in the acid chloride but not in the ring undergoing substitution, since as a strongly deactivating group it prevents the Friedel-Crafts reaction. Friedel-Crafts reactions do not succeed on aromatic rings that are substituted either by a strongly electron-withdrawing group such as carbonyl (C=O) or by an amino group (-NH_2, NHR, -NR_2).



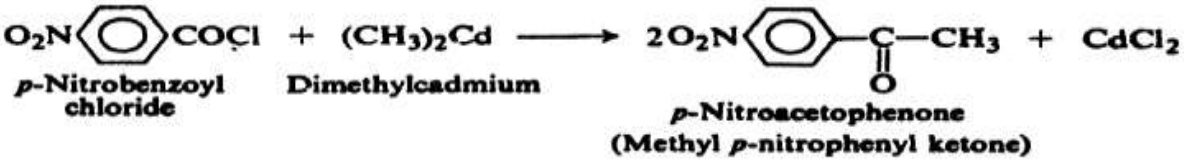
3. Formation of ketones. Reaction with organocadmium compounds.

Grignard reagents react with dry cadmium chloride to yield the corresponding organocadmium compounds, which react with acid chlorides to yield ketones:

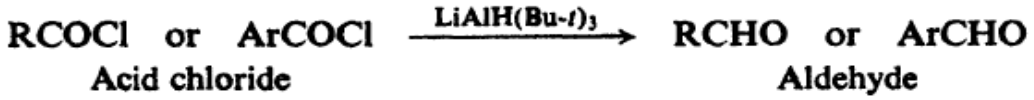


The acid chloride is undergoing nucleophilic substitution, the nucleophile being the basic alkyl or aryl group of the organometallic compound. Only

organocadmium compounds containing aryl or primary alkyl groups are stable enough for use. In spite of this limitation, the method is one of the most valuable for the synthesis of ketones. Organocadmium compounds do not react with many of the functional groups with which the Grignard reagent does react: NO_2, CN, CO, COOR, for example. Consequently, the presence of one of these groups in the acid chloride molecule does not interfere with the synthesis of a ketone. (Grignard reagents themselves react readily with acid chlorides, but the products are usually tertiary alcohols; which is result from reaction of initially formed ketones with more Grignard reagent.)



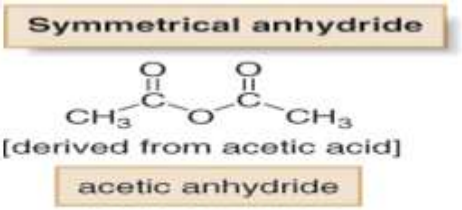
4. **Formation of aldehydes by reduction.**

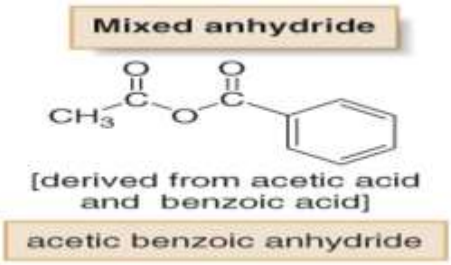


Aliphatic and aromatic aldehydes can be prepared from acid chlorides of the same carbon skeleton by reduction using Lithium tri tert-butoxy aluminum hydride.

ACID ANHYDRIDES

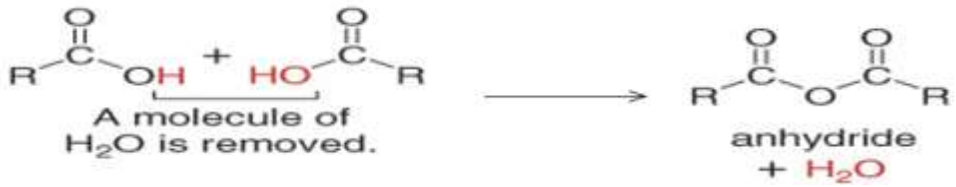
Symmetrical anhydrides, which are derived from same carboxylic acids, are named by changing the acid ending of the carboxylic acid to the word *anhydride* while mixed anhydrides, which are derived from two different carboxylic acids, are named by alphabetizing the names for both acids and replacing the word *acid* with the word *anhydride*.



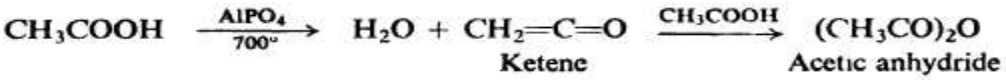


Preparation of acid anhydrides

The word anhydride means without water thus removing of one molecule of water from two carboxylic acid forms an anhydride.

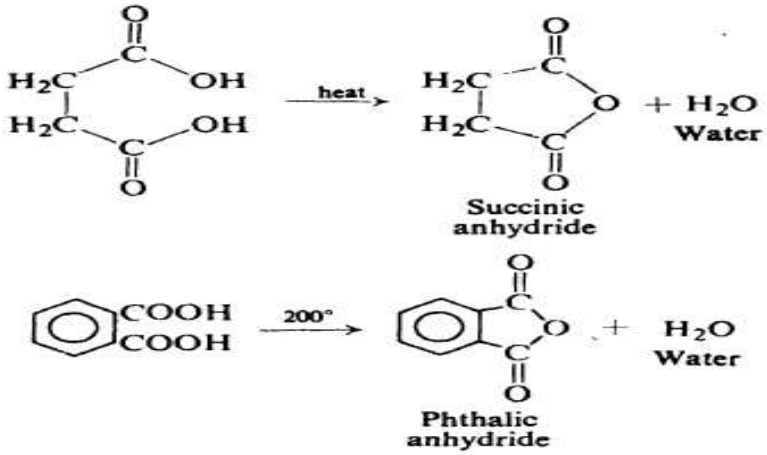


The acetic anhydride is the only one of the monocarboxylic acid anhydride that is very important and used extensively. It is prepared by the reaction of acetic acid with ketene, CH2=C=O, which itself is prepared by high-temperature dehydration of acetic acid.

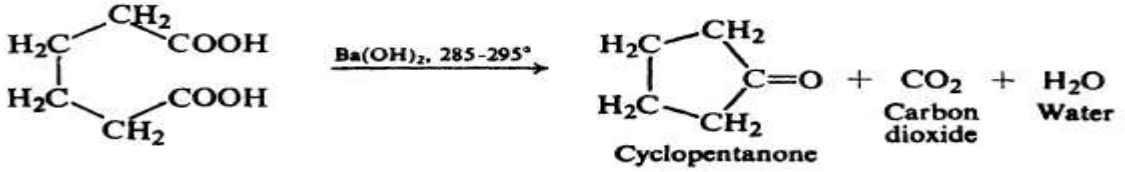


Ketene is an extremely reactive compound and it is made in the laboratory by pyrolysis of acetone, and ordinarily used as soon as it is made. (Pyrolysis is a thermochemical decomposition of organic material at elevated temperatures in the absence of oxygen (or any halogen). It involves the simultaneous change of chemical composition and physical phase, and is irreversible)

In contrast to monocarboxylic acids, certain dicarboxylic acids yield anhydrides on simple heating: in those cases where a five- or six-membered ring is produced. For example:



Ring size is crucial: with adipic acid, for example, anhydride formation would produce a seven-membered ring, and does not take place. Instead, carbon dioxide is lost and cyclopentanone, a ketone with a five-membered ring, is formed.



Reactions of acid anhydrides

Acid anhydrides undergo the same reactions as acid chlorides, but a little more slowly; where acid chlorides yield a molecule of HCl, anhydrides yield a molecule of carboxylic acid.

Compounds containing the acetyl group are often prepared from acetic anhydride; it is

- Cheap.
- Readily available.
- Less volatile.
- More easily handled than acetyl chloride.
- It does not form corrosive hydrogen chloride.

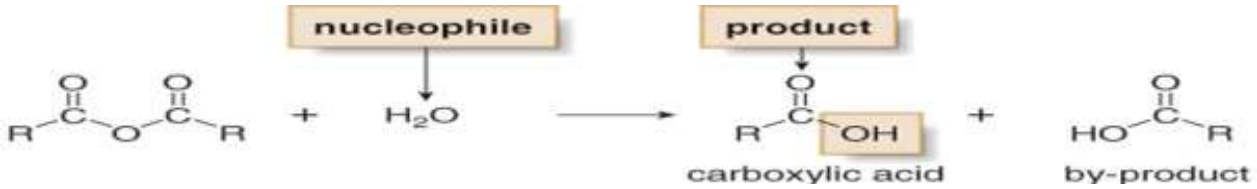
It is widely used in industrially for the esterification of the polyhydroxy compounds known as carbohydrates, especially cellulose.

1. Conversion into acids and acid derivatives

$$(RCO)_2O + HZ \longrightarrow RCOZ + RCOOH$$

Nucleophilic attack occurs at one carbonyl group, while the second carbonyl becomes part of the leaving group.

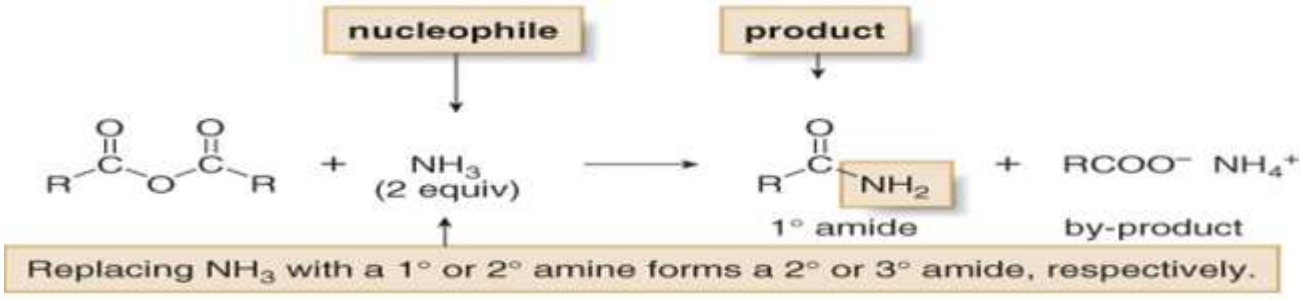
(a) Conversion into acids. Hydrolysis



$$(CH_3CO)_2O + H_2O \longrightarrow 2CH_3COOH$$

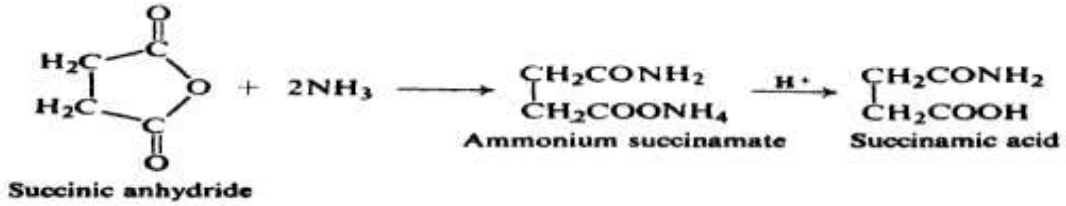
Acetic anhydride — Acetic acid

(b) Conversion into amides. Ammonolysis



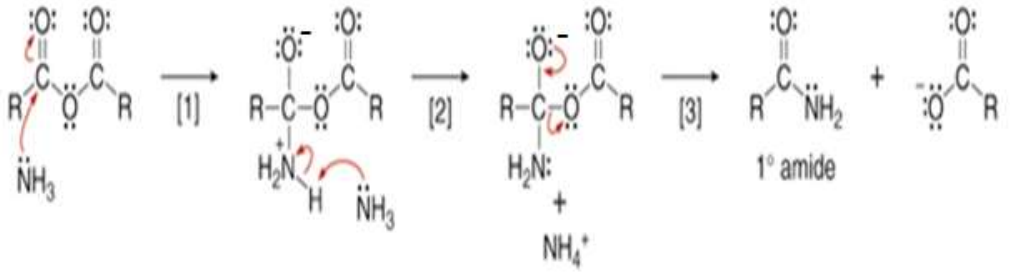
$$(CH_3CO)_2O + 2NH_3 \longrightarrow CH_3CONH_2 + CH_3COO^-NH_4^+$$

Acetic anhydride — Acetamide — Ammonium acetate



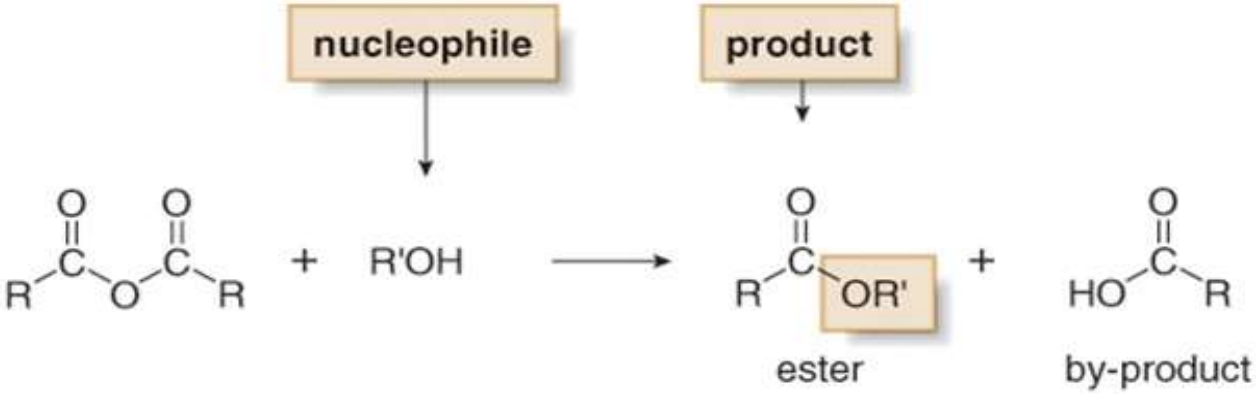
Besides the usual steps for nucleophilic addition and elimination of the leaving group, the mechanism involves an additional proton transfer.

Conversion of an Anhydride to an Amide



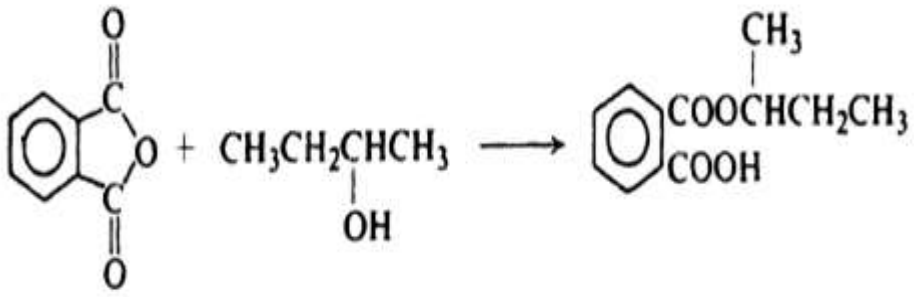
- In Step [1], **nucleophilic attack by NH_3** forms a tetrahedral intermediate.
- Removal of a proton followed by **elimination of the leaving group, $RCOO^-$** (Steps [2]–[3]), forms the substitution product, a **1° amide.**

(c) Conversion into esters. Alcoholysis



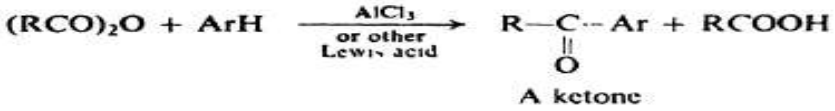
$$(CH_3CO)_2O + CH_3OH \longrightarrow CH_3COOCH_3 + CH_3COOH$$

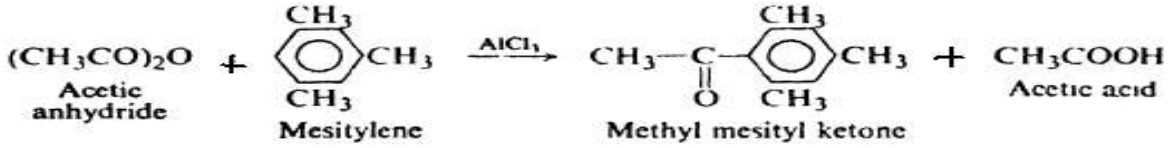
Acetic anhydride — Methyl acetate (An ester) — Acetic acid

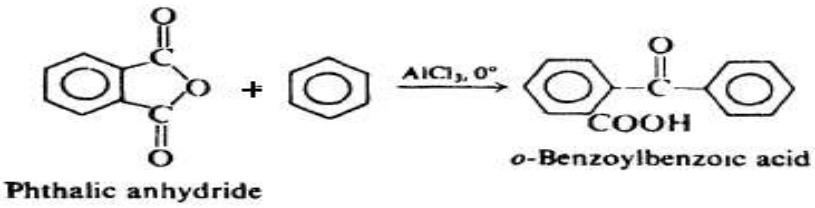


Phthalic anhydride *sec*-Butyl alcohol *sec*-Butyl phthalate

2. Formation of ketones. Friedel-Crafts acylation.





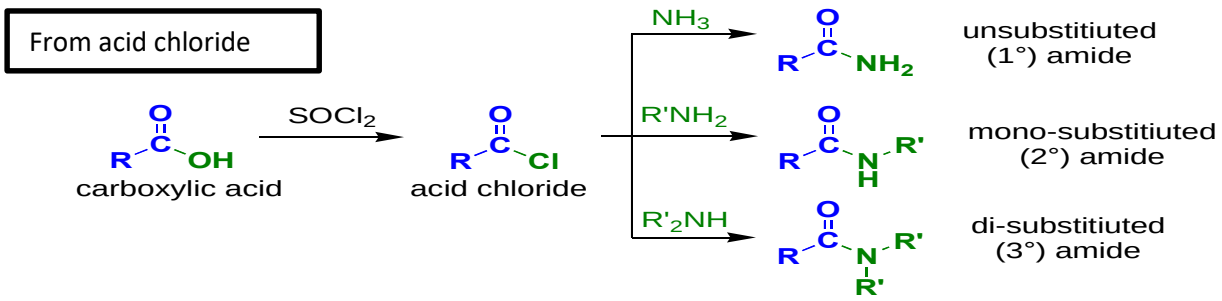


Only "half" of the anhydride appears in the acyl product; the other "half" is a carboxylic acid. A cyclic anhydride undergoes exactly the same reactions as any other anhydride. However, the acyl compound and the carboxylic acid formed will have to be a part of the same molecule, cyclic anhydrides can thus be used to make compounds containing both the acyl group and the carboxyl group: compounds that are, for example, both acids and amides, both acids and esters, etc. These bifunctional compounds are of great value in further synthesis.

AMIDES

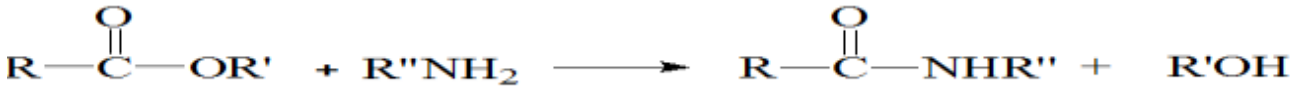
Preparation of amides

In the laboratory, amides are most commonly prepared from the reactions of ammonia, 1° or 2° amines with acids chlorides, acid anhydrides or esters. This is a nucleophilic acyl substitution reaction. When an acid chloride or anhydride is used, a mole of acid (HCl or carboxylic acid) is produced. Since amines are bases, a second equivalent (or an equivalent of another base such as hydroxide or bicarbonate) is required to neutralize the acid. In industry they are often made by heating the ammonium salts of carboxylic acids.

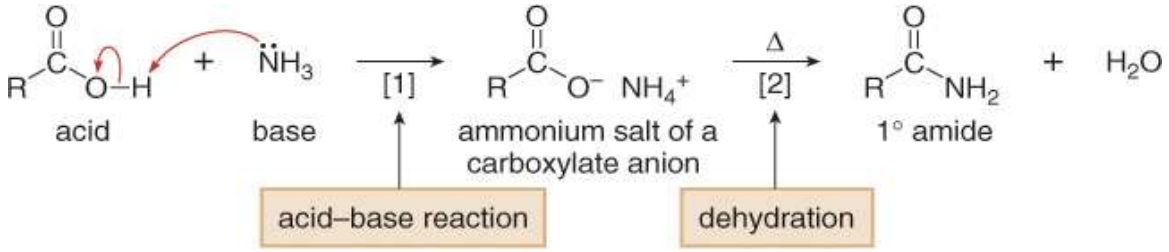


From acid anhydrides

From esters



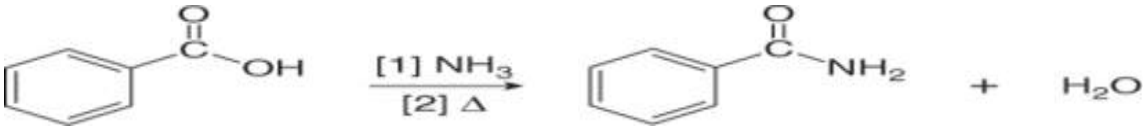
Carboxylic acids cannot be converted into amides by reaction with NH_3 or an amine because amines are bases, and undergo an acid-base reaction to form an ammonium salt before nucleophilic substitution occurs. However, heating the ammonium salt at high temperature (>100°C) dehydrates the resulting ammonium salt of the carboxylate anion to form an amide, although the yield can be low.



The overall conversion of RCOOH to $RCONH_2$ requires two steps:

[1] Acid-base reaction of RCOOH with NH_3 to form an ammonium salt.

[2] Dehydration at high temperature (>100°C).

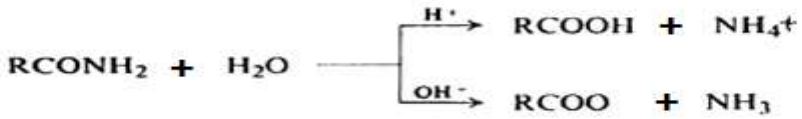


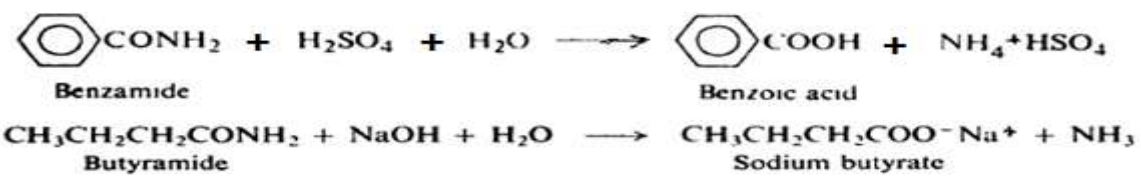
Reactions of amides

An amide is hydrolyzed when heated with aqueous acids or aqueous bases. The products are ammonia and the carboxylic acid, although one product or the other is obtained in the form of a salt, depending upon the acidity or basicity of the medium.

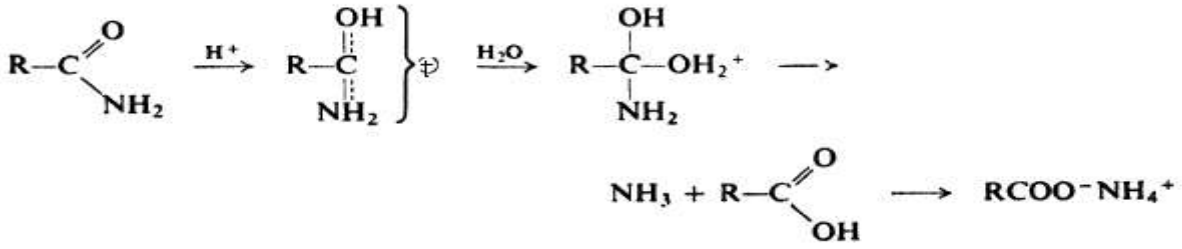
The Hoffmann degradation of amides is another important reaction of amides.

1. Hydrolysis.

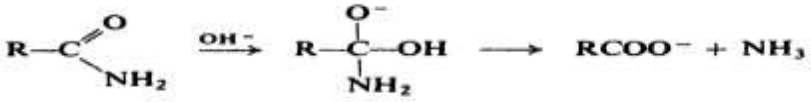


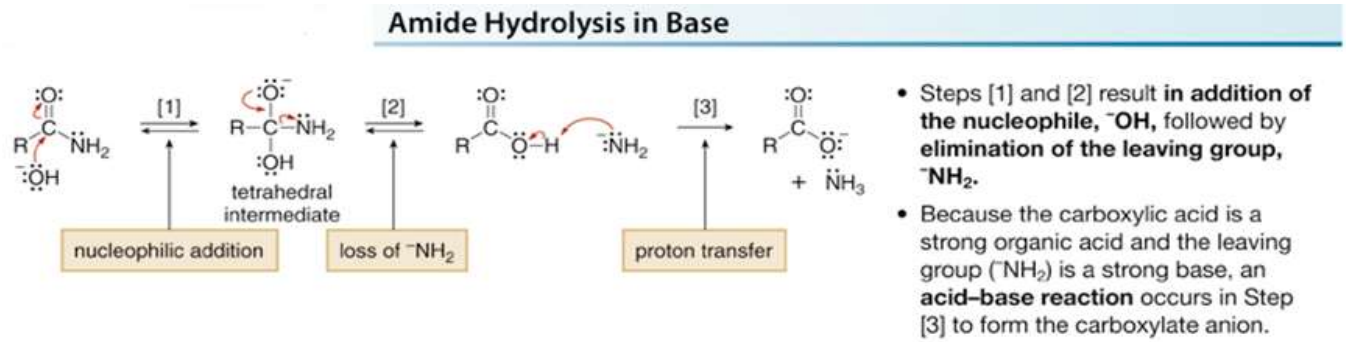


Hydrolysis of amides involves nucleophilic substitution, in which the NH_2 group is replaced by OH. Under acidic conditions hydrolysis involves attack by water on the protonated amide:



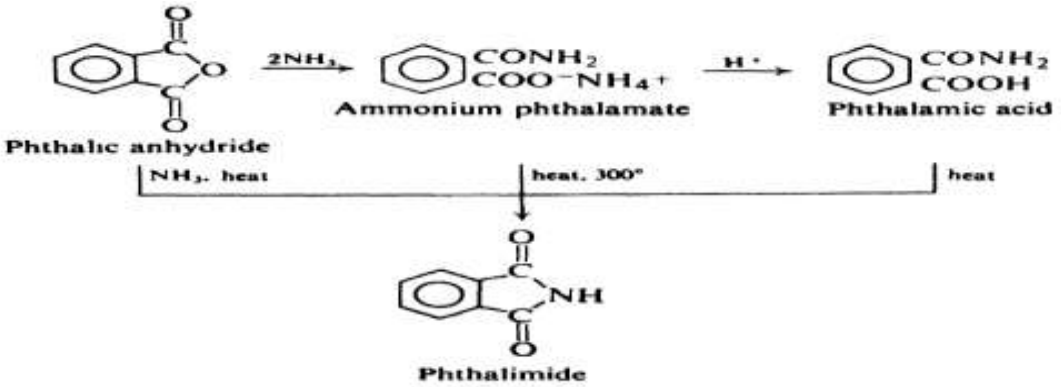
Under alkaline conditions hydrolysis involves attack by the strongly nucleophilic hydroxide ion on the amide itself:

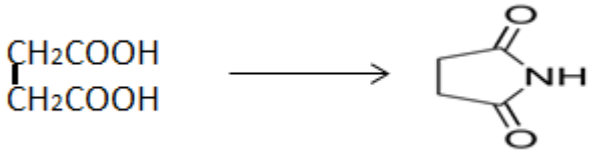




2. Conversion into imides.

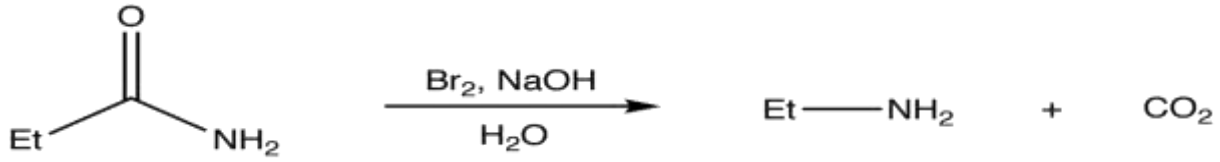
The cyclic anhydrides react with ammonia to yield amides; in this case the product contains both $CONH_2$ and COOH groups. If this acid-amide is heated, a molecule of water is lost, a ring forms, and a product is obtained in which two acyl groups have become attached to nitrogen; compounds of this form are called **imides.** Phthalic anhydride gives phthalamic acid and phthalimide:





3. Hofmann degradation of amides.

   The **Hofmann degradation of amides** is the organic reaction used to convert a **primary amide** to a primary amine using a halogen, base, water, and heat. The net effect of reaction is loss of CO_2 part of amide group lead **to primary amine with one less carbon atom than original amide.**

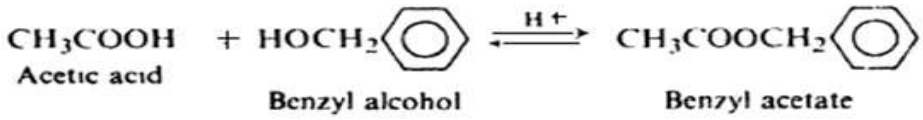


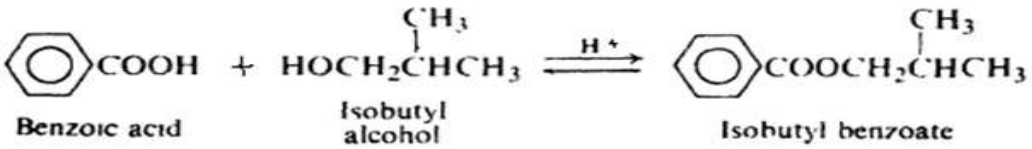
ESTERS

Preparation of esters

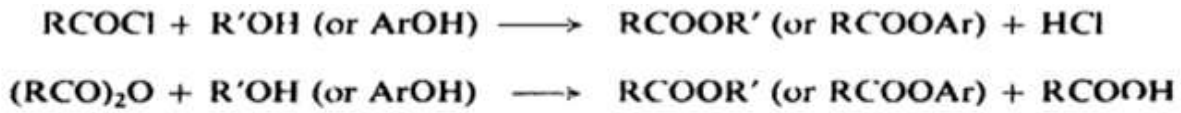
Esters are usually prepared by the reaction of alcohols or phenols with acids or acid derivatives. The most common methods are:

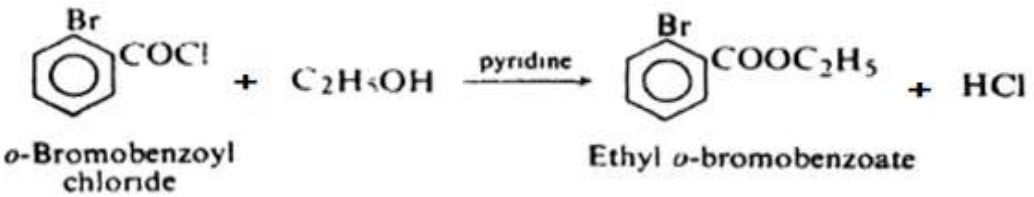
1. From acids.

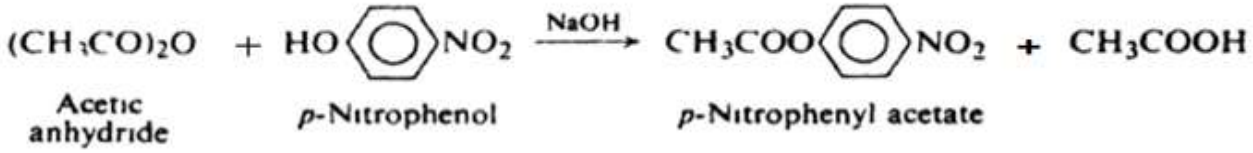




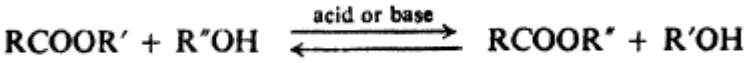
2. From acid chlorides or anhydrides.



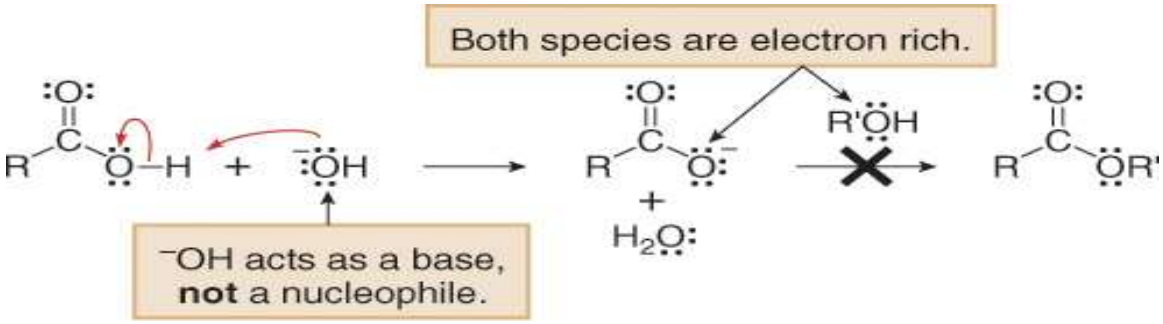




3. From esters. Transesterification.

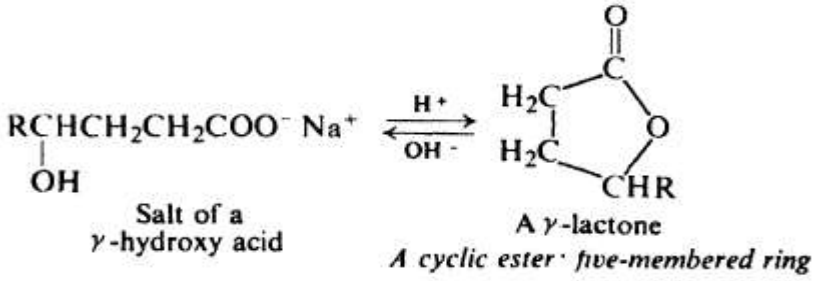


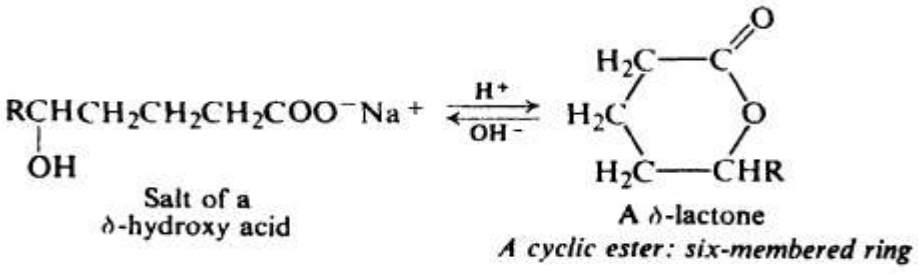
- Esterification of a carboxylic acid occurs in the presence of acid but not in the presence of base.
- Base removes a proton from the carboxylic acid, forming the carboxylate anion, which does not react with an electron-rich nucleophile.



The direct reaction of alcohols or phenols with acids involves equilibrium and especially in the case of phenols requires effort to drive to completion. In the laboratory, reaction with an acid chloride or anhydride is more commonly used.

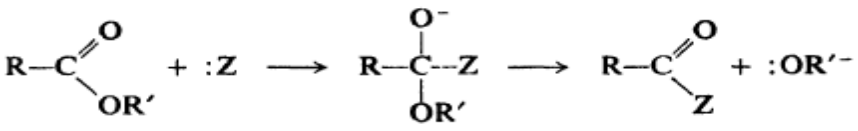
Hydroxy acid which is contain both alcohol and acid group. In those cases where a five- or six membered ring can be formed, intramolecular esterification occurs. Thus, a γ- or δ-hydroxy acid loses water spontaneously to yield a cyclic ester known as a lactone. Treatment with base (actually hydrolysis of an ester) rapidly opens the lactone ring to give the open-chain salt.





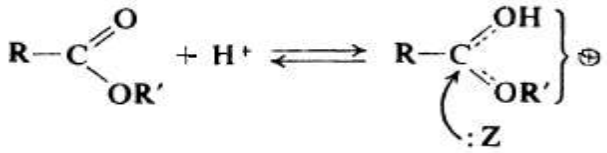
Reactions of esters

Esters undergo the nucleophilic substitution that is typical of carboxylic acid derivatives. Attack occurs at the electron-deficient carbonyl carbon, and results in the replacement of the OR' group by OH, OR", or NH_2:



$:Z = :OH^-, \quad :OR''^-, \quad :NH_3$

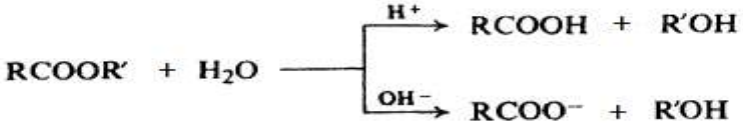
These reactions are sometimes carried out in the presence of acid. In these acid-catalyzed reactions, H^+ attaches itself to the oxygen of the carbonyl group, and thus renders carbonyl carbon even more susceptible to nucleophilic attack.

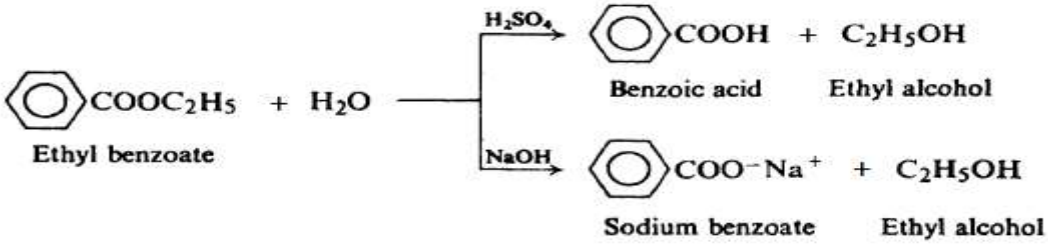


Acid catalysis:
makes carbon more susceptible to nucleophilic attack

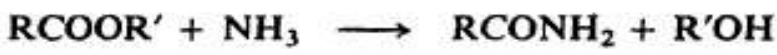
1. Conversion into acids and acid derivatives.

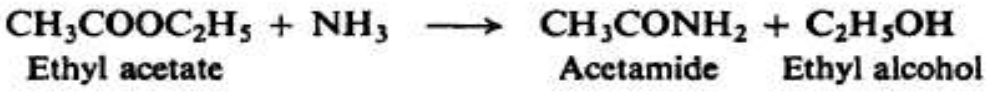
(a) Conversion into acids. Hydrolysis.



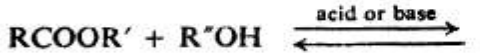


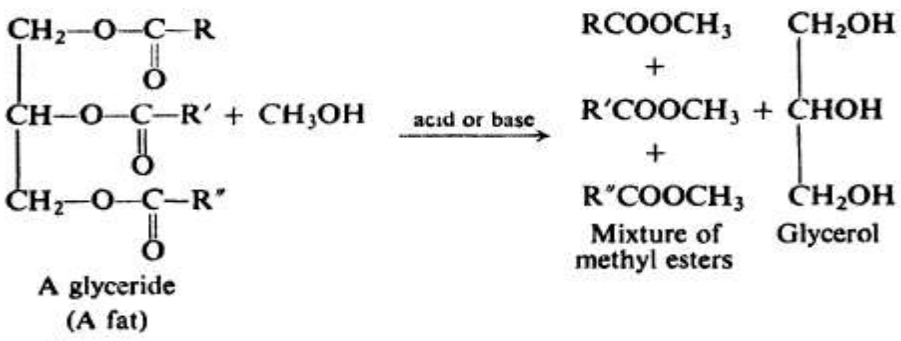
(b) Conversion into amides. Ammonolysis.



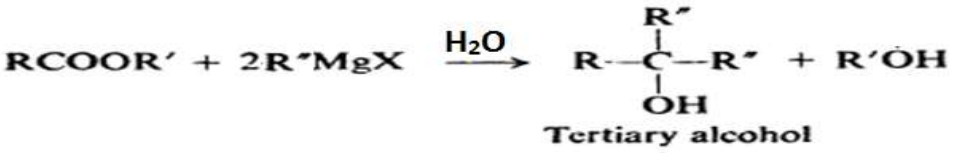


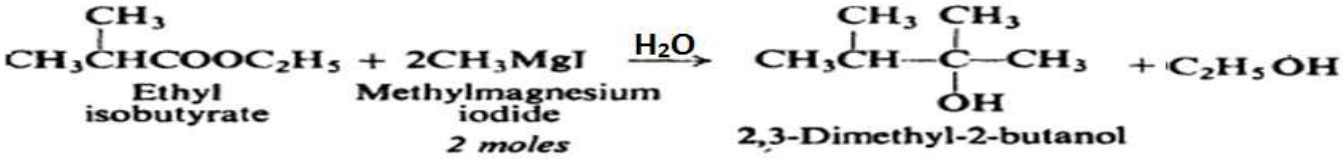
(c) Conversion into esters. Transesterification. Alcoholysis.





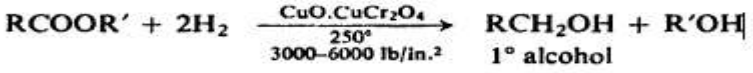
2. Reaction with Grignard reagents.

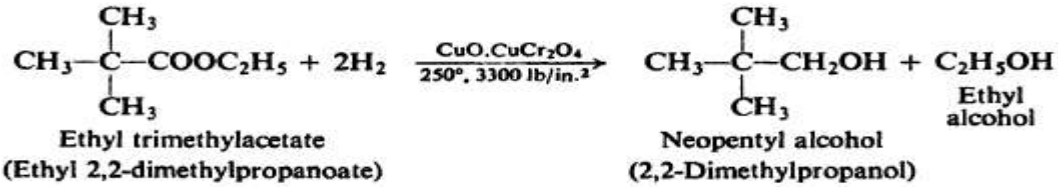




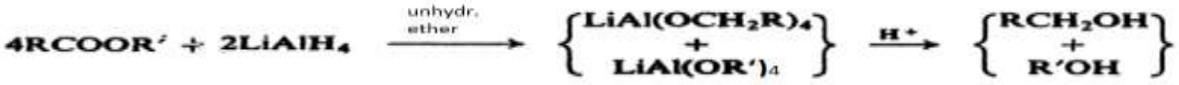
3. Reduction to alcohols.

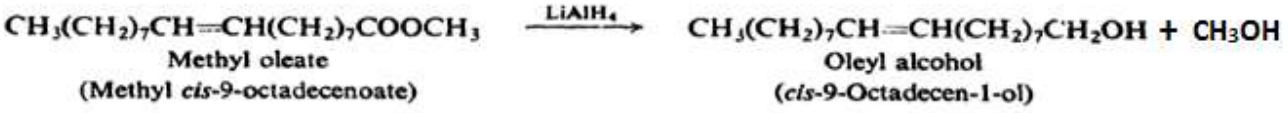
(a) Catalytic hydrogenation. Hydrogenolysis





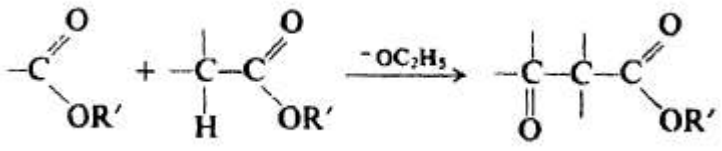
(b) Chemical reduction



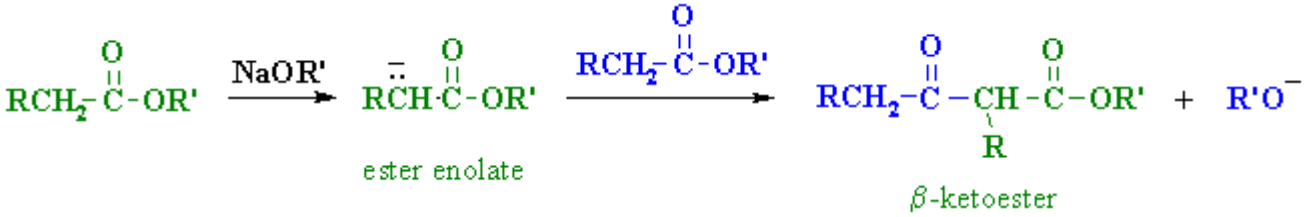


4. Reaction with carbanions. Claisen condensation

The **Claisen condensation** is a carbon–carbon bond forming reaction that occurs between two esters (same or differents) or one ester and another carbonyl compound in the presence of a strong base, resulting in a β-keto ester or a β-diketone.

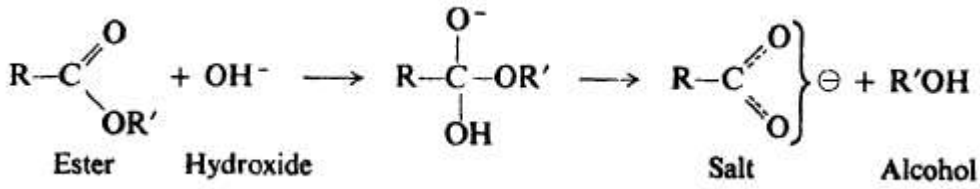


A β-keto ester



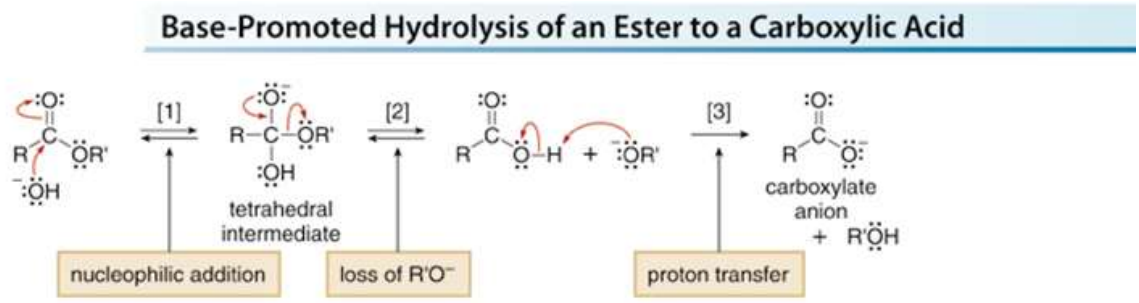
Alkaline hydrolysis of esters

A carboxylic ester is hydrolyzed to a carboxylic acid and an alcohol or phenol when heated with aqueous acid or aqueous base. Under alkaline conditions the carboxylic acid is obtained as its salt, from which it can be liberated by addition of mineral acid. Base promotes hydrolysis of esters by providing the strongly nucleophilic reagent OH^-.



This reaction is essentially irreversible, since a resonance-stabilized carboxylate anion shows little tendency to react with an alcohol.

The Hydrolysis is base promoted, <u>not</u> base catalyzed, because the base (OH^-) is the nucleophile that adds to the ester and forms part of the product. It participates in the reaction and is not regenerated later.



- Steps [1] and [2] result in **addition of the nucleophile,** ^-OH, followed by **elimination of the leaving group, $^-OR'$.** These two steps, which form the carboxylic acid, are reversible, because the stability of the reactants and products is comparable.
- Next, the carboxylic acid is a strong organic acid and the leaving group ($^-OR'$) is a strong base, so an **acid–base reaction** occurs in Step [3] to form the carboxylate anion.

The reaction first involves attack on the ester by hydroxide ion in which the rate is depending on both ester and hydroxide ion concentration. Next, hydroxide attacks at the carbonyl carbon and displaces alkoxide ion. That is to say, reaction involves cleavage of the bond between oxygen and the acyl group, RCO — OR'.

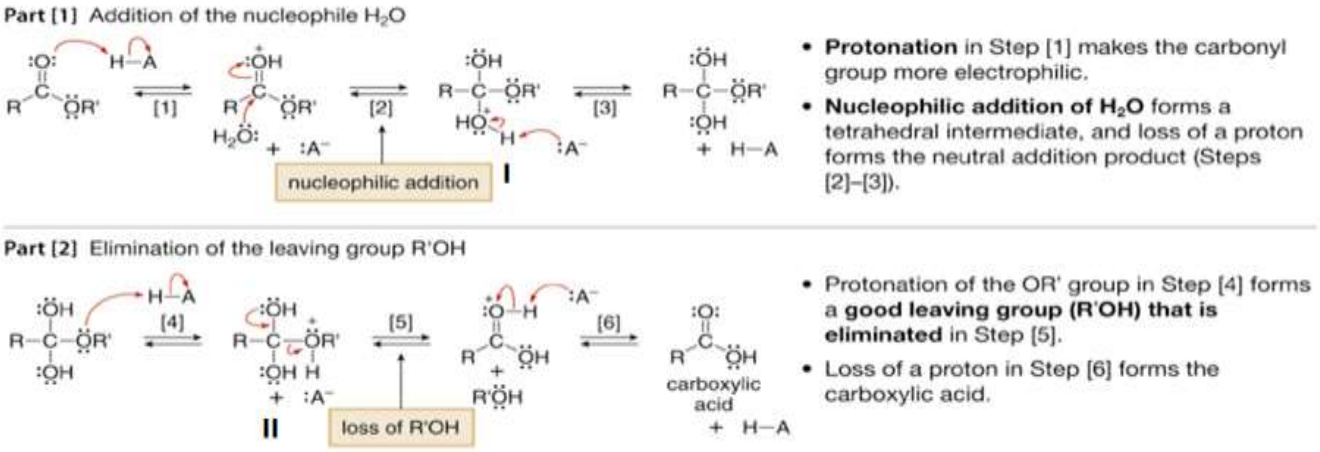
Basic hydrolysis of an ester is also called saponification.

Acidic hydrolysis of esters

Hydrolysis of esters is promoted not only by base but also by acid. Acidic hydrolysis is reversible and hence the mechanism for the hydrolysis is taken in the opposite direction the mechanism for esterification.

$$RCOOR' + H_2O \underset{H^+}{\overset{H^+}{\rightleftharpoons}} RCOOH + R'OH$$

The mechanism for acid-catalyzed hydrolysis and esterification is contained in the following equilibria:

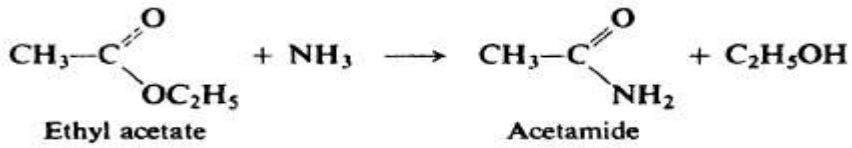


Mineral acid speeds up both processes by protonating carbonyl oxygen and thus rendering carbonyl carbon more susceptible to nucleophilic attack.

In hydrolysis, the nucleophilic is a water molecule and the leaving group is an alcohol; in esterification, the roles are exactly reversed.

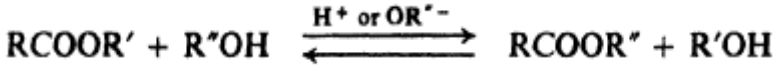
Ammonolysis of esters

Treatment of an ester with ammonia, generally in ethyl alcohol solution, yields the amide. This reaction involves nucleophilic attack by a base, ammonia, on the electron-deficient carbon; the alkoxy group, OR', is replaced by NH_2. For example:



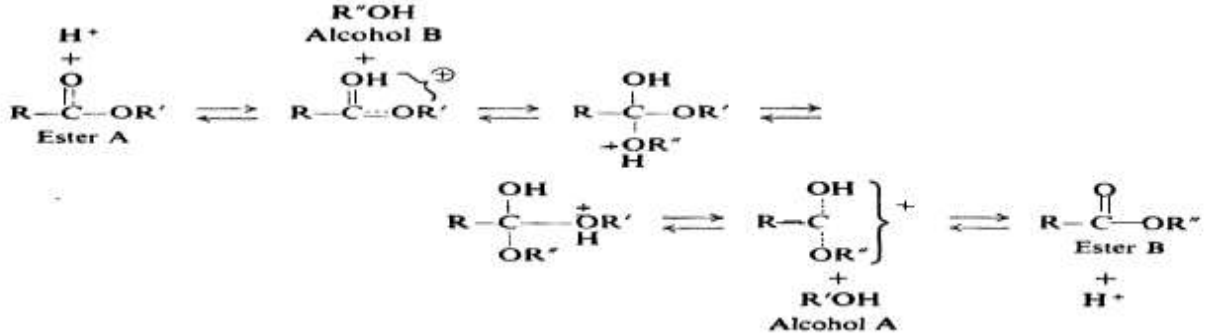
Transesterification

In the esterification of an acid, an alcohol acts as a nucleophilic reagent; in hydrolysis of an ester, an alcohol is displaced by a nucleophilic reagent. This is lead to find that one alcohol is capable of displacing another alcohol from an ester. This alcoholysis (cleavage by an alcohol) of an ester is called transesterification.

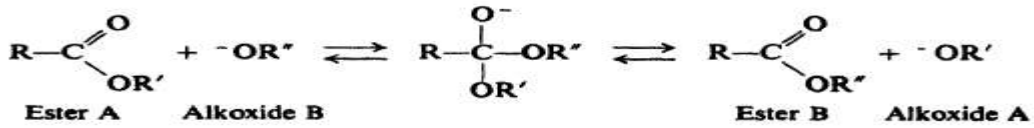


Transesterification is catalyzed by acid (H_2SO_4 or dry HCl) or base (usually alkoxide ion).

For acid-catalyzed transesterification



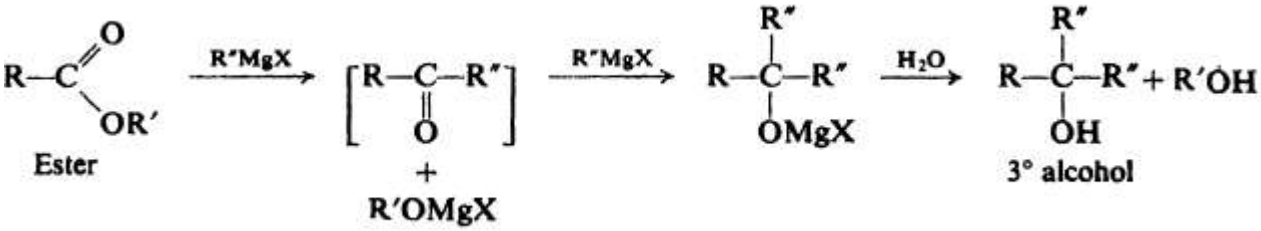
For base-catalyzed transesterification:



Transesterification is an equilibrium reaction. To shift the equilibrium to the right, it is necessary to use a large excess of the alcohol whose ester we wish to make, or else to remove one of the products from the reaction mixture.

Reaction of esters with Grignard reagents

The reaction of carboxylic esters with Grignard reagents is an excellent method for preparing tertiary alcohols. The nucleophilic (basic) alkyl or aryl group of the Grignard reagent attaches itself to the electron-deficient carbonyl carbon. Expulsion of the alkoxide group would yield a ketone, and in certain special cases ketones are indeed isolated from this reaction. However, as we know, ketones themselves readily react with Grignard reagents to yield tertiary alcohols; in the present case the products obtained correspond to the addition of the Grignard reagent to such a ketone:



(First nucleophilic acyl substitution to form ketones followed by Nucleophilic addition to form tertiary alcohols)

Two of the three groups attached to the carbon bearing the hydroxyl group in the alcohol come from the Grignard reagent and hence must be identical; this is places limits upon the alcohols that can be prepared by this method. But, where applicable, reaction of a Grignard reagent with an ester is preferred to reaction with a ketone because esters are generally more accessible.

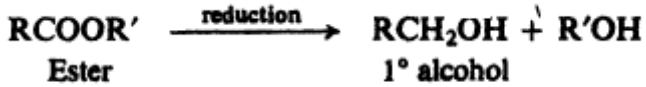
Reduction of esters

Like many organic compounds, esters can be reduced in two ways:

(a) By catalytic hydrogenation using molecular hydrogen, or

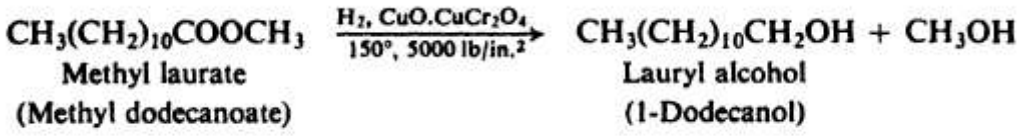
(b) By chemical reduction.

In either case, the ester is cleaved to yield (in addition to the alcohol or phenol from which it was derived) a primary alcohol corresponding to the acid portion of the ester.



Hydrogenolysis (cleavage by hydrogen) of an ester requires more severe conditions than simple hydrogenation of (addition of hydrogen to) a carbon-carbon double bond. High

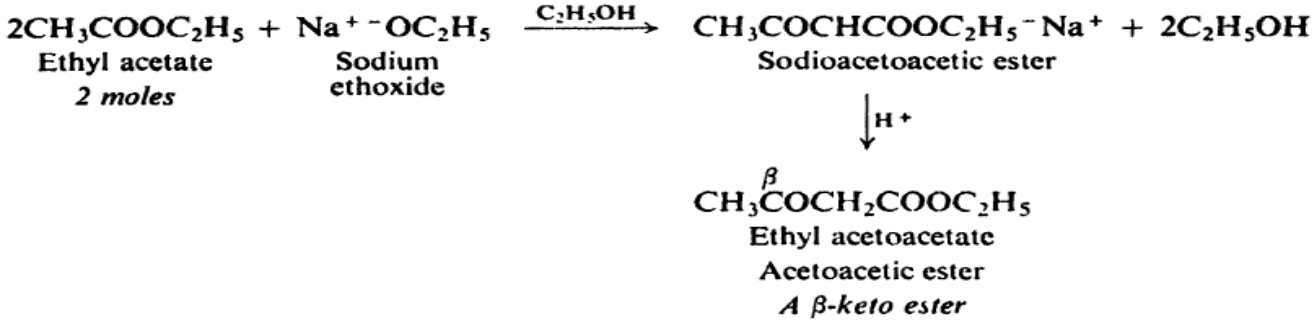
pressures and elevated temperatures are required: the catalyst used most often is a mixture of oxides known as **copper chromite**, of approximately the composition **$CuO.CuCr_2O_4$**. For example:



Chemical reduction is carried out by use of sodium metal and alcohol, or more usually by use of lithium aluminum hydride. For example:

Reaction with carbanions: Claisen condensation

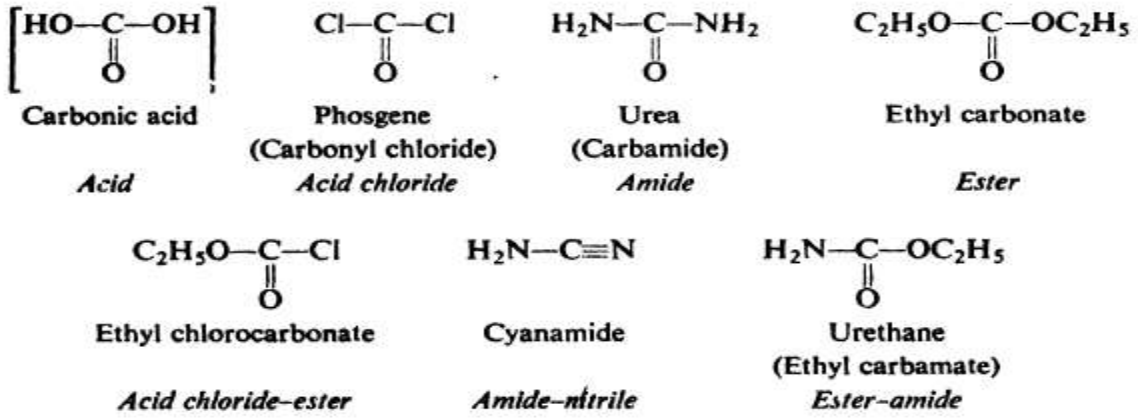
An α-hydrogen in an ester, like an α-hydrogen in an aldehyde or ketone, is weakly acidic. Through resonance, the carbonyl group helps accommodate the negative charge of the carbanion (is an anion in which carbon is tervalent (forms three bonds) and bears a formal negative charge. Carbanions are typically nucleophile and basic). When ethyl acetate is treated with sodium ethoxide, and the resulting mixture is acidified, there is obtained ethyl β-ketobutyrate (ethyl 3-oxobutanoate), generally known as ethyl acetoacetate or acetoacetic ester:



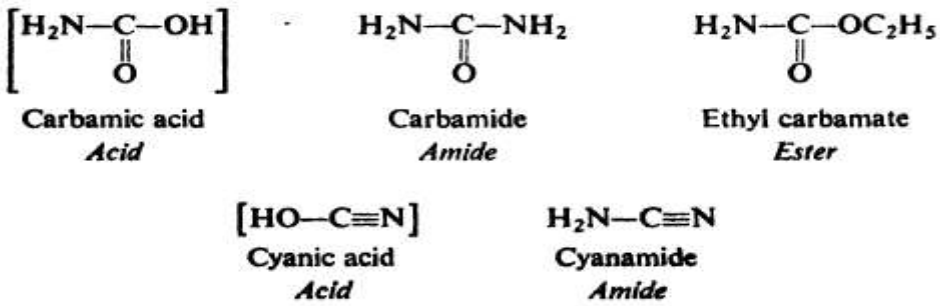
Ethyl acetoacetate is the ester of a β-keto acid; its preparation illustrates the reaction known as the Claisen condensation.

Functional derivatives of carbonic acid

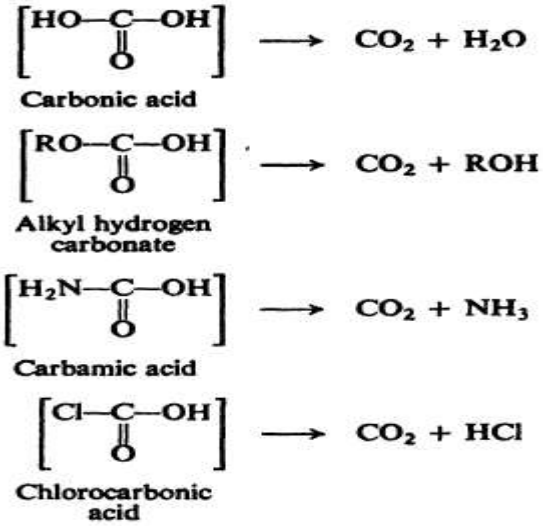
Much of the chemistry of the functional derivatives of carbonic acid is familiar through our study of carboxylic acids. The first step in dealing with one of these compounds is to recognize just how it is related to the parent acid. Since carbonic acid is **bifunctional,** each of its derivatives, too, contains **two functional groups**; these groups can be the **same or different**. For example;



Many of these compounds could be considered as derivatives of other acids, and are often so named. For example:

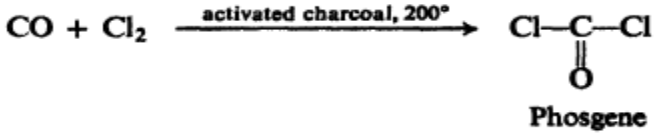


In general, a derivative of carbonic acid containing an OH group is unstable, and decomposes to carbon dioxide. For example:

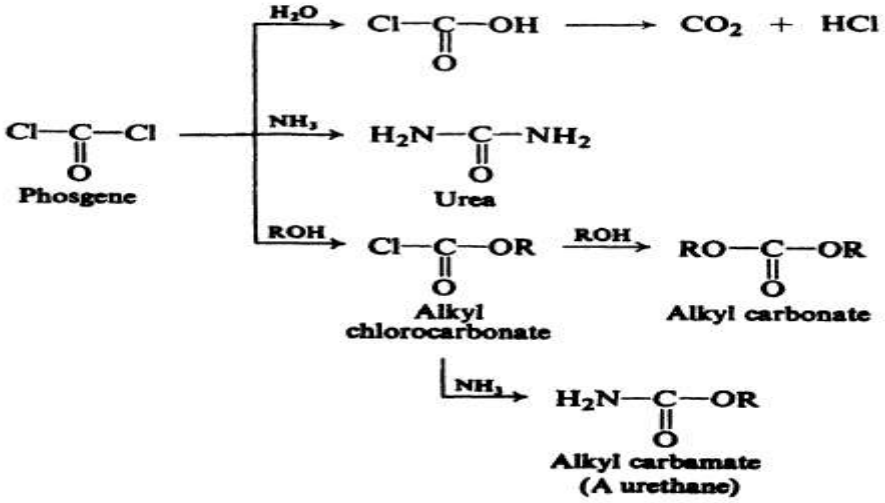


Most derivatives of carbonic acid are made from one of three industrially available compounds: **phosgene, urea, or cyanamide**.

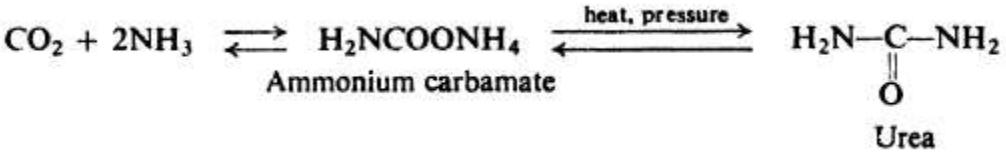
<u>Phosgene, $COCl_2$</u> , a highly poisonous gas, is manufactured by the reaction between carbon monoxide and chlorine.



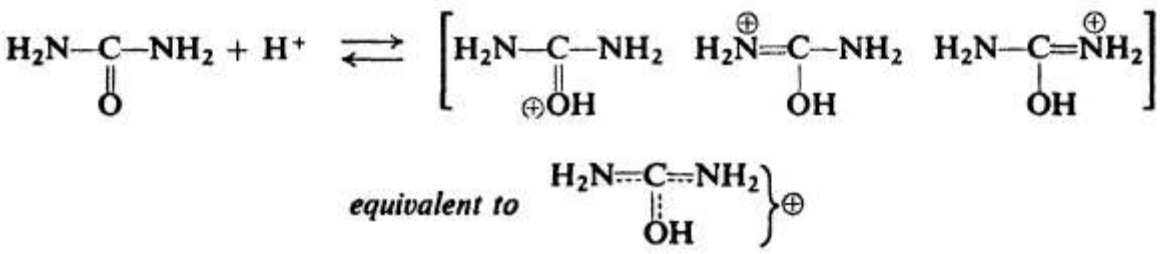
It undergoes the usual reactions of an acid chloride.



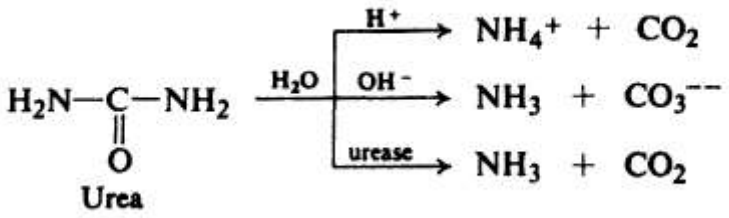
- **<u>Urea</u>**, H_2NCONH_2 ,is the diamide of carbonic acid, is excreted in the urine as the chief nitrogen-containing end product of protein metabolism. It is synthesized on a large scale for use as a
- Fertilizer and
- As a raw material in the manufacture of urea-formaldehyde plastics and of drugs.



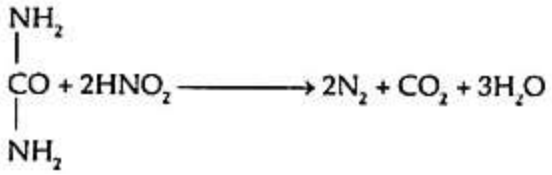
Urea is weakly basic, forming salts with strong acids. The fact that it is a stronger base than ordinary amides is attributed to resonance stabilization of the cation:



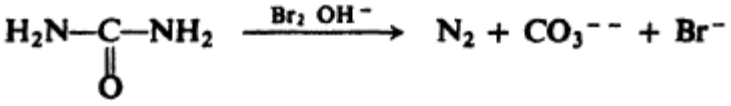
Urea undergoes hydrolysis in the presence of acids, bases, or the enzyme urease (isolable from jack beans; generated by many bacteria, such as Micrococcus ureae).



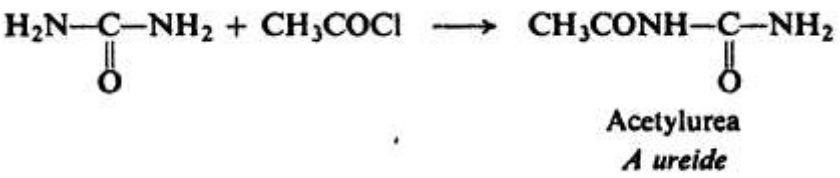
Urea reacts with nitrous acid to yield carbon dioxide and nitrogen; this is a useful way to destroy excess nitrous acid in diazotizations.



Urea is converted by hypohalites into nitrogen and carbonate.



Treatment of urea with acid chlorides or anhydrides yields ureides.



Of special importance are the cyclic ureides formed by reaction with malonic esters; these are known as barbiturates and are important hypnotics (sleep-producers). For example: