Aromatic organic compound

Ch 212

- Benzene (C_6H_6) is the simplest aromatic hydrocarbon (or arene).
- Four degrees of unsaturation.
- It is planar.
- All C—C bond lengths are equal.
- Whereas unsaturated hydrocarbons such as alkenes, alkynes and dienes readily undergo addition reactions, benzene does not.

Benzene
(an arene)

$$C_6H_6 \xrightarrow{Br_2} \text{No reaction}$$

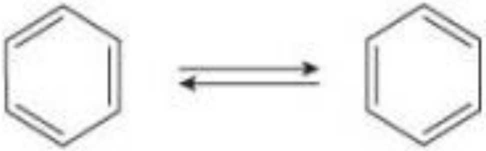
- Benzene reacts with bromine only in the presence of $FeBr_3$ (a Lewis acid), and the reaction is a substitution, not an addition.

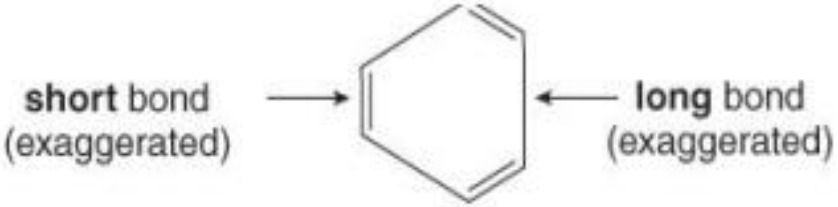
$$C_6H_6 \xrightarrow[FeBr_3]{Br_2} C_6H_5Br$$

substitution
Br replaces H

- **August Kekulé** (1865) proposed that benzene was a rapidly equilibrating mixture of two compounds, each containing a six-membered ring with three alternating π bonds.

Kekulé description:
An equilibrium

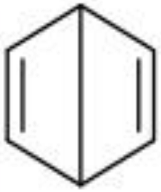




This structure implies that the C−C bonds should have **two different lengths**.

- three short bonds
- three long bonds

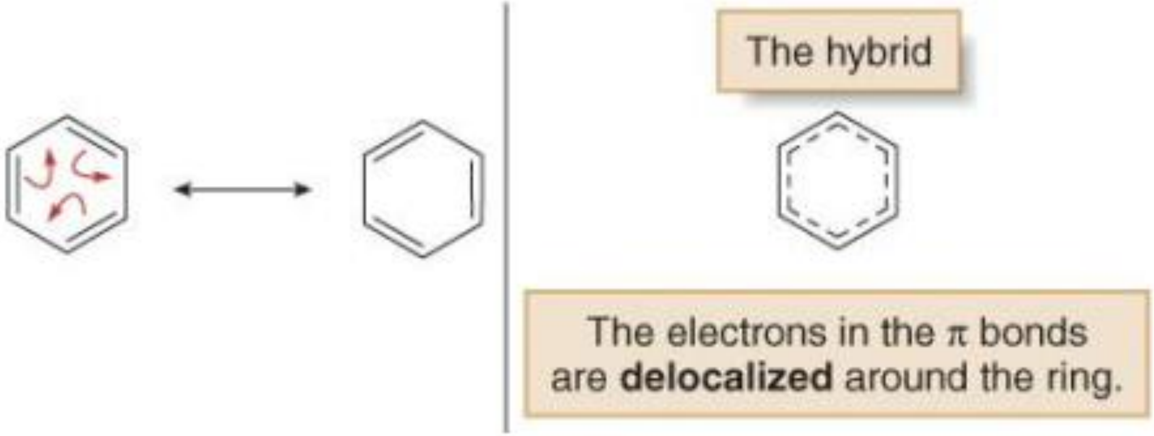
- All C—C bond lengths are equal!



James Dewar (1967) : the Dewar benzene was prepared in 1962 but it is not stable and it converts to benzene

The Structure of Benzene: Resonance

- The true structure of benzene is a resonance hybrid of the two Lewis structures.

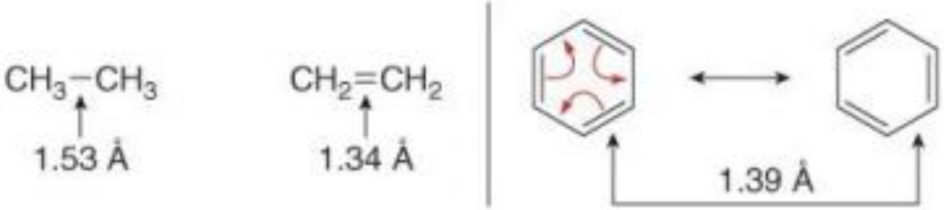


The hybrid

The electrons in the π bonds are **delocalized** around the ring.

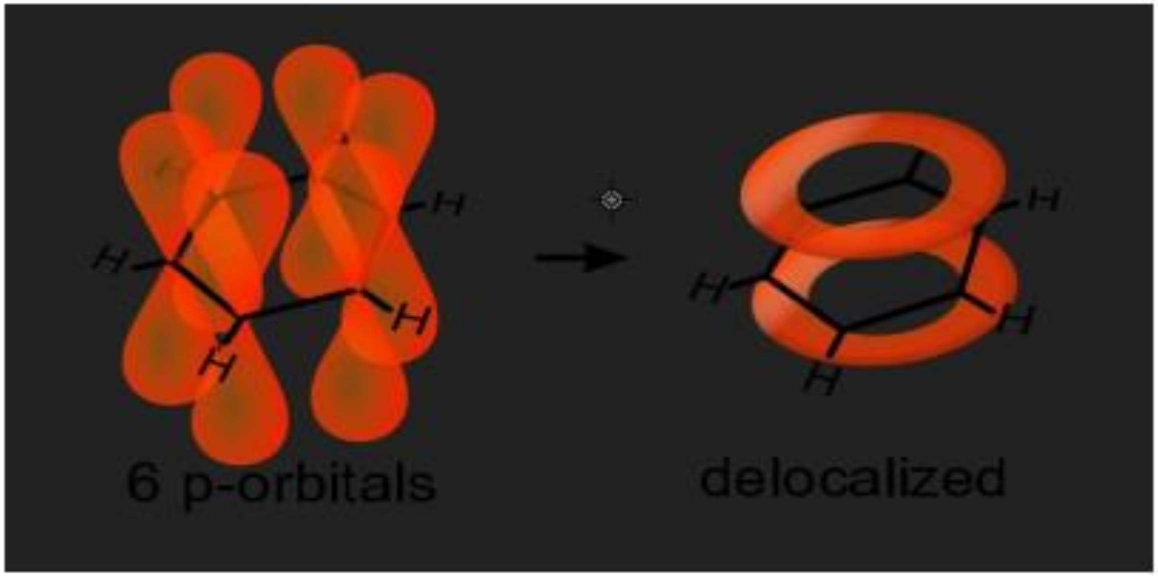
Some texts draw benzene as a hexagon with an inner circle:

The circle represents the **six π electrons,** distributed over the six atoms of the ring.

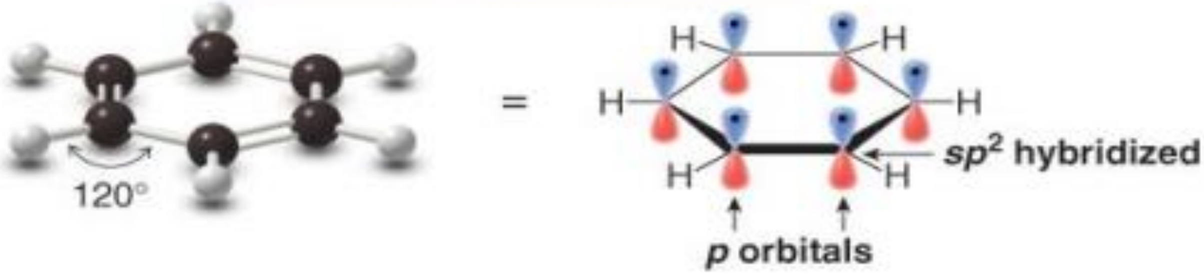


The C−C bonds in benzene are equal and intermediate in length.

The Structure of Benzene: MO

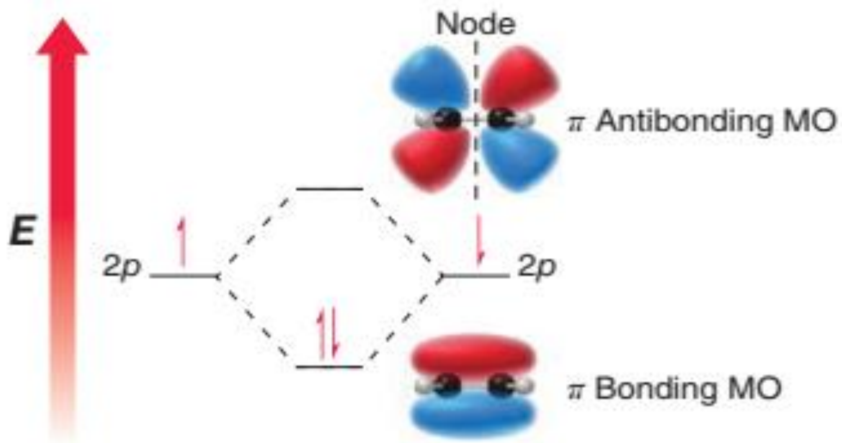


Benzene—A planar molecule

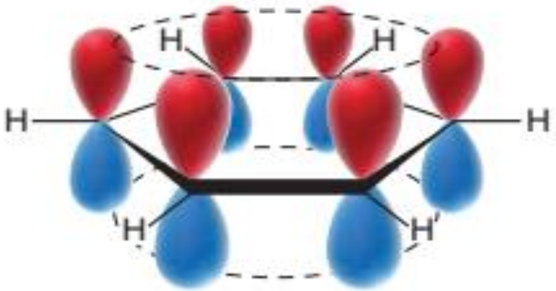


Source of Stability

In order to explain the stability of benzene, we will need to invoke MO theory. Recall that a π bond results when two atomic *p* orbitals overlap to form two new orbitals, called molecular orbitals (Figure 17.2). The lower energy MO is the bonding MO, while the higher energy MO is the antibonding MO. Both π electrons occupy the bonding MO and thereby achieve a lower energy state.

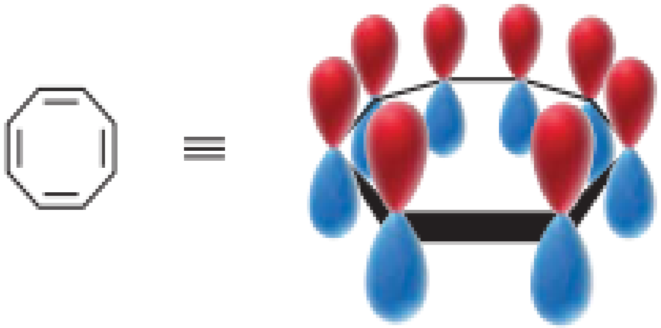


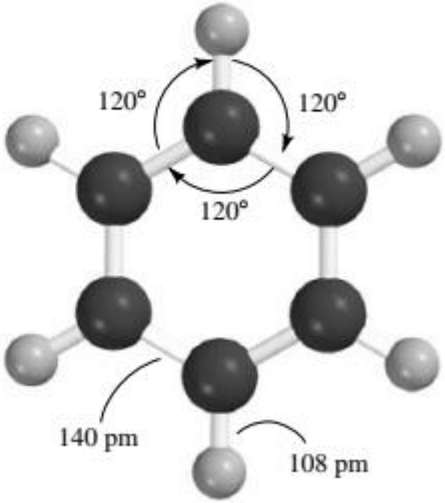
Now let's explore how MO theory describes the nature of benzene, which is comprised of six overlapping *p* orbitals (Figure 17.3). According to MO theory, these six atomic *p* orbitals are replaced



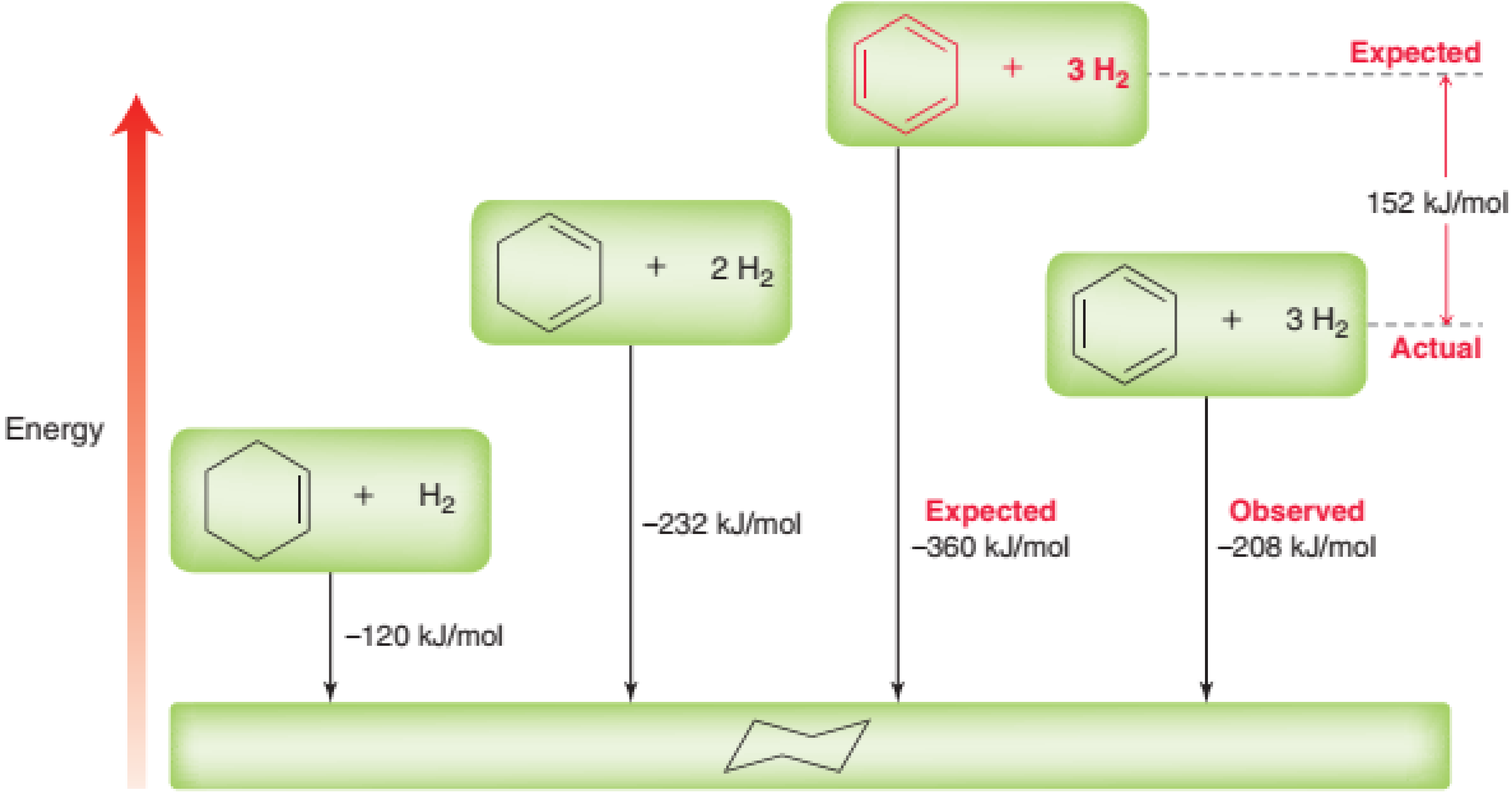
This equilibrium is achieved via a square cyclobutadiene transition state. The rectangular forms avoid much of the instability associated with an open-shell electron configuration, although they are still very high in energy. As such, cyclobutadiene is extremely unstable and highly reactive.

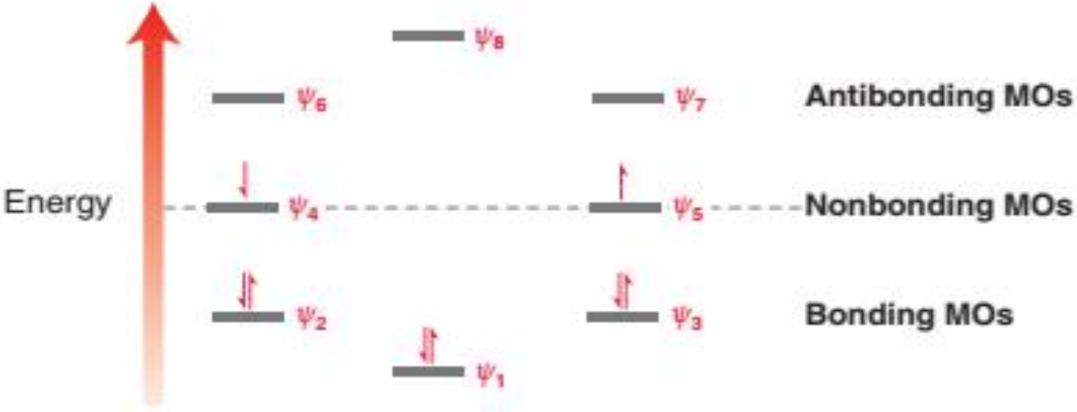
Now consider how MO theory treats planar cyclooctatetraene, which is a system constructed from the overlap of eight atomic *p* orbitals (Figure 17.7). According to MO theory, these eight





In other words, benzene is much more stable than expected. This information is graphically represented on the energy diagram in Figure 17.1. This energy diagram shows the relative heats of

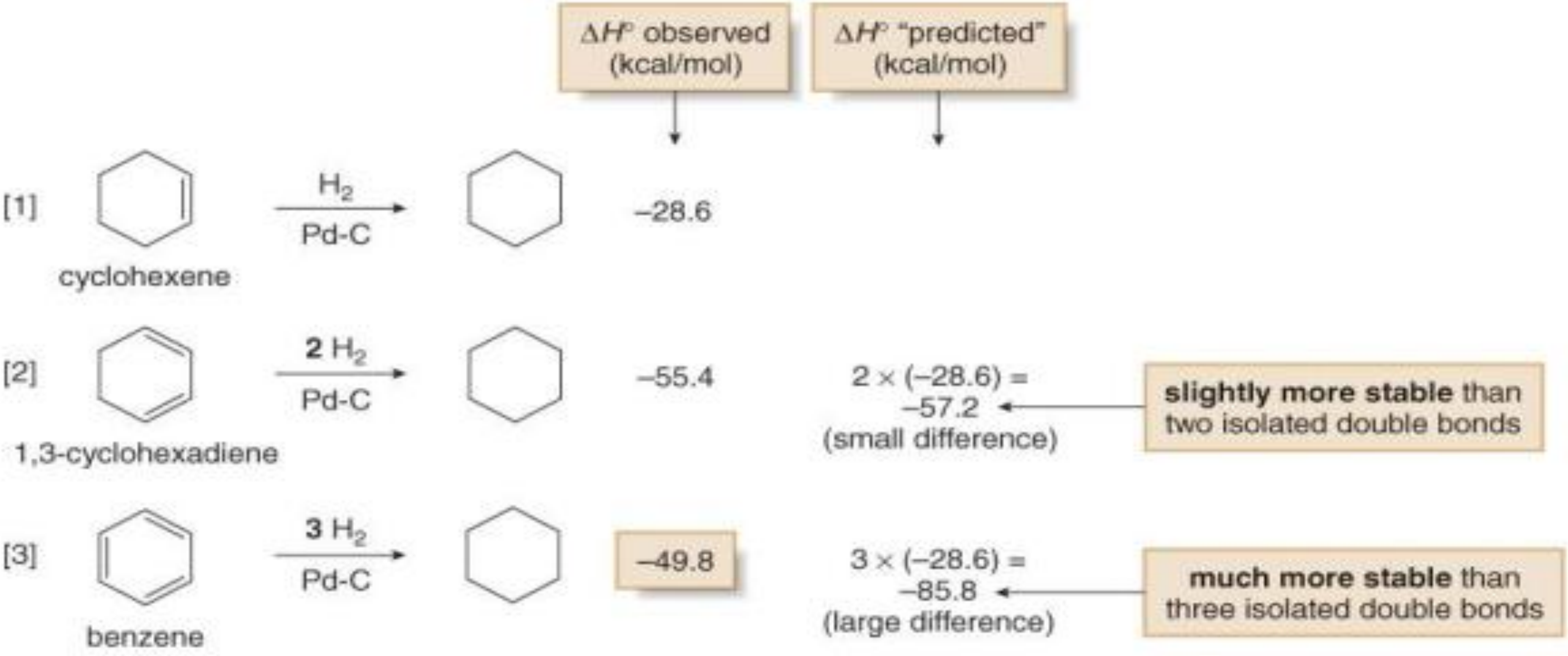




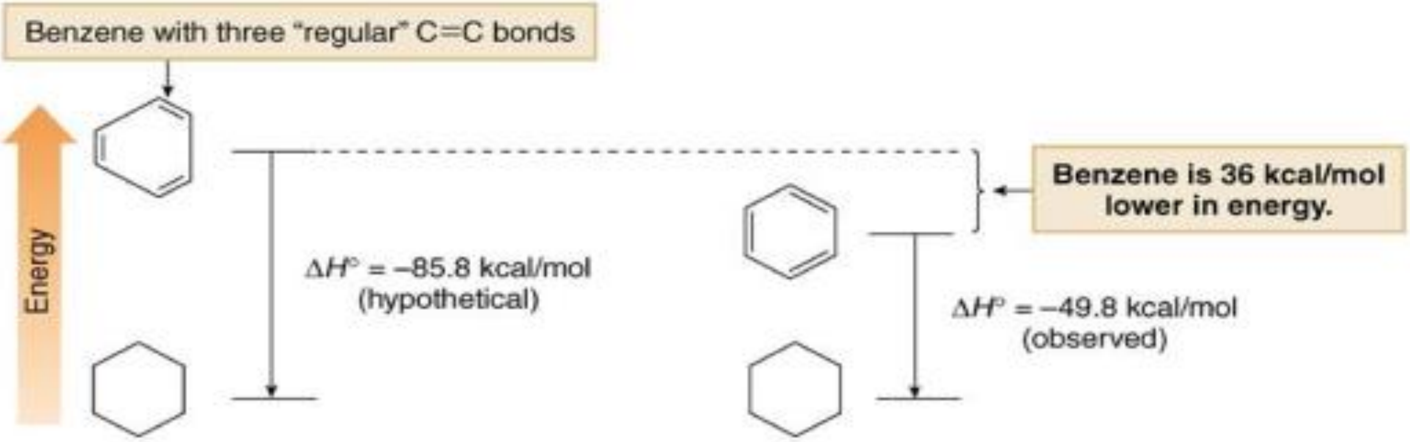
which we encountered with square cyclobutadiene—specifically, two of the electrons are unpaired and occupy nonbonding orbitals. Once again, this open-shell electron configuration is expected to be unstable, and the compound should be antiaromatic. But the compound can avoid this unnecessary instability by assuming a tub shape (Figure 17.9).

In this conformation, the eight *p* orbitals no longer overlap as one continuous system, and the energy diagram in Figure 17.8 (of the eight MOs) simply does not apply. Rather, there are four isolated π bonds, each of which contains two electrons in a bonding MO (as shown in Figure 17.2).

Aromaticity – Resonance Energy



			$\Delta H°$ observed (kcal/mol)	$\Delta H°$ "predicted" (kcal/mol)	
[1]	cyclohexene	$\xrightarrow[\text{Pd-C}]{H_2}$	–28.6		
[2]	1,3-cyclohexadiene	$\xrightarrow[\text{Pd-C}]{2\ H_2}$	–55.4	2 × (–28.6) = –57.2 (small difference)	**slightly more stable** than two isolated double bonds
[3]	benzene	$\xrightarrow[\text{Pd-C}]{3\ H_2}$	–49.8	3 × (–28.6) = –85.8 (large difference)	**much more stable** than three isolated double bonds



Benzene with three "regular" C=C bonds

$\Delta H°$ = –85.8 kcal/mol (hypothetical)

$\Delta H°$ = –49.8 kcal/mol (observed)

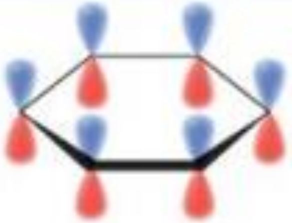
Benzene is 36 kcal/mol lower in energy.

The Criteria for Aromaticity

Four structural criteria must be satisfied for a compound to be aromatic.

[1] A molecule must be cyclic.

Cyclic compound

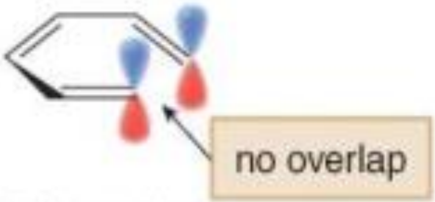


benzene

Every *p* orbital overlaps with two neighboring *p* orbitals.

aromatic

Acyclic compound



1,3,5-hexatriene

There can be no overlap between the *p* orbitals on the two terminal C's.

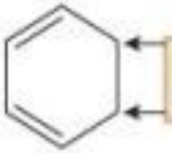
not aromatic

[2] A molecule must be completely conjugated (all atoms sp^2).

A completely conjugated ring

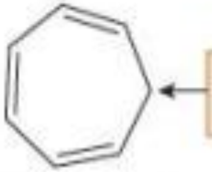
benzene
a *p* orbital on **every** C
aromatic

These rings are not completely conjugated.



no *p* orbitals

1,3-cyclohexadiene
not aromatic



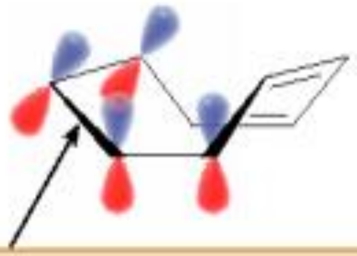
no *p* orbital

1,3,5-cycloheptatriene
not aromatic

[3] A molecule must be planar.

cyclooctatetraene
not aromatic

a tub-shaped,
eight-membered ring



Adjacent *p* orbitals cannot overlap.
Electrons cannot delocalize.

The Criteria for Aromaticity—Hückel's Rule

[4] A molecule must satisfy Hückel's rule.

- An aromatic compound must contain $4n + 2$ π electrons ($n = 0, 1, 2$, and so forth).
- Cyclic, planar, and completely conjugated compounds that contain $4n$ π electrons are especially unstable, and are said to be *antiaromatic*.

Benzene
An aromatic compound

$4n + 2 = 4(1) + 2 =$
6 π electrons
aromatic

Cyclobutadiene
An antiaromatic compound

$4n = 4(1) =$
4 π electrons
antiaromatic

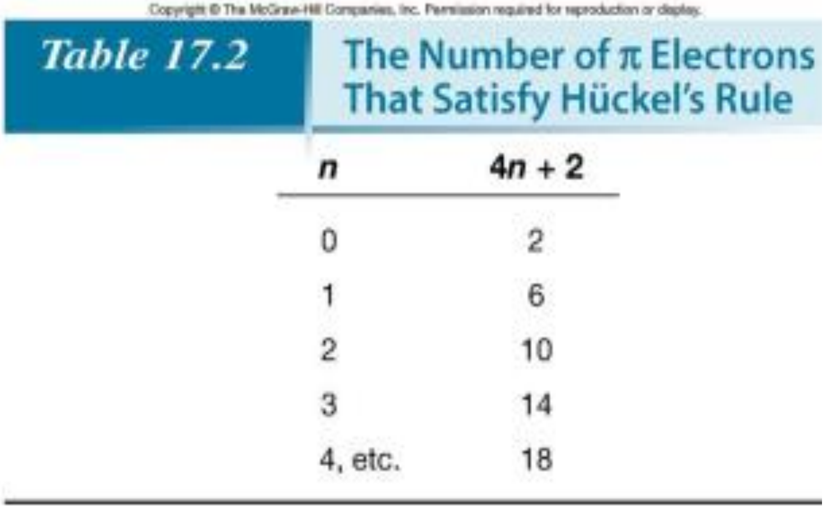
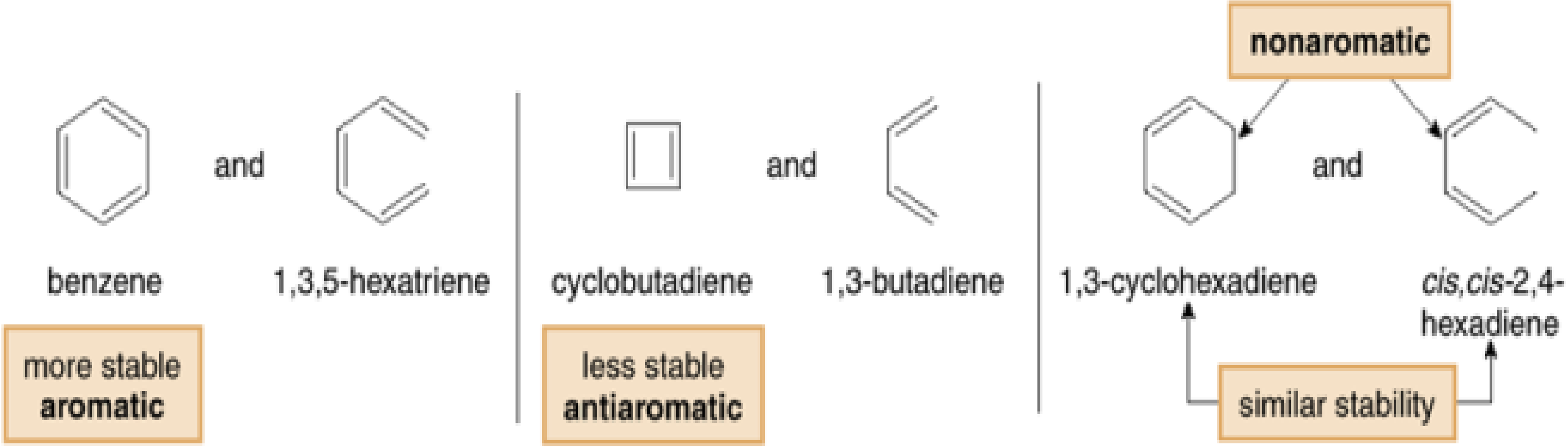


Table 17.2 The Number of π Electrons That Satisfy Hückel's Rule

n	$4n + 2$
0	2
1	6
2	10
3	14
4, etc.	18

1. Aromatic—A cyclic, planar, completely conjugated compound with $4n + 2$ π electrons.
2. Antiaromatic—A cyclic, planar, completely conjugated compound with $4n$ π electrons.
3. Not aromatic (nonaromatic)—A compound that lacks one (or more) of the following requirements for aromaticity: being cyclic, planar, and completely conjugated.


benzene and 1,3,5-hexatriene

more stable aromatic

cyclobutadiene and 1,3-butadiene

less stable antiaromatic

nonaromatic

1,3-cyclohexadiene and *cis,cis*-2,4-hexadiene

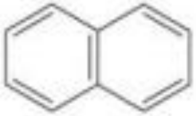
similar stability

Examples of Aromatic Rings

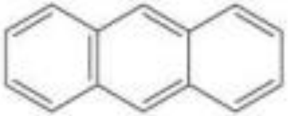
Cyclooctatetraene
8 π electrons

planar
antiaromatic

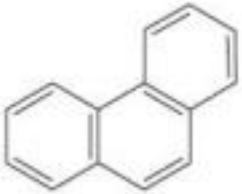
puckered
nonaromatic



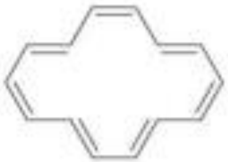
naphthalene
10 π electrons



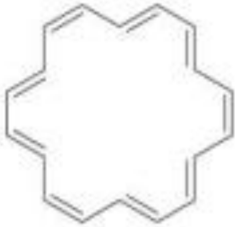
anthracene
14 π electrons



phenanthrene
14 π electrons



[14]-annulene
$4n + 2 = 4(3) + 2 =$
14 π electrons
aromatic



[18]-annulene
$4n + 2 = 4(4) + 2 =$
18 π electrons
aromatic

[10]-Annulene fits Hückel's rule, but it's **not planar**.

[10]-annulene
10 π electrons
not aromatic

=

The molecule puckers to keep these H's further away from each other.

3-D representation

Other Aromatic Compounds

cyclopentadienyl anion
- **6** π electrons
- contains $4n + 2$ π electrons

aromatic

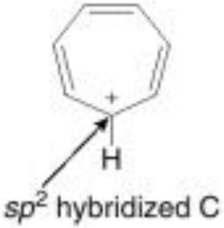
cyclopentadienyl cation
- **4** π electrons
- contains $4n$ π electrons

antiaromatic

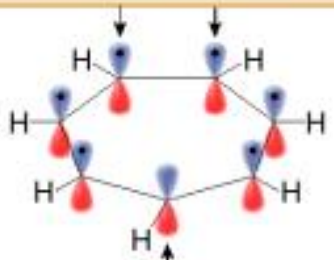
cyclopentadienyl radical
- **5** π electrons
- does not contain either $4n$ or $4n + 2$ π electrons

nonaromatic

The tropylium cation



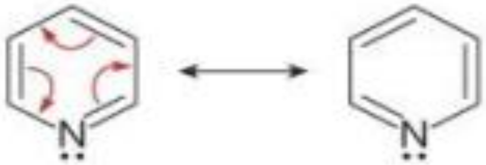
The ring is completely conjugated with **6 π electrons**.



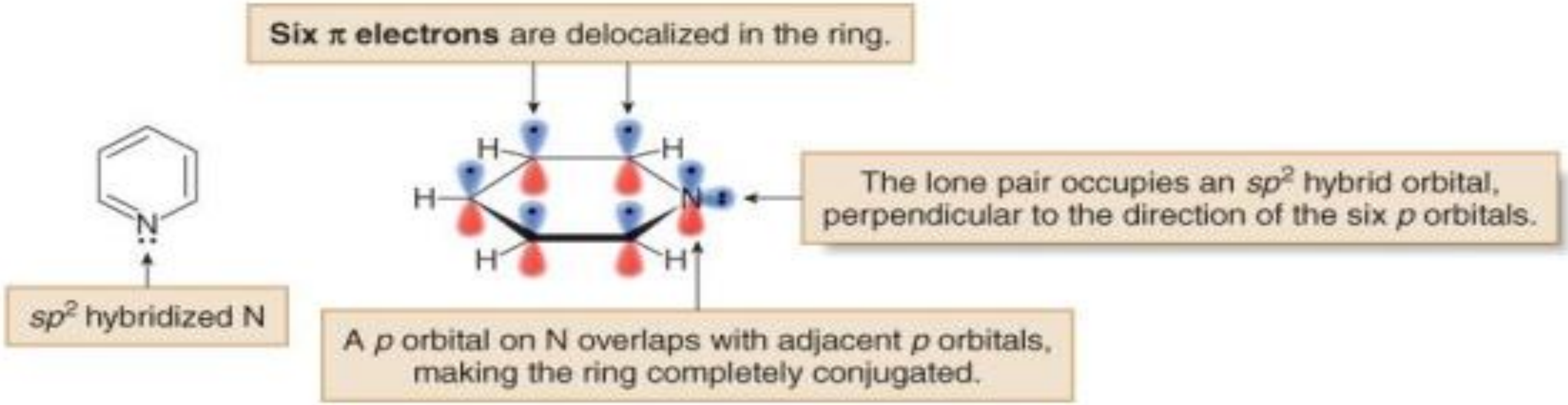
One *p* orbital is vacant.

- **The tropylium cation is aromatic because it is cyclic, planar, completely conjugated, and has six π electrons delocalized over the seven atoms of the ring.**

Aromatic Heterocycles



two resonance structures for pyridine
$6\ \pi$ electrons



Six π electrons are delocalized in the ring.

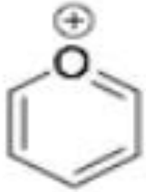
The lone pair occupies an sp^2 hybrid orbital, perpendicular to the direction of the six *p* orbitals.

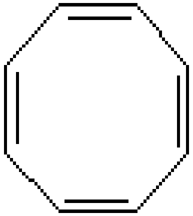
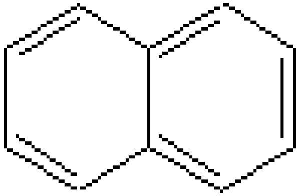
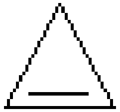
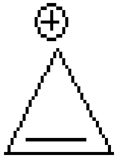
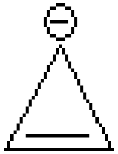
sp^2 hybridized N

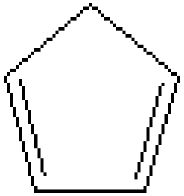
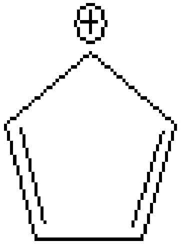
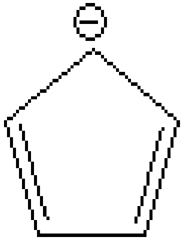
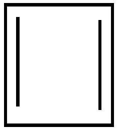
A *p* orbital on N overlaps with adjacent *p* orbitals, making the ring completely conjugated.

2H-pyran
$4\ \pi$ electrons
nonaromatic

2H-pyrilium ion
$6\ \pi$ electrons
aromatic



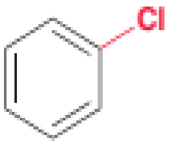
					
4n+2 =	8	10	2	2	4
n=	1.5	2	0	0	0.5

				
4n+2 =	4	4	6	4
n=	0.5	0.5	1	0.5

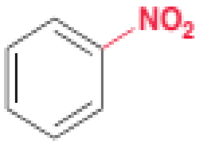
17.2 Nomenclature of Benzene Derivatives

Monosubstituted Derivatives of Benzene

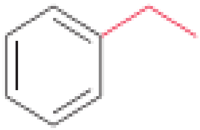
Monosubstituted derivatives of benzene are named systematically using benzene as the parent and listing the substituent as a prefix. Below are several examples.



Chlorobenzene

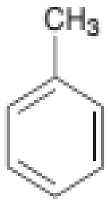


Nitrobenzene

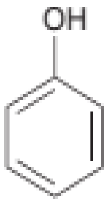


Ethylbenzene

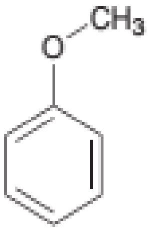
The following are some monosubstituted aromatic compounds that have common names accepted by IUPAC. You must commit these names to memory, as they will be used extensively throughout the remaining chapters.



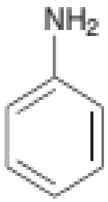
Toluene



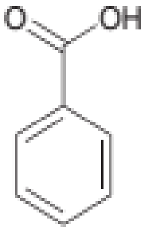
Phenol



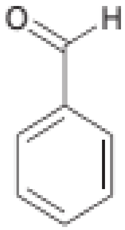
Anisole



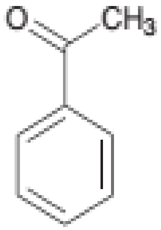
Aniline



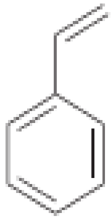
Benzoic acid



Benzaldehyde

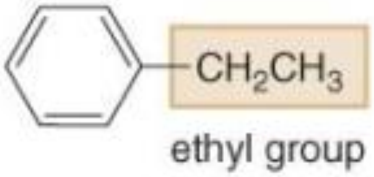


Acetophenone

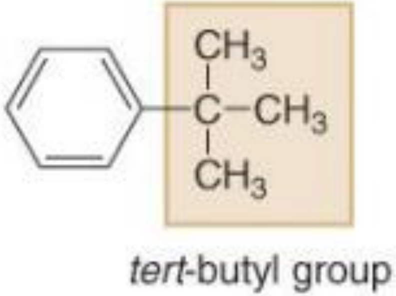


Styrene

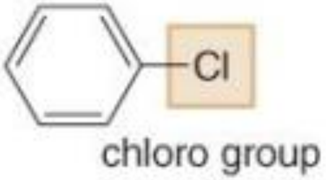
Systematic:



ethylbenzene

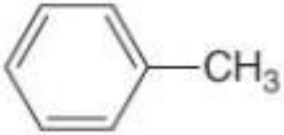


tert-butylbenzene

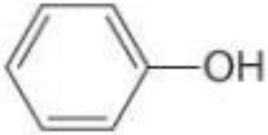


chlorobenzene

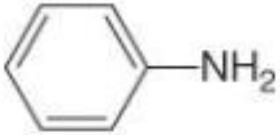
Common:



toluene
(methylbenzene)



phenol
(hydroxybenzene)

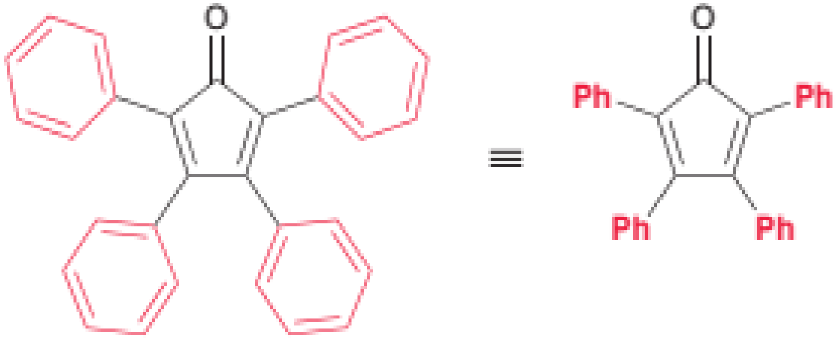


aniline
(aminobenzene)

If the substituent is larger than the benzene ring (i.e., if the substituent has more than six carbon atoms), then the benzene ring can be treated as a substituent and is called a **phenyl group**.

1-Phenylheptane

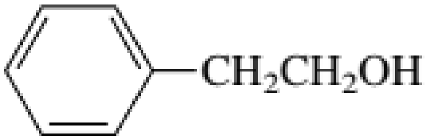
The presence of a phenyl group is often indicated with the abbreviation Ph, for example:



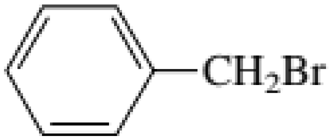
Tetraphenylcyclopentadienone

Phenyl groups bearing substituents are sometimes shown with the abbreviation Ar, indicating the presence of an aromatic ring.

When the benzene ring is named as a substituent, the word "phenyl" stands for C_6H_5—. Similarly, an arene named as a substituent is called an *aryl* group. A *benzyl* group is $C_6H_5CH_2$—.

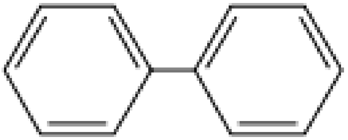


2-Phenylethanol

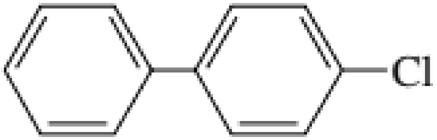


Benzyl bromide

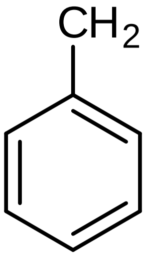
Biphenyl is the accepted IUPAC name for the compound in which two benzene rings are connected by a single bond.



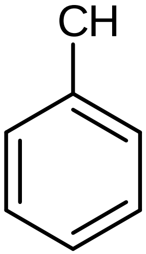
Biphenyl



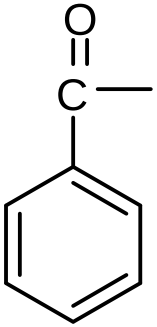
p-Chlorobiphenyl



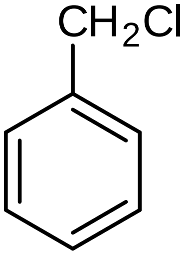
benzyl



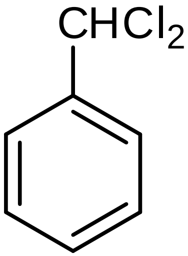
benzal



benzoyl



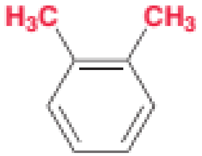
benzylchloride



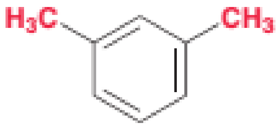
benzalchloride

Disubstituted Derivatives of Benzene

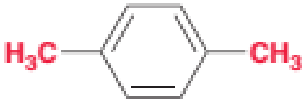
Dimethyl derivatives of benzene are called xylene, and there are three constitutionally isomeric xylenes.



ortho-Xylene
(1,2-dimethylbenzene)

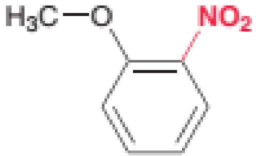


meta-Xylene
(1,3-dimethylbenzene)

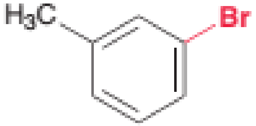


para-Xylene
(1,4-dimethylbenzene)

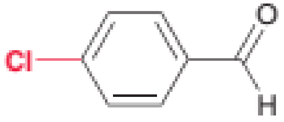
These isomers differ from each other in the relative positions of the methyl groups and can be named in two ways: (1) using the descriptors ***ortho***, ***meta***, and ***para*** or (2) using locants (i.e., 1,3 is the same as *meta*). Both methods can be used when the parent is a common name:



ortho-Nitroanisole
(2-Nitroanisole)



meta-Bromotoluene
(3-Bromotoluene)

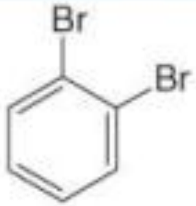


para-Chlorobenzaldehyde
(4-Chlorobenzaldehyde)

There is also a common practice to use one-letter prefixes (*o*-, *m*-, and *p*-) to represent the terms *ortho*, *meta*, and *para*. For example, the three previous compounds can be called *o*-nitroanisole, *m*-bromotoluene, and *p*-chlorobenzaldehyde, respectively.

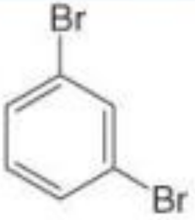
Identical:

1,2-disubstituted benzene
ortho isomer



1,2-dibromobenzene
o-dibromobenzene

1,3-disubstituted benzene
meta isomer



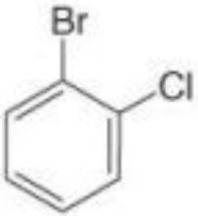
1,3-dibromobenzene
m-dibromobenzene

1,4-disubstituted benzene
para isomer

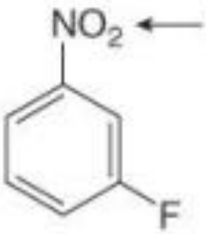
1,4-dibromobenzene
p-dibromobenzene

Different:

Alphabetize two different substituent names:



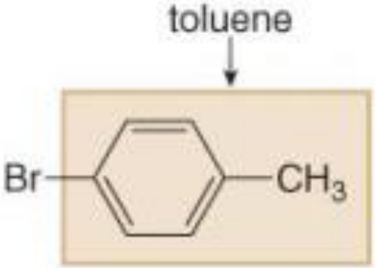
***o*-bromochloro-benzene**



nitro group

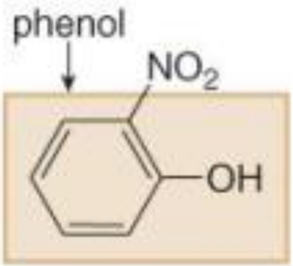
***m*-fluoronitro-benzene**

Use a common root name:



toluene

p-bromo**toluene**



phenol

o-nitro**phenol**

Polysubstituted Derivatives of Benzene

The descriptors *ortho*, *meta*, and *para* cannot be used when naming an aromatic ring bearing three or more substituents. In such a case, locants are required. That is, each substituent is designated with a number to indicate its location on the ring.

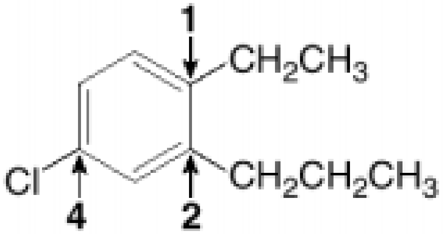
When naming a polysubstituted benzene ring, we will follow the same four-step process used for naming alkanes, alkenes, alkynes, and alcohols.

1. Identify and name the parent.
2. Identify and name the substituents.
3. Assign a locant to each substituent.
4. Arrange the substituents alphabetically.

Nomenclature: 3 or More Substituents

Examples of naming polysubstituted benzenes

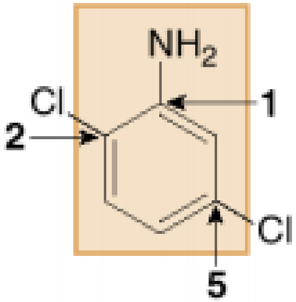
[1]



- Assign the lowest set of numbers.
- Alphabetize the names of all the substituents.

4-chloro-1-ethyl-2-propylbenzene

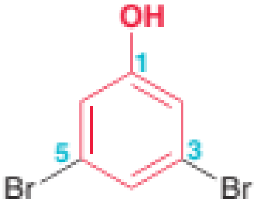
[2]



- Name the molecule as a derivative of the common root **aniline.**
- Designate the position of the NH_2 group as “1,” and then assign the lowest possible set of numbers to the other substituents.

2,5-dichloroaniline

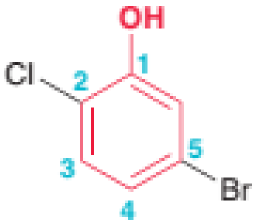
When identifying the parent, it is acceptable (and common practice) to choose a common name. Consider the following example:



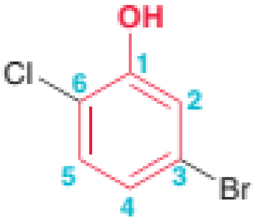
3,5-Dibromophenol

This compound could certainly be named as a trisubstituted benzene ring. However, it is much more efficient to name the parent as phenol rather than benzene and to list the two bromine atoms as substituents. When assigning locants, the carbon atom connected to the OH group receives the lowest locant (number 1). When a choice exists, place numbers so that the second substituent receives the lower possible number, for example:

Correct

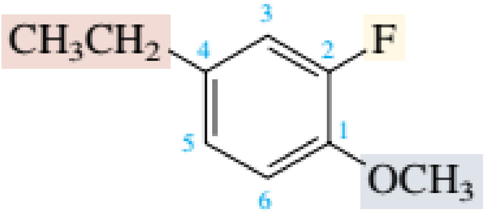


Incorrect

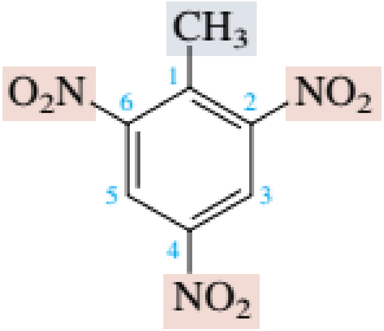


When assembling the name, make sure to alphabetize the substituents. In the example above, *b*romo is listed before *c*hloro.

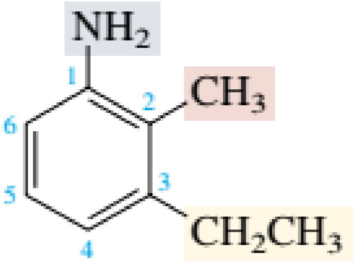
The prefixes *o*, *m*, and *p* are *not* used when three or more substituents are present on benzene; numerical locants must be used instead.



4-Ethyl-2-fluoroanisole

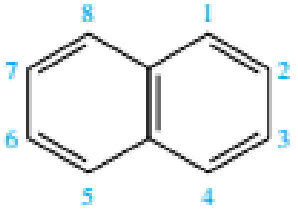


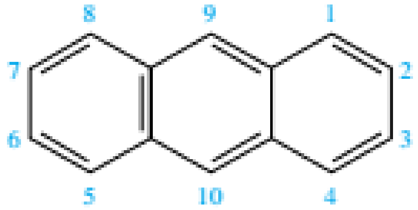
2,4,6-Trinitrotoluene

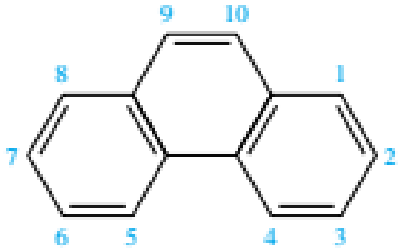


3-Ethyl-2-methylaniline

has three rings fused in a “linear” fashion, and “angular” fusion characterizes phenanthrene. The structural formulas of naphthalene, anthracene, and phenanthrene are shown along with the numbering system used to name their substituted derivatives:

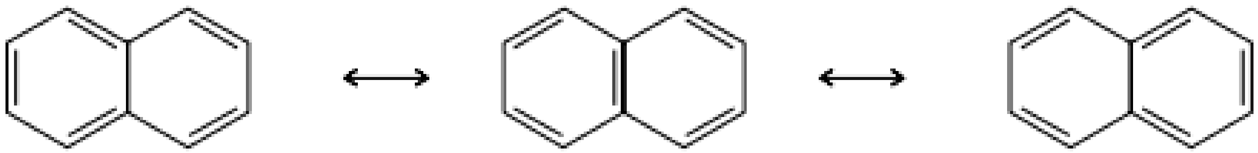






Arene:	Naphthalene	Anthracene	Phenanthrene
Resonance energy:	255 kJ/mol (61 kcal/mol)	347 kJ/mol (83 kcal/mol)	381 kJ/mol (91 kcal/mol)

In general, the most stable resonance structure for a polycyclic aromatic hydrocarbon is the one which has the greatest number of rings that correspond to Kekulé formulations of benzene. Naphthalene provides a fairly typical example:



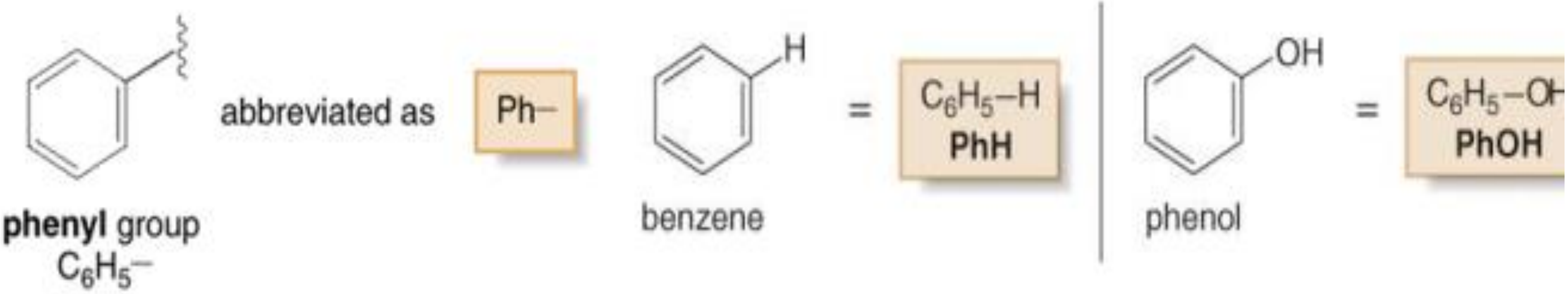
Most stable resonance form

Only left ring corresponds to Kekulé benzene.

Both rings correspond to Kekulé benzene.

Only right ring corresponds to Kekulé benzene.

- A benzene substituent is called a phenyl group, and it can be abbreviated in a structure as "Ph-".



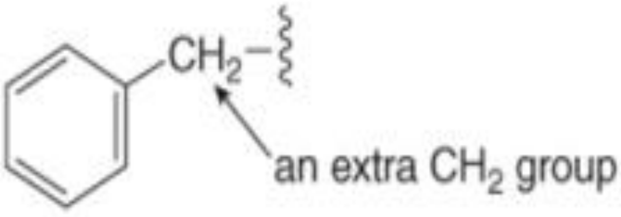
phenyl group C_6H_5-

abbreviated as **Ph–**

benzene = C_6H_5-H **PhH**

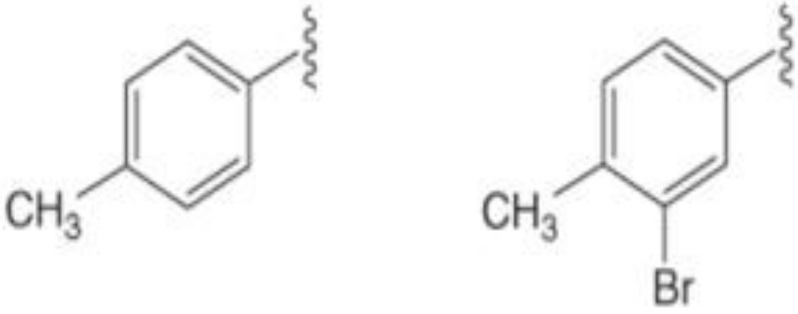
phenol = C_6H_5-OH **PhOH**

- The benzyl group:



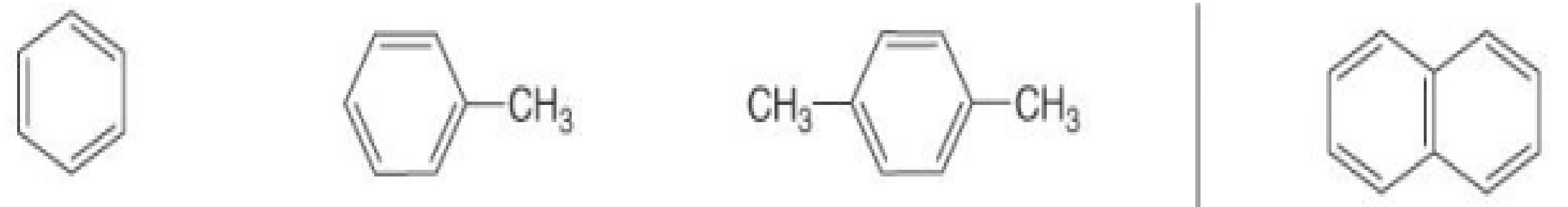
benzyl group $C_6H_5CH_2-$

- Aryl groups:



- Benzene and toluene, are obtained from petroleum refining and are useful starting materials for synthetic polymers.
- Compounds containing two or more benzene rings that share carbon—carbon bonds are called polycyclic aromatic hydrocarbons (PAHs). Naphthalene, the simplest PAH, is the active ingredient in mothballs.

The components of the gasoline additive BTX



benzene toluene *p*-xylene naphthalene (used in mothballs)

11.9 PHYSICAL PROPERTIES OF ARENES

In general, arenes resemble other hydrocarbons in their physical properties. They are nonpolar, insoluble in water, and less dense than water. In the absence of polar substituents, intermolecular forces are weak and limited to van der Waals attractions of the induced-dipole/induced-dipole type.

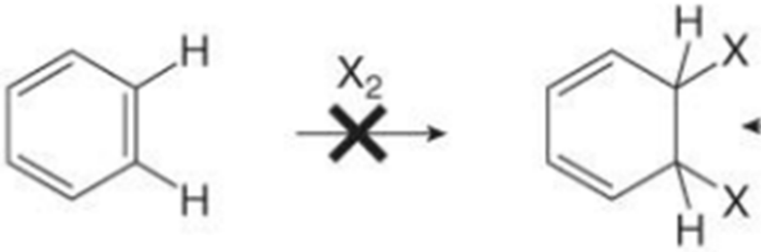
At one time, benzene was widely used as a solvent. This use virtually disappeared when statistical studies revealed an increased incidence of leukemia among workers exposed to atmospheric levels of benzene as low as 1 ppm. Toluene has replaced benzene as an inexpensive organic solvent, because it has similar solvent properties but has not been determined to be carcinogenic in the cell systems and at the dose levels that benzene is.

11.10 REACTIONS OF ARENES: A PREVIEW

We'll examine the chemical properties of aromatic compounds from two different perspectives:

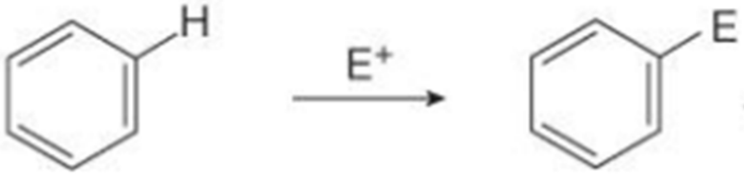
1. *One mode of chemical reactivity involves the ring itself as a functional group and includes*
   (a) Reduction
   (b) Electrophilic aromatic substitution

Addition

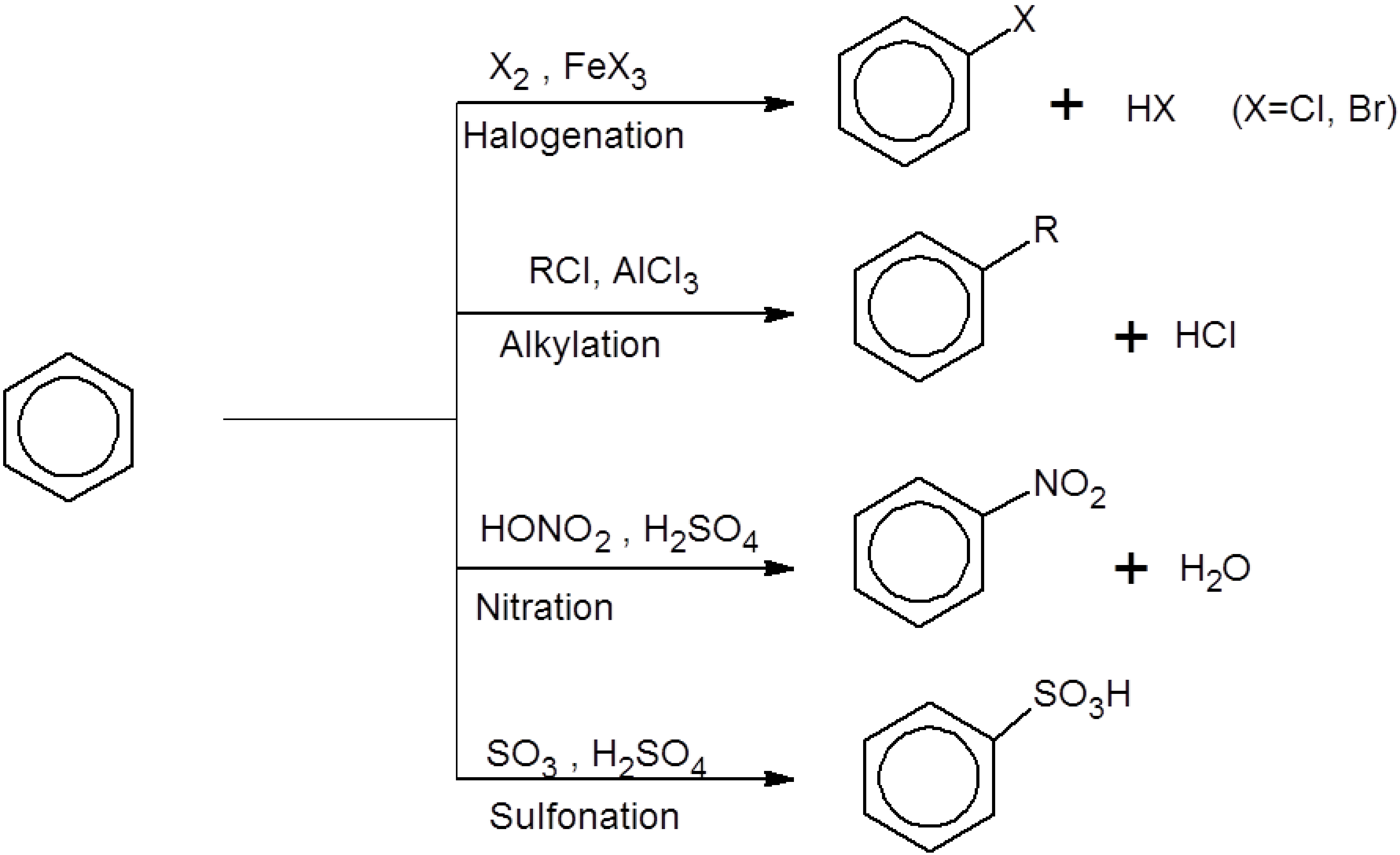


The product is *not* aromatic.

Substitution

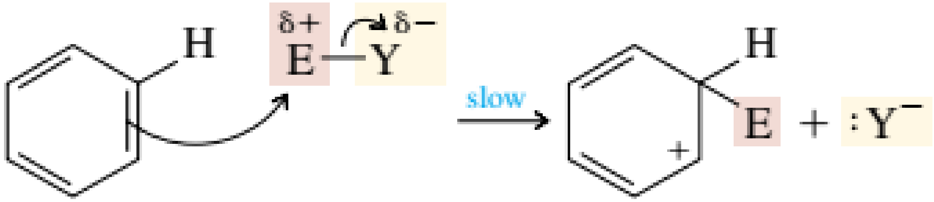


The product is aromatic.


X
X_2 , FeX_3
Halogenation
+ HX (X=Cl, Br)
R
RCl, $AlCl_3$
Alkylation
+ HCl
NO_2
$HONO_2$, H_2SO_4
Nitration
+ H_2O
SO_3H
SO_3 , H_2SO_4
Sulfonation

MECHANISTIC PRINCIPLES OF ELECTROPHILIC AROMATIC SUBSTITUTION

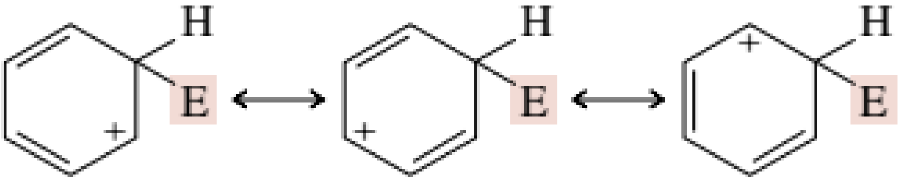
The first step in the reaction of electrophilic reagents with benzene is similar. An electrophile accepts an electron pair from the π system of benzene to form a carbocation:



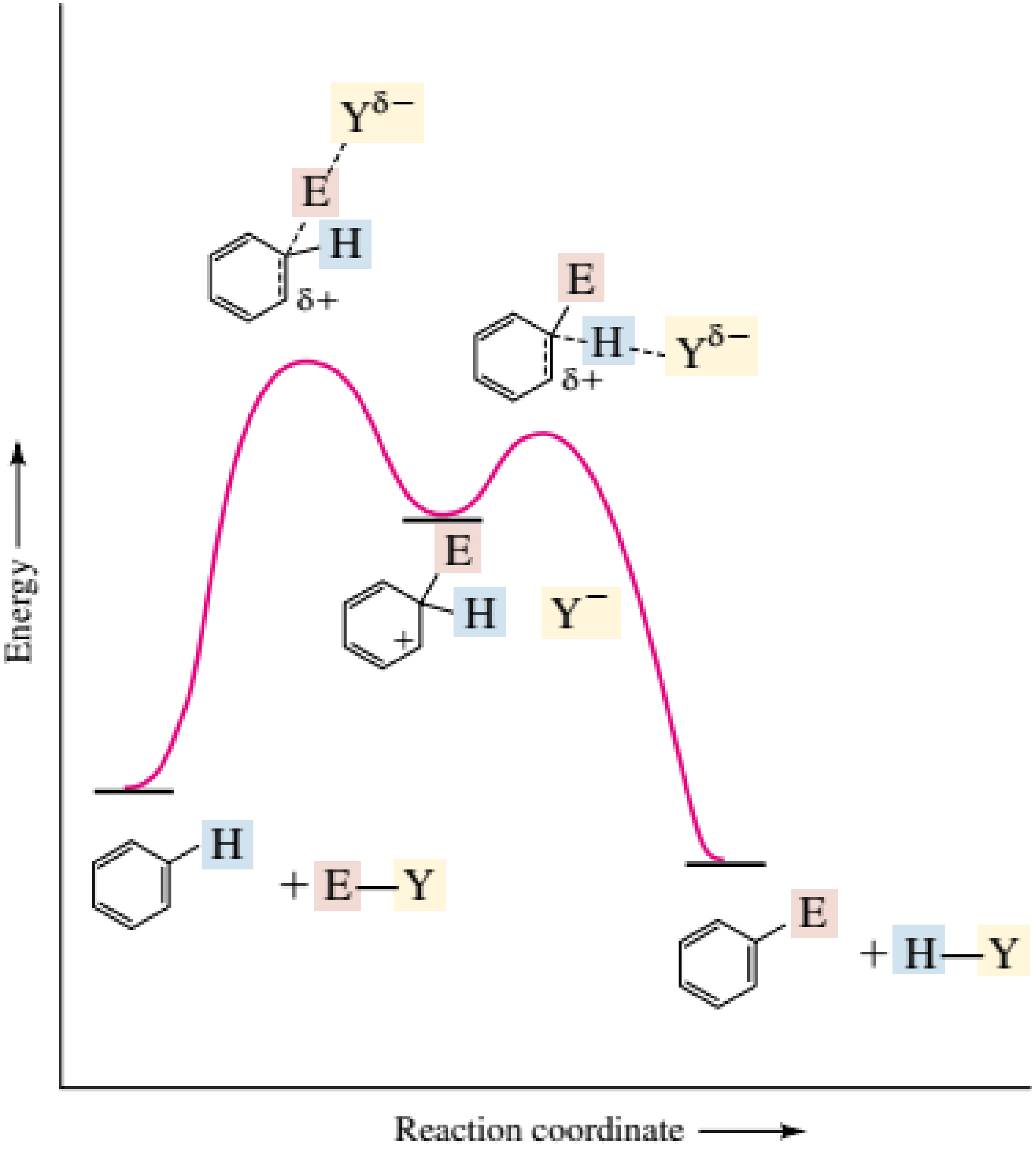
Benzene and electrophile

Carbocation

This particular carbocation is a resonance-stabilized one of the allylic type. It is a **cyclohexadienyl cation** (often referred to as an **arenium ion**).

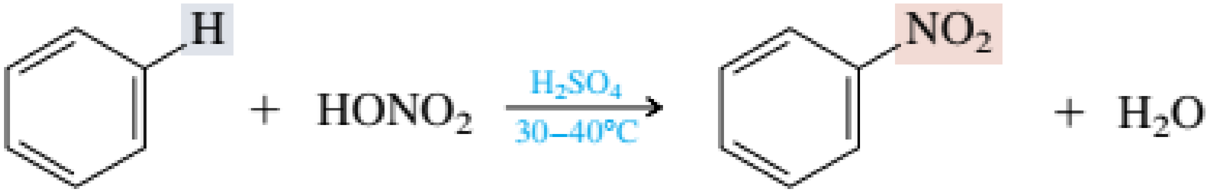


Resonance forms of a cyclohexadienyl cation

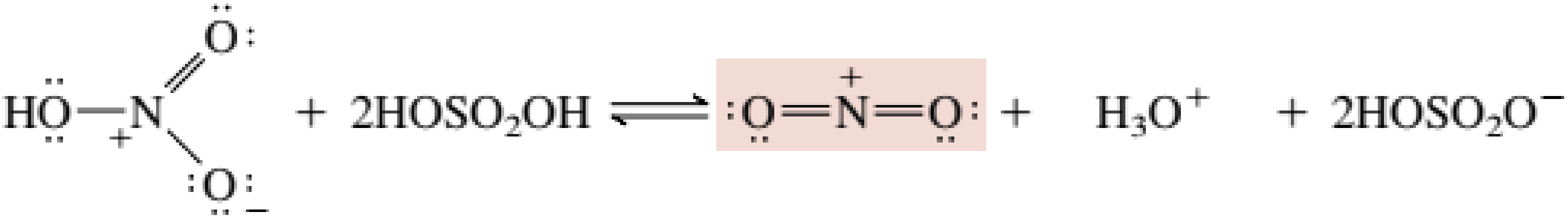

$Y^{\delta-}$
E
H
δ+
E
H
$Y^{\delta-}$
δ+
E
+
H
Y^{-}
H
+ E—Y
E
+ H—Y
Energy
Reaction coordinate

12.3 NITRATION OF BENZENE

Now that we've outlined the general mechanism for electrophilic aromatic substitution, we need only identify the specific electrophile in the nitration of benzene (see Table 12.1) to have a fairly clear idea of how the reaction occurs. Figure 12.2 shows the application of those general principles to the reaction:

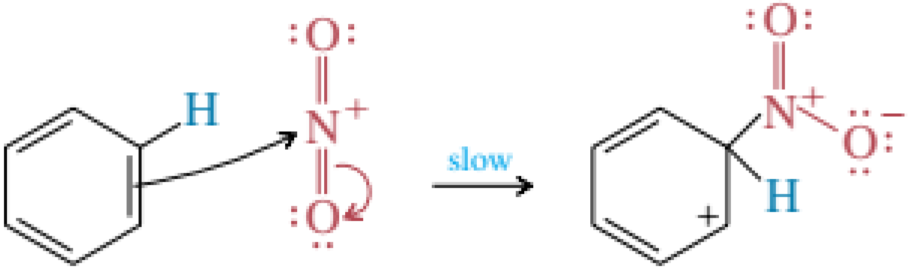


The electrophile (E^+) that reacts with benzene is *nitronium ion* (${}^+NO_2$). The concentration of nitronium ion in nitric acid alone is too low to nitrate benzene at a convenient rate, but can be increased by adding sulfuric acid.



$$HONO_2 + 2HOSO_2OH \rightleftharpoons :\ddot{O}=\overset{+}{N}=\ddot{O}: + H_3O^+ + 2HOSO_2O^-$$

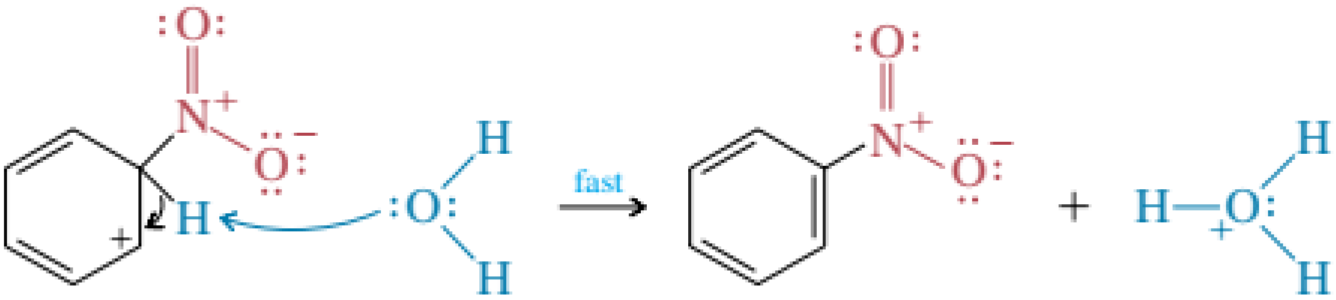
Step 1: Attack of nitronium cation on the π system of the aromatic ring



Benzene and nitronium ion

Cyclohexadienyl
cation intermediate

Step 2: Loss of a proton from the cyclohexadienyl cation



Cyclohexadienyl
cation intermediate

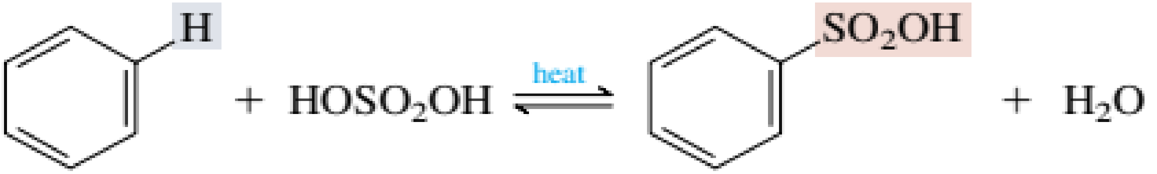
Water

Nitrobenzene

Hydronium
ion

12.4 SULFONATION OF BENZENE

The reaction of benzene with sulfuric acid to produce benzenesulfonic acid,

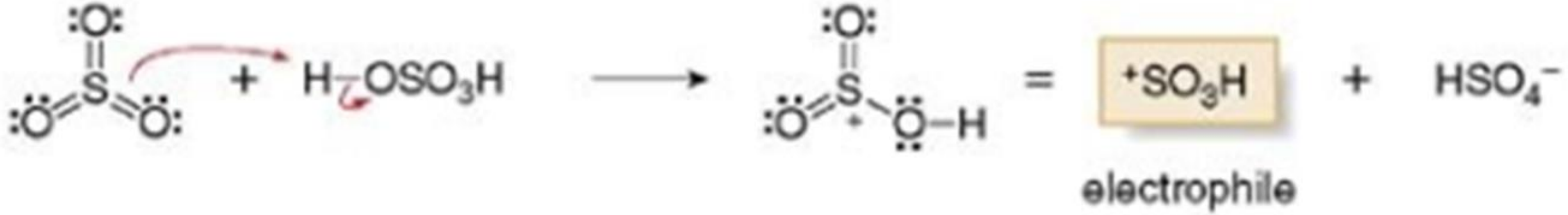


Benzene Sulfuric acid Benzenesulfonic acid Water

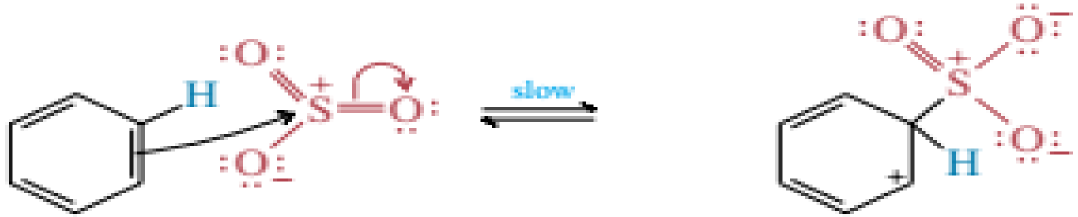
is reversible but can be driven to completion by several techniques. Removing the water formed in the reaction, for example, allows benzenesulfonic acid to be obtained in virtually quantitative yield. When a solution of sulfur trioxide in sulfuric acid is used as the sulfonating agent, the rate of sulfonation is much faster and the equilibrium is displaced entirely to the side of products, according to the equation

Benzene Sulfur trioxide Benzenesulfonic acid

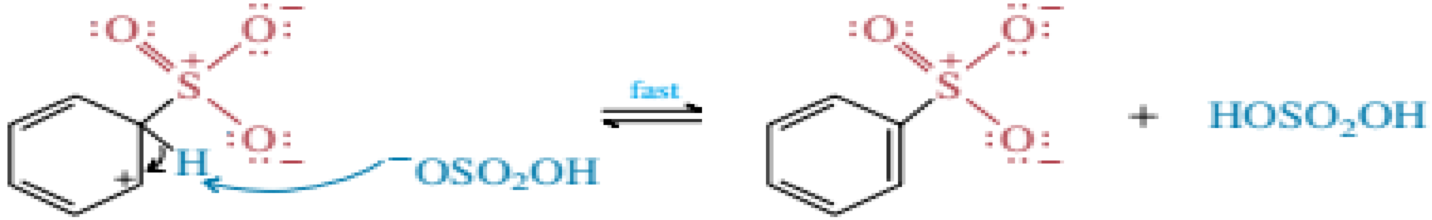
Formation of the Electrophile $^+SO_3H$ for Sulfonation



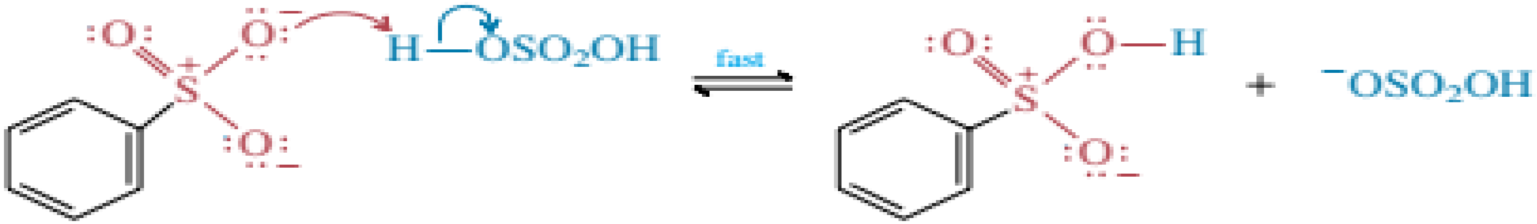
Step 1: Sulfur trioxide attacks benzene in the rate-determining step



Step 2: A proton is lost from the sp^3 hybridized carbon of the intermediate to restore the aromaticity of the ring. The species shown that abstracts the proton is a hydrogen sulfate ion formed by ionization of sulfuric acid.

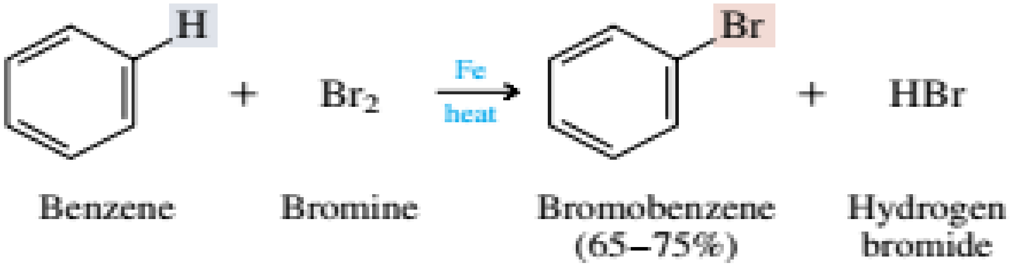


Step 3: A rapid proton transfer from the oxygen of sulfuric acid to the oxygen of benzenesulfonate completes the process.



12.5 HALOGENATION OF BENZENE

According to the usual procedure for preparing bromobenzene, bromine is added to benzene in the presence of metallic iron (customarily a few carpet tacks) and the reaction mixture is heated.



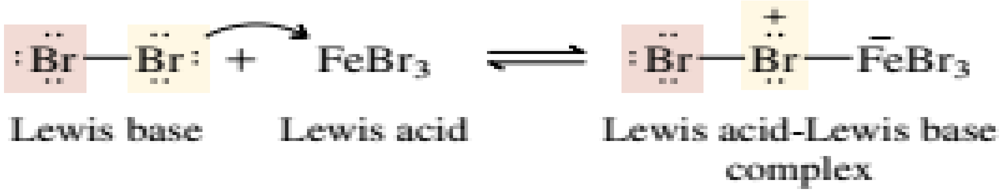
Bromine, although it adds rapidly to alkenes, is too weak an electrophile to react at an appreciable rate with benzene. A catalyst that increases the electrophilic properties of bromine must be present. Somehow carpet tacks can do this. How?

The active catalyst is not iron itself but iron(III) bromide, formed by reaction of iron and bromine.

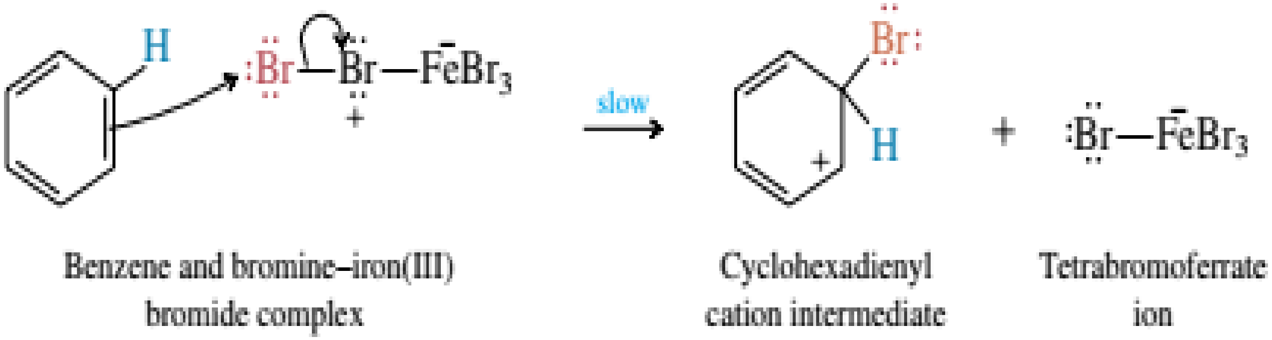
$$2Fe + 3Br_2 \longrightarrow 2FeBr_3$$

Iron   Bromine   Iron(III) bromide

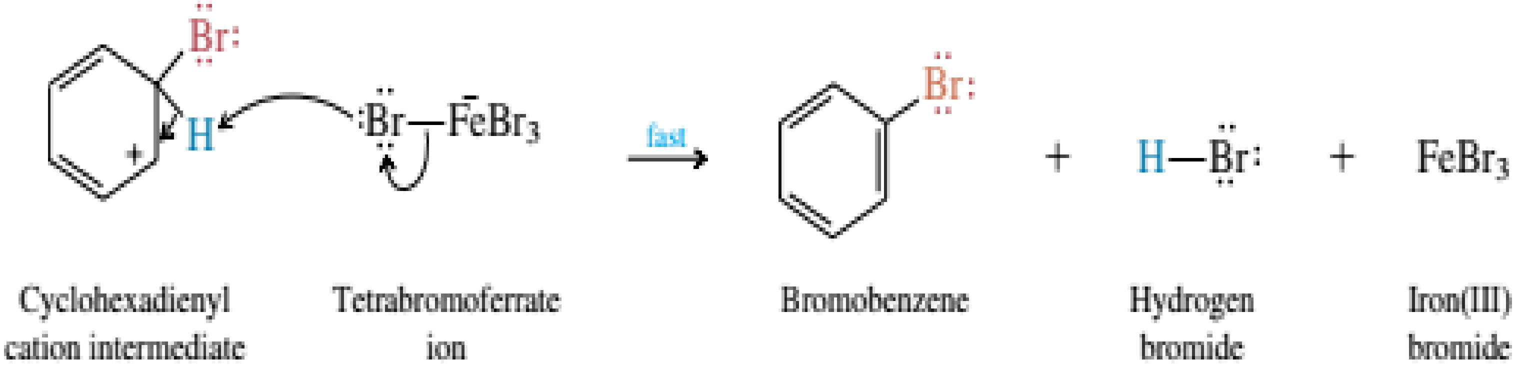
Iron(III) bromide is a weak Lewis acid. It combines with bromine to form a Lewis acid-Lewis base complex.

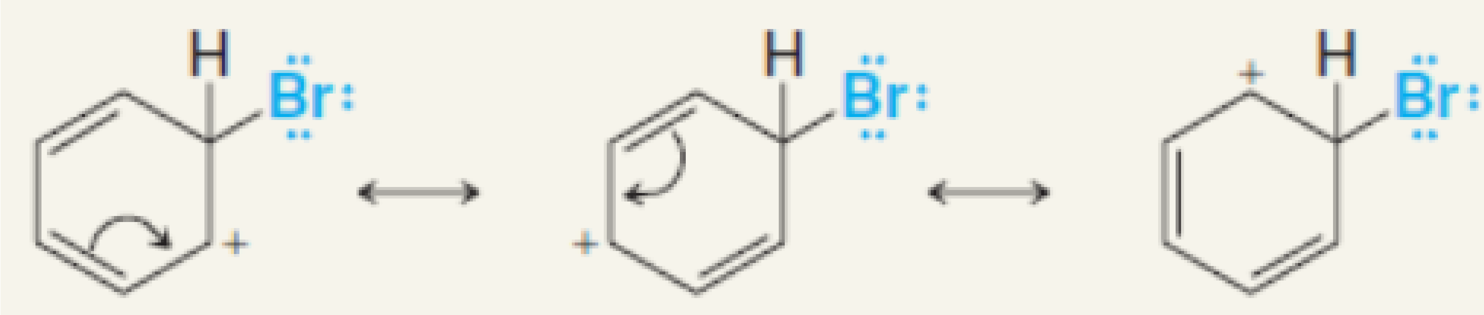


Step 1: The bromine–iron(III) bromide complex is the active electrophile that attacks benzene. Two of the π electrons of benzene are used to form a bond to bromine and give a cyclohexadienyl cation intermediate.

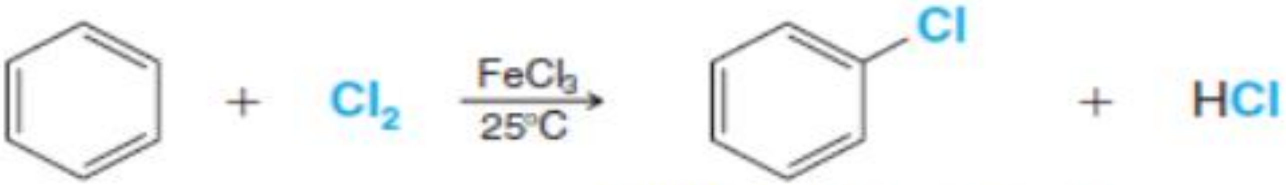


Step 2: Loss of a proton from the cyclohexadienyl cation yields bromobenzene.

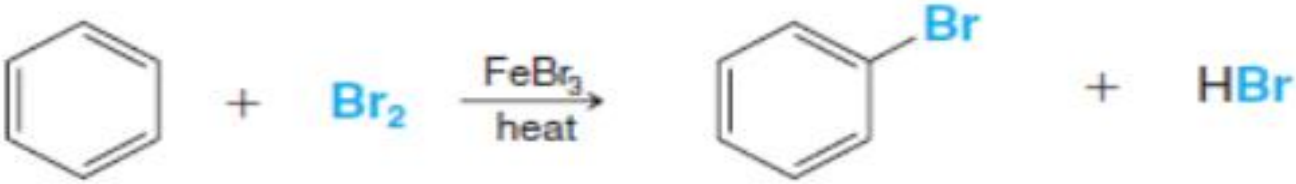




The benzene ring donates an electron pair to the terminal bromine, forming the arenium ion and neutralizing the formal positive charge on the other bromine.



Chlorobenzene (90%)



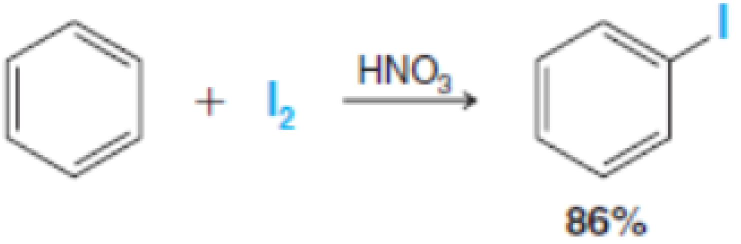
Bromobenzene (75%)

The purpose of the Lewis acid is to make the halogen a stronger electrophile.

The mechanism of the **chlorination** of benzene in the presence of *ferric chloride* is analogous to the one for bromination.

Fluorine reacts so rapidly with benzene that aromatic fluorination requires special conditions and special types of apparatus. Even then, it is difficult to limit the reaction to monofluorination. Fluorobenzene can be made, however, by an indirect method.

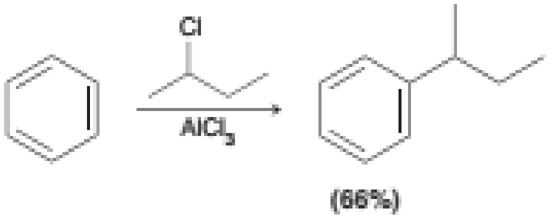
Iodine, on the other hand, is so unreactive that a special technique has to be used to effect direct iodination; the reaction has to be carried out in the presence of an oxidizing agent such as nitric acid.



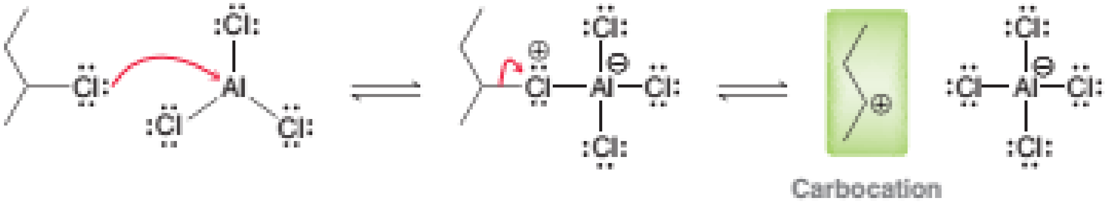
18.5 Friedel–Crafts Alkylation

In the previous sections, we have seen that a variety of electrophiles (Br^+, Cl^+, SO_3, and NO_2^+) will react with benzene in an electrophilic aromatic substitution reaction. In this section and the next, we will explore electrophiles in which the electrophilic center is a carbon atom.

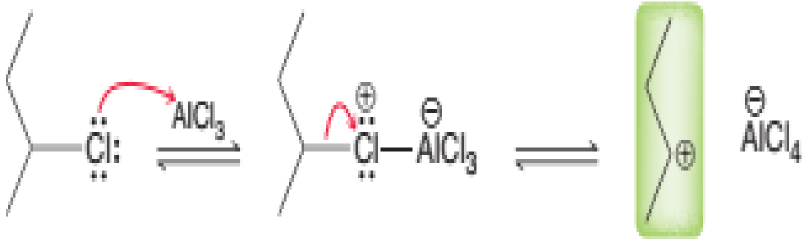
The **Friedel–Crafts alkylation**, discovered by Charles Friedel and James Crafts in 1877, makes possible the installation of an alkyl group on an aromatic ring.

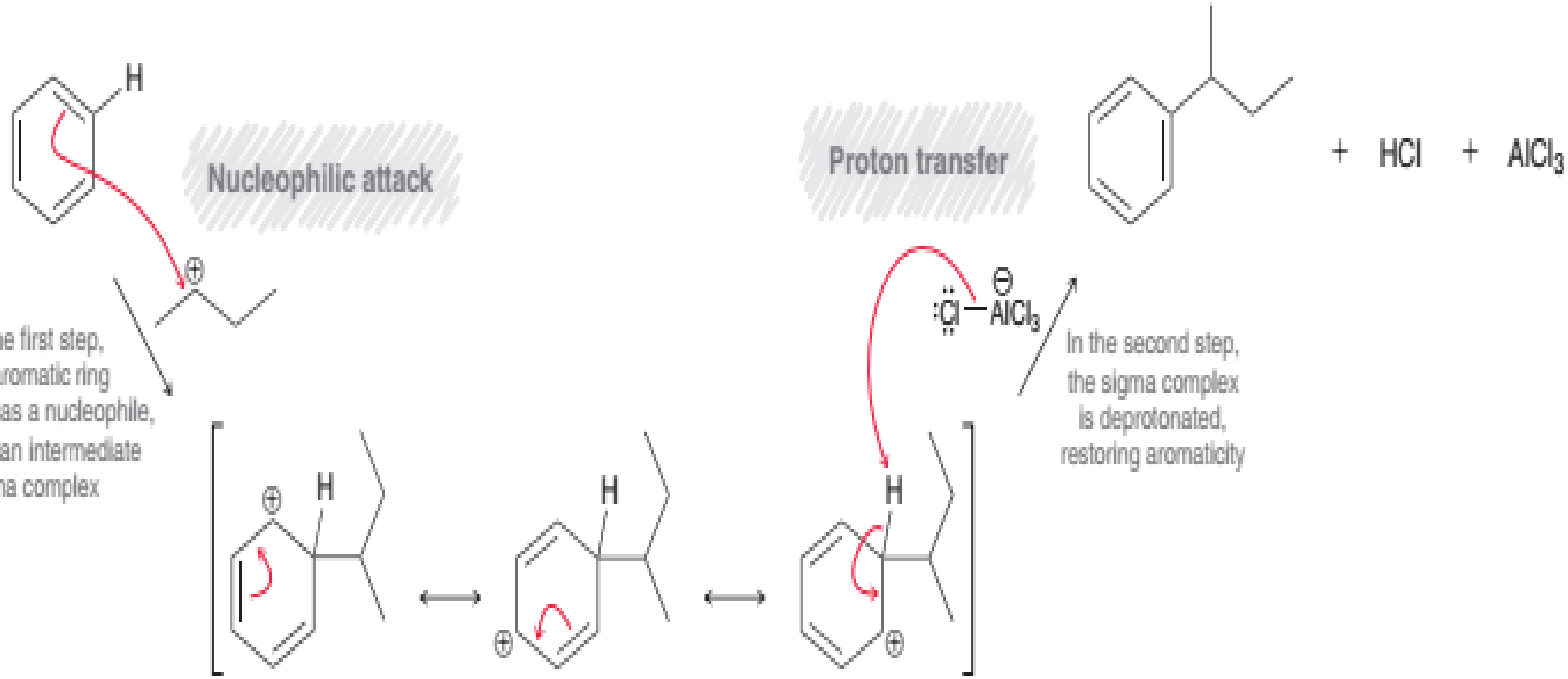


Although an alkyl halide such as 2-chlorobutane is, by itself, electrophilic, it is not sufficiently electrophilic to react with benzene. However, in the presence of a Lewis acid, such as aluminum trichloride, the alkyl halide is converted into a carbocation.



The catalyst functions exactly as expected (compare the role of $AlCl_3$ here to the role that it plays in Section 18.2). The result here is the formation of a carbocation, which is an excellent electrophile and is capable of reacting with benzene in an electrophilic aromatic substitution reaction (Mechanism 18.6).





Nucleophilic attack

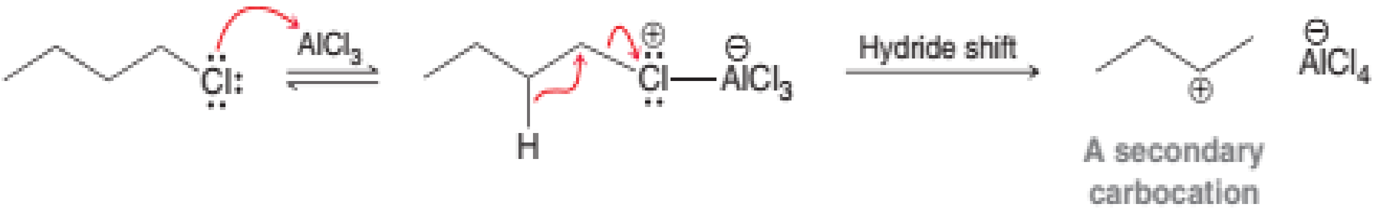
Proton transfer

In the first step,
the aromatic ring
functions as a nucleophile,
forming an intermediate
sigma complex

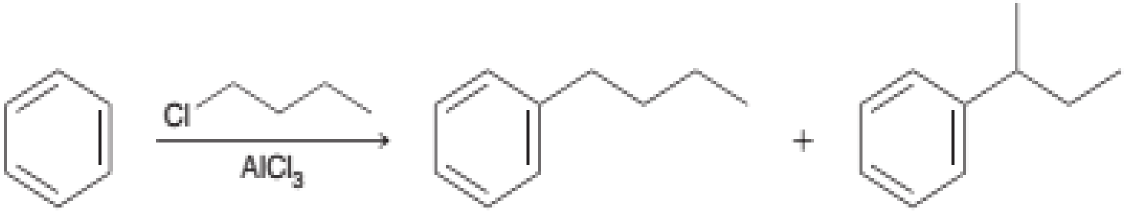
In the second step,
the sigma complex
is deprotonated,
restoring aromaticity

Sigma complex

This complex can be attacked by an aromatic ring, much like we saw during chlorination (Mechanism 18.2). Although a Friedel–Crafts alkylation is effective when ethyl chloride is used, most other primary alkyl halides cannot be used effectively, because their complexes with $AlCl_3$ readily undergo rearrangement to form secondary or tertiary carbocations. For example, when 1-chlorobutane is treated with aluminum trichloride, a secondary carbocation is formed via a hydride shift.



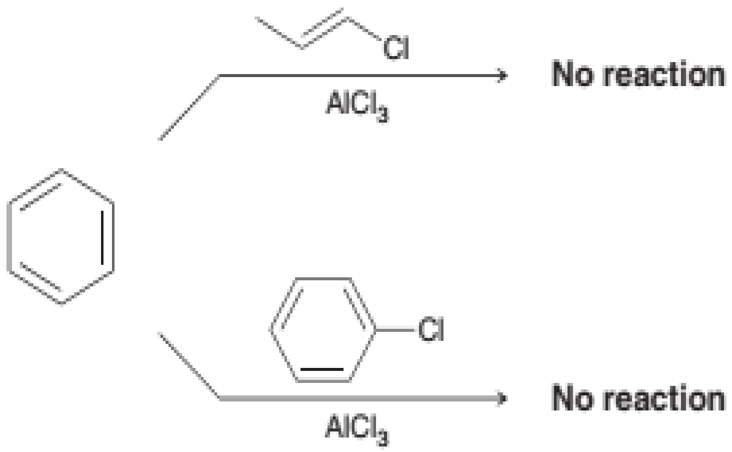
In such a case, a mixture of products is obtained.



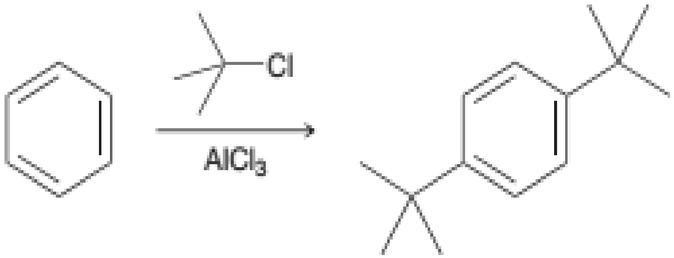
The ratio of products depends on the conditions chosen (concentrations, temperature, etc.), but a mixture of products is unavoidable. Therefore, in practice, a Friedel–Crafts alkylation is only efficient when the substrate cannot undergo rearrangement.

There are several other limitations that must be noted.

1. When choosing an alkyl halide, the carbon atom connected to the halogen must be *sp*^{3} hybridized. Vinyl carbocations and aryl carbocations are not sufficiently stable to be formed under Friedel–Crafts conditions.



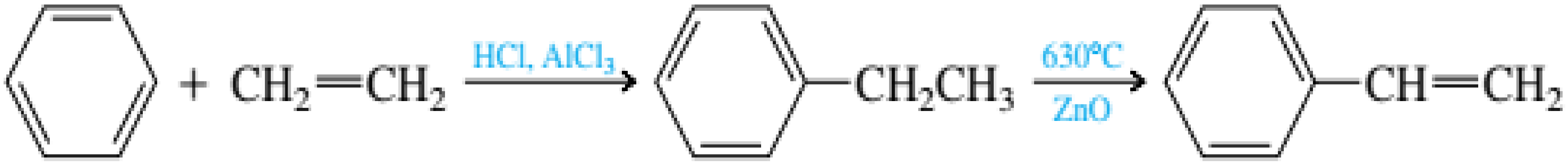
2. Installation of an alkyl group activates the ring toward further alkylation (for reasons that we will explore in the upcoming sections of this chapter). Therefore, polyalkylations often occur.



Since electrophilic attack on benzene is simply another reaction available to a carbocation, other carbocation precursors can be used in place of alkyl halides. For example, alkenes, which are converted to carbocations by protonation, can be used to alkylate benzene.

Benzene Cyclohexene Cyclohexylbenzene (65–68%)

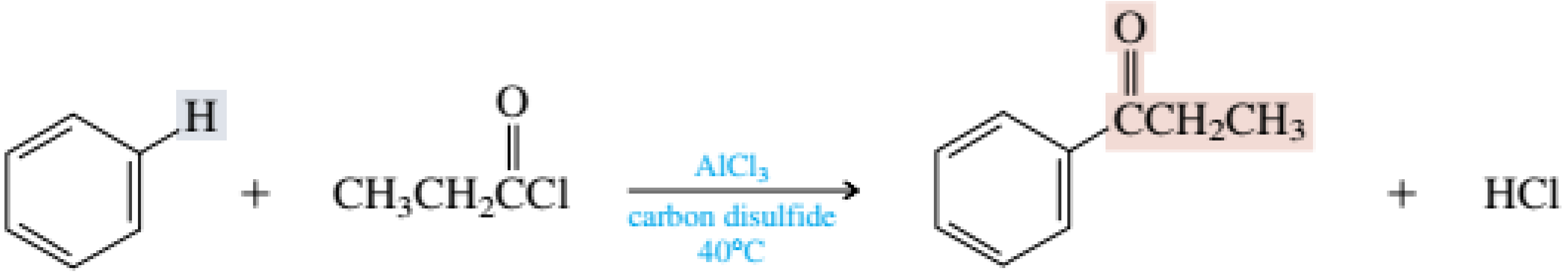
Thus, the industrial preparation of styrene from benzene and ethylene does not involve vinyl chloride but proceeds by way of ethylbenzene.



Benzene Ethylene Ethylbenzene Styrene

12.7 FRIEDEL–CRAFTS ACYLATION OF BENZENE

Another version of the Friedel–Crafts reaction uses **acyl halides** instead of alkyl halides and yields **acylbenzenes.**



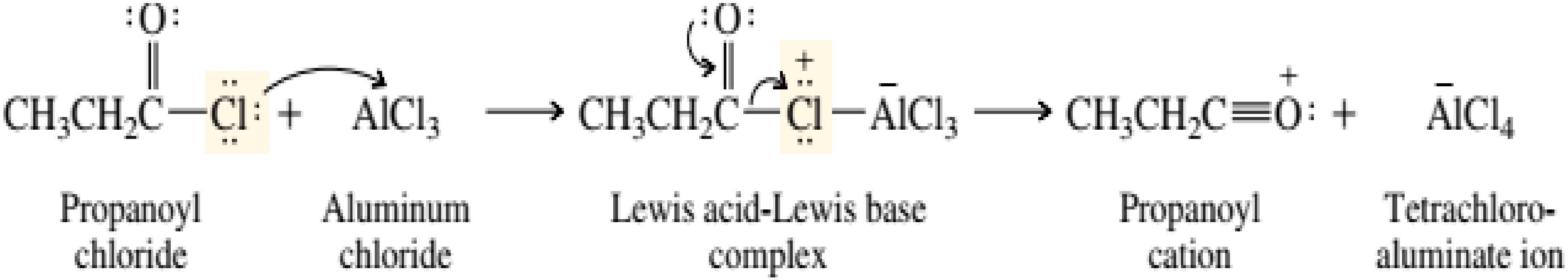
Benzene | Propanoyl chloride | 1-Phenyl-1-propanone (88%) | Hydrogen chloride

The electrophile in a Friedel–Crafts acylation reaction is an **acyl cation** (also referred to as an **acylium ion**). Acyl cations are stabilized by resonance. The acyl cation derived from propanoyl chloride is represented by the two resonance forms

$$CH_3CH_2\overset{+}{C}{=}\ddot{O}: \longleftrightarrow CH_3CH_2C{\equiv}\overset{+}{O}:$$

Most stable resonance form;
oxygen and carbon have octets of electrons

Acyl cations form by coordination of an acyl chloride with aluminum chloride, followed by cleavage of the carbon–chlorine bond.

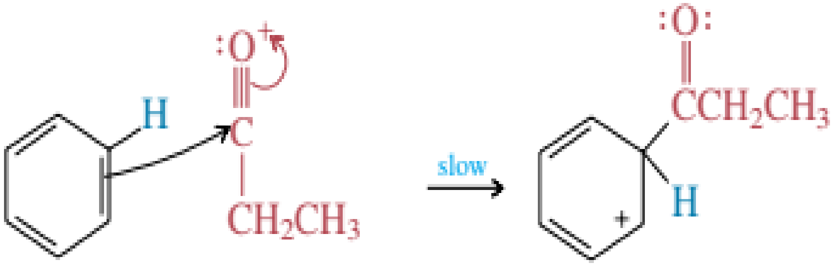


$$CH_3CH_2\overset{\overset{:O:}{\|}}{C}-\underset{..}{\overset{..}{Cl}}: + AlCl_3 \longrightarrow CH_3CH_2\overset{\overset{:O:}{\|}}{C}-\underset{..}{\overset{+}{Cl}}-\overset{-}{Al}Cl_3 \longrightarrow CH_3CH_2C\equiv\overset{+}{O}: + \overset{-}{Al}Cl_4$$

The electrophilic site of an acyl cation is its acyl carbon. An electrostatic potential map of the acyl cation from propanoyl chloride (Figure 12.6) illustrates nicely the concentration of positive charge at the acyl carbon. The mechanism of the reaction between this cation and benzene is analogous to that of other electrophilic reagents (Figure 12.7).

acylation.

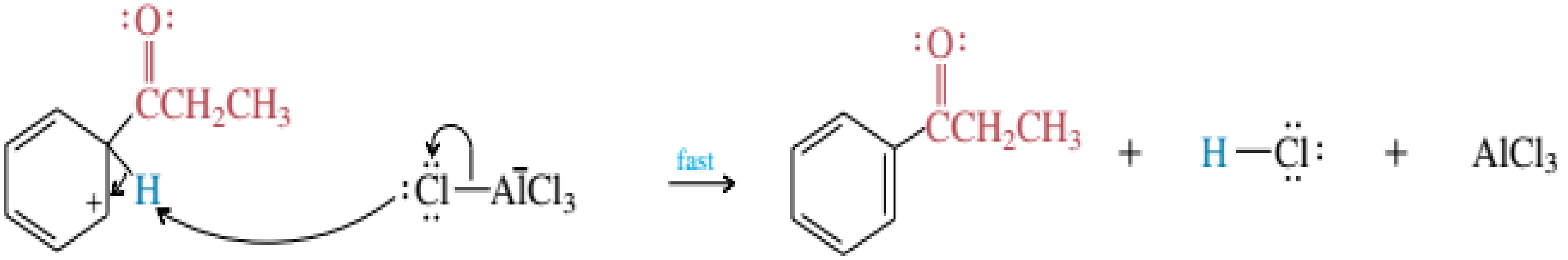
Step 1: The acyl cation attacks benzene. A pair of π electrons of benzene is used to form a covalent bond to the carbon of the acyl cation.



Benzene and propanoyl cation

Cyclohexadienyl cation intermediate

Step 2: Aromaticity of the ring is restored when it loses a proton to give the acylbenzene.



Cyclohexadienyl cation intermediate

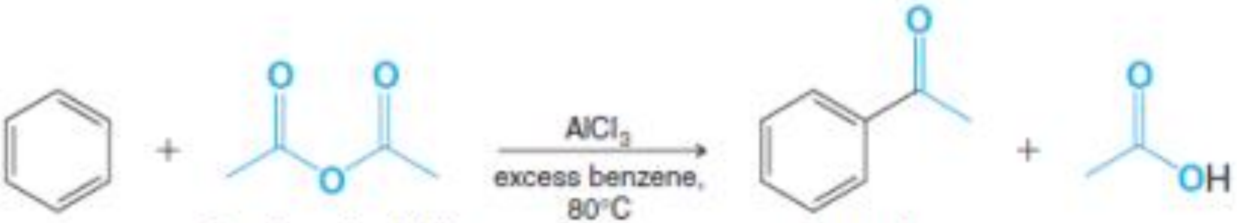
Tetrachloroaluminate ion

1-Phenyl-1-propanone

Hydrogen chloride

Aluminum chloride

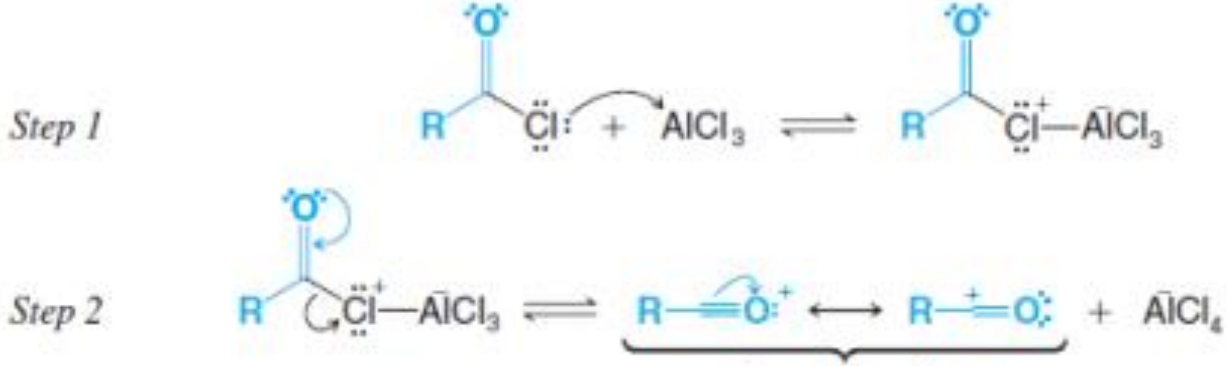
Friedel–Crafts acylations can also be carried out using carboxylic acid anhydrides.



Acetic anhydride (a carboxylic acid anhydride)

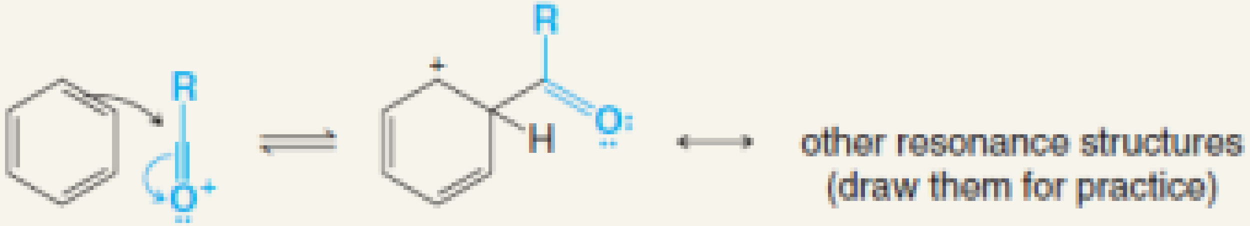
Acetophenone (82–85%)

In most Friedel–Crafts acylations the electrophile appears to be an **acylium ion** forme from an acyl halide in the following way:



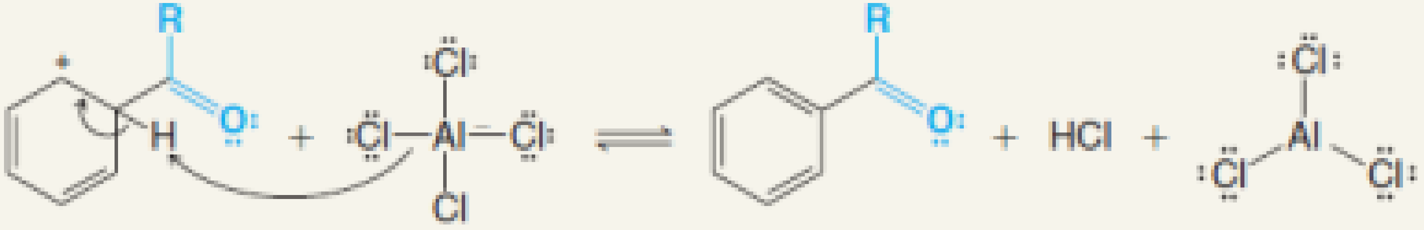
An acylium ion (a resonance hybrid)

Step 3



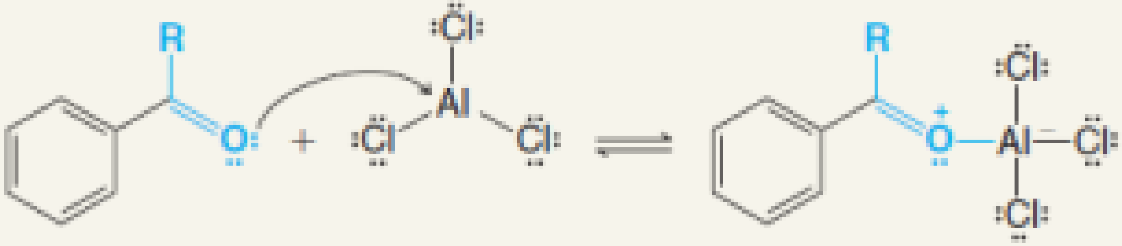
The acylium ion, acting as an electrophile, reacts with benzene to form the arenium ion.

Step 4



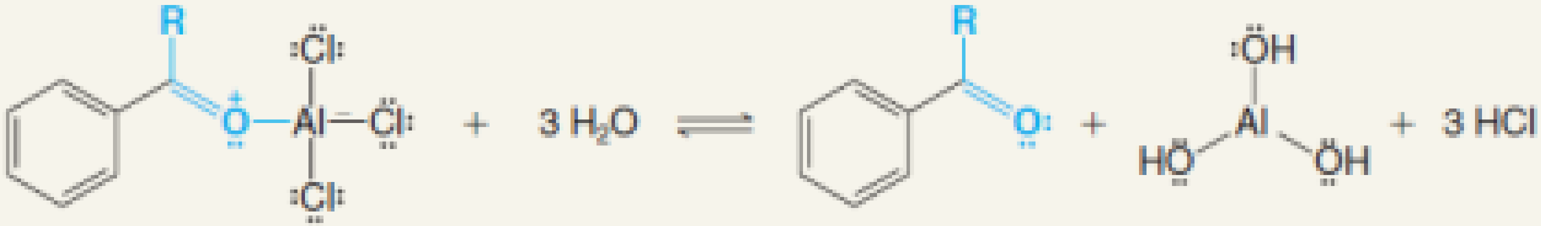
A proton is removed from the arenium ion, forming the aryl ketone.

Step 5



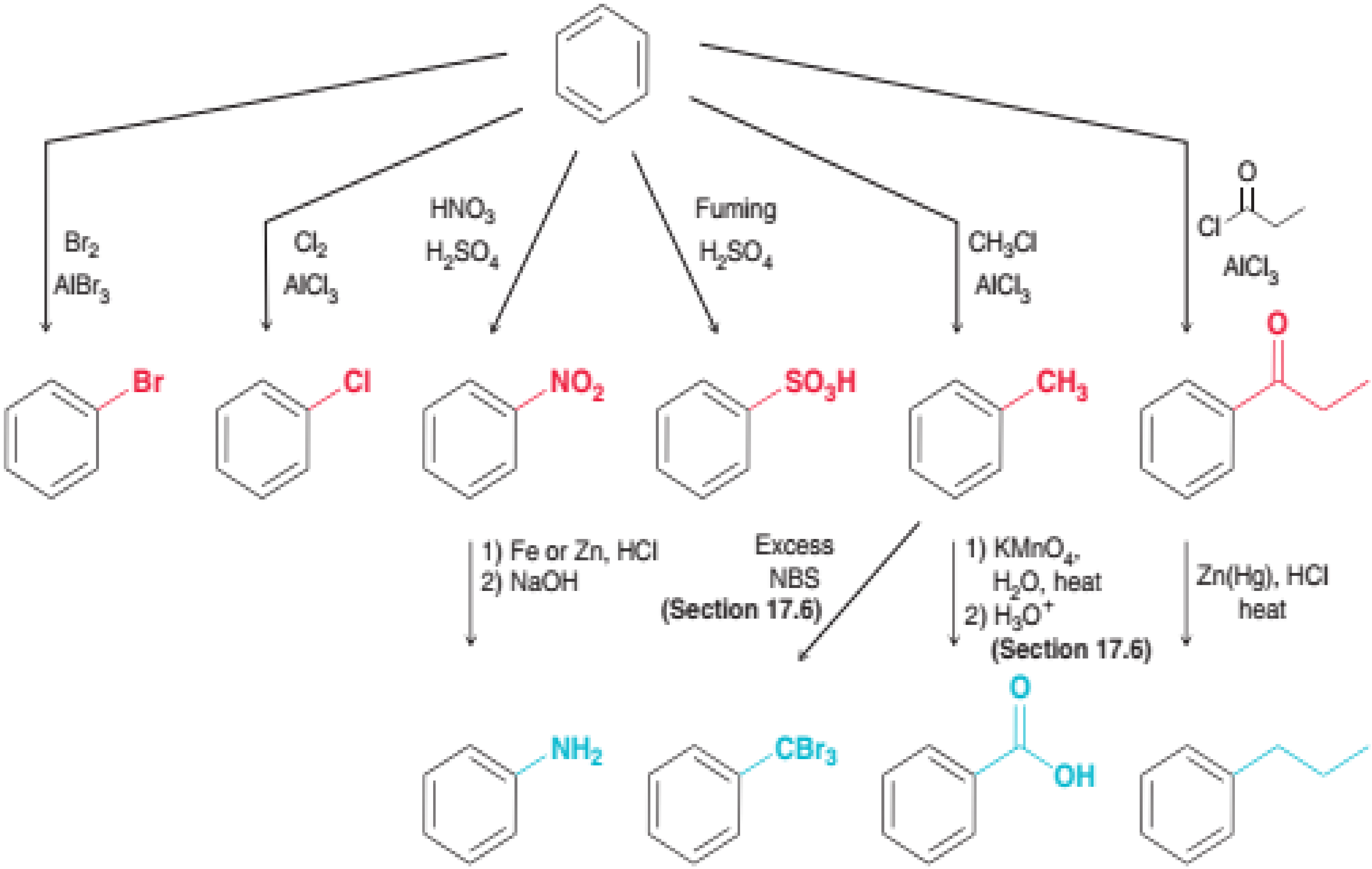
The ketone, acting as a Lewis base, reacts with aluminum chloride (a Lewis acid) to form a complex.

Step 6



Treating the complex with water liberates the ketone and hydrolyzes the Lewis acid.

Monosubstituted Benzene Rings

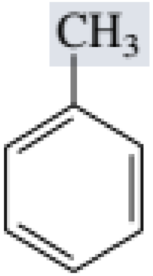


12.9 RATE AND REGIOSELECTIVITY IN ELECTROPHILIC AROMATIC SUBSTITUTION

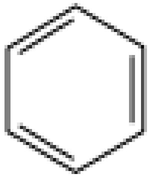
So far we've been concerned only with electrophilic substitution of benzene. Two important questions arise when we turn to analogous substitutions on rings that already bear at least one substituent:

1. What is the effect of a substituent on the *rate* of electrophilic aromatic substitution?
2. What is the effect of a substituent on the *regioselectivity* of electrophilic aromatic substitution?

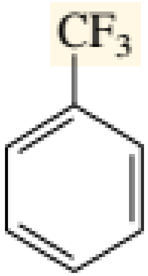
To illustrate substituent effects on rate, consider the nitration of benzene, toluene, and (trifluoromethyl)benzene.



Toluene
(most reactive)



Benzene



(Trifluoromethyl)benzene
(least reactive)

- The atoms/groups which are more electronegative than carbon gain a slight negative charge on them and withdraw the electrons of the carbon chain towards themselves are known to exert -**I Effect** (pronounced as “minus I effect”)

- The atoms/groups which are more electropositive than carbon gain a slight positive charge on them and push the electrons of the carbon chain away from themselves are known to exert +**I Effect** (pronounced as “plus I effect”)

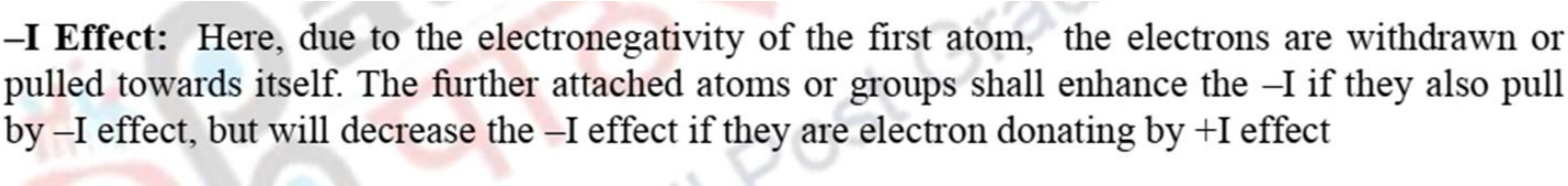
- The atoms/groups in which lone pair(or electrons of negative charge) is in conjugation with double or triple bond are electron donating and gain a formal positive charge in the resonating structure in the process and are known to exert **+M/+R Effect.**

- The atoms/groups which are in conjugation with double or triple bond and are electron withdrawing and gain a formal negative charge in the resonating structure in the process and are known to exert -**M/-R Effect.**

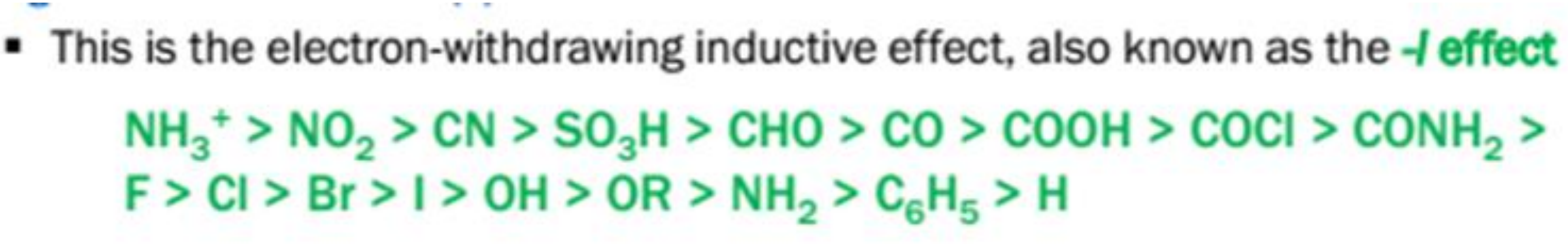
INDUCTIVE EFFECT

- *Inductive effects are electronic effects that occur through sigma σ bonds caused by electronegativity differences of atoms.*

- ***Types of Inductive effect:***

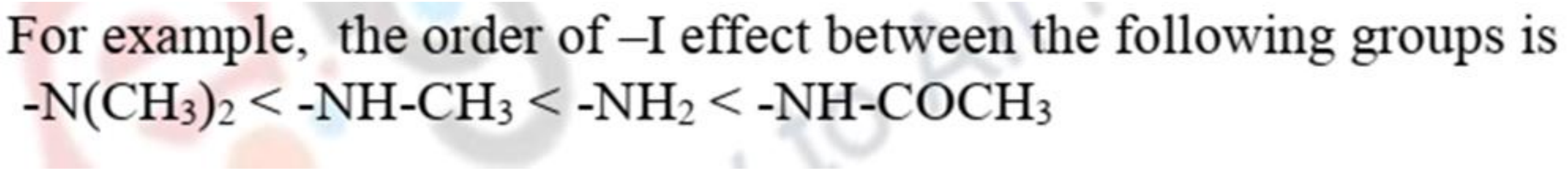


–I Effect: Here, due to the electronegativity of the first atom, the electrons are withdrawn or pulled towards itself. The further attached atoms or groups shall enhance the –I if they also pull by –I effect, but will decrease the –I effect if they are electron donating by +I effect



- This is the electron-withdrawing inductive effect, also known as the *–I effect*

  $NH_3^+ > NO_2 > CN > SO_3H > CHO > CO > COOH > COCl > CONH_2 > F > Cl > Br > I > OH > OR > NH_2 > C_6H_5 > H$



For example, the order of –I effect between the following groups is $-N(CH_3)_2 < -NH\text{-}CH_3 < -NH_2 < -NH\text{-}COCH_3$

For example, C - X (X = halogen) bond is polar with C having a δ+ charge and the halogen having a δ- charge. The magnitude or value of these fractional charges increases with an increase in the electronegativity of the halogen i.e. for halogens, it is in the order F > Cl > Br > I.

→

+I Effect: Here, due to the electropositivity of the first atom, the electrons are pushed away from itself. The further attached atoms or groups shall enhance the +I if they also push by +I effect, but will decrease the +I effect if they are electron withdrawing by -I effect

- This is electron releasing character and is indicated by the ***+I effect***

$$C(CH_3)_3 > CH(CH_3)_2 > CH_2CH_3 > CH_3 > H$$

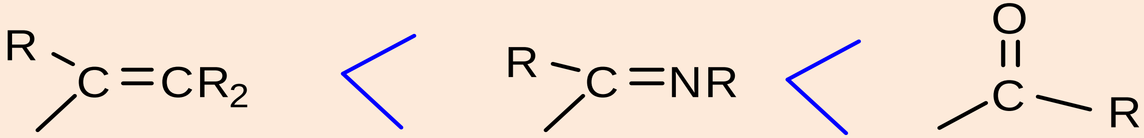
$$H\text{-} < D\text{-} < \text{-}CH_3 < \text{-}CH_2R < CHR_2 < \text{-}CR_3 < \text{-}COO^-$$

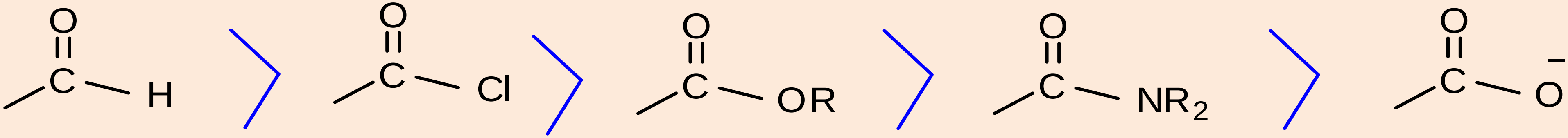
Mesomeric or Resonance Effect

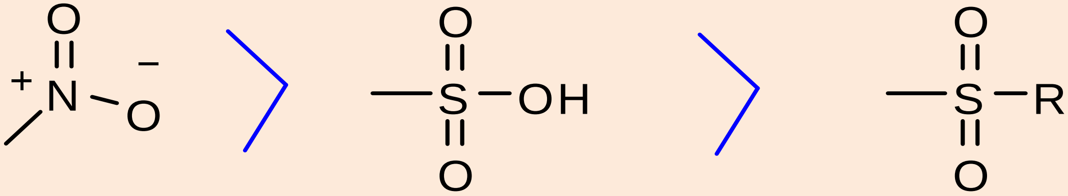
In a normal π bond, the π electrons are localised between the constituent atoms. However, if double and single bonds are present alternately in a molecule, it is called **conjugation**

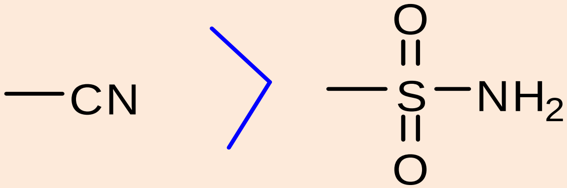
–M Effect: Here, due to the vacant p orbital on the first atom, the conjugated π electrons are withdrawn towards it. The further attached atoms or groups shall enhance the –M if they also pull by –I or –M effect, but will decrease the –M effect if they are electron donating by +I or +M effect

$-CHO > -COC_2H_5$


R
C=CR2
<
R
C=NR
<
O
C
R

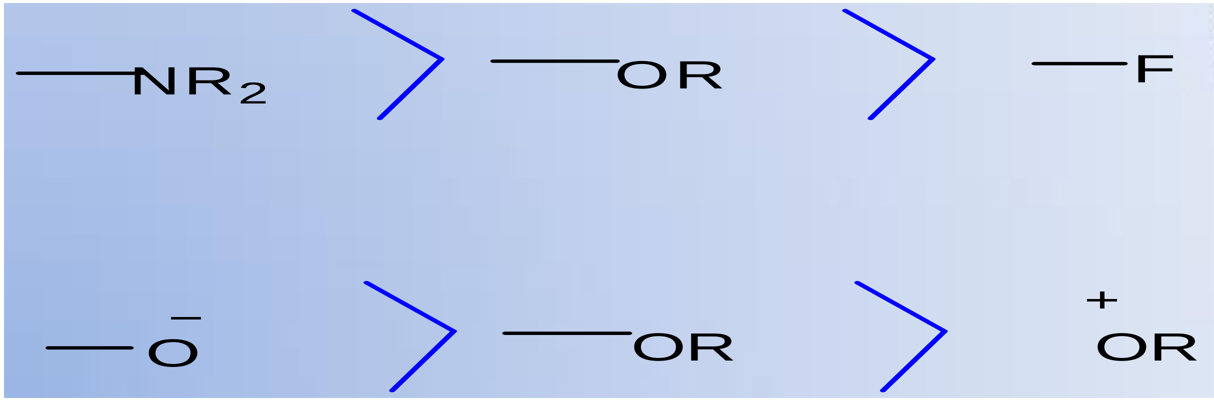

O
C
H
>
O
C
Cl
>
O
C
OR
>
O
C
NR2
>
O
C
O
–


O
+
N
O
–
>
O
S
OH
O
>
O
S
R
O


CN
>
O
S
NH2
O

+M Effect: Here, due to the lone pair or –charge in the p orbital of the first atom, the electrons are donated to the conjugated system away from itself. The further attached atoms or groups shall enhance the +M if they push by +I or +M effect, but will decrease the +M effect if they are electron withdrawing by –I or -M effect.

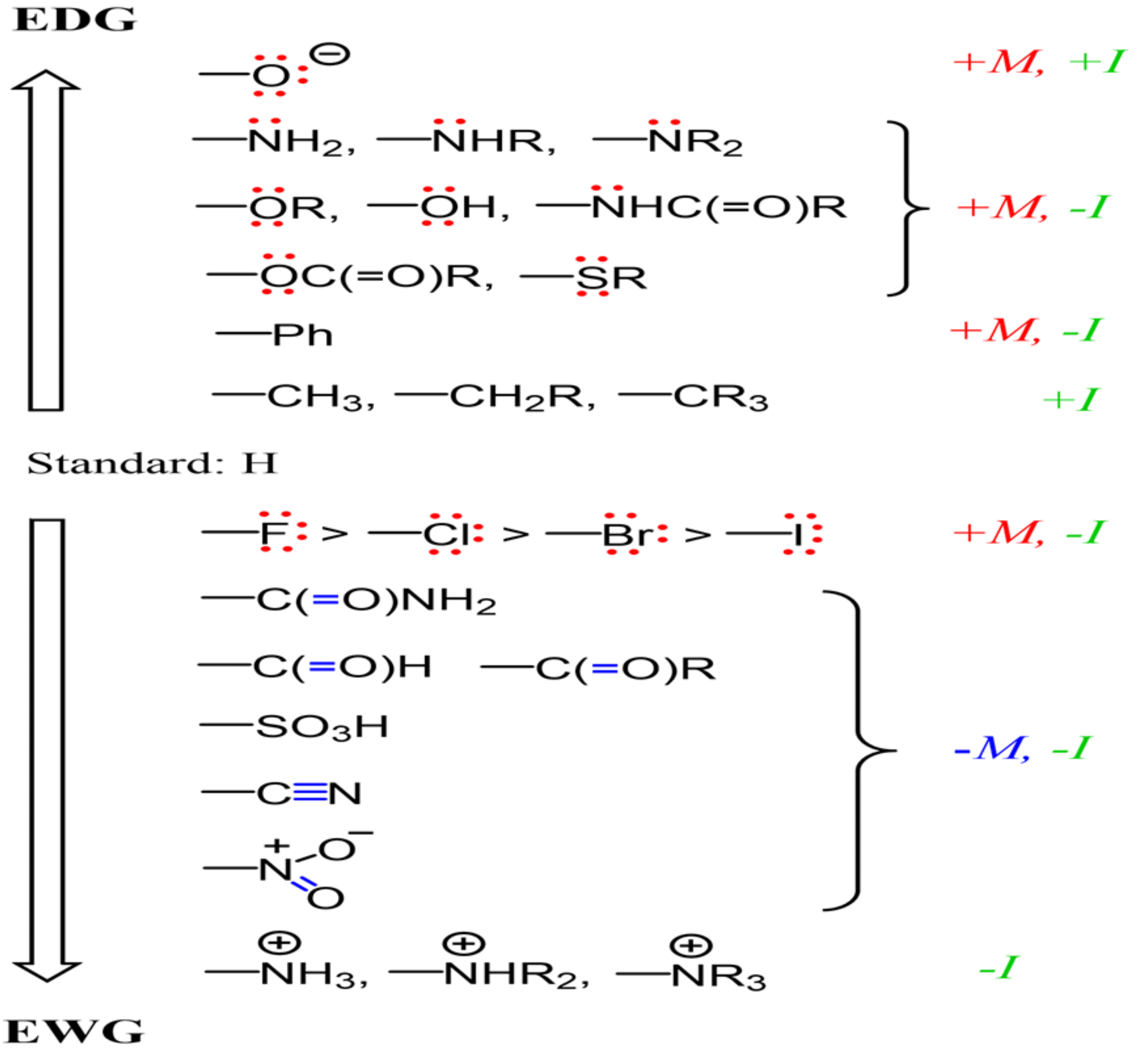
For example, the order of +M effect between the following groups is
-N(CH_3)$_2$ > -NH-CH_3 > -NH$_2$ > -NH-COCH$_3$



$$-NR_2 > -OR > -F$$

$$-\overset{-}{O} > -OR > \overset{+}{O}R$$

Inductive and Resonance (Mesomeric) Effects



EDG

$-\ddot{O}:^{\ominus}$ +*M*, +*I*

$-\ddot{N}H_2$, $-\ddot{N}HR$, $-\ddot{N}R_2$

$-\ddot{O}R$, $-\ddot{O}H$, $-\ddot{N}HC(=O)R$ +*M*, -*I*

$-\ddot{O}C(=O)R$, $-\ddot{S}R$

$-Ph$ +*M*, -*I*

$-CH_3$, $-CH_2R$, $-CR_3$ +*I*

Standard: H

$-\ddot{F}: > -\ddot{Cl}: > -\ddot{Br}: > -\ddot{I}:$ +*M*, -*I*

$-C(=O)NH_2$

$-C(=O)H$ $-C(=O)R$

$-SO_3H$

$-C\equiv N$ -*M*, -*I*

$-\overset{+}{N}(-O^{-})=O$

$-\overset{\oplus}{N}H_3$, $-\overset{\oplus}{N}HR_2$, $-\overset{\oplus}{N}R_3$ -*I*

EWG

The +M effect is due to a lone pair.

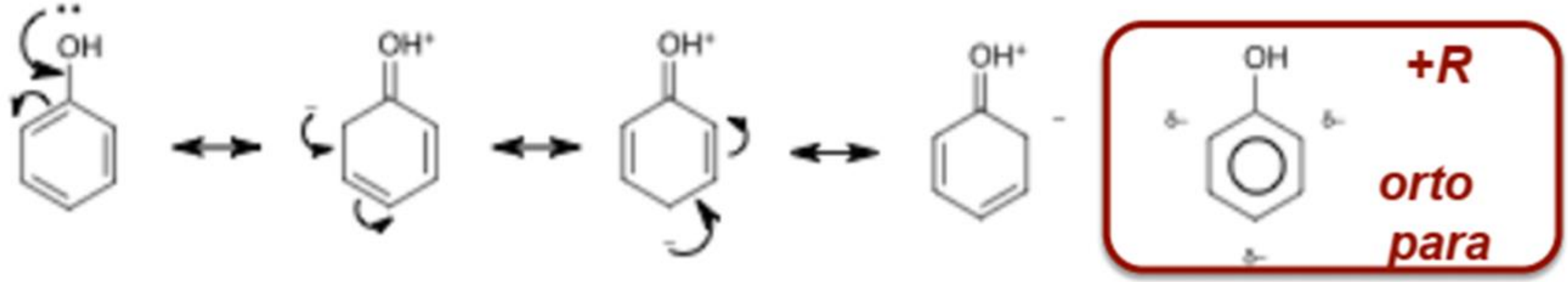
The -M effect is due to an electronegative atom and a π bond.

If in opposite directions, the resonance effect predominates.

Resonance and Inductive Effects of Various Functional Groups

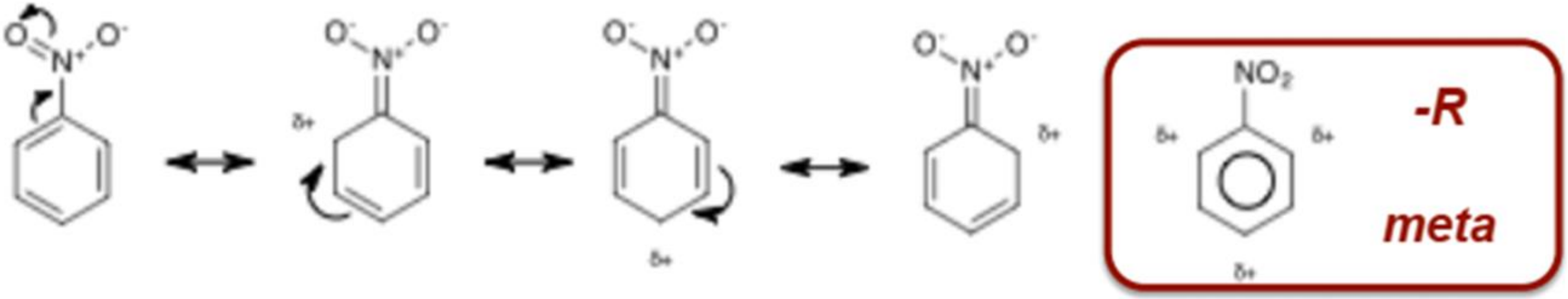
Inductive Effects: Electron-Withdrawing	**Inductive Effects: Electron-Donating**	**Resonance Effects Electron Withdrawing**	**Resonance Effects Electron Donating**
-NR_3^+ -NH_3^+	-O^- -COO^-	-COOR -COOH	-OH -OR
-COOH -COOR	-CH_3 -CHR_2 -CH_2R -CR_3	-COR -CHO	-NH_2 -NR_2
-NO_2 -CN		-SO_2R -SO_2NHR	-NHR_2 -SH
-CHO -COR		-NO_2 -CN	
-F -Cl -Br -I -CF_3		-Ar	
-OH -OR			
-NH_2			
-SH -SO_2R			

The new group is located either ortho, meta, or para to the existing substituent. The resonance effect of the first substituent determines the position of the second incoming substituent



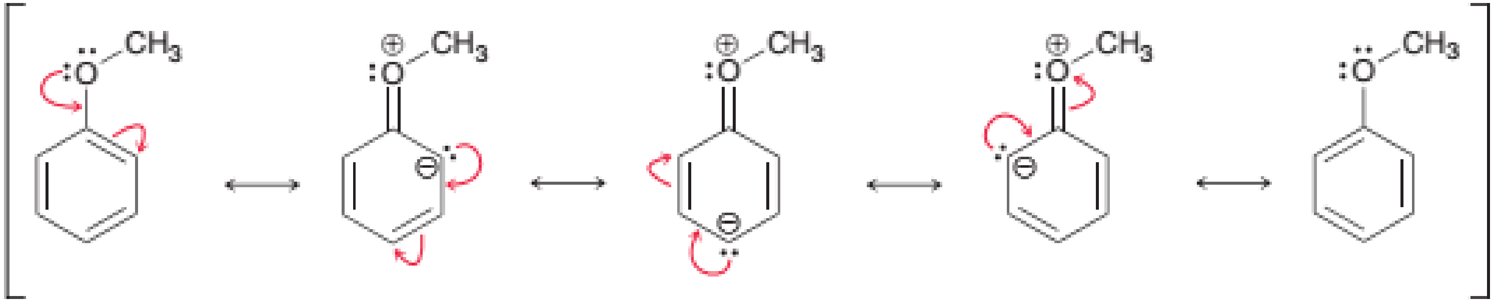
+R

orto
para

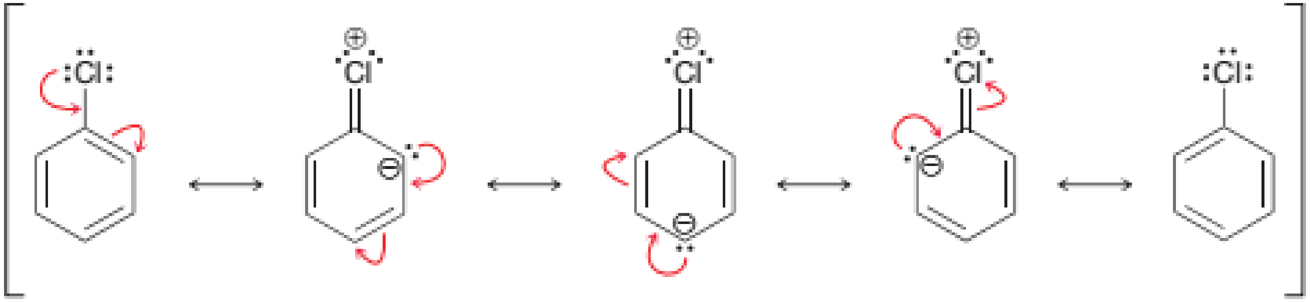


-R

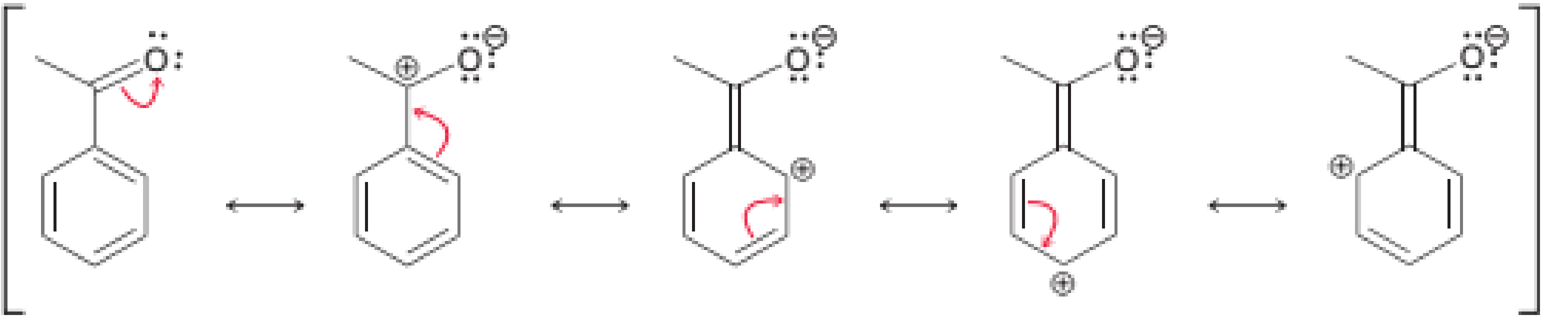
meta



Halogens are fairly electronegative (more so than carbon) and are therefore inductively electron *withdrawing*. When we draw the resonance structures, a different picture emerges.



Each of these groups withdraws electron density from the ring via resonance. For example:



Three of the resonance structures have a positive charge in the ring, indicating that the group is withdrawing electron density from the ring. This electron-withdrawing effect moderately deactivates the ring.

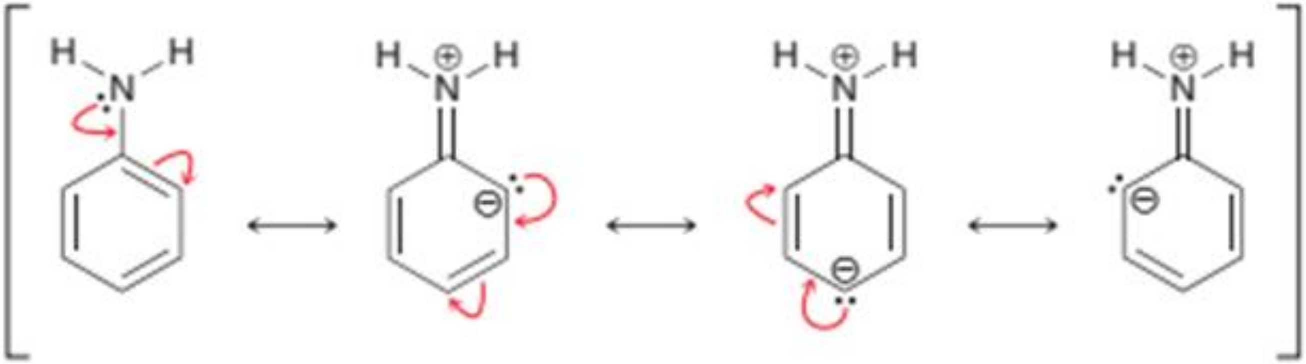
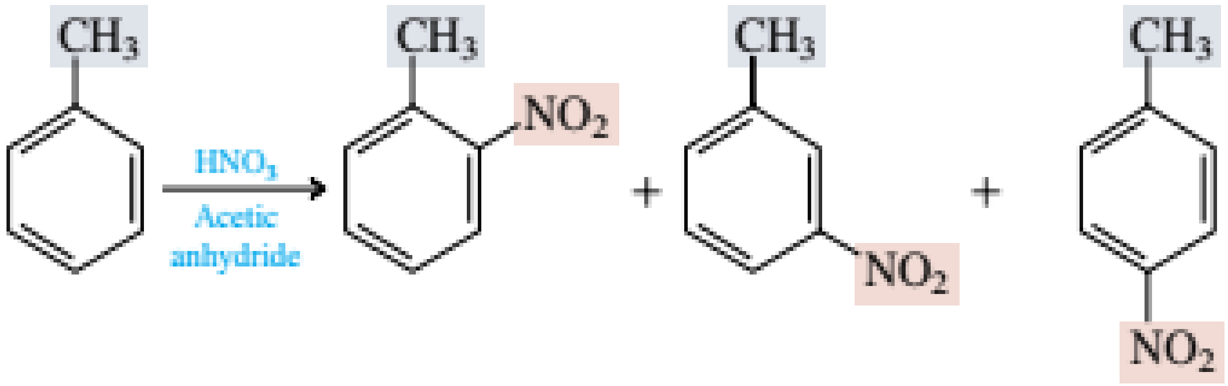


TABLE 12.2 Classification of Substituents in Electrophilic Aromatic Substitution Reactions

Effect on rate	Substituent		Effect on orientation
Very strongly activating	$-\ddot{N}H_2$	(amino)	Ortho, para-directing
	$-\ddot{N}HR$	(alkylamino)	
	$-\ddot{N}R_2$	(dialkylamino)	
	$-\ddot{\underset{..}{O}}H$	(hydroxyl)	
Strongly activating	$-\ddot{N}H\overset{O}{\overset{\|}{C}}R$	(acylamino)	Ortho, para-directing
	$-\ddot{\underset{..}{O}}R$	(alkoxy)	
	$-\ddot{\underset{..}{O}}\overset{O}{\overset{\|}{C}}R$	(acyloxy)	
Activating	$-R$	(alkyl)	Ortho, para-directing
	$-Ar$	(aryl)	
	$-CH{=}CR_2$	(alkenyl)	
Standard of comparison	$-H$	(hydrogen)	
Deactivating	$-X$ $(X = F, Cl, Br, I)$	(halogen)	Ortho, para-directing
	$-CH_2X$	(halomethyl)	
Strongly deactivating	$-\overset{O}{\overset{\|}{C}}H$	(formyl)	Meta-directing
	$-\overset{O}{\overset{\|}{C}}R$	(acyl)	
	$-\overset{O}{\overset{\|}{C}}OH$	(carboxylic acid)	
	$-\overset{O}{\overset{\|}{C}}OR$	(ester)	
	$-\overset{O}{\overset{\|}{C}}Cl$	(acyl chloride)	
	$-C{\equiv}N$	(cyano)	
	$-SO_3H$	(sulfonic acid)	
Very strongly deactivating	$-CF_3$	(trifluoromethyl)	Meta-directing
	$-NO_2$	(nitro)	

Nitration of aniline and derirtaive

Three products are possible from nitration of toluene: *o*-nitrotoluene, *m*-nitrotoluene, and *p*-nitrotoluene. All are formed, but not in equal amounts. Together, the ortho- and para-substituted isomers make up 97% of the product mixture; the meta only 3%.



Toluene

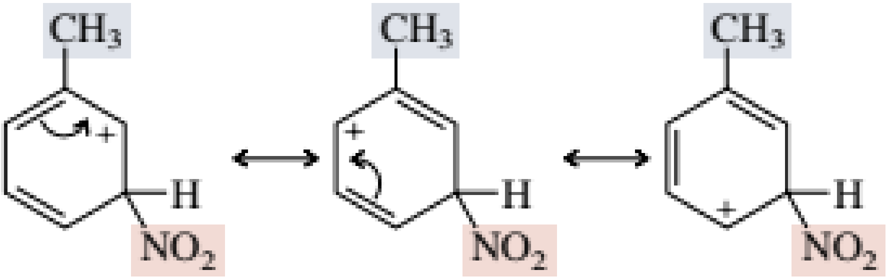
o-Nitrotoluene (63%)

m-Nitrotoluene (3%)

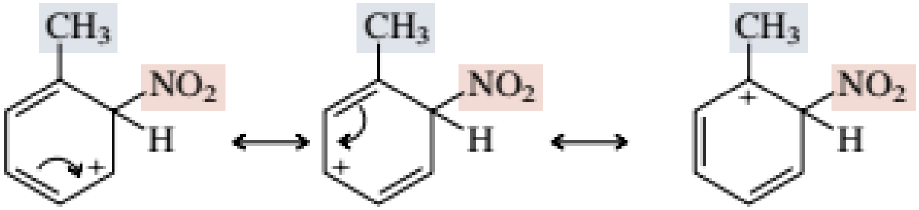
p-Nitrotoluene (34%)

Because substitution in toluene occurs primarily at positions ortho and para to methyl, we say that *a methyl substituent is an* **ortho, para director.**

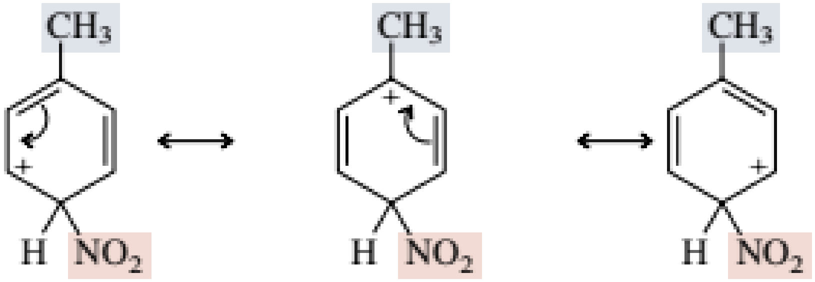
Meta attack

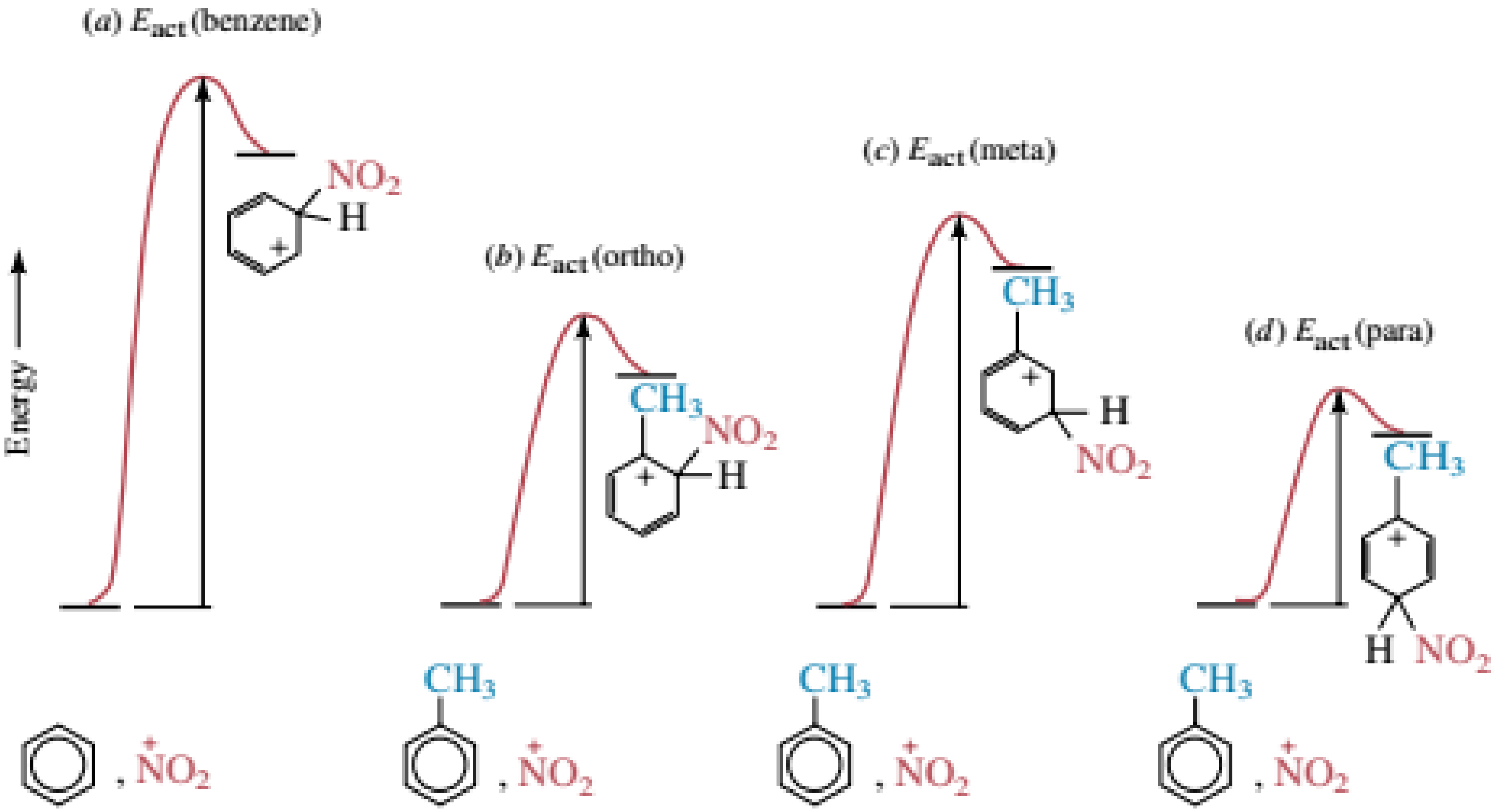


Ortho attack



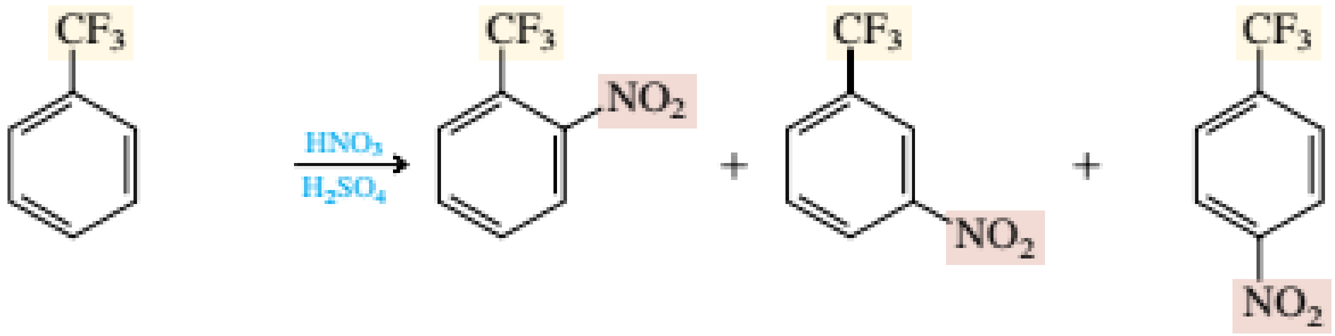
Para attack





(a) E_{act} (benzene)
(b) E_{act} (ortho)
(c) E_{act} (meta)
(d) E_{act} (para)
Energy
NO_2
H
+
CH_3
$\overset{+}{N}O_2$

Nitration of (trifluoromethyl)benzene, on the other hand, yields almost exclusively *m*-nitro(trifluoromethyl)benzene (91%). The ortho- and para-substituted isomers are minor components of the reaction mixture.



(Trifluoromethyl)benzene

o-Nitro(trifluoromethyl)benzene (6%)

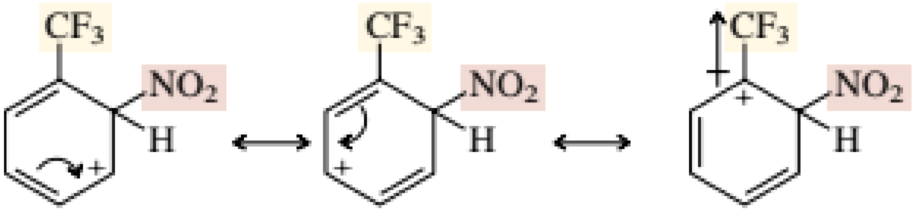
m-Nitro(trifluoromethyl)benzene (91%)

p-Nitro(trifluoromethyl)benzene (3%)

Because substitution in (trifluoromethyl)benzene occurs primarily at positions meta to the substituent, we say that *a trifluoromethyl group is a* **meta director.**

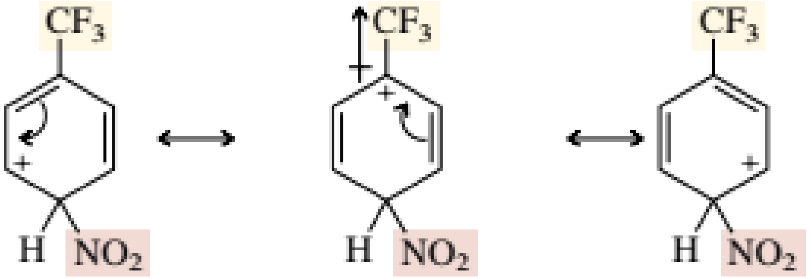
The regioselectivity of substitution, like the rate, is strongly affected by the substituent. In the following several sections we will examine the relationship between the structure of the substituent and its effect on rate and regioselectivity of electrophilic aromatic substitution.

Ortho attack



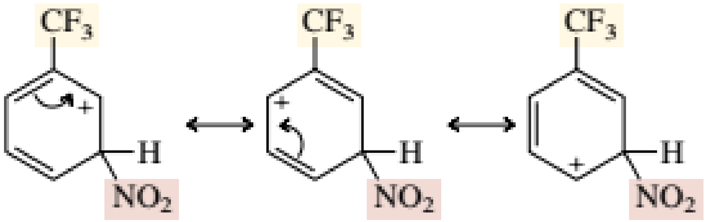
Positive charge on carbon bearing trifluoromethyl group; very unstable

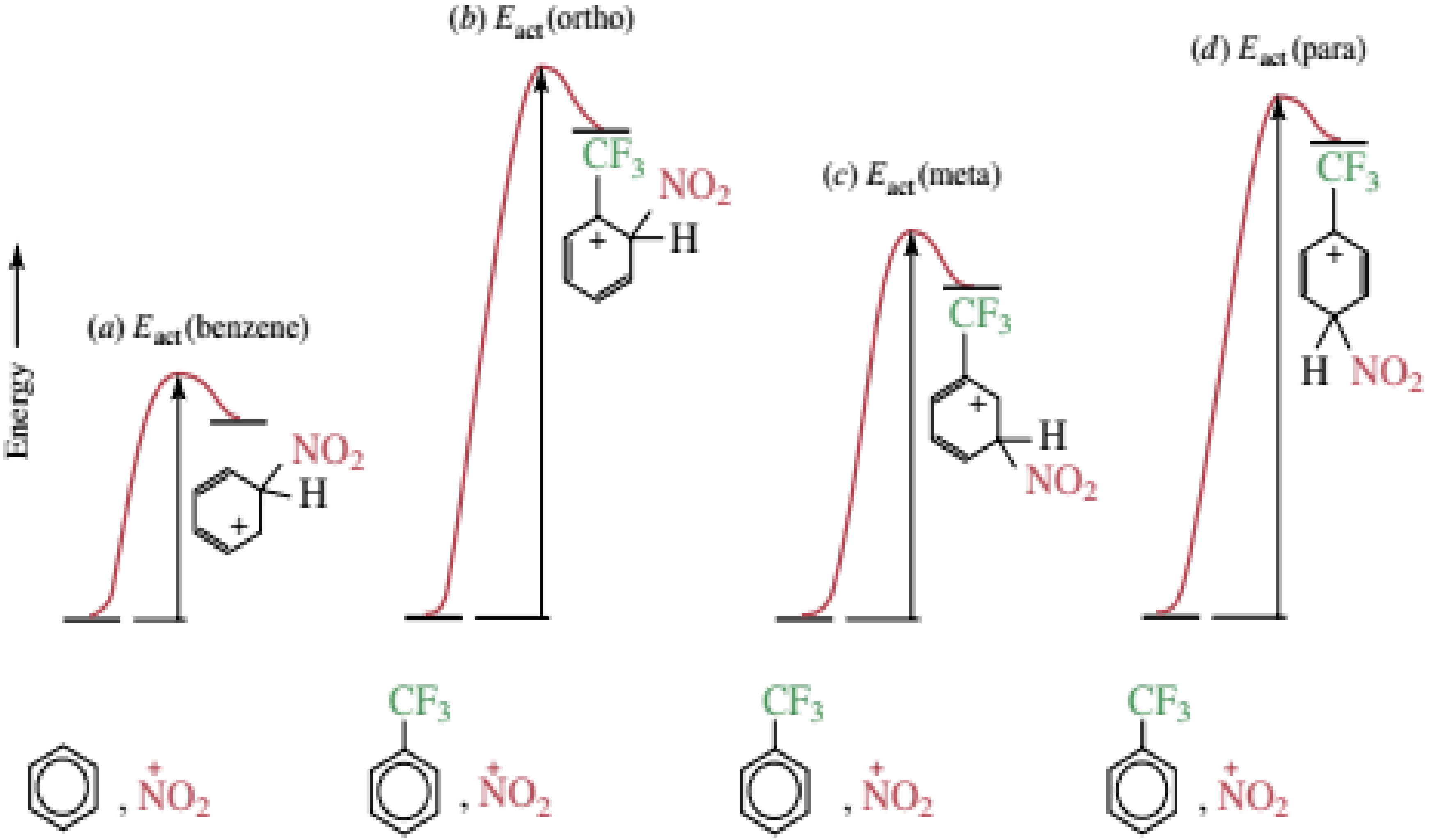
Para attack



Positive charge on carbon bearing trifluoromethyl group; very unstable

Meta attack

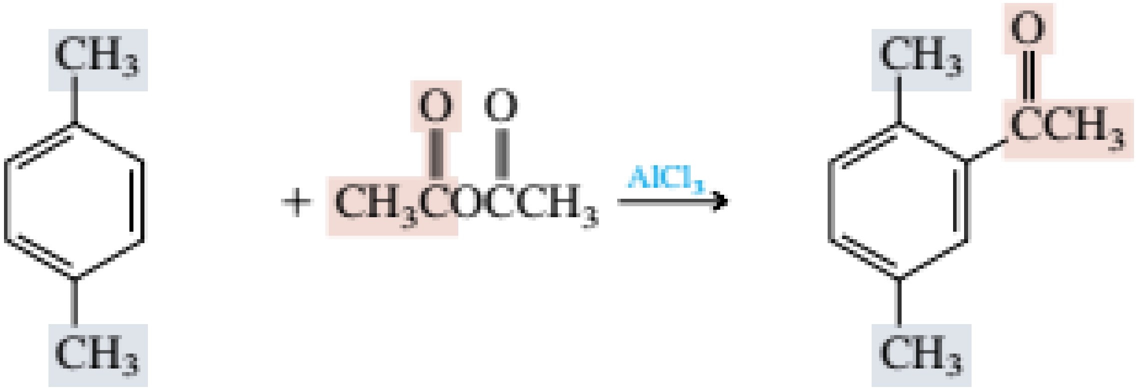



(a) E_{act} (benzene)
(b) E_{act} (ortho)
(c) E_{act} (meta)
(d) E_{act} (para)
Energy
NO_2
H
+
CF_3
$\overset{+}{N}O_2$

MULTIPLE SUBSTITUENT EFFECTS

When a benzene ring bears two or more substituents, both its reactivity and the site of further substitution can usually be predicted from the cumulative effects of its substituents.

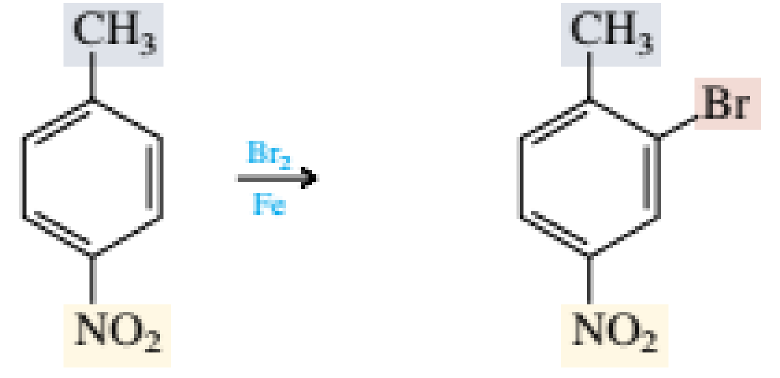
In the simplest cases all the available sites are equivalent, and substitution at any one of them gives the same product.



1,4-Dimethylbenzene
(*p*-xylene)

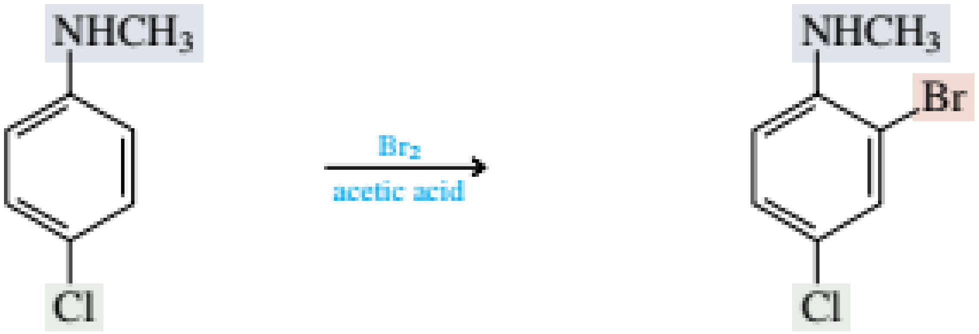
2,5-Dimethylacetophenone
(99%)

Often the directing effects of substituents reinforce each other. Bromination of *p*-nitrotoluene, for example, takes place at the position that is ortho to the ortho, para-directing methyl group and meta to the meta-directing nitro group.



p-Nitrotoluene 2-Bromo-4-nitrotoluene (86–90%)

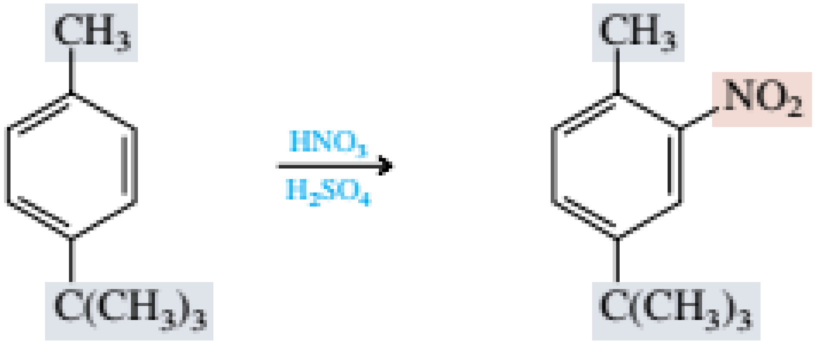
In almost all cases, including most of those in which the directing effects of individual substituents oppose each other, *it is the more activating substituent that controls the regioselectivity of electrophilic aromatic substitution*. Thus, bromination occurs ortho to the *N*-methylamino group in 4-chloro-*N*-methylaniline because this group is a very powerful activating substituent while the chlorine is weakly deactivating.



4-Chloro-*N*-methylaniline

2-Bromo-4-chloro-*N*-methylaniline (87%)

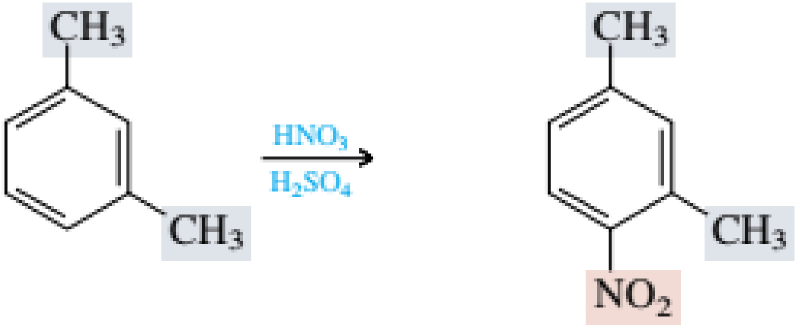
When two positions are comparably activated by alkyl groups, substitution usually occurs at the less hindered site. Nitration of *p-tert*-butyltoluene takes place at positions ortho to the methyl group in preference to those ortho to the larger *tert*-butyl group. This is an example of a *steric effect*.



p-tert-Butyltoluene

4-*tert*-Butyl-2-nitrotoluene (88%)

Nitration of *m*-xylene is directed ortho to one methyl group and para to the other.



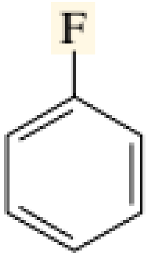
m-Xylene

2,4-Dimethyl-1-nitrobenzene (98%)

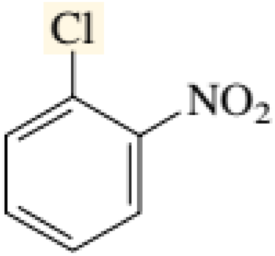
The ortho position between the two methyl groups is less reactive because it is more sterically hindered.

ARYL HALIDES

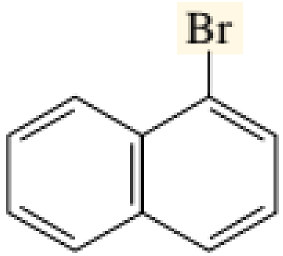
Aryl halides are compounds in which a halogen substituent is attached directly to an aromatic ring. Representative aryl halides include



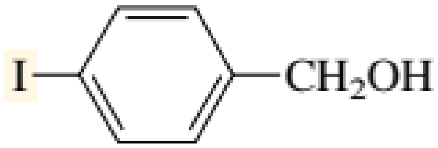
Fluorobenzene



1-Chloro-
2-nitrobenzene



1-Bromonaphthalene

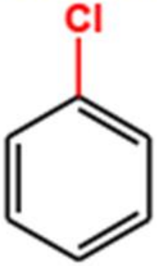


p-Iodobenzyl alcohol

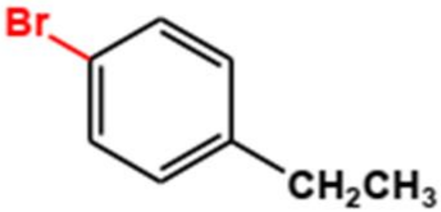
Halogen-containing organic compounds in which the halogen substituent is not directly bonded to an aromatic ring, even though an aromatic ring may be present, are not aryl halides. Benzyl chloride ($C_6H_5CH_2Cl$), for example, is not an aryl halide.

Aromatic Halogen Compounds

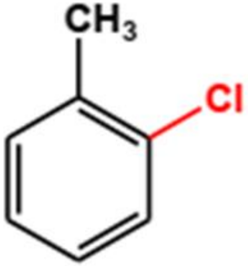
1- Aryl Halides: in which the halogen atom is directly attached to benzene ring. The substitution of halogen by nucleophiles is difficult due to strong bond between the halogen atom and benzene ring



Chlorobenzene

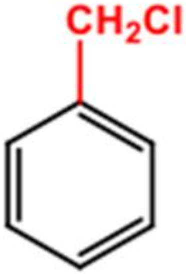


1-Bromo-4-ethylbenzene

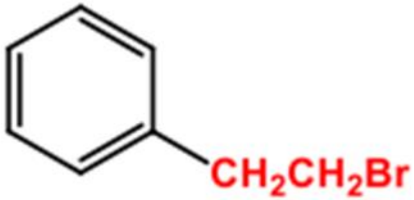


2-Chlorotoluene

2- Aralkyl Halides: in which the halogen atom is separated from benzene ring by one or more carbon atoms. The substitution of halogen by nucleophiles is easy as aliphatic halides.



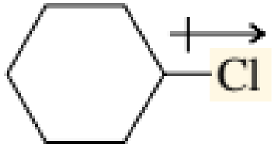
Benzyl chloride



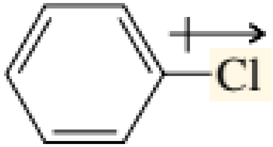
1-Bromo-2-phenylethane

Aryl halides resemble alkyl halides in many of their physical properties. All are practically insoluble in water and most are denser than water.

Aryl halides are polar molecules but are less polar than alkyl halides.



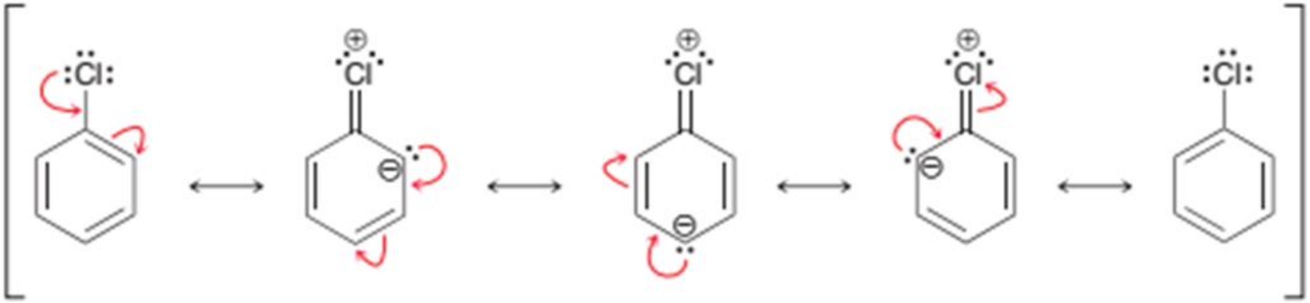
Chlorocyclohexane
μ 2.2 D



Chlorobenzene
μ 1.7 D

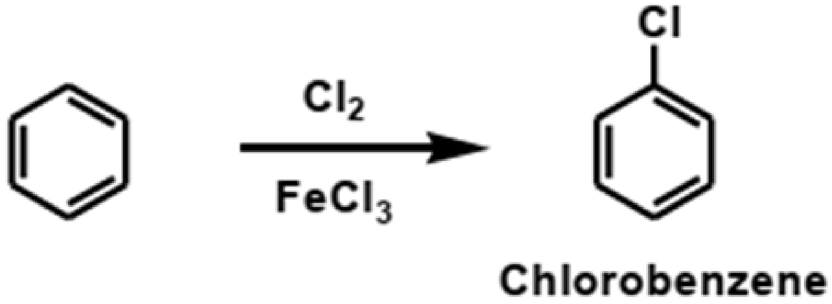
Since carbon is sp^2-hybridized in chlorobenzene, it is more electronegative than the sp^3-hybridized carbon of chlorocyclohexane. Consequently, the withdrawal of electron density away from carbon by chlorine is less pronounced in aryl halides than in alkyl halides, and the molecular dipole moment is smaller.

Halogens are fairly electronegative (more so than carbon) and are therefore inductively electron *withdrawing*. When we draw the resonance structures, a different picture emerges.

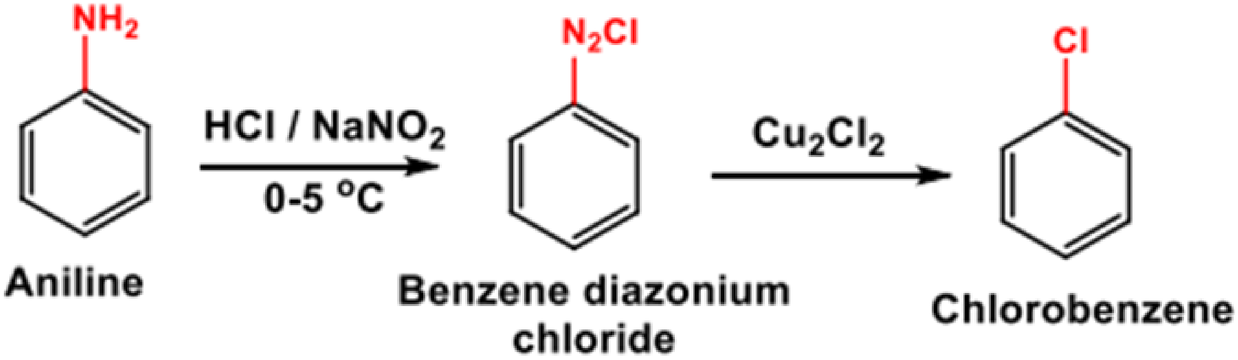


Methods of preparation of Aryl halides

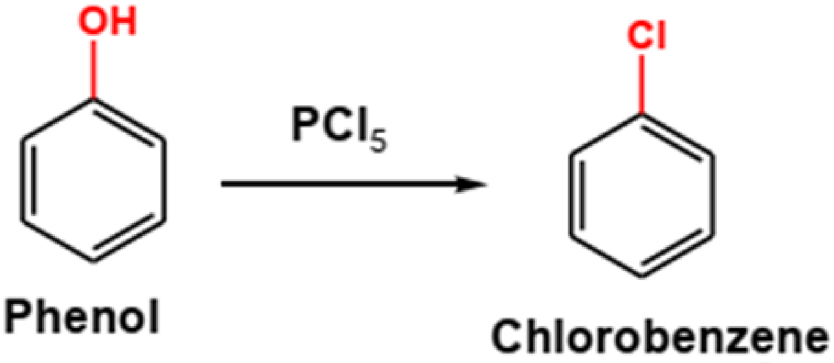
1) From benzene



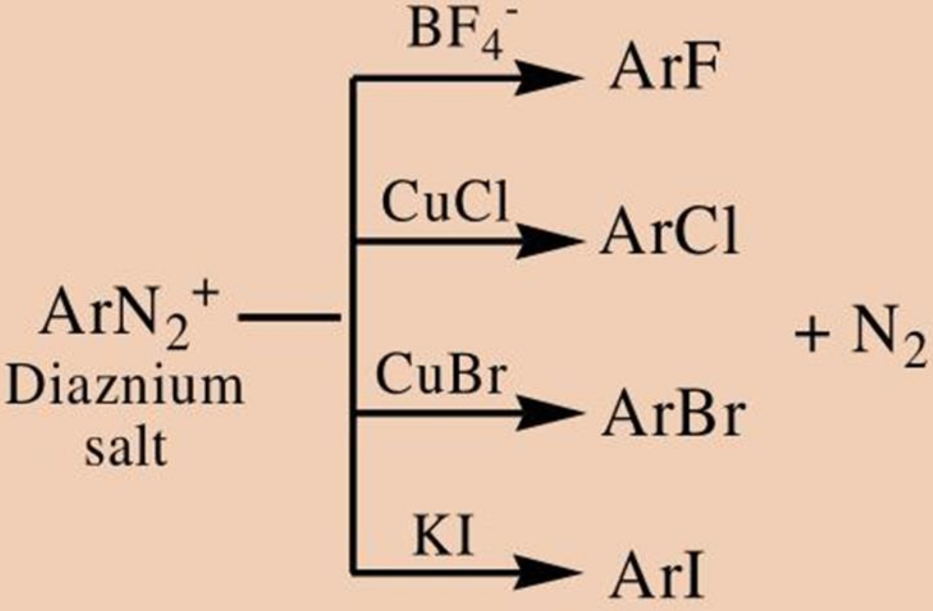
2) From aniline



3) From Phenol



2. From aryl diazonium salts



$ArN_2^+ \xrightarrow{BF_4^-} ArF + N_2$

$ArN_2^+ \xrightarrow{CuCl} ArCl + N_2$

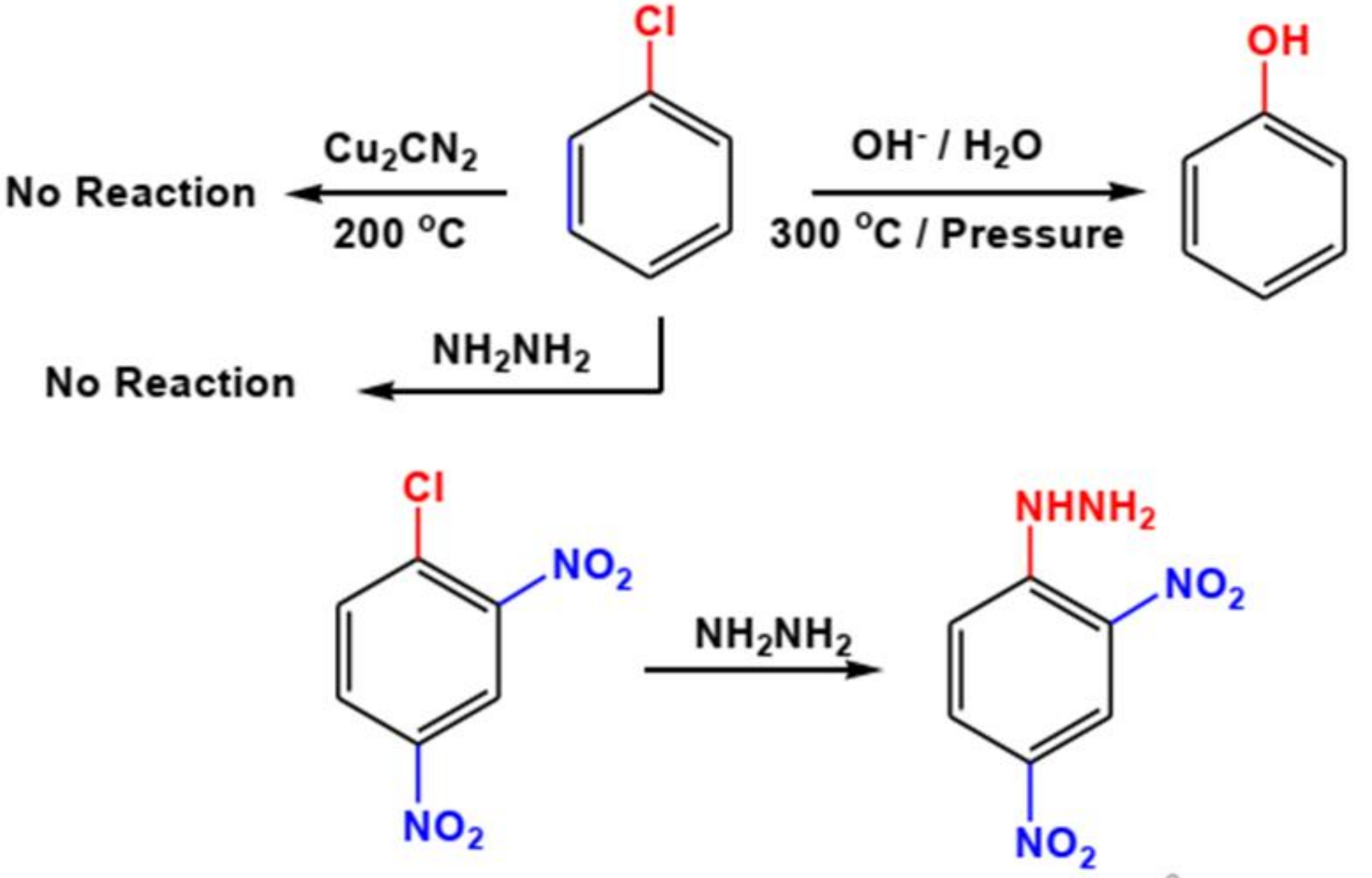
$ArN_2^+ \xrightarrow{CuBr} ArBr + N_2$

$ArN_2^+ \xrightarrow{KI} ArI + N_2$

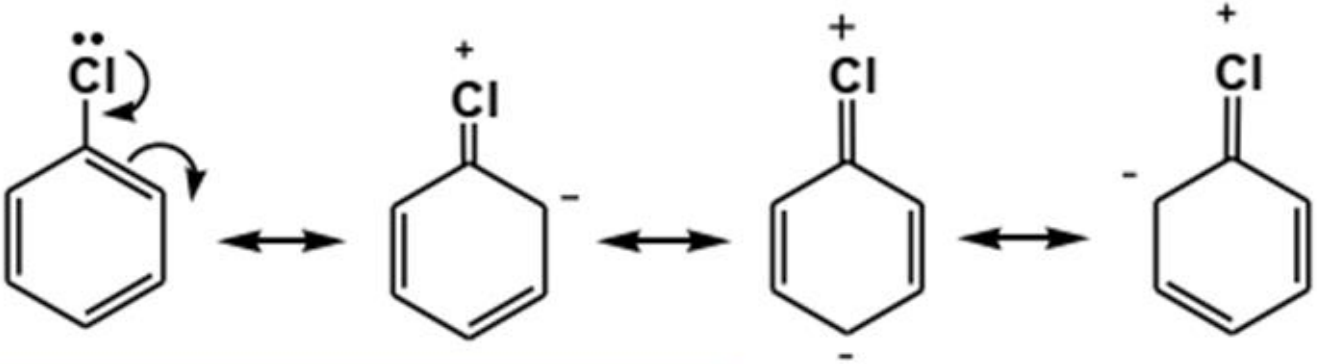
Diaznium salt

I) Nucleophilic substitution reactions of aryl halides

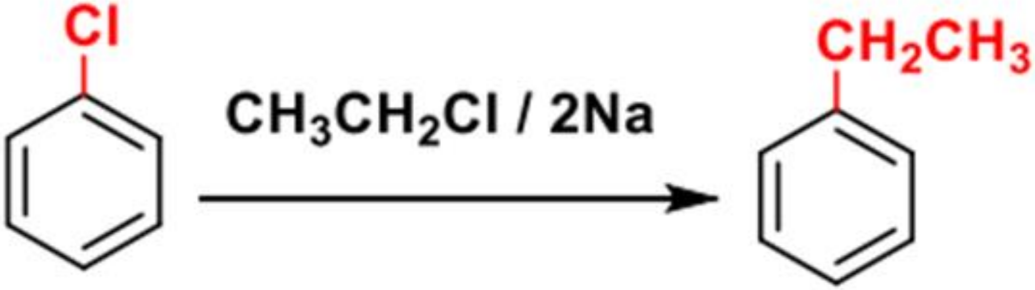
Chlorobenzene is less reactive towards nucleophilic substitution reactions. The reactions proceed under drastic condition or presence of Electron-Withdrawing groups



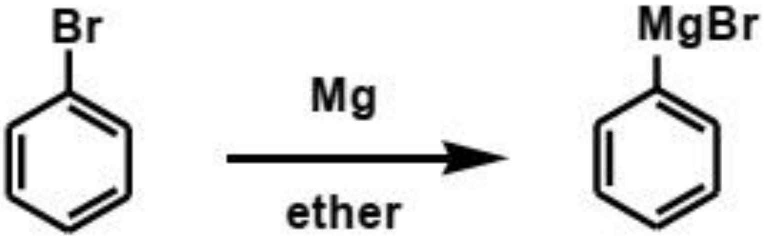
The low reactivity of chlorobenzene is due to resonance effect which increase the strength C-Cl bond (double bond character) as shown



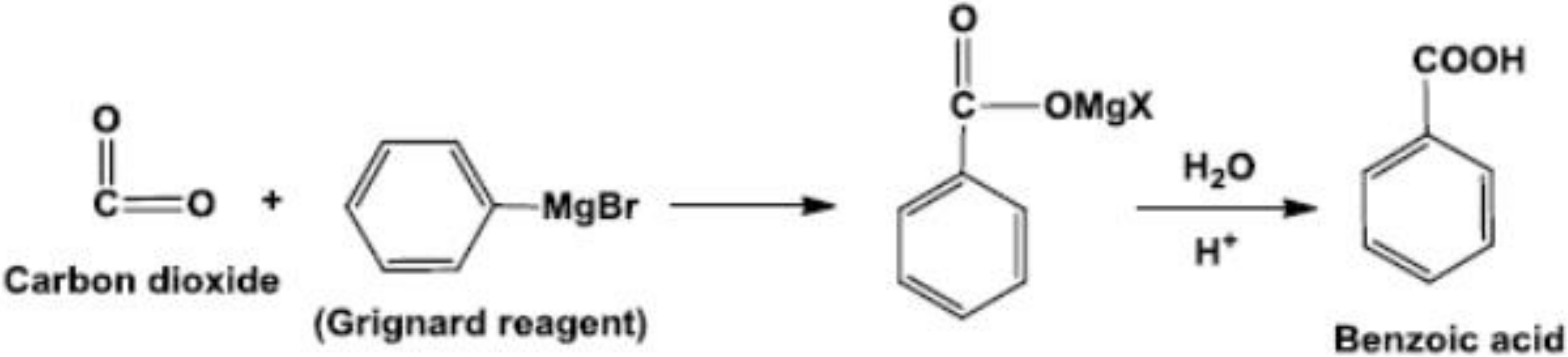
II) Wurtz-Fittig reaction

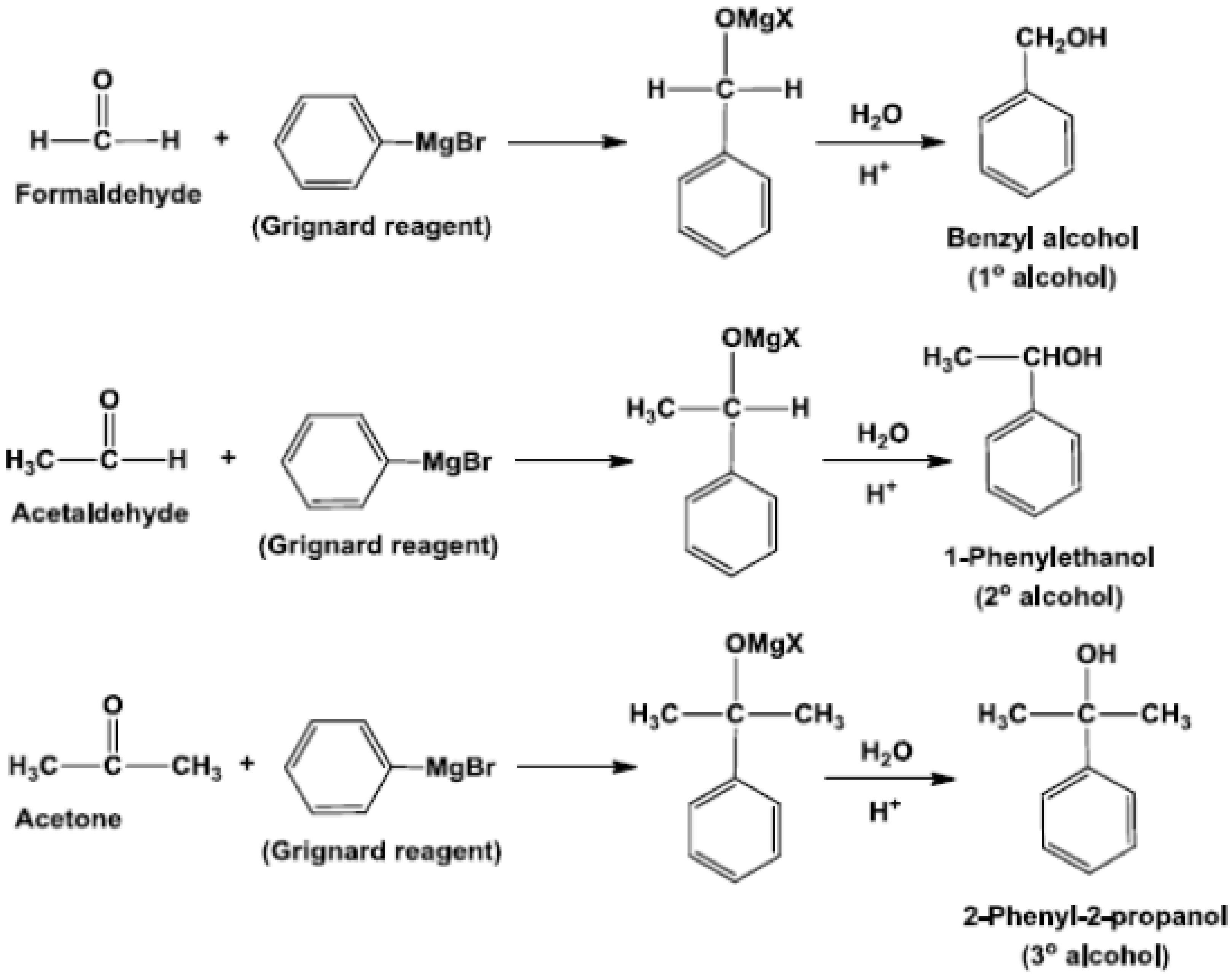


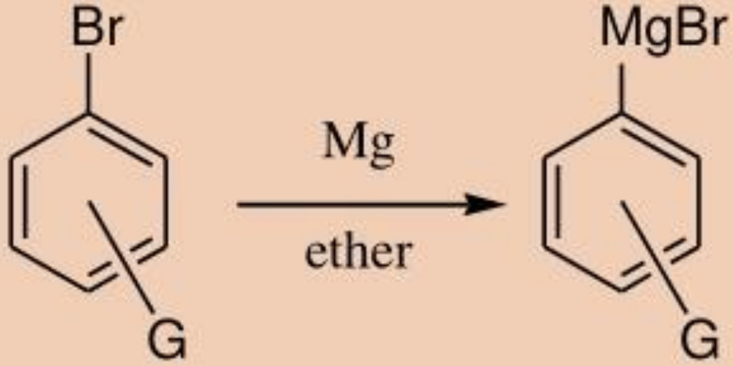
III) Reaction with magnesium metal (Grignard reagent)



Phenylmagnesium bromide
(Grignard reagent)

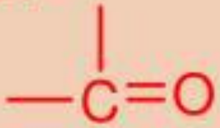



Formaldehyde
(Grignard reagent)
MgBr
OMgX
H₂O
H⁺
CH₂OH
Benzyl alcohol
(1° alcohol)
Acetaldehyde
(Grignard reagent)
MgBr
OMgX
H₂O
H⁺
H₃C—CHOH
1-Phenylethanol
(2° alcohol)
Acetone
(Grignard reagent)
MgBr
OMgX
H₂O
H⁺
OH
2-Phenyl-2-propanol
(3° alcohol)



G *may not be:*

$-COOH$


$-\overset{|}{C}=O$

$-OH$

$-COOR$

$-NH_2$

$-C\equiv N$

$-SO_3H$

$-NO_2$

and many others....

G *may be:*

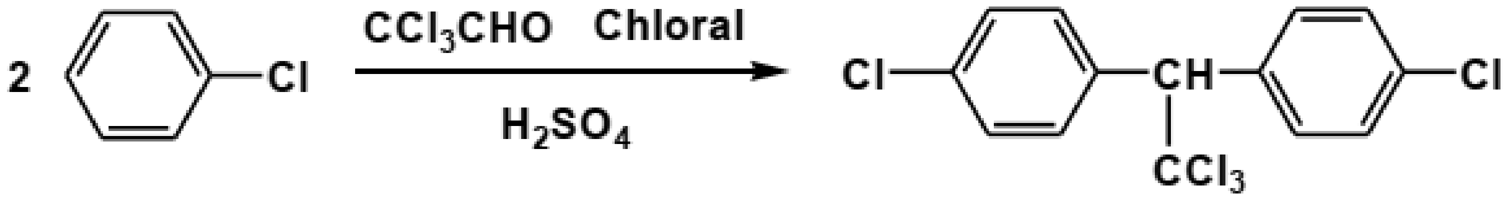
$-R$

$-OR$

$-Ar$

$-Cl$

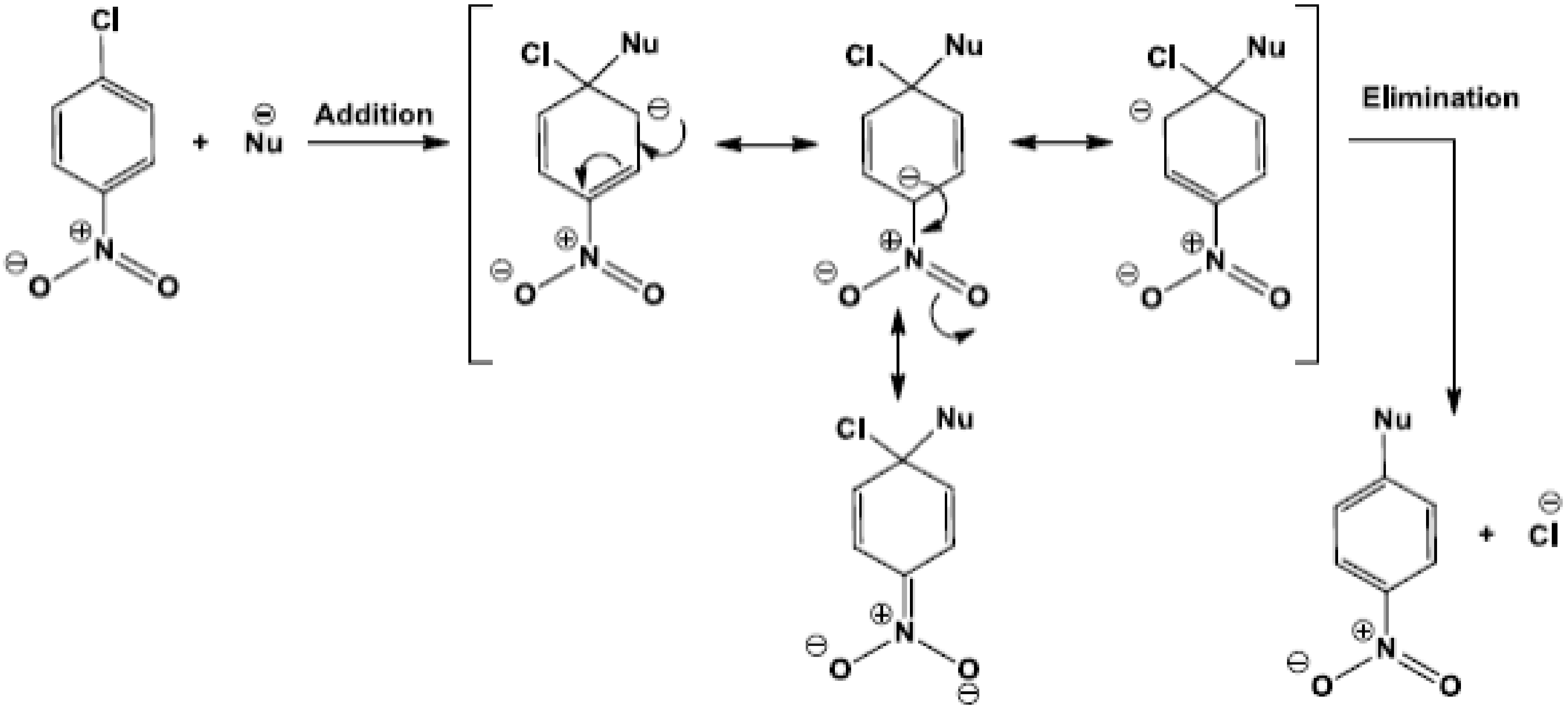
IV) D.D.T. formation



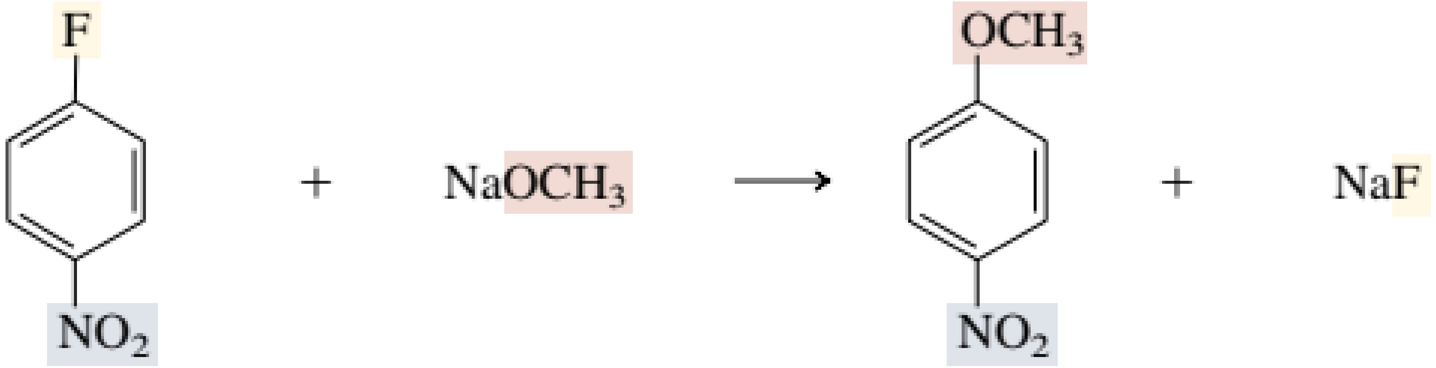
p,p`-Dichlorodiphenyl
trichloroethane (D.D.T)

V) The Addition-Elimination Mechanism

In this case, the benzene ring which has halogen atom must contain strong electron-withdrawing group(s) in ortho- and para- position with respect to the halogen atom. This group(s) will stabilize the anion formed after addition of nucleophile as shown in the given mechanism

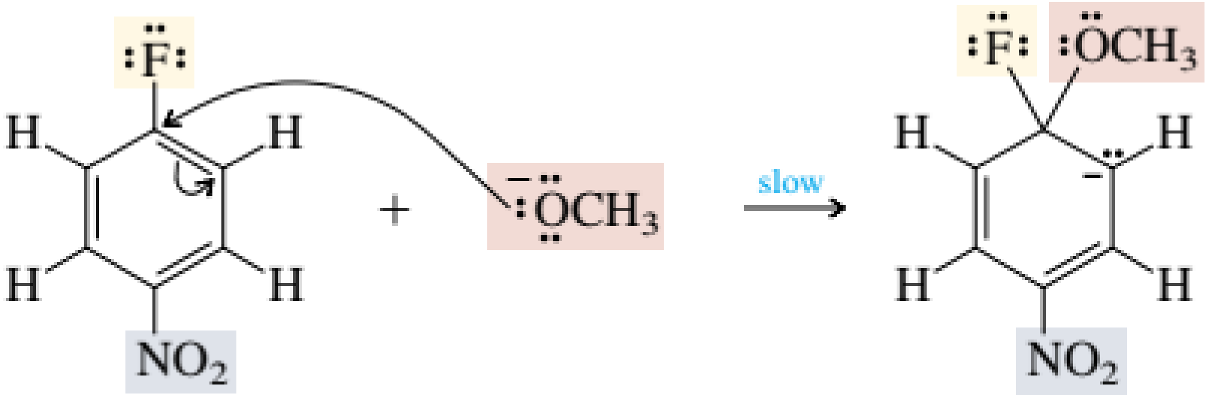


Overall reaction:



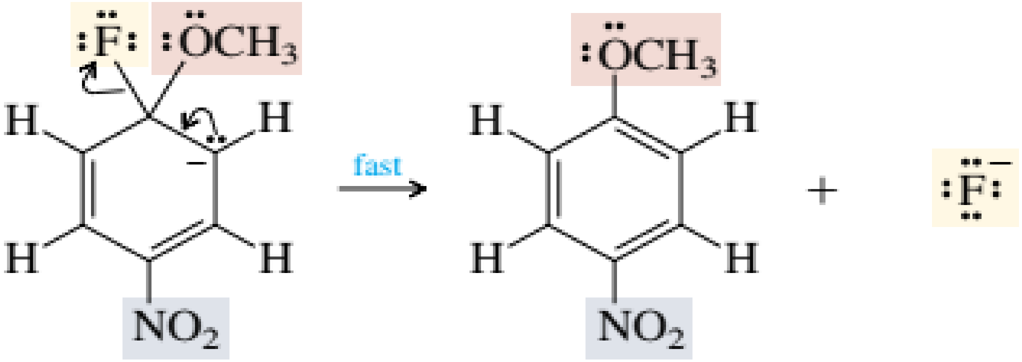
p-Fluoronitrobenzene Sodium methoxide *p*-Nitroanisole Sodium fluoride

Step 1: Addition stage. The nucleophile, in this case methoxide ion, adds to the carbo atom that bears the leaving group to give a cyclohexadienyl anion intermediate.



p-Fluoronitrobenzene Methoxide ion Cyclohexadienyl anion intermediate

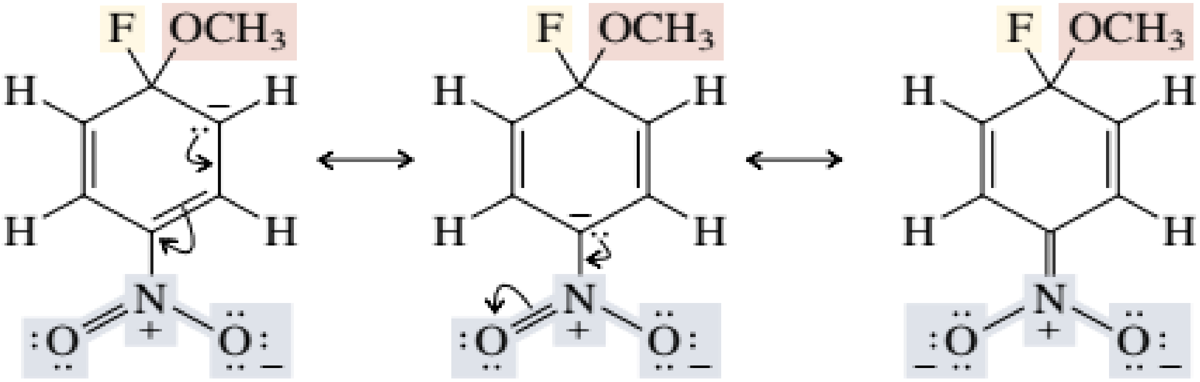
Step 2: Elimination stage. Loss of halide from the cyclohexadienyl intermediate restores the aromaticity of the ring and gives the product of nucleophilic aromatic substitution.



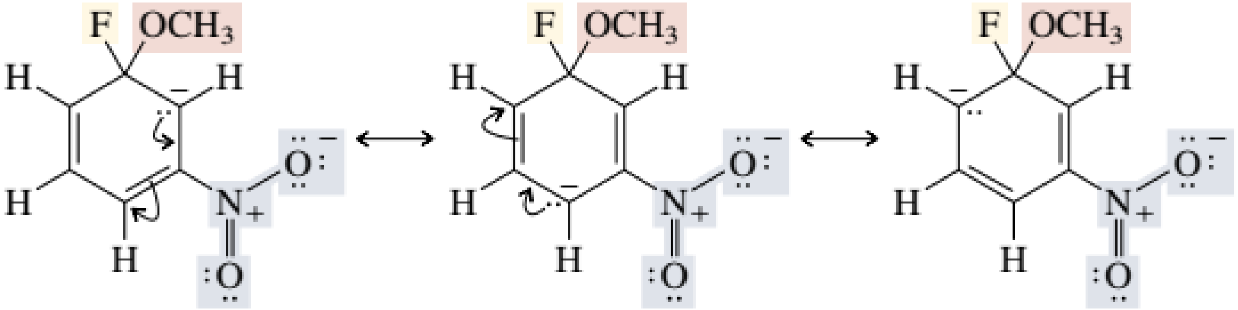
Cyclohexadienyl anion intermediate

p-Nitroanisole

Fluoride ion

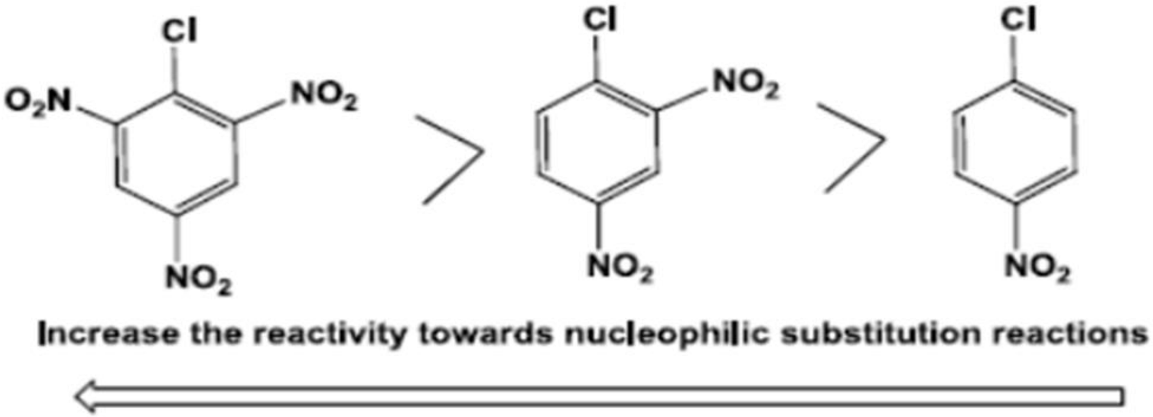


Most stable resonance structure; negative charge is on oxygen *m*-Fluoronitrobenzene reacts with sodium methoxide 10^5 times more slowly than its ortho and para isomers. According to the resonance description, direct conjugation of the negatively charged carbon with the nitro group is not possible in the cyclohexadienyl anion intermediate from *m*-fluoronitrobenzene, and the decreased reaction rate reflects the decreased stabilization afforded this intermediate.

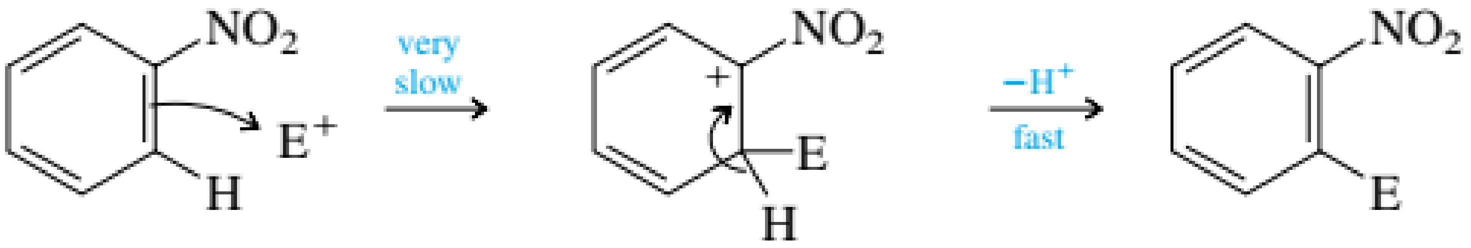


(Negative charge is restricted to carbon in all resonance forms)

As the number of electron-withdrawing groups on benzene ring increase (especially in ortho- and para- position with respect to the halogen atom), the reactivity towards nucleophilic substitution reaction will also increase and the vice-versa.



Before leaving this mechanistic discussion, we should mention that the addition–elimination mechanism for nucleophilic aromatic substitution illustrates a principle worth remembering. The words “activating” and “deactivating” as applied to substituent effects in organic chemistry are without meaning when they stand alone. When we say that a group is activating or deactivating, we need to specify the reaction type that is being considered. A nitro group is a strongly *deactivating* substituent in *electrophilic* aromatic substitution, where it markedly destabilizes the key cyclohexadienyl cation intermediate:



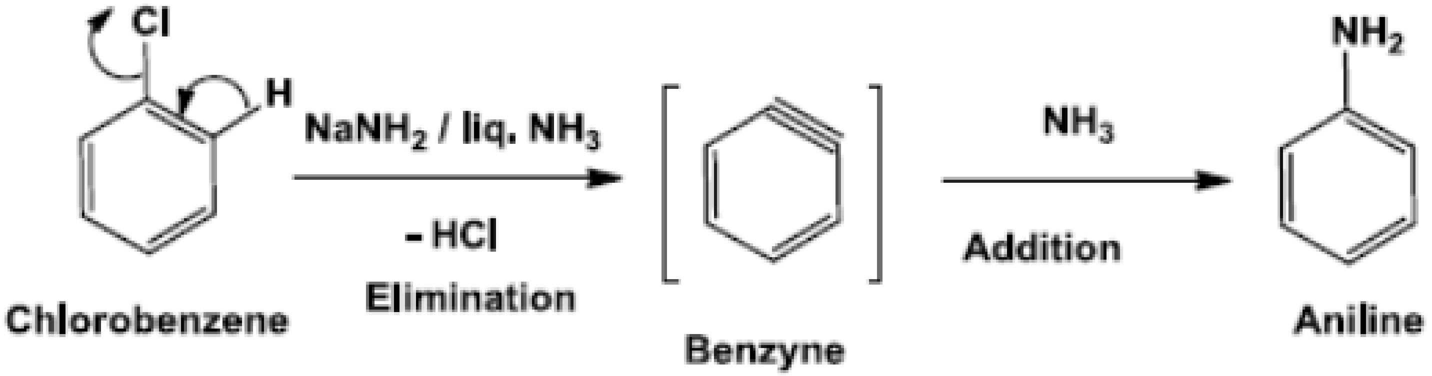
Nitrobenzene and an electrophile

Cyclohexadienyl cation intermediate; nitro group is destabilizing

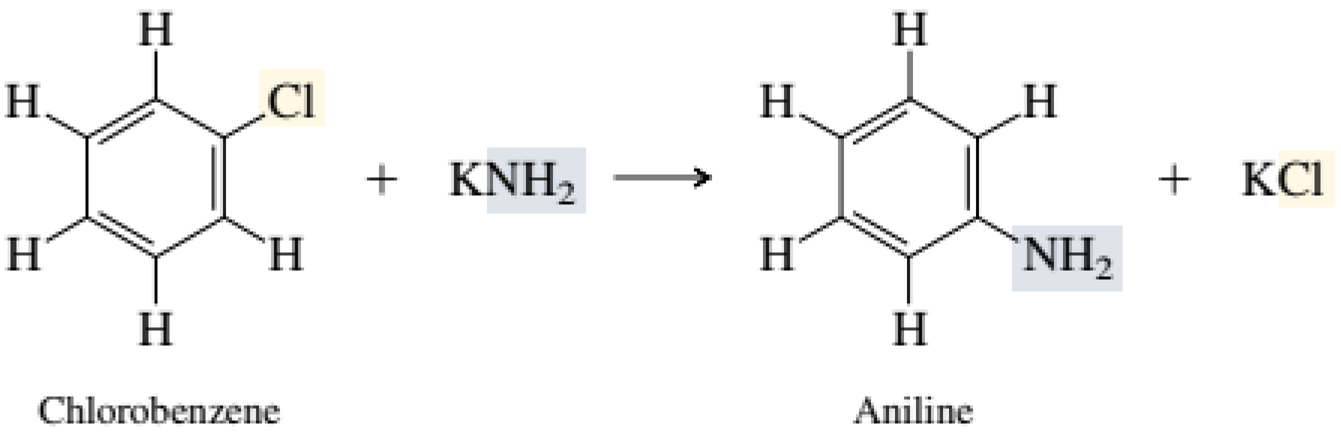
Product of electrophilic aromatic substitution

VI) The Elimination-Addition Mechanism

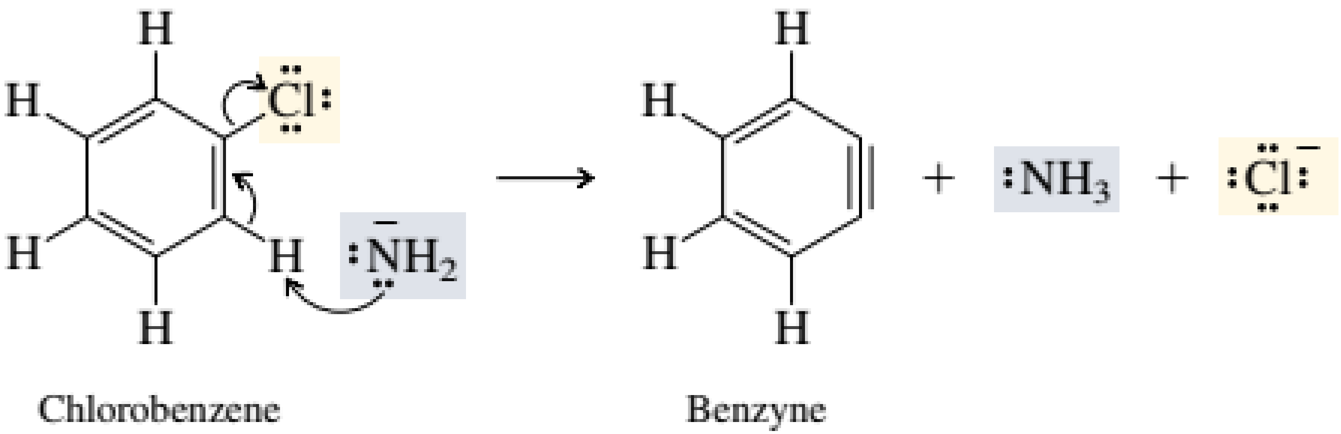
Reaction of halobenzene with strong base such as, sodium amide in liquid ammonia, (NaNH2 / liq. NH_3) will give aniline derivative. The reaction is proceeded by **benzyne intermediate as shown.**



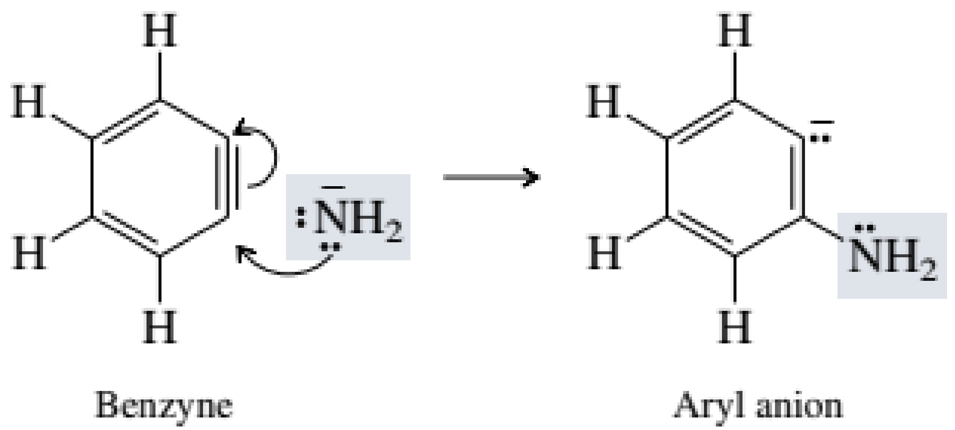
Overall reaction:



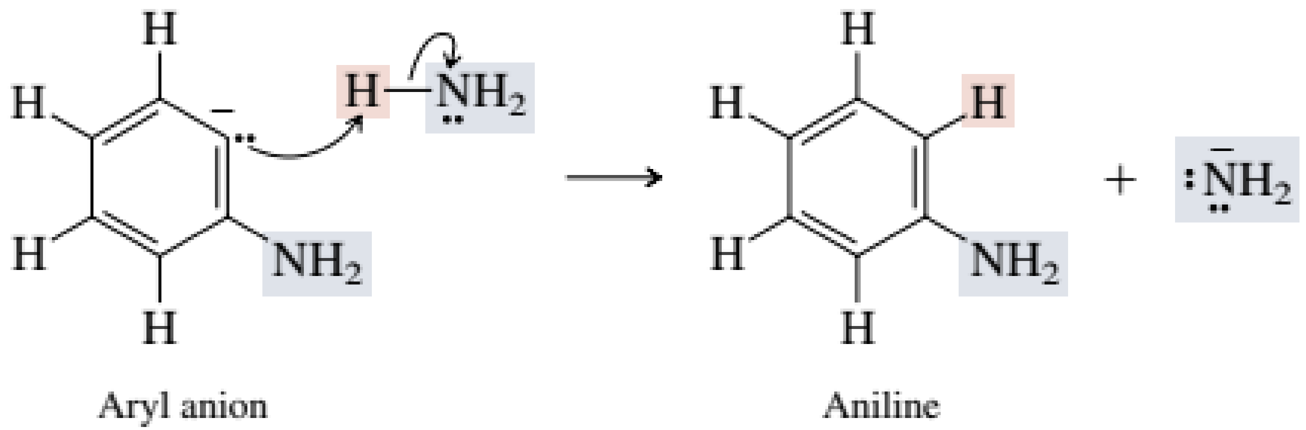
Step 1: Elimination stage. Amide ion is a very strong base and brings about the dehydrohalogenation of chlorobenzene by abstracting a proton from the carbon adjacent to the one that bears the leaving group. The product of this step is an unstable intermediate called *benzyne*.

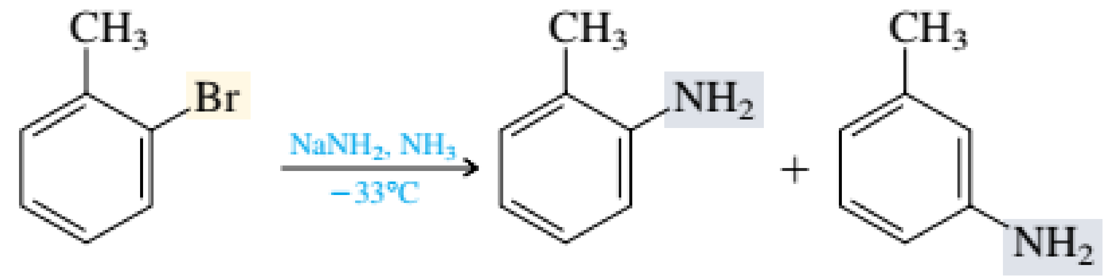


Step 2: Beginning of addition phase. Amide ion acts as a nucleophile and adds to one of the carbons of the triple bond. The product of this step is a carbanion.

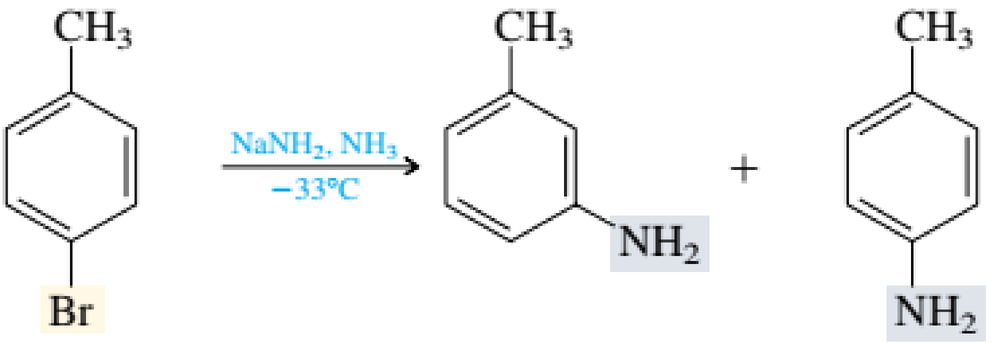


Step 3: Completion of addition phase. The aryl anion abstracts a proton from the ammonia used as the solvent in the reaction.



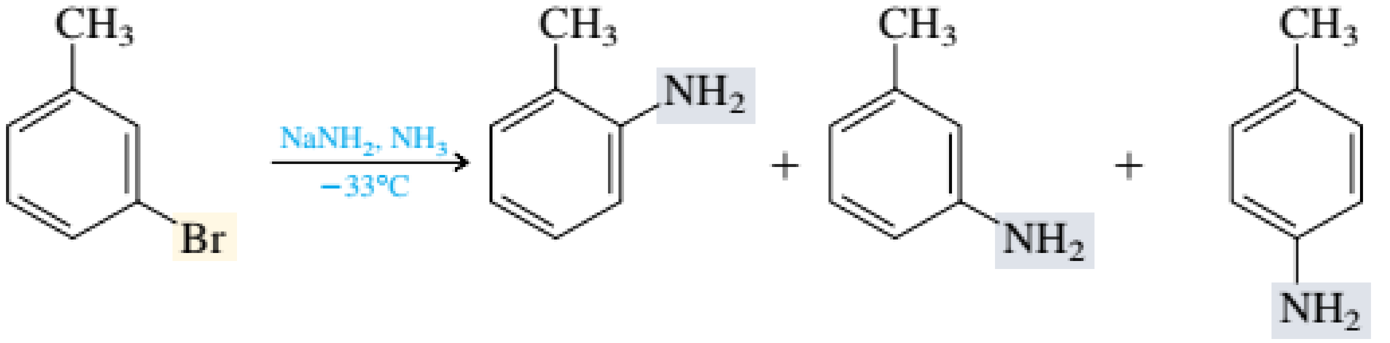


o-Bromotoluene *o*-Methylaniline *m*-Methylaniline

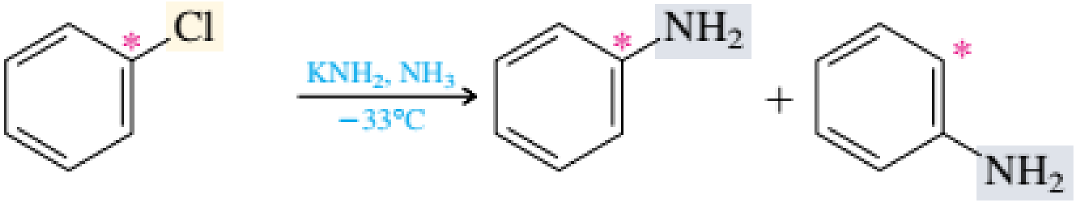


p-Bromotoluene *m*-Methylaniline *p*-Methylaniline

Three regioisomers (*o*-, *m*-, and *p*-methylaniline) were formed from *m*-bromotoluene.

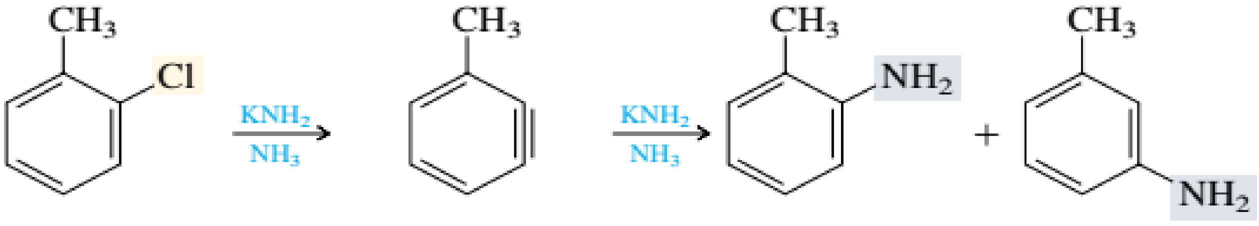


m-Bromotoluene *o*-Methylaniline *m*-Methylaniline *p*-Methylaniline



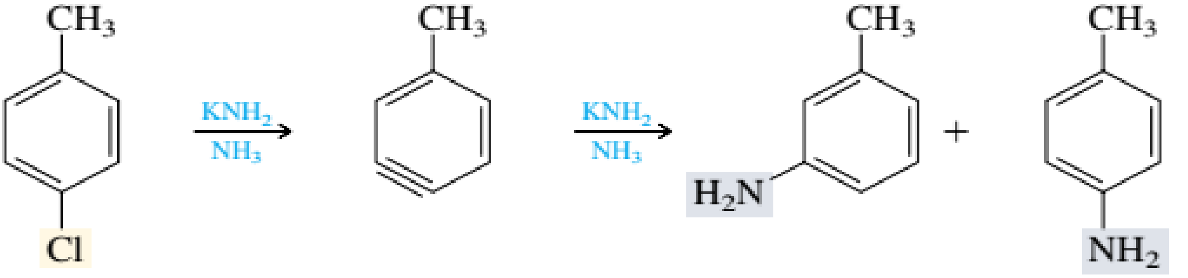
Chlorobenzene-1-^{14}C (* = ^{14}C) Aniline-1-^{14}C (48%) Aniline-2-^{14}C (52%)

Once the intermediacy of an aryne intermediate was established, the reason for the observed regioselectivity of substitution in *o*-, *m*-, and *p*-chlorotoluene became evident. Only a single aryne intermediate may be formed from *o*-chlorotoluene, but this aryne yields a mixture containing comparable amounts of *o*- and *m*-methylaniline.



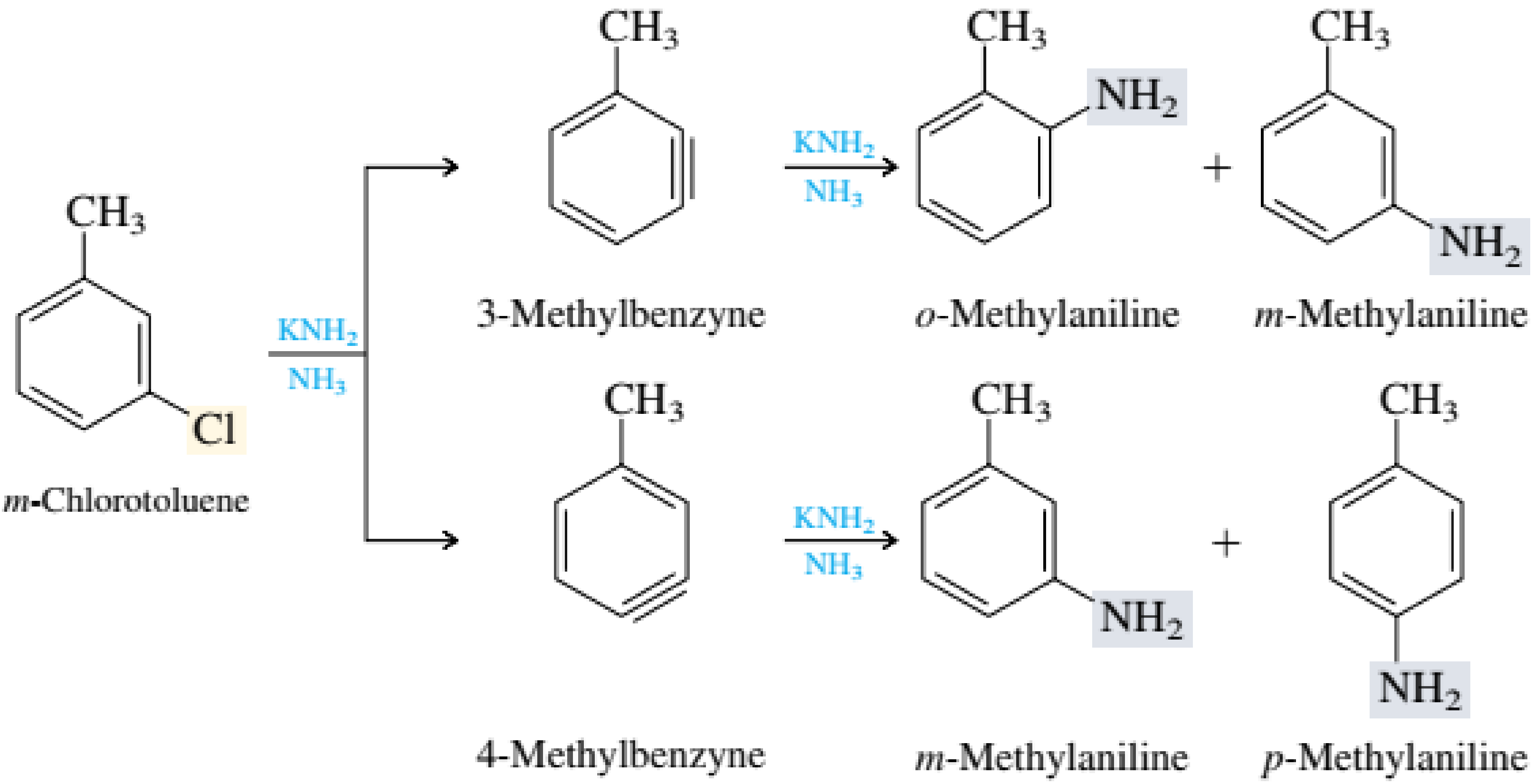
o-Chlorotoluene 3-Methylbenzyne *o*-Methylaniline *m*-Methylaniline

Similarly, *p*-chlorotoluene gives a single aryne, and this aryne gives a mixture of *m*- and *p*-methylaniline.



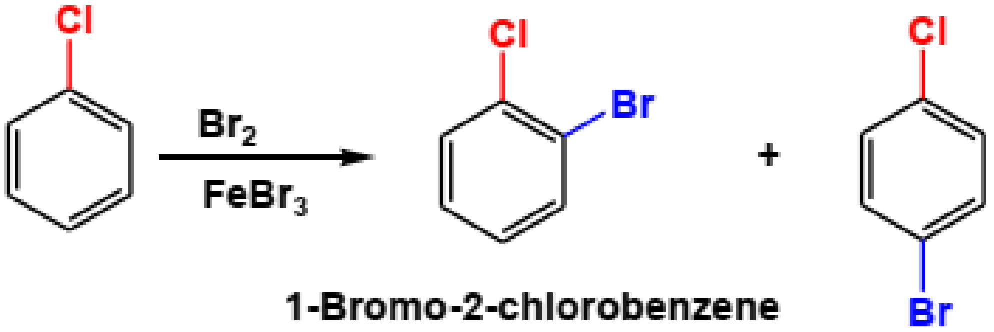
p-Chlorotoluene 4-Methylbenzyne *m*-Methylaniline *p*-Methylaniline

Two isomeric arynes give the three isomeric substitution products formed from *m*-chlorotoluene:



VII) Electrophilic substitution reactions

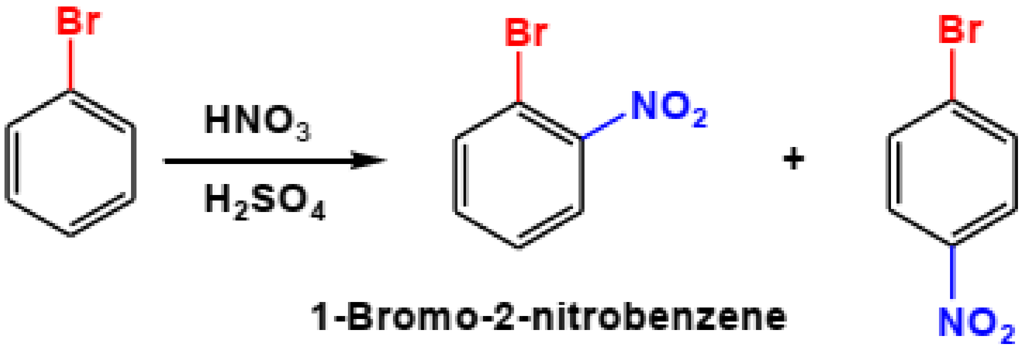
1) Halogenation



1-Bromo-2-chlorobenzene
(*o*-Bromochlorobenzene)

1-Bromo-4-chlorobenzene
(*p*-Bromochlorobenzene)

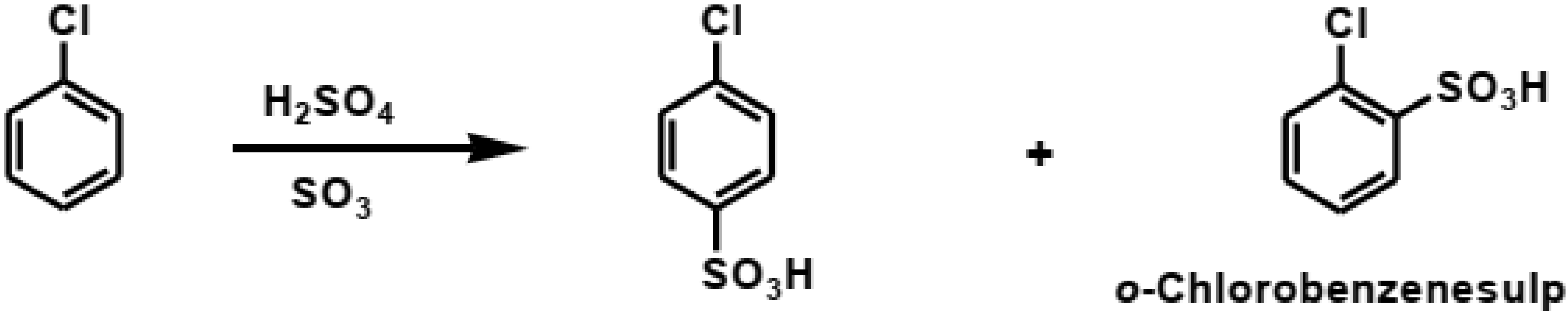
2) Nitration



1-Bromo-2-nitrobenzene
(*o*-Bromonitrobenzene)

1-Bromo-4-nitrobenzene
(*p*-Bromonitrobenzene)

3) Sulphonation



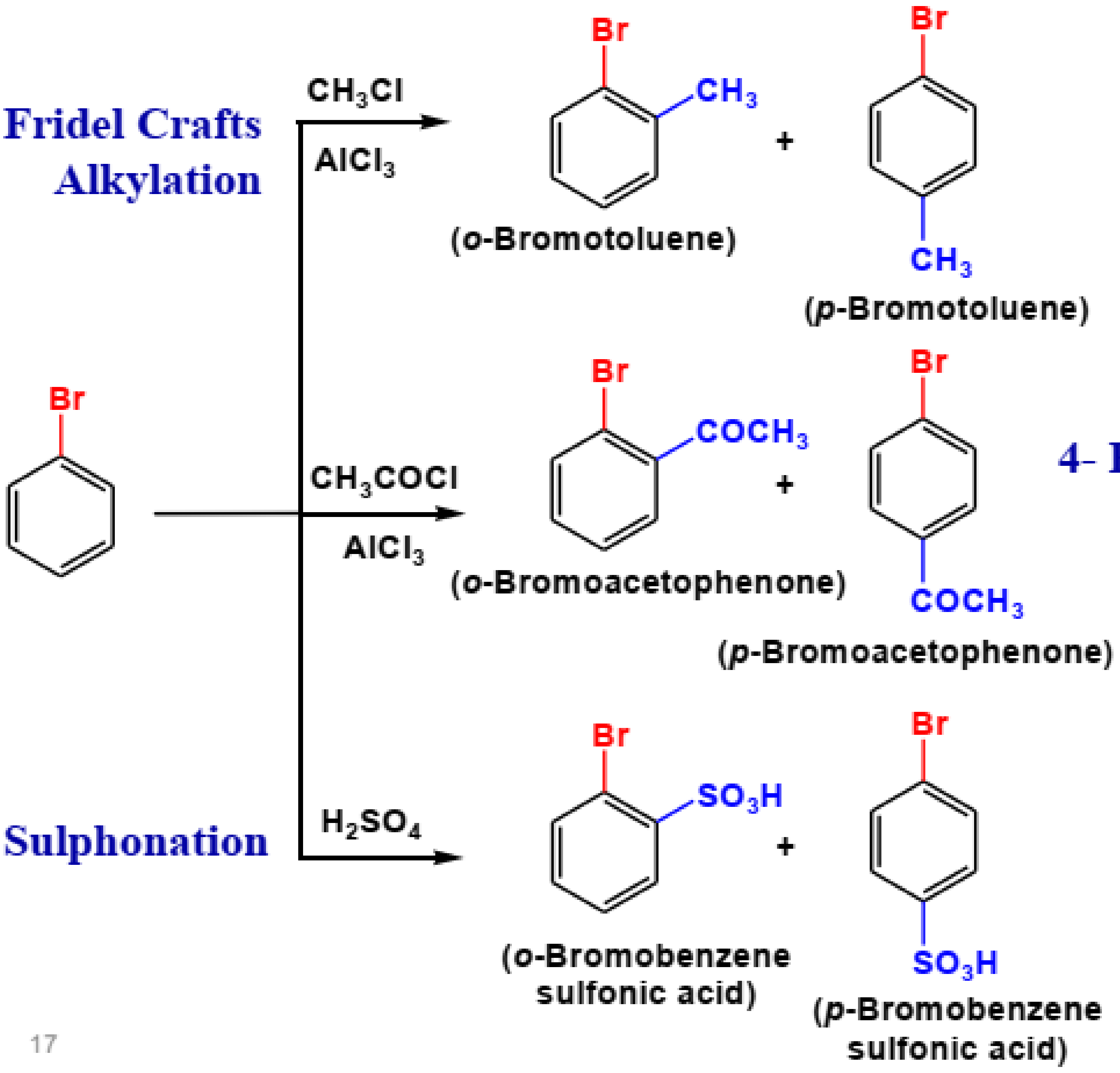
p-Chlorobenzenesulphonic acid

o-Chlorobenzenesulphonic acid

3- Fridel Crafts Alkylation

4- Fridel Crafts Acylation

5- Sulphonation



(*o*-Bromotoluene)

(*p*-Bromotoluene)

(*o*-Bromoacetophenone)

(*p*-Bromoacetophenone)

(*o*-Bromobenzene sulfonic acid)

(*p*-Bromobenzene sulfonic acid)

23.9 DIELS–ALDER REACTIONS OF BENZYNE

Alternative methods for its generation have made it possible to use benzyne as an intermediate in a number of synthetic applications. One such method involves treating *o*-bromofluorobenzene with magnesium, usually in tetrahydrofuran as the solvent.

o-Bromofluorobenzene Benzyne

The reaction proceeds by formation of the Grignard reagent from *o*-bromofluorobenzene. Since the order of reactivity of magnesium with aryl halides is ArI > ArBr > ArCl > ArF, the Grignard reagent has the structure shown and forms benzyne by loss of the salt FMgBr: