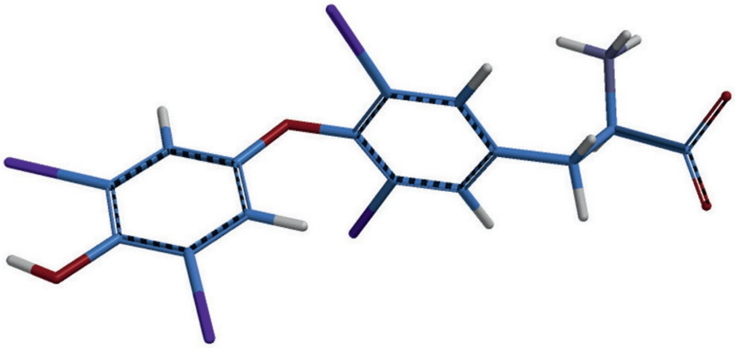
Electrophilic Aromatic Substitution

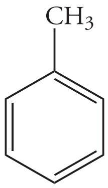


Thyroxine

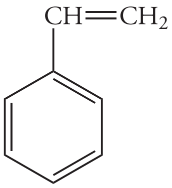
NOMENCLATURE OF BENZENE DERIVATIVES

Benzene is the “parent” of many aromatic compounds, which have both common and IUPAC names. The common names of substituted benzenes often came from their sources. One example is toluene, which used to be obtained from the South American gum tree, T*oluifera balsamum*. A few benzene compounds are shown below. Their common names are shown in parentheses below their IUPAC names. The common names have been used for so long that they have become accepted by IUPAC.

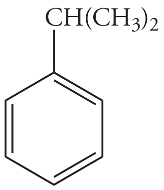
IUPAC names
(Common names)



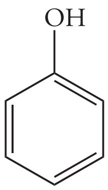
methylbenzene
(toluene)



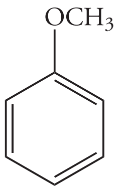
vinylbenzene
(styrene)



isopropylbenzene
(cumene)

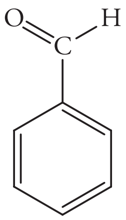


benzol
(phenol)

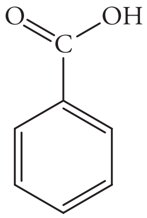


methoxybenzene
(anisole)

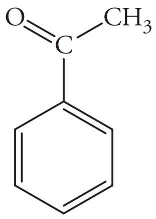
IUPAC Names
(Common names)



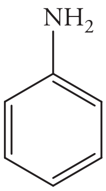
benzenecarboxaldehyde
(benzaldehyde)



benzenecarboxylic acid
(benzoic acid)

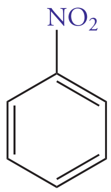


1-phenylethanone
(acetophenone)

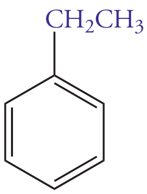


benzenamine
(aniline)

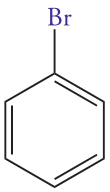
The IUPAC system of naming substituted aromatic hydrocarbons uses the names of the substituents as prefixes to benzene. Examples include the compounds listed below.



nitrobenzene



ethylbenzene



bromobenzene

In this section we will always write a substituent at a “12 o’clock” position. However, the six positions on the benzene ring are equivalent, so if a single substituent is bonded to a benzene ring, it does not matter where we place it.

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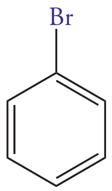
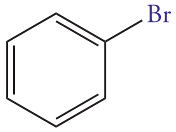
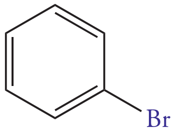


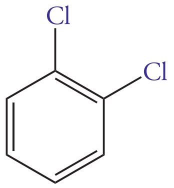
is the same as



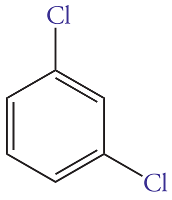
is the same as



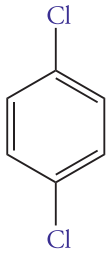
Many benzene derivatives contain two substituents. They give rise to three isomers. Groups located on adjacent carbons, are *ortho* (*o*), groups separated by one carbon are *meta* (*m*), and groups separated by two carbon atoms, which lie at opposite ends of the ring, are *para* (*p*). That is, *ortho* compounds are 1,2-substituted, *meta* compounds are 1,3-substituted, and *para* compounds are 1,4-substituted.



o-dichlorobenzene
(1,2-dichlorobenzene)

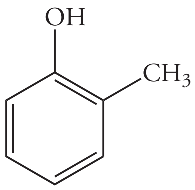


m-dichlorobenzene
(1,3-dichlorobenzene)

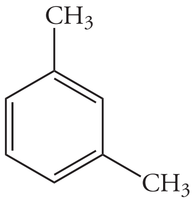


p-dichlorobenzene
(1,4-dichlorobenzene)

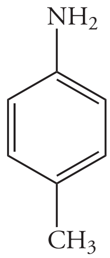
Many disubstituted compounds have common names. Examples include the xylenes, cresols, and toluidines, all of which can be *ortho*, *meta*, or *para* isomers.



2-methylphenol
(*o*-cresol)

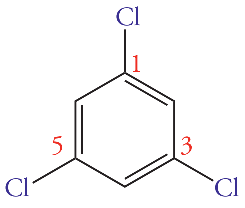


1,3-dimethylbenzene
(*m*-xylene)

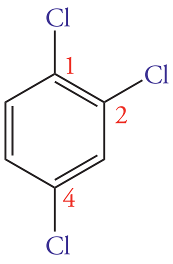


p-methylaniline
(*p*-toluidine)

To obtain the IUPAC name of a trisubstituted aromatic compound, we number the benzene ring to give the lowest possible numbers to the carbon atoms bearing the substituents. Thus, each substituent has both a name and a number.

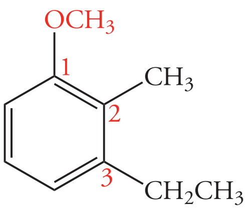


1,3,5-trichlorobenzene

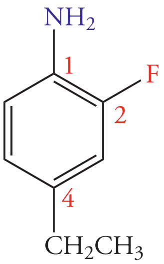


1,2,4-trichlorobenzene

Many derivatives of benzene are named with the common name of the monosubstituted aromatic compound as the parent. The position of the substituent of the parent compound is automatically designated C-1, but the number is not used in the name. The other substituents are prefixes named in alphabetical order along with numbers indicating their locations.

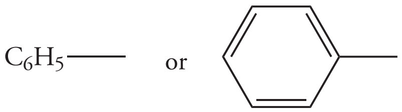


3-ethyl-2-methylanisole

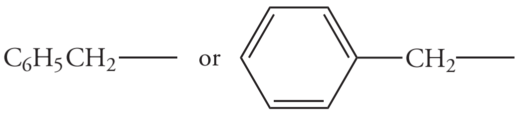


4-ethyl-2-fluoroanline

An aromatic ring residue attached to a larger parent structure is called an **aryl** group. It is abbreviated Ar. The aryl group derived from benzene, C_6H_5—, is a *phenyl* group. A *benzyl* group, derived from toluene, has the formula $C_6H_5CH_2$—.

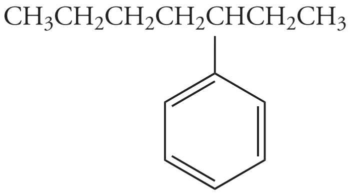


phenyl group



benzyl group

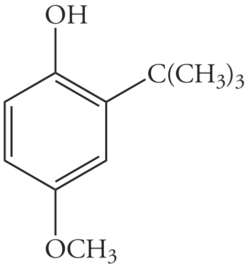
If alkyl groups containing fewer than six carbon atoms are bonded to a benzene ring, the compound is named as an alkyl-substituted benzene. For more complex molecules, the term phenyl is named as a substituent on the parent chain of carbon atoms, as in 3-phenylheptane.



3-phenylheptane

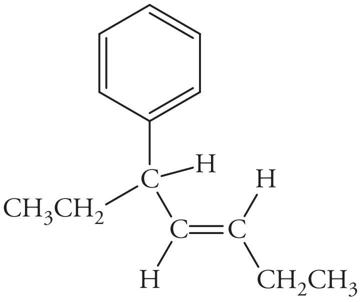
Problem 1

What is the name of the following trisubstituted compound?



Problem 2

What is the name of the following trisubstituted compound?



Sample Solution

The compound is an alkene with an aromatic ring as a substituent. First, we determine that the chain has seven carbon atoms; it is a heptene. Next, we number the chain from right to left so that the double bond is assigned to C-3. The phenyl group is then located on C-5. Also, we note that the compound is the (*E*) isomer. The complete name is (*E*)-5-phenyl-3-heptene.

Problem 13.

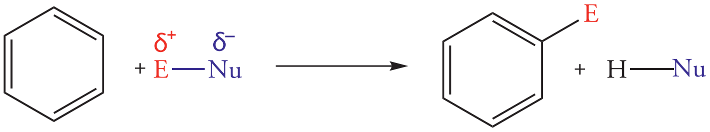
Write the structure of each of the following compounds.

(a) 2,4,6-trinitrophenol (b) 3,5-dibromoaniline (c) 2,4-dinitrotoluene

(d) *p*-methylbenzoic acid (e) *p*-chloroanisole (f) *o*-methylacetophenone

MECHANISM OF ELECTROPHILIC AROMATIC SUBSTITUTION

Aromatic rings do not undergo the electrophilic addition reactions we discussed for alkenes. Instead, they react with electrophiles— and even then only in the presence of a catalyst—to give a substitution product. In these reactions an electrophile (E^+) substitutes for H^+. The general process is shown below.

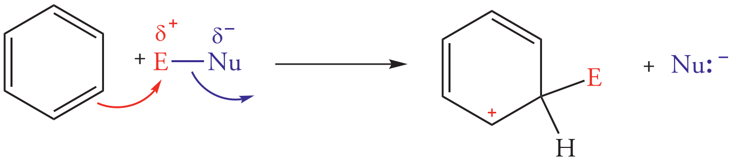


Many electrophiles can replace a hydrogen atom on an aromatic ring. A halogen atom, usually chlorine or bromine, adds to the ring through a halogenation reaction. The nitro group (—NO_2) and the sulfonic acid group (—SO_3H) add in nitration and sulfonation reactions. Alkylation and acylation reactions introduce alkyl (—R) and acyl groups (—COR). These reactions all occur by the same general reaction mechanism.

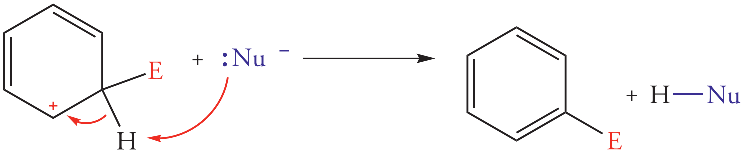
Mechanism of Electrophilic Aromatic Substitution

In the first step of electrophilic aromatic substitution, which resembles the addition of electrophiles to alkenes, the electrophile accepts a pair of electrons from the aromatic ring. However, because this electron pair forms part of a delocalized aromatic sextet, aromatic compounds are significantly less reactive than alkenes. They are so much less reactive that a Lewis acid, such as $FeBr_3$ in bromination, and $AlCl_3$ in alkylation and acylation, is required as a catalyst to generate an electrophile that is potent enough to react with the aromatic ring.

When the electrophile adds to the aromatic ring, it produces a carbocation intermediate. The first step of electrophilic aromatic substitution is usually the rate-determining step. Because a new sigma bond forms in the first step, the intermediate is called a **sigma complex**.



This carbocation is resonance stabilized, but is not aromatic because it has only four 2p electrons. Therefore, the sigma complex is much more reactive than the original aromatic ring.



The formation of the sigma complex in electrophilic aromatic substitution of a benzene ring has a higher activation energy than electrophilic addition to an alkene (Figure 13.1). Therefore, the rates of electrophilic aromatic substitution reactions are slower than the rates of electrophilic addition reactions to alkenes for the same electrophile. For example, bromine reacts instantly with alkenes, but does not react at all with benzene except in the presence of a strong Lewis acid catalyst.

In the faster second step of the electrophilic substitution mechanism, the proton bound to the sp^3-hybridized ring carbon atom leaves, restoring the aromatic π system. A nucleophile, acting as a base, extracts the leaving proton.

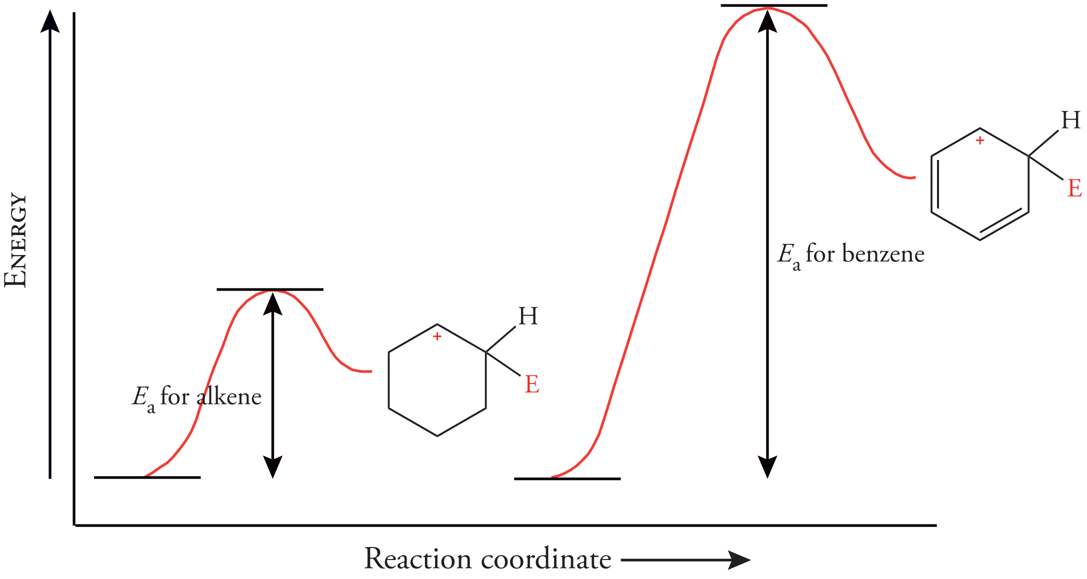
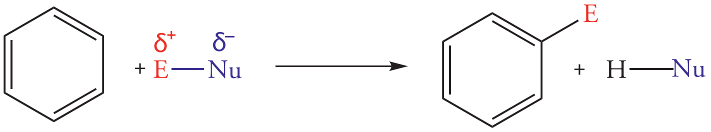


Figure 1 Electrophilic Addition to Hexene Compared to Benzene
The activation energy for adding an electrophile to benzene is higher than for the activation energy for adding an electrophilic to an alkene because some of the resonance energy of benzene is lost in the transition state.

COMMON ELECTROPHILIC AROMATIC SUBSTITUTION REACTIONS

In the preceding discussion we used a generic electrophile, E^+, in our electrophilic substitution mechanism. In this section we will consider some specific examples of electrophiles that react with aromatic rings.

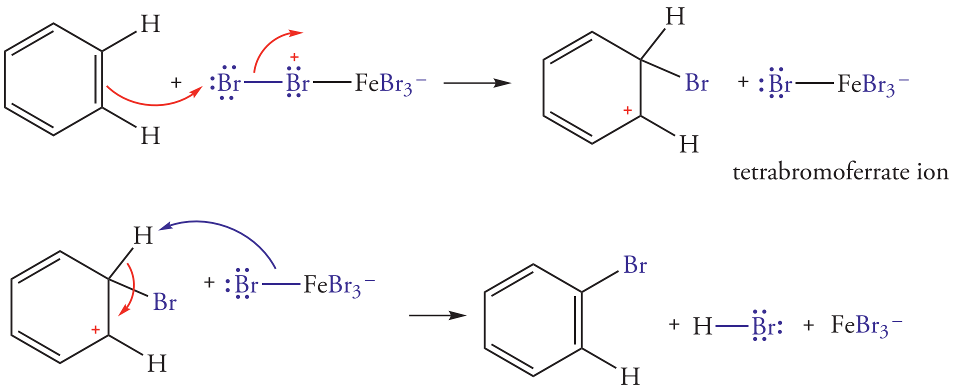


Halogenation

In the presence of a strong Lewis acid, bromine and chlorine halogenate aromatic rings. Bromination requires both Br_2 and a Lewis acid catalyst, $FeBr_3$. The catalyst generates a Lewis acid-Lewis base complex with a weakened Br—Br bond. The bromine atom bonded to iron carries a formal positive charge. It is the electrophile.

Lewis-acid–Lewis-base complex

The Lewis acid-base complex reacts with the benzene ring to form a cyclohexadienyl cation. This step also forms a tetrabromoferrate ion, which removes a proton from the cyclohexadienyl cation in a subsequent step. This step also regenerates the iron(III) bromide, which continues to act as a catalyst in the reaction.

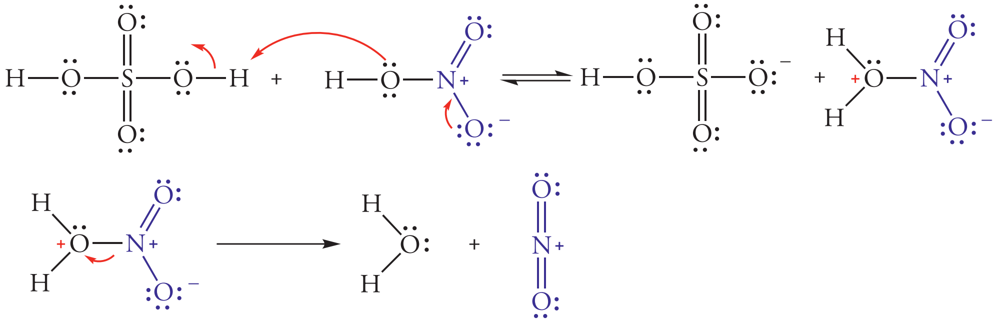


tetrabromoferrate ion

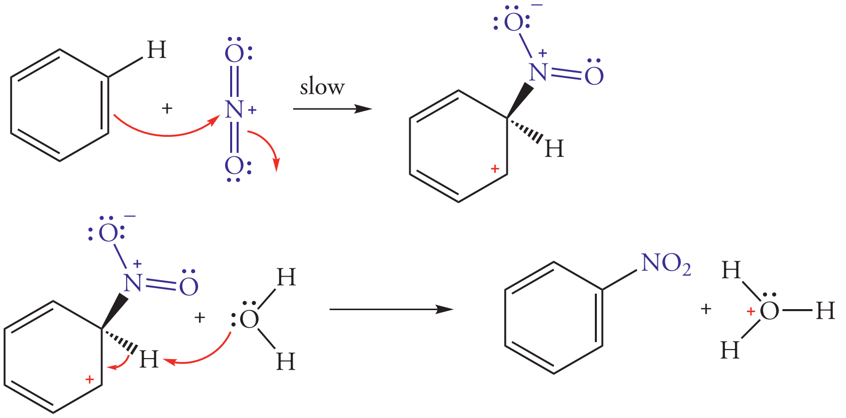
Chlorination, which proceeds in a similar manner, requires $FeCl_3$ as the Lewis acid catalyst. Fluorine reacts so strongly that multiple substitution reactions occur. Iodine, on the other hand, does not react with benzene by this mechanism. We will discuss alternative methods for aromatic substitution that allow iodination later in this chapter.

Nitration

Nitration adds a nitro group ($—NO_2$) to an aromatic ring. Electrophilic aromatic substitution requires nitric acid (HNO_3), with sulfuric acid as a catalyst. Nitronium ion, (NO_2^+), is the electrophile. It forms in two steps by the reaction of nitric acid with sulfuric acid.



The nitronium ion reacts with the π system of the aromatic ring to give a sigma complex. A water molecule then extracts a proton from the cyclohexadienyl carbocation to give the product.



Nitration of aromatic rings is an important reaction because the nitro group can readily be reduced to an amino group, a common functional group required in many pharmaceutical compounds. Other substituents can subsequently replace the amino group (Section 13.8).

Sulfonation

Sulfonation reaction is less exothermic than halogenation or nitration. Hence, it is reversible, and desulfonation occurs in dilute aqueous acid. The reversibility of sulfonation forms the basis of the synthesis of some aromatic compounds because the sulfonic acid group may block a position on an aromatic ring, preventing substitution at that point. The sulfonic acid group is removed at the end of the synthesis.

$$SO_3 + H_2SO_4 \rightleftharpoons {}^{+}SO_3H + HSO_4^-$$