22: ARENES, ELECTROPHILIC AROMATIC SUBSTITUTION

John D. Roberts and Marjorie C. Caserio
California Institute of Technology

CHAPTER OVERVIEW

22: Arenes, Electrophilic Aromatic Substitution

Benzene and other aromatic hydrocarbons usually have such strikingly different properties from typical open-chain conjugated polyenes, such as 1,3,5-hexatriene, that it is convenient to consider them as a separate class of compounds called **arenes**. In this chapter we shall outline the essential features of the chemistry of arenes, particularly their reactions with electrophilic reagents which result in the substitution of a ring hydrogen with other functional groups. Some of the important properties of benzene were discussed in Chapter 21 in connection with the valence-bond and molecular-orbital theories, which rationalize the bonding in benzene and account for the remarkable stability and low reactivity of benzene (Section 21-3A). This chapter is especially concerned with chemical properties of benzene and its derivatives as well as related ring systems.

22.1: Contributors and Attributions

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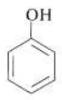
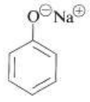
22.1: Nomenclature of Arenes

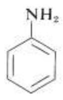
The naming of benzene derivatives was considered in Section 3-5 and is relatively straightforward. However, many benzene derivatives have acquired trivial names, and we draw your attention to a few of these below. The accepted name for the C_6H_5- group as a substituent is **phenyl**.



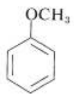
benzenol
(phenol)



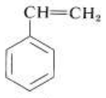
sodium
benzenolate
(sodium phenoxide)



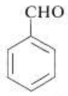
benzenamine
(aniline)



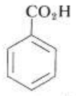
methoxybenzene
methyl phenyl ether
(anisole)



ethenylbenzene
(phenylethene,
styrene)



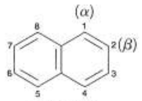
benzenecarbaldehyde
(benzaldehyde)



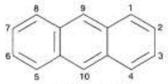
benzenecarboxylic acid
(benzoic acid)

The more complex ring systems having two or more fused benzene rings have nonsystematic names and illogical numbering systems. They are described as polynuclear aromatic hydrocarbons, the three most important examples being naphthalene, anthracene, and phenanthrene. In anthracene the rings are connected in a *linear* manner, whereas in phenanthrene they are connected *angularly*:

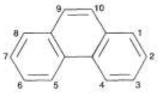
benzene



naphthalene

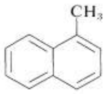


anthracene

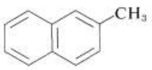


phenanthrene

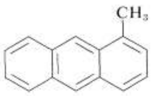
The accepted numbering system for these hydrocarbons is as shown in the structures. The 1- and 2-positions of the naphthalene ring sometimes are designated as α and β, but we prefer not to use these designations. Some illustrative substitution products are:



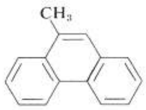
1-methylnaphthalene



2-methylnaphthalene



1-methylanthracene



9-methylphenanthrene

The names that have been give to these and other more elaborate types of polynuclear aromatic hydrocarbons are for the most part distressingly uninformative with respect to their structures.[1]

[1] A thorough summary of names and numbering systems has been published by A. M. Patterson, L. T. Capell, and D. F. Walker, *Ring Index*, 2nd ed., American Chemical Society, 1960. Less complete but useful summaries are given in various handbooks of chemistry.

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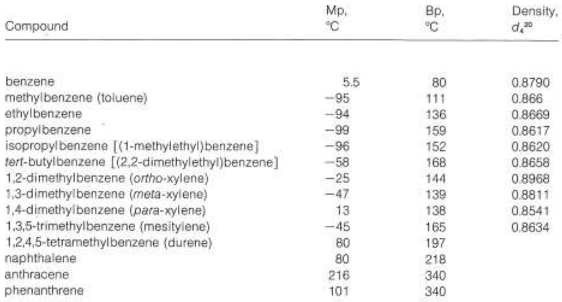
22.2: Physical Properties of Arenes

The pleasant odors of the derivatives of many arenes is the origin of the name **aromatic** hydrocarbons. The arenes themselves generally are quite toxic; some are carcinogenic and inhalation of their vapors should be avoided. The volatile arenes are highly flammable and burn with a luminous sooty flame, in contrast to alkanes and alkenes, which usually burn with a bluish flame leaving little carbon residue.

The more common arenes and their physical properties are given in Table 22-1. They are less dense than water and are highly insoluble. Boiling points increase regularly with increasing molecular weight, but there is little correlation between melting point and molecular weight. The melting point is highly dependent on the symmetry of the compound; thus benzene melts 100° higher than methylbenzene, and the more symmetrical 1,4-dimethylbenzene (*para*-xylene) has a higher boiling point than either the 1,2- or the 1,3-isomer. This latter fact is utilized in the separation by fractional crystallization of 1,4-dimethylbenzene from mixtures of isomers produced from petroleum.

***Table 22-1:** Physical Properties of Arenes*



Compound	Mp, °C	Bp, °C	Density, d_4^{20}
benzene	5.5	80	0.8790
methylbenzene (toluene)	−95	111	0.866
ethylbenzene	−94	136	0.8669
propylbenzene	−99	159	0.8617
isopropylbenzene [(1-methylethyl)benzene]	−96	152	0.8620
tert-butylbenzene [(2,2-dimethylethyl)benzene]	−58	168	0.8658
1,2-dimethylbenzene (*ortho*-xylene)	−25	144	0.8968
1,3-dimethylbenzene (*meta*-xylene)	−47	139	0.8811
1,4-dimethylbenzene (*para*-xylene)	13	138	0.8541
1,3,5-trimethylbenzene (mesitylene)	−45	165	0.8634
1,2,4,5-tetramethylbenzene (durene)	80	197	
naphthalene	80	218	
anthracene	216	340	
phenanthrene	101	340	

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22.3: Spectral Properties of Arenes

22.3.1: Infrared Spectra

The presence of a phenyl group in a compound can be ascertained with a fair degree of certainty from its infrared spectrum. For example, in Figure 22-1 we see the infrared spectra of methylbenzene, and of 1,2-, 1,3-, and 1,4-dimethylbenzene. That each spectrum is of a benzene derivative is apparent from certain common features. The two bands near $1600\ \text{cm}^{-1}$ and $1500\ \text{cm}^{-1}$, although of variable intensity, have been correlated with the stretching vibrations of the carbon-carbon bonds of the aromatic ring; also, the sharp bands near $3030\ \text{cm}^{-1}$ are characteristic of aromatic $\text{C}-\text{H}$ bonds. Other bands in the spectra, especially those between $1650\ \text{cm}^{-1}$ and $2000\ \text{cm}^{-1}$, between $1225\ \text{cm}^{-1}$ and $950\ \text{cm}^{-1}$, and below $900\ \text{cm}^{-1}$, have been correlated with the number and position of ring substituents. Although we shall not document all these various bands in detail, each of the spectra in Figure 22-1 is marked to show some of the correlations that have been made.

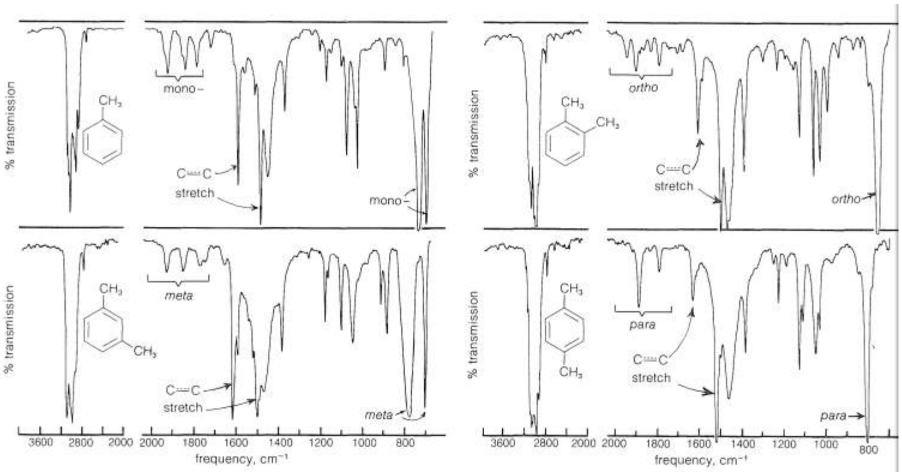


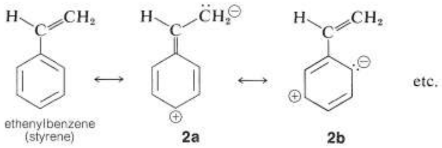
Figure 22-1: Infrared spectra of methylbenzene and the 1,2-, 1,3-, and 1,4-dimethylbenzenes. The number and positions of ring substituents determine the pattern of the low-intensity bands in the region $2000\ \text{cm}^{-1}$ to $1650\ \text{cm}^{-1}$ and the positions of the stronger bands in the region 800 cm^{-1} to 690 cm^{-1}. The sharp bands near 3030 cm^{-1} arise from $\text{C}-\text{H}$ stretching vibrations.

22.3.2: Electronic Absorption Spectra

Compared to straight-chain conjugated polyenes, aromatic compounds have relatively complex absorption spectra with several bands in the ultraviolet region. Benzene and the alkylbenzenes show two bands in which we shall be primarily interested, one near $200\ \text{nm}$ and the other near $260\ \text{nm}$. The 200-nm band is of fairly high intensity and corresponds to excitation of a π electron of the conjugated system to a π^* orbital (i.e., a $\pi \rightarrow \pi^8*$ transition). The excited state has significant contributions from dipolar structures such as 1:

1

This is analogous to the absorption bands of conjugated dienes (Section 9-9B) except that the wavelength of absorption of benzenes is shorter. In fact, the 200-nm absorptions of benzene and the alkylbenzenes are just beyond the range of most commercial quartz spectrometers. However, these absorptions (which we say arise from the benzene **chromophore**[2]) are intensified and shifted to longer wavelengths when the conjugated system is extended by replacement of the ring hydrogens by unsaturated groups (e.g., $-\text{CH}=\text{CH}_2$, $-\text{C}\equiv\text{CH}$, $-\text{CH}=\text{O}$, and $-\text{C}\equiv\text{N}$; see Table 22-2). The delocalized π-electron system of the absorbing chromophore now includes the electrons of the unsaturated substituent as well as those of the ring. In the specific case of ethenylbenzene the excited state is a hybrid structure composite of $2a$ and $2b$ and other related dipolar structures:

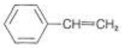
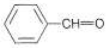
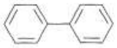
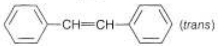


ethenylbenzene (styrene)

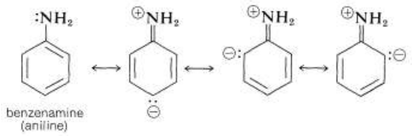
2a

2b

Table 22-2: *Effect of Conjugation on Electronic Absorption by the Benzene Chromophore*

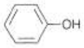
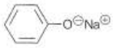
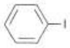
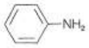
Compound	λ_{max}, nm^a	ϵ_{max}
	203	8,000
	244	12,000
	244	15,000
	250	18,000
	295	27,000

Similar effects are observed for benzene derivatives in which the substituent has unshared electron pairs that can be conjugated with the benzene ring (e.g., $-\mathrm{NH_2}$, $-\mathrm{OH}$, $-\mathrm{Cl}$). An unshared electron pair is to some extent delocalized to become a part of the aromatic π-electron system in both the ground and excited states, but more importantly in the excited state. This is illustrated for benzenamine (aniline) by the following structures, which contribute to the hybrid structure:



The data of Table 22-3 show the effect on the benzene chromophore of this type of substituent - the substituent often being called an **auxochrome**.[2] This term means that, although the substituent itself is not responsible for the absorption band, it shifts the absorption of the chromophoric group, in this case the benzene ring, toward *longer* wavelengths. The auxochromic groups usually increase the intensity of the absorption also.

Table 22-3: *Effect of Auxochromic Substituents on Electronic Absorption by the Benzene Chromophore*

Compound	λ_{max}, nm^a	ϵ_{max}
	203	8,000
	210	6,200
	235	9,400
	226	13,000
	230	8,600

^{a}In ethanol or water

Figure 22-3, is of relatively low intensity and is found under high resolution to be a composite of several narrow peaks. It appears to be characteristic of aromatic hydrocarbons because no analogous band is found in the spectra of conjugated acyclic polyenes. For this reason it often is called the benzenoid band. The position and intensity of this band, like the one at shorter wavelengths, is affected by the nature of the ring substituents, particularly by those that extend the conjugated system, as may be seen from the date in Table 22-4.

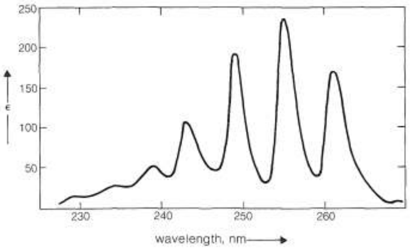
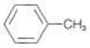
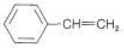
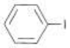
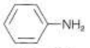
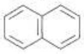
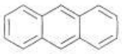
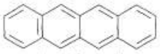
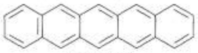


Figure 22-3: Ultraviolet absorption spectrum of benzene (in cyclohexane) showing the "benzenoid" band.

Table 22-4: *Effects of Structure on Electronic Absorption Corresponding to the Benzenoid Band*

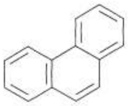
Compound	λ_{max}, nm[a]	ϵ_{max}
	255	230
	261	300
	282	450
	256	800
	280	1,430
	314	316
	380	7,900
 (naphthacene)	480	11,000
 (pentacene)	580	12,600

[a] Mostly in ethanol solution

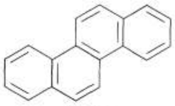
The benzenoid band corresponds to a low-energy $\pi \rightarrow \pi^*$ transition of the benzene molecules. The absorption intensity is weak because the π^* state involved has the same electronic symmetry as the ground state of benzene, and transitions between symmetrical states usually are forbidden. The transitions are observed in this case only because the vibrations of the ring cause it to be slightly distorted at given instants. In the valence-bond treatment this excited state of benzene is an antibonding state of the π electrons.

The electronic spectra of polynuclear aromatic hydrocarbons such as naphthalene and anthracene, in which aromatic rings are fused together in a linear manner, resemble the spectrum of benzene except that the bands are shifted to longer wavelengths. In fact, with the four linearly connected rings of naphthacene, the benzenoid band is shifted far enough to longer wavelengths to be in the visible region of the spectrum (see Table 22-4). Accordingly, naphthacene is yellow. The next higher member, pentacene, is blue.

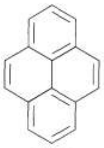
Compounds such as phenanthrene, chrysene, and pyrene, in which the aromatic rings are fused in an angular manner, have complex electronic spectra with considerable fine structure. The λ_{max} values normally are at shorter wavelengths than those of their linear isomers.



phenanthrene



chrysene



pyrene

22.3.3: Nuclear Magnetic Resonance Spectra

The chemical shifts of arene protons ($6.5\,\text{ppm}$ to $8.0\,\text{ppm}$) characteristically are toward lower magnetic fields than those of protons attached to ordinary double bonds ($4.6\,\text{ppm}$ to $6.9\,\text{ppm}$). The difference of about $2\,\text{ppm}$ cannot be easily explained because the hydrogens in both types of systems are bonded to carbon through sp^2-σ bonds (Sections 6-4C and 6-5A).

At least part of the chemical-shift difference between arene protons and alkene protons is the result of the special property of π electrons in aromatic systems of circulating freely above and below the plane of the carbon nuclei, as shown in Figure 22-4. When a molecule such as benzene is subjected to a magnetic field that has a component *perpendicular* to the plane of the ring, the electrons circulate around the ring in such a way as to produce a local magnetic dipole in the direction *opposite* to the applied field. This *diamagnetic shielding* effect acts to reduce the applied field in the center of the ring. Therefore, if a proton could be located in the center of the ring, the applied field would have to be higher than normal to counteract the local diamagnetic field and bring the proton into resonance. A proton outside the ring is affected in the opposite way (*paramagnetic deshielding* effect) because, as can be seen from the diagram, such protons are located in the return path of the lines of force associated with the local field and thus are in a field greater than that arising from the external magnet alone. When the plane of the molecule is oriented parallel to the field, the diamagnetic circulation is cut off. As a result, as the molecules tumble over and over in the liquid the component of magnetization perpendicular to the plane of the ring varies rapidly. Nonetheless, a substantial *net* paramagnetic effect is experienced by the ring hydrogens. The resonance line positions therefore are shifted to lower magnetic fields.

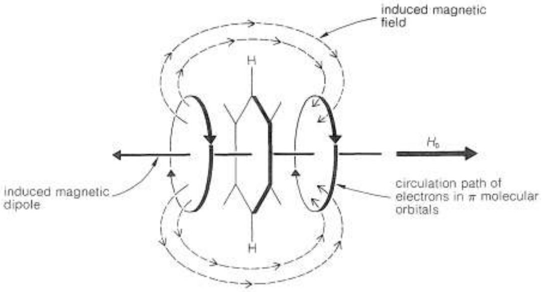
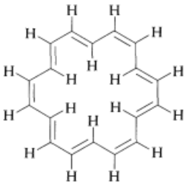


Figure 9-26. The strength of the induced magnetic field, or dipole, is proportional to the applied field.

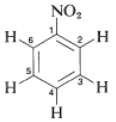
Strong evidence in confirmation of the above explanation of the chemical shifts of aromatic hydrogens is provided by a study of the cyclic conjugated polyene [18]annulene, which has hydrogens both "inside" and "outside" the ring:



[18]annulene

The *inside* hydrogens are strongly deshielded, coming at 1.9 ppm *upfield* from tetramethylsilane, while the *outside* hydrogens are deshielded and come at 8.8 ppm *downfield* from TMS. As we shall see, the ring current effect is quite general and constitutes a widely used test for aromatic character in conjugated polyene ring systems.

In general, the spin-spin splittings observed between the five protons of a phenyl group can be extremely complex. An example is afforded by nitrobenzene (Figure 22-5), which has different chemical shifts for its ortho, meta, and para hydrogens and six different spin-spin interaction constants: J_{23}, J_{24}, J_{25}, J_{26}, J_{34}, J_{35}, (the subscripts correspond to position numbers of the protons):



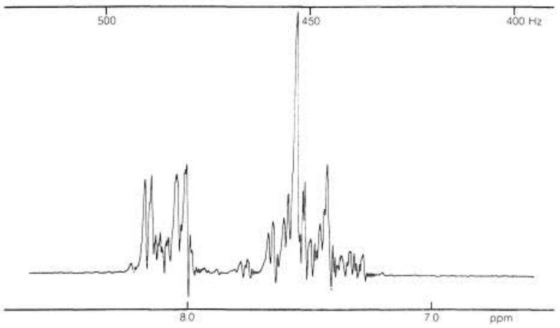
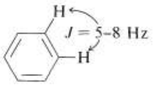
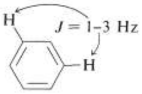
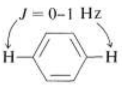


Figure 22-5: Nmr spectrum of nitrobenzene at 60 MHz with reference to TMS at 0.00 ppm.

Such a spectrum is much too complex to be analyzed by any simple procedure. Nonetheless, nuclear magnetic resonance can be useful in assigning structures to aromatic derivatives, particularly in conjunction with integrated line intensities and approximate values of the coupling constants between the ring hydrogens, as shown below:







[2] A chromophore is a grouping of atoms in an organic molecule that gives rise to color, or has the potential of doing so when other groups called **auxochromes** are present (also see Section 28-4).

22.3.4: Contributors and Attributions

John D. Robert and Marjorie C. Caserio (1977) *Basic Principles of Organic Chemistry, second edition.* W. A. Benjamin, Inc. , Menlo Park, CA. ISBN 0-8053-8329-8. This content is copyrighted under the following conditions, "You are granted permission for individual, educational, research and non-commercial reproduction, distribution, display and performance of this work in any format."

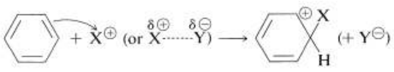
22.4: Electrophilic Aromatic Substitution

22.4.1: Scope and Mechanism

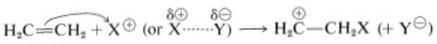
In this section we shall be mainly interested in the reactions of arenes that involve attack on the carbon atoms of the aromatic ring. We shall not elaborate now on the reactions of substituent groups around the ring.

The principal types of reactions involving aromatic rings are substitution, addition, and oxidation. Of these, the most common type is electrophilic substitution. A summary of the more important substitution reactions of benzene is given in Figure 22-7. Many of the reagents used to achieve these substitutions will be familiar to you in connection with electrophilic addition reactions to alkenes (e.g., Cl_2, Br_2, H_2SO_4, and $HOCl$; Section 10-3). Electrophilic addition to alkenes and electrophilic aromatic substitution are both polar, stepwise processes, and the key step for each is attack of an electrophile at carbon to form a cationic intermediate. We may represent this type of reaction by the following general equations, in which the attacking reagent is represented either formally as a cation, $X^{\ominus}$, or as a neutral but polarized molecule, $\overset{\delta\oplus}{X}\text{---}\overset{\delta\ominus}{Y}$:

electrophilic aromatic substitution (first step)



electrophilic addition to alkenes (first step)



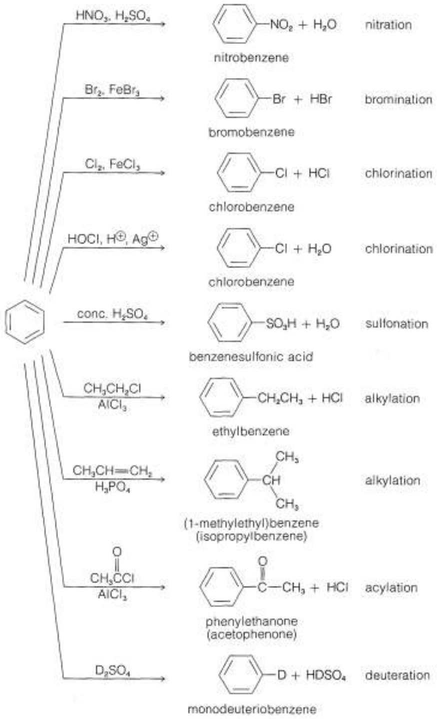
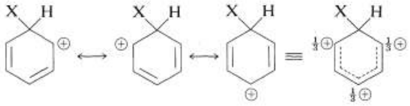


Figure 22-7: Typical benzene substitution reactions.

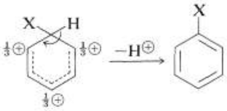
The intermediate shown for aromatic substitution no longer has an aromatic structure; rather, it is a cation with four π electrons delocalized over five carbon nuclei, the sixth carbon being saturated with sp^3-hybrid bonds. It may be formulated in terms of the following contributing structures, which are assumed to contribute essentially equally:



The importance of writing the hybrid structure with the partial charges at these three positions will become evident later. This kind of ion is referred to as a σ *complex* or a *benzenium ion*.

The aromatic ring is regenerated from this cationic intermediate by loss of a proton from the sp^3-hybridized carbon. The electron pair of this $\text{C}-\text{H}$ bond then becomes part of the aromatic π-electron system and a substitution product of benzene, $\text{C}_6\text{H}_5\text{X}$, is formed.

electrophilic aromatic substitution (second step)



The gain in stabilization attendant on regeneration of the aromatic ring is sufficiently advantageous that this, rather than combination of the cation with $\text{Y}^\ominus$, normally is the favored course of reaction. Herein lies the difference between aromatic substitution and alkene addition. In the case of alkenes there usually is no substantial resonance energy to be gained by loss of a proton from the intermediate, which tends therefore to react by combination with a nucleophilic reagent.

electrophilic addition to alkenes (second step)

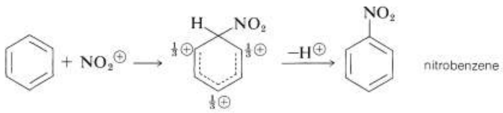
$$\overset{\oplus}{\text{C}}\text{H}_2-\text{CH}_2\text{X}+\text{Y}^\ominus\rightarrow\text{YCH}_2-\text{CH}_2\text{X} \tag{22.4.1}$$

22.4.2: Nature of the Substituting Agent

It is important to realize that in aromatic substitution the actual electrophilic substituting agent, $\overset{\oplus}{\text{X}}$ or $\overset{\delta\oplus}{\text{X}}-\overset{\delta\ominus}{\text{Y}}$, is not necessarily the reagent that is added to the reaction mixture. For example, nitration in mixtures of nitric and sulfuric acids is not brought about by attack of the nitric acid molecule on the aromatic compound, but by attack of a more electrophilic species, the nitronium ion, NO_2^+. This ion is formed from nitric acid and sulfuric acid according to the following equation:

$$\text{HNO}_3+2\text{H}_2\text{SO}_4\rightleftharpoons\text{NO}_2^++\text{H}_3\text{O}^++2\text{HSO}_4^- \tag{22.4.2}$$

The nitronium ion attacks the aromatic ring to give first a nitrobenzenium ion and then an aromatic nitro compound:

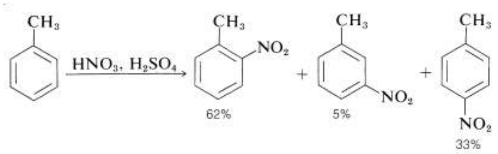


In general, the function of a catalyst (which is so often necessary to promote aromatic substitution) is to generate an electrophilic substituting agent from the given reagents. Thus it is necessary to consider carefully for each substitution reaction what the actual substituting agent may be. This problem does not arise to the same degree in electrophilic additions to alkenes, because alkenes are so much more reactive than arenes that the reagents employed (e.g., Br_2, Cl_2, HCl, HOCl, HOBr, $\text{H}_3\text{O}^\oplus$) themselves are sufficiently electrophilic to react with alkenes without the aid of a catalyst. In fact, conditions that lead to substitution of arenes, such as nitration in mixtures of nitric and sulfuric acid, often will degrade the carbon skeleton of alkenes.

Now we shall consider the individual substitution reactions listed in Figure 22-1 with regard to the nature of the substituting agent and the utility for synthesis of various classes of aromatic compounds.

22.4.3: Nitration

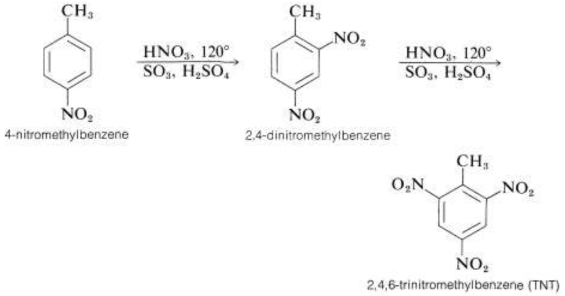
The nitronium ion, NO_2^+, is the active nitrating agent in nitric acid-sulfuric acid mixtures. The nitration of methylbenzene (toluene) is a typical example of a nitration that proceeds well using nitric acid in a 1:2 mixture with sulfuric acid. The nitration product is a mixture of 2-, 3-, and 4-nitromethylbenzenes:



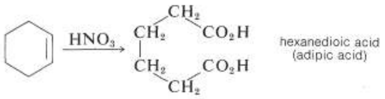
The presence of appreciable amounts of water in the reaction mixture is deleterious because water tends to reverse the reaction by which nitronium ion is formed:

$$NO_2^+ + H_2O \overset{HSO_4^-}{\rightleftharpoons} HNO_3 + H_2SO_4 \tag{22.4.3}$$

For this reason the potency of a nitric-sulfuric acid mixture can be considerably increased by using fuming nitric and fuming sulfuric acids. With such mixtures nitration of relatively unreactive compounds can be achieved. For example, 4-nitromethylbenzene is far less reactive than methylbenzene, but when heated with an excess of nitric acid in fuming sulfuric acid, it can be converted successively to 2,4-dinitromethylbenzene and to 2,4,6-trinitromethylbenzene (TNT):

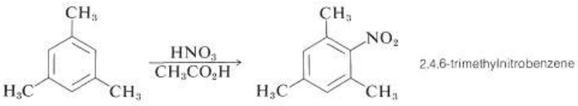


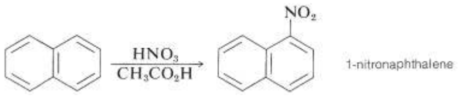
There are several interesting features about the nitration reactions thus far discussed. For instance, the conditions required for nitration of 4-nitromethylbenzene would rapidly oxidize an alkene by cleavage of the double bond:



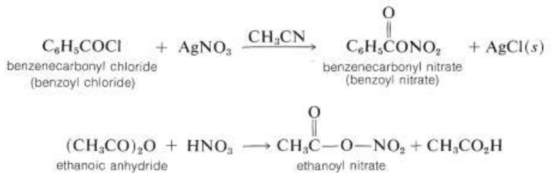
Also the mononitration of methylbenzene does not lead to equal amounts of the three possible products. The methyl substituent apparently orients the entering substituent preferentially to the 2 and 4 positions. This aspect of aromatic substitution will be discussed in Section 22-5 in conjunction with the effect of substituents on the reactivity of aromatic compounds.

Some compounds are sufficiently reactive that they can be nitrated with nitric acid in ethanoic acid. Pertinent examples are 1,3,5-trimethylbenzene and naphthalene:

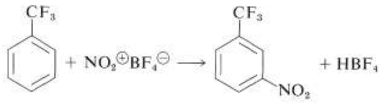




Other convenient nitrating reagents are benzoyl nitrate, $C_6H_5COONO_2$, and ethanoyl nitrate, CH_3COONO_2. These reagents provide a source of NO_2^+ and have some advantage over $HNO_3 \cdot H_2SO_4$ mixtures in that they are soluble in organic solvents such as ethanenitrile or nitromethane. Having homogeneous solutions is especially important for kinetic studies of nitration. The reagents usually are prepared in solution as required from the corresponding acyl chloride and silver nitrate or from the acid anhydride and nitric acid. Such reagents are hazardous materials and must be handles with care.

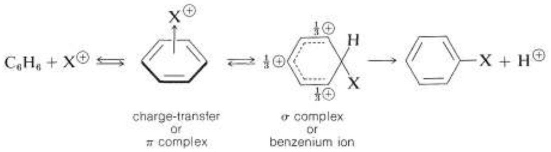


Nitronium salts of the type $NO_2^+X^-$ are very powerful nitrating agents. The counterion, X^-, must be non-nucleophilic and usually is fluoroborate, BF_4^- or SbF_4^-:



22.4.4: Halogenation

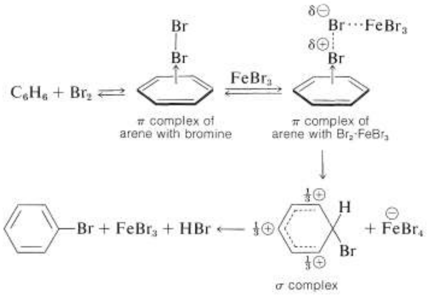
To some degree we have oversimplified electrophilic substitution by neglecting the possible role of the 1:1 charge-transfer complexes that most electrophiles form with arenes (see Section 10-3C for discussion of analogous complexes of alkenes):



With halogens, especially iodine, complex formation is visually evident from the color of solutions of the halogen in arenes. Although complex formation may assist substitution by bringing the halogen and arene in close proximity, substitution does not necessarily occur. A catalyst usually is required, and the catalysts most frequently used are metal halides that are capable of accepting electrons (i.e., Lewis acids such as $FeBr_3$, $AlCl_3$, and $ZnCl_2$). Their catalytic activity may be attributed to their ability to polarize the halogen-halogen bond in the following way:

$$\overset{\delta\oplus}{Br}\cdots\overset{\delta\ominus}{Br}\cdots FeBr_3 \tag{22.4.4}$$

The positive end of the dipole attacks the aromatic compound while the negative end is complexed with the catalyst. We can represent the reaction sequence as follows, with the slow step being formation of a σ bond between $Br^{\oplus}$ and the aromatic ring:



The order of reactivity of the halogens is $F_2 > Cl_2 > Br_2 > I_2$. Fluorine is too reactive to be of practical use for the preparation of aromatic fluorine compounds and indirect methods are necessary (see Section 23-10B). Iodine usually is unreactive. It has been stated that iodination fails because the reaction is reversed as the result of the reducing properties of the hydrogen iodide that is formed:

$$C_6H_6 + I_2 \overset{\rightharpoonup}{\longleftarrow} C_6H_5I + HI \tag{22.4.5}$$

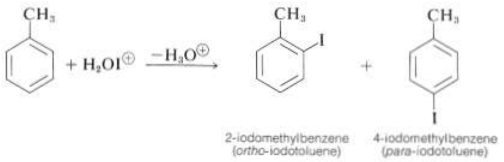
This view is not correct because, as Kekule himself showed, iodobenzene is not reduced by hydroiodic acid except at rather high temperatures.

The way to achieve direct iodination in the absence of powerful activating substituent groups is to convert molecular iodine to some more active species (perhaps $H_2OI^{\oplus}$ or $I^{\oplus}$) with an oxidizing agent such as nitric acid or hydrogen peroxide:

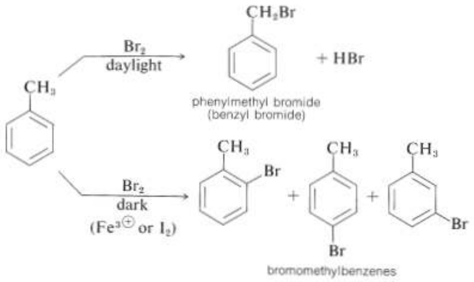
$$I_2 + 4HNO_3 \rightarrow 2H_2O{-}I^+ + 2NO_2 + 2NO_3^- \tag{22.4.6}$$

$$I_2 + H_2O_2 + 2H^+ \rightarrow 2H_2OI^+ \tag{22.4.7}$$

With combinations of this kind good yields of iodination products are obtained:



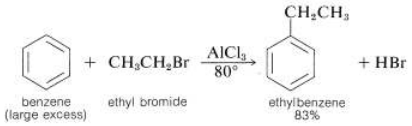
Halogen substitution reactions with chlorine or bromine must be carried out with adequate protection from strong light. If such precautions are not taken, an *alkyl*benzene will react rapidly with halogen by a photochemical process to substitute a hydrogen of the alkyl group rather than of the aromatic ring. The reaction has a light-induced, radical-chain mechanism of the kind discussed for the chlorination of propene (Section 14-3A). Thus methylbenzene reacts with bromine when illuminated to give phenylmethyl bromide; but when light is excluded and a Lewis acid catalyst is present, substitution occurs to give principally the 2- and 4-bromomethylbenzenes. Much less of the 3-bromomethylbenzene is formed:



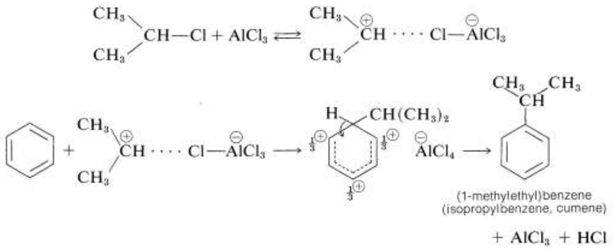
Benzene itself can be induced to *add* halogens on strong irradiation to give polyhalocyclohexanes (see Sections 21-3A and 22-9C):

22.4.5: Alkylation

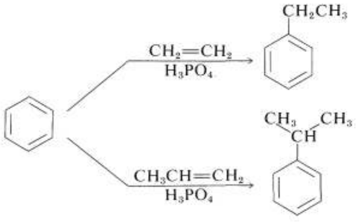
An important method of synthesis of alkylbenzenes utilizes an alkyl halide as the alkylating agent and a metal halide, usually aluminum chloride, as catalyst:



This class of reaction is called **Friedel-Crafts alkylation** in honor of its discoverers, C. Friedel (a French chemist) and J. M. Crafts (an American chemist). The metal-halide catalyst functions much as it does in halogenation reactions to provide a source of a positive substituting agent, which in this case is a carbocation:



Alkylation is not restricted to alkyl halides; alcohols and alkenes may be used to advantage in the presence of acidic catalysts such as H_3PO_4, H_2SO_4, HF, BF_3, or $HF{-}BF_3$. Ethylbenzene is made commercially from benzene and ethene using phosphoric acid as the catalyst. Isopropylbenzene is made similarly from benzene and propene:

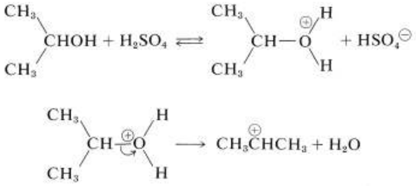


Under these conditions the carbocation, which is the active substituting agent, is generated by protonation of the alkene:

$$CH_2{=}CH_2 + H^+ \rightleftharpoons CH_3CH_2^+ \tag{22.4.8}$$

$$CH_3CH{=}CH_2 + H^+ \rightleftharpoons CH_3\overset{+}{C}HCH_3 \tag{22.4.9}$$

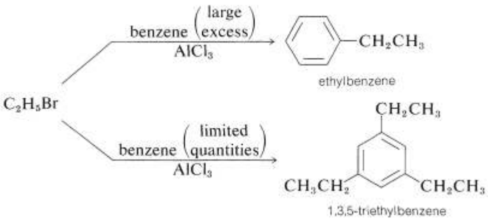
With alcohols the electrophile can be formed by initial protonation by the acid catalyst and subsequent cleavage to a carbocation:



22.4.5.1: Limitations of Alkylation Reactions

Polysubstitution

There are several factors that limit the usefulness of alkylation reactions. First, it may be difficult to limit reaction to monosubstitution because introduction of one alkyl substituent tends to activate the ring towards a second substitution (see Section 22-5). Therefore, to obtain reasonable yields of a monoalkylbenzene, it usually is necessary to use a large excess relative to the alkylating agent:



Rearrangement of the alkylating agent

A second limitation is the penchant for the alkylating reagent to give rearrangement products. As an example, the alkylation of benzene with 1-chloropropane leads to a mixture of propylbenzene and isopropylbenzene. We may write the reaction as first involving formation of a propyl cation, which is a *primary* carbocation:

$$CH_3CH_2CH_2Cl + AlCl_3 \rightarrow CH_3CH_2CH_2^+ + \overset{-}{A}lCl_4 \tag{22.4.10}$$

This ion either can alkylate benzene to give propylbenzene,

$$C_6H_6 + CH_3CH_2CH_2^+ \rightarrow C_6H_5CH_2CH_2CH_3 + H^+ \tag{22.4.11}$$

or it can rearrange to a more stable secondary ion by the transfer of a hydrogen from a neighboring carbon together with its bonding electron pair (i.e., 1,2-hydride shift). The positive charge is thereby transferred from C_1 to C_2:

$$CH_3-\overset{H}{C}H-\overset{\oplus}{C}H_2 \longrightarrow CH_3-\overset{\oplus}{C}H-\overset{H}{C}H_2$$

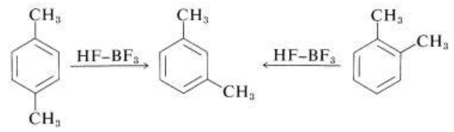
Alkylation of benzene with the isopropyl cation then produces isopropylbenzene:

$$C_6H_6 + CH_3\overset{\oplus}{C}HCH_3 \rightarrow C_6H_5CH(CH_3)_2 + H^{\oplus} \tag{22.4.12}$$

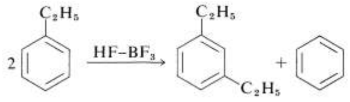
Rearrangements of this type involving carbocation intermediates often occur in Friedel-Crafts alkylations with primary and secondary alkyl groups larger than C_2 and C_3. Related carbocation rearrangements are discussed in Sections 8-9B and 15-5E.

Rearrangement of products

Further complications arise from the fact that the alkylation reactions sometimes are under equilibrium control rather than kinetic control. Products often isomerize and disproportionate, particularly in the presence of large amounts of catalyst. Thus 1,2- and 1,4-dimethylbenzenes (*ortho*- and *para*-xylenes) are converted by large amounts of Friedel-Crafts catalysts into 1,3-dimethylbenzene (*meta*-xylene):

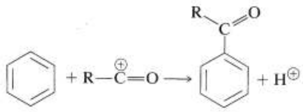


Ethylbenzene disproportionates under the influence of excess $HF-BF_3$ to benzene and 1,3-diethylbenzene:

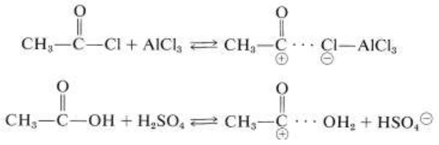


22.4.6: Acylation

Acylation and alkylation of arenes are closely related. Both reactions were developed as the result of the collaboration between Friedel and Crafts, in 1877. The acylation reaction introduces an acyl group, RCO, into an aromatic ring and the product is an aryl ketone:



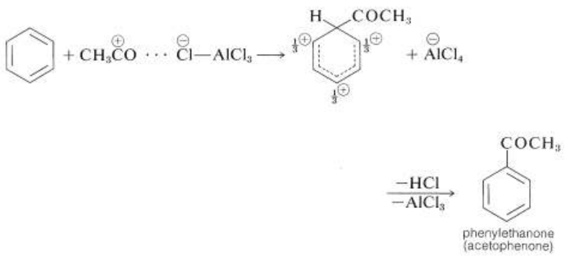
The acylating reagents commonly used are carboxylic acid halides, $RCOCl$, anhydrides, $(RCO)_2O$, or the acid itself, RCO_2H. A strong proton or other Lewis-acid catalyst is essential. The catalyst functions to generate the acyl cation:



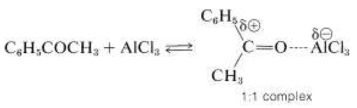
$$CH_3-\overset{O}{\overset{\|}{C}}-Cl + AlCl_3 \rightleftharpoons CH_3-\underset{\oplus}{\overset{O}{\overset{\|}{C}}}\cdots\underset{\ominus}{Cl}-AlCl_3$$

$$CH_3-\overset{O}{\overset{\|}{C}}-OH + H_2SO_4 \rightleftharpoons CH_3-\underset{\oplus}{\overset{O}{\overset{\|}{C}}}\cdots OH_2 + HSO_4^{\ominus}$$

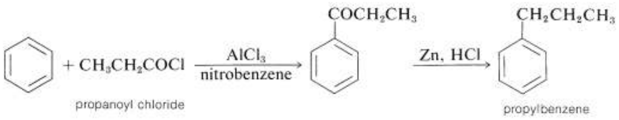
The catalyst most commonly used with acyl halides and anhydrides is aluminum chloride:



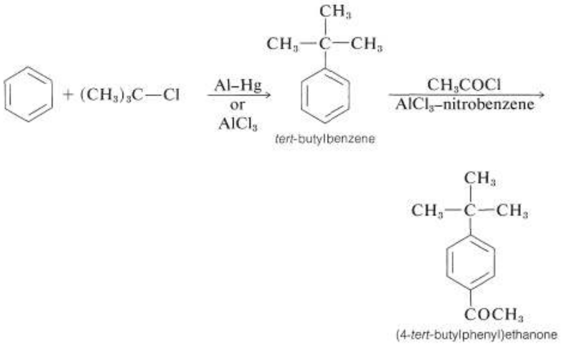
Acylation differs from alkylation in that the reaction usually is carried out in a solvent, commonly carbon disulfide, CS_2, or nitrobenzene. Furthermore, acylation requires more catalyst than alkylation, because much of the catalyst is tied up and inactivated by complex formation with the product ketone:



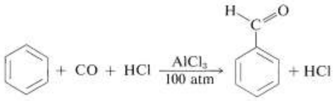
Unlike alkylation, acylation is controlled easily to give monosubstitution, because once an acyl group is attached to a benzene ring, it is not possible to introduce a second acyl group into the same ring. Because of this, a convenient synthesis of alkylbenzenes starts with acylation, followed by reduction of the carbonyl group with zinc and hydrochloric acid (Section 16-6). For example, propylbenzene is prepared best by this two-step route because, as we have noted, the direct alkylation of benzene with propyl chloride produces considerable amounts of isopropylbenzene and polysubstitution products:



In the acylation of alkylbenzene the product almost always is the *para* isomer. The synthesis of (4-*tert*-butylphenyl)ethanone illustrates this as well as the sequential use of alkylation and acylation reactions:



Chemists are inclined to give names to reactions that associate them either with their discoverers or with the products they give. This practice can be confusing because many named reactions (or "name reactions") which once were thought to be quite unrelated, have turned out to have very similar mechanisms. Thus we have two closely related acylation reactions: one is the Friedel-Crafts ketone synthesis, in which the electrophile is $R-\overset{\oplus}{C}=O$; and the other is the **Gattermann-Koch aldehyde synthesis**, in which the electrophile is $H-\overset{\oplus}{C}=O$:

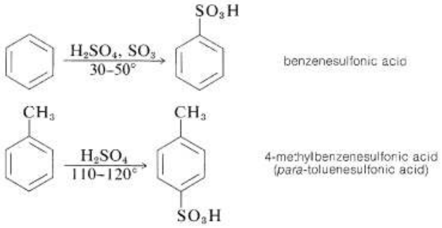


The latter reaction utilizes carbon monoxide and HCl under pressure in the presence of aluminum chloride. The electrophile may be considered to be formed as follows:

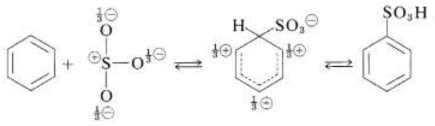
$$C=O+HCl+AlCl_3 \rightleftharpoons H-\overset{\oplus}{C}=O+\overset{\ominus}{A}lCl_4 \tag{22.4.13}$$

22.4.7: Sulfonation

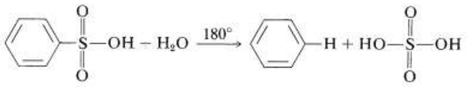
Substitution of the sulfonic acid $\left(-SO_3H\right)$ group for a hydrogen of an aromatic hydrocarbon can be carried out by heating the hydrocarbon with a slight excess of concentrated or fuming sulfuric acid:



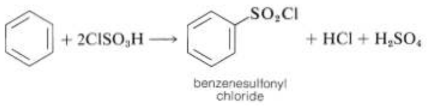
The actual sulfonating agent normally is the SO_3 molecule, which, although neutral, has a powerfully electrophilic sulfur atom:



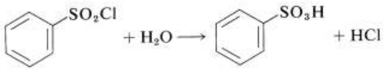
Sulfonation is reversible and the $-SO_3H$ group can be removed by hydrolysis at 180^o:



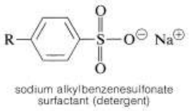
A useful alternative preparation of sulfonyl derivatives is possible with chlorosulfonic acid:



This procedure has an advantage over direct sulfonation in that sulfonyl chlorides usually are soluble in organic solvents and may be easily separated from the reaction mixture. Also, the sulfonyl chloride is a more useful intermediate than the sulfonic acid, but can be converted to the acid by hydrolysis if desired:



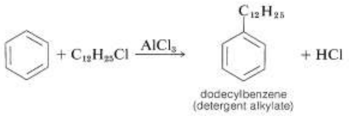
Sulfonation is important in the commercial production of an important class of detergents - the sodium alkylbenzenesulfonates:



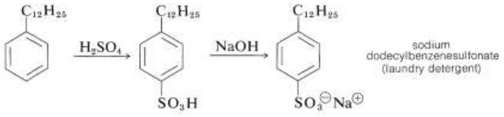
The synthesis illustrates several important types of reactions that we have discussed in this and previous chapters. First, the alkyl group R usually is a C_{12} group derived from the straight-chain hydrocarbon, dodecane, which on photochlorination gives a mixture of chlorododecanes:

$$\underset{\text{dodecane}}{C_{12}H_{26}} + Cl_2 \xrightarrow{h\nu} \underset{\substack{\text{chlorododecanes}\\\text{(primary and secondary)}}}{C_{12}H_{25}Cl} + HCl$$

This mixture of chlorododecanes is used to alkylate benzene, thereby giving a mixture of isomeric dodecylbenzenes, called *detergent alkylate*:



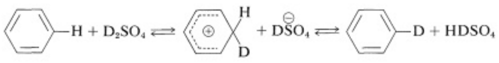
Sulfonation of the detergent alkylate gives exclusively the 4-dodecylbenzenesulfonic acids, which with sodium hydroxide form water-soluble dodecylbenzenesulfonates:



In many countries it is prohibited by law to market detergents of this type, which have highly branched alkyl groups. The reason is that quaternary carbons and, to a lesser extent, tertiary carbons are not degraded readily by bacteria in sewage treatment plants:

22.4.8: Hydrogen Exchange

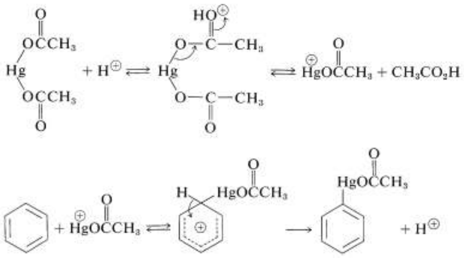
It is possible to replace the ring hydrogens of many aromatic compounds by exchange with strong acids. When an isotopically labeled acid such as D_2SO_4 is used, this reaction is an easy way to introduce deuterium. The mechanism is analogous to other electrophilic substitutions:



Perdeuteriobenzene[3] can be made from benzene in good yield if a sufficiently large excess of deuteriosulfuric acid is used. Deuteration might appear to be competitive with sulfonation, but deuteration actually occurs under much milder conditions.

22.4.9: Aromatic Substitution by Electrophilic Metalation

Because metals are electropositive elements they can be considered potential electrophiles. Their reactions with arenes have been investigated most thoroughly for mercury. Benzene can be substituted with $HgX^{\oplus}$ derived from a mercuric salt, HgX_2, in the presence of an acid catalyst. The salt most commonly used is mercuric ethanoate, $Hg(OOCCH_3)_2$. The catalyst is considered to function by assisting the generation of the active electrophile, $HgX^{\oplus}$. Other metals that may be introduced directly into an aromatic ring in this manner include thallium and lead.



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[3] The prefix *per*, as in perdeuterio- or perfluoro-, means that *all* the hydrogens have been replaced with the named substituent, D or F. Perhydro means saturated or fully hydrogenated.

22.4.10: Contributors and Attributions

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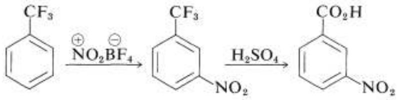
22.5: Effect of Substituents on Reactivity and Orientation in Electrophilic Aromatic Substitution

In planning syntheses based on substitution reactions of substituted benzenes, it is imperative to be able to predict in advance which of the available positions of the ring are likely to be most reactive. This is now possible with a rather high degree of certainty, thanks to the work of many chemists during the past 100 years. Few, if any, other problems in organic chemistry have received so much attention over so many years, and there are now sufficient data on the orientation and reactivity effects of ring substituents in electrophilic substitution to permit the formation of some very valuable generalizations.

Basically, three experimental problems are involved in the substitution reactions of aromatic compounds: (1) proof of structure of the isomers that are formed; (2) determination of the percentage of each isomer formed, if the product is a mixture; and (3) measurement of the reactivity of the compound being substituted relative to some standard substance, usually benzene.

For benzenoid compounds, structures can be established by the historically important substitution method (Section 1-1F) or with the aid of correlations between spectroscopic properties and positions of substitution, as we indicated in Section 22-3. Also, it is often possible to identify the isomers by converting them to compounds of known structure. For example, trifluoromethylbenzene on nitration gives only one product, which has been shown to be the 3-nitro derivative by conversion to the known 3-nitrobenzoic acid by concentrated sulfuric acid:

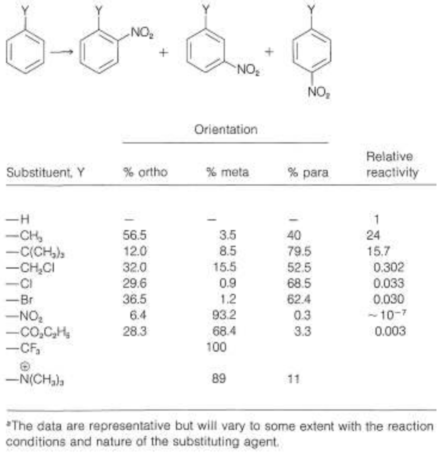


The ratios of isomers formed in substitution reactions can be determined by spectroscopic means or by the analytical separation methods discussed in Section 9-2. We mainly are concerned in this chapter with the reactivity and orientation observed in aromatic substitution.

22.5.1: The Pattern of Orientation in Aromatic Substitution

The reaction most studied in connection with the orientation problem is nitration, but the principles established also apply for the most part to the related reactions of halogenation, sulfonation, alkylation, and acylation. Some illustrative data for the nitration of a number of mono-substituted benzene derivatives are given in Table 22-5. The table includes the percentage of ortho, meta, and para isomers formed, along with their reactivities relative to benzene. We see that there is a wide range of reactivity according to the nature of the substituent, and that the ortho, meta, and para positions are *not* equally reactive. Although these substituent effects may appear complex, they are related closely to substituted alkenes (Section 10-4), as will be explained in the following section.

Table 22-5: *Orientation and Rate Data for Nitration of Some Monosubstituted Benzene Derivatives*^{a}



	Orientation			
Substituent, Y	% ortho	% meta	% para	Relative reactivity
$-H$	–	–	–	1
$-CH_3$	56.5	3.5	40	24
$-C(CH_3)_3$	12.0	8.5	79.5	15.7
$-CH_2Cl$	32.0	15.5	52.5	0.302
$-Cl$	29.6	0.9	68.5	0.033
$-Br$	36.5	1.2	62.4	0.030
$-NO_2$	6.4	93.2	0.3	$\sim 10^{-7}$
$-CO_2C_2H_5$	28.3	68.4	3.3	0.003
$-CF_3$		100		
$-\overset{\oplus}{N}(CH_3)_3$		89	11	

[a] The data are representative but will vary to some extent with the reaction conditions and nature of the substituting agent.

22.5.2: Electronic Effects

It is helpful to construct an energy diagram for substitution by an electrophilic $X^{\oplus}$ of a benzene derivative, C_6H_5Y, in which Y is a substituent group (Figure 22-8). The rate of substitution at any one position (we have arbitrarily chosen in Figure 22-8 to compare the 3 and 4 positions) will depend on the height of the energy barrier between the reactants and the transition state. Effects that act to lower the heights of the barriers increase the rates of substitution. Because the transition state and the positively charged intermediate for aromatic substitution have much the same energy, any effect that stabilizes this intermediate is likely to lower the energy of the transition state and increase the rate of substitution. Thus under conditions of *kinetic control* the preferred arene substitution product, as in alkene addition, will be that derived from the most stable of the possible intermediates. Therefore the problem of predicting relative rates and orientation in aromatic substitution becomes one of deciding what factors are likely to stabilize or destabilize the various possible intermediates relative to one another and to the ground state.

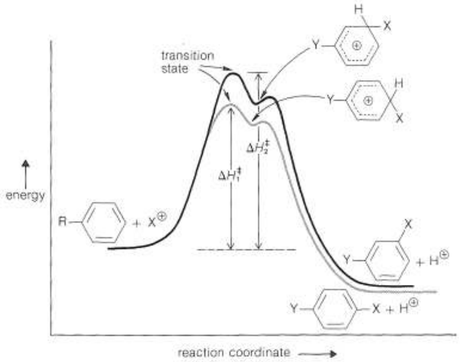
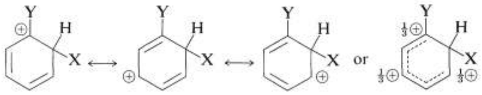


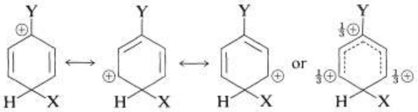
Figure 22-8: Energy diagram for the substitution of a compound C_6H_5Y in the 3 and 4 positions. It is assumed here that the relative rates are determined by differences in $\Delta H^\ddagger$ and not in $\Delta S^\ddagger$. Because $\Delta H_1^\ddagger$ is less than $\Delta H_2^\ddagger$, substitution to give the 4-isomer is "kinetically preferred".

We now can examine the structures of the three substitution intermediates with a view to deciding how the substituent might affect their stability. According to the valence-bond method, the positive charge in the ring is dispersed mainly on alternate carbons, as shown below.

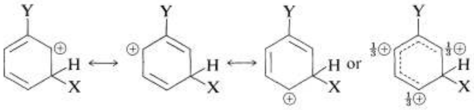
ortho substitution



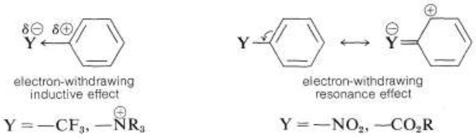
para substitution



meta substitution



The substituent Y should (and does) exert its electronic influence more strongly from the ortho and para positions than from the meta position because Y in the ortho and the para positions is close to a positively charged ring carbon. This electronic influence will be stabilizing if Y has a net electron-donating effect, and destabilizing if Y is electron withdrawing. A group can withdraw electrons relative to hydrogen if it is more electronegative than hydrogen and this is called the electron-withdrawing inductive effect (also see Section 18-2B). A group also can withdraw electrons by the **resonance effect**:

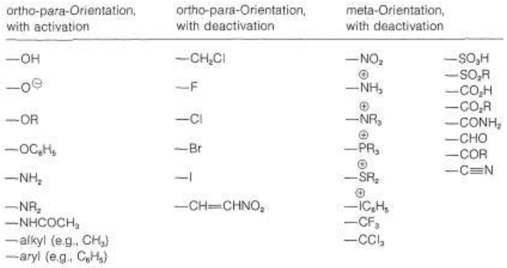


Accordingly, substituents fall into one of the following categories.

22.5.2.1: Meta-directing substituents

A ring substituent Y that is electron withdrawing relative to hydrogen and has no capacity to donate electrons by a resonance effect will *decrease* the reactivity of $\mathrm{C_6H_5Y}$, especially at the ortho and para positions. The result is a sluggish reaction (**deactivation**) with substitution occurring preferentially at the meta position. Substituents in this category are $-\mathrm{NO_2}$, $-\mathrm{CF_3}$, $-\mathrm{CO_2R}$, $-\overset{\oplus}{\mathrm{N}}\mathrm{R_3}$, and so on (also see Tables 22-5 and 22-6). No groups are known that direct the electrophile to the meta position and, at the same time, make the phenyl derivative *more* reactive relative to benzene.

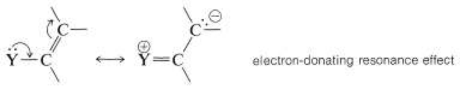
***Table 22-6:** Orientation and Reactivity Effects of Ring Substituents*



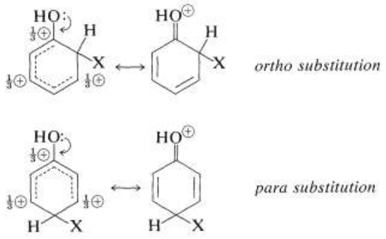
ortho-para-Orientation, with activation	ortho-para-Orientation, with deactivation	meta-Orientation, with deactivation	
$-\mathrm{OH}$	$-\mathrm{CH_2Cl}$	$-\mathrm{NO_2}$	$-\mathrm{SO_3H}$
$-\mathrm{O}^{\ominus}$	$-\mathrm{F}$	$-\overset{\oplus}{\mathrm{N}}\mathrm{H_3}$	$-\mathrm{SO_2R}$
$-\mathrm{OR}$	$-\mathrm{Cl}$	$-\overset{\oplus}{\mathrm{N}}\mathrm{R_3}$	$-\mathrm{CO_2H}$
$-\mathrm{OC_6H_5}$	$-\mathrm{Br}$	$-\overset{\oplus}{\mathrm{P}}\mathrm{R_3}$	$-\mathrm{CO_2R}$
$-\mathrm{NH_2}$	$-\mathrm{I}$	$-\overset{\oplus}{\mathrm{S}}\mathrm{R_2}$	$-\mathrm{CONH_2}$
$-\mathrm{NR_2}$	$-\mathrm{CH{=}CHNO_2}$	$-\overset{\oplus}{\mathrm{I}}\mathrm{C_6H_5}$	$-\mathrm{CHO}$
$-\mathrm{NHCOCH_3}$		$-\mathrm{CF_3}$	$-\mathrm{COR}$
—alkyl (e.g., $\mathrm{CH_3}$)		$-\mathrm{CCl_3}$	$-\mathrm{C{\equiv}N}$
—aryl (e.g., $\mathrm{C_6H_5}$)			

22.5.2.2: Ortho-para directing substituents

1. A ring substituent, $-\mathrm{Y}$, that has an electron pair on the atom adjacent to the ring gives ortho-para substitution in preference to meta substitution. The reason is that the intermediate can be stabilized by an electron-donating resonance effect from Y that is effective from the ortho and para positions only:



This effect is made clear in the valence-bond structures for the ortho-para substitution intermediates from benzenol (phenol):



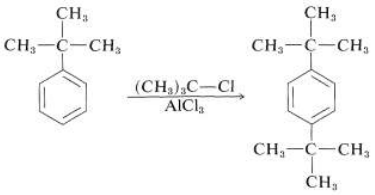
Substituents of the type $-\mathrm{Y}$ include $-\mathrm{OH}$, $-\mathrm{OR}$, $-\mathrm{SR}$, $-\mathrm{NH_2}$, and halogens. Most of these groups also are electron withdrawing by an inductive effect that opposes their resonance effect. However, as we saw in the case of alkene additions (Section 10-4C), even when $-\mathrm{Y}$ is an electronegative group, stabilization of the intermediate cation by donation of unshared electrions of Y to the adjacent positive carbon more than compensates for the polar electron-withdrawing properties of Y. Electron donation thus controls the orientation. If, however, the group is *strongly* electron withdrawing (e.g., $-\mathrm{Y} = -\mathrm{F}$, $-\mathrm{Cl}$, $-\mathrm{Br}$, $-\mathrm{I}$), the reactivity of the compound $\mathrm{C_6H_5Y}$ may be reduced. Groups of this kind are ortho-para directing with deactivation.

But if the polar effect is not pronounced, then substitution can be powerfully assisted by the substituent. This is ortho-para direction with activation and is provided by groups such as $-\mathrm{OH}$, $-\mathrm{OR}$, $-\mathrm{SR}$, and $-\mathrm{NH_2}$. A more comprehensive list of substituents and their orientation effects is provided in Table 22-6.

2. When no important π-electron effect is possible, as with alkyl groups, the orientation effect of a substituent is controlled by its polar effect and the degree to which it polarizes the bonding electrons of the ring. Alkyl groups actually are electron donating and therefore are ortho-para directing with activation.

22.5.3: Steric Effects

Thus far we have made no distinction between the reactivities of the ortho and the para positions, yet they clearly are not equal. If they were equal, the ortho:para ratio would be 2:1, thereby reflecting the fact that there are two ortho positions but only one para position in monosubstituted benzenes. Most substitution reactions favor the para product, sometimes by a considerable amount (see Table 22-5). A reasonable explanation is that ortho substitution is subject to steric hindrance between the substituent and the entering group. *tert*-Butylbenzene, for example, gives much less ortho nitration than methylbenzene (Table 22-5), thereby suggesting that the size of the substituent is important. Also, *tert*-butylbenzene gives no ortho alkylation with *tert*-butyl chloride, suggesting that the size of the entering group is also important:



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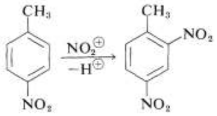
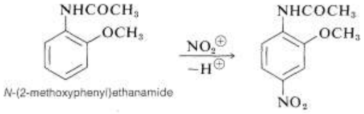
22.6: Orientation in Disubstituted Benzenes

The orientation and reactivity effects of substituents discussed for the substitution of monosubstituted benzenes also hold for disubstituted benzenes, except that the directing influences now come from two groups. Qualitatively, the effects of the two substituents are additive on the reactivity. We therefore would expect 4-nitromethylbenzene to be less reactive than methylbenzene because of the deactivating effect of a nitro group. Also, the most likely position of substiuttion should be, and is, ortho to the methyl group and meta to the nitro group:



When the two substituents have opposed orientation effects, it is not always easy to predict what products will be obtained. For example, N-(2-methoxyphenyl)ethanamide has two powerful *o*,*p*-directing substituents, $-\mathrm{OCH_3}$ and $-\mathrm{NHCOCH_3}$. Nitration of this compound gives mainly the 4-nitro derivative, which indicates that the $-\mathrm{NHCOCH_3}$ exerts a stronger influence than $-\mathrm{OCH_3}$:



Seemingly anomalous effects of substituents are known, but such effects may be due to equilibrium control. One example is the aluminum chloride-catalyzed alkylation of benzene, which leads to the formation of a 1,3,5-trialkylbenzene in preference to the expected 1,2,4-isomer (see Section 22-4E). The preferred reaction occurs particularly readily because alkylation is reversible and because alkylation is one of the least selective of the electrophilic aromatic substitutions (considerable meta isomer is formed even under conditions where kinetic control is dominant). Equilibrium control, which favors the 1,3,5-product rather than the less stable 1,2,4-product, becomes most evident when the reaction time, the reaction temperature, and aluminum chloride concentration are increased. Another source of anomalous substituent effects is discussed in the next section.

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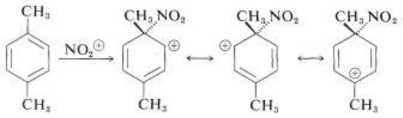
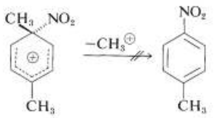
22.7: IPSO Substitution

For all practical purposes, electrophilic aromatic substitution is confined to the substitution of a ring hydrogen. Does this mean that an electrophile such as NO_2^+ only attacks hydrogen-bearing carbons? What about substituted ring carbons?

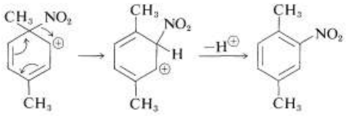
Electrophilic attack at methyl-bearing carbons, particularly in *ortho*- and *para*-dimethylbenzenes, would appear quite reasonable because the electron-donating character of the other methyl group should activate the ring by stabilizing the intermediate ion:



Attack at the substituted (*ipso*) carbon evidently does occur, but it does not lead directly to substitution products because demethylation, unlike deprotonation, does not occur:

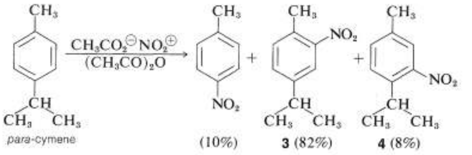


Instead, the nitro group changes positions to the neighboring ring carbon, which then can eliminate a proton to form a substitution product:



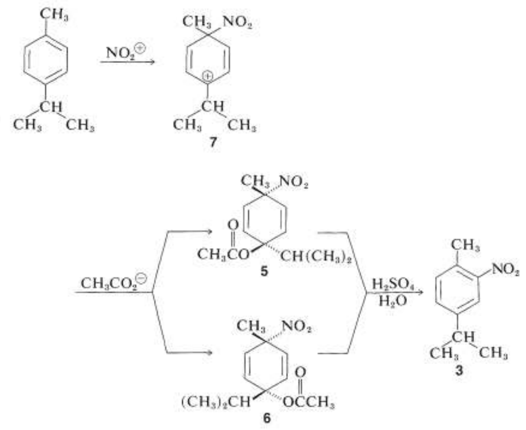
Because the product obtained indirectly (by *ipso* substitution) is indistinguishable from that expected by direct electrophilic attack at C_2, it is not possible to say how much, if any, product is formed by the *ipso* route in this reaction.

In general, orientation effects in the substitution of alkylbenzenes are complicated by *ipso* attack. For example, in the nitration of 4-methylisopropylbenzene (*para*-cymene) about 10% of the nitration product is 4-nitromethylbenzene:



(22-1)

The 4-nitromethylbenzene arises from *ipso* attack of NO_2^+ at the isopropyl-substituted ring carbon. Unlike methyl, the isopropyl group is eliminated rapidly as propene. Can we say that the other products, **3** and **4**, arise by direct substitution? Evidently not, because nitration at 0° gives two other products, **5** and **6**, which must be formed by *ipso* attack at the *methyl*-bearing carbon. At low temperatures, intermediate ion **7** is attacked by the weakly nucleophilic ethanoate ion to give **5** and **6**. Both of these adducts solvolyze rapidly in 78% sulfuric acid to give **3** only:



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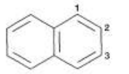
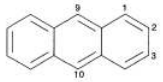
22.8: Substitution Reactions of Polynuclear Aromatic Hydrocarbons

Although naphthalene, phenanthrene, and anthracene resemble benzene in many respects, they are more reactive than benzene in both substitution and addition reactions. This increased reactivity is expected on theoretical grounds because quantum-mechanical calculations show that the net loss in stabilization energy for the first step in electrophilic substitution or addition decreases progressively from benzene to anthracene; therefore the reactivity in substitution and addition reactions should increase from benzene to anthracene.

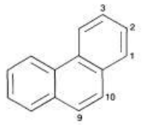
In considering the properties of the polynuclear hydrocarbons relative to benzene, it is important to recognize that we neither expect nor find that all the carbon-carbon bonds in polynuclear hydrocarbons are alike or correspond to benzene bonds in being halfway between single and double bonds.



naphthalene



anthracene

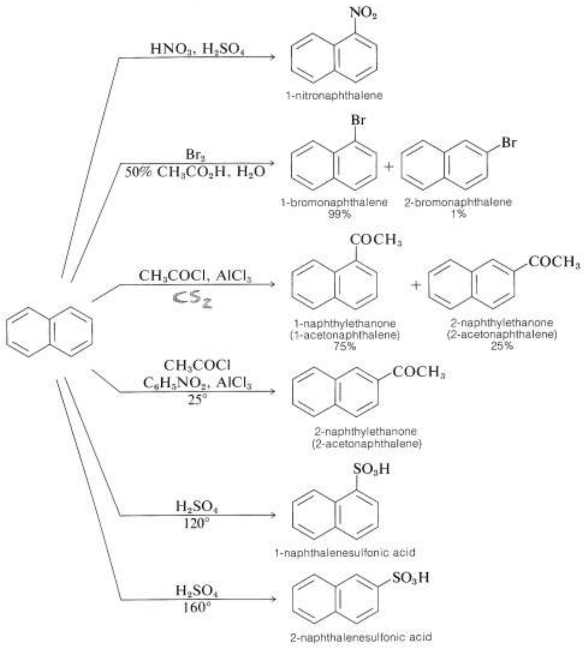


phenanthrene

The 1,2 bonds in both naphthalene and antracene are in fact shorter than the other ring bonds, whereas the 9,10 bond in phenanthrene closely resembles an alkene double bond in both its length and chemical reactivity.

22.8.1: Naphthalene

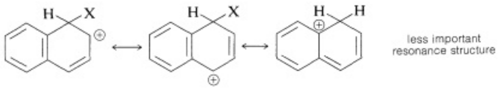
Orientation in the substitution of naphthalene can be complex, although the 1 position is the most reactive. Some examples follow.



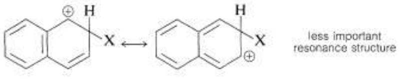
Sometimes, small changes in the reagents and conditions change the pattern of orientation. One example is sulfonation, in which the orientation changes with reaction temperature. Another example is Friedel-Crafts acylation; in carbon disulfide the major product is the 1-isomer, whereas in nitrobenzene the major product is the 2-isomer.

Substitution usually occurs more readily at the 1 position than at the 2 position because the intermediate for 1-substitution is more stable than that for 2-substitution. The reason is that the most favorable resonance structures for either intermediate are those that have *one fully aromatic* ring. We can see that 1-substitution is more favorable because the positive charge can be distributed over two positions, leaving one aromatic ring unchanged. Only one resonance structure is possible for the 2-substitution intermediate that retains a benzenoid-bond arrangement for one of the rings.

1-substitution

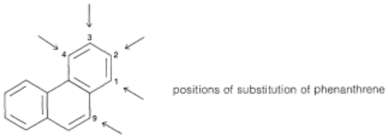


2-substitution

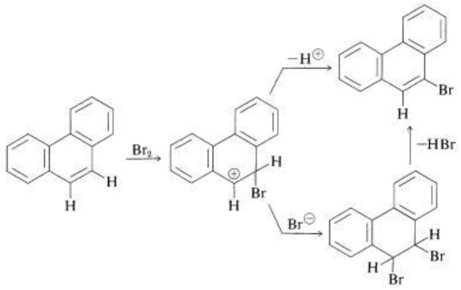


22.8.2: Phenanthrene

The reactions of the higher hydrocarbons with electrophilic reagents are more complex than of naphthalene. For example, phenanthrene can be nitrated and sulfonated, and the products are mixtures of 1-, 2-, 3-, 4-, and 9-substituted phenanthrenes:



However, the 9,10 bond in phenanthrene is quite reactive; in fact is is almost as reactive as an alkene double bond. Addition therefore occurs fairly readily; halogenation can give both 9,10-addition and 9-substitution products by the following scheme:



22.8.3: Anthracene

Anthracene is even more reactive than phenanthrene and has a greater tendency to add at the 9,10 positions than to substituted. However, the addition products of nitration and halogenation readily undergo elimination to form the 9-substitution products:

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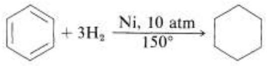
22.9: Addition Reactions of Arenes

22.9.1: Catalytic Hydrogenation

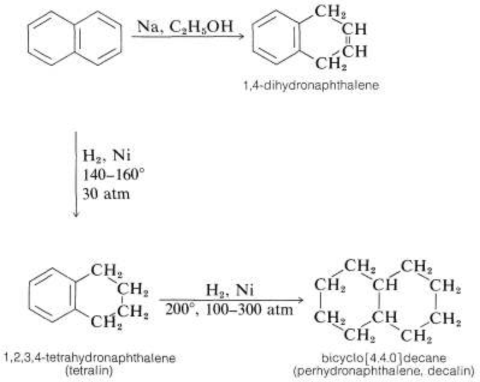
Benzenoid compounds are not readily converted to cyclohexane derivatives. Nevertheless, several addition reactions are carried out on an industrial scale. Mention was made previously of the hydrogenation of benzene to cyclohexane in the presence of a nickel catalyst:



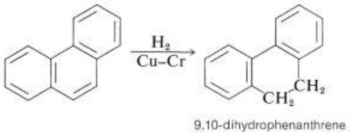
The reaction is very important because cyclohexane is used widely as a solvent and also is oxidized to cyclohexanone, and important intermediate in the synthesis of hexanedioic (adipic) acid and azacycloheptan-2-one (caprolactam), which are used in the preparation of nylon (Section 24-3C).

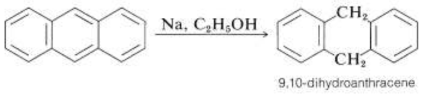
Other cyclohexyl compounds are obtained by catalytic hydrogenation of the corresponding benzene derivatives. Thus cyclohexanol is obtained from benzenol, and cyclohexanamine is obtained from benzenamine (aniline):

Naphthalene can be reduced more easily than benzene. With sodium in alcohol, 1,4-dihydronaphthalene is formed. Catalytic hydrogenation gives tetralin (1,2,3,4-tetrahydronaphthalene). Further reduction to give perhydronaphthalene (decalin) can be achieved on prolonged catalytic hydrogenation at relatively high temperatures and pressures:



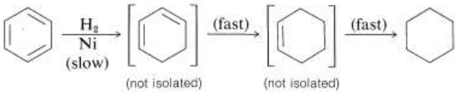
Phenanthrene and anthracene are reduced readily to the dihydro level by addition to the 9,10 positions. Further reduction of the terminal benzene rings is relatively difficult:





22.9.2: Reduction of Arenes with Metals

Catalytic hydrogenation of benzene cannot be stopped at cyclohexane or cyclohexadiene; it proceeds to cyclohexane. This is because the rate of the first addition step is much slower than of the subsequent steps:



However, benzene and its derivatives can be reduced to cyclohexadienes by solutions of metals such as Li, Na, K, Zn, and Hg in a weakly acidic solvent, such as liquid ammonia, amines, or ether-alcohol mixtures. This general type of reaction is known as the **Birch reduction** after the Australian chemist, A. J. Birch. With benzene, reduction with metals leads to 1,4-cyclohexadiene:

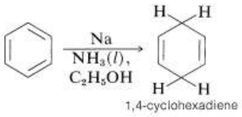
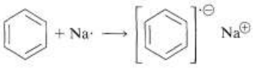
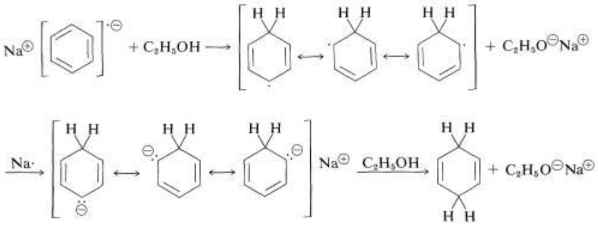


Figure 21-5) to form a radical anion:

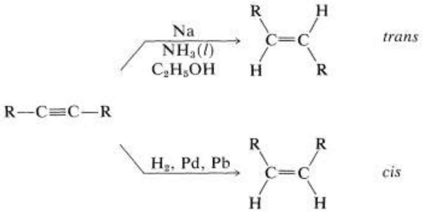


Subsequent steps include a sequence of proton- and electron-transfer steps as follows:



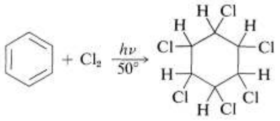
Substituent effects observed for this reaction are entirely consisent with those described for electrophilic substitution and addition - only reversed. That is, the reactivity of an arene in metal reductions is increased by electron-withdrawing groups and decreased by electron-donating groups. Substituents that can stabilize the anion-radical intermediate facilitate the reduction.

Reduction with metals in weakly acidic solvents is not restricted to arenes. A useful related reaction reduces alkynes to *trans*-alkenes, and provides a useful alternative to catalytic hydrogenation, which favors formation of *cis*-alkenes (Section 11-2A):

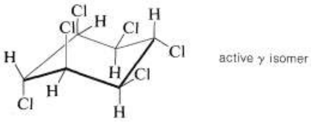


22.9.3: Halogen Addition

Benzene will add chlorine on irradiation with light to give the fully saturated hexachlorocyclohexane as a mixture of stereoisomers:

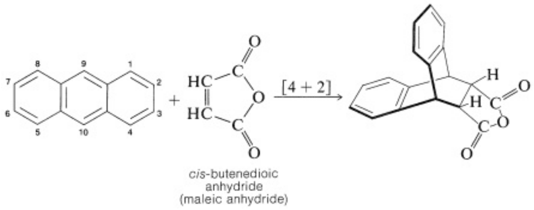


The reaction is commercially important because one of the isomers is a potent insecticide. The product is marketed as a mixture of isomers in which the active isomer (γ) is optimally about 40% by weight. It has a variety of trade names: Fortified, BHC, Lindane, Gammexane, Hexachlor.

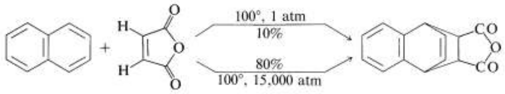


22.9.4: Cycloaddition

In Chapter 13 we encountered the Diels-Aler reaction, which involves addition of a reactive alkene (dienophile) to the 1,4 positions of a conjugated diene. Neither benzene nor naphthalene reacts significantly with dienophiles on simple heating, but anthracene does react. Cycloaddition occurs between the 9,10 positions:



Reactions in which the transition state has a *smaller* volume than the reactants are speeded up by an increase in pressure. This is the case with naphthalene and *cis*-butenedioic anhydride. An 80% yield of adduct is obtained at 100^o at 15,000 atmospheres pressure, whereas at one atmosphere and 100^o, the yield is only 10%.



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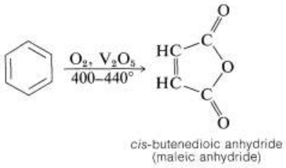
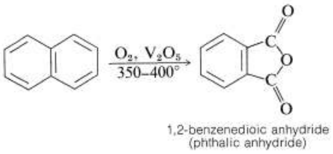
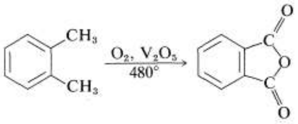
22.10: Oxidation Reactions

The reagents usually employed for the oxidation of alkenes (e.g., CrO_3, $KMnO_4$, H_2O_2, OsO_4) normally do not attack benzene. At high temperatures, benzene can be oxidized to *cis*-butenedioic (maleic) anhydride by air with a vanadium pentoxide catalyst. Naphthalene can be similarly oxidized to 1,2-benzenedioic (phthalic) anhydride:



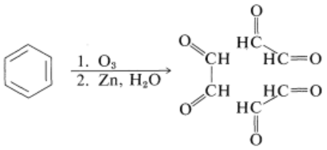


Both anhydrides are prepared in this manner on a large scale for use in the production of ester polymers (Section 29-5A). Phthalic anhydride also is prepared by the oxidation of 1,2-dimethylbenzene:

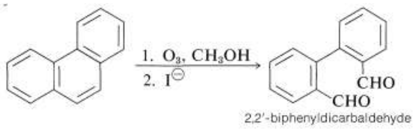


Phthalic anhydride is used to make anthraquinone and to make esters of phthalic acid, which are used widely to plasticize polymers.

Ozonization of aromatic hydrocarbons is possible. Benzene itself gives ethanedial (glyoxal):



The double-bond character of the 9,10 bond in phenanthrene is particularly evident in ozonization. This bond is attacked preferentially, which leads to the formation of a dialdehyde when the ozonide is reduced with iodide ion:



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22.11: Sources and Uses of Aromatic Hydrocarbons

Benzene and many of its derivatives are manufactured on a large scale for use in high-octane gasolines and in the production of polymers, insecticides, detergents, dyes, and many miscellaneous chemicals. Prior to World War II, coal was the only important source of aromatic hydrocarbons, but during the war and thereafter, the demand for benzene, methylbenzene, and the dimethylbenzenes rose so sharply that other sources had to be found. Today, most of the benzene and almost all of the methylbenzene and the dimethylbenzenes produced in the United States are derived from petroleum.

Coal tar, which is a distillate obtained in the coking of coal (Section 4-2), is a source of an amazing number of aromatic compounds. Some of these are listed in Table 22-7, which includes nitrogen, oxygen, and sulfur compounds, as well as hydrocarbons. Although petroleum from some locations contains fairly substantial amounts of aromatic hydrocarbons, it is not a principal source for such compounds. Rather, aromatic compounds are synthesized from the C_6-C_{10} gasoline fraction from petroleum refining by a process referred to in the petroleum industry as **catalytic re-forming** or **hydroforming**. This involves heating a C_6-C_{10} fraction with hydrogen in the presence of a catalyst to modify the molecular structure of its components. Some amazing transformations take place, and the C_6-C_7 alkanes can be converted to cycloalkanes, which, in turn, are converted to arenes. Benzene, methylbenzene (toluene), and the dimethylbenzenes (xylenes) are produced primarily in this way:

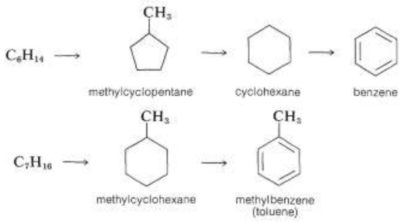
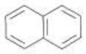
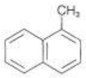


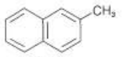
Table 22-7: *Principal Compounds Obtained from Coal Tar*[a,b]

Hydrocarbons[c]

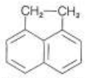

naphthalene



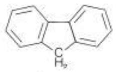
1-methyl-
naphthalene



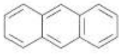
2-methyl-
naphthalene

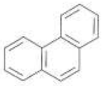


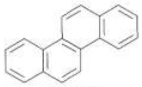
acenaphthene

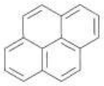


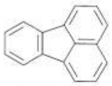
fluorene


anthracene


phenanthrene

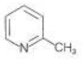

chrysene


pyrene

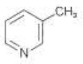

fluoranthene

Nitrogen compounds

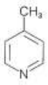
azabenzene
(pyridine)



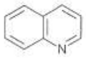
2-methylazabenzene
(α-picoline)



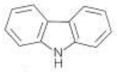
3-methylazabenzene
(β-picoline)



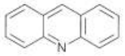
4-methylazabenzene
(γ-picoline)



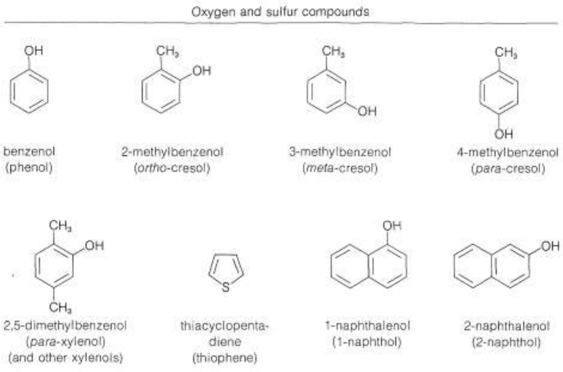
1-azanaphthalene
(quinoline)



9-azafluorene
(carbazole)



9-azaanthracene
(acridine)



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[a] Compiled from *Chemistry of Coal Utilization*, National Research Council Committee, H. H. Lowry (Ed.), John Wiley and Sons, Inc., 1945.

[b] None of the compounds listed are very abundant in coal tar. Even naphthalene, which is present in the largest amount, constitutes only 10–11% of coal tar.

[c] Benzene and the mono- and dimethylbenzenes are present in very small amount (0.3% total) in coal tar.

Figures 22-9 and 22-10.

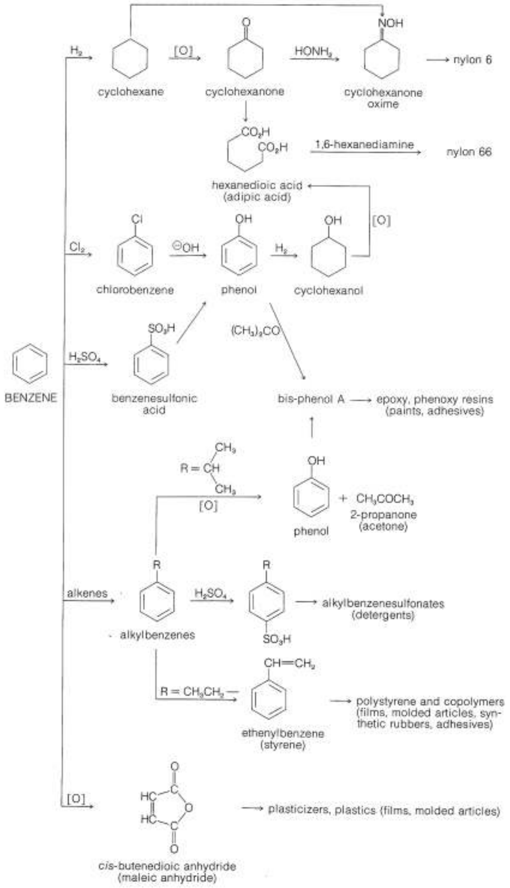

Figure 22-9: Important chemicals derived from benzene.

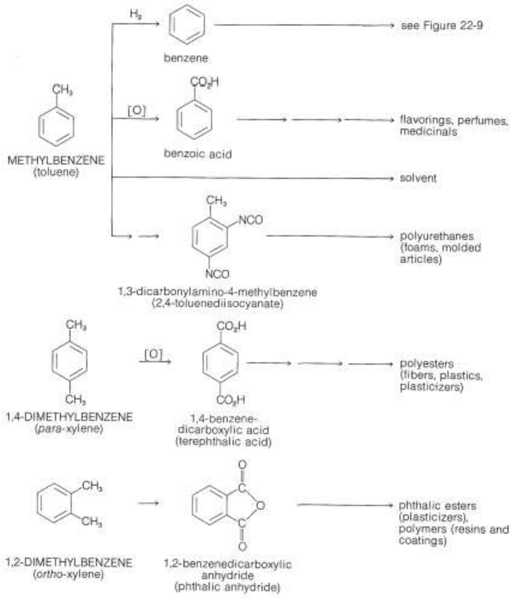

Figure 22-10: Important chemicals derived from methyl-substituted benzenes.

22.11.1: Contributors and Attributions

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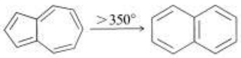
22.12: Some Conjugated Cyclic Polyenes

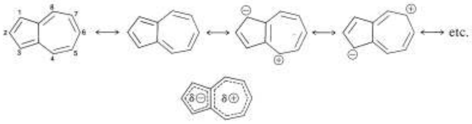
22.12.1: Azulene

There are several compounds that possess some measure of aromatic character typical of benzene, but do not possess a benzenoid ring. Appropriately, they have $(4n+2)$ π electrons and are classified as nonbenzenoid aromatic compounds (Section 21-9). An example is azulene, which is isomeric with naphthalene and has a five- and a seven-membered ring fused through adjacent carbons:

As the name implies, it is deep blue. It is less stable than naphthalene, to which it isomerizes quantitatively on heating above $350°$ in the absence of air:

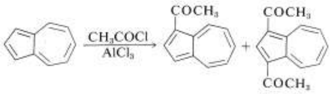


Azulene has a significant polarity, with the five-membered ring negative and the seven-membered ring positive. The structure can be represented as a hybrid of neutral and ionic structures:

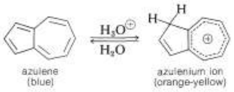


The polarization that has the five-membered ring negative and the seven-membered ring positive corresponds to ionic structures that have *six* (i.e., $4n+2$) electrons in both the five- and seven-membered rings (Section 21-9B).

In keeping with its aromatic character and unsymmetrical charge distribution, azulene undergoes certain typical electrophilic substitution reactions at the 1 and 3 positions. Thus Friedel-Crafts acylation leads to a mixture of 1-ethanoylazulene and 1,3-diethanoylazulene:

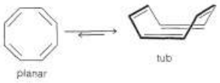


Furthermore, in the presence of strong acids the 1 position is protonated to give a derivative of the relatively stable cycloheptatrienyl (tropylium) ion (Section 21-9B):



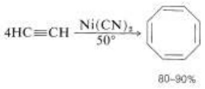
22.12.2: Cyclooctatetraene

1,3,5,7-Cyclooctatetraene (or simply cyclooctatetraene) is a bright-yellow, nonplanar, nonaromatic compound (Section 21-9A). Apparently the resonance energy of a planar structure is insufficient to overcome the unfavorable angle strain of a planar structure would have with its $C-C-C$ bond angles of $135°$. Cyclooctatetraene normally assumes a "tub" structure with alternating single and double bonds:



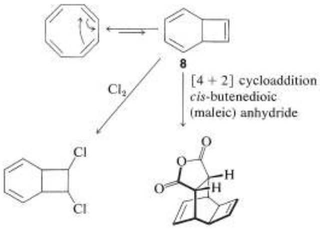
There is, however, nmr evidence that indicates that the tub form is in rapid equilibrium with a very small amount of the planar form at room temperature. There is about a 15-kcal mol^{-1} energy difference between the two forms. The dication, $C_8H_8{}^{2+}$, and the dianion of cyclooctatetraene, $C_8H_8{}^{2-}$, which have $(4n+2)$ π electrons, appear to exist in planar conformation.

Cyclooctatetraene can be prepared readily by polymerization of ethyne in the presence of nickel cyanide:

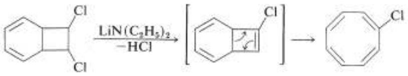


It could be manufactured on a large scale, but no large-scale commercial uses of the substance have yet been developed.

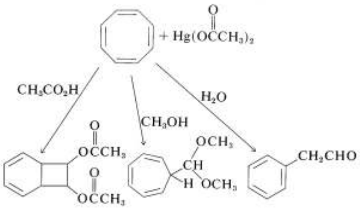
The chemistry of cyclooctatetraene is interesting and unusual. Particularly noteworthy is the way in which it undergoes addition reactions to form products that appear to be derived from the bicyclic isomer, bicyclo[4.2.0]2,4,7-octatriene, 8. In fact, there is an electrocyclic equilibrium between cyclooctatetraene and 8 (Section 21-10D) and, although the position of equilibrium lies far on the side of cyclooctatetraene, 8 is more reactive and leads to the observed addition products:



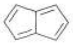
Treatment of the bridged dichloride with strong bases causes elimination of hydrogen chloride and formation of chlorocyclooctatetraene:



The diverse ways in which cyclooctatetraene can react with a give reagent under different conditions is well illustrated by the variety of products obtained with mercuric ethanoate in ethanoic acid, methanol, and water:



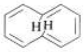
Efforts to prepare "pentalene", a bridged analog of cyclooctatetraene, have not been very successful so far. A substance that appears to be a methylpentalene has been characterized at −180° by its spectral properties. On warming to −105° it forms a dimer.


pentalene

22.12.3: Annulenes

Cyclooctatetraene is nonplanar. One reason is that the angle strain is severe in the planar form. Is it possible that larger-ring conjugated polyalkenes may have strainless planar structures? Models show that a strainless structure can be achieved with two or more of the double bonds only in *trans* configurations, and then only with a large enough ring that the "inside" hydrogens do not interfere with one another.

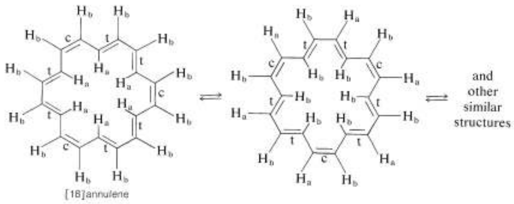
In discussing compounds of this type, it will be convenient to use the name *[n]annulene* to designate the simple conjugated cyclic polyalkenes, with *n* referring to the number of carbons in the ring - benzene being [6]annulene. The simplest conjugated cyclic polyolefin that could have a strainless planar ring containing trans double bonds, except for interferences between the inside hydrogens, is [10]annulene:



[10]annulene

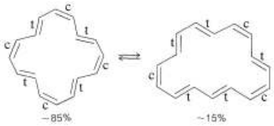
Inside-hydrogen interferences are likely to be of some importancee in all annulenes up to [30]annulene. Many annulenes have been synthesized by F. Sondheimer.

We have mentioned already (Section 22-3C) the large differences in nmr chemical shifts between the inside and outside hydrogens of [18]annulene - a substance which with 18 π electrons should be aromatic by the $4n+2$ rule. These differences are observed only at low temperatures. The proton nmr spectrum of [18]annulene at room temperature is a single resonance, which indicates that the inside (H_a) and outside (H_b) hydrogens are equilibrating rapidly. This can take place only if cis-trans interconversion occurs about the double bonds (marked c and t):



At low temperatures, this equilibrium is slow enough that separate groups of resonances for the inside and outside hydrogens can be discerned in an nmr experiment (see Sections 9-10C and 27-2).

A theoretical prediction that has been borne out by experiment is that an annulene with $4n$ π electrons should have a *paramagnetic* circulation of electrons - that is, opposite in direction to that shown in Figure 22-4 for benzene. For example, [16]annulene, which has $4n$ electrons, is not very stable and exists as a very rapidly interconverting mixture of two configurational isomers:



At very low temperatures $(-155°)$, the proton nmr spectrum shows the *inner* hydrogens at $\delta 12.9$-10.5 and the outer hydrogens at $\delta 5.7$ -6.4, which is in exactly the opposite order to the shifts with [18]annulene and the other known $[4n+2]$ π-electron annulenes.

The annulenes generally are not stable compounds, but the $[4n+2]$annulenes clearly show typical aromatic reactions. For instance [18]annulene has been converted to the nitro, ethanoyl, bromo, and carbaldehyde derivatives by electrophilic substitution reactions.

22.12.4: Contributors and Attributions

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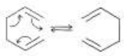
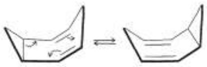
22.13: Fluxional Compounds

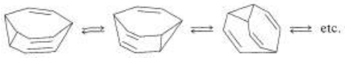
A number of compounds are known to rearrange from one structure to an entirely equivalent structure, sometimes with extraordinary facility. Such compounds are said to be **fluxional** to distinguish from tautomers (which usually involve rearrangements between nonequivalent structures). Simple examples are the Cope rearrangement of 1,5-hexadiene,



and the electrocyclic rearrangement of bicyclo[5.1.0]-2,5-octadiene,


9a 9b

If the two methylenes of 9 are bridged with two double-bonded carbons, we get the remarkable structure 10, called "bullvalene", which rapidly interconverts amongst equivalent structures:



10a 10b

Equilibration of fluxional molecules must not be confused with resonance. In each electrocyclic reaction, the nuclei alter their positions as bond lengths and angles change. Interconversion of fluxional molecules also must not be confused with conformational changes (as in the interconversion of two equivalent chair forms of cyclohexane). In the interconversion of fluxional molecules, chemical bonds are broken and made; in conformational changes, no bonds are broken and no bonds are made.

> *Equilibration of fluxional molecules must not be confused with resonance.*

A theoretical prediction is that the very-large-ring annulenes, even those with $[4n+2]$ π electrons, may not have sufficient resonance energy to maintain equal bond lengths between the carbons and hence would be most stable with alternating double and single bonds. These substances then would be as Kekule thought benzene to be - a fluxional, equilibrating mixture of cyclohexatrienes! This does *not* mean that there would be no π-electron delocalization in fluxional cyclic polyenes; it means only that the VB structures would *not* be exactly equivalent and the MO model would have a σ-bond framework with alternating short and long $\mathrm{C{-}C}$ bonds. The theory suggests that if alternation in bond lengths occurs, then neither diamagnetic nor paramagnetic circulation of the π electrons should be important. The synthesis and study of [26]- and [30]annulenes seems to bear out this prediction, in that with these substances there appears to be no ring-current effect on the proton chemical shifts.

22.13.1: Contributors and Attributions

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22.E: Arenes, Electrophilic Aromatic Substitution (Exercises)

Exercise 22-1 How many structurally different monomethyl derivatives are possible for each of the following compounds? Name each.

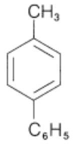
a. naphthalene
b. anthracene
c. phenanthrene

Exercise 22-2 How many isomeric products could each of the dimethylbenzenes give on introduction of a third substituent? Name each isomer, using chlorine as the third substituent.

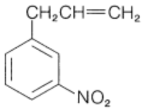
Exercise 22-3 Name each of the following compounds by the IUPAC system:

a. $(C_6H_5)_2CHCl$
b. $C_6H_5CHCl_2$
c. $C_6H_5CCl_3$

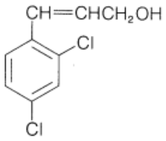
d.



e.



f.



Exercise 22-4 Identify the two compounds with molecular formula C_7H_7Cl from the infrared spectra shown in Figure 22-2.

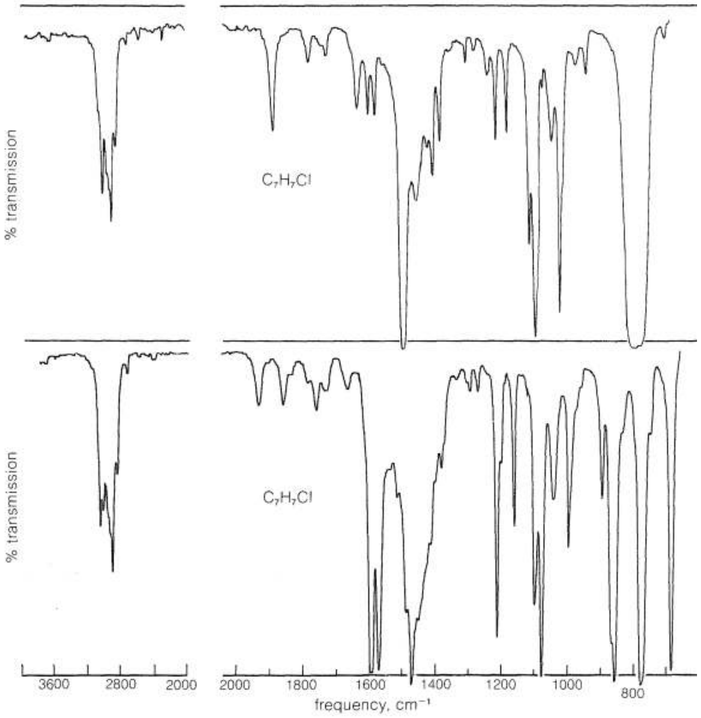
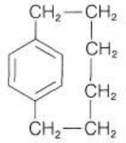


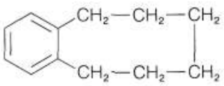
Figure 22-2: *Infrared spectra of two isomeric compounds of formula* C_7H_7Cl *(see Exercise 22-4)*

Exercise 22-5 Predict the effect on the ultraviolet spectrum of a water solution of benzenamine when hydrochloric acid is added. Explain why a solution of sodium benzenoxide absorbs at longer wavelengths than a solution of benzenol (see Table 22-3).

Exercise 22-6* Estimate the chemical shifts of the protons of (a) the separate CH_2 of "1,4-hexamethylenebenzene" as compared with "1,2-hexamethylenebenzene"; and (b) cyclooctatetraene (see Section 21-9A).



"1,4-hexamethylenebenzene"



"1,2-hexamethylenebenzene"

Exercise 22-7 Establish the structures of the following benzene derivatives on the basis of their empirical formulas and NMR spectra shown in Figure 22-6. Remember that equivalent protons normally do not split each other's resonances.

a. C_8H_{10}
b. C_8H_7OCl
c. $C_9H_{10}O_2$
d. C_9H_{12}

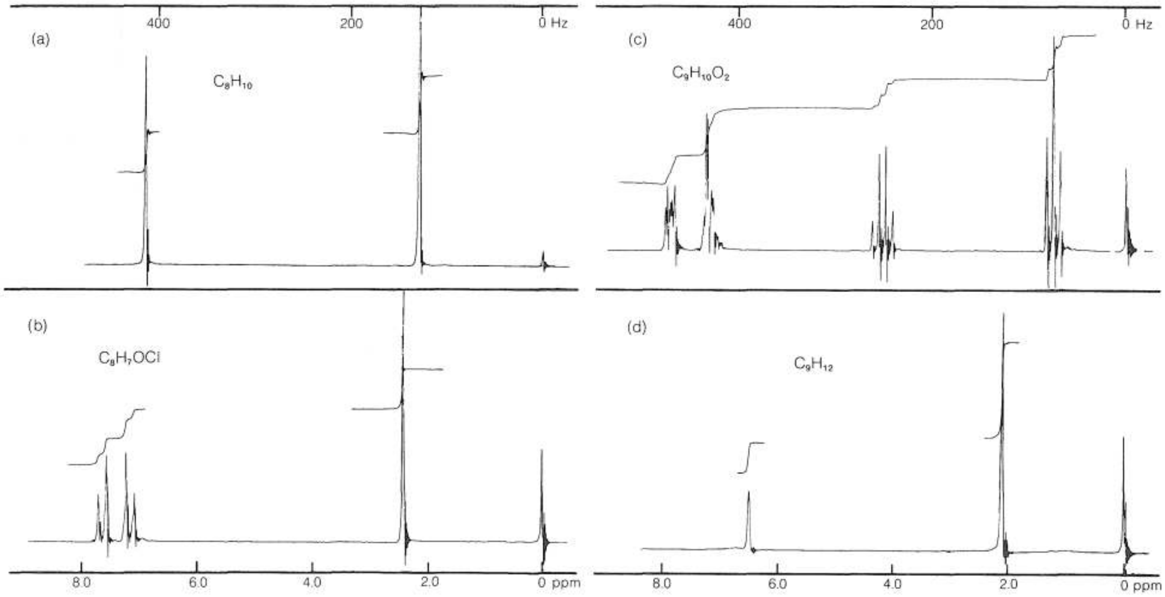
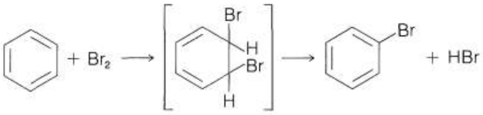


Figure 22-6: Proton NMR spectra of some benzene derivatives at 60 MHz *with reference to TMS at* 0 ppm *(see Exercise 22-7).*

Exercise 22-8 Calculate from appropriate bond-energy and stabilization-energy tables (4-3 and 21-1) the heats of chlorine with benzene to give (a) chlorobenzene and (b) 5,6-dichloro-1,3-cyclohexadiene. Your answer should indicate that substitution is energetically more favorable than addition.

Exercise 22-9 Devise an *experimental* test to determine whether the following addition-elimination mechanism for bromination of benzene actually takes place.



Exercise 22-10 Why is nitration with ethanoyl nitrate accelerated by added fluoroboric acid, HBF_4, but retarded by added hydrochloric acid?

Exercise 22-11 Why do fairly reactive arenes, such as benzene, methylbenzene, and ethylbenzene, react with excess nitric acid in nitromethane solution at a rate that is *independent of the concentration of the arene* (i.e., zero order in arene concentration)? Does this lack of dependencies on arene concentration mean that nitration of an equimolar mixture of benzene and methylbenzene would necessarily give an equimolar mixture of nitrobenzene and nitromethylbenzenes? Why or why not?

Exercise 22-12 Reagents, besides the molecular halogens, that effect halogen substitution include hypochlorous and hypobromous acids. They are most effective when a strong acid is present and care is taken to exclude formation of halide ions. Account for the catalytic effect of acid and the anticatalytic effect of halide ions.

Exercise 22-13 Arrange the following bromine-containing species in order of their expected reactivity in achieving electrophilic aromatic bromination: $HOBr$, Br_2, $Br^{\oplus}$, $Br^{\ominus}$, HBr, $H_2OBr^{\oplus}$, $BrCl$.

Exercise 22-14 Aluminum chloride is a much more powerful catalyst than ferric bromide for bromination of benzene. Would you expect the combination of aluminum chloride and bromine to give much chlorobenzene in reaction with benzene? Explain.

Exercise 22-15

a. The bromination of benzene is catalyzed by small amounts of iodine. Devise a possible explanation for this catalytic effect.

b. The kinetic expression for the bromination of naphthalene in ethanoic acid involves a term that is first order in naphthalene and second order in bromine. How can two molecules of bromine and one of naphthalene be involved in the rate-determining step of bromination? Explain why the kinetic expression simplifies to first order in naphthalene and first order in bromine in 50% aqueous ethanoic acid.

Exercise 22-16 Write a mechanism for the alkylation of benzene with 2-propanol catalyzed by boron trifluoride.

Exercise 22-17 Explain how it is possible that the ratio of products isolated from equilibration of 1,2-, 1,3-, and 1,4-dimethylbenzenes is 18:58:24 if the presence of a small amount of $HF-BF_3$, but is essentially 0:100:0 in the presence of excess $HF-BF_3$. Notice that HBF_4 is an extremely strong acid.

Exercise 22-18 Account for the following observations:

a. 3-Methyl-2-butanol alkylates benzene in HF to give (1,1-dimethylpropyl)benzene.

b. 1-Chloronorbornane will not alkylate in the presence of $AlCl_3$.

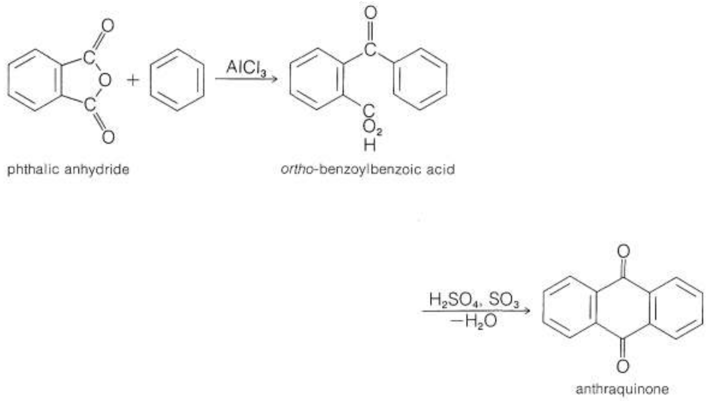
c. 1-Methylcyclopentyl cation is formed from each of the compounds shown below under the indicated conditions at low temperatures (-70^{o}).

chlorocyclohexane $\xrightarrow{SbF_5-SO_2}$

cyclohexene $\xrightarrow{HF-SbF_5-SO_2}$

cyclohexanol $\xrightarrow{FSO_3H-SbF_5}$

Exercise 22-19 Anthraquinone can be synthesized from phthalic anhydride and benzene in two steps. The first step is catalyzed by $AlCl_3$, the second by fuming sulfuric acid. Write mechanisms for both reactions and suggest why fuming sulfuric is required in the second step but not in the first.



Exercise 22-20 Suggest possible routes for the synthesis of the following compounds:

a. diphenylmethane from benzoic acid and benzene
b. 1-ethyl-4-methylbenzene from methylbenzene

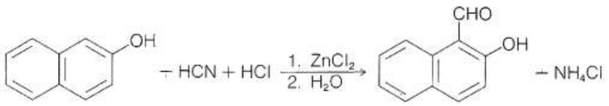
Exercise 22-21

a. Substitution of a chloromethyl group, $-CH_2Cl$, on an aromatic ring is **chloromethylation** and is accomplished using methanal, HCl, and a metal-halide catalyst $(ZnCl_2)$. Write reasonable mechanistic steps that could be involved in this reaction:

$$C_6H_6 + CH_2O + HCl \xrightarrow{ZnCl_2} C_6H_5CH_2Cl + CH_2O \tag{22.E.1}$$

b. Phenylmethyl chloride can be formed from benzene and chloromethyl methyl ether, $ClCH_2OCH_3$, in the presence of stannic chloride, $SnCl_4$. Write reasonable mechanistic steps, again supported by analogy, for this reaction. Notice that $SnCl_4$ is a Lewis acid.

Exercise 22-22 The **Gattermann reaction** (not to be confused with the Gattermann-Koch aldehyde synthesis) introduces the $H-C{=}O$ function into reactive aromatic compounds such as 2-naphthalenol. The necessary reagents are HCN, HCl, and a metal-halide catalyst ($ZnCl_2$ or $AlCl_3$), and the initial product must be treated with water. Write a mechanism for this reaction that is supported by analogy to other reactions discussed in this chapter.



Exercise 22-23 Show explicitly how an alkyl side chain of alkylbenzenesulfonates could be formed with a quaternary carbon, if the C_{12} alkane used at the start of the synthesis contained any branched-chain C_{12} isomers.

Exercise 22-24 Draw the structures of the intermediate cations for nitration of nitrobenzene in the 2, 3, and 4 positions. Use the structures to explain why the nitro group is meta-orienting with deactivation. Use the same kind of arguments to explain the orientation observed with $-CF_3$, $-CHO$, $-CH_2Cl$, and $-NH_2$ groups in electrophilic aromatic substitution (Table 22-6).

Exercise 22-25* The product distribution in the bromination of methylbenzene (toluene) depends on the nature of the brominating agent. Pertinent information follows:

reagent	% of isomeric bromomethylbenzenes		
	2-	3-	4-
Br_2	33	<1	67
$H_2OBr^{\oplus}$	58	19	23

Explain why the distribution varies with the nature of the substituting agent. Predict the product distribution of isomeric ions if $Br^{\oplus}$ were to add to methylbenzene in the *gas phase*.

Exercise 22-26 Construct an energy diagram, similar to Figure 22-8, for nitration of phenyltrimethylammonium ion in the meta and para positions.

Exercise 22-27 Using the rationale developed in Section 22-5, predict the major products of nitration of the following compounds. It will help to work out the Lewis structures of the substituent groups.

a. phenylnitromethane, $C_6H_5CH_2NO_2$
b. methylthiobenzene, $C_6H_5SCH_3$
c. nitrosobenzene, C_6H_5NO
d. phenyldimethylphosphine oxide, $C_6H_5PO(CH_3)_2$

Exercise 22-28 The energy diagram in Figure 22-8 represents a two-step reaction in which the first step is slower than the second. This circumstance is found in nitration and halogenation reactions. Show how this diagram would change when (a) the rate-determining step is loss of a proton from the intermediate ion, (b) the reactants rapidly form a π complex prior to the slow step of the electrophilic attack at carbon, and (c) the rate-determining step is π-complex formation.

Exercise 22-29 Predict the favored position(s) of substitution in the nitration of the following compounds:

a. 4-nitro-1-phenylbenzene
b. 4-methylbenzenecarboxylic acid
c. 3-methylbenzenecarboxylic acid
d. 1,3-dibromobenzene
e. 1-fluoro-3-methoxybenzene
f. 1,3-dimethylbenzene

Exercise 22-30*

a. In the nitration of *para*-cymene by ethanoyl nitrate in ethanoic anhydride, the observed product composition at 0^o is 41% 5 and 6, 41% 3, 8% 4, and 10% of 4-nitromethylbenzene. Use these results to determine the relative reactivities of the *para*-cymene ring carbons towards NO_2^+. Give your answer relative to C_3 as unity (C_3 is the carbon next to the isopropyl group). determine the relative reactivities based on the data obtained in Equation 22-1. How does neglect of *ipso* substitution affect calculation of relative reactivities of the ring carbons?

b. Write a mechanism for the solvolytic conversion of 5 and 6 to 3.

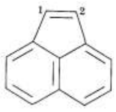
Exercise 22-31 Draw the Kekulé-type valence-bond structures for napthalene, anthracene, and phenanthrene. Estimate the percentage of double-bond character for the 9,10 bond of phenanthrene, assuming that each of the valence-bond structures contributes equally to the hybrid structure.

Exercise 22-32 Devise an experiment that would establish whether the acylation of naphthalene in the 2 position in nitrobenzene solution is the result of *thermodynamic control* of the orientation.

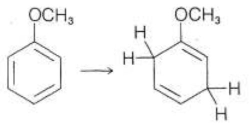
Exercise 22-33 Predict the orientation in the following reactions:

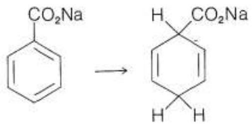
a. 1-methylnaphthalene $+Br_2$
b. 2-methylnaphthalene $+HNO_3$
c. 2-napthalenecarboxylic acid $+HNO_3$

Exercise 22-34 Show how one can predict qualitatively the character of the 1,2 bond in acenapthylene.



Exercise 22-35* Explain why sodium in liquid ammonia reduces methoxybenzene (anisole) to 1-methoxy-1,4-cyclohexadiene, whereas it reduces sodium benzoate to sodium 2,5-cyclohexadienecarboxylate:





Exercise 22-36 Predict the Birch reduction products of the following reactions:

a. anthracene $\xrightarrow[C_2H_5OH]{Na}$

b. naphthalene $\xrightarrow[\text{NH}_3(l)]{\text{Na}}$

c.* methylbenzene $\xrightarrow[\text{NH}_3(l)]{\text{Na, C}_2\text{H}_5\text{OH}}$

Exercise 22-37* A side reaction when reducing benzene derivatives to 1,4-cyclohexadienes with lithium or sodium in liquid ammonia is over-reduction to give cyclohexenes. Addition of ethanol greatly reduces the importance of this side reaction. Explain what role ethanol plays in preventing over-reduction.

Exercise 22-38 Neglecting steric-hindrance effects use the stabilization energies in Table 21-1 to explain why *cis*-butenedioic anhydride adds more readily to anthracene than to benzene and adds across the 9,10 positions but not the 1,4 positions of anthracene.

Exercise 22-39 What products would you expect to be formed in the ozonization of the following substances? Consider carefully which bonds are likely to be most reactive.

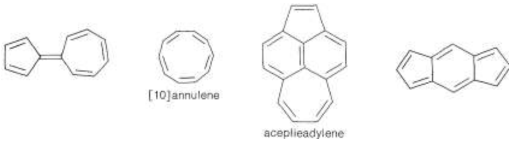
a. 1,2-dimethylbenzene
b. naphthalene
c. acenaphthylene (see Exercise 22-34)

Exercise 22-40* The rate of the Diels-Alder addition between cyclooctatetraene and tetracyanoethene is proportional to the tetracyanoethene concentration, $[C_2(CN)_4]$, at low concentrations of the addends but becomes independent of $[C_2(CN)_4]$ at high concentrations. Write a mechanism that accounts for this behavior.

Exercise 22-41* Write reasonable mechanisms for the different oxidation reactions of cyclooctatetraene with mercuric ethanoate in ethanoic acid, methanol, and water solutions. Notice that compounds of the type $Hg(OR)_2$ appear to act in some cases as $^{\oplus}OR$-donating agents and also that the oxide produced from cyclooctatetraene and peroxyacids (Section 15-11C) rearranges readily in the presence of acids to phenylethanal.

Exercise 22-42* The dianion $C_8H_6^{2-}$, which corresponds to pentalene, has been prepared and appears to be reasonably stable. Why may the dianon be more stable than pentalene itself? (See Section 21-9B.)

Exercise 22-43* Predict which of the following compounds may have some aromatic character. Give your reasons.



Exercise 22-44 Write structural formulas for all of the possible isomers of C_8H_{10} that contain one benzene ring. Show how many different mononitration products each could give if no carbon skeleton rearrangements occur but nitration is possible either in the ring or side chain. Name all of the mononitration products by an accepted system.

Exercise 22-45 Write structural formulas (more than one may be possible) for aromatic substances that fit the following descriptions:

a. C_8H_{10}, which can give only one theoretically possible ring nitration product
b. $C_6H_3Br_3$, which can give three theoretically possible nitration products.
c. $C_6H_3Br_2Cl$, which can give two theoretically possible nitration products.
d. $C_8H_8(NO_2)_2$, which can give only two theoretically possible different ring monobromosubstitution products.

Exercise 22-46 Predict the most favorable position for mononitration for each of the following substances. Indicate whether the rate is greater, or less, than for the nitration of benzene. Give your reasoning in each case.

a. fluorobenzene
b. trifluoromethylbenzene
c. phenylethanone
d. phenylmethyldimethylamine oxide, $C_6H_5CH_2\overset{\oplus}{N}(CH_3)_2\overset{\ominus}{O}$
e. diphenylmethane
f. 4-bromo-1-methoxybenzene

g. phenylsulfinylbenzene, $C_6H_5SOC_6H_5$

h. 1-*tert*-butyl-4-methylbenzene

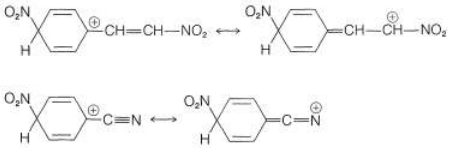
i. diphenyliodonium nitrate, $(C_6H_5)_2\overset{\oplus}{I}\overset{\ominus}{N}$ \ce{O_3}\)

j. 1,3-diphenylbenzene (*meta*-terphenyl)

k. N-(4-phenylphenyl)ethanamide

Exercise 22-47 Explain why the bromination of benzenamine (aniline) gives 2,4,6-tribromobenzenamine (2,4,6-tribromoaniline), whereas the nitration with mixed acids gives 3-nitrobenzenamine (*meta*-nitroaniline).

Exercise 22-48 Explain how comparison of the following resonance structures for para substitution with the corresponding ones for meta substitution may (or may not) lead to the expectation that ortho-para orientation would be favored for the nitro, cyano, and $-CH{=}CHNO_2$ groups.



Exercise 22-49 Starting with benzene, show how the following compounds could be prepared. Specify the required reagents and catalysts.

a. 1-bromo-4-nitrobenzene

b. 4-isopropyl-3-nitrobenzenesulfonic acid

c. 4-*tert*-butylbenzenecarbaldehyde

d. $C_6H_5COCH_2CH_2CO_2H$

e. 1,2,4,5-tetrachlorocyclohexane

Exercise 22-50 Offer a suitable explanation of each of the following facts:

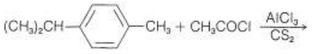
a. Nitration of arenes in concentrated nitric acid is retarded by added nitrate ions and strongly accelerated by small amounts of sulfuric acid.

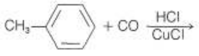
b. Nitrobenzene is a suitable solvent to use in Friedel-Crafts acylation of benzene derivatives.

c. Benzene and other arenes usually do not react with *nucleophiles* by either addition or substitution.

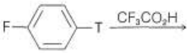
d. Pyridine is almost inert to nitration with mixed nitric and sulfuric acids, a reaction the proceeds readily with benzene.

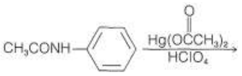
Exercise 22-51 Indicate the structures of the major product(s) expected in the following reactions:

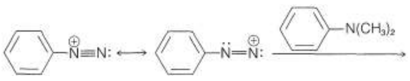
a. 

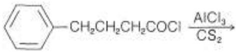
b. 

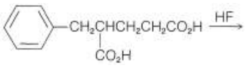
c. 

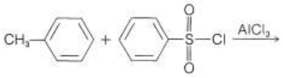
d.  (T is ^3H, or tritium)

e. 

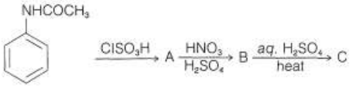
f. 

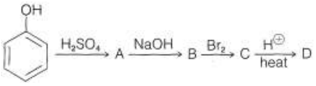
g. 

h. 

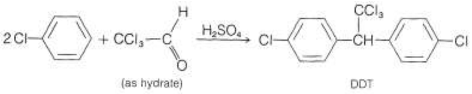
i. 

Exercise 22-52 Draw the structures of the products A, B, C, and D in the stepwise reaction sequences shown.

a. 

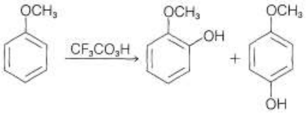
b. 

Exercise 22-53 The pesticide DDT is made commercially by the reaction of chlorobenzene with trichloroethanal (chloral) in the presence of an acid catalyst $(\mathrm{H_2SO_4})$. Show the steps that are likely to be involved in this reaction:



Exercise 22-54 Hexachlorophene, the controversial germicide, is prepared from 2,4,5-trichlorobenzenol (2 moles) and methanal (1 mole) in the presence of concentrated sulfuric acid. Show the steps involved and the expected orientation of the substituents in the final product.

Exercise 22-55 Trifluoroperoxyethanoic acid, $\mathrm{CF_3C(O)O{-}OH}$ reacts with methoxybenzene to give 2- and 4-methoxybenzenols:



Explain the nature of this reaction. What is likely to be the substituting agent? What products would you expect from trifluoroperoxyethanoic acid and fluorobenzene? Would fluorobenzene be more, or less, reactive than methoxybenzene?

Exercise 22-56 Ethanoic anhydride reacts with concentrated nitric acid to yield the rather unstable ethanoyl nitrate (acetyl nitrate), which is a useful nitrating agent. With mixtures of benzene and methylbenzene, ethanoyl nitrate products a mixture of nitrobenzene and 2- and 4-nitromethylbenzenes. When nitrated separately, each compound reacts at the **same** overall rate, but when mixed together, 25 times more nitromethylbenzene is formed than nitrobenzene.

a. Write equations for the formation of ethanoyl nitrate and its use in nitration of benzene derivatives.

b. Consider possible mechanisms for nitrations with ethanoyl nitrate and show how the above observations with benzene and methylbenzene alone or in mixtures can be rationalized by proper choice of the rate-determining step.

Exercise 22-57 4-Nitromethylbenzene-2,6-$\mathrm{D_2}$ is nitrated by a mixture of nitric and sulfuric acids at the same rate as ordinary 4-nitromethylbenzene under conditions in which the rate of nitration v is given by $v = k\,[\text{nitromethylbenzene}]\left[\mathrm{NO_2^+}\right]$. (Review Section 15-6B.)

a. Explain what conclusion may be drawn from this result as to the mechanism of nitration under these conditions.

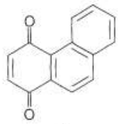
b. What would you expect the nitration rate of $\mathrm{C_6D_6}$ to be as compared with $\mathrm{C_6H_6}$ in the ethanoyl nitrate nitration in Exercise 22-56?

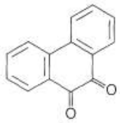
Exercise 22-58

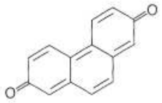
a. From the data of Table 21-1 estimate the overall loss in stabilization energy for the addition of chlorine to the 1,4-positions of naphthalene and to the 9,10 positions of phenanthrene. Which is likely to be the more favorable reaction?

b. Predict whether anthracene is more likely to undergo electrophilic substitution at the 1,2 or 9 position. Show your reasoning.

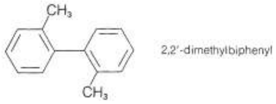
Exercise 22-59 Phenanthrene is oxidized more easily than benzene or naphthalene. Chromic acid oxidation of phenanthrene forms a substance known as phenanthraquinone. Which structure, A, B, or C, would you expect to be formed most readily by oxidation of phenanthrene? Explain.


A


B


C

Exercise 22-60 Explain why the nitration and halogenation of biphenyl (phenylbenzene) goes with activation at the ortho and para positions but with deactivation at the meta position. Suggest a reason why biphenyl is more reactive than 2,2'-dimethylbiphenyl in nitration.



22.E.1: Contributors

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