# 11

# AROMATIC ELECTROPHILIC SUBSTITUTION

Most substitutions at an aliphatic carbon are nucleophilic. In aromatic systems the situation is reversed, because the high electron density at the aromatic ring attracts positive species and not negative ones. In electrophilic substitutions the attacking species is a positive ion or the positive end of a dipole or induced dipole. The leaving group (the electrofuge) must necessarily depart without its electron pair. In nucleophilic substitutions, the chief leaving groups are those best able to carry the unshared pair: $Br^-$, $H_2O$, $OTs^-$, etc., that is, the weakest bases. In electrophilic substitutions the most important leaving groups are those that can best exist without the pair of electrons necessary to fill the outer shell, that is, the weakest Lewis acids. The most common leaving group in electrophilic aromatic substitutions is the proton.

## MECHANISMS

Electrophilic aromatic substitutions are unlike nucleophilic substitutions in that the large majority proceed by just one mechanism with respect to the substrate.[1] In this mechanism, which we call the *arenium ion mechanism*, the electrophile attacks in the first step, giving rise to a positively charged intermediate (the arenium ion), and the leaving group departs in the second step, so there is a resemblance to the tetrahedral mechanism of Chapter 10, but with the charges reversed. The IUPAC designation for this mechanism is $A_E + D_E$. Another mechanism, much less common, consists of the opposite behavior: the leaving group departs *before* the electrophile arrives. This mechanism, the SE1 mechanism, corresponds to the SN1 mechanism of nucleophilic substitution. Simultaneous attack and departure mechanisms (corresponding to SN2) are not found at all. An addition–elimination mechanism has been postulated in one case (see **1-6**).

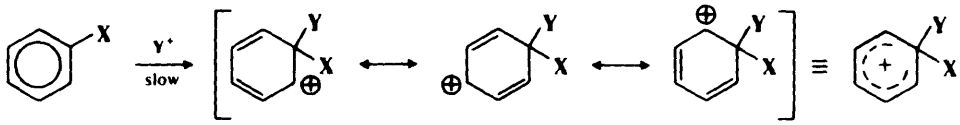
### The Arenium Ion Mechanism[2]

In the arenium ion mechanism the attacking species may be produced in various ways, but what happens to the aromatic ring is basically the same in all cases. For this reason most attention in the study of this mechanism centers around the identity of the attacking entity and how it is produced.

[1]For monographs, see Taylor *Electrophilic Aromatic Substitution*; Wiley: New York, 1990; Katritzky; Taylor *Electrophilic Substitution of Heterocycles: Quantitative Aspects* (Vol. 47 of *Adv. Heterocycl. Chem.*); Academic Press: New York, 1990. For a review, see Taylor, in Bamford; Tipper *Comprehensive Chemical Kinetics*, vol. 13; Elsevier: New York, 1972, pp. 1-406.

[2]This mechanism is sometimes called the SE2 mechanism because it is bimolecular, but in this book we reserve that name for aliphatic substrates (see Chapter 12).

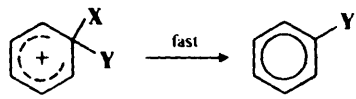
The electrophile may be a positive ion or a dipole. If it is a positive ion, it attacks the ring, removing a pair of electrons from the sextet to give a carbocation, which is a resonance hybrid, as shown in **1**, and is frequently represented as in **2**. Ions of this type are called[3]



**1** **2**

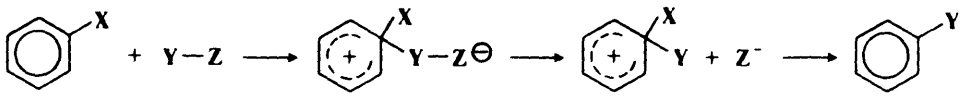
*Wheland intermediates*, σ *complexes*, or *arenium ions*.[4] In the case of benzenoid systems they are cyclohexadienyl cations. It is easily seen that the great stability associated with an aromatic sextet is no longer present in **1**, though the ion is stabilized by resonance of its own. The arenium ion is generally a highly reactive intermediate and must stabilize itself by a further reaction, although it has been isolated (see p. 504).

Carbocations can stabilize themselves in various ways (see p. 174), but for this type of ion the most likely way[5] is by loss of either $X^+$ or $Y^+$. The aromatic sextet is then restored, and in fact this is the second step of the mechanism:



The second step is nearly always faster than the first, so the first is rate-determining and the reaction is second order (unless the formation of the attacking species is slower still, in which case the aromatic compound does not take part in the rate expression at all). If $Y^+$ is lost, there is no net reaction, but if $X^+$ is lost, an aromatic substitution has taken place. If $X^+$ is a proton, a base is necessary to help remove it.

If the attacking species is not an ion but a dipole, the product must have a negative charge unless part of the dipole, with its pair of electrons, is broken off somewhere in the process, e.g.,



The attacking entity in each case and how it is formed are discussed for each reaction in the reactions section of this chapter.

The evidence for the arenium ion mechanism is mainly of two kinds:

**1.** *Isotope effects.* If the hydrogen ion departs before the arrival of the electrophile (SE1 mechanism) or if the arrival and departure are simultaneous, there should be a substantial isotope effect (i.e., deuterated substrates should undergo substitution more slowly than

[3]General agreement on what to call these ions has not yet been reached. The term σ complex is a holdover from the time when much less was known about the structure of carbocations and it was thought they might be complexes of the type discussed in Chapter 3. Other names have also been used. We will call them arenium ions, following the suggestion of Olah *J. Am. Chem. Soc.* **1971**, *94*, 808.

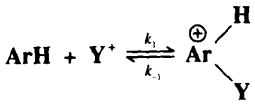
[4]For reviews of arenium ions formed by addition of a proton to an aromatic ring, see Brouwer; Mackor; MacLean, in Olah; Schleyer *Carbonium Ions*, vol. 2; Wiley: New York, 1970, pp. 837-897; Perkampus *Adv. Phys. Org. Chem.* **1966**, *4*, 195-304.

[5]For a discussion of cases in which **1** stabilizes itself in other ways, see de le Mare *Acc. Chem. Res.* **1974**, 7, 361-368.

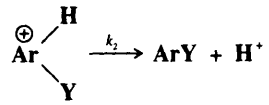
nondeuterated compounds) because, in each case, the C—H bond is broken in the rate-determining step. However, in the arenium ion mechanism, the C—H bond is not broken in the rate-determining step, so no isotope effect should be found. Many such studies have been carried out and, in most cases, especially in the case of nitrations, there is no isotope effect.[6] This result is incompatible with either the SE1 or the simultaneous mechanism.

However, in many instances, isotope effects have been found. Since the values are generally much lower than expected for either the SE1 or the simultaneous mechanisms (e.g., 1 to 3 for $k_H/k_D$ instead of 6 to 7), we must look elsewhere for the explanation. For the case where hydrogen is the leaving group, the arenium ion mechanism can be summarized:

Step 1

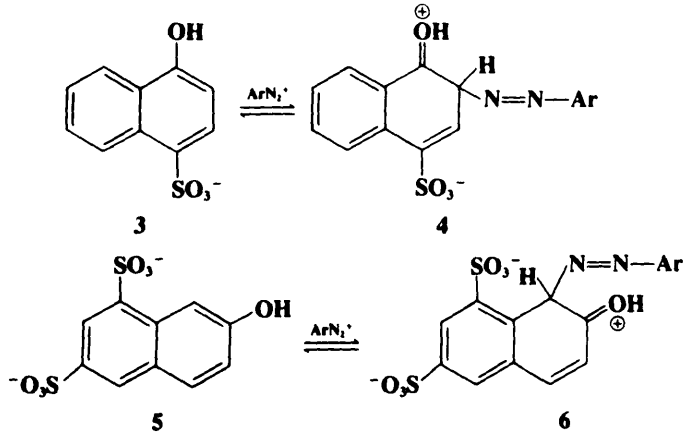


Step 2



The small isotope effects found most likely arise from the reversibility of step 1 by a *partitioning effect*.[7] The rate at which $ArHY^+$ reverts to ArH should be essentially the same as that at which $ArDY^+$ (or $ArTY^+$) reverts to ArD (or ArT), since the Ar—H bond is not cleaving. However, $ArHY^+$ should go to ArY faster than either $ArDY^+$ or $ArTY^+$, since the Ar—H bond is broken in this step. If $k_2 \gg k_{-1}$, this does not matter; since a large majority of the intermediates go to product, the rate is determined only by the slow step ($k_1[ArH][Y^+]$) and no isotope effect is predicted. However, if $k_2 \lessapprox k_{-1}$, reversion to starting materials is important. If $k_2$ for $ArDY^+$ (or $ArTY^+$) is less than $k_2$ for $ArHY^+$, but $k_{-1}$ is the same, then a larger proportion of $ArDY^+$ reverts to starting compounds. That is, $k_2/k_{-1}$ (the *partition factor*) for $ArDY^+$ is less than that for $ArHY^+$. Consequently, the reaction is slower for ArD than for ArH and an isotope effect is observed.

One circumstance that could affect the $k_2/k_{-1}$ ratio is steric hindrance. Thus, diazonium coupling of **3** gave no isotope effect, while coupling of **5** gave a $k_H/k_D$ ratio of 6.55.[8] For



[6]The pioneering studies were by Melander; Melander *Ark. Kemi* **1950,** *2*, 211; Berglund-Larsson; Melander *Ark. Kemi* **1953,** *6*, 219. See also Zollinger, *Adv. Phys. Org. Chem.* **1964,** *2*, 163-200.

[7]For a discussion, see Hammett *Physical Organic Chemistry*, 2nd ed.; McGraw-Hill: New York, 1970 pp. 172-182.

[8]Zollinger *Helv. Chim. Acta* **1955,** *38*, 1597, 1617, 1623.

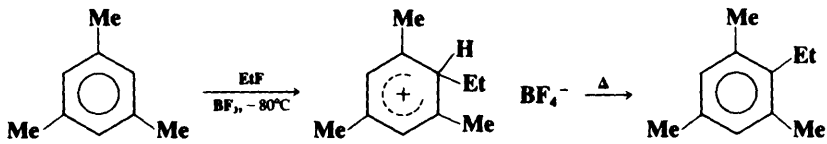
steric reasons it is much more difficult for **6** to lose a proton (it is harder for a base to approach) than it is for **4**, so $k_2$ is greater for the latter. Since no base is necessary to remove $ArN_2^+$, $k_{-1}$ does not depend on steric factors[9] and is about the same for each. Thus the partition factor $k_2/k_{-1}$ is sufficiently different for **4** and **6** that **5** exhibits a large isotope effect and **3** exhibits none.[10] Base catalysis can also affect the partition factor, since an increase in base concentration increases the rate at which the intermediate goes to product without affecting the rate at which it reverts to starting materials. In some cases, isotope effects can be diminished or eliminated by a sufficiently high concentration of base.

Evidence for the arenium ion mechanism has also been obtained from other kinds of isotope-effect experiments, involving substitutions of the type

$$ArMR_3 + H_3O^+ \longrightarrow ArH + R_3MOH_2^+$$

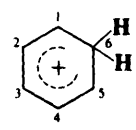
where M is Si, Ge, Sn, or Pb, and R is methyl or ethyl. In these reactions the proton is the electrophile. If the arenium ion mechanism is operating, then the use of $D_3O^+$ should give rise to an isotope effect, since the D—O bond would be broken in the rate-determining step. Isotope effects of 1.55 to 3.05 were obtained,[11] in accord with the arenium ion mechanism.

**2.** *Isolation of arenium ion intermediates.* Very strong evidence for the arenium ion mechanism comes from the isolation of arenium ions in a number of instances.[12] For example, **7** was isolated as a solid with melting point −15°C from treatment of mesitylene with ethyl




mesitylene **7** **8**

fluoride and the catalyst $BF_3$ at −80°C. When **7** was heated, the normal substitution product **8** was obtained.[13] Even the simplest such ion, the benzenonium ion (**9**) has been prepared in $HF–SbF_5–SO_2ClF–SO_2F_2$ at −134°C, where it could be studied spectrally.[14] $^{13}C$ nmr




**9**

[9]Snyckers; Zollinger *Helv. Chim. Acta* **1970,** *53*, 1294.

[10]For some other examples of isotope effects caused by steric factors, see Helgstrand *Acta Chem. Scand.* **1965,** *19*, 1583; Nilsson *Acta Chem. Scand.* **1967,** *21*, 2423; Baciocchi; Illuminati; Sleiter; Stegel *J. Am. Chem. Soc.* **1967,** *89*, 125; Myhre; Beug; James *J. Am. Chem. Soc.* **1968,** *90*, 2105; Dubois; Uzan *Bull. Soc. Chim. Fr.* **1968,** 3534; Mårton *Acta Chem. Scand.* **1969,** *23*, 3321, 3329.

[11]Bott; Eaborn; Greasley J. Chem. Soc. **1964,** 4803.

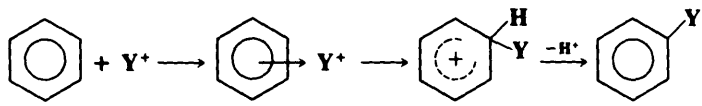
[12]For reviews, see Koptyug *Top. Curr. Chem.* **1984,** *122*, 1-245, *Bull. Acad. Sci. USSR, Div. Chem. Sci.* **1974,** *23*, 1031-1045. For a review of polyfluorinated arenium ions, see Shteingarts *Russ. Chem. Rev.* **1981,** *50*, 735-749. For a review of the protonation of benzene and simple alkylbenzenes, see Fărcaşiu *Acc. Chem. Res.* **1982,** *15*, 46-51.

[13]Olah; Kuhn *J. Am. Chem. Soc.* **1958,** *80*, 6541. For some other examples, see Ershov; Volod'kin *Bull. Acad. Sci. USSR, Div. Chem. Sci.* **1962,** 680; Farrell; Newton; White *J. Chem. Soc. B* **1967,** 637; Kamshii; Koptyug *Bull. Acad. Sci. USSR, Div. Chem. Sci.* **1974,** *23*, 232; Olah; Spear; Messina; Westerman *J. Am. Chem. Soc.* **1975,** *97*, 4051; Nambu; Hiraoka; Shigemura; Hamanaka; Ogawa *Bull. Chem. Soc. Jpn.* **1976,** *49*, 3637; Chikinev; Bushmelev; Shakirov; Shubin *J. Org. Chem. USSR* **1986,** *22*, 1311; Knoche; Schoeller; Schomäcker; Vogel *J. Am. Chem. Soc.* **1988,** *110*, 7484; Effenberger *Acc. Chem. Res.* **1989,** *22*, 27-35.

[14]Olah; Schlosberg; Porter; Mo; Kelly; Mateescu *J. Am. Chem. Soc.* **1972,** *94*, 2034.

spectra of the benzenonium ion[15] and the pentamethylbenzenonium ion[16] give graphic evidence for the charge distribution shown in **1.** According to this, the 1, 3, and 5 carbons, each of which bears a charge of about $+\frac{1}{3}$, should have a greater chemical shift in the nmr than the 2 and 4 carbons, which are uncharged. The spectra bear this out. For example, $^{13}C$ nmr chemical shifts for **9** are C-3: 178.1; C-1 and C-5: 186.6; C-2 and C-4: 136.9, and C-6: 52.2.[15]

In Chapter 3 it was mentioned that positive ions can form addition complexes with π systems. Since the initial step of electrophilic substitution involves attack by a positive ion on an aromatic ring, it has been suggested[17] that such a complex, called a π *complex* (represented as **10**), is formed first and then is converted to the arenium ion **11.** Stable solutions of arenium ions or π complexes (e.g., with $Br_2$, $I_2$, picric acid, $Ag^+$, or HCl) can




**10** **11**

be formed at will. For example, π complexes are formed when aromatic hydrocarbons are treated with HCl alone, but the use of HCl plus a Lewis acid (e.g., $AlCl_3$) gives arenium ions. The two types of solution have very different properties. For example, a solution of an arenium ion is colored and conducts electricity (showing positive and negative ions are present), while a π complex formed from HCl and benzene is colorless and does not conduct a current. Furthermore, when DCl is used to form a π complex, no deuterium exchange takes place (because there is no covalent bond between the electrophile and the ring), while formation of an arenium ion with DCl and $AlCl_3$ gives deuterium exchange. The relative stabilities of some methylated arenium ions and π complexes are shown in Table 11.1. The arenium ion stabilities listed were determined by the relative basicity of the substrate toward HF.[18] The π complex stabilities are relative equilibrium constants for the reaction[19] between

**TABLE 11.1** Relative stabilities of arenium ions and π complexes and relative rates of chlorination and nitration
*In each case, p-xylene = 1.00*

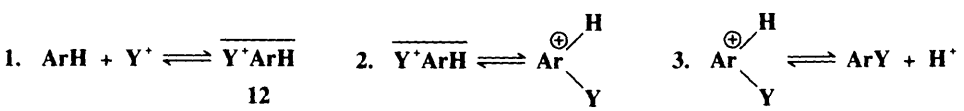
| Substituents | Relative arenium ion stability[18] | Relative π-complex stability[18] | Rate of chlorination[19] | Rate of nitration[23] |
|---|---|---|---|---|
| None (benzene) | 0.09 | 0.61 | 0.0005 | 0.51 |
| **Me** | 0.63 | 0.92 | 0.157 | 0.85 |
| *p*-$\mathbf{Me_2}$ | 1.00 | 1.00 | 1.00 | 1.00 |
| *o*-$\mathbf{Me_2}$ | 1.1 | 1.13 | 2.1 | 0.89 |
| *m*-$\mathbf{Me_2}$ | 26 | 1.26 | 200 | 0.84 |
| 1,2,4-$\mathbf{Me_3}$ | 63 | 1.36 | 340 | |
| 1,2,3-$\mathbf{Me_3}$ | 69 | 1.46 | 400 | |
| 1,2,3,4-$\mathbf{Me_4}$ | 400 | 1.63 | 2000 | |
| 1,2,3,5-$\mathbf{Me_4}$ | 16,000 | 1.67 | 240,000 | |
| $\mathbf{Me_5}$ | 29,000 | | 360,000 | |

[15]Olah; Staral; Asencio; Liang; Forsyth; Mateescu *J. Am. Chem. Soc.* **1978,** *100,* 6299.
[16]Lyerla; Yannoni; Bruck; Fyfe *J. Am. Chem. Soc.* **1979,** *101,* 4770.
[17]Dewar *Electronic Theory of Organic Chemistry*; Clarendon Press: Oxford, 1949.
[18]Kilpatrick; Luborsky *J. Am. Chem. Soc.* **1953,** *75,* 577.
[19]Brown; Brady *J. Am. Chem. Soc.* **1952,** *74,* 3570.

the aromatic hydrocarbon and HCl. As shown in Table 11.1, the relative stabilities of the two types of species are very different: the $\pi$ complex stability changes very little with methyl substitution, but the arenium ion stability changes a great deal.

How can we tell if **10** is present on the reaction path? If it is present, there are two possibilities: (1) The formation of **10** is rate-determining (the conversion of **10** to **11** is much faster), or (2) the formation of **10** is rapid, and the conversion **10** to **11** is rate-determining. One way to ascertain which species is formed in the rate-determining step in a given reaction is to use the stability information given in Table 11.1. We measure the relative rates of reaction of a given electrophile with the series of compounds listed in Table 11.1. If the relative rates resemble the arenium ion stabilities, we conclude that the arenium ion is formed in the slow step; but if they resemble the stabilities of the $\pi$ complexes, the latter are formed in the slow step.[20] When such experiments are carried out, it is found in most cases that the relative rates are similar to the arenium ion and not to the $\pi$ complex stabilities. For example, Table 11.1 lists chlorination rates.[19] Similar results were obtained in room-temperature bromination with $Br_2$ in acetic acid[21] and in acetylation with $CH_3CO^+$ $SbF_6^-$.[22] It is clear that in these cases the $\pi$ complex either does not form at all, or if it does, its formation is not rate-determining (unfortunately, it is very difficult to distinguish between these two possibilities).

On the other hand, in nitration with the powerful electrophile $NO_2^+$ (in the form of $NO_2^+$ $BF_4^-$), the relative rates resembled $\pi$ complex stabilities much more than arenium ion stabilities (Table 11.1).[23] Similar results were obtained for bromination with $Br_2$ and $FeCl_3$ in nitromethane. These results were taken to mean[24] that in these cases $\pi$ complex formation is rate-determining. However, graphical analysis of the $NO_2^+$ data showed that a straight line could not be drawn when the nitration rate was plotted against $\pi$ complex stability,[25] which casts doubt on the rate-determining formation of a $\pi$ complex in this case.[26] There is other evidence, from positional selectivities (discussed on p. 520), that *some* intermediate is present before the arenium ion is formed, whose formation can be rate-determining with powerful electrophiles. Not much is known about this intermediate, which is given the nondescriptive name *encounter complex* and generally depicted as **12.** The arenium complex mechanism is therefore written as[27]




[20]Condon *J. Am. Chem. Soc.* **1952,** *74*, 2528.

[21]Brown; Stock *J. Am. Chem. Soc.* **1957,** *79*, 1421.

[22]Olah; Kuhn; Flood; Hardie *J. Am. Chem. Soc.* **1964,** *86*, 2203.

[23]Olah; Kuhn; Flood *J. Am. Chem. Soc.* **1961,** *83*, 4571, 4581.

[24]Olah; Kuhn; Flood; Hardie *J. Am. Chem. Soc.* **1964,** *86*, 1039, 1044; Ref. 23.

[25]Rys; Skrabal; Zollinger *Angew. Chem. Int. Ed. Engl.* **1972,** *11*, 874-883 [*Angew. Chem. 84*, 921-930]. See also DeHaan; Covey; Delker; Baker; Feigon; Miller; Stelter *J. Am. Chem. Soc.* **1979,** *101*, 1336; Santiago; Houk; Perrin *J. Am. Chem. Soc.* **1979,** *101*, 1337.

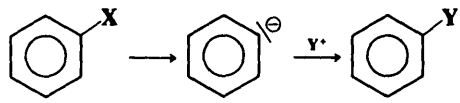
[26]For other evidence against $\pi$ complexes, see Tolgyesi *Can. J. Chem.* **1965,** *43*, 343; Caille; Corriu *Chem. Commun.* **1967,** 1251, *Tetrahedron* **1969,** *25*, 2005; Coombes; Moodie; Schofield *J. Chem. Soc. B* **1968**, 800; Hoggett; Moodie; Schofield *J. Chem. Soc. B* **1969,** 1; Christy; Ridd; Stears *J. Chem. Soc. B* **1970,** 797; Ridd *Acc. Chem. Res.* **1971,** *4*, 248-253; Taylor; Tewson *J. Chem. Soc., Chem. Commun.* **1973,** 836; Naidenov; Guk; Golod *J. Org. Chem. USSR* **1982,** *18*, 1731. For further support for $\pi$ complexes, see Olah; Overchuk *Can. J. Chem.* **1965,** *43*, 3279; Olah *Acc. Chem. Res.* **1971,** *4*, 240-248; Olah; Lin *J. Am. Chem. Soc.* **1974,** *96*, 2892; Koptyug; Rogozhnikova; Detsina *J. Org. Chem. USSR* **1983,** *19*, 1007; El-Dusouqui; Mahmud; Sulfab *Tetrahedron Lett.* **1987,** *28*, 2417; Sedaghat-Herati; Sharifi *J. Organomet. Chem.* **1989,** *363*, 39. For an excellent discussion of the whole question, see Banthorpe *Chem. Rev.* **1970,** *70*, 295-322, especially sections VI and IX.

[27]For discussions, see Stock *Prog. Phys. Org. Chem.* **1976,** *12*, 21-47; Ridd *Adv. Phys. Org. Chem.* **1978,** *16*, 1-49.

For the reason given above and for other reasons, it is unlikely that the encounter complex is a π complex, but just what kind of attraction exists between $Y^+$ and ArH is not known, other than the presumption that they are together within a solvent cage (see also p. 520). There is evidence (from isomerizations occurring in the alkyl group, as well as other observations) that π complexes are present on the pathway from substrate to arenium ion in the gas phase protonation of alkylbenzenes.[28]

### The SE1 Mechanism

The SE1 mechanism (*substitution electrophilic unimolecular*) is rare, being found only in certain cases in which carbon is the leaving atom (see **1-38, 1-39**) or when a very strong base is present (see **1-1, 1-11,** and **1-42**).[29] It consists of two steps with an intermediate carbanion. The IUPAC designation is $D_E + A_E$.




Reactions **2-41, 2-45,** and **2-46** also take place by this mechanism when applied to aryl substrates.

## ORIENTATION AND REACTIVITY

### Orientation and Reactivity in Monosubstituted Benzene Rings[30]

When an electrophilic substitution reaction is performed on a monosubstituted benzene, the new group may be directed primarily to the ortho, meta, or para position and the substitution may be slower or faster than with benzene itself. The group already on the ring determines which position the new group will take and whether the reaction will be slower or faster than with benzene. Groups that increase the reaction rate are called *activating* and those that slow it *deactivating*. Some groups are predominantly meta-directing; all of these are deactivating. Others are mostly ortho-para directing; some of these are deactivating too, but most are activating. Groups direct *predominantly*, but usually not *exclusively*. For example, nitration of nitrobenzene gave 93% *m*-dinitrobenzene, 6% of the ortho, and 1% of the para isomer.

The orientation and reactivity effects of each group are explained on the basis of resonance and field effects on the stability of the intermediate arenium ion. To understand why we can use this approach, it is necessary to know that in these reactions the product is usually kinetically and not thermodynamically controlled (see p. 214). Some of the reactions are irreversible and the others are usually stopped well before equilibrium is reached. Therefore, which of the three possible intermediates is formed is dependent not on the thermodynamic stability of the products but on the activation energy necessary to form each of the three

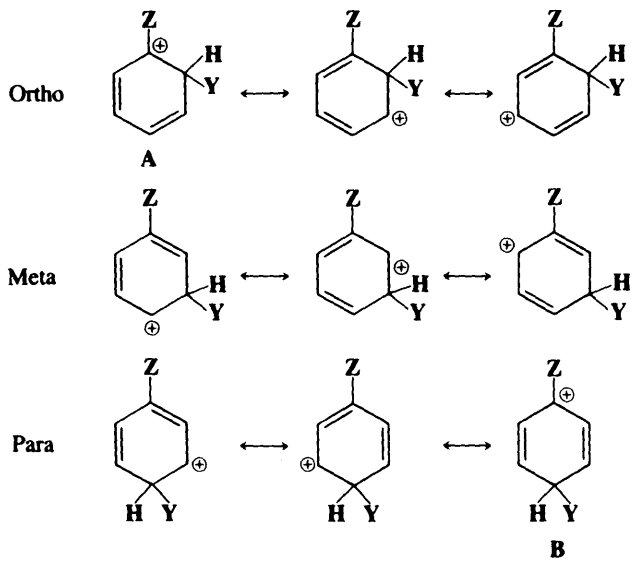
[28]Holman; Gross *J. Am. Chem. Soc.* **1989,** *111,* 3560.

[29]It has also been found with a metal ($SnMe_3$) as electrofuge: Eaborn; Hornfeld; Walton *J. Chem. Soc. B* **1967,** 1036.

[30]For a review of orientation and reactivity in benzene and other aromatic rings, see Hoggett; Moodie; Penton; Schofield *Nitration and Aromatic Reactivity;* Cambridge University Press: Cambridge, 1971, pp. 122-145, 163-220.

intermediates. It is not easy to predict which of the three activation energies is lowest, but we make the assumption that the free-energy profile resembles either Figure 6.2(*a*) or (*b*). In either case, the transition state is closer in energy to the arenium ion intermediate than to the starting compounds. Invoking the Hammond postulate (p. 215), we can then assume that the geometry of the transition state also resembles that of the intermediate and that anything that increases the stability of theintermediate will also lower the activation energy necessary to attain it. Since the intermediate, once formed, is rapidly converted to products, we can use the relative stabilities of the three intermediates as guides to predict which products will predominantly form. Of course, if reversible reactions are allowed to proceed to equilibrium, we may get product ratios that are quite different. For example, the sulfonation of naphthalene at 80°C, where the reaction does not reach equilibrium, gives mostly α-naphthalenesulfonic acid,[31] while at 160°C, where equilibrium is attained, the β isomer predominates[32] (the α isomer is thermodynamically less stable because of steric interaction between the $SO_3H$ group and the hydrogen at the 8 position).

These are the three possible ions:



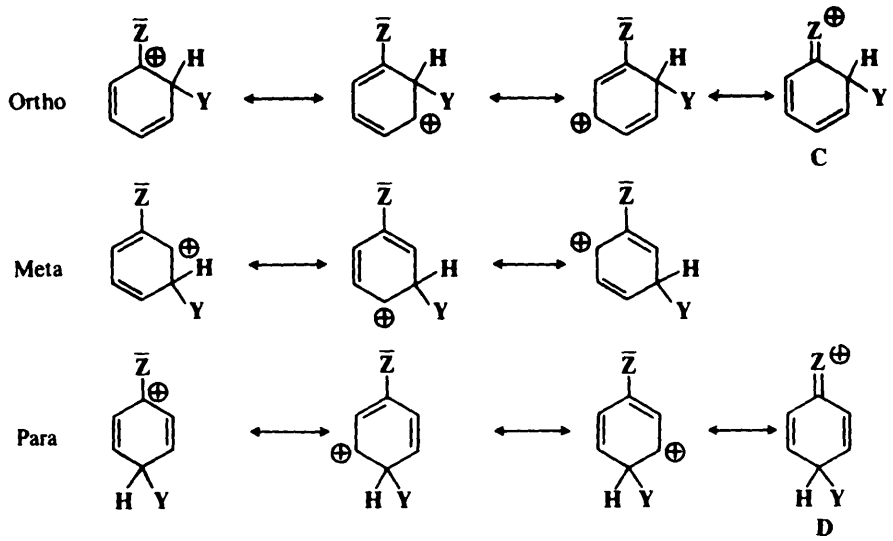

For each ion we see that the ring has a positive charge. We can therefore predict that any group Z that has an electron-donating field effect ( + *I*) should stabilize all three ions (relative to **1**), but that electron-withdrawing groups, which increase the positive charge on the ring, should destabilize them. We can also make a further prediction concerning field effects. These taper off with distance and are thus strongest at the carbon connected to the group Z. Of the three arenium ions, only the ortho and para have any positive charge at this carbon. None of the canonical forms of the meta ion has a positive charge there and so the hybrid has none either. Therefore, + *I* groups should stabilize all three ions but mostly the ortho and para, so they should be not only activating but ortho-para-directing as well. On the other hand, − *I* groups, by removing electron density, should destabilize all three ions but mostly the ortho and para, and should be not only deactivating but also meta-directing.

These conclusions are correct as far as they go, but they do not lead to the proper results in all cases. In many cases there is *resonance interaction* between Z and the ring; this also

[31]Fierz; Weissenbach *Helv. Chim. Acta* **1920,** *3*, 312.
[32]Witt, *Ber.* **1915,** *48*, 743.

affects the relative stability, in some cases in the same direction as the field effect, in others differently.

Some substituents have a pair of electrons (usually unshared) that may be contributed *toward* the ring. The three arenium ions would then look like this:




For each ion the same three canonical forms can be drawn as before, but now we can draw an extra form for the ortho and para ions. The stability of these two ions is increased by the extra form not only because it is another canonical form, but because it is more stable than the others and makes a greater contribution to the hybrid. Every atom (except of course hydrogen) in these forms (**C** and **D**) has a complete octet, while all the other forms have one carbon atom with a sextet. No corresponding form can be drawn for the meta isomer. The inclusion of this form in the hybrid lowers the energy not only because of rule 6 (p. 35), but also because it spreads the positive charge over a larger area—out onto the group Z. Groups with a pair of electrons to contibute would be expected, then, in the absence of field effects, not only to direct ortho and para, but also to activate these positions for electrophilic attack.

On the basis of these discussions, we can distinguish three types of groups.

**1.** Groups that contain an unshared pair of electrons on the atom connected to the ring. In this category are $O^-$, $NR_2$, NHR, $NH_2$,[33] OH, OR, NHCOR, OCOR, SR, and the four halogens.[34] The SH group would probably belong here too, except that in the case of thiophenols electrophiles usually attack the sulfur rather than the ring, and ring substitution is not feasible with these substrates.[35] The resonance explanation predicts that all these

[33]It must be remembered that in acid solution amines are converted to their conjugate acids, which for the most part are meta-directing (type 2). Therefore in acid (which is the most common medium for electrophilic substitutions) amino groups may direct meta. However, unless the solution is highly acidic, there will be a small amount of free amine present, and since amino groups are activating and the conjugate acids deactivating, ortho-para direction is often found even under acidic conditions.

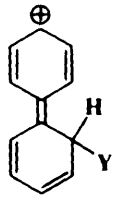
[34]For a review of the directing and orienting effects of amino groups, see Chuchani, in Patai *The Chemistry of the Amino Group*; Wiley: New York, 1968, pp. 250-265; for ether groups see Kohnstam; Williams, in Patai *The Chemistry of the Ether Linkage*; Wiley: New York, 1967, pp. 132-150.

[35]Tarbell; Herz *J. Am. Chem. Soc.* **1953,** *75*, 4657. Ring substitution *is* possible if the SH group is protected. For a method of doing this, see Walker *J. Org. Chem.* **1966,** *31*, 835.

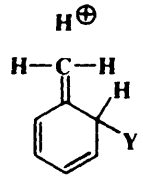
groups should be ortho-para-directing, and they are, though all except $O^-$ are electron-withdrawing by the field effect (p. 18). Therefore, for these groups, resonance is more important than the field effect. This is especially true for $NR_2$, NHR, $NH_2$, and OH, which are *strongly* activating, as is $O^-$. The other groups are mildly activating, except for the halogens, which are deactivating. Fluorine is the least deactivating, and fluorobenzenes usually show a reactivity approximating that of benzene itself. The other three halogens deactivate about equally. In order to explain why chlorine, bromine, and iodine deactivate the ring, even though they direct ortho-para, we must assume that the canonical forms **C** and **D** make such great contributions to the respective hybrids that they make the ortho and para arenium ions more stable than the meta, even though the $-I$ effect of the halogen is withdrawing sufficient electron density from the ring to deactivate it. The three halogens make the ortho and para ions more stable than the meta, but less stable than the unsubstituted arenium ion (**1**). For the other groups that contain an unshared pair, the ortho and para ions are more stable than either the meta ion or the unsubstituted ion. For most of the groups in this category, the meta ion is more stable than **1**, so that groups such as $NH_2$, OH, etc. activate the meta positions too, but not as much as the ortho and para positions (see also the discussion on pp. 516-517).

**2.** Groups that lack an unshared pair on the atom connected to the ring and that are $-I$. In this category are, in approximate order of decreasing deactivating ability, $NR_3^+$, $NO_2$, $CF_3$, CN, $SO_3H$, CHO, COR, COOH, COOR, $CONH_2$, $CCl_3$, and $NH_3^+$. Also in this category are all other groups with a positive charge on the atom directly connected to the ring[36] ($SR_2^+$, $PR_3^+$, etc.) and many groups with positive charges on atoms farther away, since often these are still powerful $-I$ groups. The field-effect explanation predicts that these should all be meta-directing and deactivating, and (except for $NH_3^+$) this is the case. The $NH_3^+$ group is an anomaly, since this group directs para about as much as or a little more than it directs meta.[37] The $NH_2Me^+$, $NHMe_2^+$, and $NMe_3^+$ groups all give more meta than para substitution, the percentage of para product decreasing with the increasing number of methyl groups.[38]

**3.** Groups that lack an unshared pair on the atom connected to the ring and that are ortho-para-directing. In this category are alkyl groups, aryl groups, and the $COO^-$ group,[39] all of which activate the ring. We shall discuss them separately. Since aryl groups are $-I$ groups, they might seem to belong to category 2. They are nevertheless ortho-para-directing and activating. This can be explained in a similar manner as in category 1, with a pair of electrons from the aromatic sextet playing the part played by the unshared pair, so that we have forms like **E**. The effect of negatively charged groups like $COO^-$ is easily explained




**E**




**F**

[36]For discussions, see Gastaminza; Modro; Ridd; Utley *J. Chem. Soc. B* **1968,** 534; Gastaminza; Ridd; Roy *J. Chem. Soc. B* **1969,** 684; Gilow; De Shazo; Van Cleave *J. Org. Chem.* **1971,** *36,* 1745; Hoggett; Moodie; Penton; Schofield, Ref. 30, pp. 167-176.

[37]Brickman; Ridd *J. Chem. Soc.* **1965,** 6845; Hartshorn; Ridd *J. Chem. Soc. B.* **1968,** 1063. For a discussion, see Ridd, in *Aromaticity, Chem. Soc. Spec. Publ.* no. 21, 1967, pp. 149-162.

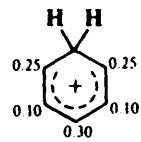
[38]Brickman; Utley; Ridd *J. Chem. Soc* **1965,** 6851.

[39]Spryskov; Golubkin *J. Gen. Chem. USSR* **1961,** *31,* 833. Since the $COO^-$ group is present only in alkaline solution, where electrophilic substitution is not often done, it is seldom met with.

by the field effect (negatively charged groups are of course electron-donating), since there is no resonance interaction between the group and the ring. The effect of alkyl groups can be explained in the same way, but, in addition, we can also draw canonical forms, even though there is no unshared pair. These of course are hyperconjugation forms like **F.** This effect, like the field effect, predicts activation and ortho-para direction, so that it is not possible to say how much each effect contributes to the result. Another way of looking at the effect of alkyl groups (which sums up both field and hyperconjugation effects) is that (for Z = R) the ortho and para arenium ions are more stable because each contains a form (**A** and **B**) that is a tertiary carbocation, while all the canonical forms for the meta ion and for **1** are secondary carbocations. In activating ability, alkyl groups usually follow the Baker–Nathan order (p. 68), but not always.[40]

## The Ortho/Para Ratio[41]

When an ortho-para-directing group is on a ring, it is usually difficult to predict how much of the product will be the ortho isomer and how much the para isomer. Indeed, these proportions can depend greatly on the reaction conditions. For example, chlorination of toluene gives an ortho/para ratio anywhere from 62:38 to 34:66.[42] Nevertheless, certain points can be made. On a purely statistical basis there would be 67% ortho and 33% para, since there are two ortho positions and only one para. However, the phenonium ion **9,**




**9**

which arises from protonation of benzene, has the approximate charge distribution shown.[43] If we accept this as a model for the arenium ion in aromatic substitution, a para substituent would have a greater stabilizing effect on the adjacent carbon than an ortho substituent. If other effects are absent, this would mean that more than 33% para and less than 67% ortho substitution would be found. In hydrogen exchange (reaction **1-1**), where other effects are absent, it has been found for a number of substituents that the average ratio of the logarithms of the partial rate factors for these positions (see p. 516 for a definition of partial rate factor) was close to 0.865,[44] which is not far from the value predicted from the ratio of charge densities in **9.** This picture is further supported by the fact that meta-directing groups, which destabilize a positive charge, give ortho/para ratios greater than 67:33[45] (of course the total amount of ortho and para substitution with these groups is small, but the *ratios* are generally greater than 67:33). Another important factor is the steric effect. If either the group on the ring or the attacking group is large, steric hindrance inhibits formation of the ortho product and increases the amount of the para isomer. An example may be seen in the nitration, under the same conditions, of toluene and *t*-butylbenzene. The former gave 58% of the ortho compound and 37% of the para, while the more bulky *t*-butyl group gave 16% of the

[40]For examples of situations where the Baker–Nathan order is not followed, see Eaborn; Taylor, *J. Chem. Soc.* **1961,** 247; Stock *J. Org. Chem.* **1961,** *26,* 4120; Utley; Vaughan *J. Chem. Soc. B* **1968,** 196; Schubert; Gurka *J. Am. Chem. Soc.* **1969,** *91,* 1443; Himoe; Stock *J. Am. Chem. Soc.* **1969,** *91,* 1452.

[41]For a discussion, see Pearson; Buehler *Synthesis* **1971,** 455-477, pp. 455-464.

[42]Stock; Himoe *J. Am. Chem. Soc.* **1961,** *83,* 4605.

[43]Olah *Acc. Chem. Res.* **1970,** *4,* 240, p. 248.

[44]Bailey; Taylor *J. Chem. Soc. B* **1971,** 1446; Ansell; Le Guen; Taylor *Tetrahedron Lett.* **1973,** 13.

[45]Hoggett; Moodie; Penton; Schofield, Ref. 30, pp. 176-180.

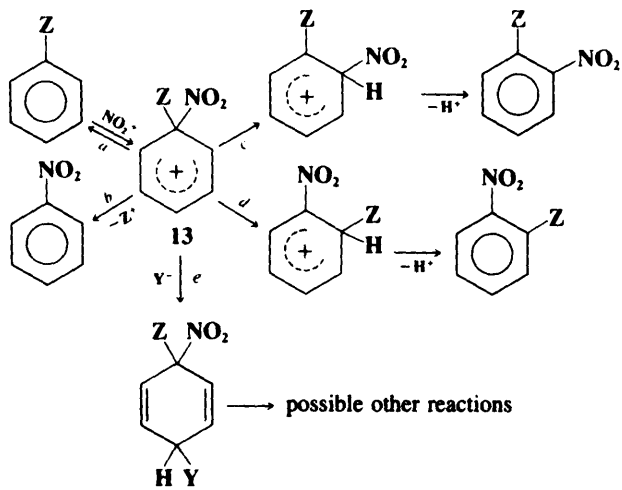
ortho product and 73% of the para.[46] Some groups are so large that they direct almost entirely para.

When the ortho-para-directing group is one with an unshared pair (this of course applies to most of them), there is another effect that increases the amount of para product at the expense of the ortho. A comparison of the intermediates involved (p. 509) shows that **C** is a canonical form with an ortho-quinonoid structure, while **D** has a para-quinonoid structure. Since we know that *para*-quinones are more stable than the ortho isomers, it seems reasonable to assume that **D** is more stable than **C** and therefore contributes more to the hybrid and increases its stability compared to the ortho intermediate.

It has been shown that it is possible to compel regiospecific para substitution by enclosing the substrate molecules in a cavity from which only the para position projects. Anisole was chlorinated in solutions containing a cyclodextrin, a molecule in which the anisole is almost entirely enclosed (see Fig. 3.4). With a high enough concentration of cyclodextrin, it was possible to achieve a para/ortho ratio of 21.6[47] (in the absence of the cyclodextrin the ratio was only 1.48). This behavior is a model for the regioselectivity found in the action of enzymes.

## Ipso Attack

We have discussed orientation in the case of monosubstituted benzenes entirely in terms of attack at the ortho, meta, and para positions, but attack at the position bearing the substituent (called the *ipso position*[48]) can also be important. Ipso attack has mostly been studied for nitration.[49] When $NO_2^+$ attacks at the ipso position there are at least five possible fates for the resulting arenium ion (**13**).




[46]Nelson; Brown *J. Am. Chem. Soc.* **1951,** *73*, 5605. For product ratios in the nitration of many monoalkylbenzenes, see Baas; Wepster *Recl. Trav. Chim. Pays-Bas* **1971,** *90*, 1081, 1089, **1972,** *91*, 285, 517, 831.

[47]Breslow; Campbell *J. Am. Chem. Soc.* **1969,** *91*, 3085, *Bioorg. Chem.* **1971,** *1*, 140. See also Chen; Kaeding; Dwyer *J. Am. Chem. Soc.* **1979,** *101*, 6783; Konishi; Yokota; Ichihashi; Okano; Kiji *Chem. Lett.* **1980,** 1423; Komiyama; Hirai *J. Am. Chem. Soc.* **1983,** *105*, 2018, **1984,** *106*, 174; Chênevert; Ampleman *Can. J. Chem.* **1987,** *65*, 307; Komiyama *Polym. J. (Tokyo)* **1988,** *20*, 439.

[48]Perrin; Skinner *J. Am. Chem. Soc.* **1971,** *93*, 3389. For a review of ipso substitution, see Traynham *J. Chem. Educ.* **1983,** *60*, 937-941.

[49]For a review, see Moodie; Schofield *Acc. Chem. Res.* **1976,** *9*, 287-292. See also Fischer; Henderson; RayMahasay *Can. J. Chem.* **1987,** *65*, 1233, and other papers in this series.

*Path a.* The arenium ion can lose $NO_2^+$ and revert to the starting compounds. This results in no net reaction and is often undetectable.

*Path b.* The arenium ion can lose $Z^+$, in which case this is simply aromatic substitution with a leaving group other than H (see **1-37** to **1-44**).

*Path c.* The electrophilic group (in this case $NO_2^+$) can undergo a 1,2-migration, followed by loss of the proton. The product in this case is the same as that obtained by direct attack of $NO_2^+$ at the ortho position of PhZ. It is not always easy to tell how much of the ortho product in any individual case arises from this pathway,[50] though there is evidence that it can be a considerable proportion. Because of this possibility, many of the reported conclusions about the relative reactivity of the ortho, meta, and para positions are cast into doubt, since some of the product may have arisen not from direct attack at the ortho position, but from attack at the ipso position followed by rearrangement.[51]

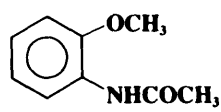
*Path d.* The ipso substituent (Z) can undergo 1,2-migration, which also produces the ortho product (though the rearrangement would become apparent if there were other substituents present). The evidence is that this pathway is very minor, at least when the electrophile is $NO_2^+$.[52]

*Path e.* Attack of a nucleophile on **13.** In some cases the products of such an attack (cyclohexadienes) have been isolated[53] (this is 1,4-addition to the aromatic ring), but further reactions are also possible.

## Orientation in Benzene Rings with More than One Substituent[54]

It is often possible in these cases to predict the correct isomer. In many cases the groups already on the ring reinforce each other. Thus, 1,3-dimethylbenzene is substituted at the 4 position (ortho to one group and para to the other), but not at the 5 position (meta to both). Likewise the incoming group in *p*-chlorobenzoic acid goes to the position ortho to the chloro and meta to the carboxyl group.

When the groups oppose each other, predictions may be more difficult. In a case such as




where two groups of about equal directing ability are in competing positions, all four products can be expected, and it is not easy to predict the proportions, except that steric hindrance should probably reduce the yield of substitution ortho to the acetamido group, especially for large electrophiles. Mixtures of about equal proportions are frequent in such cases. Nevertheless, even when groups on a ring oppose each other, there are some regularities.

**1.** If a strong activating group competes with a weaker one or with a deactivating group, the former controls. Thus *o*-cresol gives substitution mainly ortho and para to the *hydroxyl* group and not to the methyl. For this purpose we can arrange the groups in the following

[50]For methods of doing so, see Gibbs; Moodie; Schofield *J. Chem. Soc., Perkin Trans. 2* **1978,** 1145.

[51]This was first pointed out by Myhre *J. Am. Chem. Soc.* **1972,** *94,* 7921.

[52]For examples of such migration, where Z = Me, see Hartshorn; Readman; Robinson; Sies; Wright *Aust. J. Chem.* **1988,** *41,* 373.

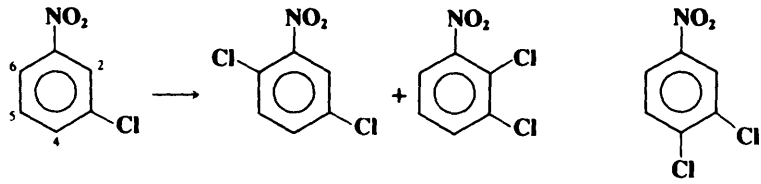
[53]For examples, see Banwell; Morse; Myhre; Vollmar *J. Am. Chem. Soc.* **1977,** 99, 3042; Fischer; Greig *Can. J. Chem.* **1978,** 56, 1063.

[54]For a quantitative discussion, see pp. 516-517.

order: $NH_2$, OH, $NR_2$, $O^-$ > OR, OCOR, NHCOR > R, Ar > halogen > meta-directing groups.

**2.** All other things being equal, a third group is least likely to enter between two groups in the meta relationship. This is the result of steric hindrance and increases in importance with the size of the groups on the ring and with the size of the attacking species.[55]

**3.** When a meta-directing group is meta to an ortho-para-directing group, the incoming group primarily goes ortho to the meta-directing group rather than para. For example, chlorination of **14** gives mostly **15.** The importance of this effect is underscored by the fact that **16,** which is in violation of the preceding rule, is formed in smaller amounts, but **17** is




**14** **15** **16** **17**

not formed at all. This is called the *ortho effect*,[56] and many such examples are known.[57] Another is the nitration of *p*-bromotoluene, which gives 2,3-dinitro-4-bromotoluene. In this case, once the first nitro group came in, the second was directed ortho to it rather than para, even though this means that the group has to come in between two groups in the meta position. There is no good explanation yet for the ortho effect, though possibly there is intramolecular assistance from the meta-directing group.

It is interesting that chlorination of **14** illustrates all three rules. Of the four positions open to the electrophile, the 5 position violates rule 1, the 2 position rule 2, and the 4 position rule 3. The principal attack is therefore at position 6.

## Orientation in Other Ring Systems[58]

In fused ring systems the positions are not equivalent and there is usually a preferred orientation, even in the unsubstituted hydrocarbon. The preferred positions may often by predicted as for benzene rings. Thus it is possible to draw more canonical forms for the arenium ion when naphthalene is attacked at the α position than when it is attacked at the β position, and the α position is the preferred site of attack,[59] though, as previously mentioned (p. 508), the isomer formed by substitution at the β position is thermodynamically more stable and is the product if the reaction is reversible and equilibrium is reached. Because of the more extensive delocalization of charges in the corresponding arenium ions, naphthalene is more reactive than benzene and substitution is faster at both positions. Similarly,

[55]In some cases, an electrophile preferentially attacks the position between two groups in the meta relationship. For a list of some of these cases and a theory to explain them, see Kruse; Cha *J. Chem. Soc., Chem. Commun.* **1982,** 1333.

[56]This is not the same as the ortho effect mentioned on p. 286.

[57]See Hammond; Hawthorne, in Newman *Steric Effects in Organic Chemistry*; Wiley: New York, 1956, pp. 164-200, 178-182.

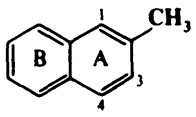
[58]For a review of substitution on nonbenzenoid aromatic systems, see Hafner; Moritz, in Olah *Friedel-Crafts and Related Reactions*, vol. 4; Wiley: New York, 1965, pp. 127-183. For a review of aromatic substitution on ferrocenes, see Bublitz; Rinehart, *Org. React.* **1969,** *17*, 1-154.

[59]For a discussion on the preferred site of attack for many ring systems, see de la Mare; Ridd *Aromatic Substitution—Nitration and Halogenation*; Academic Press: New York, 1959, pp. 169-209.

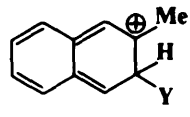
anthracene, phenanthrene, and other fused polycyclic aromatic hydrocarbons are also substituted faster than benzene.

Heterocyclic compounds, too, have nonequivalent positions, and the principles are similar.[60] Furan, thiophene, and pyrrole are chiefly substituted at the 2 position, and all are substituted faster than benzene.[61] Pyrrole is particularly reactive, with a reactivity approximating that of aniline or the phenoxide ion. For pyridine[62] it is not the free base that is attacked but the conjugate acid, pyridinium ion.[63] The 3 position is most reactive, but the reactivity in this case is much less than that of benzene, being similar to that of nitrobenzene. However, groups can be introduced into the 4 position of a pyridine ring indirectly, by performing the reaction on the corresponding pyridine N-oxide.[64]

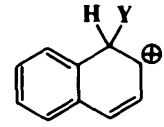
When fused ring systems contain substituents, successful predictions can often be made by using a combination of the above principles. Thus, ring A of 2-methylnaphthalene (**18**)




**18**



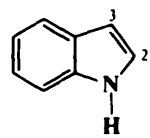

**19**



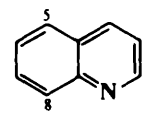

**20**

is activated by the methyl group; ring B is not (though the presence of a substituent in a fused ring system affects all the rings,[65] the effect is generally greatest on the ring to which it is attached). We therefore expect substitution in ring A. The methyl group activates positions 1 and 3, which are ortho to itself, but not position 4, which is meta to it. However, substitution at the 3 position gives rise to an arenium ion for which it is impossible to write a low-energy canonical form in which ring B has a complete sextet. All we can write are forms like **19,** in which the sextet is no longer intact. In contrast, substitution at the 1 position gives rise to a more stable arenium ion, for which two canonical forms (one of them is **20**) can be written in which ring B is benzenoid. We thus predict predominant substitution at C-1, and that is what is generally found.[66] However, in some cases predictions are much harder to make. For example, chlorination or nitration of **21** gives mainly the 4 derivative, but bromination yields chiefly the 6 compound.[67]


**21**




**indole**




**quinoline**

[60]For a monograph, see Katritzky; Taylor, Ref. 1.

[61]For a review of electrophilic substitution on five-membered aromatic heterocycles, see Marino *Adv. Heterocycl. Chem.* **1971,** *13*, 235-314.

[62]For reviews of substitution on pyridines and other six-membered nitrogen-containing aromatic rings, see Comins; O'Connor *Adv. Heterocycl. Chem.* **1988,** *44*, 199-267; Aksel'rod; Berezovskii *Russ. Chem. Rev.* **1970,** *39*, 627-643; Katritzky; Johnson *Angew. Chem. Int. Ed. Engl.* **1967,** *6*, 608-615 [*Angew. Chem. 79*, 629-636]; Abramovitch; Saha *Adv. Heterocycl. Chem.* **1966,** *6*, 229-345. For a review of methods of synthesizing 3-substituted pyrroles, see Anderson; Loader *Synthesis* **1985,** 353-364.

[63]Olah; Olah; Overchuk *J. Org. Chem.* **1965,** *30*, 3373; Katritzky; Kingsland *J. Chem. Soc. B* **1968,** 862.

[64]Jaffé *J. Am. Chem.* **1954,** *76*, 3527.

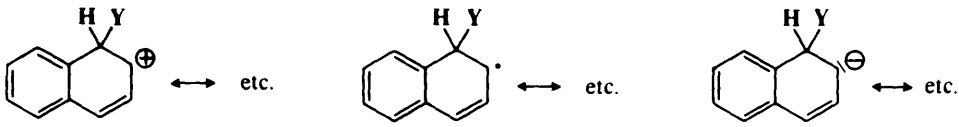
[65]See, for example, Ansell; Sheppard; Simpson; Stroud; Taylor *J. Chem. Soc., Perkin Trans 2* **1979,** 381.

[66]For example, see Alcorn; Wells *Aust. J. Chem.* **1965,** *18*, 1377, 1391; Eaborn; Golborn; Spillett; Taylor *J. Chem. Soc. B* **1968,** 1112; Kim, Chen, Krieger, Judd, Simpson, Berliner *J. Am. Chem. Soc.* **1970,** *92*, 910. For discussions, see Taylor *Chimia* **1968,** *22*, 1-8; Gore; Siddiquei; Thorburn *J. Chem. Soc., Perkin Trans 1* **1972,** 1781.

[67]Bell *J. Chem. Soc.* **1959,** 519.

For fused heterocyclic systems too, we can often make predictions based on the above principles, though many exceptions are known. Thus, indole is chiefly substituted in the pyrrole ring (at position 3) and reacts faster than benzene, while quinoline generally reacts in the benzene ring, at the 5 and 8 positions, and slower than benzene, though faster than pyridine.

In alternant hydrocarbons (p. 50) the reactivity at a given position is similar for electrophilic, nucleophilic, and free-radical substitution, because the same kind of resonance can be shown in all three types of intermediate (compare **20, 22,** and **23**). Attack at the position



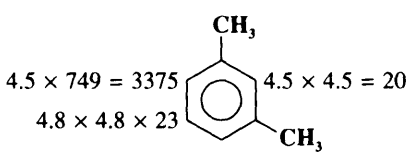

**20** **22** **23**

that will best delocalize a positive charge will also best delocalize a negative charge or an unpaired electron. Most results are in accord with these predictions. For example, naphthalene is attacked primarily at the 1 position by $NO_2^+$, $NH_2^-$, and Ph•, and always more readily than benzene.

## Quantitative Treatments of Reactivity in the Substrate

Quantitative rate studies of aromatic substitutions are complicated by the fact that there are usually several hydrogens that can leave, so that measurements of overall rate ratios do not give a complete picture as they do in nucleophilic substitutions, where it is easy to compare substrates that have only one possible leaving group in a molecule. What is needed is not, say, the overall rate ratio for acetylation of toluene vs. that for benzene, but the *rate ratio at each position.* These can be calculated from the overall rates and a careful determination of the proportion of isomers formed, provided that the products are kinetically controlled, as is usually the case. We may thus define the *partial rate factor* for a given group and a given reaction as the rate of substitution at a single position relative to a single position in benzene. For example, for acetylation of toluene the partial rate factors are: for the ortho position $o_f^{Me} = 4.5$, for the meta $m_f^{Me} = 4.8$, and for the para $p_f^{Me} = 749$.[68] This means that toluene is acetylated at the ortho position 4.5 times as fast as a single position in benzene, or 0.75 times as fast as the overall rate of acetylation of benzene. A partial rate factor greater than 1 for a given position indicates that the group in question activates that position for the given reaction. Partial rate factors differ from one reaction to another and are even different, though less so, for the same reaction under different conditions.

Once we know the partial rate factors, we can predict the proportions of isomers to be obtained when two or more groups are present on a ring, *if we make the assumption that the effect of substituents is additive.* For example, if the two methyl groups in *m*-xylene have the same effect as the methyl group in toluene, we can calculate the theoretical partial rate factors at each position by multiplying those from toluene, so they should be as indicated:

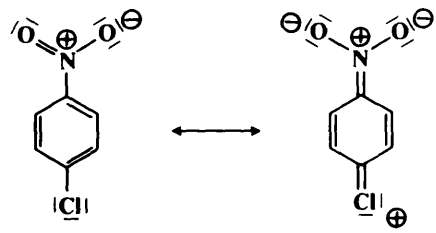



[68]Brown; Marino; Stock *J. Am. Chem. Soc.* **1959,** *81,* 3310.

**TABLE 11.2** Calculated and experimental isomer distributions in the acetylation of *m*-xylene[69]

| | Isomer distribution, % | |
|---|---|---|
| **Position** | **Calculated** | **Observed** |
| 2 | 0.30 | 0 |
| 4 | 99.36 | 97.5 |
| 5 | 0.34 | 2.5 |

From this it is possible to calculate the overall theoretical rate ratio for acetylation of *m*-xylene relative to benzene, since this is one-sixth the sum of the partial rate factors (in this case 1130), and the isomer distribution if the reaction is kinetically controlled. The overall rate ratio actually is 347[69] and the calculated and observed isomer distributions are listed in Table 11.2.[69] In this case, and in many others, agreement is fairly good, but many cases are known where the effects are not additive.[70] For example, the treatment predicts that for 1,2,3-trimethylbenzene there should be 35% 5 substitution and 65% 4 substitution, but acetylation gave 79% 5 substitution and 21% of the 4 isomer. The treatment is thrown off by steric effects, such as those mentioned earlier (p. 511), by products arising from ipso attack (p. 512) and by resonance interaction *between* groups (for example, **24**), which must make the results deviate from simple additivity of the effects of the groups.



**24**

Another approach that avoids the problem created by having competing leaving groups present in the same substrate is the use of substrates that contain only one leaving group. This is most easily accomplished by the use of a leaving group other than hydrogen. By this means overall rate ratios can be measured for specific positions.[71] Results obtained in this way[72] give a reactivity order quite consistent with that for hydrogen as leaving group.

A quantitative scale of reactivity for aromatic substrates (fused, heterocyclic, and substituted rings) has been devised, based on the hard-soft concept (p. 261).[73] From molecular orbital theory, a quantity, called *activation hardness,* can be calculated for each position of an aromatic ring. The smaller the activation hardness, the faster the attack at that position; hence the treatment predicts the most likely orientations for incoming groups.

[69]Marino; Brown *J. Am. Chem. Soc.* **1959,** *81,* 5929.

[70]For some examples where additivity fails, see Fischer; Vaughan; Wright *J. Chem. Soc. B* **1967,** 368; Coombes; Crout; Hoggett; Moodie; Schofield *J. Chem. Soc. B* **1970,** 347; Richards; Wilkinson; Wright *Aust. J. Chem.* **1972,** *25,* 2369; Cook; Phillips; Ridd *J. Chem. Soc., Perkin Trans. 2* **1974,** 1166. For a theoretical treatment of why additivity fails, see Godfrey *J. Chem. Soc. B* **1971,** 1545.

[71]For a review of aryl-silicon and related cleavages, see Eaborn *J. Organomet. Chem.* **1975,** *100,* 43-57.

[72]See, for example, Deans and Eaborn *J. Chem. Soc.* **1959,** 2299; Eaborn; Jackson *J. Chem. Soc. B* **1969,** 21.

[73]Zhou; Parr *J. Am. Chem. Soc.* **1990,** *112,* 5720.

## A Quantitative Treatment of Reactivity of the Electrophile. The Selectivity Relationship

Not all electrophiles are equally powerful. The nitronium ion attacks not only benzene but also aromatic rings that contain a strongly deactivating group. On the other hand, diazonium ions couple only with rings containing a powerful activating group. Attempts have been made to correlate the influence of substituents with the power of the attacking group. The most obvious way to do this is with the Hammett equation (p. 278):

$$\log \frac{k}{k_0} = \rho\sigma$$

For aromatic substitution, $k_0$ is divided by 6 and, for meta substitution, $k$ is divided by 2, so that comparisons are made for only one position (consequently, $k/k_0$ for, say, the methyl group at a para position is identical to the partial rate factor $p_f^{Me}$). It was soon found that, while this approach worked fairly well for electron-withdrawing groups, it failed for those that are electron-donating. However, if the equation is modified by the insertion of the Brown $\sigma^+$ values instead of the Hammett $\sigma$ values (because a positive charge develops during the transition state), more satisfactory correlations can be made, even for electron-donating groups (see Table 9.4 for a list of $\sigma^+$ values).[74] Groups with a negative value of $\sigma_p^+$ or $\sigma_m^+$ are activating for that position; groups with a positive value are deactivating. The $\rho$ values correspond to the susceptibility of the reaction to stabilization or destabilization by the Z group and to the reactivity of the electrophile. The $\rho$ values vary not only with the electrophile but also with conditions. A large negative value of $\rho$ means an electrophile of relatively low reactivity. Of course, this approach is completely useless for ortho substitution, since the Hammett equation does not apply there.

A modification of the Hammett approach, suggested by Brown, called the *selectivity relationship*,[75] is based on the principle that reactivity of a species varies inversely with selectivity. Table 11.3 shows how electrophiles can be arranged in order of selectivity as measured by two indexes: (1) their selectivity in attacking toluene rather than benzene, and (2) their selectivity between the meta and para positions in toluene.[76] As the table shows, an electrophile more selective in one respect is also more selective in the other. In many

**TABLE 11.3** Relative rates and product distributions in some electrophilic substitutions on toluene and benzene[76]

| | Relative rate | Product distribution, % | |
|---|---|---|---|
| **Reaction** | $k_{toluene}/k_{benzene}$ | *m* | *p* |
| Bromination | 605 | 0.3 | 66.8 |
| Chlorination | 350 | 0.5 | 39.7 |
| Benzoylation | 110 | 1.5 | 89.3 |
| Nitration | 23 | 2.8 | 33.9 |
| Mercuration | 7.9 | 9.5 | 69.5 |
| Isopropylation | 1.8 | 25.9 | 46.2 |

[74]For a discussion of the limitations of the Hammett equation approach, see Koptyug; Salakhutdinov; Detsina *J. Org. Chem. USSR* **1984**, *20*, 1039.

[75]Stock; Brown *Adv. Phys. Org. Chem.* **1963**, *1*, 35-154.

[76]Ref. 75, p. 45.

cases, electrophiles known to be more stable (hence less reactive) than others show a higher selectivity, as would be expected. For example, the *t*-butyl cation is more stable and more selective than the isopropyl (p. 166), and $Br_2$ is more selective than $Br^+$. However, deviations from the relationship are known.[77] Selectivity depends not only on the nature of the electrophile but also on the temperature. As expected, it normally decreases with increasing temperature.

Brown assumed that a good measurement of selectivity was the ratio of the para and meta partial rate factors in toluene. He defined the selectivity $S_f$ of a reaction as

$$S_f = \log \frac{p_f^{Me}}{m_f^{Me}}$$

That is, the more reactive an attacking species, the less preference it has for the para position compared to the meta. If we combine the Hammett–Brown $\sigma^+\rho$ relationship with the linearity between log $S_f$ and log $p_f^{Me}$ and between log $S_f$ and log $m_f^{Me}$, it is possible to derive the following expressions:

$$\log p_f^{Me} = \frac{\sigma_p^+}{\sigma_p^+ - \sigma_m^+} S_f$$

$$\log m_f^{Me} = \frac{\sigma_m^+}{\sigma_p^+ - \sigma_m^+} S_f$$

$S_f$ is related to $\rho$ by

$$S_f = \rho(\sigma_p^+ - \sigma_m^+)$$

The general validity of these equations is supported by a great deal of experimental data on aromatic substitution reactions of toluene. Examples of values for some reactions obtained from these equations are given in Table 11.4.[78] For other substituents, the treatment works well with groups that, like methyl, are not very polarizable. For more polarizable groups the correlations are sometimes satisfactory and sometimes not, probably because each electrophile in the transition state makes a different demand on the electrons of the substituent group.

Not only are there substrates for which the treatment is poor, but it also fails with very powerful electrophiles; this is why it is necessary to postulate the encounter complex mentioned on p. 506. For example, relative rates of nitration of *p*-xylene, 1,2,4-trimethylbenzene, and 1,2,3,5-tetramethylbenzene were 1.0, 3.7, and 6.4,[79] though the extra methyl groups

**TABLE 11.4** Values of $m_f^{Me}$, $p_f^{Me}$, $s_f$, and $\rho$ for three reactions of toluene[78]

| Reaction | $m_f^{Me}$ | $p_f^{Me}$ | $S_f$ | $\rho$ |
|---|---|---|---|---|
| PhMe + EtBr $\xrightarrow[\text{benzene, 25°C}]{GaBr_3}$ | 1.56 | 6.02 | 0.587 | −2.66 |
| PhMe + $HNO_3$ $\xrightarrow[45°C]{90\%\ HOAc}$ | 2.5 | 58 | 1.366 | −6.04 |
| PhMe + $Br_2$ $\xrightarrow[25°C]{85\%\ HOAc}$ | 5.5 | 2420 | 2.644 | −11.40 |

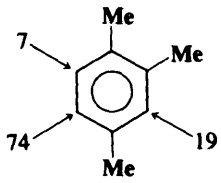
[77]At least some of these may arise from migration of groups already on the ring; see Olah; Olah; Ohyama *J. Am. Chem. Soc.* **1984,** *106,* 5284.

[78]Stock; Brown *J. Am. Chem. Soc.* **1959,** *81,* 3323. Ref. 75 presents many tables of these kinds of data. See also DeHaan; Chan; Chang; Ferrara; Wainschel *J. Org. Chem.* **1986,** *51,* 1591, and other papers in this series.

[79]Olah; Lin, Ref. 26.

should enhance the rates much more (*p*-xylene itself reacted 295 times faster than benzene). The explanation is that with powerful electrophiles the reaction rate is so rapid (reaction taking place at virtually every encounter[80] between an electrophile and substrate molecule)[81] that the presence of additional activating groups can no longer increase the rate.[82]

Given this behavior (little selectivity in distinguishing between different substrate molecules), the selectivity relationship would predict that positional selectivity should also be very small. However, it is not. For example, under conditions where nitration of *p*-xylene and 1,2,4-trimethylbenzene takes place at about equal rates, there was no corresponding lack of selectivity at positions *within* the latter.[83] Though steric effects are about the same at both positions, more than 10 times as much 5-nitro product was formed as 6-nitro product.




relative rate ratios

It is clear that the selectivity relationship has broken down and it becomes necessary to explain why such an extremely rapid reaction should occur with positional selectivity. The explanation offered is that the rate-determining step is formation of an encounter complex (**12**, p. 506).[84] Since the position of attack is not determined in the rate-determining step, the 5/6 ratio is not related to the reaction rate. Essentially the same idea was suggested earlier[85] and for the same reason (failure of the selectivity relationship in some cases), but the earlier explanation specifically pictured the complex as a $\pi$ complex, and we have seen (p. 506) that there is evidence against this.

One interesting proposal[86] is that the encounter pair is a radical pair $\overline{NO_2\bullet\ ArH^{\bullet+}}$ formed by an electron transfer (SET), which would explain why the electrophile, once in the encounter complex, can acquire the selectivity that the free $NO_2^+$ lacked (it is not proposed that a radical pair is present in all aromatic substitutions; only in those that do not obey the selectivity relationship). The radical pair subsequently collapses to the arenium ion. There is evidence[87] both for and against this proposal.[88]

## The Effect of the Leaving Group

In the vast majority of aromatic electrophilic substitutions, the leaving group is $H^+$ (it is certainly one of the best), and very little work has been done on the relative electrofugal

[80]See Coombes; Moodie; Schofield, Ref. 29; Moodie; Schofield; Thomas *J. Chem. Soc., Perkin Trans. 2* **1978,** 318.

[81]For a review of diffusion control in electrophilic aromatic substitution, see Ridd, Ref. 27.

[82]Coombes; Moodie; Schofield, Ref. 26; Hoggett; Moodie; Schofield, Ref. 26; Hartshorn; Moodie; Schofield; Thompson *J. Chem. Soc. B* **1971,** 2447; Manglik; Moodie; Schofield; Dedeoglu; Dutly; Rys *J. Chem. Soc., Perkin Trans 2* **1981,** 1358.

[83]Barnett; Moodie; Schofield; Weston *J. Chem. Soc., Perkin Trans. 2* **1975,** 648; Barnett; Moodie; Schofield; Taylor; Weston *J. Chem. Soc., Perkin Trans. 2* **1979,** 747.

[84]For kinetic evidence in favor of encounter complexes, see Sheats; Strachan *Can. J. Chem.* **1978,** *56*, 1280. For evidence for such complexes in the gas phase, see Attinà; Cacace; de Petris *Angew. Chem. Int. Ed. Engl.* **1987,** *26*, 1177 [*Angew. Chem. 99*, 1174].

[85]Olah, Ref. 26.

[86]Perrin *J. Am. Chem. Soc.* **1977,** *99*, 5516.

[87]For evidence in favor of the proposal, see Reents; Freiser *J. Am. Chem. Soc.* **1980,** *102*, 271; Morkovnik; Dobaeva; Panov; Okhlobystin *Doklad. Chem.* **1980,** *251*, 116; Sankararaman; Haney; Kochi *J. Am. Chem. Soc.* **1987,** *109*, 5235; Keumi; Hamanaka; Hasegawa; Minamide; Inoue; Kitajima *Chem. Lett.* **1988,** 1285; Johnston; Ridd; Sandall *J. Chem. Soc., Chem. Commun.* **1989,** 244. For evidence against it, see Barnes; Myhre *J. Am. Chem. Soc.* **1978,** *100*, 975; Eberson; Radner *Acc. Chem. Res.* **1987,** *20*, 53-59; Baciocchi; Mandolini *Tetrahedron* **1987,** *43*, 4035.

[88]For a review, see Morkovnik *Russ. Chem. Rev.* **1988,** *57*, 144-160.

ability of other leaving groups. However, the following orders of leaving-group ability have been suggested:[89] (1) for leaving groups that depart without assistance (SN1 process with respect to the leaving group), $NO_2^+$[90] < iso-$Pr^+$ ~ $SO_3$ < *t*-$Bu^+$ ~ $ArN_2^+$ < $ArCHOH^+$ < $NO^+$ < $CO_2$; (2) for leaving groups that depart with assistance from an outside nucleophile (SN2 process), $Me^+$ < $Cl^+$ < $Br^+$ < $D^+$ ~ $RCO^+$ < $H^+$ ~ $I^+$ < $Me_3Si^+$. We can use this kind of list to help predict which group, X or Y, will cleave from an arenium ion **1** once it has been formed, and so obtain an idea of which electrophilic substitutions are feasible. However, a potential leaving group can also affect a reaction in another way: by influencing the rate at which the original electrophile attacks directly at the ipso position. Partial rate factors for electrophilic attack at a position substituted by a group other than hydrogen are called ipso partial rate factors ($i_f^X$).[48] Such factors for the nitration of *p*-haloanisoles are 0.18, 0.08, and 0.06, for *p*-iodo, *p*-bromo-, and *p*-chloroanisole, respectively.[91] This means, for example, that the electrophile in this case attacks the 4 position of 4-iodoanisole 0.18 times as fast as a single position of benzene. Note that this is far slower than it attacks the 4 position of anisole itself so that the presence of the iodo group greatly slows the reaction at that position. A similar experiment on *p*-cresol showed that ipso attack at the methyl position was 6.8 times slower than attack at the para position of phenol.[92] Thus, in these cases, both an iodo and a methyl group deactivate the ipso position.[93]

## REACTIONS

The reactions in this chapter are classified according to leaving group. Hydrogen replacements are treated first, then rearrangements in which the attacking entity is first cleaved from another part of the molecule (hydrogen is also the leaving group in these cases), and finally replacements of other leaving groups.

### Hydrogen as the Leaving Group in Simple Substitution Reactions

#### A. Hydrogen as the Electrophile

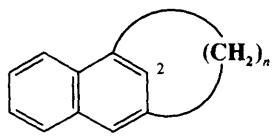
**1-1** Hydrogen Exchange
**Deuterio-de-hydrogenation** or **Deuteriation**

$$\mathbf{ArH + D^+ \rightleftharpoons ArD + H^+}$$

Aromatic compounds can exchange hydrogens when treated with acids. The reaction is used chiefly to study mechanic questions[94] (including substituent effects), but can also be useful to deuterate or tritate aromatic rings selectively. The usual directive effects apply and, for example, phenol treated with $D_2O$ gives slow exchange on heating, with only ortho and para hydrogens being exchanged.[95] Strong acids, of course, exchange faster with aromatic substrates, and this exchange must be taken into account when studying the mechanism of any aromatic substitution catalyzed by acids. There is a great deal of evidence that exchange

[89]Perrin *J. Org. Chem.* **1971,** *36*, 420.
[90]For examples where $NO_2^+$ is a leaving group (in a migration), see Bullen; Ridd; Sabek *J. Chem. Soc., Perkin Trans. 2* **1990,** 1681, and other papers in this series.
[91]Ref. 48. See also Fischer; Zollinger *Helv. Chim. Acta* **1972,** *55*, 2139.
[92]Tee; Iyengar; Bennett *J. Org. Chem.* **1986,** *51*, 2585.
[93]For other work on ipso reactivity, see Baciocchi; Illuminati *J. Am. Chem. Soc.* **1967,** *89*, 4017; Berwin *J. Chem. Soc., Chem. Commun.* **1972,** 237; Galley; Hahn *J. Am. Chem. Soc.* **1974,** *96*, 4337; Clemens; Hartshorn; Richards; Wright *Aust. J. Chem.* **1977,** *30*, 103, 113.
[94]For a review, see Taylor, in Bamford; Tipper, Ref. 1, pp. 194-277.
[95]Small; Wolfenden *J. Chem. Soc.* **1936,** 1811.

takes place by the ordinary arenium ion mechanism. Among the evidence are the orientation effects noted above and the finding that the reaction is general-acid-catalyzed, which means that a proton is transferred in the slow step[96] (p. 259). Furthermore, many examples have been reported of stable solutions of arenium ions formed by attack of a proton on an aromatic ring.[4] Simple aromatic compounds can be extensively deuterated in a convenient fashion by treatment with $D_2O$ and $BF_3$.[97] It has been shown that tritium exchange takes place readily at the 2 position of **25**, despite the fact that this position is hindered by the bridge. The




$n$ = 7, 8, 10

**25**

rates were not very different from the comparison compound 1,3-dimethylnaphthalene.[98]

Hydrogen exchange can also be effected with strong bases,[99] such as $NH_2^-$. In these cases the slow step is the proton transfer:

$$\mathbf{ArH + B \longrightarrow Ar^- + BH^+}$$

so the SE1 mechanism and not the usual arenium ion mechanism is operating.[100] Aromatic rings can also be deuterated by treatment with $D_2O$ and a rhodium(III) chloride[101] or platinum[102] catalyst or with $C_6D_6$ and an alkylaluminum dichloride catalyst,[103] though rearrangements may take place during the latter procedure. Tritium can be introduced by treatment with $T_2O$ and an alkylaluminum dichloride catalyst.[103] Tritiation at specific sites (e.g. more than 90% para in toluene) has been achieved with $T_2$ gas and a microporous aluminophosphate catalyst.[104]

## B. Nitrogen Electrophiles

### 1-2 Nitration or Nitro-de-hydrogenation

$$\mathbf{ArH + HNO_3 \xrightarrow{H_2SO_4} ArNO_2}$$

Most aromatic compounds, whether of high or low reactivity, can be nitrated, because a wide variety of nitrating agents is available.[105] For benzene, the simple alkylbenzenes, and less reactive compounds, the most common reagent is a mixture of concentrated nitric and

[96]For example, see Challis; Long *J. Am. Chem. Soc.* **1963,** *85*, 2524; Batts; Gold *J. Chem. Soc.* **1964,** 4284; Kresge; Chiang; Sato *J. Am. Chem. Soc.* **1967,** *89*, 4418; Gruen; Long *J. Am. Chem. Soc.* **1967,** *89*, 1287; Butler; Hendry *J. Chem. Soc. B* **1970,** 852.

[97]Larsen; Chang *J. Org. Chem.* **1978,** *43*, 3602.

[98]Laws; Neary; Taylor *J. Chem. Soc., Perkin Trans. 2* **1987,** 1033.

[99]For a review of base-catalyzed hydrogen exchange on heterocycles, see Elvidge; Jones; O'Brien; Evans; Sheppard *Adv. Heterocycl. Chem.* **1974,** *16*, 1-31.

[100]Shatenshtein *Tetrahedron* **1962,** *18*, 95.

[101]Lockley *Tetrahedron Lett.* **1982,** *23*, 3819, *J. Chem. Res. (S)* **1985,** 178.

[102]See, for example, Leitch *Can. J. Chem.* **1954,** *32*, 813; Fraser; Renaud *J. Am. Chem. Soc.* **1966,** *88*, 4365; Fischer; Puza *Synthesis* **1973,** 218; Blake; Garnett; Gregor; Hannan; Hoa; Long *J. Chem. Soc., Chem. Commun.* **1975,** 930. See also Parshall *Acc. Chem. Res.* **1975,** *8*, 113-117.

[103]Garnett; Long; Vining; Mole *J. Am. Chem. Soc.* **1972,** *94*, 5913, 8632; Long; Garnett; West *Tetrahedron Lett.* **1978,** 4171.

[104]Garnett; Kennedy; Long; Than; Watson *J. Chem. Soc., Chem. Commun.* **1988,** 763.

[105]For monographs, see Olah; Malhotra; Narang *Nitration: Methods and Mechanisms*; VCH: New York, 1989; Schofield *Aromatic Nitration*; Cambridge University Press: Cambridge, 1980; Hoggett; Moodie; Penton; Schofield, Ref. 30. For reviews, see Weaver, in Feuer *Chemistry of the Nitro and Nitroso Groups*, pt. 2; Wiley: New York, 1970, pp. 1-48; de la Mare; Ridd, Ref. 59, pp. 48-93. See also Ref. 1. For a review of side reactions, see Suzuki *Synthesis* **1977,** 217-238.

sulfuric acids, but for active substrates, the reaction can be carried out with nitric acid alone, or in water, acetic acid, or acetic anhydride. In fact, these milder conditions are necessary for active compounds such as amines, phenols, and pyrroles, since reaction with mixed nitric and sulfuric acids would oxidize these substrates. If anhydrous conditions are required, nitration can be effected with $N_2O_5$[106] in $CCl_4$ in the presence of $P_2O_5$, which removes the water formed in the reaction.[107] Nitration in alkaline media can be accomplished with esters of nitric acid such as ethyl nitrate ($EtONO_2$). These reagents can also be used with proton or Lewis-acid catalysts. Other nitrating agents are $NaNO_2$ and trifluoroacetic acid,[108] $N_2O_4$ (which gives good yields with polycyclic hydrocarbons[109]), and nitronium salts[110] such as $NO_2^+$ $BF_4^-$, $NO_2^+$ $PF_6^-$, and $NO_2^+$ $CF_3SO_3^-$. The last-mentioned salt gives a very high yield of products at low temperatures.[111] Aromatic hydrocarbons and halobenzenes are nitrated in high yields with clay-supported cupric nitrate (claycop),[112] with predominant para regioselectivity.[113] With active substrates such as amines and phenols, nitration can be accomplished by nitrosation under oxidizing conditions with a mixture of dilute nitrous and nitric acids.[114] Active substrates can also be nitrated, conveniently and under mild conditions, with nitrocyclohexadienones such as 2,3,5,6-tetrabromo-4-methyl-4-nitro-1,4-cyclohexadienone.[115]

When amines are nitrated under strong-acid conditions, meta orientation is generally observed, because the species undergoing nitration is actually the conjugate acid of the amine. If the conditions are less acidic, the free amine is nitrated and the orientation is ortho-para. Although the free base may be present in much smaller amounts than the conjugate acid, it is far more susceptible to aromatic substitution (see also p. 510). Because of these factors and because they are vulnerable to oxidation by nitric acid, primary aromatic amines are often protected before nitration by treatment with acetyl chloride (**0-52**) or acetic anhydride (**0-53**). Nitration of the resulting acetanilide derivative avoids all these problems. There is evidence that when the reaction takes place on the free amine, it is the nitrogen that is attacked to give an N-nitro compound Ar—NH—$NO_2$ which rapidly undergoes rearrangement (see **1-32**) to give the product.[116]

Since the nitro group is deactivating, it is usually easy to stop the reaction after one group has entered the ring, but a second and a third group can be introduced if desired, especially when an activating group is also present. Even *m*-dinitrobenzene can be nitrated if vigorous conditions are applied. This has been accomplished with $NO_2^+$ $BF_4^-$ in $FSO_3H$ at 150°C.[117]

[106]For a review of $N_2O_5$ see Fischer, in Feuer; Nielsen *Nitro Compounds, Recent Advances in Synthesis and Chemistry*; VCH: New York, 1990, pp. 267-365.

[107]For another method, see Olah; Krishnamurthy; Narang *J. Org. Chem.* **1982,** *47*, 596.

[108]Uemura; Toshimitsu; Okano *J. Chem. Soc., Perkin Trans. 1.* **1978,** 1076.

[109]Radner *Acta Chem. Scand., Ser. B* **1983,** *37*, 65.

[110]Olah; Kuhn *J. Am. Chem. Soc.* **1962,** *84*, 3684. These have also been used together with crown ethers: Masci *J. Chem. Soc., Chem. Commun.* **1982,** 1262, *J. Org. Chem.* **1985,** *50*, 4081. For a review of nitronium salts in organic chemistry, see Guk; Ilyushin; Golod; Gidaspov *Russ. Chem. Rev.* **1983,** *52*, 284-297.

[111]Coon; Blucher; Hill *J. Org. Chem.* **1973,** *38*, 4243; Effenberger; Geke *Synthesis* **1975,** 40.

[112]For reviews of clay-supported nitrates, see Cornélis; Laszlo *Synthesis* **1985,** 909-918; Laszlo *Acc. Chem. Res.* **1986,** 121-127; Laszlo; Cornélis *Aldrichimica Acta* **1988,** *21*, 97-103.

[113]Laszlo; Pennetreau *J. Org. Chem.* **1987,** *52*, 2407; Cornélis; Delaude; Gerstmans; Laszlo *Tetrahedron Lett.* **1988,** *29*, 5657; Cornélis; Gerstmans; Laszlo *Chem. Lett.* **1988,** 1839; Laszlo; Vandormael *Chem. Lett.* **1988,** 1843. See also Smith; Fry; Butters; Nay *Tetrahedron Lett.* **1989,** *30*, 5333. For similar nitrations of phenols, see Cornélis; Laszlo; Pennetreau *Bull. Soc. Chim. Belg.* **1984,** *93*, 961; Poirier; Vottero *Tetrahedron* **1989,** *45*, 1415. For a method of nitrating phenols in the ortho position, see Pervez; Onyiriuka; Rees; Rooney; Suckling *Tetrahedron* **1988,** *44*, 4555.

[114]For discussions of the mechanism in this case, see Giffney; Ridd *J. Chem. Soc., Perkin Trans. 2* **1979,** 618; Bazanova; Stotskii *J. Org. Chem. USSR* **1980,** *16*, 2070, 2075; Ross; Moran; Malhotra *J. Org. Chem.* **1983,** *48*, 2118; Dix; Moodie *J. Chem. Soc., Perkin Trans. 2* **1986,** 1097; Leis; Peña; Ridd *Can. J. Chem.* **1989,** *67*, 1677. For a review, see Ridd, Ref. 122a.

[115]Lemaire; Guy; Roussel; Guette *Tetrahedron* **1987,** *43*, 835.

[116]Ridd; Scriven *J. Chem. Soc., Chem. Commun.* **1972,** 641. See also Helsby; Ridd *J. Chem. Soc., Perkin Trans. 2* **1983,** 1191.

[117]Olah; Lin *Synthesis* **1974,** 444.

With most of the reagents mentioned, the attacking species is the nitronium ion $NO_2^+$. Among the ways in which this ion is formed are:

**1.** In concentrated sulfuric acid, by an acid–base reaction in which nitric acid is the base:

$$HNO_3 + 2H_2SO_4 \rightleftharpoons NO_2^+ + H_3O^+ + 2HSO_4^-$$

This ionization is essentially complete.

**2.** In concentrated nitric acid alone,[118] by a similar acid-base reaction in which one molecule of nitric acid is the acid and another the base:

$$2HNO_3 \rightleftharpoons NO_2^+ + NO_3^- + H_2O$$

This equilibrium lies to the left (about 4% ionization), but enough $NO_2^+$ is formed for nitration to occur.

**3.** The equilibrium just mentioned occurs to a small extent even in organic solvents.

**4.** With $N_2O_5$ in $CCl_4$, there is spontaneous dissociation:

$$N_2O_5 \rightleftharpoons NO_2^+ + NO_3^-$$

but in this case there is evidence that some nitration also takes place with undissociated $N_2O_5$ as the electrophile.

**5.** When nitronium salts are used, $NO_2^+$ is of course present to begin with. Esters and acyl halides of nitric acid ionize to form $NO_2^+$. Nitrocyclohexadienones are converted to $NO_2^+$ and the corresponding phenol.[115]

There is a great deal of evidence that $NO_2^+$ is present in most nitrations and that it is the attacking entity,[119] e.g.,

**1.** Nitric acid has a peak in the Raman spectrum. When nitric acid is dissolved in concentrated sulfuric acid, the peak disappears and two new peaks appear, one at 1400 $cm^{-1}$ attributable to $NO_2^+$ and one at 1050 $cm^{-1}$ due to $HSO_4^-$.[120]

**2.** On addition of nitric acid, the freezing point of sulfuric acid is lowered about four times the amount expected if no ionization has taken place.[121] This means that the addition of one molecule of nitric acid results in the production of four particles, which is strong evidence for the ionization reaction between nitric and sulfuric acids given above.

**3.** The fact that nitronium salts in which nitronium ion is known to be present (by x-ray studies) nitrate aromatic compounds shows that this ion does attack the ring.

**4.** The rate of the reaction with most reagents is proportional to the concentration of $NO_2^+$, not to that of other species.[122] When the reagent produces this ion in small amounts, the attack is slow and only active substrates can be nitrated. In concentrated and aqueous mineral acids the kinetics are second order: first order each in aromatic substrate and in nitric acid (unless pure nitric acid is used in which case there are pseudo-first-order kinetics). But in organic solvents such as nitromethane, acetic acid, and $CCl_4$, the kinetics are first order in nitric acid alone and zero order in aromatic substrate, because the rate-determining step is formation of $NO_2^+$ and the substrate does not take part in this.

In a few cases, depending on the substrate and solvent, there is evidence that the arenium ion is not formed directly, but via the intermediacy of a radical pair (see p. 520):[122a]

[118]See Belson; Strachan *J. Chem. Soc., Perkin Trans. 2* **1989,** 15.

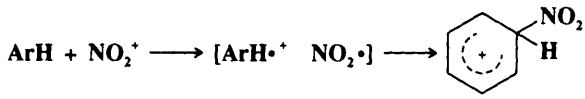
[119]For an exhaustive study of this reaction, see Hughes; Ingold; and co-workers *J. Chem. Soc.* **1950,** 2400-2684.

[120]Ingold; Millen; Poole *J. Chem. Soc.* **1950,** 2576.

[121]Gillespie; Graham; Hughes; Ingold; Peeling *J. Chem. Soc.* **1950,** 2504.

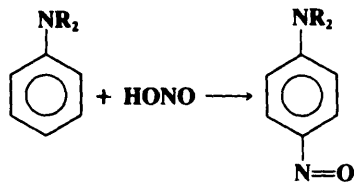
[122]This is not always strictly true. See Ross; Kuhlmann; Malhotra *J. Am. Chem. Soc.* **1983,** *105,* 4299.

[122a]For a review of radical processes in aromatic nitration, see Ridd *Chem. Soc. Rev.* **1991,** *20,* 149-165. For a review of aromatic substitutions involving radical cations, see Kochi *Adv. Free Radical Chem. (Greenwich, Conn.)* **1990,** *1,* 53-119.



OS **I,** 372, 396, 408 (see also OS **53,** 129); **II,** 254, 434, 438, 447, 449, 459, 466; **III,** 337, 644, 653, 658, 661, 837; **IV,** 42, 364, 654, 711, 722, 735; **V,** 346, 480, 829, 1029, 1067.

### 1-3 Nitrosation or Nitroso-de-hydrogenation



Ring nitrosation[123] with nitrous acid is normally carried out only with active substrates such as amines and phenols. However, primary aromatic amines give diazonium ions (**2-49**) when treated with nitrous acid,[124] and secondary amines tend to give N-nitroso rather than C-nitroso compounds (**2-51**); hence this reaction is normally limited to phenols and tertiary aromatic amines. Nevertheless secondary aromatic amines can be C-nitrosated in two ways. The N-nitroso compound first obtained can be isomerized to a C-nitroso compound (**1-33**), or it can be treated with another mole of nitrous acid to give an N,C-dinitroso compound. Also, a successful nitrosation of anisole has been reported, where the solvent was $CF_3COOH$–$CH_2Cl_2$.[125]

Much less work has been done on the mechanism of this reaction than on the preceding one.[126] In some cases the attacking entity is $NO^+$, but in others it is apparently NOCl, NOBr, $N_2O_3$, etc., in each of which there is a carrier of $NO^+$. NOCl and NOBr are formed during the normal process of making nitrous acid—the treatment of sodium nitrite with HCl or HBr. Nitrosation requires active substrates because $NO^+$ is much less reactive than $NO_2^+$. Kinetic studies have shown that $NO^+$ is at least $10^{14}$ times less reactive than $NO_2^+$.[127] A consequence of the relatively high stability of $NO^+$ is that this species is easily cleaved from the arenium ion, so that $k_{-1}$ competes with $k_2$ (p. 503) and isotope effects are found.[128] With phenols, there is evidence that nitrosation may first take place at the OH group, after which the nitrite ester thus formed rearranges to the C-nitroso product.[129] Tertiary aromatic amines substituted in the ortho position generally do not react with HONO, probably because the ortho substituent prevents planarity of the dialkylamino group, without which the ring is no longer activated. This is an example of steric inhibition of resonance (p. 36).

OS **I,** 214, 411, 511; **II,** 223; **IV,** 247.

### 1-4 Diazonium Coupling
### Arylazo-de-hydrogenation

$$ArH + Ar'N_2^+ \longrightarrow Ar{-}N{=}N{-}Ar'$$

[123]For a review, see Williams *Nitrosation*; Cambridge University Press: Cambridge, 1988, pp. 58-76.

[124]For examples of formation of C-nitroso compounds from primary and secondary amines, see Hoefnagel; Wepster *Recl. Trav. Chim. Pays-Bas* **1989,** *108*, 97.

[125]Radner; Wall; Loncar *Acta Chem. Scand.* **1990,** *44*, 152.

[126]For a review of nitrosation mechanisms at C and other atoms, see Williams *Adv. Phys. Org. Chem.* **1983,** *19*, 381-428. See also Ref. 123.

[127]Challis; Higgins; Lawson *J. Chem. Soc., Perkin Trans. 2*, **1972,** 1831; Challis; Higgins *J. Chem. Soc., Perkin Trans. 2* **1972,** 2365.

[128]Challis; Lawson *J. Chem. Soc. B* **1971,** 770; Challis; Higgins *J. Chem. Soc., Perkin Trans. 2* **1973,** 1597.

[129]Gosney; Page *J. Chem. Soc., Perkin Trans. 2* **1980,** 1783.

Aromatic diazonium ions normally couple only with active substrates such as amines and phenols.[130] Many of the products of this reaction are used as dyes (*azo dyes*).[131] Presumably because of the size of the attacking species, substitution is mostly para to the activating group, unless that position is already occupied, in which case ortho substitution takes place. The pH of the solution is important both for phenols and amines. For amines, the solutions may be mildly acidic or neutral. The fact that amines give ortho and para products shows that even in mildly acidic solution they react in their un-ionized form. If the acidity is too high, the reaction does not occur, because the concentration of free amine becomes too small. Phenols must be coupled in slightly alkaline solution where they are converted to the more reactive phenoxide ions, because phenols themselves are not active enough for the reaction. However, neither phenols nor amines react in moderately alkaline solution, because the diazonium ion is converted to a diazo hydroxide Ar—N=N—OH. Primary and secondary amines face competition from attack at the nitrogen.[132] However, the resulting N-azo compounds (aryl triazenes) can be isomerized to C-azo compounds (**1-34**). In at least some cases, even when the C-azo compound is isolated, it is the result of initial N-azo compound formation followed by isomerization. It is therefore possible to synthesize the C-azo compound directly in one laboratory step.[133] Acylated amines and phenolic ethers and esters are ordinarily not active enough for this reaction, though it is sometimes possible to couple them (as well as such polyalkylated benzenes as mesitylene and pentamethylbenzene) to diazonium ions containing electron-withdrawing groups in the para position, since such groups increase the concentration of the positive charge and thus the electrophilicity of the $ArN_2^+$. Some coupling reactions which are otherwise very slow (in cases where the coupling site is crowded) are catalyzed by pyridine for reasons discussed on p. 504. Phase transfer catalysis has also been used.[134] Coupling of a few aliphatic diazonium compounds to aromatic rings has been reported. All the examples reported so far involve cyclopropanediazonium ions and brigehead diazonium ions, in which loss of $N_2$ would lead to very unstable carbocations.[135]

OS **I,** 49, 374; **II,** 35, 39, 145.

## 1-5 Direct Introduction of the Diazonium Group
## **Diazoniation** or **Diazonio-de-hydrogenation**

$$ArH \xrightarrow[HX]{2HONO} ArN_2^+ X^-$$

Diazonium salts can be prepared directly by replacement of an aromatic hydrogen without the necessity of going through the amino group.[136] The reaction is essentially limited to active substrates (amines and phenols), since otherwise poor yields are obtained. Since the reagents and the substrate are the same as in reaction **1-3,** the first species formed is the nitroso compound. In the presence of excess nitrous acid, this is converted to the diazonium ion.[137] The reagent (azidochloromethylene)dimethylammonium chloride $Me_2\overset{\oplus}{N}{=}C(Cl)N_3\ Cl^-$ can also introduce the diazonium group directly into a phenol.[138]

[130]For reviews, see Szele; Zollinger *Top. Curr. Chem.* **1983,** *112*, 1-66; Hegarty, in Patai *The Chemistry of Diazonium and Diazo Groups*, pt. 2; Wiley: New York, 1978, pp. 545-551.

[131]For reviews of azo dyes, see Zollinger *Color Chemistry*; VCH: New York, 1987, pp. 85-148; Gordon; Gregory *Organic Chemistry in Colour*; Springer: New York, 1983, pp. 95-162.

[132]See Penton; Zollinger *Helv. Chim. Acta* **1981,** *64*, 1717, 1728.

[133]Kelly; Penton; Zollinger *Helv. Chim. Acta* **1982,** *65*, 122.

[134]Hashida; Kubota; Sekiguchi *Bull. Chem. Soc. Jpn.* **1988,** *61*, 905.

[135]See Szele; Zollinger, Ref. 130, pp. 3-6.

[136]Tedder *J. Chem. Soc.* **1957,** 4003.

[137]Tedder; Theaker *Tetrahedron* **1959,** *5*, 288; Kamalova; Nazarova; Solodova; Yaskova *J. Org. Chem. USSR* **1988,** *24*, 1004.

[138]Kokel; Viehe *Angew. Chem. Int. Ed. Engl.* **1980,** *19*, 716 [*Angew. Chem. 92*, 754].

## 1-6 Amination or Amino-de-hydrogenation[139]

$$ArH + HN_3 \xrightarrow{AlCl_3} ArNH_2$$

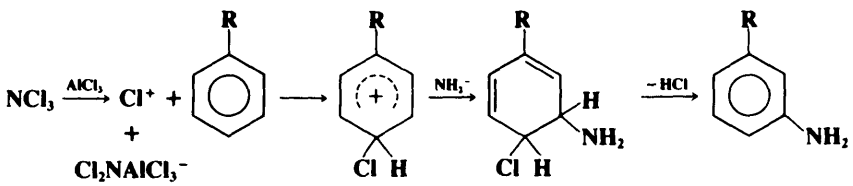
Aromatic compounds can be converted to primary aromatic amines, in 10 to 65% yields, by treatment with hydrazoic acid $HN_3$ in the presence of $AlCl_3$ or $H_2SO_4$.[140] Higher yields (> 90%) have been reported with trimethylsilyl azide $Me_3SiN_3$ and triflic acid $F_3CSO_2OH$.[141] Tertiary amines have been prepared in fairly good yields (about 50 to 90%) by treatment of aromatic hydrocarbons with N-chlorodialkylamines, by heating in 96% sulfuric acid; or with $AlCl_3$ or $FeCl_3$ in nitroalkane solvents; or by irradiation.[142]

Tertiary (and to a lesser extent, secondary) aromatic amines can also be prepared in moderate to high yields by amination with an N-chlorodialkylamine (or an N-chloroalkylamine) and a metallic-ion catalyst (e.g., $Fe^{2+}$, $Ti^{3+}$, $Cu^{+}$, $Cr^{2+}$) in the presence of sulfuric acid.[143] The attacking species in this case is the aminium radical ion $R_2\overset{\oplus}{N}H\bullet$ formed by[144]

$$R_2\overset{\oplus}{N}HCl + M^{+} \longrightarrow R_2\overset{\oplus}{N}H\bullet + M^{2+} + Cl^{-}$$

Because attack is by a positive species (even though it is a free radical), orientation is similar to that in other electrophilic substitutions (e.g., phenol and acetanilide give ortho and para substitution, mostly para). When an alkyl group is present, attack at the benzylic position competes with ring substitution. Aromatic rings containing only meta-directing groups do not give the reaction at all. Fused ring systems react well.[145]

Unusual orientation has been reported for amination with halomines and with $NCl_3$ in the presence of $AlCl_3$. For example, toluene gave predominately meta amination.[146] It has been suggested that initial attack in this case is by $Cl^{+}$ and that a nitrogen nucleophile (whose structure is not known but is represented here as $NH_2^{-}$ for simplicity) adds to the resulting arenium ion, so that the initial reaction is addition to a carbon-carbon double bond followed by elimination of HCl:[147]




According to this suggestion, the electrophilic attack is at the para position (or the ortho, which leads to the same product) and the meta orientation of the amino group arises indirectly. This mechanism is called the *σ-substitution mechanism*.

Aromatic compounds that do not contain meta-directing groups can be converted to diarylamines by treatment with aryl azides in the presence of phenol at −60°C: ArH +

[139]For a review, see Kovacic, in Olah, Ref. 58, vol. 3, 1964, pp. 1493-1506.
[140]Kovacic; Russell; Bennett *J. Am. Chem. Soc.* **1964,** *86*, 1588.
[141]Olah; Ernst *J. Org. Chem.* **1989,** *54*, 1203.
[142]Bock; Kompa *Angew. Chem. Int. Ed. Engl.* **1965,** *4*, 783 [*Angew. Chem. 77*, 807]. *Chem. Ber.* **1966,** *99*, 1347, 1357, 1361.
[143]For reviews, see Minisci *Top. Curr. Chem.* **1976,** *62*, 1-48, pp. 6-16, *Synthesis* **1973,** 1-24, pp. 2-12, Sosnovsky; Rawlinson *Adv. Free-Radical Chem.* **1972,** *4*, 203-284, pp. 213-238.
[144]For a review of aminium radical ions, see Chow *React. Intermed. (Plenum)* **1980,** *1*, 151-262.
[145]The reaction has been extended to the formation of primary aromatic amines, but the scope is narrow: Citterio; Gentile; Minisci; Navarrini; Serravalle; Ventura *J. Org. Chem.* **1984,** *49*, 4479.
[146]See Kovacic; Lange; Foot; Goralski; Hiller; Levisky *J. Am. Chem. Soc.* **1964,** *86*, 1650; Strand; Kovacic *J. Am. Chem. Soc.* **1973,** *95*, 2977.
[147]Kovacic; Levisky *J. Am. Chem. Soc.* **1966,** *88*, 1000.

$Ar'N_3 \rightarrow ArNHAr'$.[148] Diarylamines are also obtained by the reaction of N-arylhydroxylamines with aromatic compounds (benzene, toluene, anisole) in the presence of $F_3CCOOH$: $ArH + Ar'NHOH \rightarrow ArNHAr'$.[149]

Direct *amidation* can be carried out if an aromatic compound is heated with a hydroxamic acid in polyphosphoric acid, though the scope is essentially limited to phenolic ethers.[150]

$$ArH + R{-}\overset{\overset{O}{\|}}{C}{-}NH{-}OH \longrightarrow Ar{-}NH{-}\overset{\overset{O}{\|}}{C}{-}R$$

Also see **3-18** and **3-19.**

## C. Sulfur Electrophiles

### 1-7 Sulfonation or Sulfo-de-hydrogenation

$$ArH + H_2SO_4 \longrightarrow ArSO_2OH$$

The sulfonation reaction is very broad in scope and many aromatic hydrocarbons (including fused ring systems), aryl halides, ethers, carboxylic acids, amines,[151] acylated amines, ketones, nitro compounds, and sulfonic acids have been sulfonated.[152] Phenols can also be successfully sulfonated, but attack at oxygen may compete.[153] Sulfonation is often accomplished with concentrated sulfuric acid, but it can also be done with fuming sulfuric acid, $SO_3$, $ClSO_2OH$, or other reagents. As with nitration (**1-2**), reagents of a wide variety of activity are available to suit both highly active and highly inactive substrates. Since this is a reversible reaction (see **1-41**), it may be necessary to drive the reaction to completion. However, at low temperatures the reverse reaction is very slow and the forward reaction is practically irreversible.[154] $SO_3$ reacts much more rapidly than sulfuric acid—with benzene it is nearly instantaneous. Sulfones are often side products. When sulfonation is carried out on a benzene ring containing four or five alkyl and/or halogen groups, rearrangements usually occur (see **1-40**).

A great deal of work has been done on the mechanism,[155] chiefly by Cerfontain and coworkers. Mechanistic study is made difficult by the complicated nature of the solutions. Indications are that the electrophile varies with the reagent, though $SO_3$ is involved in all cases, either free or combined with a carrier. In aqueous $H_2SO_4$ solutions the electrophile is thought to be $H_3SO_4^+$ (or a combination of $H_2SO_4$ and $H_3O^+$) at concentrations below about 80 to 85% $H_2SO_4$, and $H_2S_2O_7$ (or a combination of $H_2SO_4$ and $SO_3$) at concentrations higher than this[156] (the changeover point varies with the substrate[157]). Evidence for a change

[148]Nakamura; Ohno; Oka *Synthesis* **1974,** 882. See also Takeuchi; Takano *J. Chem. Soc., Perkin Trans. 1* **1986,** 611.

[149]Shudo; Ohta; Okamoto *J. Am. Chem. Soc.* **1981,** *103,* 645.

[150]Wassmundt; Padegimas *J. Am. Chem. Soc.* **1967,** *89,* 7131; March; Engenito *J. Org. Chem.* **1981,** *46,* 4304.

[151]See Khelevin *J. Org. Chem. USSR* **1984,** *20,* 339, 1173, 1723, **1987,** *23,* 1709, **1988,** *24,* 535.

[152]For reviews, see Nelson, in Olah, Ref. 58, vol. 3, 1964, pp. 1355-1392; Gilbert, *Sulfonation and Related Reactions*; Wiley: New York, 1965, pp. 62-83, 87-124.

[153]See, for example de Wit; Woldhuis; Cerfontain *Recl. Trav. Chim. Pays-Bas* **1988,** *107,* 668.

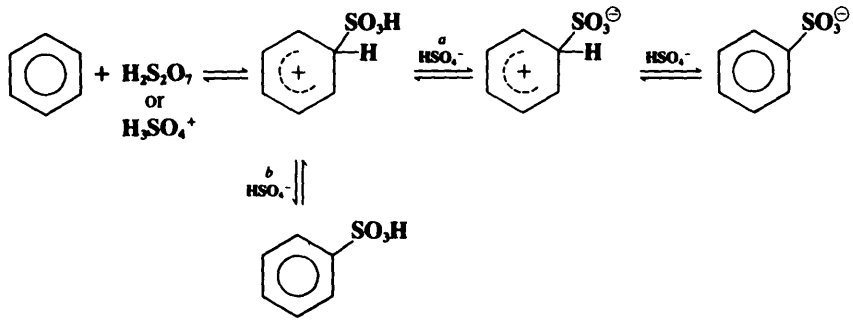
[154]Spryskov *J. Gen. Chem. USSR* **1960,** *30,* 2433.

[155]For a monograph, see Cerfontain *Mechanistic Aspects in Aromatic Sulfonation and Desulfonation*; Wiley: New York, 1968. For reviews, see Cerfontain *Recl. Trav. Chim. Pays-Bas* **1985,** *104,* 153-165; Cerfontain; Kort *Int. J. Sulfur Chem. C* **1971,** *6,* 123-136; Taylor, in Bamford; Tipper, Ref. 1, pp. 56-77.

[156]Kort; Cerfontain *Recl. Trav. Chim. Pays-Bas* **1968,** *87,* 24, **1969,** *88,* 860; Maarsen; Cerfontain *J. Chem. Soc., Perkin Trans. 2* **1977,** 1003; Cerfontain; Lambrechts; Schaasberg-Nienhuis; Coombes; Hadjigeorgiou; Tucker *J. Chem. Soc., Perkin Trans. 2* **1985,** 659.

[157]See, for example, Kaandorp; Cerfontain *Recl. Trav. Chim. Pays-Bas* **1969,** *88,* 725.

in electrophile is that in the dilute and in the concentrated solutions the rate of the reaction was proportional to the activity of $H_3SO_4^+$ and $H_2S_2O_7$, respectively. Further evidence is that with toluene as substrate the two types of solution gave very different ortho/para ratios. The mechanism is essentially the same for both electrophiles and may be shown as:[156]




The other product of the first step is $HSO_4^-$ or $H_2O$ from $H_2S_2O_7$ or $H_3SO_4^+$, respectively. Path *a* is the principal route, except at very high $H_2SO_4$ concentrations, when path *b* becomes important. With $H_3SO_4^+$ the first step is rate-determining under all conditions, but with $H_2S_2O_7$ the first step is the slow step only up to about 96% $H_2SO_4$, when a subsequent proton transfer becomes partially rate-determining.[158] $H_2S_2O_7$ is more reactive than $H_3SO_4^+$. In fuming sulfuric acid ($H_2SO_4$ containing excess $SO_3$), the electrophile is thought to be $H_3S_2O_7^+$ (protonated $H_2S_2O_7$) up to about 104% $H_2SO_4$ and $H_2S_4O_{13}$ ($H_2SO_4$ + $3SO_3$) beyond this concentration.[159] Finally, when pure $SO_3$ is the reagent in aprotic solvents, $SO_3$ itself is the actual electrophile.[160] Free $SO_3$ is the most reactive of all these species, so that attack here is generally fast and a subsequent step is usually rate-determining, at least in some solvents.

OS **II,** 42, 97, 482, 539; **III,** 288, 824; **IV,** 364; **VI,** 976.

### 1-8 Halosulfonation or Halosulfo-de-hydrogenation

$$\mathbf{ArH + ClSO_2OH \longrightarrow ArSO_2Cl}$$

Aromatic sulfonyl chlorides can be prepared directly, by treatment of aromatic rings with chlorosulfuric acid.[161] Since sulfonic acids can also be prepared by the same reagent (**1-7**), it is likely that they are intermediates, being converted to the halides by excess chlorosulfuric acid.[162] The reaction has also been effected with bromo- and fluorosulfuric acids.

OS **I,** 8, 85.

### 1-9 Sulfurization

$$\mathbf{ArH + SCl_2 \xrightarrow{AlCl_3} ArSAr}$$

[158]Kort; Cerfontain *Recl. Trav. Chim. Pays-Bas* **1967,** *86*, 865.

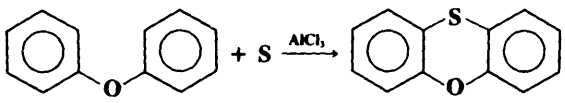
[159]Kort; Cerfontain *Recl. Trav. Chim. Pays-Bas* **1969,** *88*, 1298; Koeberg-Telder; Cerfontain *J. Chem. Soc., Perkin Trans. 2* **1973,** 633.

[160]Koeberg-Telder; Cerfontain *Recl. Trav. Chim. Pays-Bas* **1971,** *90*, 193, **1972,** *91*, 22; Lammertsma; Cerfontain *J. Chem. Soc., Perkin Trans. 2* **1980,** 28.

[161]For a review, see Gilbert, Ref. 152, pp. 84-87.

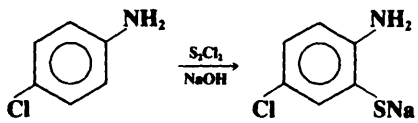
[162]For a discussion of the mechanism with this reagent, see van Albada; Cerfontain *J. Chem. Soc., Perkin Trans. 2* **1977,** 1548, 1557.

Diaryl sulfides can be prepared by treating aromatic compounds with $SCl_2$ and a Friedel–Crafts catalyst. Other reagents that can bring about the same result are $S_2Cl_2$, thionyl chloride, and even sulfur itself. A catalyst is not always necessary. The reaction has been used for ring closure:




When thionyl chloride is used, diaryl sulfoxides are usually the main products.[163] Unsymmetrical diaryl sulfides can be obtained by treatment of an aromatic compound with an aryl sulfenyl chloride (ArSCl) in the presence of a trace amount of iron powder.[164] Aromatic amines and phenols can be alkylthiolated (giving mostly ortho product) by treatment with an alkyl disulfide and a Lewis acid catalyst.[165]

With certain substrates (primary amines with a chloro group, or a group not replaceable by chloro, in the para position), treatment with $S_2Cl_2$ and NaOH gives thiophenolate salts:




This is called the *Herz reaction*.[166]

OS **II**, 242, 485. Also see OS **I**, 574; **III**, 76.

## 1-10 Sulfonylation
### Alkylsulfonylation or Alkylsulfo-de-hydrogenation

$$ArH + Ar'SO_2Cl \xrightarrow{AlCl_3} ArSO_2Ar'$$

Diaryl sulfones can be formed by treatment of aromatic compounds with aryl sulfonyl chlorides and a Friedel–Crafts catalyst.[167] This reaction is analogous to Friedel–Crafts acylation with carboxylic acid halides (**1-14**). In a better procedure, the aromatic compound is treated with an aryl sulfonic acid and $P_2O_5$ in polyphosphoric acid.[168] Still another method uses an arylsulfonic trifluoromethanesulfonic anhydride $ArSO_2OSO_2CF_3$ (generated in situ from $ArSO_2Br$ and $CF_3SO_3Ag$) without a catalyst.[169]

The reaction can be extended to the preparation of alkyl aryl sulfones by the use of a sulfonyl fluoride.[170]

[163]Nikolenko; Krizhechkovskaya *J. Gen. Chem. USSR* **1963**, *33*, 3664; Oae; Zalut *J. Am. Chem. Soc.* **1960**, *82*, 5359.

[164]Fujisawa; Kobori; Ohtsuka; Tsuchihashi *Tetrahedron Lett.* **1968**, 5071.

[165]Ranken; McKinnie *Synthesis* **1984**, 117, *J. Org. Chem.* **1989**, *54*, 2985.

[166]For a review, see Warburton *Chem. Rev.* **1957**, *57*, 1011-1020.

[167]For reviews, see Taylor, in Bamford; Tipper, Ref. 1, pp. 77-83; Jensen; Goldman, in Olah, Ref. 58, vol. 3, 1964, pp. 1319-1347.

[168]Graybill *J. Org. Chem.* **1967**, *32*, 2931; Sipe; Clary; White *Synthesis* **1984**, 283. See also Ueda; Uchiyama; Kano *Synthesis* **1984**, 323.

[169]Effenberger; Huthmacher *Chem. Ber.* **1976**, *109*, 2315. For similar methods, see Hancock; Tyobeka; Weigel *J. Chem. Res., (S)* **1980**, 270; Ono; Nakamura; Sato; Itoh *Chem. Lett.* **1988**, 395.

[170]Hyatt; White *Synthesis* **1984**, 214.

## D. Halogen Electrophiles

### 1-11 Halogenation[171] or Halo-de-hydrogenation

$$ArH + Br_2 \xrightarrow{Fe} ArBr$$

**1.** *Chlorine and bromine.* Aromatic compounds can be brominated or chlorinated by treatment with bromine or chlorine in the presence of a catalyst, most often iron. However, the real catalyst is not the iron itself, but the ferric bromide or ferric chloride formed in small amounts from the reaction between iron and the reagent. Ferric chloride and other Lewis acids are often directly used as catalysts, as is iodine. When thallium(III) acetate is the catalyst, many substrates are brominated with high regioselectivity para to an ortho-para-directing group.[172] For active substrates, including amines, phenols, naphthalene, and polyalkylbenzenes[173] such as mesitylene and isodurene, no catalyst is needed. Indeed, for amines and phenols the reaction is so rapid that it is carried out with a dilute solution of $Br_2$ or $Cl_2$ in water at room temperature. Even so, with amines it is not possible to stop the reaction before all the available ortho and para positions are substituted, because the initially formed haloamines are weaker bases than the original amines and are less likely to be protonated by the liberated HX.[174] For this reason, primary amines are often converted to the corresponding anilides if monosubstitution is desired. With phenols it is possible to stop after one group has entered.[175] The rapid room-temperature reaction with amines and phenols is often used as a test for these compounds. Chlorine is a more active reagent than bromine. Phenols can be brominated exclusively in the ortho position (disubstitution of phenol gives 2,6-dibromophenol) by treatment about $-70°C$ with $Br_2$ in the presence of *t*-butylamine or triethylenediamine, which precipitates out the liberated HBr.[176] Predominant ortho chlorination[177] of phenols has been achieved with chlorinated cyclohexadienes,[178] while para chlorination of phenols, phenolic ethers, and amines can be accomplished with N-chloroamines[179] and with N-chlorodimethylsulfonium chloride $Me_2\overset{\oplus}{S}Cl\ Cl^-$.[180] The last method is also successful for bromination. On the other hand, certain alkylated phenols can be brominated in the meta positions with $Br_2$ in the super-acid solution $SbF_5$–HF.[181] It is likely that the meta orientation is the result of conversion by the super acid of the OH group

[171]For a monograph, see de la Mare *Electrophilic Halogenation*; Cambridge University Press: Cambridge, 1976. For reviews, see Buehler; Pearson *Survey of Organic Synthesis*; Wiley: New York, 1970, pp. 392-404; Braendlin; McBee, in Olah, Ref. 58, vol. 3, 1964, pp. 1517-1593. For a review of the halogenation of heterocyclic compounds, see Eisch *Adv. Heterocycl. Chem.* **1966,** *7*, 1-37. For a list of reagents, with references, see Larock *Comprehensive Organic Transformations*; VCH: New York, 1989, pp. 315-318.

[172]McKillop; Bromley; Taylor *J. Org. Chem.* **1972,** *37*, 88.

[173]For a review of aromatic substitution on polyalkylbenzenes, see Baciocchi; Illuminati *Prog. Phys. Org. Chem.* **1967,** *5*, 1-79.

[174]Monobromination (para) of aromatic amines has been achieved with tetrabutylammonium tribromide: Berthelot; Guette; Desbène; Basselier; Chaquin; Masure *Can. J. Chem.* **1989,** *67*, 2061. For another procedure, see Onaka; Izumi *Chem. Lett.* **1984,** 2007.

[175]For a review of the halogenation of phenols, see Brittain; de la Mare, in Patai; Rappoport *The Chemistry of Functional Groups, Supplement D*, pt. 1; Wiley: New York, 1983, pp. 522-532.

[176]Pearson; Wysong; Breder *J. Org. Chem.* **1967,** *32*, 2358.

[177]For other methods of regioselective chlorination or bromination, see Schmitz; Pagenkopf *J. Prakt. Chem.* **1985,** *327*, 998; Watson *J. Org. Chem.* **1985,** *50*, 2145; Smith; Butters; Paget; Nay *Synthesis* **1985,** 1157, *Tetrahedron Lett.* **1988,** *29*, 1319; Kodomari; Takahashi; Yoshitomi *Chem. Lett.* **1987,** 1901; Kamigata; Satoh; Yoshida; Matsuyama; Kameyama *Bull. Chem. Soc. Jpn.* **1988,** *61*, 2226; de la Vega; Sasson *J. Chem. Soc., Chem. Commun.* **1989,** 653.

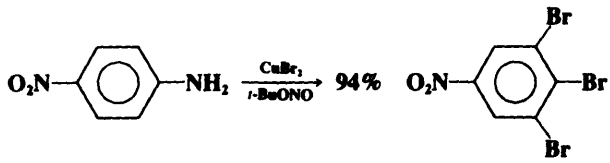
[178]Guy; Lemaire; Guette *Tetrahedron* **1982,** *38*, 2339, 2347; Lemaire; Guy; Guette *Bull. Soc. Chim. Fr.* **1985,** 477.

[179]Lindsay Smith; McKeer; Taylor *J. Chem. Soc., Perkin Trans. 2* **1987,** 1533, **1988,** 385, **1989,** 1529, 1537. See also Minisci; Vismara; Fontana; Platone; Faraci *J. Chem. Soc., Perkin Trans. 2* **1989,** 123.

[180]Olah; Ohannesian; Arvanaghi *Synthesis* **1986,** 868.

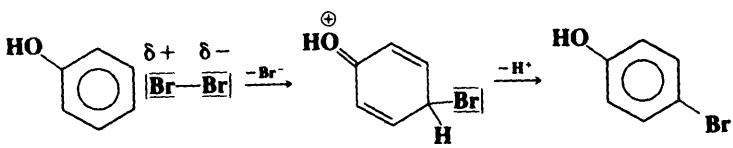
[181]Jacquesy; Jouannetaud; Makani *J. Chem. Soc., Chem. Commun.* **1980,** 110.

to the $OH_2^+$ group, which should be meta-directing because of its positive charge. Bromination and the Sandmeyer reaction (**4-25**) can be carried out in one laboratory step by treatment of an aromatic primary amine with $CuBr_2$ and *t*-butyl nitrite, e.g.,[182]




Other reagents have been used, among them HOCl,[183] HOBr, and N-chloro and N-bromo amides (especially N-bromosuccinimide and tetraalkylammonium polyhalides[184]). In all but the last of these cases the reaction is catalyzed by the addition of acids. Dibromoisocyanuric acid in $H_2SO_4$ is a very good brominating agent[185] for substrates with strongly deactivating substituents.[186] Two particularly powerful reagents consist of (1) $S_2Cl_2$ and $AlCl_3$ in sulfuryl chloride ($SO_2Cl_2$) (the *BMC reagent*)[187] and (2) dichlorine oxide $Cl_2O$ and a strong acid such as sulfuric.[188] If the substrate contains alkyl groups, side-chain halogenation (**4-1**) is possible with most of the reagents mentioned, including chlorine and bromine. Since side-chain halogenation is catalyzed by light, the reactions should be run in the absence of light wherever possible.

For reactions in the absence of a catalyst, the attacking entity is simply $Br_2$ or $Cl_2$ that has been polarized by the ring.[189]




**26**

Evidence for molecular chlorine or bromine as the attacking species in these cases is that acids, bases, and other ions, especially chloride ion, accelerate the rate about equally, though if chlorine dissociated into $Cl^+$ and $Cl^-$, the addition of chloride should decrease the rate and the addition of acids should increase it. The conjugate base of **26** (4-bromo-2,5-cyclohexadienone) has been detected spectrally in the aqueous bromination of phenol.[190]

When a Lewis-acid catalyst is used with chlorine or bromine, the attacking entity may be $Cl^+$ or $Br^+$, formed by $FeCl_3 + Br_2 \rightarrow FeCl_3Br^- + Br^+$, or it may be $Cl_2$ or $Br_2$, polarized by the catalyst. With other reagents, the attacking entity in brominations may be $Br^+$ or a species such as $H_2OBr^+$ (the conjugate acid of HOBr), in which $H_2O$ is a carrier of $Br^+$.[191]

[182]Doyle; Van Lente; Mowat; Fobare *J. Org. Chem.* **1980,** *45*, 2570.

[183]For the use of calcium hypochlorite, see Nwaukwa; Keehn *Synth. Commun.* **1989,** *19*, 799.

[184]See Kajigaeshi; Moriwaki; Tanaka; Fujisaki; Kakinami; Okamoto *J. Chem. Soc., Perkin Trans. 1* **1990,** 897, and other papers in this series.

[185]Nitrobenzene is pentabrominated in 1 min with this reagent in 15% oleum at room temperature.

[186]Gottardi *Monatsh. Chem.* **1968,** *99*, 815, **1969,** *100*, 42.

[187]Ballester; Molinet; Castañer *J. Am. Chem. Soc.* **1960,** *82*, 4254; Andrews, Glidewell; Walton *J. Chem. Res. (S)* **1978,** 294.

[188]Marsh; Farnham; Sam; Smart *J. Am. Chem. Soc.* **1982,** *104*, 4680.

[189]For reviews of the mechanism of halogenation, see de le Mare, Ref. 171; de la Mare; Swedlund, in Patai *The Chemistry of the Carbon–Halogen Bond*, pt. 1; Wiley: New York, 1973; pp. 490-536; Taylor, in Bamford; Tipper, Ref. 1, pp. 83-139; Berliner *J. Chem. Educ.* **1966,** *43*, 124-133. See also Schubert; Dial *J. Am. Chem. Soc.* **1975,** *97*, 3877; Keefer; Andrews *J. Am. Chem. Soc.* **1977,** *99*, 5693; Briggs; de la Mare; Hall *J. Chem. Soc., Perkin Trans. 2* **1977,** 106; Tee; Paventi; Bennett *J. Am. Chem. Soc.* **1989,** *111*, 2233.

[190]Tee; Iyengar; Paventi *J. Org. Chem.* **1983,** *48*, 759. See also Tee; Iyengar *J. Am. Chem. Soc.* **1985,** *107*, 455, *Can. J. Chem.* **1990,** *68*, 1769.

[191]For discussions, see Gilow; Ridd *J. Chem. Soc., Perkin Trans. 2* **1973,** 1321; Rao; Mali; Dangat *Tetrahedron* **1978,** *34*, 205.

With HOCl in water the electrophile may be $Cl_2O$, $Cl_2$, or $H_2OCl^+$; in acetic acid it is generally AcOCl. All these species are more reactive than HOCl itself.[192] It is extremely doubtful that $Cl^+$ is a significant electrophile in chlorinations by HOCl.[192] It has been demonstrated in the reaction between N-methylaniline and calcium hypochlorite that the chlorine attacking entity attacks the *nitrogen* to give N-chloro-N-methylaniline, which rearranges (as in **1-35**) to give a mixture of ring-chlorinated N-methylanilines in which the ortho isomer predominates.[193]

$FeCl_3$ itself, and also $CuCl_2$, $SbCl_5$, etc.,[194] can give moderate yields of aryl chlorides.[195] The electrophile might be a species such as $FeCl_2^+$, but the reactions can also take place by a free-radical mechanism.[196]

When chlorination or bromination is carried out at high temperatures (e.g., 300 to 400°C), ortho-para-directing groups direct meta and vice versa.[197] A different mechanism operates here, which is not completely understood. It is also possible for bromination to take place by the SE1 mechanism, e.g., in the *t*-BuOK-catalyzed bromination of 1,3,5-tribromobenzene.[198]

**2.** *Iodine.* Iodine is the least reactive of the halogens in aromatic substitution.[199] Except for active substrates, an oxidizing agent must normally be present to oxidize $I_2$ to a better electrophile.[200] Examples of such oxidizing agents are $HNO_3$, $HIO_3$, $SO_3$, peracetic acid, and $H_2O_2$.[201] ICl is a better iodinating agent than iodine itself.[202] Among other reagents used have been IF (prepared directly from the elements),[203] benzyltrimethylammonium dichloroiodate (which iodinates phenols, aromatic amines, and N-acylated aromatic amines),[204] and the combination of iodine cyanide ICN and a Lewis acid, which is a good reagent for active substrates.[205] Iodination can also be accomplished by treatment of the substrate with $I_2$ in the presence of copper salts,[206] $SbCl_5$,[207] silver trifluoromethanesulfonate $CF_3SO_3Ag$,[208] HgO–$BF_4$,[209] $Al_2O_3$,[210] $AgNO_3$,[211] $Ag_2SO_4$,[212] or thallium(I) acetate.[213] The TlOAc method is regioselective for ortho iodination.

The actual attacking species is less clear than with bromine or chlorine. Iodine itself is too unreactive, except for active species such as phenols, where there is good evidence that

[192]Swain; Crist *J. Am. Chem. Soc.* **1972,** *94*, 3195.

[193]Haberfield; Paul *J. Am. Chem. Soc.* **1965,** *87*, 5502; Gassman; Campbell *J. Am. Chem. Soc.* **1972,** *94*, 3891; Paul; Haberfield *J. Org. Chem.* **1976,** *41*, 3170.

[194]Kovacic; Wu; Stewart *J. Am. Chem. Soc.* **1960,** *82*, 1917; Ware; Borchert *J. Org. Chem.* **1961,** *26*, 2267; Commandeur; Mathais; Raynier; Waegell *Nouv. J. Chim.* **1979,** *3*, 385; Makhon'kov; Cheprakov; Rodkin; Beletskaya *J. Org. Chem. USSR* **1988,** *24*, 211; Kodomari; Satoh; Yoshitomi *J. Org. Chem.* **1988,** *53*, 2093.

[195]For a review of halogenations with metal halides, see Kovacic, in Olah, Ref. 58, vol. 4, 1965, pp. 111-126.

[196]Nonhebel *J. Chem. Soc.* **1963,** 1216; Nonhebel; Russell *Tetrahedron* **1969,** *25*, 3493.

[197]For a review of this type of reaction, see Kooyman *Pure. Appl. Chem.* **1963,** *7*, 193-202.

[198]Mach; Bunnett *J. Am. Chem. Soc.* **1974,** *96*, 936.

[199]For reviews of $I_2$ as an electrophilic reagent, see Pizey, in Pizey *Synthetic Reagents*, vol. 3; Wiley: New York, 1977, pp. 227-276. For reviews of aromatic iodination, see Merkushev *Synthesis* **1988,** 923-937, *Russ. Chem. Rev.* **1984,** *53*, 343-350.

[200]Butler *J. Chem. Educ.* **1971,** *48*, 508.

[201]For a discussion, see Makhon'kov; Cheprakov; Beletskaya *J. Org. Chem. USSR* **1989,** *24*, 2029.

[202]For a review of ICl, see McCleland, in Pizey, Ref. 199, vol. 5, 1983, pp. 85-164.

[203]Rozen; Zamir *J. Org. Chem.* **1990,** *55*, 3552.

[204]See Kajigaeshi; Kakinami; Watanabe; Okamoto *Bull. Chem. Soc. Jpn.* **1989,** *62*, 1349, and references cited therein.

[205]Radner *Acta Chem. Scand.* **1989,** *43*, 481. For another method, see Edgar; Falling *J. Org. Chem.* **1990,** *55*, 5287.

[206]Baird; Surridge *J. Org. Chem.* **1970,** *35*, 3436; Horiuchi; Satoh *Bull. Chem. Soc. Jpn.* **1984,** *57*, 2691; Makhon'kov; Cheprakov; Rodkin; Beletskaya *J. Org. Chem. USSR* **1986,** *22*, 1003.

[207]Uemura; Onoe; Okano *Bull. Chem. Soc. Jpn.* **1974,** *47*, 147.

[208]Kobayashi; Kumadaki; Yoshida *J. Chem. Res. (S)* **1977,** 215. For a similar procedure, see Merkushev; Simakhina; Koveshnikova *Synthesis* **1980,** 486.

[209]Barluenga; Campos; González; Asensio *J. Chem. Soc., Perkin Trans. 1* **1984,** 2623.

[210]Pagni; Kabalka; Boothe; Gaetano; Stewart; Conaway; Dial; Gray; Larson; Luidhart *J. Org. Chem.* **1988,** *53*, 4477.

[211]Sy; Lodge *Tetrahedron Lett.* **1989,** *30*, 3769.

[212]Sy; Lodge; By *Synth. Commun.* **1990,** *20*, 877.

[213]Cambie; Rutledge; Smith-Palmer; Woodgate *J. Chem. Soc., Perkin Trans. 1* **1976,** 1161.

$I_2$ is the attacking entity.[214] There is evidence that AcOI may be the attacking entity when peroxyacetic acid is the oxidizing agent,[215] and $I_3^+$ when $SO_3$ or $HIO_3$ is the oxidizing agent.[216] $I^+$ has been implicated in several procedures.[216a] For an indirect method for accomplishing aromatic iodination, see **2-30.**

**3.** *Fluorine.* Direct fluorination of aromatic rings with $F_2$ is not feasible at room temperature, because of the extreme reactivity of $F_2$.[217] It has been accomplished at low temperatures (e.g., $-70$ to $-20°C$, depending on the substrate),[218] but the reaction is not yet of preparative significance. Fluorination has also been reported with silver difluoride $AgF_2$,[219] with cesium fluoroxysulfate $CsSO_4F$,[220] with acetyl hypofluorite $CH_3COOF$ (generated from $F_2$ and sodium acetate),[221] with $XeF_2$,[222] with an N-fluoroperfluoroalkyl sulfonamide, e.g., $(CF_3SO_2)_2NF$,[223] and with fluoroxytrifluoromethane $CF_3OF$[224] under various conditions and with various yields, in some cases by electrophilic and in other cases by free-radical mechanisms. However, none of these methods seems likely to displace the Schiemann reaction (**3-24**) as the most common method for introducing fluorine into aromatic rings.

The overall effectiveness of reagents in aromatic substitution is $Cl_2 > BrCl > Br_2 > ICl > I_2$.

OS **I,** 111, 121, 123, 128, 207, 323; **II,** 95, 97, 100, 173, 196, 343, 347, 349, 357, 592; **III,** 132, 134, 138, 262, 267, 575, 796; **IV,** 114, 166, 256, 545, 547, 872, 947; **V,** 117, 147, 206, 346; **VI,** 181, 700; **67,** 222. Also see OS **II,** 128.

**E. Carbon Electrophiles** In the reactions in this section, a new carbon–carbon bond is formed. With respect to the aromatic ring, they are electrophilic substitutions, because a positive species attacks the ring. We treat them in this manner because it is customary. However, with respect to the electrophile, most of these reactions are nucleophilic substitutions, and what was said in Chapter 10 is pertinent to them.

## 1-12 Friedel–Crafts Alkylation
## Alkylation or Alkyl-de-hydrogenation

$$\mathbf{ArH + RCl \xrightarrow{AlCl_3} ArR}$$

[214]Grovenstein; Aprahamian; Bryan; Gnanapragasam; Kilby; McKelvey; Sullivan *J. Am. Chem. Soc.* **1973,** *95,* 4261.

[215]Ogata; Urasaki *J. Chem. Soc. C* **1970,** 1689.

[216]Arotsky; Butler; Darby *J. Chem. Soc. C* **1970,** 1480.

[216a]Galli *J. Org. Chem.* **1991,** *56,* 3238.

[217]For a monograph on fluorinating agents, see German; Zemskov *New Fluorinating Agents in Organic Synthesis*; Springer: New York, 1989. For reviews of $F_2$ in organic synthesis, see Purrington; Kagen; Patrick *Chem. Rev.* **1986,** *86,* 997-1018; Grakauskas, *Intra-Sci. Chem. Rep.* **1971,** *5,* 85-104. For a review of fluoroaromatic compounds, see Hewitt; Silvester *Aldrichimica Acta* **1988,** *21,* 3-10.

[218]Grakauskas *J. Org. Chem.* **1970,** *35,* 723; Cacace; Giacomello; Wolf *J. Am. Chem. Soc.* **1980,** *102,* 3511; Stavber; Zupan *J. Org. Chem.* **1983,** *48,* 2223. See also Purrington; Woodard *J. Org. Chem.* **1991,** *56,* 142.

[219]Zweig; Fischer; Lancaster *J. Org. Chem.* **1980,** *45,* 3597.

[220]Ip; Arthur; Winans; Appelman *J. Am. Chem. Soc.* **1981,** *103,* 1964; Stavber; Zupan *J. Org. Chem.* **1985,** *50,* 3609; Appelman; Basile; Hayatsu *Tetrahedron* **1984,** *40,* 189; Patrick; Darling *J. Org. Chem.* **1986,** *51,* 3242.

[221]See Hebel; Lerman; Rozen *Bull. Soc. Chim. Fr.* **1986,** 861; Visser; Bakker; van Halteren; Herscheid; Brinkman; Hoekstra *J. Org. Chem.* **1986,** *51,* 1886.

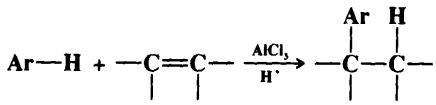
[222]Shaw; Hyman; Filler *J. Am. Chem. Soc.* **1969,** *91,* 1563, **1970,** *92,* 6498, *J. Org. Chem.* **1971,** *36,* 2917; Mackenzie; Fajer *J. Am. Chem. Soc.* **1970,** *92,* 4994; Filler *Isr. J. Chem.* **1978,** *17,* 71.

[223]Singh; DesMarteau; Zuberi; Witz; Huang *J. Am. Chem. Soc.* **1987,** *109,* 7194.

[224]Barton; Ganguly; Hesse; Loo; Pechet *Chem. Commun.* **1968,** 806; Kollonitsch; Barash; Doldouras *J. Am. Chem. Soc.* **1970,** *92,* 7494; Patrick; Cantrell; Chang *J. Am. Chem. Soc.* **1979,** *101,* 7434; Fifolt; Olczak; Mundhenke; Bieron *J. Org. Chem.* **1985,** *50,* 4576. For a review of this reagent, see Barton *Pure. Appl. Chem.* **1977,** *49,* 1241-1249.

The alkylation of aromatic rings, called *Friedel–Crafts alkylation*, is a reaction of very broad scope.[225] The most important reagents are alkyl halides, olefins, and alcohols, but many other types of reagent have also been employed.[225] When alkyl halides are used, the reactivity order is F > Cl > Br > I[226]; e.g., $FCH_2CH_2CH_2Cl$ reacts with benzene to give $PhCH_2CH_2CH_2Cl$[227] when the catalyst is $BCl_3$. By the use of this catalyst, it is therefore possible to place a haloalkyl group on a ring (see also **1-24**).[228] Di- and trihalides, when all the halogens are the same, usually react with more than one molecule of aromatic compound; it is usually not possible to stop the reaction earlier.[229] Thus, benzene with $CH_2Cl_2$ gives not $PhCH_2Cl$, but $Ph_2CH_2$; benzene with $CHCl_3$ gives $Ph_3CH$. With $CCl_4$, however, the reaction stops when only three rings have been substituted to give $Ph_3CCl$.

Olefins are especially good alkylating agents. With respect to them the reaction is addition of ArH to a C=C double bond:



Acetylene reacts with 2 moles of aromatic compound to give 1,1-diarylethanes, but other alkynes react poorly, if at all. Alcohols are more active than alkyl halides, though if a Lewis-acid catalyst is used, more catalyst is required, since the catalyst complexes with the OH group. However, proton acids, especially $H_2SO_4$, are often used to catalyze alkylation with alcohols. When carboxylic esters are the reagents, there is competition between alkylation and acylation (**1-14**). Though this competition can often be controlled by choice of catalyst, and alkylation is usually favored, carboxylic esters are not often employed in Friedel–Crafts reactions. Other alkylating agents are ethers, thiols, sulfates, sulfonates, alkyl nitro compounds,[230] and even alkanes and cycloalkanes, under conditions where these are converted to carbocations. Notable here are ethylene oxide, which puts the $CH_2CH_2OH$ group onto the ring, and cyclopropane. For all types of reagent the reactivity order is allylic ~ benzylic > tertiary > secondary > primary.

Regardless of which reagent is used, a catalyst is nearly always required.[231] Aluminum chloride and boron trifluoride are the most common, but many other Lewis acids have been used, and also proton acids such as HF and $H_2SO_4$.[232] For active halides a trace of a less

[225]For a monograph, see Roberts; Khalaf *Friedel–Crafts Alkylation Chemistry*; Marcel Dekker: New York, 1984. For a treatise on Friedel–Crafts reactions in general, see Olah *Friedel–Crafts and Related Reactions*; Wiley: New York, 1963-1965. Volume 1 covers general aspects, such as catalyst activity, intermediate complexes, etc. Volume 2 covers alkylation and related reactions. In this volume the various reagents are treated by the indicated authors as follows: alkenes and alkanes, Patinkin; Friedman, pp. 1-288; dienes and substituted alkenes, Koncos; Friedman, pp. 289-412; alkynes, Franzen, pp. 413-416; alkyl halides, Drahowzal, pp. 417-475; alcohols and ethers, Schriesheim, pp. 477-595; sulfonates and inorganic esters, Drahowzal, pp. 641-658. For a monograph in which five chapters of the above treatise are reprinted and more recent material added, see Olah *Friedel–Crafts Chemistry*; Wiley: New York, 1973.

[226]For example, see Calloway *J. Am. Chem. Soc.* **1937,** *59*, 1474; Brown; Jungk *J. Am. Chem. Soc.* **1955,** *77*, 5584.

[227]Olah; Kuhn *J. Org. Chem.* **1964,** *29*, 2317.

[228]For a review of selectivity in this reaction, i.e., which group preferentially attacks when the reagent contains two or more, see Olah, in Olah, Ref. 225, vol. 1, pp. 881-905. This review also covers the case of alkylation vs. acylation.

[229]It has proven possible in some cases. Thus, arenes ArH have been converted to $ArCCl_3$ with $CCl_4$ and excess $AlCl_3$: Raabe; Hörhold *J. Prakt. Chem.* **1987,** *329*, 1131; Belen'kii; Brokhovetsky; Krayushkin *Chem. Scr.* **1989,** *29*, 81.

[230]Bonvino; Casini; Ferappi; Cingolani; Pietroni *Tetrahedron* **1981,** *37*, 615.

[231]There are a few exceptions. Certain alkyl and vinylic triflates alkylate aromatic rings without a catalyst; see Gramstad; Haszeldine *J. Chem. Soc.* **1957,** 4069; Olah; Nishimura *J. Am. Chem. Soc.* **1974,** *96*, 2214; Stang; Anderson *Tetrahedron Lett.* **1977,** 1485, *J. Am. Chem. Soc.* **1978,** *100*, 1520.

[232]For a review of catalysts and solvents in Friedel–Crafts reactions, see Olah, in Olah, Ref. 225, vol. 1, pp. 201-366, 853-881.

active catalyst, e.g., $ZnCl_2$, may be enough. For an unreactive halide, such as chloromethane, a more powerful catalyst is needed, for example, $AlCl_3$, and in larger amounts. In some cases, especially with olefins, a Lewis-acid catalyst causes reaction only if a small amount of proton-donating cocatalyst is present. Catalysts have been arranged in the following order of overall reactivity: $AlBr_3 > AlCl_3 > GaCl_3 > FeCl_3 > SbCl_5$[233] $> ZrCl_4$, $SnCl_4 > BCl_3$, $BF_3$, $SbCl_3$;[234] but the reactivity order in each case depends on the substrate, reagent, and conditions. Nafion-H, a superacidic perfluorinated resinsulfonic acid, is a very good catalyst for gas phase alkylations with alkyl halides, alcohols, or olefins.[235]

Friedel–Crafts alkylation is unusual among the principal aromatic substitutions in that the entering group is activating so that di- and polyalkylation are frequently observed. However, the activating effect of simple alkyl groups (e.g., ethyl, isopropyl) is such that compounds with these groups as substituents are attacked in Friedel–Crafts alkylations only about 1.5 to 3 times as fast as benzene,[236] so it is often possible to obtain high yields of monoalkyl product. Actually, the fact that di- and polyalkyl derivatives are frequently obtained is not due to the small difference in reactivity but to the circumstance that alkylbenzenes are preferentially soluble in the catalyst layer, where the reaction actually takes place.[237] This factor can be removed by the use of a suitable solvent, by high temperatures, or by high-speed stirring.

Also unusual is the fact that the OH, OR, $NH_2$, etc., groups do not facilitate the reaction, since the catalyst coordinates with these basic groups. Although phenols give the usual Friedel–Crafts reactions, orienting ortho and para, the reaction is very poor for amines. However, amines can undergo the reaction if olefins are used as reagents and aluminum anilides as catalysts.[238] In this method the catalyst is prepared by treating the amine to be alkylated with $\frac{1}{3}$ mole of $AlCl_3$. A similar reaction can be performed with phenols, though here the catalyst is $Al(OAr)_3$.[239] Primary aromatic amines (and phenols) can be methylated regioselectively in the ortho position by an indirect method (see **1-26**). For an indirect method for regioselective ortho methylation of phenols, see p. 872.

Naphthalene and other fused ring compounds generally give poor yields in Friedel–Crafts alkylation, because they are so reactive that they react with the catalyst. Heterocyclic rings are usually also poor substrates for the reaction. Although some furans and thiophenes have been alkylated, a true alkylation of a pyridine or a quinoline has never been described.[240] However, alkylation of pyridine and other nitrogen heterocycles can be accomplished by a free radical (**4-23**) and by a nucleophilic method (**3-17**).

In most cases, meta-directing groups make the ring too inactive for alkylation. Nitrobenzene cannot be alkylated, and there are only a few reports of successful Friedel–Crafts alkylations when electron-withdrawing groups are present.[241] This is not because the attacking species is not powerful enough; indeed we have seen (p. 518) that alkyl cations are among the most powerful of electrophiles. The difficulty is caused by the fact that, with inactive substrates, degradation and polymerization of the electrophile occurs before it can attack the ring. However, if an activating and a deactivating group are both present on a

[233]For a review of $SbCl_5$ as a Friedel–Crafts catalyst, see Yakobson; Furin *Synthesis* **1980**, 345-364.

[234]Russell *J. Am. Chem. Soc.* **1959**, *81*, 4834.

[235]For a review of Nafion-H in organic synthesis, see Olah; Iyer; Prakash *Synthesis* **1986**, 513-531.

[236]Condon *J. Am. Chem. Soc.* **1948**, *70*, 2265; Olah; Kuhn; Flood *J. Am. Chem. Soc.* **1962**, *84*, 1688.

[237]Francis *Chem. Rev.* **1948**, *43*, 257.

[238]For a review, see Stroh; Ebersberger; Haberland; Hahn *Newer Methods Prep. Org. Chem.* **1963**, *2*, 227-252. This article also appeared in *Angew. Chem.* **1957**, *69*, 124-131.

[239]Koshchii; Kozlikovskii; Matyusha *J. Org. Chem. USSR* **1988**, *24*, 1358; Laan; Giesen; Ward *Chem. Ind. (London)* **1989**, 354. For a review, see Stroh; Seydel; Hahn *Newer Methods Prep. Org. Chem.* **1963**, *2*, 337-359. This article also appeared in *Angew. Chem.* **1957**, *69*, 669-706.

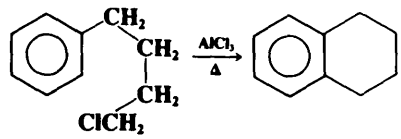
[240]Drahowzal, in Olah, Ref. 225, vol. 2, p. 433.

[241]Campbell; Spaeth *J. Am. Chem. Soc.* **1959**, *81*, 5933; Yoneda; Fukuhara; Takahashi; Suzuki *Chem. Lett.* **1979**, 1003; Shen; Liu; Chen *J. Org. Chem.* **1990**, *55*, 3961.

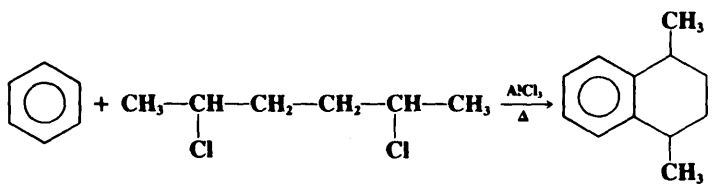
ring, Friedel–Crafts alkylation can be accomplished.[242] Aromatic nitro compounds can be methylated by a nucleophilic mechanism (**3-17**).

An important synthetic limitation of Friedel–Crafts alkylation is that rearrangement frequently takes place in the reagent. For example, benzene treated with *n*-propyl bromide gives mostly isopropylbenzene (cumene) and much less *n*-propylbenzene. Rearrangement is usually in the order primary → secondary → tertiary and occurs mostly by migration of $H^-$ but also of $R^-$ (see discussion of rearrangement mechanisms in Chapter 18). It is therefore not usually possible to put a primary alkyl group (other than methyl and ethyl) onto an aromatic ring by Friedel–Crafts alkylation. Because of these rearrangements, *n*-alkylbenzenes are often prepared by *acylation* (**1-14**), followed by reduction (**9-37**).

An important use of the Friedel–Crafts alkylation reaction is to effect ring closure.[243] The most common method is to heat with aluminum chloride an aromatic compound having a halogen, hydroxy, or olefinic group in the proper position, as, for example, in the preparation of tetralin:




Another way of effecting ring closure through Friedel–Crafts alkylation is to use a reagent containing two groups, e.g.,




These reactions are most successful for the preparation of 6-membered rings,[244] though 5- and 7-membered rings have also been closed in this manner. For other Friedel–Crafts ring-closure reactions, see **1-13, 1-14,** and **1-23.**

From what has been said thus far it is evident that the electrophile in Friedel–Crafts alkylation is a carbocation, at least in most cases.[245] This is in accord with the knowledge that carbocations rearrange in the direction primary → secondary → tertiary (see Chapter 18). In each case the cation is formed from the attacking reagent and the catalyst. For the three most important types of reagent these reactions are:

From alkyl halides: $$RCl + AlCl_3 \longrightarrow R^+ + AlCl_4^-$$

From alcohols and Lewis acids:

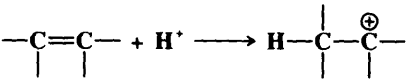
$$ROH + AlCl_3 \longrightarrow ROAlCl_2 \longrightarrow R^+ + {}^-OAlCl_2$$

From alcohols and proton acids:

$$ROH + H^+ \longrightarrow ROH_2^+ \longrightarrow R^+ + H_2O$$

[242]Olah, in Olah, Ref. 225, vol. 1, p. 34.
[243]For a review, see Barclay, in Olah, Ref. 225, vol. 2, pp. 785-977.
[244]See Khalaf; Roberts *J. Org. Chem.* **1966,** *31,* 89.
[245]For a discussion of the mechanism see Taylor *Electrophilic Aromatic Substitution*, Ref. 1, pp. 188-213.

From olefins (a supply of protons is always required):



There is direct evidence, from ir and nmr spectra, that the *t*-butyl cation is quantitatively formed when *t*-butyl chloride reacts with $AlCl_3$ in anhydrous liquid HCl.[246] In the case of olefins, Markovnikov's rule (p. 750) is followed. Carbocation formation is particularly easy from some reagents, because of the stability of the cations. Triphenylmethyl chloride[247] and 1-chloroadamantane[248] alkylate activated aromatic rings (e.g., phenols, amines) with no catalyst or solvent. Ions as stable as this are less reactive than other carbocations and often attack only active substrates. The tropylium ion, for example, alkylates anisole but not benzene.[249] It was noted on p. 337 that relatively stable vinylic cations can be generated from certain vinylic compounds. These have been used to introduce vinylic groups into aryl substrates.[250]

However, there is much evidence that many Friedel–Crafts alkylations, especially with primary reagents, do not go through a completely free carbocation. The ion may exist as a tight ion pair with, say, $AlCl_4^-$ as the counterion or as a complex. Among the evidence is that methylation of toluene by methyl bromide and methyl iodide gave different ortho/para/meta ratios,[251] though if the same species attacked in each case we would expect the same ratios. Other evidence is that, in some cases, the reaction kinetics are third order; first order each in aromatic substrate, attacking reagent, and catalyst.[252] In these instances a mechanism in which the carbocation is slowly formed and then rapidly attacks the ring is ruled out since, in such a mechanism, the substrate would not appear in the rate expression. Since it is known that free carbocations, once formed, rapidly attack the ring, there are no free carbocations here. Another possibility (with alkyl halides) is that some alkylations take place by an SN2 mechanism (with respect to the halide), in which case no carbocations would be involved at all. However, a completely SN2 mechanism requires inversion of configuration. Most investigations of Friedel–Crafts stereochemistry, even where an SN2 mechanism might most be expected, have resulted in total racemization, or at best a few percent inversion. A few exceptions have been found,[253] most notably where the reagent was optically active propylene oxide, in which case 100% inversion was reported.[254]

Rearrangement is possible even with a noncarbocation mechanism. The rearrangement could occur *before* the attack on the ring takes place. It has been shown that treatment of $CH_3{}^{14}CH_2Br$ with $AlBr_3$ in the absence of any aromatic compound gave a mixture of the starting material and $^{14}CH_3CH_2Br$.[255] Similar results were obtained with $PhCH_2{}^{14}CH_2Br$, in which case the rearrangement was so fast that the rate could be measured only below

[246]Kalchschmid; Mayer *Angew. Chem. Int. Ed. Engl.* **1976,** *15*, 773 [*Angew. Chem. 88*, 849].

[247]See, for example, Chuchani *J. Chem. Soc.* **1960,** 325; Hart; Cassis *J. Am. Chem. Soc.* **1954,** *76*, 1634; Hickinbottom *J. Chem. Soc.* **1934,** 1700; Chuchani and Zabicky *J. Chem. Soc. C* **1966,** 297.

[248]Takaku; Taniguchi; Inamoto *Synth. Commun.* **1971,** *1*, 141.

[249]Bryce-Smith; Perkins *J. Chem. Soc.* **1962,** 5295.

[250]Kitamura; Kobayashi; Taniguchi; Rappoport *J. Org. Chem.* **1982,** *47*, 5503.

[251]Brown; Jungk *J. Am. Chem. Soc.* **1956,** *78*, 2182.

[252]For examples, see Brown; Grayson *J. Am. Chem. Soc.* **1953,** *75*, 6285; Jungk; Smoot; Brown *J. Am. Chem. Soc.* **1956,** *78*, 2185; Choi; Brown *J. Am. Chem. Soc.* **1963,** *85*, 2596.

[253]Some instances of retention of configuration have been reported; a neighboring-group mechanism is likely in these cases: see Masuda; Nakajima; Suga *Bull. Chem. Soc. Jpn.* **1983,** *56*, 1089; Effenberger; Weber *Angew. Chem. Int. Ed. Engl.* **1987,** *26*, 142 [*Angew. Chem. 99*, 146].

[254]Nakajima; Suga; Sugita; Ichikawa *Tetrahedron* **1969,** *25*, 1807. For cases of almost complete inversion, with acyclic reagents, see Piccolo; Spreafico; Visentin; Valoti *J. Org. Chem.* **1985,** *50*, 3945; Piccolo; Azzena; Melloni; Delogu; Valoti *J. Org. Chem.* **1991,** *56*, 183.

[255]Sixma; Hendriks *Recl. Trav. Chim. Pays-Bas* **1956,** *75*, 169; Adema; Sixma *Recl. Trav. Chim. Pays-Bas* **1962,** *81*, 323, 336.

$-70°C$.[256] Rearrangement could also occur *after* formation of the product, since alkylation is reversible (see **1-37**).[257]

See **4-21** and **4-23** for free-radical alkylation.

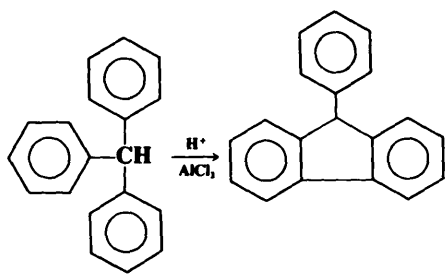
OS **I**, 95, 548; **II**, 151, 229, 232, 236, 248; **III**, 343, 347, 504, 842; **IV**, 47, 520, 620, 665, 702, 898, 960; **V**, 130, 654; **VI**, 109, 744.

### **1-13** Friedel–Crafts Arylation. The Scholl Reaction
### **De-hydrogen-coupling**

$$2ArH \xrightarrow[H^+]{AlCl_3} Ar—Ar + H_2$$

The coupling of two aromatic molecules by treatment with a Lewis acid and a proton acid is called the *Scholl reaction*.[258] Yields are low and the synthesis is seldom useful. High temperatures and strong-acid catalysts are required, and the reaction fails for substrates that are destroyed by these conditions. Because the reaction becomes important with large fused-ring systems, ordinary Friedel–Crafts reactions (**1-12**) on these systems are rare. For example, naphthalene gives binaphthyl under Friedel–Crafts conditions. Yields can be increased by the addition of a salt such as $CuCl_2$ or $FeCl_3$, which acts as an oxidant.[259]

Intramolecular Scholl reactions, e.g.,




are much more successful than the intermolecular kind. The mechanism is not clear, but it may involve attack by a proton to give an arenium ion of the type **9** (p. 504), which would be the electrophile that attacks the other ring.[260] Sometimes arylations have been accomplished by treating aromatic substrates with particularly active aryl halides, especially fluorides. For free-radical arylations, see reactions **4-18** to **4-22.**

OS **IV**, 482. Also see OS **V**, 102, 952.

### **1-14** Friedel–Crafts Acylation
### **Acylation** or **Acyl-de-hydrogenation**

$$ArH + RCOCl \xrightarrow{AlCl_3} ArCOR$$

The most important method for the preparation of aryl ketones is known as *Friedel–Crafts acylation*.[261] The reaction is of wide scope. Reagents used[262] are not only acyl halides but

[256]For a review of the use of isotopic labeling to study Friedel–Crafts reactions, see Roberts; Gibson *Isot. Org. Chem.* **1980**, *5*, 103-145.

[257]For an example, see Lee; Hamblin; Uthe *Can. J. Chem.* **1964**, *42*, 1771.

[258]For reviews, see Kovacic; Jones *Chem. Rev.* **1987**, *87*, 357-79; Balaban; Nenitzescu, in Olah, Ref. 225, vol. 2, pp. 979-1047.

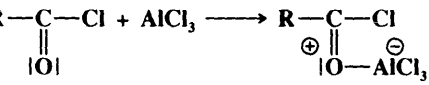
[259]Kovacic; Koch *J. Org. Chem.* **1963**, *28*, 1864, **1965**, *30*, 3176; Kovacic; Wu *J. Org. Chem.* **1961**, *26*, 759, 762. For examples, with references, see Larock, Ref. 171, pp. 45-46.

[260]For a discussion, see Clowes *J. Chem. Soc. C* **1968**, 2519.

[261]For reviews of Friedel–Crafts acylation, see Olah *Friedel–Crafts and Related Reactions*; Wiley: New York, 1963-1964, as follows: vol. 1, Olah, pp. 91-115; vol. 3, Gore, pp. 1-381; Peto, pp. 535-910; Sethna, pp. 911-1002; Jensen; Goldman, pp. 1003-1032. For another review, see Gore *Chem. Ind.* (*London*) **1974**, 727-731.

[262]For a list of reagents, with references, see Larock, Ref. 171, pp. 703-704.

also carboxylic acids, anhydrides, and ketenes. Carboxylic esters usually give predominant alkylation (see **1-12**). R may be aryl as well as alkyl. The major disadvantages of Friedel–Crafts alkylation are not present here. Rearrangement of R is never found, and, because the RCO group is deactivating, the reaction stops cleanly after one group is introduced. All four acyl halides can be used, though chlorides are most commonly employed. The order of activity is usually, but not always, I > Br > Cl > F.[263] Catalysts are Lewis acids, similar to those in reaction **1-12**, but in acylation a little more than 1 mole of catalyst is required per mole of reagent, because the first mole coordinates with the oxygen of the reagent.[264]

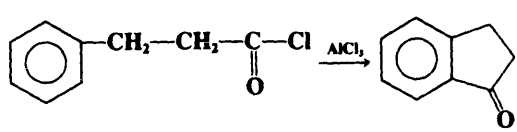


Proton acids can be used as catalysts when the reagent is a carboxylic acid. The mixed carboxylic sulfonic anhydrides $RCOOSO_2CF_3$ are extremely reactive acylating agents and can smoothly acylate benzene without a catalyst.[265] With active substrates (e.g., aryl ethers, fused-ring systems, thiophenes), Friedel–Crafts acylation can be carried out with very small amounts of catalyst, often just a trace, or even sometimes with no catalyst at all. Ferric chloride, iodine, zinc chloride, and iron are the most common catalysts when the reactions is carried out in this manner.[266]

The reaction is quite successful for many types of substrate, including fused ring systems, which give poor results in **1-12**. Compounds containing ortho-para-directing groups, including alkyl, hydroxy, alkoxy, halogen, and acetamido groups, are easily acylated and give mainly or exclusively the para products, because of the relatively large size of the acyl group. However, aromatic amines give poor results. With amines and phenols there may be competition from N- or O-acylation; however, O-acylated phenols can be converted to C-acylated phenols by the Fries rearrangement (**1-30**). Friedel–Crafts acylation is usually prevented by meta-directing groups. Indeed, nitrobenzene is often used as a solvent for the reaction. Many heterocyclic systems, including furans, thiophenes, pyrans, and pyrroles but not pyridines or quinolines, can be acylated in good yield (however, pyridines and quinolines can be acylated by a free-radical mechanism, reaction **4-23**). Gore, in Ref. 261 (pp. 36–100; with tables, pp. 105–321), presents an exhaustive summary of the substrates to which this reaction has been applied.

When a mixed anhydride RCOOCOR′ is the reagent, two products are possible—ArCOR and ArCOR′. Which product predominates depends on two factors. If R contains electron-withdrawing groups, then ArCOR′ is chiefly formed, but if this factor is approximately constant in R and R′, the ketone with the larger R group predominantly forms.[267] This means that *formylations* of the ring do not occur with mixed anhydrides of formic acid HCOOCOR.

An important use of the Friedel–Crafts acylation is to effect ring closure.[268] This can be done if an acyl halide, anhydride, or acid group is in the proper position. An example is



[263]Yamase *Bull. Chem. Soc. Jpn.* **1961**, *34*, 480; Corriu *Bull. Soc. Chim. Fr.* **1965**, 821.

[264]The crystal structures of several of these complexes have been reported: Rasmussen; Broch *Acta Chem. Scand.* **1966**, *20*, 1351; Chevrier; Le Carpentier; Weiss *J. Am. Chem. Soc.* **1972**, *94*, 5718. For a review of these complexes, see Chevrier; Weiss *Angew. Chem. Int. Ed. Engl.* **1974**, *13*, 1-10 [*Angew. Chem. 86*, 12-21].

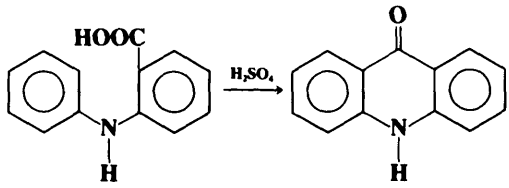
[265]Effenberger; Sohn; Epple *Chem. Ber.* **1983**, *116*, 1195. See also Keumi; Yoshimura; Shimada; Kitajima *Bull. Chem. Soc. Jpn.* **1988**, *44*, 455.

[266]For a review, see Pearson; Buehler *Synthesis* **1972**, 533-542.

[267]Edwards; Sibelle *J. Org. Chem.* **1963**, *28*, 674.

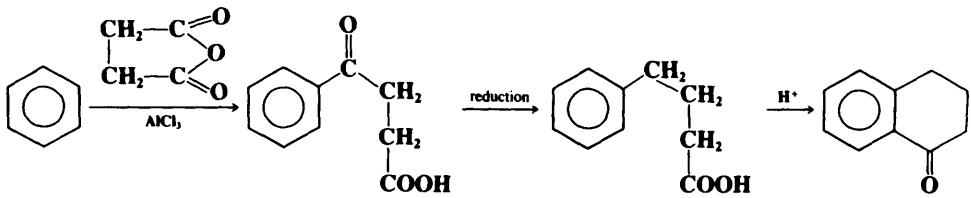
[268]For a review, see Sethna, Ref. 261. For examples, with references, see Larock, Ref. 171, pp. 704-708.

The reaction is used mostly to close 6-membered rings, but has also been done for 5- and 7-membered rings, which close less readily. Even larger rings can be closed by high-dilution techniques.[269] Tricyclic and larger systems are often made by using substrates containing one of the acyl groups on a ring. An example is the formation of acridone:




Many fused ring systems are made in this manner. If the bridging group is CO, the product is a quinone.[270] One of the most common catalysts for intramolecular Friedel–Crafts acylation is polyphosphoric acid[271] (because of its high potency), but $AlCl_3$, $H_2SO_4$, and other Lewis and proton acids are also used, though acylations with acyl halides are not generally catalyzed by proton acids.

Friedel–Crafts acylation can be carried out with cyclic anhydrides,[272] in which case the product contains a carboxyl group in the side chain. When succinic anhydride is used, the product is $ArCOCH_2CH_2COOH$. This can be reduced (**9-37**) to $ArCH_2CH_2CH_2COOH$, which can then be cyclized by an internal Friedel–Crafts acylation. The total process is called the *Haworth reaction*:[273]




The mechanism of Friedel–Crafts acylation is not completely understood, but at least two mechanisms probably operate, depending on conditions.[274] In most cases the attacking species is the acyl cation, either free or as an ion pair, formed by[275]

$$RCOCl + AlCl_3 \longrightarrow RCO^+ + AlCl_4^-$$

If R is tertiary, $RCO^+$ may lose CO to give $R^+$, so that the alkylarene ArR is often a side product or even the main product. This kind of cleavage is much more likely with relatively unreactive substrates, where the acylium ion has time to break down. For example, pivaloyl chloride $Me_3CCOCl$ gives the normal acyl product with anisole, but the alkyl product $Me_3CPh$ with benzene. In the other mechanism an acyl cation is not involved, but the 1:1 complex attacks directly.[276]

[269]For example, see Schubert; Sweeney; Latourette *J. Am. Chem. Soc.* **1954,** *76*, 5462.

[270]For discussions, see Naruta; Maruyama, in Patai; Rappoport *The Chemistry of the Quinonoid Compounds*, vol. 2, pt. 1; Wiley: New York, 1988, pp. 325-332; Thomson, in Patai *The Chemistry of the Quinonoid Compounds*, vol. 1, pt. 1; Wiley: New York, 1974; pp. 136-139.

[271]For a review of polyphosphoric acid, see Rowlands, in Pizey, Ref. 199, vol. 6, 1985, pp. 156-414.

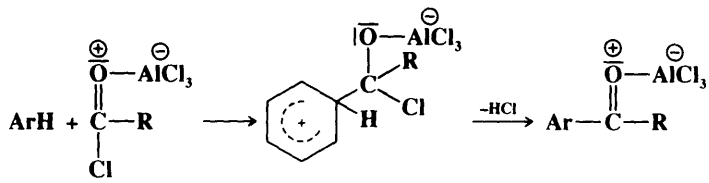
[272]For a review see Peto, Ref. 261.

[273]See Agranat; Shih *J. Chem. Educ.* **1976,** *53*, 488.

[274]For a review of the mechanism see Taylor *Electrophilic Aromatic Substitution*, Ref. 1, pp. 222-237.

[275]After 2 min, exchange between PhCOCl and $Al(^{36}Cl)_3$ is complete: Oulevey; Susz *Helv. Chim. Acta* **1964,** *47*, 1828.

[276]For example, see Corriu; Coste *Bull. Soc. Chim. Fr.* **1967,** 2562, 2568, 2574; **1969,** 3272; Corriu; Dore; Thomassin *Tetrahedron* **1971,** *27*, 5601, 5819; Tan; Brownstein *J. Org. Chem.* **1983,** *48*, 302.

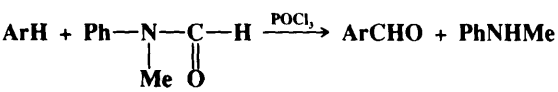


Free-ion attack is more likely for sterically hindered R.[277] The ion $CH_3CO^+$ has been detected (by ir spectroscopy) in the liquid complex between acetyl chloride and aluminum chloride, and in polar solvents such as nitrobenzene; but in nonpolar solvents such as chloroform, only the complex and not the free ion is present.[278] In any event, 1 mole of catalyst certainly remains complexed to the product at the end of the reaction. When the reaction is performed with $RCO^+$ $SbF_6^-$, no catalyst is required and the free ion[279] (or ion pair) is undoubtedly the attacking entity.[280]

OS **I,** 109, 353, 476, 517; **II,** 3, 8, 15, 81, 156, 169, 304, 520, 569; **III,** 6, 14, 23, 53, 109, 183, 248, 272, 593, 637, 761, 798; **IV,** 8, 34, 88, 898, 900; **V,** 111; **VI,** 34, 618, 625.

Reactions **1-15** through **1-18** are direct formylations of the ring.[281] Reaction **1-14** has not been used for formylation, since neither formic anhydride nor formyl chloride is stable at ordinary temperatures. Formyl chloride has been shown to be stable in chloroform solution for 1 hr at $-60°C$,[282] but it is not useful for formylating aromatic rings under these conditions. Formic anhydride has been prepared in solution, but has not been isolated.[283] Mixed anhydrides of formic and other acids are known[284] and can be used to formylate amines (see **0-53**) and alcohols, but no formylation takes place when they are applied to aromatic rings. See **3-17** for a nucleophilic method for the formylation of aromatic rings.

### 1-15 Formylation with Disubstituted Formamides
### Formylation or Formyl-de-hydrogenation



The reaction with disubstituted formamides and phosphorus oxychloride, called the *Vilsmeier* or the *Vilsmeier–Haack reaction*, is the most common method for the formylation of aromatic rings.[285] However, it is applicable only to active substrates, such as amines and phenols. Aromatic hydrocarbons and heterocycles can also be formylated, but only if they are much more active than benzene (e.g., azulenes, ferrocenes). Though N-phenyl-N-methylform-

[277]Yamase *Bull. Chem. Soc. Jpn.* **1961,** *34*, 484; Gore *Bull. Chem. Soc. Jpn.* **1962,** *35*, 1627; Satchell *J. Chem. Soc.* **1961,** 5404.

[278]Cook *Can. J. Chem.* **1959,** *37*, 48; Cassimatis; Bonnin; Theophanides *Can. J. Chem.* **1970,** *48*, 3860.

[279]Crystal structures of solid $RCO^+$ $SbF_6^-$ salts have been reported: Boer *J. Am. Chem. Soc.* **1968,** *90*, 6706; Chevrier; Le Carpentier; Weiss *Acta Crystallogr., Sect. B* **1972,** *28*, 2673, *J. Am. Chem. Soc.* **1972,** *94*, 5718.

[280]Olah; Kuhn; Flood; Hardie *J. Am. Chem. Soc.* **1964,** *86*, 2203; Olah; Lin; Germain *Synthesis* **1974,** 895. For a review of acylium salts in organic synthesis, see Al-Talib; Tashtoush *Org. Prep. Proced. Int.* **1990,** *22*, 1-36.

[281]For a review, see Olah; Kuhn, in Olah, Ref. 261, vol. 3, 1964, pp. 1153-1256. For a review of formylating agents, see Olah; Ohannesian; Arvanaghi *Chem. Rev.* **1987,** *87*, 671-686. For a list of reagents, with references, see Larock, Ref. 171, pp. 702-703.

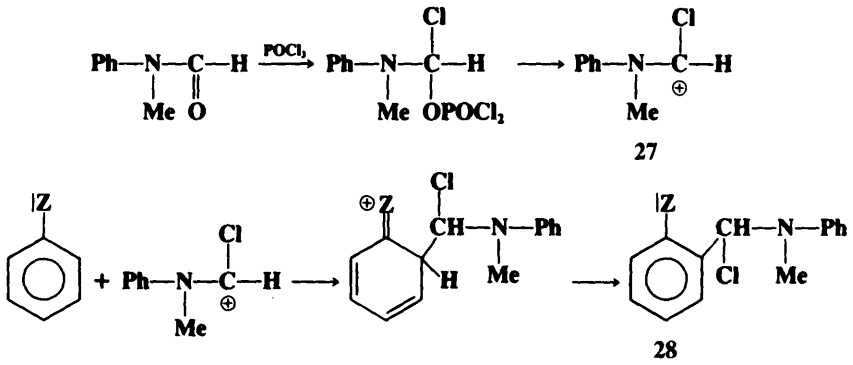
[282]Staab; Datta *Angew. Chem. Int. Ed. Engl.* **1964,** *3*, 132 [*Angew. Chem.* **1963,** *75*, 1203].

[283]Olah; Vankar; Arvanaghi; Sommer *Angew. Chem. Int. Ed. Engl.* **1979,** *18*, 614 [*Angew. Chem. 91*, 649]; Schijf; Scheeren; van Es; Stevens *Recl. Trav. Chim. Pays-Bas* **1965,** *84*, 594.

[284]Stevens; van Es *Recl. Trav. Chim. Pays-Bas* **1964,** *83*, 863.

[285]For a review, see Jutz *Adv. Org. Chem.* **1976,** *9*, pt. 1, 225-342.

amide is a common reagent, other arylalkyl amides and dialkyl amides are also used.[286] Phosgene $COCl_2$ has been used in place of $POCl_3$. The reaction has also been carried out with other amides to give ketones (actually an example of **1-14**), but not often. The attacking species[287] is **27**,[288] and the mechanism is probably:




**28** is unstable and easily hydrolyzes to the product. Either formation of **27** or the reaction of **27** with the substrate can be rate-determining, depending on the reactivity of the substrate.[289]

When $(CF_3SO_2)_2O$ was used instead of $POCl_3$, the reaction was extended to some less-active compounds, including naphthalene and phenanthrene.[290]

OS **I**, 217; **III**, 98, **IV**, 331, 539, 831, 915.

## 1-16 Formylation with Zinc Cyanide and HCl. The Gatterman Reaction
**Formylation** or **Formyl-de-hydrogenation**

$$ArH + Zn(CN)_2 \xrightarrow{HCl} ArCH{=}NH_2^+\ Cl^- \xrightarrow{H_2O} ArCHO$$

Formylation with $Zn(CN)_2$ and HCl is called the *Gatterman reaction*.[291] It can be applied to alkylbenzenes, phenols and their ethers, and many heterocyclic compounds. However, it cannot be applied to aromatic amines. In the original version of this reaction the substrate was treated with HCN, HCl, and $ZnCl_2$, but the use of $Zn(CN)_2$ and HCl (HCN and $ZnCl_2$ are generated in situ) makes the reaction more convenient to carry out and does not reduce yields. The mechanism of the Gatterman reaction has not been investigated very much, but there is an initial nitrogen-containing product that is normally not isolated but is hydrolyzed to aldehyde. The above structure is presumed for this product. When benzene was treated with NaCN under super acidic conditions ($F_3CSO_2OH$—$SbF_5$), a good yield of product was obtained, leading to the conclusion that the electrophile in this case was $H\overset{\oplus}{C}{=}\overset{\oplus}{N}H_2$.[292] The Gatterman reaction may be regarded as a special case of **1-27.**

[286]For a review of dimethylformamide, see Pizey, Ref. 199, vol. 1, 1974, pp. 1-99.

[287]For a review of such species, see Kantlehner *Adv. Org. Chem.* **1979**, *9*, pt. 2, 5-172.

[288]See Arnold; Holý *Collect. Czech. Chem. Commun.* **1962**, *27*, 2886; Martin; Martin *Bull. Soc. Chim. Fr.* **1963**, 1637; Fritz; Oehl *Liebigs Ann. Chem.* **1971**, *749*, 159; Jugie; Smith; Martin *J. Chem. Soc., Perkin Trans. 2* **1975**, 925.

[289]Alunni; Linda; Marino; Santini; Savelli *J. Chem. Soc., Perkin Trans. 2* **1972**, 2070.

[290]Martínez; Alvarez; Barcina; Cerero; Vilar; Fraile; Hanack; Subramanian *J. Chem. Soc., Chem. Commun.* **1990**, 1571.

[291]For a review, see Truce *Org. React.* **1957**, *9*, 37-72.

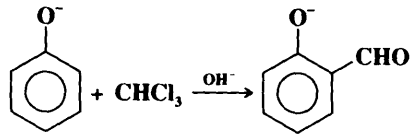
[292]Yato; Ohwada; Shudo *J. Am. Chem. Soc.* **1991**, *113*, 691.

Another method, formylation with CO and HCl in the presence of $AlCl_3$ and $CuCl$[293] (the *Gatterman–Koch reaction*), is limited to benzene and alkylbenzenes.[294]

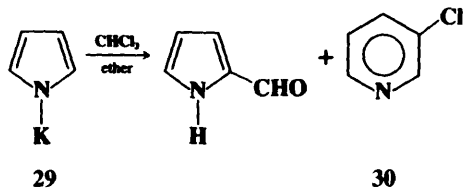
OS **II**, 583; **III**, 549.

## 1-17 Formylation with Chloroform. The Reimer–Tiemann Reaction

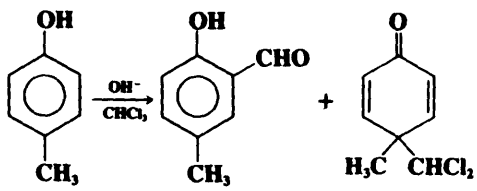
**Formylation** or **Formyl-de-hydrogenation**




In the *Reimer–Tiemann reaction* chloroform and hydroxide ion are used to formylate aromatic rings.[295] The method is useful only for phenols and certain heterocyclic compounds such as pyrroles and indoles. Unlike the previous formylation methods (**1-15** and **1-16**), this one is conducted in basic solution. Yields are generally low, seldom rising above 50%.[296] The incoming group is directed ortho, unless both ortho positions are filled, in which case the attack is para.[297] Certain substrates have been shown to give abnormal products instead of or in addition to the normal ones. For example, **29** and **31** gave, respectively, **30** and **32** as well as the normal aldehyde products. From the nature of the reagents and from the kind




**29** **30**




**31** **32**

of abnormal products obtained, it is clear that the attacking entity in this reaction is dichlorocarbene $CCl_2$.[298] This in known to be produced by treatment of chloroform with bases (p. 371); it is an electrophilic reagent and is known to give ring expansion of aromatic rings

[293]The CuCl is not always necessary: see Toniolo; Graziani *J. Organomet. Chem.* **1980**, *194*, 221.

[294]For a review, see Crounse *Org. React.* **1949**, *5*, 290-300.

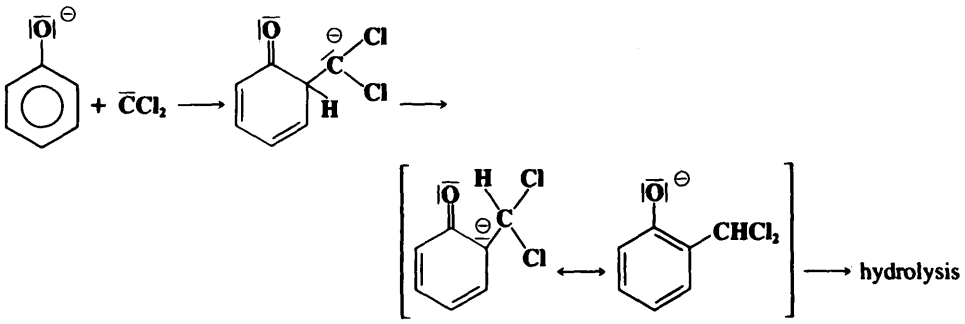
[295]For a review, see Wynberg; Meijer *Org. React.* **1982**, *28*, 1-36.

[296]For improved procedures, see Thoer; Denis; Delmas; Gaset *Synth. Commun.* **1988**, *18*, 2095; Cochran; Melville *Synth. Commun.* **1990**, *20*, 609.

[297]Increased para selectivity has been achieved by the use of polyethylene glycol: Neumann; Sasson *Synthesis* **1986**, 569.

[298]For a review of carbene methods for introducing formyl and acyl groups into organic molecules, see Kulinkovich *Russ. Chem. Rev.* **1989**, *58*, 711-719.

(see **5-50**), accounting for products like **30.** The mechanism of the normal reaction is thus something like this.[299]




The formation of **32** in the case of **31** can be explained by attack of some of the $CCl_2$ ipso to the $CH_3$ group. Since this position does not contain a hydrogen, normal proton loss cannot take place and the reaction ends when the $CCl_2^-$ moiety acquires a proton.

A method closely related to the Reimer–Tiemann reaction is the *Duff reaction*, in which hexamethylenetetramine $(CH_2)_6N_4$ is used instead of chloroform. This reaction can be applied only to phenols and amines; ortho substitution is generally observed and yields are low. A mechanism[300] has been proposed that involves initial aminoalkylation(**1-25**) to give $ArCH_2NH_2$, followed by dehydrogenation to ArCH=NH and hydrolysis of this to the aldehyde product. When $(CH_2)_6N_4$ is used in conjunction with $F_3CCOOH$, the reaction can be applied to simple alkylbenzenes; yields are much higher and a high degree of regioselectively para substitution is found.[301] In this case too an imine seems to be an intermediate.

OS **III,** 463; **IV,** 866

## 1-18 Other Formylations
### Formylation or Formyl-de-hydrogenation

$$ArH + Cl_2CHOMe \xrightarrow{AlCl_3} ArCHO$$

Besides **1-15** to **1-17,** several other formylation methods are known.[302] In one of these, dichloromethyl methyl ether formylates aromatic rings with Friedel–Crafts catalysts.[303] ArCHClOMe is probably an intermediate. Orthoformates have also been used.[304] In another method, aromatic rings are formylated with formyl fluoride HCOF and $BF_3$.[305] Unlike formyl chloride, formyl fluoride is stable enough for this purpose. This reaction was successful for benzene, alkylbenzenes, PhCl, PhBr, and naphthalene. Phenols can be regioselectively formylated in the ortho position in high yields by treatment with two equivalents of paraformaldehyde in aprotic solvents in the presence of $SnCl_4$ and a tertiary amine.[306] Phenols

[299]Robinson *J. Chem. Soc.* **1961,** 1663; Hine; van der Veen *J. Am. Chem. Soc.* **1959,** *81,* 6446. See also Langlois *Tetrahedron Lett.* **1991,** *32,* 3691.

[300]Ogata; Kawasaki; Sugiura *Tetrahedron* **1968,** *24,* 5001.

[301]Smith *J. Org. Chem.* **1972,** *37,* 3972.

[302]For methods other than those described here, see Smith; Manas *Synthesis* **1984,** 166; Olah; Laali; Farooq *J. Org. Chem.* **1985,** *50,* 1483; Nishino; Tsunoda; Kurosawa *Bull. Chem. Soc. Jpn.* **1989,** *62,* 545.

[303]Rieche; Gross; Höft *Chem. Ber.* **1960,** *93,* 88; Lewin; Parker; Fleming; Carroll *Org. Prep. Preced. Int.* **1978,** *10,* 201.

[304]Gross; Rieche; Matthey *Chem. Ber.* **1963,** *96,* 308.

[305]Olah; Kuhn *J. Am. Chem. Soc.* **1960,** *82,* 2380.

[306]Casiraghi; Casnati; Puglia; Sartori; Terenghi *J. Chem. Soc., Perkin Trans. 1* **1980,** 1862.

have also been formylated indirectly with 2-ethoxy-1,3-dithiolane.[307] See also the indirect method mentioned at **1-26.**

OS **V,** 49; **VII,** 162.

Reactions **1-19** and **1-20** are direct carboxylations[308] of aromatic rings.[309]

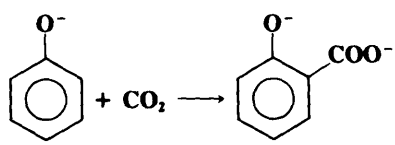
### 1-19 Carboxylation with Carbonyl Halides
**Carboxylation** or **Carboxy-de-hydrogenation**

$$\mathbf{ArH + COCl_2 \xrightarrow{AlCl_3} ArCOOH}$$

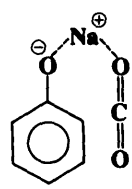
Phosgene, in the presence of Friedel–Crafts catalysts, can carboxylate the ring. This process is analogous to **1-14,** but the ArCOCl initially produced hydrolyzes to the carboxylic acid. However, in most cases the reaction does not take this course, but instead the ArCOCl attacks another ring to give a ketone ArCOAr. A number of other reagents have been used to get around this difficulty, among them oxalyl chloride, urea hydrochloride, chloral $Cl_3CCHO$,[310] carbamoyl chloride $H_2NCOCl$, and N,N-diethylcarbamoyl chloride.[311] With carbamoyl chloride the reaction is called the *Gatterman amide synthesis* and the product is an amide. Among compounds carboxylated by one or another of these reagents are benzene, alkylbenzenes, and fused ring systems.[312]

OS **V,** 706; **VII,** 420.

### 1-20 Carboxylation with Carbon Dioxide. The Kolbe–Schmitt Reaction
**Carboxylation** or **Carboxy-de-hydrogenation**




Sodium phenoxides can be carboxylated, mostly in the ortho position, by carbon dioxide (*the Kolbe–Schmitt reaction*). The mechanism is not clearly understood, but apparently some kind of a complex is formed between the reactants,[313] making the carbon of the $CO_2$ more




[307]Jo; Tanimoto; Sugimoto; Okano *Bull. Chem. Soc. Jpn.* **1981,** *54,* 2120.

[308]For other carboxylation methods, one of which leads to the anhydride, see Sakakibara; Odaira *J. Org. Chem.* **1976,** *41,* 2049; Fujiwara; Kawata; Kawauchi; Taniguchi *J. Chem. Soc., Chem. Commun.* **1982,** 132.

[309]For a review, see Olah; Olah, in Olah, Ref. 261, vol. 3, 1964, pp. 1257-1273.

[310]Menegheli; Rezende; Zucco *Synth. Commun.* **1987,** *17,* 457.

[311]Naumov; Isakova; Kost; Zakharov; Zvolinskii; Moiseikina; Nikeryasova *J. Org. Chem. USSR* **1975,** *11,* 362.

[312]For the use of phosgene to carboxylate phenols, see Sartori; Casnati; Bigi; Bonini *Synthesis* **1988,** 763.

[313]Hales; Jones; Lindsey *J. Chem. Soc.* **1954,** 3145.

positive and putting it in a good position to attack the ring. Potassium phenoxide, which is less likely to form such a complex,[314] is chiefly attacked in the para position.[315] Carbon tetrachloride can be used instead of $CO_2$ under Reimer–Tiemann (**1-17**) conditions.

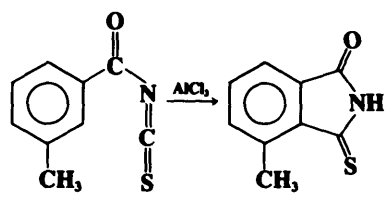
Sodium or potassium phenoxide can be carboxylated regioselectively in the para position in high yield by treatment with sodium or potassium carbonate and carbon monoxide.[316] $^{14}C$ labeling showed that it is the carbonate carbon that appears in the *p*-hydroxybenzoic acid product.[317] The CO is converted to sodium or potassium formate. Carbon monoxide has also been used to carboxylate aromatic rings with palladium compounds as catalysts.[318] In addition, a palladium-catalyzed reaction has been used directly to prepare acyl fluorides ArH → ArCOF.[319]

OS **II,** 557.

## 1-21 Amidation with Isocyanates *N*-Alkylcarbamoyl-de-hydrogenation

$$\mathbf{ArH + RNCO \xrightarrow{AlCl_3} ArCONHR}$$

N-Substituted amides can be prepared by direct attack of isocyanates on aromatic rings.[320] R may be alkyl or aryl, but if the latter, dimers and trimers are also obtained. Isothiocyanates similarly give thioamides.[321] The reaction has been carried out intramolecularly both with aralkyl isothiocyanates and acyl isothiocyanates.[322] In the latter case, the product is easily hydrolyzable to a dicarboxylic acid; this is a way of putting a carboxyl group on a ring ortho




**33**

to one already there (**33** is prepared by treatment of the acyl halide with lead thiocyanate). The reaction gives better yields with substrates of the type $ArCH_2CONCS$, where six-membered rings are formed. Ethyl carbamate $NH_2COOEt$ (with $P_2O_5$ in xylene)[323] and biscarbamoyl diselenides $R_2NCOSeSeCONR_2$[324] (with $HgBr_2$ or $SnCl_4$) have also been used to amidate aromatic rings.

OS **V,** 1051; **VI,** 465.

[314]There is evidence that, in the complex formed from potassium salts, the bonding is between the aromatic compound and the carbon atom of $CO_2$: Hirao; Kito *Bull. Chem. Soc. Jpn.* **1973,** *46*, 3470.

[315]Actually, the reaction seems to be more complicated than this. At least part of the potassium *p*-hydroxybenzoate that forms comes from a rearrangement of initially formed potassium salicylate. Sodium salicylate does not rearrange. See Shine, Ref. 375, pp. 344-348. See also Ota *Bull. Chem. Soc. Jpn.* **1974,** *47*, 2343.

[316]Yasuhara; Nogi *J. Org. Chem.* **1968,** *33*, 4512, *Chem. Ind.* (*London*) **1967,** 229, **1969,** 77.

[317]Yasuhara; Nogi; Saishō *Bull. Chem. Soc. Jpn.* **1969,** *42*, 2070.

[318]See Sakakibara; Odaira, Ref. 308; Jintoku; Taniguchi; Fujiwara *Chem. Lett.* **1987,** 1159; Ugo; Chiesa *J. Chem. Soc., Perkin Trans. 1* **1987,** 2625.

[319]Sakakura; Chaisupakitsin; Hayashi; Tanaka *J. Organomet. Chem.* **1987,** *334*, 205.

[320]Effenberger; Gleiter *Chem. Ber.* **1964,** *97*, 472; Effenberger; Gleiter; Heider; Niess *Chem. Ber.* **1968,** *101*, 502; Piccolo; Filippini; Tinucci; Valoti; Citterio *Tetrahedron* **1986,** *42*, 885.

[321]Jagodziński *Synthesis* **1988,** 717.

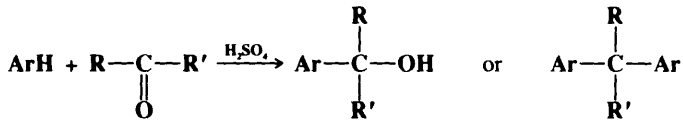
[322]Smith; Kan *J. Am. Chem. Soc.* **1960,** *82*, 4753, *J. Org. Chem.* **1964,** *29*, 2261.

[323]Chakraborty; Mandal; Roy *Synthesis* **1981,** 977.

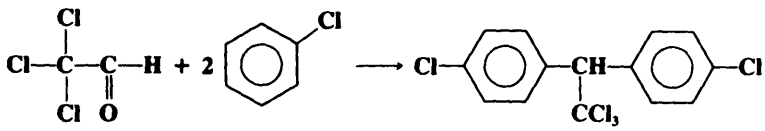
[324]Fujiwara; Ogawa; Kambe; Ryu; Sonoda *Tetrahedron Lett.* **1988,** *29*, 6121.

Reactions **1-22** to **1-26** involve the introduction of a $CH_2Z$ group, where Z is halogen, hydroxyl, amino, or alkylthio. They are all Friedel–Crafts reactions of aldehydes and ketones and, with respect to the carbonyl compound, additions to the C=O double bond. They follow mechanisms discussed in Chapter 16.

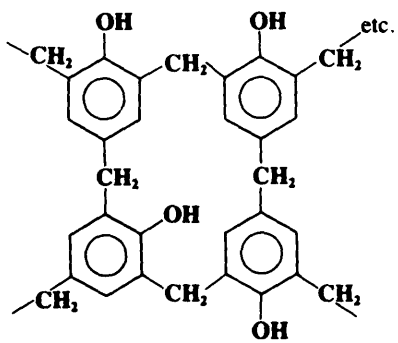
### 1-22 Hydroxyalkylation or Hydroxyalkyl-de-hydrogenation



The condensation of aromatic rings with aldehydes or ketones is called *hydroxyalkylation*.[325] The reaction can be used to prepare alcohols,[326] though more often the alcohol initially produced reacts with another molecule of aromatic compound (**1-12**) to give diarylation. For this the reaction is quite useful, an example being the preparation of DDT:



The diarylation reaction is especially common with phenols (the diaryl product here is called a *bisphenol*). The reaction is normally carried out in alkaline solution on the phenolate ion.[327] The hydroxymethylation of phenols with formaldehyde is called the *Lederer-Manasse reaction*. This reaction must be carefully controlled,[328] since it is possible for the para and both ortho positions to be substituted and for each of these to be rearylated, so that a polymeric structure is produced:



However, such polymers, which are of the Bakelite type (phenol–formaldehyde resins), are of considerable commercial importance.

The attacking species is the carbocation, $R-\overset{\oplus}{C}(OH)-R'$, formed from the aldehyde or ketone and the acid catalyst, except when the reaction is carried out in basic solution

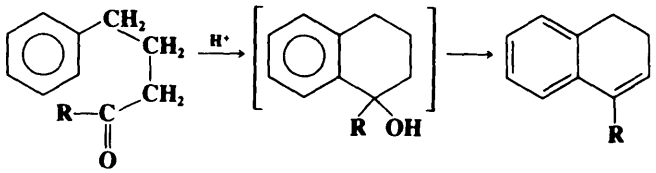
[325]For a review, see Hofmann; Schriesheim, in Olah, Ref. 261, vol. 2, pp. 597-640.
[326]See, for example, Casiraghi; Casnati; Puglia; Sartori *Synthesis* **1980**, 124.
[327]For a review, see Schnell; Krimm *Angew. Chem. Int. Ed. Engl.* **1963**, *2*, 373-379 [*Angew. Chem.* 75, 662-668].
[328]See, for example, Casiraghi; Casnati; Pochini; Puglia; Ungaro; Sartori *Synthesis* **1981**, 143.

When an aromatic ring is treated with diethyl oxomalonate $(EtOOC)_2C{=}O$, the product is an arylmalonic acid derivative $ArC(OH)(COOEt)_2$, which can be converted to an arylmalonic acid $ArCH(COOEt)_2$.[329] This is therefore a way of applying the malonic ester synthesis (**0-94**) to an aryl group (see also **3-14**). Of course, the opposite mechanism applies here: the aryl species is the nucleophile.

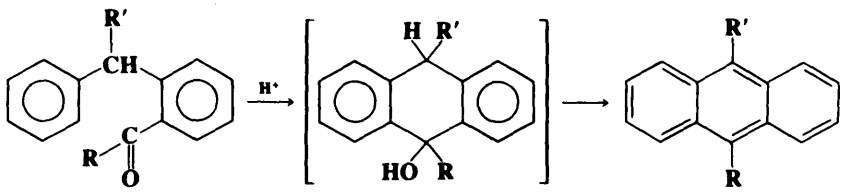
Two methods, both involving boron-containing reagents, have been devised for the regioselective ortho hydroxymethylation of phenols or aromatic amines.[330]

OS **III,** 326; **V,** 422; **VI,** 471, 856; **68,** 234, 238, 243. Also see OS **I,** 214.

## **1-23** Cyclodehydration of Aldehydes and Ketones

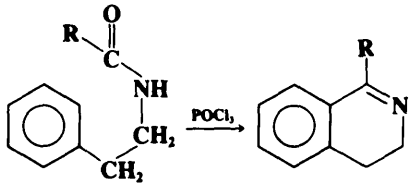



When an aromatic compound contains an aldehyde or ketone function in a position suitable for closing a six-membered ring, treatment with acid results in cyclodehydration. The reaction is a special case of **1-22,** but in this case dehydration almost always takes place to give a double bond conjugated with the aromatic ring.[331] The method is very general and is widely used to close both carbocyclic and heterocyclic rings.[332] Polyphosphoric acid is a common reagent, but other acids have also been used. In a variation known as the *Bradsher reaction*,[333]




diarylmethanes containing a carbonyl group in the ortho position can be cyclized to anthracene derivatives. In this case 1,4-dehydration takes place, at least formally.

Among the many applications of cyclodehydration to the formation of heterocyclic systems is the *Bischler–Napieralski reaction*.[334] In this reaction amides of the type **34** are cyclized with phosphorous oxychloride:




**34**

[329]Ghosh; Pardo; Salomon *J. Org. Chem.* **1982,** *47*, 4692.

[330]Sugasawa; Toyoda; Adachi; Sasakura *J. Am. Chem. Soc.* **1978,** *100*, 4842; Nagata; Okada; Aoki *Synthesis* **1979,** 365.

[331]For examples where the hydroxy compound was the principal product (with R = $CF_3$), see Fung; Abraham; Bellini; Sestanj *Can. J. Chem.* **1983,** *61*, 368; Bonnet-Delpon; Charpentier-Morize; Jacquot *J. Org. Chem.* **1988,** *53*, 759.

[332]For a review, see Bradsher *Chem. Rev.* **1987,** *87*, 1277-1297.

[333]For examples, see Bradsher *J. Am. Chem. Soc.* **1940,** *62*, 486; Saraf; Vingiello *Synthesis* **1970,** 655; Ref. 332, pp. 1287-1294.

[334]For a review of the mechanism, see Fodor; Nagubandi *Tetrahedron* **1980,** *36*, 1279-1300.

If the starting compound contains a hydroxyl group in the α position, an additional dehydration takes place and the product is an isoquinoline. Higher yields can be obtained if the amide is treated with $PCl_5$ to give an imino chloride $ArCH_2CH_2N{=}CR{-}Cl$, which is isolated and then cyclized by heating.[335] The nitrilium ion $ArCH_2CH_2\overset{\oplus}{N}{\equiv}CR$ is an intermediate.

OS **I,** 360, 478; **II,** 62, 194; **III,** 281, 300, 329, 568, 580, 581; **IV,** 590; **V,** 550; **VI,** 1. Also see OS **I,** 54.

### 1-24 Haloalkylation or Haloalkyl-de-hydrogenation

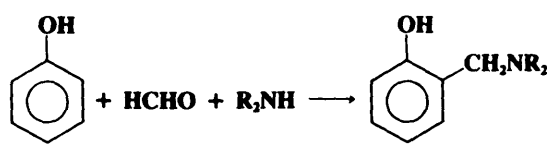
$$ArH + HCHO + HCl \xrightarrow{ZnCl_2} ArCH_2Cl$$

When certain aromatic compounds are treated with formaldehyde and HCl, the $CH_2Cl$ group is introduced into the ring in a reaction called *chloromethylation*. The reaction has also been carried out with other aldehydes and with HBr and HI. The more general term *haloalkylation* covers these cases.[336] The reaction is successful for benzene, and alkyl-, alkoxy-, and halobenzenes. It is greatly hindered by meta-directing groups, which reduce yields or completely prevent the reactions. Amines and phenols are too reactive and usually give polymers unless deactivating groups are also present, but phenolic ethers and esters successfully undergo the reaction. Compounds of lesser reactivity can often be chloromethylated with chloromethyl methyl ether $ClCH_2OMe$, bis(chloromethyl) ether $(ClCH_2)_2O$,[337] methoxyacetyl chloride $MeOCH_2COCl$,[338] or 1-chloro-4-(chloromethoxy)butane.[339] Zinc chloride is the most common catalyst, but other Friedel–Crafts catalysts are also employed. As with reaction **1-22** and for the same reason, an important side product is the diaryl compound $Ar_2CH_2$ (from formaldehyde).

Apparently, the initial step involves reaction of the aromatic compound with the aldehyde to form the hydroxyalkyl compound, exactly as in **1-22,** and then the HCl converts this to the chloroalkyl compound.[340] The acceleration of the reaction by $ZnCl_2$ has been attributed[341] to the raising of the acidity of the medium, causing an increase in the concentration of $HOCH_2^+$ ions.

OS **III,** 195, 197, 468, 557; **IV,** 980.

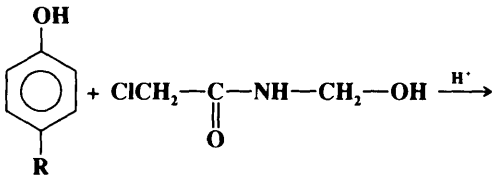
### 1-25 Aminoalkylation and Amidoalkylation
### Dialkylaminoalkylation or Dialkylamino-de-hydrogenation

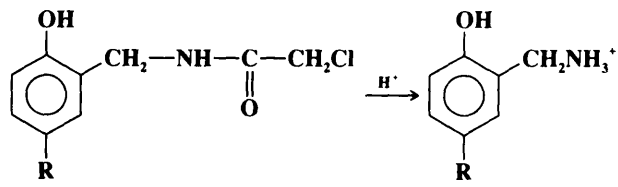



Phenols, secondary and tertiary aromatic amines,[342] pyrroles, and indoles can be aminomethylated by treatment with formaldehyde and a secondary amine. Other aldehydes have

[335]Fodor; Gal; Phillips *Angew. Chem. Int. Ed. Engl.* **1972,** *11*, 919 [*Angew. Chem. 84*, 947].
[336]For reviews, see Belen'kii; Vol'kenshtein; Karmanova *Russ. Chem. Rev.* **1977,** *46*, 891-903; Olah; Tolgyesi, in Olah, Ref. 261, vol. 2, pp. 659-784.
[337]Suzuki *Bull. Chem. Soc. Jpn.* **1970,** *43*, 3299; Kuimova; Mikhailov *J. Org. Chem. USSR* **1971,** 7, 1485.
[338]McKillop; Madjdabadi; Long *Tetrahedron Lett.* **1983,** *24*, 1933.
[339]Olah; Beal; Olah *J. Org. Chem.* **1976,** *41*, 1627.
[340]Ziegler; Hontschik; Milowiz *Monatsh. Chem.* **1948,** 79, 142; Ogata; Okano *J. Am. Chem. Soc.* **1956,** *78*, 5423. See also Olah; Yu *J. Am. Chem. Soc.* **1975,** *97*, 2293.
[341]Lyushin; Mekhtiev; Guseinova *J. Org. Chem. USSR* **1970,** *6*, 1445.
[342]Miocque; Vierfond *Bull. Soc. Chim. Fr.* **1970,** 1896, 1901, 1907.

sometimes been employed. Aminoalkylation is a special case of the Mannich reaction (**6-16**). When phenols and other activated aromatic compounds are treated with N-hydroxymethylchloroacetamide, *amidomethylation* takes place[343] to give **35,** which is often hydro-



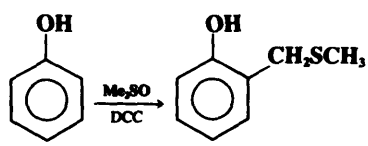


**35**

lyzed in situ to the aminoalkylated product. Other N-hydroxyalkyl and N-chlorinated compounds have also been used.[343]

OS **I,** 381; **IV,** 626; **V,** 434; **VI,** 965; **VII,** 162.

## **1-26** Thioalkylation
## **Alkylthioalkylation** or **Alkylthioalkyl-de-hydrogenation**



A methylthiomethyl group can be inserted into the ortho position of phenols by heating with dimethyl sulfoxide and dicyclohexylcarbodiimide (DCC).[344] Other reagents can be used instead of DCC, among them pyridine–$SO_3$,[345] $SOCl_2$,[346] and acetic anhydride.[347] Alternatively, the phenol can be treated with dimethyl sulfide and N-chlorosuccinimide, followed by triethylamine.[348] The reaction can be applied to amines (to give *o*-$NH_2C_6H_4CH_2SMe$) by treatment with *t*-BuOCl, $Me_2S$, and NaOMe in $CH_2Cl_2$.[349] It is possible to convert the $CH_2SMe$ group to the CHO group,[350] so that this becomes an indirect method for the preparation of ortho-amino and ortho-hydroxy aromatic aldehydes; or to the $CH_3$ group (with Raney nickel—reaction **4-36**), which makes this an indirect method[351] for the intro-

[343]For a review, see Zaugg *Synthesis* **1984,** 85-110.

[344]Burdon; Moffatt *J. Am. Chem. Soc.* **1966,** *88,* 5855, **1967,** *89,* 4725; Olofson; Marino *Tetrahedron* **1971,** *27,* 4195.

[345]Claus *Monatsh. Chem.* **1971,** *102,* 913.

[346]Sato; Inoue; Ozawa; Tazaki *J. Chem. Soc., Perkin Trans. 1* **1984,** 2715.

[347]Hayashi; Oda *J. Org. Chem.* **1967,** *32,* 457; Pettit; Brown *Can. J. Chem.* **1967,** *45,* 1306; Claus *Monatsh. Chem.* **1968,** *99,* 1034.

[348]Gassman; Amick *J. Am. Chem. Soc.* **1978,** *100,* 7611.

[349]Gassman; Gruetzmacher *J. Am. Chem. Soc.* **1973,** *95,* 588; Gassman; van Bergen *J. Am. Chem. Soc.* **1973,** *95,* 590, 591.

[350]Gassman; Drewes *J. Am. Chem. Soc.* **1978,** *100,* 7600; Ref. 348.

[351]For another indirect method, in this case for alkylation ortho to an amino group, see Gassman; Parton *Tetrahedron Lett.* **1977,** 2055.

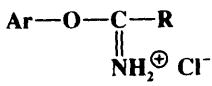
duction of a $CH_3$ group ortho to an OH or $NH_2$ group.[349] Aromatic hydrocarbons have been thioalkylated with ethyl α-(chloromethylthio)acetate $ClCH_2SCH_2COOEt$ (to give $ArCH_2SCH_2COOEt$)[352] and with methyl methylsulfinylmethyl sulfide $MeSCH_2SOMe$ or methylthiomethyl *p*-tolyl sulfone $MeSCH_2SO_2C_6H_4Me$ (to give $ArCH_2SMe$),[353] in each case with a Lewis acid catalyst.

OS **VI,** 581, 601.

## 1-27 Acylation with Nitriles. The Hoesch Reaction
**Acylation** or **Acyl-de-hydrogenation**

$$ArH + RCN \xrightarrow[ZnCl_2]{HCl} ArCOR$$

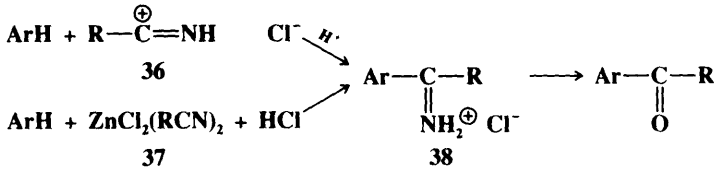
Friedel–Crafts acylation with nitriles and HCl is called the *Hoesch* or the *Houben–Hoesch reaction*.[354] In most cases, a Lewis acid is necessary; zinc chloride is the most common. The reaction is generally useful only with phenols, phenolic ethers, and some reactive heterocyclic compounds, e.g., pyrrole, but it can be extended to aromatic amines by the use of $BCl_3$.[355] Acylation in the case of amines is regioselectively ortho. Monohydric phenols, however, generally do not give ketones[356] but are attacked at the oxygen to produce imino esters.



An imino ester

Many nitriles have been used. Even aryl nitriles give good yields if they are first treated with HCl and $ZnCl_2$ and then the substrate added at 0°C.[357] In fact, this procedure increases yields with any nitrile. If thiocyanates RSCN are used, thiol esters ArCOSR can be obtained. The Gatterman reaction (**1-16**) is a special case of the Hoesch synthesis.

The reaction mechanism is complex and not completely settled.[358] The first stage consists of an attack on the substrate by a species containing the nitrile and HCl (and the Lewis acid, if present) to give an imine salt (**38**). Among the possible attacking species are **36** and **37.** In the second stage, the salts are hydrolyzed to the products:



Ketones can also be obtained by treating phenols or phenolic ethers with a nitrile in the presence of $F_3CSO_2OH$.[359] The mechanism in this case is different.

OS **II,** 522.

[352]Tamura; Tsugoshi; Annoura; Ishibashi *Synthesis* **1984,** 326.
[353]Torisawa; Satoh; Ikegami *Tetrahedron Lett.* **1988,** *29,* 1729.
[354]For a review, see Ruske, in Olah, Ref. 261, vol. 3, 1964, pp. 383-497.
[355]Sugasawa et al., Ref. 330; Sugasawa; Adachi; Sasakura; Kitagawa *J. Org. Chem.* **1979,** *44,* 578.
[356]For an exception, see Toyoda; Sasakura; Sugasawa *J. Org. Chem.* **1981,** *46,* 189.
[357]Zil'berman; Rybakova *J. Gen. Chem. USSR* **1960,** *30,* 1972.
[358]For discussions, see Ref. 354 and Jeffery; Satchell *J. Chem. Soc. B.* **1966,** 579.
[359]Booth; Noori *J. Chem. Soc., Perkin Trans. I* **1980,** 2894; Amer; Booth; Noori; Proença *J. Chem. Soc., Perkin Trans. I* **1983,** 1075.

### 1-28 Cyanation or Cyano-de-hydrogenation

$$ArH + Cl_3CCN \xrightarrow{HCl} Ar{-}\underset{\underset{NH_2^{\oplus}\ Cl^-}{\|}}{C}{-}CCl_3 \xrightarrow{NaOH} ArCN$$

Aromatic hydrocarbons (including benzene), phenols, and phenolic ethers can be cyanated with trichloroacetonitrile, BrCN, or mercury fulminate $Hg(ONC)_2$.[360] In the case of $Cl_3CCN$, the actual attacking entity is probably $Cl_3C{-}\overset{\oplus}{C}{=}NH$, formed by addition of a proton to the cyano nitrogen. Secondary aromatic amines ArNHR, as well as phenols, can be cyanated in the ortho position with $Cl_3CCN$ and $BCl_3$.[361]

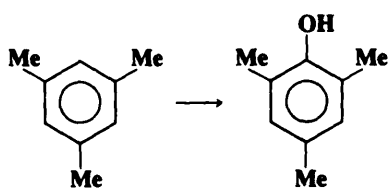
OS **III,** 293.

**F. Oxygen Electrophiles** Oxygen electrophiles are very uncommon, since oxygen does not bear a positive charge very well. However, there is one reaction that can be mentioned.

### 1-29 Hydroxylation or Hydroxy-de-hydrogenation

$$ArH + F_3C{-}\underset{\underset{O}{\|}}{C}{-}O{-}OH \xrightarrow{BF_3} ArOH$$

There have been only a few reports of direct hydroxylation[362] by an electrophilic process (see, however, **2-26** and **4-5**).[363] In general, poor results are obtained, partly because the introduction of an OH group activates the ring to further attack. Quinone formation is common. However, alkyl-substituted benzenes such as mesitylene or durene can be hydroxylated in good yield with trifluoroperacetic acid and boron trifluoride.[364] In the case of mesitylene, the product is not subject to further attack:




In a related procedure, even benzene and substituted benzenes (e.g., PhMe; PhCl; xylenes) can be converted to phenols in good yields with sodium perborate–$F_3CSO_2OH$.[365] Low to moderate yields of phenols can be obtained by treatment of simple alkylbenzenes with $H_2O_2$

[360]Olah, in Olah, Ref. 225, vol. 1, 1963, pp. 119-120.
[361]Adachi; Sugasawa *Synth. Commun.* **1990,** *20,* 71.
[362]For a list of hydroxylation reagents, with references, see Larock, Ref. 171, pp. 485-486.
[363]For reviews of electrophilic hydroxylation, see Jacquesy; Gesson; Jouannetaud *Rev. Chem. Intermed.* **1988,** *9,* 1-26, pp. 5-10; Haines *Methods for the Oxidation of Organic Compounds*; Academic Press: New York, 1985, pp. 173-176, 347-350.
[364]Hart; Buehler *J. Org. Chem.* **1964,** *29,* 2397. See also Hart *Acc. Chem. Res.* **1971,** *4,* 337-343.
[365]Prakash; Krass; Wang; Olah *Synlett* **1991,** 39.

in $HF–BF_3$[366] or $H_2O_2$ catalyzed by $AlCl_3$[367] or liquid HF, in some cases under $CO_2$ pressure.[368] With the last procedure even benzene could be converted to phenol in 37% yield (though 37% hydroquinone and 16% catechol were also obtained). Aromatic amines, N-acyl amines, and phenols were hydroxylated with $H_2O_2$ in $SbF_5–HF$.[369] Pyridine and quinoline were converted to their 2-acetoxy derivatives in high yields with acetyl hypofluorite AcOF at $-75°C$.[370]

Another hydroxylation reaction is the *Elbs reaction*.[371] In this method phenols can be oxidized to *p*-diphenols with $K_2S_2O_8$ in alkaline solution.[372] Primary, secondary, or tertiary aromatic amines give predominant or exclusive ortho substitution unless both ortho positions are blocked, in which case para substitution is found. The reaction with amines is called the *Boyland–Sims oxidation*. Yields are low with either phenols or amines, generally under 50%. The mechanisms are not clear,[373] but for the Boyland–Sims oxidation there is evidence that the $S_2O_8^{2-}$ ion attacks at the ipso position, and then a migration follows.[374]

**G. Metal Electrophiles** Reactions in which a metal replaces the hydrogen of an aromatic ring are considered along with their aliphatic counterparts in Chapter 12 (**2-21** and **2-22**).

## Hydrogen as the Leaving Group in Rearrangement Reactions

In these reactions a group is detached from a *side chain* and then attacks the ring, but in other aspects they resemble the reactions already treated in this chapter.[375] Since a group moves from one position to another in a molecule, these are rearrangements. In all these reactions the question arises as to whether the group that cleaves from a given molecule attacks the same molecule or another one, i.e., is the reaction intramolecular or intermolecular? For intermolecular reactions the mechanism is the same as ordinary aromatic substitution, but for intramolecular cases the migrating group could never be completely free, or else it would be able to attack another molecule. Since the migrating species in intramolecular rearrangements is thus likely to remain near the atom from which it cleaved, it has been suggested that intramolecular reactions are more likely to lead to ortho products than are the intermolecular type. This characteristic has been used, among others, to help decide whether a given rearrangement is inter- or intramolecular, though there is evidence that at least in some cases, an intermolecular mechanism can still result in a high degree of ortho migration.[376]

[366]Olah; Fung; Keumi *J. Org. Chem.* **1981,** *46*, 4305. See also Gesson; Jacquesy; Jouannetaud *Nouv. J. Chem.* **1982,** *6*, 477.

[367]Kurz; Johnson *J. Org. Chem.* **1971,** *36*, 3184.

[368]Vesely; Schmerling *J. Org. Chem.* **1970,** *35*, 4028. For other hydroxylations, see Chambers; Goggin; Musgrave *J. Chem. Soc.* **1959,** 1804; Hamilton; Friedman *J. Am. Chem. Soc.* **1963,** *85*, 1008; Kovacic; Kurz *J. Am. Chem. Soc.* **1965,** *87*, 4811, *J. Org. Chem.* **1966,** *31*, 2011, 2549; Walling; Camaioni *J. Am. Chem. Soc.* **1975,** *97*, 1603; So; Miller *Synthesis* **1976,** 468; Ogata; Sawaki; Tomizawa; Ohno *Tetrahedron* **1981,** *37*, 1485; Galliani; Rindone *Tetrahedron* **1981,** *37*, 2313.

[369]Jacquesy; Joannetaud; Morellet; Vidal *Tetrahedron Lett.* **1984,** *25*, 1479; Berrier; Carreyre; Jacquesy; Joannetaud *New J. Chem.* **1990,** *14*, 283, and references cited in these papers.

[370]Rozen; Hebel; Zamir *J. Am. Chem. Soc.* **1987,** *109*, 3789.

[371]For a review of the Elbs and Boyland–Sims reactions, see Behrman *Org. React.* **1988,** *35*, 421-511.

[372]For a method for the ortho hydroxylation of phenols, see Capdevielle; Maumy *Tetrahedron Lett.* **1982,** *23*, 1573, 1577.

[373]Behrman *J. Am. Chem. Soc.* **1967,** *89*, 2424; Ogata; Akada *Tetrahedron* **1970,** *26*, 5945; Walling; Camaioni; Kim *J. Am. Chem. Soc.* **1978,** *100*, 4814.

[374]Srinivasan; Perumal; Arumugam *J. Chem. Soc., Perkin Trans. 2* **1985,** 1855.

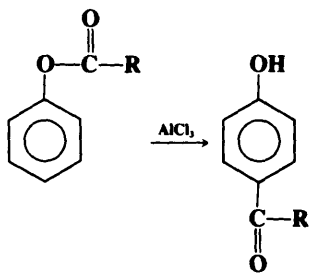
[375]For a monograph, see Shine *Aromatic Rearrangements*; Elsevier: New York, 1967. For reviews, see Williams; Buncel *Isot. Org. Chem.* **1980,** *5*, 147-230; Williams, in Bamford; Tipper, Ref. 1, pp. 433-486.

[376]See Dawson; Hart; Littler *J. Chem. Soc., Perkin Trans. 2* **1985,** 1601.

The Claisen (**8-35**) and benzidine (**8-38**) rearrangements, which superficially resemble those in this section, have different mechanisms and are treated in Chapter 18.

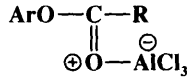
## A. Groups Cleaving From Oxygen

### 1-30 The Fries Rearrangement
### 1/*C*-Hydro,5/*O*-acyl-interchange[377]




Phenolic esters can be rearranged by heating with Friedel–Crafts catalysts in a synthetically useful reaction known as the *Fries rearrangement*.[378] Both *o*- and *p*-acylphenols can be produced, and it is often possible to select conditions so that either one predominates. the ortho/para ratio is dependent on the temperature, solvent, and amount of catalyst used. Though exceptions are known, low temperatures generally favor the para product and high temperatures the ortho product. R may be aliphatic or aromatic. Any meta-directing substituent on the ring interferes with the reactions, as might be expected for a Friedel–Crafts process. In the case of aryl benzoates treated with $F_3CSO_2OH$, the Fries rearrangement was shown to be reversible and an equilibrium was established.[379]

The exact mechanism has still not been completely worked out. Opinions have been expressed that it is completely intermolecular,[380] completely intramolecular,[381] and partially inter- and intramolecular.[382] One way to decide between inter- and intramolecular processes is to run the reaction of the phenolic ester in the presence of another aromatic compound, say, toluene. If some of the toluene is acylated, the reaction must be, at least in part, intermolecular. If the toluene is not acylated, the presumption is that the reaction is intramolecular, though this is not certain, for it may be that the toluene is not attacked because it is less active than the other. A number of such experiments (called *crossover experiments*) have been carried out; sometimes crossover products have been found and sometimes not. As in **1-14**, an initial complex (**39**) is formed between the substrate and the catalyst, so that a catalyst/substrate molar ratio of at least 1:1 is required.




**39**

[377]This is the name for the para migration. For the ortho migration, the name is 1/*C*-hydro,3/*O*-acyl-interchange.

[378]For reviews, see Shine, Ref. 375, pp. 72-82, 365-368; Gerecs, in Olah, Ref. 261, vol. 3, 1964, pp. 499-533. For a list of references, see Larock, Ref. 171, pp. 642.

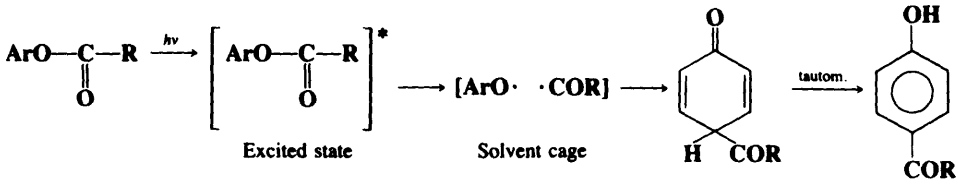
[379]Effenberger; Gutmann *Chem. Ber.* **1982,** *115*, 1089.

[380]Krausz; Martin *Bull. Soc. Chim. Fr.* **1965,** 2192; Martin *Bull. Soc. Chim. Fr.* **1974,** 983, **1979,** II-373; Martin; Gavard; Delfly; Demerseman; Tromelin *Bull. Soc. Chim. Fr.* **1986,** 659.

[381]Ogata; Tabuchi *Tetrahedron* **1964,** *20*, 1661.

[382]Munavilli *Chem. Ind.* (*London*) **1972,** 293; Warshawsky; Kalir; Patchornik *J. Am. Chem. Soc.* **1978,** *100*, 4544; Ref. 376.

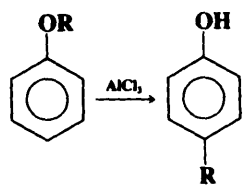
The Fries rearrangement can also be carried out with uv light, in the absence of a catalyst.[383] This reaction, called the *photo-Fries rearrangement*,[384] is predominantly an intramolecular free-radical process. Both ortho and para migration are observed.[385] Unlike the Lewis-acid-catalyzed Fries rearrangement, the photo-Fries reaction can be accomplished, though often in low yields, when meta-directing groups are on the ring. The available evidence strongly suggests the following mechanism[386] for the photo-Fries rearrangement[387] (illustrated for para attack):




The phenol ArOH is always a side product, resulting from some ArO• that leaks from the solvent cage and abstracts a hydrogen atom from a neighboring molecule. When the reaction was performed on phenyl acetate in the gas phase, where there are no solvent molecules to form a cage (but in the presence of isobutane as a source of abstractable hydrogens), phenol was the chief product and virtually no *o*- or *p*-hydroxyacetophenone was found.[388] Other evidence[389] for the mechanism is that CIDNP has been observed during the course of the reaction[390] and that the ArO• radical has been detected by flash photolysis[391] and by nanosecond time-resolved Raman spectroscopy.[392]

OS **II,** 543; **III,** 280, 282.

## 1-31 Rearrangement of Phenolic Ethers 1/*C*-Hydro,5/*O*-alkyl-interchange




This reaction bears the same relationship to **1-30** that **1-12** bears to **1-14.**[393] However, yields are generally low and this reaction is much less useful synthetically. Isomerization of the R

[383]Kobsa *J. Org. Chem.* **1962,** *27,* 2293; Anderson; Reese *J. Chem. Soc.* **1963,** 1781; Finnegan; Matice *Tetrahedron* **1965,** *21,* 1015.

[384]For reviews, see Belluš *Adv. Photochem.* **1971,** *8* 109-159; Belluš; Hrdlovič *Chem. Rev.* **1967,** *67,* 599-609; Stenberg *Org. Photochem.* **1967,** *1,* 127-153.

[385]The migration can be made almost entirely ortho by cyclodextrin encapsulation (see p. 91): Syamala; Rao; Ramamurthy *Tetrahedron* **1988,** *44,* 7234. See also Veglia; Sanchez; de Rossi *J. Org. Chem.* **1990,** *55,* 4083.

[386]Proposed by Kobsa, Ref. 383.

[387]It has been suggested that a second mechanism, involving a four-center transition state, is also possible: Belluš; Schaffner; Hoigné *Helv. Chim. Acta* **1968,** *51,* 1980; Sander; Hedaya; Trecker *J. Am. Chem. Soc.* **1968,** *90,* 7249; Belluš Ref. 384.

[388]Meyer; Hammond *J. Am. Chem. Soc.* **1970,** *92,* 2187, **1972,** *94,* 2219.

[389]For evidence from isotope effect studies, see Shine; Subotkowski *J. Org. Chem.* **1987,** *52,* 3815.

[390]Adam; Arce de Sanabia; Fischer *J. Org. Chem.* **1973,** *38,* 2571; Adam *J. Chem. Soc., Chem. Commun.* **1974,** 289.

[391]Kalmus; Hercules *J. Am. Chem. Soc.* **1974,** *96,* 449.

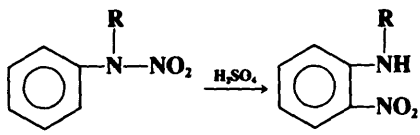
[392]Beck; Brus *J. Am. Chem. Soc.* **1982,** *104,* 1805.

[393]For reviews, see Dalrymple; Kruger; White, in Patai *The Chemistry of the Ether Linkage*, Ref. 34, pp. 628-635; Shine, Ref. 375, pp. 82-89, 368-370.

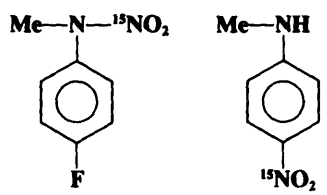
group is usually found when that is possible. Evidence has been found for both inter- and intramolecular processes.[394] The fact that dialkylphenols can often be isolated shows that at least some intermolecular processes occur. Evidence for intramolecular reaction is that conversion of optically active *p*-tolyl *sec*-butyl ether to 2-*sec*-butyl-4-methylphenol proceeded with some retention of configuration.[395] The mechanism is probably similar to that of **1-14.**

**B. Groups Cleaving from Nitrogen**[396] It has been shown that $PhN\overset{\oplus}{H}_2D$ rearranges to *o*- and *p*-deuterioaniline.[397] The migration of OH, formally similar to reactions **1-32** to **1-36,** is a nucleophilic substitution and is treated in Chapter 13 (**3-27**).

## 1-32 Migration of the Nitro Group
## 1/*C*-Hydro,3/*N*-nitro-interchange




N-Nitro aromatic amines rearrange on treatment with acids to *o*- and *p*-nitroamines with the ortho compounds predominating.[398] Aside from this indication of an intramolecular process, there is also the fact that virtually no meta isomer is produced in this reaction,[399] though direct nitration of an aromatic amine generally gives a fair amount of meta product. Thus a mechanism in which $NO_2^+$ is dissociated from the ring and then attacks another molecule must be ruled out. Further results indicating an intramolecular process are that rearrangement of several substrates in the presence of $K^{15}NO_3$ gave products containing no $^{15}N$[400] and that rearrangement of a mixture of $PhNH^{15}NO_2$ and unlabeled *p*-$MeC_6H_4NHNO_2$ gave 2-nitro-4-methylaniline containing no $^{15}N$.[401] On the other hand, rearrangement of **40**




**40** **41**

in the presence of unlabeled $PhNMeNO_2$ gave labeled **41,** which did not arise by displacement of F.[402] R may be hydrogen or alkyl. Two principal mechanisms have been suggested, one

[394]For mechanistic discussions, see Tarbell; Petropoulos *J. Am. Chem. Soc.* **1952,** *74*, 244; Hart; Waddington *J. Chem. Soc., Perkin Trans. 2* **1985,** 1607.

[395]Sprung; Wallis *J. Am. Chem. Soc.* **1934,** *56*, 1715. See also Hart; Elia *J. Am. Chem. Soc.* **1954,** *76*, 3031.

[396]For a review, see Stevens; Watts *Selected Molecular Rearrangements*; Van Nostrand-Reinhold: Princeton, 1973, pp. 192-199.

[397]Okazaki; Okumura *Bull. Chem. Soc. Jpn.* **1961,** *34*, 989.

[398]For reviews, see Williams, in Patai *The Chemistry of Functional Groups, Supplement F*, pt. 1; Wiley: New York, 1982, pp. 127-153; White, *Mech. Mol. Migr.* **1971,** *3*, 109-143; Shine, Ref. 375, pp. 235-249.

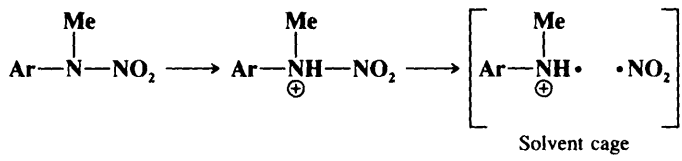
[399]Hughes; Jones *J. Chem. Soc.* **1950,** 2678.

[400]Brownstein; Bunton; Hughes *J. Chem. Soc.* **1958,** 4354; Banthorpe; Thomas; Williams *J. Chem. Soc.* **1965,** 6135.

[401]Geller; Dubrova *J. Gen. Chem. USSR* **1960,** *30*, 2627.

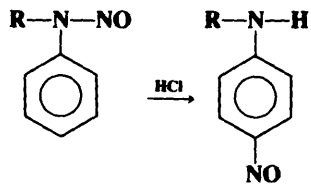
[402]White; Golden *J. Org. Chem.* **1970,** *35*, 2759.

involving cyclic attack by the oxygen of the nitro group at the ortho position before the group cleaves,[403] and the other involving a cleavage into a radical and a radical ion held together in a solvent cage.[404] Among the evidence for the latter view[405] are the effects of




substituents on the rate of the reaction,[406] $^{15}N$ and $^{14}C$ kinetic isotope effects that show nonconcertedness,[407] and the fact that both N-methylaniline and nitrous acid are produced in sizable and comparable amounts in addition to the normal products *o*- and *p*-nitro-N-methylaniline.[408] These side products are formed when the radicals escape from the solvent cage.

## 1-33 Migration of the Nitroso Group. The Fischer–Hepp Rearrangement 1/*C*-Hydro-5/*N*-nitroso-interchange




The migration of a nitroso group, formally similar to **1-32,** is important because *p*-nitroso secondary aromatic amines cannot generally be prepared by direct C-nitrosation of secondary aromatic amines (see **2-51**). The reaction, known as the *Fischer–Hepp rearrangement*,[409] is brought about by treatment of N-nitroso secondary aromatic amines with HCl. Other acids give poor or no results. In benzene systems the para product is usually formed exclusively.[410] The mechanism of the rearrangement is not completely understood. The fact that the reaction takes place in a large excess of urea[411] shows that it is intramolecular[412] since, if $NO^+$, NOCl,

[403]Banthorpe; Hughes; Williams *J. Chem. Soc.* **1964,** 5349; Banthorpe; Thomas *J. Chem. Soc.* **1965,** 7149, 7158. Also see Ref. 400.

[404]White; Lazdins; White *J. Am. Chem. Soc.* **1964,** *86,* 1517; White; White; Fentiman *J. Org. Chem.* **1976,** *41,* 3166.

[405]For additional evidence, see White; Hathaway; Huston *J. Org. Chem.* **1970,** *35,* 737; White; Golden; Lazdins *J. Org. Chem.* **1970,** *35,* 2048; White; Klink *J. Org. Chem.* **1977,** *42,* 166; Ridd; Sandall *J. Chem. Soc., Chem. Commun.* **1982,** 261.

[406]White; Klink *J. Org. Chem.* **1970,** *35,* 965.

[407]Shine; Zygmunt; Brownawell; San Filippo *J. Am. Chem. Soc.* **1984,** *106,* 3610.

[408]White; White *J. Org. Chem.* **1970,** *35,* 1803.

[409]For reviews, see Williams, Ref. 123, pp. 113-128; Williams, Ref. 398; Shine, Ref. 375, pp. 231-235.

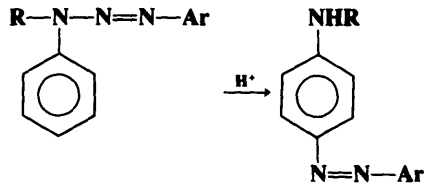
[410]For a report of formation of about 15% ortho product in the case of N,N-diaryl-N-nitroso amides, see Titova; Arinich; Gorelik *J. Org. Chem. USSR* **1986,** *22,* 1407.

[411]Aslapovskaya; Belyaev; Kumarev; Porai-Koshits *Org. React. USSR* **1968,** *5,* 189; Morgan; Williams *J. Chem. Soc., Perkins Trans. 2* **1972,** 74.

[412]See also Belyaev; Nikulicheva *Org. React. USSR* **1971,** *7,* 165; Williams; Wilson *J. Chem. Soc., Perkin Trans. 2* **1974,** 13; Williams *Tetrahedron* **1975,** *31,* 1343, *J. Chem. Soc., Perkin Trans 2* **1975,** 655, **1982,** 801.

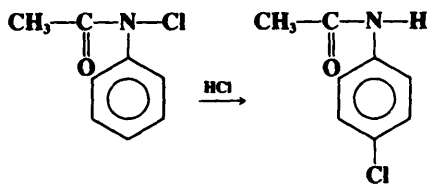
or some similar species were free in the solution, it would be captured by the urea, preventing the rearrangement.

## 1-34 Migration of an Arylazo Group
### 1/C-Hydro-5/N-arylazo-interchange




Rearrangement of aryl triazenes can be used to prepare azo derivatives of primary and secondary aromatic amines.[413] These are first diazotized at the amino group (see **1-4**) to give triazenes, which are then rearranged by treatment with acid. The rearrangement always gives the para isomer, unless that position is occupied.

## 1-35 Migration of Halogen. The Orton Rearrangement
### 1/C-Hydro-5/N-halo-interchange




Migration of a halogen from a nitrogen side chain to the ring by treatment with HCl is called the *Orton rearrangement.*[414] The main product is the para isomer, though some ortho product may also be formed. The reaction has been carried out with N-chloro- and N-bromoamines and less often with N-iodo compounds. The amine must be acylated, except that $PhNCl_2$ gives 2,4-dichloroaniline. The reaction is usually performed in water or acetic acid. There is much evidence (cross-halogention, labeling, etc.) that this is an intermolecular process.[415] First the HCl reacts with the starting material to give $ArNHCOCH_3$ and $Cl_2$; then the chlorine halogenates the ring as in **1-11.** Among the evidence is that chlorine has been isolated from the reaction mixture. The Orton rearrangement can also be brought about photochemically[416] and by heating in the presence of benzoyl peroxide.[417] These are free-radical processes.

[413]For a review, see Shine, Ref. 375, pp. 212-221.

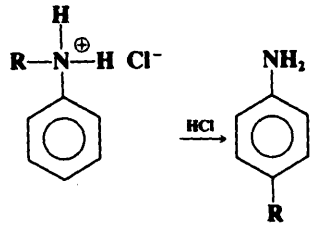
[414]For reviews, see Shine, Ref. 375, pp. 221-230, 362-364: Bieron; Dinan, in Zabicky *The Chemistry of Amides*; Wiley: New York, 1970, pp. 263-269.

[415]The reaction has been found to be intramolecular in aprotic solvents: Golding; Reddy; Scott; White; Winter *Can. J. Chem.* **1981,** *59,* 839.

[416]For example, see Hodges *J. Chem. Soc.* **1933,** 240.

[417]For example, Ayad; Beard; Garwood; Hickinbottom *J. Chem. Soc.* **1957,** 2981; Coulson; Williams; Johnston *J. Chem. Soc. B* **1967,** 174.

## 1-36 Migration of an Alkyl Group[418]
### 1/*C*-Hydro-5/*N*-alkyl-interchange




When HCl salts of arylalkylamines are heated at about 200 to 300°C, migration occurs. This is called the *Hofmann–Martius reaction*. It is an intermolecular reaction, since crossing is found. For example, methylanilinium bromide gave not only the normal products *o*- and *p*-toluidine but also aniline and di- and trimethylanilines.[419] As would be expected for an intermolecular process, there is isomerization when R is primary.

With primary R, the reaction probably goes through the alkyl halide formed initially in an SN2 reaction:

$$\overset{\oplus}{\text{R}}\text{NH}_2\text{Ar} + \text{Cl}^- \longrightarrow \text{RCl} + \text{ArNH}_2$$

Evidence for this view is that alkyl halides have been isolated from the reaction mixture and that $Br^-$, $Cl^-$, and $I^-$ gave different ortho/para ratios, which indicates that the halogen is involved in the reaction.[419] Further evidence is that the alkyl halides isolated are unrearranged (as would be expected if they are formed by an SN2 mechanism), even though the alkyl groups in the ring are rearranged. Once the alkyl halide is formed, it reacts with the substrate by a normal Friedel–Crafts alkylation process (**1-12**), accounting for the rearrangement. When R is secondary or tertiary, carbocations may be directly formed so that the reaction does not go through the alkyl halides.[420]

It is also possible to carry out the reaction by heating the amine (not the salt) at a temperature between 200 and 350°C with a metal halide such as $CoCl_2$, $CdCl_2$, or $ZnCl_2$. When this is done, the reaction is called the *Reilly–Hickinbottom rearrangement*. Primary R groups larger than ethyl give both rearranged and unrearranged products.[421] The reaction is not generally useful for secondary and tertiary R groups, which are usually cleaved to olefins under these conditions.

When acylated arylamines are photolyzed, migration of an acyl group takes place[422] in a process that resembles the photo-Fries reaction (**1-30**).

[418]For reviews, see Grillot *Mech. Mol. Migr.* **1971,** *3* 237-270; Shine, Ref. 375, pp. 249-257.
[419]Ogata; Tabuchi; Yoshida *Tetrahedron* **1964,** *20*, 2717.
[420]Hart; Kosak *J. Org. Chem.* **1962,** *27*, 116.
[421]For example, see Birchall; Clark; Goldwhite; Thorpe *J. Chem. Soc., Perkin Trans. 1* **1972,** 2579.
[422]For examples, see Elad; Rao; Stenberg *J. Org. Chem.* **1965,** *30*, 3252; Shizuka; Tanaka *Bull. Chem. Soc. Jpn.* **1968,** *41*, 2343, **1969,** *42*, 909; Fischer *Tetrahedron Lett.* **1968,** 4295; Hageman *Recl. Trav. Chim. Pays-Bas* **1972,** *91*, 1447; Chênevert; Plante *Can. J. Chem.* **1983,** *61*, 1092; Abdel-Malik; de Mayo *Can. J. Chem.* **1984,** *62*, 1275; Nassetta; de Rossi; Cosa *Can. J. Chem.* **1988,** *66*, 2794.

## Other Leaving Groups

Three types of reactions are considered in this section.

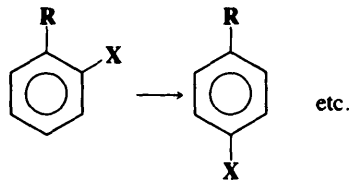
1. Reactions in which hydrogen replaces another leaving group:

$$\mathbf{ArX + H^+ \longrightarrow ArH}$$

2. Reactions in which an electrophile other than hydrogen replaces another leaving group:

$$\mathbf{ArX + Y^+ \longrightarrow ArY}$$

3. Reactions in which a group (other than hydrogen) migrates from one position in a ring to another. Such migrations can be either inter- or intramolecular:



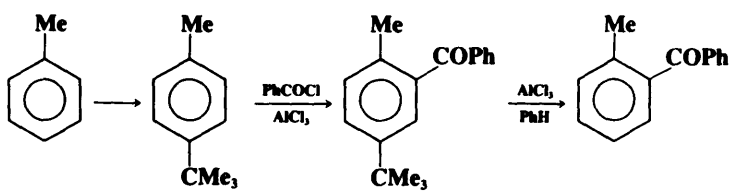

The three types are not treated separately, but reactions are classified by leaving group.

### A. Carbon Leaving Groups

### 1-37 Reversal of Friedel–Crafts Alkylation
**Hydro-de-alkylation** or **Dealkylation**

$$\mathbf{ArR + H^+ \xrightarrow{AlCl_3} ArH}$$

Alkyl groups can be cleaved from aromatic rings by treatment with proton and/or Lewis acids. Tertiary R groups are the most easily cleaved; because this is true, the *t*-butyl group is occasionally introduced into a ring, used to direct another group, and then removed.[423] For example,[424]

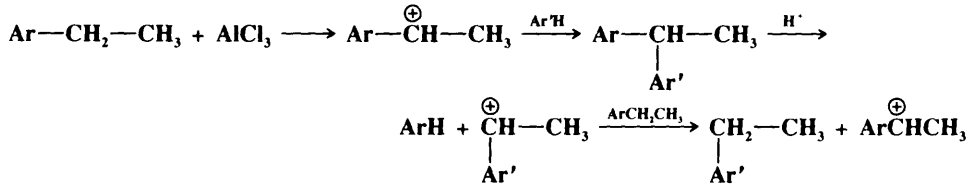



Secondary R groups are harder to cleave, and primary R harder still. Because of this reaction, care must be taken when using Friedel–Crafts catalysts (Lewis or proton acids) on aromatic compounds containing alkyl groups. True cleavage, in which the R becomes an olefin, occurs only at high temperatures—above 400°C.[425] At ordinary temperatures, the R group attacks

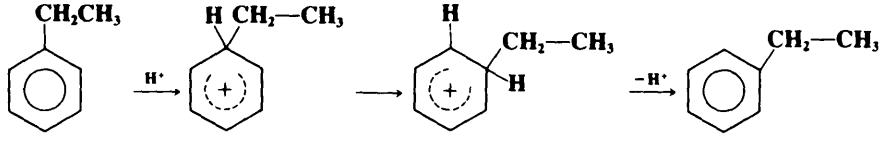
[423]For reviews of such reactions, where the blocking group is *t*-butyl, benzyl, or a halogen, see Tashiro, *Synthesis* **1979**, 921-936; Tashiro; Fukata *Org. Prep. Proced. Int.* **1976**, *8*, 51-74.
[424]Hofman; Reiding; Nauta *Recl. Trav. Chim. Pays-Bas* **1960**, 79, 790.
[425]Olah, in Olah, Ref. 261, vol. 1, 1963, pp. 36-38.

another ring, so that the bulk of the product may be dealkylated, but there is a residue of heavily alkylated material. The isomerization reaction, in which a group migrates from one position in a ring to another or to a different ring, is therefore more important than true cleavage. In these reactions, the meta isomer is generally the most favored product among the dialkylbenzenes; and the 1,3,5 product the most favored among the trialkylbenzenes, because they have the highest thermodynamic stabilities. Alkyl migrations can be inter- or intramolecular, depending on the conditions and on the R group. The following experiments can be cited: Ethylbenzene treated with HF and $BF_3$ gave, almost completely, benzene and diethylbenzenes[426](entirely intermolecular); propylbenzene labeled in the β position gave benzene, propylbenzene, and di- and tripropylbenzenes, but the propylbenzene recovered was partly labeled in the α position and not at all in the γ position[427] (both intra- and intermolecular); *o*-xylene treated with HBr and $AlBr_3$ gave a mixture of *o*- and *m*- but no *p*-xylene, while *p*-xylene gave *p*- and *m*- but no *o*-xylene, and no trimethyl compounds could be isolated in these experiments[428] (exclusively intramolecular rearrangement). Apparently, methyl groups migrate only intramolecularly, while other groups may follow either path.[429]

The mechanism[430] of intermolecular rearrangement can involve free alkyl cations, but there is much evidence to show that this is not necessarily the case. For example, many of them occur without rearrangement within the alkyl group. The following mechanism has been proposed for intermolecular rearrangement without the involvement of carbocations that are separated from the ring.[431]




Evidence for this mechanism is that optically active $PhCHDCH_3$ labeled in the ring with $^{14}C$ and treated with $GaBr_3$ in the presence of benzene gave ethylbenzene containing no deuterium and two deuteriums and that the rate of loss of radioactivity was about equal to the rate of loss of optical activity.[431] The mechanism of intramolecular rearrangement is not very clear. 1,2 shifts of this kind have been proposed:[432]




There is evidence from $^{14}C$ labeling that intramolecular migration occurs only through 1,2 shifts.[433] Any 1,3 or 1,4 migration takes place by a series of two or more 1,2 shifts.

[426]McCaulay; Lien *J. Am. Chem. Soc.* **1953,** *75*, 2407. For similar results, see Roberts; Roengsumran *J. Org. Chem.* **1981,** *46*, 3689; Bakoss; Roberts; Sadri *J. Org. Chem.* **1982,** *47*, 4053.

[427]Roberts; Brandenberger *J. Am. Chem. Soc.* **1957,** *79*, 5484; Roberts; Douglass *J. Org. Chem.* **1963,** *28*, 1225.

[428]Brown; Jungk *J. Am. Chem. Soc.* **1955,** *77*, 5579; Allen; Yats *J. Am. Chem. Soc.* **1959,** *81*, 5289.

[429]Allen; Alfrey; Yats *J. Am. Chem. Soc.* **1959,** *81*, 42; Allen *J. Am. Chem. Soc.* **1960,** *82*, 4856.

[430]For a review of the mechanism of this and closely related reactions, see Shine, Ref. 375, pp. 1-55.

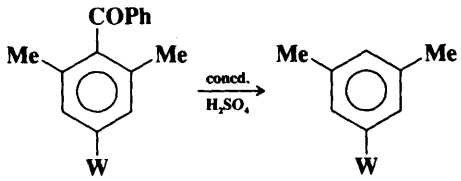
[431]Streitwieser; Reif *J. Am. Chem. Soc.* **1964,** *86*, 1988.

[432]Olah; Meyer; Overchuk *J. Org. Chem.* **1964,** *29*, 2313.

[433]See, for example, Steinberg; Sixma, *Recl. Trav. Chim. Pays-Bas* **1962,** *81*, 185; Koptyug; Isaev; Vorozhtsov *Doklad. Akad. Nauk SSSR* **1963,** *149*, 100.

Phenyl groups have also been found to migrate. Thus *o*-terphenyl, heated with $AlCl_3$–$H_2O$, gave a mixture containing 7% *o*-, 70% *m*-, and 23% *p*-terphenyl.[434] Alkyl groups have also been replaced by groups other than hydrogen, e.g., nitro groups.

Unlike alkylation, Friedel–Crafts *acylation* has been generally considered to be irreversible, but a number of instances of electrofugal acyl groups have been reported,[435] especially where there are two ortho substituents, for example, the hydro-de-benzoylation of **42**.[436]




**42** W = Me, Cl, OH, etc.

OS **V**, 332. Also see OS **III**, 282, 653; **V**, 598.

## 1-38 Decarbonylation of Aromatic Aldehydes
## Hydro-de-formylation or Deformylation

$$\mathbf{ArCHO} \xrightarrow{H_2SO_4} \mathbf{ArH + CO}$$

The decarbonylation of aromatic aldehydes with sulfuric acid[437] is the reverse of the Gatterman–Koch reaction (**1-16**). It has been carried out with trialkyl- and trialkoxybenzaldehydes. The reaction takes place by the ordinary arenium ion mechanism: the attacking species is $H^+$ and the leaving group is $HCO^+$, which can lose a proton to give CO or combine with $OH^-$ from the water solvent to give formic acid.[438] Aromatic aldehydes have also been decarbonylated with basic catalysts.[439] When basic catalysts are used, the mechanism is probably similar to the SE1 process of **1-39.** See also **4-41.**

## 1-39 Decarboxylation of Aromatic Acids
## Hydro-de-carboxylation or Decarboxylation

$$\mathbf{ArCOOH} \xrightarrow[\text{quinoline}]{Cu} \mathbf{ArH + CO_2}$$

The decarboxylation of aromatic acids is most often carried out by heating with copper and quinoline. However, two other methods can be used with certain substrates. In one method the salt of the acid ($ArCOO^-$) is heated, and in the other the carboxylic acid is heated with a strong acid, often sulfuric. The latter method is accelerated by the presence of electron-donating groups in ortho and para positions and by the steric effect of groups in the ortho positions; in benzene systems it is generally limited to substrates that contain such groups.

[434]Olah; Meyer *J. Org. Chem.* **1962,** *27*, 3682.

[435]For some other examples, see Agranat; Bentor; Shih *J. Am. Chem. Soc.* **1977,** *99*, 7068; Bokova; Buchina *J. Org. Chem. USSR* **1984,** *20*, 1199; Benedikt; Traynor *Tetrahedron Lett.* **1987,** *28*, 763; Gore; Moonga; Short *J. Chem. Soc., Perkin Trans. 2* **1988,** 485; Keumi; Morita; Ozawa; Kitajima *Bull. Chem. Soc. Jpn.* **1989,** *62*, 599; Giordano; Villa; Annunziata *Synth. Commun.* **1990,** *20*, 383.

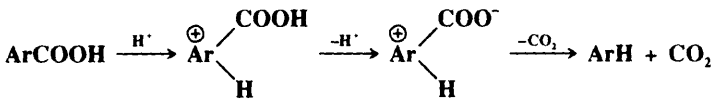
[436]Al-Ka'bi; Farooqi; Gore; Moonga; Waters *J. Chem. Res. (S)* **1989,** 80.

[437]For reviews of the mechanism, see Taylor, in Bamford; Tipper, Ref. 1, pp. 316-323; Schubert; Kintner, in Patai *The Chemistry of the Carbonyl Group*, vol. 1; Wiley: New York, 1966, pp. 695-760.

[438]Burkett; Schubert; Schultz; Murphy; Talbott *J. Am. Chem. Soc.* **1959,** *81*, 3923.

[439]Bunnett; Miles; Nahabedian *J. Am. Chem. Soc.* **1961,** *83*, 2512; Forbes; Gregory *J. Chem. Soc. B* **1968,** 205.

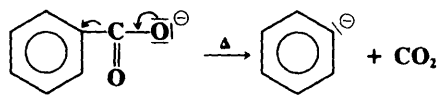
In this method decarboxylation takes place by the arenium ion mechanism,[440] with $H^+$ as the electrophile and $CO_2$ as the leaving group.[441] Evidently, the order of electrofugal ability



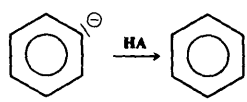
is $CO_2 > H^+ > COOH^+$, so that it is necessary, at least in most cases, for the COOH to lose a proton before it can cleave.

When carboxylate *ions* are decarboxylated, the mechanism is entirely different, being of the SE1 type. Evidence for this mechanism is that the reaction is first order and that electron-withdrawing groups, which would stabilize a carbanion, facilitate the reaction.[442]

Step 1



Step 2



Despite its synthetic importance, the mechanism of the copper–quinoline method has been studied very little, but it has been shown that the actual catalyst is cuprous ion.[443] In fact, the reaction proceeds much faster if the acid is heated in quinoline with cuprous oxide instead of copper, provided that atmospheric oxygen is rigorously excluded. A mechanism has been suggested in which it is the cuprous salt of the acid that actually undergoes the decarboxylation.[443] It has been shown that cuprous salts of aromatic acids are easily decarboxylated by heating in quinoline[444] and that arylcopper compounds are intermediates that can be isolated in some cases.[445] Metallic silver has been used in place of copper, with higher yields.[446]

In certain cases the carboxyl group can be replaced by electrophiles other than hydrogen, e.g., NO,[446] I,[447] Br,[448] or Hg.[449]

Rearrangements are also known to take place. For example, when the phthalate ion is heated with a catalytic amount of cadmium, the terphthalate ion (**43**) is produced:[450]

[440]For a review, see Taylor, in Bamford; Tipper, Ref. 1, pp. 303-316. For a review of isotope effect studies of this reaction, see Willi *Isot. Org. Chem.* **1977,** *3*, 257-267.

[441]See, for example, Los; Rekker; Tonsbeeck *Recl. Trav. Chim. Pays-Bas* **1967,** *86*, 622; Huang; Long *J. Am. Chem. Soc.* **1969,** *91*, 2872; Willi; Cho; Won *Helv. Chim. Acta* **1970,** *53*, 663.

[442]See, for example, Segura; Bunnett; Villanova *J. Org. Chem.* **1985,** *50*, 1041.

[443]Cohen; Schambach *J. Am. Chem. Soc.* **1970,** *92*, 3189. See also Aalten; van Koten; Tromp; Stam; Goubitz; Mak *Recl. Trav. Chim. Pays-Bas* **1989,** *108*, 295.

[444]Cairncross; Roland; Henderson; Sheppard *J. Am. Chem. Soc.* **1970,** *92*, 3187; Cohen; Berninger; Wood *J. Org. Chem.* **1978,** *43*, 37.

[445]For example, see Ibne-Rasa *J. Am. Chem. Soc.* **1962,** *84*, 4962; Tedder; Theaker *J. Chem. Soc.* **1959,** 257.

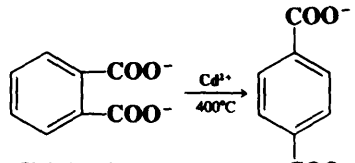
[446]Chodowska-Palicka; Nilsson *Acta Chem. Scand.* **1970,** *24*, 3353.

[447]Singh; Just *Synth. Commun.* **1988,** *18*, 1327.

[448]For example, see Grovenstein; Ropp *J. Am. Chem. Soc.* **1956,** *78*, 2560.

[449]For a review, see Larock *Organomercury Compounds in Organic Synthesis*; Springer: New York, 1985, pp. 101-105.

[450]Raecke *Angew. Chem.* **1958,** *70*, 1; Riedel; Kienitz *Angew. Chem.* **1960,** 72, 738; McNelis *J. Org. Chem.* **1965,** *30*, 1209; Ogata; Nakajima *Tetrahedron* **1965,** *21*, 2393; Ratuský; Šorm *Chem. Ind. (London)* **1966,** 1798.




Phthalate ion

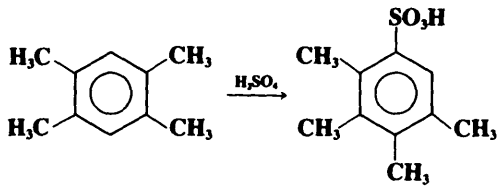
**43**

In a similar process, potassium benzoate heated with cadmium salts disproportionates to benzene and **43.** The term *Henkel reaction* (named for the company that patented the process) is used for these rearrangements.[451] An SE1 mechanism has been suggested.[452] The terphthalate is the main product because it crystallizes from the reaction mixture, driving the equilibrium in that direction.[453]

For aliphatic decarboxylation, see **2-40.**

OS **I,** 274, 455, 541; **II,** 100, 214, 217, 341; **III,** 267, 272, 471, 637; **IV,** 590, 628; **V,** 635, 813, 982, 985. Also see OS **I,** 56.

**1-40** The Jacobsen Reaction




When polalkyl- or polyhalobenzenes are treated with sulfuric acid, the ring is sulfonated, but rearrangement also takes place. The reaction, known as the *Jacobsen reaction*, is limited to benzene rings that have at least four substituents, which can be any combination of alkyl and halogen groups, where the alkyl groups can be ethyl or methyl and the halogen iodo, chloro, or bromo. When isopropyl or *t*-butyl groups are on the ring, these groups are cleaved to give olefins. Since a sulfo group can later be removed (**1-41**), the Jacobsen reaction can be used as a means of rearranging polyalkylbenzenes. The rearrangement always brings the alkyl or halo groups closer together than they were originally. Side products in the case illustrated above are pentamethylbenzenesulfonic acid, 2,4,5-trimethylbenzenesulfonic acid, etc., indicating an intermolecular process, at least partially.

The mechanism of the Jacobsen reaction is not established,[454] but there is evidence, at least for polymethylbenzenes, that the rearrangement is intermolecular, and that the species to which the methyl group migrates is a polymethylbenzene, not a sulfonic acid. Sulfonation takes place after the migration.[455] It has been shown by labeling that ethyl groups migrate without internal rearrangement.[456]

[451]For a review, see Ratuský, in Patai *The Chemistry of Acid Derivatives*, pt. 1; Wiley: New York, 1979, pp. 915-944.

[452]See, for example, Ratuský *Collect. Czech. Chem. Commun.* **1967,** *32*, 2504, **1972,** *37*, 2436, **1973,** *38*, 74, 87.

[453]Ratuský *Chem. Ind. (London)* **1967,** 1093, *Collect. Czech. Chem. Commun.* **1968,** *33*, 2346.

[454]For discussions, see Suzuki *Bull. Chem. Soc. Jpn.* **1963,** *36*, 1642; Koeberg-Telder; Cerfontain *J. Chem. Soc., Perkin Trans. 2* **1977,** 717; Cerfontain, *Mechanistic Aspects in Aromatic Sulfonation and Desulfonation*, Ref. 155, pp. 214-226; Taylor, in Bamford; Tipper, Ref. 1, pp. 22-32, 48-55.

[455]Koeberg-Telder; Cerfontain *Recl. Trav. Chim. Pays-Bas* **1987,** *106*, 85; Cerfontain; Koeberg-Telder *Can. J. Chem.* **1988,** *66*, 162.

[456]Marvell; Webb *J. Org. Chem.* **1962,** *27*, 4408.

## B. Sulfur Leaving Groups

### 1-41 Desulfonation or Hydro-de-sulfonation

$$ArSO_3H \xrightarrow[\text{dil. } H_2SO_4]{135\text{–}200^\circ C} ArH + H_2SO_4$$

The cleavage of sulfo groups from aromatic rings is the reverse of **1-7.**[457] By the principle of microscopic reversibility, the mechanism is also the reverse.[458] Dilute $H_2SO_4$ is generally used, as the reversibility of sulfonation decreases with increasing $H_2SO_4$ concentration. The reaction permits the sulfo group to be used as a blocking group to direct meta and then to be removed. The sulfo group has also been replaced by nitro and halogen groups. Sulfo groups have also been removed from the ring by heating with an alkaline solution of Raney nickel.[459] In another catalytic process, aromatic sulfonyl bromides or chlorides are converted to aryl bromides or chlorides, respectively, on heating with chlorotris(triphenylphosphine)rhodium(I).[460] This reaction is similar to the decarbonylation of aromatic acyl halides mentioned in **4-41.**

$$ArSO_2Br \xrightarrow{RhCl(PPh_3)_3} ArBr$$

OS **I,** 388; **II,** 97; **III,** 262; **IV,** 364. Also see OS **I,** 519; **II,** 128; **V,** 1070.

## C. Halogen Leaving Groups

### 1-42 Dehalogenation or Hydro-de-halogenation

$$ArX \xrightarrow{AlCl_3} ArH$$

Aryl halides can be dehalogenated by Friedel–Crafts catalysts. Iodine is the most easily cleaved. Dechlorination is seldom performed and defluorination apparently never. The reaction is most successful when a reducing agent, say, $Br^-$ or $I^-$ is present to combine with the $I^+$ or $Br^+$ coming off.[461] Except for deiodination, the reaction is seldom used for preparative purposes. Migration of halogen is also found,[462] both intramolecular[463] and intermolecular.[464] The mechanism is probably the reverse of that of **1-11.**[465]

Rearrangement of polyhalobenzenes can also be catalyzed by very strong bases; e.g., 1,2,4-tribromobenzene is converted to 1,3,5-tribromobenzene by treatment with PhNHK.[466]

[457]For reviews, see Cerfontain, Ref. 454, pp. 185-214; Taylor, in Bamford; Tipper, Ref. 1, pp. 349-355; Gilbert, Ref. 152, pp. 427-442. See also Krylov *J. Org. Chem. USSR* **1988,** *24,* 709.

[458]For a discussion, see Kozlov; Bagrovskaya *J. Org. Chem. USSR* **1989,** *25,* 1152.

[459]Feigl *Angew. Chem.* **1961,** *73,* 113.

[460]Blum; Scharf *J. Org. Chem.* **1970,** *35,* 1895.

[461]Pettit; Piatak *J. Org. Chem.* **1960,** *25,* 721.

[462]Olah; Tolgyesi; Dear *J. Org. Chem.* **1962,** *27,* 3441, 3449, 3455; De Valois; Van Albada; Veenland *Tetrahedron* **1968,** *24,* 1835; Olah; Meidar; Olah *Nouv. J. Chim.* **1979,** *3,* 275.

[463]Koptyug; Isaev; Gershtein; Berezovskii *J. Gen. Chem. USSR* **1964,** *34,* 3830; Erykalov; Becker; Belokurova *J. Org. Chem. USSR* **1968,** *4,* 2054; Jacquesy; Jouannetaud *Tetrahedron Lett.* **1982,** *23,* 1673.

[464]Kooyman; Louw *Recl. Trav. Chim. Pays-Bas* **1962,** *81,* 365; Augustijn; Kooyman; Louw *Recl. Trav. Chim. Pays-Bas* **1963,** *82,* 965.

[465]Choguill; Ridd *J. Chem. Soc.* **1961,** 822; Ref. 430; Ref. 462.

[466]Moyer; Bunnett *J. Am. Chem. Soc.* **1963,** *85,* 1891.

This reaction, which involves aryl carbanion intermediates (SE1 mechanism), has been called the *halogen dance*.[467]

Removal of halogen from aromatic rings can also be accomplished by various reducing agents, among them $Ph_3SnH$,[468] HI, Sn and HBr, $Ph_3P$,[469] Zn and an acid or base,[470] catalytic hydrogenolysis,[471] catalytic transfer hydrogenolysis,[472] Zn–Ag couple,[473] Na–Hg in liquid $NH_3$,[474] $LiAlH_4$,[475] $LiAlH_4$ irradiated with light[476] or with ultrasound,[477] $NaAlH_4$,[478] $NaBH_4$ and a catalyst,[479] NaH,[480] and Raney nickel in alkaline solution,[481] the last method being effective for fluorine as well as for the other halogens. Carbon monoxide, with potassium tetracarbonylhydridoferrate $KHFe(CO)_4$ as a catalyst, specifically reduces aryl iodides.[482] Not all these reagents operate by electrophilic substitution mechanisms. Some are nucleophilic substitutions and some are free-radical processes. Photochemical[483] and electrochemical[484] reduction are also known. Halogen can also be removed from aromatic rings indirectly by conversion to Grignard reagents (**2-38**) followed by hydrolysis (**1-44**).

OS **III,** 132, 475, 519; **V,** 149, 346, 998; **VI,** 82, 821.

**1-43** Formation of Organometallic Compounds

$$\mathbf{ArBr + M \longrightarrow ArM}$$

$$\mathbf{ArBr + RM \longrightarrow ArM + RBr}$$

These reactions are considered along with their aliphatic counterparts at reactions **2-38** and **2-39**.

## D. Metal Leaving Groups

**1-44** Hydrolysis of Organometallic Compounds
**Hydro-de-metallation** or **Demetallation**

$$\mathbf{ArM + H^+ \longrightarrow ArH + M^+}$$

Organometallic compounds can be hydrolyzed by acid treatment. For active metals such as Mg, Li, etc., water is sufficiently acidic. The most important example of this reaction is

[467]Bunnett; McLennan *J. Am. Chem. Soc.* **1968,** *90*, 2190; Bunnett *Acc. Chem. Res.* **1972,** *5*, 139-147; Mach; Bunnett *J. Org. Chem.* **1980,** *45*, 4660; Sauter; Fröhlich; Kalt *Synthesis*, **1989,** 771.

[468]Lorenz; Shapiro; Stern; Becker *J. Org. Chem.* **1963,** *28*, 2332; Neumann; Hillgärtner *Synthesis* **1971,** 537.

[469]Hoffmann; Michael *Chem. Ber.* **1962,** *95*, 528.

[470]Tashiro; Fukuta *J. Org. Chem.* **1977,** *42*, 835. See also Colon *J. Org. Chem.* **1982,** *47*, 2622.

[471]For example, see Subba Rao; Mukkanti; Choudary *J. Organomet. Chem.* **1989,** *367*, C29.

[472]Anwer; Spatola *Tetrahedron Lett.* **1985,** *26*, 1381.

[473]Chung; Ho; Lun; Wong; Wong; Tam *Synth. Commun.* **1988,** *18*, 507.

[474]Austin; Alonso; Rossi *J. Chem. Res. (S)* **1990,** 190.

[475]Karabatsos; Shone *J. Org. Chem.* **1968,** *33*, 619; Brown; Krishnamurthy *J. Org. Chem.* **1969,** *34*, 3918; Virtanen; Jaakkola *Tetrahedron Lett.* **1969,** 1223; Ricci; Danieli; Pirazzini *Gazz. Chim. Ital.* **1975,** *105*, 37; Chung; Chung *Tetrahedron Lett.* **1979,** 2473. Evidence for a free-radical mechanism has been found in this reaction; see Chung; Filmore *J. Chem. Soc., Chem Commun.* **1983,** 358; Beckwith; Goh *J. Chem. Soc., Chem Commun.* **1983,** 905.

[476]Beckwith; Goh *J. Chem. Soc., Chem. Commun.* **1983,** 907.

[477]Han; Baudjouk *Tetrahedron Lett.* **1982,** *23*, 1643.

[478]Zakharkin; Gavrilenko; Rukasov *Dokl. Chem.* **1972,** *205*, 551.

[479]Egli *Helv. Chim. Acta* **1968,** *51*, 2090; Bosin; Raymond; Buckpitt *Tetrahedron Lett.* **1974,** 4699; Lin; Roth *J. Org. Chem.* **1979,** *44*, 309; Narisada; Horibe; Watanabe; Takeda *J. Org. Chem.* **1989,** *54*, 5308. See also Epling; Florio *J. Chem. Soc., Perkin Trans. 1* **1988,** 703.

[480]Nelson; Gribble *J. Org. Chem.* **1974,** *39*, 1425.

[481]Buu-Hoï; Xuong; van Bac *Bull. Soc. Chim. Fr.* **1963,** 2442; de Koning *Org. Prep. Proced. Int.* **1975,** *7*, 31.

[482]Brunet; Taillefer *J. Organomet. Chem.* **1988,** *348*, C5.

[483]See, for example, Pinhey; Rigby *Tetrahedron Lett.* **1969,** 1267, 1271; Barltrop; Bradbury *J. Am. Chem. Soc.* **1973,** *95*, 5085.

[484]See Fry *Synthetic Organic Electrochemistry*, 2nd ed.; Wiley: New York, 1989, pp. 142-143.

hydrolysis of Grignard reagents, but M may be many other metals or metalloids. Examples are $SiR_3$, HgR, Na, and $B(OH)_2$. Since aryl Grignard and aryllithium compounds are fairly easy to prepare, they are often used to prepare salts of weak acids, e.g.,

$$\mathbf{PhMgBr + H{-}C{\equiv}C{-}H \longrightarrow H{-}C{\equiv}C^{-}\ \ MgBr^{+} + PhH}$$

Where the bond between the metal and the ring is covalent, the usual arenium ion mechanism operates.[485] Where the bonding is essentially ionic, this is a simple acid–base reaction. For the aliphatic counterpart of this reaction, see reaction **2-24.**

Other reactions of aryl organometallic compounds are treated with their aliphatic analogs: reactions **2-25** through **2-36.**

[485]For a discussion of the mechanism, see Taylor, in Bamford; Tipper, Ref. 1, pp. 278-303, 324-349.