QUARTERLY REVIEWS

MECHANISM AND REACTIVITY IN AROMATIC NUCLEOPHILIC SUBSTITUTION REACTIONS

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ALTHOUGH nucleophilic substitutions at aromatic carbon atoms had been encountered as early as 1854,[1] and although many such reactions had found wide use in synthesis, questions of mechanism and reactivity received only scattered attention before the present decade. About 1950, active research in this area was commenced independently in several laboratories. In 1951, a comprehensive review by the Reviewer and the late Roland Zahler [2] and a shorter review by Joseph Miller [3] were published. At that time relatively few definite conclusions about mechanisms could be reached, but today a rather satisfactory picture can be drawn.

For years, "aromatic substitution" meant to chemists a group of reactions now recognised to involve electrophilic substitution reagents almost without exception. Certain outstanding problems were recognised. One was to determine why, of the five nuclear hydrogen atoms in a monosubstituted benzene, sometimes one of the two *meta* to the substituent was replaced and at other times one of the three in the *ortho*- and *para*-positions. Another problem was to establish the identity of the effective electrophilic entities provided by the various chemicals used to effect substitution. In *nucleophilic* aromatic substitution the analogous problems have only subordinate interest. Hydrogen is seldom displaced, the readily displaceable groups being those which can depart with the bonding electron pair as stable anions or molecules. There is usually only one displaceable group per molecule and so the directing effects of other substituents are not often considered. The effective form of the nucleophilic reagent is usually obvious. On the other hand, nucleophilic substitutions are generally strongly dependent on the assistance of activating groups and therefore much attention is paid to establishing the activating powers of substituents. Changes in rate with changes in the displaceable group are another focus of interest. Other intriguing questions arise from the availability of at least three mechanisms for nucleophilic aromatic substitution.

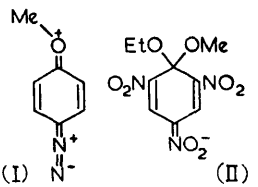
[1] Williamson and Scrugham, *J.*, 1854, **7**, 237; *Annalen*, 1854, **92**, 316; Pisani, *Compt. rend.*, 1854, **39**, 852; *Annalen*, 1854, **92**, 326.
[2] Bunnett and Zahler, *Chem. Rev.*, 1951, **49**, 273.
[3] Miller, *Rev. Pure Appl. Chem.*, 1951, **1**, 171.

The S_N1 mechanism

Although aliphatic nucleophilic substitution frequently occurs by the S_N1 mechanism,[4] this mechanism is rare for substitution at aromatic carbon atoms. It is well established only for the thermal decomposition of diazonium cations in aqueous solution. The diazonium ion splits to form an aryl cation and a nitrogen molecule, $ArN_2^+ \longrightarrow Ar^+ + N_2$, and the aryl cation rapidly combines with water to form a phenol, with a halide ion (if available) to form an aryl halide, or with whatever other nucleophilic reagents may be at hand. The evidence for this mechanism is manifold. Necessary but not sufficient is that the reaction is kinetically of first order.[5] More decisive is the fact that the rate of decomposition is independent of the nature or concentration of added metal halide salts [6] even though at high concentrations of such salts the product is to a large extent the aryl halide.[7, 8] The effects of substituents on rate also support the S_N1 mechanism: the reaction is accelerated by electron-releasing *meta*-substituents and retarded by electron-attracting *meta*- and *para*-substituents.[8] [Surprisingly, electron-releasing *para*-substituents *retard* the reaction. The reason is that, in furnishing electrons by mesomeric or hyperconjugative interaction, *para*-substituents strengthen the C–N bond which must be broken by increasing its double-bond character; [9] *e.g.*, see structure (I).]

In special circumstances, as in the reaction of bromide ion with the *p*-nitrobenzenediazonium ion,[9b] bimolecular displacement of a diazo-group may also occur.

Decomposition of diazonium ions in the presence of a variety of neutral organic molecules of low nucleophilic reactivity has yielded products to be expected only through the intermediacy of a highly electrophilic species such



(I) (II)

as an aryl cation.[10] Thus, decomposing benzenediazonium fluoroborate phenylates nitrobenzene and benzotrifluoride in *meta*-positions, and methyl acrylate in the α-position. The same reagent converts benzonitrile into

[4] Ingold, " Structure and Mechanism in Organic Chemistry ", Cornell Univ. Press, 1953, p. 306.

[5] Moelwyn-Hughes and Johnson, *Trans. Faraday Soc.*, 1940, **36**, 948.

[6] Cain, *Ber.*, 1905, **38**, 2511; Pray, *J. Phys. Chem.*, 1926, **30**, 1417.

[7] Hantzsch, *Ber.*, 1900, **33**, 2517.

[8] Crossley, Kienle, and Benbrook, *J. Amer. Chem. Soc.*, 1940, **62**, 1400; see also ref. 2, p. 294.

[9] (*a*) Hughes, quoted in ref. 2, p. 295; (*b*) Lewis and Hinds, *J. Amer. Chem. Soc.*, 1952, **74**, 304.

[10] Nesmeyanov, Makarova, and Tolstaya, *Tetrahedron*, 1957, **1**, 145.

benzanilide,[11] bromobenzene into diphenylbromonium ion, and diphenyl ether into triphenyloxonium ion.

Nesmeyanov and his co-workers[10] aver that diphenyliodonium fluoroborate also may act as a source of phenyl cations. Thus, $Ph_2I^+BF_4^-$ reacts with diphenyl sulphide to form the triphenylsulphonium ion, although $Ph_2I^+Cl^-$ does not yield that product. However, kinetic studies on reactions of the diphenyliodonium ion with weak nucleophilic reagents in solution [12] indicate a bimolecular reaction with no evidence for a unimolecular mechanism. The reaction of Ph_2I^+ with Ph_2S may also be bimolecular in mechanism ; chloride ion may interfere because it is a stronger nucleophilic reagent than diphenyl sulphide.

The bimolecular mechanism

The great majority of aromatic nucleophilic substitutions occur by a bimolecular mechanism. In this type of reaction second-order kinetics, first order in both substrate and reagent, are regularly observed, as are greater rates with stronger nucleophilic reagents and with substrates carrying substituents of greater electron-attracting character.

After the establishment of the S_N2 mechanism of substitution at saturated carbon atoms by Hughes, Ingold, and their co-workers, [4, 13] it was often assumed that bimolecular aromatic nucleophilic substitution occurs by an analogous one-step mechanism of synchronous bond-formation and bond-breaking. An alternative two-step, intermediate complex mechanism was occasionally mentioned but was first forcefully advocated in 1951 by Zahler and the Reviewer,[2] who showed that one-step, S_N2-like substitution at an aromatic carbon atom was quantum-mechanically improbable, whilst the intermediate complex mechanism was not only acceptable in this regard but was also supported by significant analogies with other phenomena. The latter included electrophilic aromatic substitution, for which the intermediate complex mechanism was being recognised on experimental grounds,[14] and the formation of isolable addition complexes by the interaction of nucleophilic reagents with highly activated aromatic substrates. Foremost of these was complex (II), formed by addition of methoxide ion to 2 : 4 : 6-trinitrophenetole or of ethoxide ion to 2 : 4 : 6-trinitroanisole. Evidence for the structure of (II) was adduced at the turn of the century [15] and the structure assigned has received further support recently.[16, 17] It was argued that if highly activated substrates formed isolable addition complexes as intermediates in substitution reactions, and indeed (II) can be considered to be such an intermediate, then less highly activated substrates ought also to form actual

[11] Cf. Benson and Ritter, *J. Amer. Chem. Soc.*, 1949, **71**, 4128.

[12] Beringer and Gindler, *J. Amer. Chem. Soc.*, 1955, **77**, 3203 ; Beringer, Geering, and Kuntz, Abst. Amer. Chem. Soc. Meeting, New York, Sept. 1954, p. 97–O.

[13] Hughes, *Trans. Faraday Soc.*, 1941, **37**, 603.

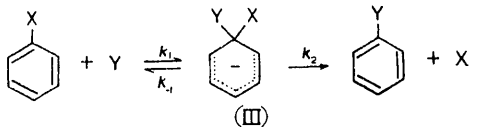
[14] Melander, *Arkiv Kemi*, 1950, **2**, 211 ; Hughes, Ingold, and Reed, *J.*, 1950, 2428.

[15] Jackson and Gazzolo, *Amer. Chem. J.*, 1900, **23**, 376 ; Jackson and Earle, *ibid.* 1903, **29**, 89 ; Meisenheimer, *Annalen*, 1902, **323**, 205.

[16] Foster and Hammick, *J.*, 1954, 2153 ; Foster, *Nature*, 1955, **176**, 746.

[17] Ainscough and Caldin, *J.*, 1956, 2528.

intermediates of type (III) although of stability insufficient to allow isolation. Bimolecular aromatic nucleophilic substitution was therefore represented as in equation (1). It was stressed that either the first or the second step of the mechanism might be rate-determining, depending on the relative magni-



(III) (1)

tudes of k_2 and k_{-1}. Thus if $k_2 \gg k_{-1}$, the rate of the first step would in effect be the rate of the overall reaction whilst if $k_{-1} \gg k_2$ the rate would depend on the equilibrium concentration of the intermediate complex (III) and on k_2.

Nevertheless, the one-step S_N2-like mechanism continued to be advocated,[18, 19] especially for the reactions of iodide ion [19] and of *N*-methylaniline [20] with 1-halogeno-2 : 4-dinitrobenzenes in which the order of halogen mobility, Br > Cl > F, resembled that for aliphatic S_N2 reactions. The order F $\gg$ Cl $\sim$ Br $\sim$ I is usually observed in aromatic displacements. The order Br > Cl > F is however not incompatible with the intermediate-complex mechanism.[20, 21] Thus if, in intermediate (III) of scheme (1), X is a poorer leaving group than Y (*e.g.*, if X is fluorine and Y is iodine), then $k_{-1} > k_2$ and the rate will depend on k_2. With a given Y group, k_2 will be greater for X = Br than for X = F.

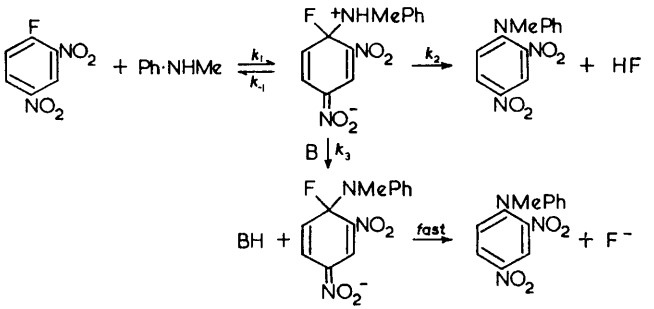
Three powerful lines of support for the intermediate-complex mechanism have come from recent research. They prove the mechanism for certain reactions and make it probable for all bimolecular aromatic nucleophilic substitutions. The first takes account of the fact that the C–F bond characteristically is broken more slowly than other carbon–halogen bonds. This has been established for S_N1 and S_N2 reactions of alkyl halides [22] and for the formation of " benzyne " from *o*-halogenophenyl anions [23] (see p. 7). It follows that in any reaction series in which fluorine is displaced more rapidly than the other halogens, breaking of the C–F bond cannot have made significant progress in the rate-determining transition state.[20, 21] Since in the intermediate-complex mechanism the C–X bond is intact in the rate-determining transition state (if $k_2 \gg k_{-1}$), whilst in the S_N2-like mechanism it is partially broken, the former mechanism is indicated for the many displacements in which fluorine is the most mobile of the halogens.

Secondly, it has been found that piperidine reacts with several 1-substituted-2 : 4-dinitrobenzenes to form 2 : 4-dinitrophenylpiperidine at nearly the same rate.[21] The maximum variation in rate of displacement of Cl, Br, I, SOPh, SO_2Ph, and $O{\cdot}C_6H_4{\cdot}NO_2$-*p* is less than five-fold, and this

[18] Chapman and Russell-Hill, *J.*, 1956, 1563.
[19] Fierens *et al.*, *Bull. Soc. chim. belges*, 1955, **64**, 696, 704, 709, 717.
[20] Hammond and Parks, *J. Amer. Chem. Soc.*, 1955, **77**, 340.
[21] Bunnett, Garbisch, and Pruitt, *ibid.*, 1957, **79**, 385.
[22] Cooper and Hughes, *J.*, 1937, 1183 ; Chapman and Levy, *J.*, 1952, 1673.
[23] Roberts *et al.*, *J. Amer. Chem. Soc.*, 1953, **75**, 3290 ; 1956, **78**, 601, 611.

sameness in rate is derived from a sameness in energy and entropy of activation. In these six reactions, bonds from carbon to five different elements are broken. Since in general bonds such as C–S, C–I, and C–O undergo heterolysis at widely different rates, the lack of a kinetic " element effect " shows that these various bonds are not broken in rate-determining steps. Again, the S_N2-like mechanism is vitiated and the intermediate complex mechanism upheld. Formation of a C–N bond, and thus of a complex of type (III), is the slow step in each reaction.

Thirdly, the reaction of *N*-methylaniline with 1-fluoro-2 : 4-dinitrobenzene, which occurs more slowly than with 1-bromo-2 : 4-dinitrobenzene,[20] has been found [24] to be subject to base-catalysis, whereas the reactions of this and other amines with 1-chloro-2 : 4-dinitrobenzene and related substrates are not.[25] In ethanol, 0·1M-potassium acetate accelerates the reaction 14-fold, far in excess of a simple salt effect. Added acetic acid does not decelerate the acetate-catalysed reaction ; this shows that the base-catalysis does not concern a prior equilibrium and that acetate ion participates as such in the rate-determining step. The rate of the catalysed reaction in ethanol is linearly dependent on acetate concentration, but the hydroxide-catalysed reaction in aqueous dioxan shows a somewhat less than linear response to increasing base concentration. These observations uniquely establish the following mechanism :



The kinetic expression for this mechanism is

$$k_{obs} = (k_1k_2 + k_1k_3[B])/(k_{-1} + k_2 + k_3[B])$$

In ethanol with B = OAc^- the inequalities $k_{-1} \gg k_3[B] > k_2$ prevail.[24]

For some time a distinction in mechanism between activated and unactivated substitutions has been inferred on grounds of differing orders of halogen mobility. The order $F \gg Cl \sim Br \sim I$ commonly observed in reactions of nitroaryl halides contrasts with the order $I > Br > Cl > F$ reported by Tronov and Krüger [26] for reactions of unsubstituted phenyl halides with piperidine and with sodium methoxide. Substantially the latter order was also observed in reactions of phenyl halides with metal

[24] Bunnett and Randall, *J. Amer. Chem. Soc.*, in the press.
[25] Bunnett and Pruitt, *J. Elisha Mitchell Sci. Soc.*, 1957, **73**, 297.
[26] Tronov and Krüger, *J. Russ. Phys. Chem. Soc.*, 1926, **58**, 1270 ; *Chem Zentr.*, 1927, II, 1145.

amides in liquid ammonia,[27] reactions now known to occur *via* benzyne.[23] For a time it was thought [20] that Tronov and Kruger's reactions also went by the benzyne mechanism, but it has been established that certain substitutions in unactivated naphthyl halides do occur by a straightforward displacement mechanism.[28] In these reactions fluorine appears to be more readily displaced than the other halogens. Tronov and Krüger's order, and consequently the basis for a categorical distinction between unactivated and activated substitutions, are therefore placed in doubt. The intermediate complex mechanism, established for activated substitutions, is thus indicated at least provisionally for unactivated bimolecular displacements as well.

Charge-transfer Complexes.—Charge-transfer complexes [29] have been shown to be preliminary intermediates in certain electrophilic aromatic substitutions.[30] The charge-transfer complex is a loose association of reagent with substrate; the rate-determining step or steps concern the formation and/or decomposition of a covalent intermediate complex analogous to (III).

Amongst nucleophilic substitutions, the part played by charge-transfer complexes is not yet clear. They may precede the formation of the covalent intermediate complex, or the covalent complex may be formed directly from reagent and substrate. The condensation of aniline with 1-chloro-2 : 4-dinitrobenzene is decelerated somewhat by charge-transfer complex formation,[31] but whether the charge-transfer complex is a preliminary intermediate in the substitution is not known. Ethoxide ion and 2 : 4 : 6-trinitroanisole form two complexes : a charge-transfer complex formed extremely rapidly, and a covalent complex (II) formed subsequently.[17] The rates of both processes have been measured, but it is not known whether they are consecutive or competitive. Iodide ion and *N*-methylpyridinium ion also form a charge-transfer complex; it has been suggested [32] that charge-transfer complex formation determines the position of nucleophilic attack on the pyridinium ring.

In early discussions of the intermediate-complex mechanism [33] some confusion arose from failure to distinguish rapidly-formed, loose charge-transfer complexes from the covalent intermediate complexes which are formed more slowly. Increasing understanding of the nature of charge-transfer complexes [29] and increasing evidence for covalent intermediate complexes of type (III) have dispelled the confusion.

The elimination–addition (benzyne) mechanism

During the early years of the war, Wittig *et al.*[34] adduced evidence that

[27] Bergstrom, Wright, Chandler, and Gilkey, *J. Org. Chem.*, 1936, **1**, 170.

[28] (*a*) Bunnett and Brotherton, *J. Amer. Chem. Soc.*, 1956, **78**, 155, 6265; (*b*) Huisgen and Sauer, *Angew. Chem.*, 1957, **69**, 390.

[29] Mulliken, *J. Amer. Chem. Soc.*, 1952, **74**, 811.

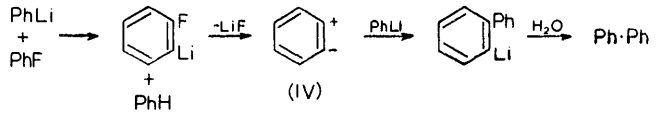
[30] Keefer, Ottenberg, and Andrews, *ibid.*, 1956, **78**, 255 and earlier papers; Gold and Satchell, *J.*, 1955, 3619; 1956, 2743.

[31] Ross and Kuntz, *J. Amer. Chem. Soc.*, 1954, **76**, 3000.

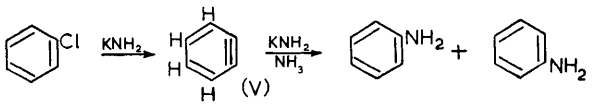
[32] Kosower, *ibid.*, 1956, **78**, 3497. [33] Cavell and Chapman, *J.*, 1953, 3392.

[34] Wittig *et al.*, *Ber.*, 1940, **73**, 1193; 1941, **74**, 1480; *Naturwiss.*, 1942, **30**, 700.

the reaction of phenyl-lithium with fluorobenzene to form diphenyl proceeds *via* the unusual intermediate (IV) :



Later, Roberts *et al.*[23] showed that the C_6H_4 intermediate is also involved in the transformation of chlorobenzene into aniline through the action of potassamide in liquid ammonia. They found that [1-^{14}C]chlorobenzene yielded, after allowance for small kinetic isotope effects, equal parts of [1-^{14}C]aniline and [2-^{14}C]aniline. A symmetrical intermediate was thus indicated, and the mechanism was represented as follows :



The reaction of [1-^{14}C] fluorobenzene with phenyl-lithium was similarly shown [35] to proceed *via* a symmetrical intermediate which Roberts preferred to represent as (V) and to call " benzyne ". The existence of this intermediate is now widely accepted, but there is no general agreement on the manner of bonding in this extraordinary unsaturated species. It has been suggested that benzyne can be considered analogous to the *cis*-bent excited state of acetylene.[36]

o-Deuterated phenyl halides react more slowly than analogous plain phenyl halides with potassamide in ammonia ; [23] the elimination–addition mechanism is thus further supported. Fluorobenzene does not yield benzyne at −33° but it quickly exchanges *ortho*-hydrogen with KNH_2 in ammonia. Bromobenzene does not exchange without undergoing loss of bromine, and chlorobenzene has intermediate character. These results show that elimination is initiated by removal of an *ortho*-hydrogen atom by NH_2^-. The resulting *o*-halogenophenyl anion may either lose halide ion to yield benzyne or recapture a proton from the solvent. If the halogen is bromine, halide ion is lost ; if it is fluorine, a proton is recaptured ; and if it is chlorine, reactions of each type occur.

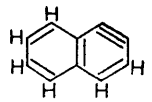
The reaction of *o*-iodoanisole with sodium amide to form *m*-anisidine [37] is one of a large number of cine-substitutions (see p. 15) which occur by the benzyne mechanism.[38] Amide ion converts this halide into 3-methoxybenzyne which then adds an amide ion and a proton so as to form *m*-anisidine. Orientation in addition to benzyne derivatives appears to be governed mainly by inductive effects of substituents ; [23] steric factors are relatively unimportant.[39]

Cine-substitution so characteristically accompanies reactions occurring

[35] Jenny and Roberts, *Helv. Chim. Acta*, 1955, **38**, 1248.
[36] Ingold, *J.*, 1954, 2991.
[37] Gilman and Avakian, *J. Amer. Chem. Soc.*, 1945, **67**, 349.
[38] An extensive summary is given in ref. 2, p. 384.
[39] Huisgen and Zirngibl, *Angew. Chem.*, 1957, **69**, 389.

by the benzyne mechanism that it tends to be diagnostic for the mechanism. One other mechanism of cine-substitution is known (see p. 15) and yet others may exist. However, if a strongly basic reagent is involved and if nitro-groups are absent, the occurrence of cine-substitution may reasonably be taken as evidence for the benzyne mechanism. If the direction of addition of a given reagent to a given benzyne derivative is known from other experience, the non-incidence of cine-substitution may also be significant. The point of reference for the detection of rearrangement during substitution may be either a substituent or an isotopic label.

Application of this criterion of mechanism has served to define the limits of the benzyne mechanism. By use of both isotopically and methyl-labelled phenyl halides, it was shown [40] that hydrolysis to phenols by aqueous sodium hydroxide at 250—340° goes partly by the benzyne mechanism and partly by direct substitution; the proportions of the two can be varied by suitable choice of conditions. 1-Naphthalyne (VI) is known [28] to add piperidine to form 1- and 2-naphthylpiperidines in the ratio 1 : 2. One may therefore conclude that any reaction of a 1-substituted naphthalene with piperidine and/or piperidide ions which gives these naphthylpiperidines in this ratio proceeds *via* (VI); and further, that any reaction which gives 1-naphthylpiperidine in excess of 33% yield proceeds in whole or in part by direct displacement. In the latter case, the ratio of the two mechanisms is calculable from the ratio of the two naphthylpiperidines. It was thus shown [28a] that sodamide in boiling piperidine acts upon 1-chloro-, 1-bromo-, and 1-iodo-naphthalenes entirely *via* (VI), upon methyl 1-naphthyl sulphone entirely by direct displacement, and upon 1-fluoronaphthalene in part by each mechanism. Also, 1-bromonaphthalene and piperidine (without sodamide) were shown to react entirely by direct displacement. The reaction of 1-fluoronaphthalene with lithium piperidide in ether goes entirely *via* (VI) but with excess of piperidine increasing amounts of direct displacement occur.[28b]


(VI)

There are other interesting facets to benzyne chemistry.[41] Our purpose has been to show that the elimination–addition mechanism is an important mechanism of nucleophilic aromatic substitution, but one which has its limitations in scope.

Reactivity in bimolecular displacements

Electronic Effects.—The displacement reaction is facilitated by electron-attracting and retarded by electron-releasing substituents. The electronic effects of substituents *meta* or *para* to the site of substitution can be correlated by the Hammett equation,[42, 43] $\log (k/k_0) = \rho\sigma$. The large ρ values (+ 3·5

[40] Bottini and Roberts, *J. Amer. Chem. Soc.*, 1957, **79**, 1458.

[41] See Wittig, *Angew, Chem.*, 1957, **69**, 245.

[42] Hammett, "Physical Organic Chemistry", McGraw-Hill, 1940, p. 186; Jaffe, *Chem. Rev.*, 1953, **53**, 191.

[43] Berliner and Monack, *J. Amer. Chem. Soc.*, 1952, **74**, 1574; Bunnett, Moe, and Knutson, *ibid.*, 1954, **76**, 3936; Miller, *Austral. J. Chem.*, 1956, **9**, 61.

to + 5) observed, and the requirement that the special σ^- (formerly [44] designated σ^*) values of *para*-substituents capable of mesomeric interaction be used, reflect the large demand of this reaction that substituents accept electrons in the transition state. Space does not permit discussion of the many valuable studies [45, 46] of the effects of particular substituents. The strong activating effect of the $-N_2^+$ group of diazonium salts is, however, especially noteworthy. It sometimes facilitates unexpected displacement of *ortho*- or *para*-substituents by relatively weak nucleophilic reagents.[47] A most interesting manifestation is the " self-diazotisation " of certain nitroanilines by hydrochloric acid in acetic acid ; [48] 2 : 5-dinitroaniline, for example, is converted into 2-chloro-5-nitrobenzenediazonium ion.

ortho : para-*Ratio.*—Groups such as nitro, given to accepting electrons by mesomeric interaction, generally activate about equivalently from the *ortho*- and *para*-positions and much less from the *meta*-position. Yet the *ortho* : *para*-ratio of activation, for example, by the nitro-group, is by no means constant. The preferential displacement of the 2-halogen atom from 2 : 4-dihalogenonitrobenzenes by nucleophilic reagents of all types, and the fact that *o*-halogenonitrobenzenes react faster than their *para*-isomers with amines, suggest *ortho*-activation to predominate, but the fact that *p*-halogenonitrobenzenes react faster with alkoxide and thiophenoxide ions suggests the opposite.[49] These seeming anomalies are interpreted as follows : (*a*) All other things being equal, the nitro-group is preferentially *ortho*-activating ; its inductive effect is probably responsible. This situation is most nearly encountered in reactions of 2 : 4-dihalogenonitrobenzenes as mentioned. (*b*) In transition states for reactions of *o*-halogenonitrobenzenes with alkoxides, steric interference with attainment of coplanarity by the nitro-group (see p. 11) diminishes the reactivity of the *ortho*-isomer below that of the *para*-isomer in which the nitro-group is unhindered. (*c*) In the dipolar transition states for reactions of *o*-halogenonitrobenzenes with amines, electrostatic interaction between the adjacent negative (oxygen atoms of the nitro-group) and positive (nitrogen atom of the amine) ends of the dipole reduces the requirement for solvation by external molecules, as compared to the *para*-transition state which requires normal solvation, and therefore increases the entropy of activation ; this effect, dubbed " built-in solvation ", once again swings the delicate balance of factors back in favour of *ortho*-substitution.[49]

Stage (*a*) of this interpretation is an assertion in accord with general experience and theory. Stage (*b*) is theoretically sound and receives experimental support from the fact that the usual inversion in *ortho* : *para*-ratio is suppressed when the activating group (methylsulphonyl) is immune to

[44] Okamoto and Brown, *J. Org. Chem.*, 1957, **22**, 493.

[45] See especially Miller *et al.*, *J. Amer. Chem. Soc.*, 1957, **79**, 93 ; *J.*, 1956, 2329 and earlier papers ; Brieux and Deulofeu, *J.*, 1954, 2519.

[46] Bevan and Bye, *J.*, 1954, 3091 and earlier papers.

[47] See, *e.g.*, Burawoy *et al.*, *J.*, 1953, 959 ; 1954, 82 ; Schiemann and Ley, *Ber.*, 1936, **69**, 960.

[48] Sihlbom, *Acta Chem. Scand.*, 1953, **7**, 1197.

[49] Bunnett and Morath, *J. Amer. Chem. Soc.*, 1955, **77**, 5051.

steric interference with its mesomeric interaction [50] and in reactions of fluoronitrobenzenes [46] in which the *ortho*-fluorine atom is not big enough to interfere very much with attainment of coplanarity by the nitro-group. Stage (*c*) is supported by measurements [49] of the rates and energies and entropies of activation for reactions of piperidine with *o*- and *p*-chloronitrobenzene in various solvents. Reactions of the *para*-isomer showed the typical variation with change from less polar to more polar solvents: a small increase in $\Delta H^{\ddagger}$, a large increase in $\Delta S^{\ddagger}$, and a large increase in rate. Typical requirement for transition-state solvation was thus revealed.[51] Reactions of the *ortho*-isomer showed similar tendencies but in severely repressed form, indicating reduced requirement for solvation of the *ortho*-transition state. Because of the strong variation in *para*-rate and the comparative constancy in *ortho*-rate, the *o* : *p*-ratio changed from 80 in xylene to 1·4 in water containing 1% of dioxan.

The inversion in *o* : *p*-ratio has been given an alternative interpretation [52] which makes reference to an assumed set of relative energy levels for the reactants, transition states, and intermediate complexes involved in reactions of *o*- and *p*-chloronitrobenzenes with alkoxides and amines. Unfortunately, the critical assumptions have not been supported or tested by experiment.

" Built-in solvation " is also evident in the *o* : *p*-ratios for activation by the carboxylate group.[53] This group is mildly *para*-activating for displacement of chlorine by both alkoxides [54] and amines, but is distinctly *ortho*-deactivating for methoxy-dechlorination [55] and strongly *ortho*-activating for piperidinodechlorination.[55] These *ortho*-effects reflect, respectively, unfavourable [54] and favourable [53] local electrostatic interactions in the transition states; the latter cause acceleration by increasing the entropy of activation.

A number of substituents of the —COR type (—COMe, —COPh, —CO_2Me) show an *o* : *p*-ratio of < 1 for methoxydechlorination, owing largely to less effective conjugation in the *ortho*-position, but the ratio for —CO·NH_2 is > 1.[56] Hydrogen-bonding in the *ortho*-transition state for —CO·NH_2 is inferred.

Heterocyclic Bases.—The hetero-nitrogen atom in bases such as pyridine, quinoline, and thiazole is an activating structure nearly as strong as the nitro-group.[18] The amount of activation provided at various positions in numerous heterocyclic systems has been studied.[57] Positions α and γ to

[50] Ogata and Tsuchida, *J. Org. Chem.*, 1955, **20**, 1631; Kloosterziel and Backer, *Rec. Trav. chim.*, 1953, **72**, 185.

[51] Pearson, *J. Chem. Phys.*, 1952, **20**, 1478.

[52] Hawthorne, *J. Amer. Chem. Soc.*, 1954, **76**, 6358; Hammond and Hawthorne, in Newman, " Steric Effects in Organic Chemistry ", Wiley, New York, 1956, p. 191.

[53] Bunnett, Morath, and Okamoto, *J. Amer. Chem. Soc.*, 1955, **77**, 5055.

[54] Miller and Williams, *J.*, 1953, 1475.

[55] This systematic name for a substitution reaction comprises the parts: name of entering group + " de " + name (slightly contracted) of group displaced + " ation "; see Bunnett, *J.*, 1954, 4717.

[56] Miller and Williams, *J. Amer. Chem. Soc.*, 1954, **76**, 5482.

[57] See especially Chapman *et al.*, ref. 18 and previous papers; Amstutz *et al.*, *J. Org. Chem.*, 1954, **19**, 1830 and earlier papers.

the nitrogen atom are most strongly activated, and the rates and/or activation energies in many cases correlate well with quantum-mechanical calculations.[18, 58]

Conversion of the hetero-nitrogen atom into the 'onium condition amplifies its activating power. Quaternisation of 2-halogenopyridines greatly increases the mobility of the halogen.[59] Protonation also has this effect, and thus nucleophilic substitution in heterocyclic halides is subject to acid catalysis,[18, 60] sometimes of much use in synthesis. *N*-Oxidation has the same influence, and nucleophilic displacement of nitro-groups from the easily accessible *N*-oxides of 4-nitropyridine and 4-nitroquinoline has synthetic value.[61]

The hetero-oxonium atom in pyrylium salts is a significant activating structure.[62] There is evidence that the hetero-oxygen atom in furan and the sulphur in thiophen are somewhat activating.[63]

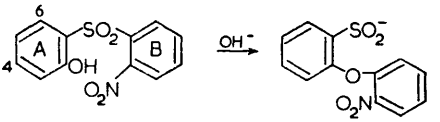
Steric Effects.—Because the reagent attacks almost perpendicularly to the plane of the ring, aromatic substitution is comparatively insensitive to the bulk of *ortho*-substituents providing the reagent has moderate steric requirements. Thus in reactions of iodide ion with 6-alkyl-1-bromo-2 : 4-dinitrobenzenes only the *tert.*-butyl group, of the set Me, Et, Pr^i, Bu^t, exerted a steric decelerating effect.[19] Steric hindrance by *ortho*-methyl becomes evident as the steric requirements of reagents increase. The diminution of rate caused by introduction of a methyl group in the 6-position of 1-chloro-2 : 4-dinitrobenzene is 14-fold, 22-fold, and 276-fold, respectively, for reactions with methoxide, aniline, and piperidine.[64] The first two figures are but slightly greater than expected from electronic considerations but the effective bulk of piperidine is evidently considerable. Another demonstration of steric interaction between reagent and *ortho*-alkyl group is the 1·22-fold difference in rates of condensation of (+)- and (−)-6-*sec.*-butyl-1-chloro-2 : 4-dinitrobenzenes with L-(+)-1-phenylethylamine.[65] In reactions with 1-chloro-2 : 4-dinitrobenzene, a set of primary and secondary aliphatic amines display differences in rate unrelated to their basicities but closely correlated with front-side interference by alkyl groups branching from the nitrogen atom or adjacent carbons.[66]

Many important activating groups, nitro above all, must be coplanar with the ring to exert their maximum activating effect. One substituent *ortho* to such a group interferes noticeably with the attainment of coplanarity, and two *ortho*-substituents severely weaken the influence of the activating

[58] Chapman, Chem. Soc. Special Pub. No. 3, 1955, p. 155.
[59] See, *e.g.*, Bradlow and Vanderwerf, *J. Org. Chem.*, 1951, **16**, 1143.
[60] Banks, *J. Amer. Chem. Soc.*, 1944, **66**, 1127.
[61] Ochiai, *J. Org. Chem.*, 1953, **18**, 534.
[62] King and Ozog, *ibid.*, 1955, **20**, 448 ; Anker and Cook, *J.*, 1946, 117.
[63] Hurd and Kreuz, *J. Amer. Chem. Soc.*, 1952, **74**, 2965 ; Manly and Amstutz, *J. Org. Chem.*, 1957, **22**, 133.
[64] Capon and Chapman, *J.*, 1957, 600 ; see also Bevan, Fayiga, and Hirst, *J.*, 1956, 4284 ; van Berk *et al.*, *Rec. Trav. chim.*, 1956, **75**, 1137.
[65] Hawthorne and Cram, *J. Amer. Chem. Soc.*, 1952, **74**, 5859.
[66] Brady and Cropper, *J.*, 1950, 507 ; ref. 2, p. 342.

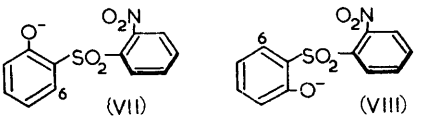
group. This effect was recognised years ago and is abundantly substantiated.[67] A recent example concerns the effect of methyl groups in positions *meta* to the chlorine atom on the rate of reaction of piperidine with 1-chloro-2 : 4-dinitrobenzene ; 5-Me (*ortho* to 4-NO_2) decelerates the reaction 3·6-fold, whilst 3-Me (the first group *ortho* to 4-NO_2 and the second group *ortho* to 2-NO_2) slows it 970-fold.[64] Groups like cyano, whose mesomeric interaction with the ring cannot be disturbed by *ortho*-substituents, are not subject to this secondary steric effect.[68]

The Smiles rearrangement [69] comprises a group of intramolecular nucleophilic substitutions of which the following is representative :



Substituents in the 6-position of the A-ring exert an enormous steric accelerative effect which eclipses the curious but moderate electronic effects of A-ring substituents. Methyl, chlorine, or bromine in the 6-position accelerates rearrangement about 500,000-fold, as judged by comparing rates of rearrangement of isomeric 4- and 6-substituted sulphones in which electronic effects are roughly equivalent.[70]

This enormous effect is interpreted with reference to two limiting rotational conformations of the hydroxy-sulphone anion, the species which actually undergoes rearrangement.[70] Conformation (VIII) is prerequisite to rearrangement because it brings the $-O^-$ group against the flat face of the B-ring close to the carbon which must be attacked. There are steric compressions in (VIII), because $-O^-$ with its solvent shell is rather large, and ordinarily conformation (VII), geometrically unsuitable for rearrangement, is preferred.



In (VII) and (VIII) the right-hand (nitrated) ring is to be regarded as perpendicular to the plane of the paper with the " thick " edge forward, the other ring lying in the plane of the paper.

However, if a substituent such as methyl is introduced into the 6-position, conformation (VII) is no longer so favoured because energy is required to compress the 6-substituent against the B-ring ; the population in rearranging conformations similar to (VIII) is increased and consequently rearrangement occurs faster.

[67] See ref. 2, p. 324.
[68] Spitzer and Wheland, *J. Amer. Chem. Soc.*, 1940, **62**, 2995.
[69] McClement and Smiles, *J.*, **1937**, 1016 and other papers ; ref. 2, p. 362.
[70] Okamoto and Bunnett, *J. Amer. Chem. Soc.*, 1956, **78**, 5357, 5363.

The Group Displaced.—The halogens are the most familiar groups displaced. Numerous studies [21, 71] have shown that the order of mobility $F \gg Cl \sim Br \sim I$ is common but that inversions may occur [19, 20] if the second step of the intermediate-complex mechanism enters into rate determination.[24] Many other groups can be displaced and several equal or surpass the halogens in replaceability. 'Onium groups such as $—NMe_3^+$ and $—SMe_2^+$ are exceptionally mobile [72] and $—NO_2$ rivals F in replaceability.[21, 72] Groups which approximate to or excel Cl in mobility include *p*-toluenesulphonoxy, *p*-nitrophenoxy, and phenylsulphonyl.[21]

Fuson and his co-workers [73] have observed, in reactions of Grignard reagents with hindered ketones such as duryl 4-substituted-phenyl ketones, displacement of a variety of nuclear substituents including halogens, —OMe, —OPh, —O·COMe, $—SO_2Me$, $—S·C_6H_5$ and, perhaps most interesting of all, the cyano-group. Another unusual displaceable group is $—CCl_3$.[74]

The Nucleophilic Reagent.—Comparison of reaction rates with a common substrate has given the following orders of reactivity : $PhS^- \gg$ piperidine $> PhO^- > H_2N·NH_2 > OH^- > Ph·NH_2$ (with 1-chloro-2 : 4-dinitrobenzene in 60% dioxan),[75] $MeO^- > N_3^- > SCN^-$ (with 1-iodo-2 : 4-dinitrobenzene in methanol),[45] $MeO^- \sim PhS^- > PhO^- > Ph·NH_2$ (with 1-fluoro-4-nitrobenzene in methanol),[76] $Ph·NH_2 > m\text{-}NO_2·C_6H_4·NH_2 > Cl^-$ > MeOH (with picryl chloride in methanol),[76] EtO^- > piperidine > $Ph·NH_2$ (with 3-chloro-2 : 6-dinitrotoluene in ethanol),[64] $MeO^- \sim$ piperidine (with 1-chloro-2 : 4-dinitrobenzene in methanol),[77] and piperidine > morpholine (several substrates in ethanol).[71b] The low reactivity of OH^- (in the first series) is particularly remarkable : it emphasises that nucleophilic reactivity and basicity frequently diverge widely from one another.

The PhS^- : MeO^- ratio of reactivity varies with the substrate. The ratio is approximately 1·0 with *p*-fluoronitrobenzene [76] but increases with increasing activation (59 with 1-fluoro-2 : 4-dinitrobenzene) and with increasing size and weight of the halogen displaced (16,800 with 1-iodo-2 : 4-dinitrobenzene).[71d] The latter is a manifestation of a general trend in bimolecular nucleophilic substitution : reagents of higher polarisability are relatively more effective with substrates having substituents of higher polarisability at or near the site of substitution.[78]

2 : 4-Dinitrophenyl toluene-*p*-sulphonate is susceptible to nucleophilic attack at two sites : the 1-position in the dinitrophenyl group and the sulphur

[71] (*a*) Bevan, *J.*, 1951, 2340 ; (*b*) Chapman, Parker, and Soanes, *J.*, 1954, 2109 ; (*c*) Miller *et al.*, *J.*, 1955, 2926 and earlier papers ; (*d*) Bunnett and Merritt, *J. Amer. Chem. Soc.*, 1957, **79**, 5967 ; (*e*) Brieux and Deulofeu, *Anales Asoc. quim. argentina*, 1951, **39**, 189.

[72] Bolto and Miller, *Austral. J. Chem.*, 1956, **9**, 74.

[73] Fuson *et al.*, *J. Amer. Chem. Soc.*, 1954, **76**, 5782 ; 1955, **77**, 1138 and earlier papers.

[74] Kreutzberger, *ibid.*, 1957, **79**, 2629.

[75] Bunnett and Davis, *ibid.*, 1954, **76**, 3011 and unpublished results.

[76] Bevan and Hirst, *J.*, 1956, 254.

[77] Ref. 2, p. 357, and ref. 21.

[78] Bunnett, *J. Amer. Chem. Soc.*, 1957, **79**, 5969.

atom. The proportions of attack at the two positions vary with the reagent employed, from 83% attack on sulphur by MeO^- to 100% attack on carbon by PhS^-; reagents of higher polarisability prefer to attack carbon, suggesting that the vicinity of the 1-position has higher effective polarisability than that of the sulphur atom.[79]

Basic reagents may interact with alcohols to form alkoxide ions, and therefore alcoholysis is a possible side-reaction whenever substitution is conducted in an alcoholic solvent. This complication is often insignificant [33] but is occasionally a minor [21] and sometimes a major side-reaction. The reaction of *p*-fluoronitrobenzene with sodium phenoxide in methanol gives 99% of *p*-nitroanisole and only 1% of 4-nitrodiphenyl ether.[80]

In series of reagents of similar type, such as series of substituted anilines,[81] pyridines,[81] or phenoxides,[82] reactivity is closely correlated with basicity; good Hammett plots [42] are obtained. Reactivity in a set of polynuclear aromatic amines has been successfully related to charge densities calculated quantum-mechanically.[83]

Medium Effects.—The reaction of methoxide ion with 1-chloro-2 : 4-dinitrobenzene is accelerated somewhat by change from methanol to methanol–methyl acetate or methanol–benzene solvent,[84] in accord with prediction of the Hughes–Ingold theory of solvent action.[4] However, the rate also increases somewhat on change to 80% methanol : 20% water solvent.[85] As predicted, reactions of amines with neutral substrates tend to go faster in more polar solvents [49] although sometimes the change is very small.[86]

With 1-chloro-2 : 4-dinitrobenzene in methanol, the order of reactivity, KOMe > NaOMe > LiOMe, has been observed.[87] Addition of potassium salts to LiOMe or NaOMe reactions increases the rate as much as 48% and addition of lithium salts to NaOMe or KOMe reactions diminishes the rate somewhat. With the cations held constant, rates depend on the anions of added salts: rates are highest with acetates and lowest with perchlorates. Ion-pairing phenomena underlie these interesting effects.[87] The results are consistent with the assumptions that free methoxide ion is a more effective reagent than any methoxide–metal ion pair and that the orders of ion-pairing tendency are $Li^+ > Na^+ > K^+$ for cations and $OAc^- > ClO_4^-$ for anions. In methanol–benzene solution similar effects occur but in magnified form.[84b]

The kinetics of reaction of Ph_2I^+ with PhO^- to form Ph_2O and PhI indicate the ion pair to be an intermediate.[12] Rates of reactions of MeO^-

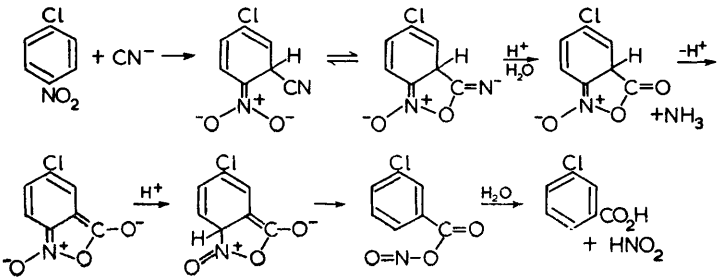
[79] Bunnett and Bassett, unpublished results.
[80] England, *Chem. and Ind.*, 1954, 1145.
[81] Singh and Peacock, *J. Phys. Chem.*, 1936, **40**, 669; ref. 33 and earlier papers.
[82] Leahy, Liveris, Miller, and Parker, *Austral. J. Chem.*, 1956, **9**, 382.
[83] Sixma, *Rec. Trav. chim.*, 1955, **74**, 168.
[84] (*a*) Briner and Miller, *J.*, 1954, 4682; (*b*) Reinheimer and Cochran, personal communication.
[85] Bevan and Bye, *J.*, 1956, 469.
[86] Bunnett and Morath, *J. Amer. Chem. Soc.*, 1955, **77**, 5165.
[87] Reinheimer, Kieffer, Frey, Cochran, and Barr, *ibid.*, 1958, **80**, 164.

with p-$O_2N{\cdot}C_6H_4{\cdot}NMe_3^+$ and with p-$O_2N{\cdot}C_6H_4{\cdot}SMe_2^+$ vary with ionic strength as expected for an anion–cation reaction.[72]

Cine-substitutions

This is a category of reactions in which the entering group takes a position other than that vacated by the leaving group. As discussed on p. 7, several such reactions occur *via* benzyne intermediates. At least one other mechanism has been demonstrated, and a number of cases await thorough study.[88]

The von Richter reaction is exemplified by the conversion, through the action of potassium cyanide in aqueous ethanol, of p-chloronitrobenzene into m-chlorobenzoic acid. The entering $-CO_2H$ group specifically takes a position *ortho* to $-NO_2$, not *para*, not the position vacated by $-NO_2$. A proton from the solvent becomes attached to carbon. Most remarkably, the nitrile and amide corresponding to the eventual acid product are *not* intermediates; thus, α-naphthonitrile and α-naphthamide are not isolable from the reaction of β-nitronaphthalene with potassium cyanide to form α-naphthoic acid although the nitrile and the amide resist hydrolysis under the conditions used. The following mechanism[89] is consistent with the facts:



Several cases of cine-substitution have been observed in tropone derivatives; it has been suggested that the elimination–addition mechanism may go more readily in a 7-membered ring because of less strain in the formation of " acetylenic " intermediates.[90]

The Hauser rearrangement

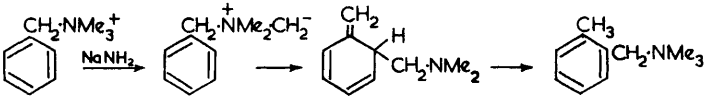
Benzyltrimethylammonium ion (IX), on treatment with sodamide in liquid ammonia, is converted into the tertiary amine (XII).[91] Hauser and his co-workers have provided evidence that intermediate (X), formed by removal of a proton from a methyl group, mounts an intramolecular nucleophilic attack at an *ortho*-position to form (XI) which quickly gives (XII); (XII) can be quaternised and the rearrangement repeated, etc., until all the ring

[88] Brower and Amstutz, *J. Org. Chem.*, 1954, **19**, 411; Bradley and Waller, *J.*, 1953, 3783; ref. 2, p. 382.

[89] Bunnett and Rauhut, *J. Org. Chem.*, 1956, **21**, 944 and earlier papers.

[90] Johns, Johnson, and Tisler, *J.*, 1954, 4604.

[91] (*a*) Hauser *et al.*, *J. Amer. Chem. Soc.*, 1951, **73**, 4122; (*b*) 1953, **75**, 2660; (*c*) 1956, **78**, 5698.



(IX) (X) (XI) (XII)

positions are filled. If both *ortho*-positions are blocked, an analogue of (XI) can be isolated.[91c] Benzyl methyl sulphide undergoes a similar rearrangement.[91b]

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