Mechanisms for Nucleophilic and Photonucleophilic Aromatic Substitution Reactions

By Francesco Pietra
DEPARTMENT OF CHEMISTRY, UNIVERSITY OF PISA, PISA, ITALY

Nucleophilic aromatic substitutions are those processes in which a charged or neutral nucleophilic species replaces an atom or group from a ring position of an aromatic compound (substrate). Usually such an atom or group is displaced with its bonding electrons although cases have been also suggested in which such bonding electrons are left on the aromatic ring.[1, 2]

A wide variety of substrate–nucleophile couples which are able to lead to substitution is known. In general, reaction with weakly basic nucleophiles only occurs if strongly electron-attracting groups are present at the *ortho* or *para* position with respect to the group to be displaced. With very strong bases, however, even substrates without such activating groups but possessing only a displaceable group with anionic stability undergo nucleophilic substitution as well.

A short review by Bunnett appeared in 1958[3] summarising the achievements of *ca.* 15 yrs. research on the mechanisms of nucleophilic aromatic substitutions. Three main mechanisms were clearly recognised at that time: the elimination–addition (benzyne), the addition–elimination, and the unimolecular mechanism. Since then the basic ideas about the first two mechanisms are mostly unchanged, even though important mechanistic details have recently been reported. However, ideas about the unimolecular mechanism have changed drastically.

In the last decade new mechanisms have been disclosed; these, like the elimination–addition mechanism, may lead to rearranged products. These substitutions accompanied by rearrangement are discussed in a separate section.

A further important achievement in recent studies is the discovery of photonucleophilic aromatic substitution reactions. The outstanding feature of these reactions is that the course of the reaction is often drastically altered relative to the corresponding thermal reactions. A section of this Review is devoted to these photochemical reactions whose mechanism is still uncertain.

1 The Unimolecular Mechanism

The aromatic counterpart of the aliphatic limiting S_N1 mechanism, *i.e.* slow ionisation of the aromatic substrate, ArX, into X^- and an aromatic cation, Ar^+, which is rapidly captured by the nucleophiles to give reaction products, has rarely been suggested. Most such proposals are confined to the thermal decomposition of diazonium cations in aqueous non-basic solutions and are

---

[1] J. D. Loudon and D. M. Smith, *J. Chem. Soc.*, 1964, 2806.

[2] R. L. Letsinger, O. B. Ramsay, and J. H. McCain, *J. Amer. Chem. Soc.*, 1965, **87**, 2945.

[3] J. F. Bunnett, *Quart. Rev.*, 1958, **12**, 1.

based on the evidence that the hydrolyses are (*a*) kinetically first-order and (*b*) insensitive to added salts.[4] The hypothesis of the aryl cation intermediate is also able to accommodate both the observed effects of substituents on the reaction rate in terms of consideration of inductive and mesomeric effects on both the initial and the transition state,[4] and the low selectivity of the diazonium salts toward the nucleophiles available in the reaction medium in terms of the expected high energy of aryl cations.[4]

However, conditions (*a*) and (*b*) do not always obtain. Thus, for example, the first-order rate coefficient for the reaction of *p*-nitrobenzene diazonium ion in acidic aqueous sodium bromide increases linearly with bromide ion concentration.[5] At least three mechanisms are consistent with such an observation. The first includes two parallel steps, one unimolecular and the other bimolecular.[6] However, results of experiments on the influence of hydrostatic pressure on the reaction rate are inconsistent with the presence of a bimolecular path.[7]

In another mechanism the first (reversible) step, $ArN_2^+ \rightleftharpoons ArN_2^{+*}$, gives a species, ArN_2^{+*}, which, when not attacked by the nucleophiles to afford reaction products, is able to revert to reagents.[6] Although the mode of partitioning of the intermediate ArN_2^{+*} would clearly accommodate the observed rate law, no acceptable structure can be suggested for ArN_2^{+*} to account for the very small extent of the rearrangement $Ar^{15}N^+{\equiv}N \longrightarrow ArN^+{\equiv}{}^{15}N$ observed.[6]

A third mechanism, kinetically equivalent to the last one, has been preferred.[6] This involves irreversible displacement of nitrogen from the substrate by water or by another nucleophile, B^-, (equations 1 and 2) and rearrangement (equation 3). To account for the peculiar features of these reactions, the

$$Ar^{15}N^+{\equiv}N + H_2O \longrightarrow ArOH \tag{1}$$
$$Ar^{15}N^+{\equiv}N + B^- \longrightarrow ArB \tag{2}$$
$$Ar^{15}N^+{\equiv}N \longrightarrow ArN^+{\equiv}{}^{15}N \tag{3}$$

transition states for steps (1) and (2) are visualised as very close to those expected for nucleophilic attack on an aromatic cation,[6] as distinct from the Meisenheimer-like transition state suggested for reactions occurring by the addition–elimination mechanism.

Less detailed studies are available for other reactions and therefore the conclusions reached are even less reliable.

2 The Addition–Elimination Mechanism

These are the most common nucleophilic aromatic substitutions, *i.e.* those in which the entering group directly replaces the group expelled; higher rates are generally obtained by either changing to a stronger nucleophile or to a substrate with a stronger electron-attracting group, or both.

---

[4] S. D. Ross, *Progr. Phys. Org. Chem.*, 1963, **1**, 31.

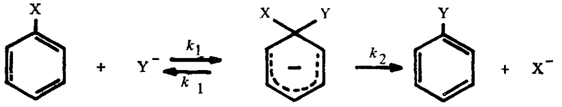
[5] E. S. Lewis and W. H. Hinds, *J. Amer. Chem. Soc.*, 1952, **74**, 304.

[6] E. S. Lewis, L. D. Hartung, and B. M. McKay, *J. Amer. Chem. Soc.*, 1969, **91**, 419.

[7] K. R. Brower, *J. Amer. Chem. Soc.*, 1960, **82**, 4535.

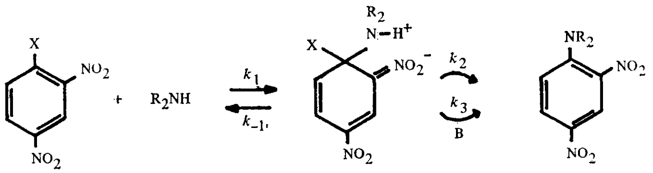
The main mechanistic question is whether these reactions are to be visualised as one-step or as multi-step processes. The present position is that while certain observations require a multi-step mechanism and all other observations can be satisfactorily rationalised in terms of such a mechanism, there is no single finding whose rationalisation requires a one-step mechanism.

A. The Multi-step Nature of the Reaction.—The addition–elimination mechanism of equation (4) is widely accepted for these processes on the basis of much evidence which can be summarised along three main lines. The first, and strongest, is the occurrence and form of base catalysis which has been observed for some of these reactions by primary or secondary amines. In this case a proton must be transferred to a base at some stage and equation (4) may be rewritten as equation (5) for the case of a 2,4-dinitro substrate and a secondary amine. If the steady-state treatment applies, the mechanism of equation (5) gives the rate equation (6) where k is the second-order rate coefficient (Rate/[substrate][R_2NH]). Equation (6) predicts that when the magnitude of $k_2 + k_3$ [B] becomes comparable with that of k_{-1}, a less than linear dependence of k on base concentration should be observed. In other words it is predicted that the rate-limiting step changes from rate-limiting decomposition of the intermediate (Ib) into products at low catalyst concentration to rate-limiting formation of the intermediate (Ib) at high catalyst concentration. The fact that such a prediction has been verified for several such reactions, and that more trivial causes like nucleophile or catalyst extraction by complexing of the substrate or removal of the catalyst by complexing with the nucleophile have



(4)

(Ia)



(5)

(Ib)

$$k = (k_1k_2 + k_1k_3[B]) / (k_{-1} + k_2 + k_3[B]) \qquad (6)$$

been ruled out, is considered as unequivocal proof for the multi-step nature of the reactions.[8]

Equation (6) predicts also that under appropriate circumstances the reaction rate should either (*a*) be insensitive to base catalysis (when $k_2 \gg k_{-1}$) or (*b*) increase linearly with base concentration (when $k_{-1} \gg k_2 + k_3$ [B]). Case (*a*) occurs when a change is made to a better leaving group.[8] The same is also brought about by a mere change of solvent as observed from the reaction of fluoro-2,4-dinitrobenzene with n-butylamine which is base-catalysed in benzene[8c] but not in the much more polar mixture of 60% dioxan–40% water.[9] This can be understood because the value of k_{-1} should be reduced in changing to a more polar solvent since this process leads to a charge neutralisation. In contrast, the first stage of the forward reaction (k_2) probably leads to proton loss to the solvent and thus to further charge separation. This process should be facilitated in a more polar and more basic solvent. Case (*b*) occurs when the opposite change, to a poorer leaving group[8, 10] or to a less nucleophilic amine,[8] is made although some anomalies are also known.[11]

It is also clear that as the nucleophile is a base itself some of these reactions are more than first-order in reacting amine.[8] Therefore, second-order overall kinetics are not general for these reactions and so the terminology addition–elimination mechanism is preferable to that of bimolecular mechanism which was also frequently used.

At this point a warning is pertinent against interpreting slight accelerations by a variety of substances as base catalysis. The accelerations include those observed with amines. This interpretation has been criticised by Bunnett[9] mainly on the ground that change to a stronger base failed to bring about a more efficient catalysis.

According to the addition–elimination mechanism it is conceivable that reactions of a given nucleophile with various substrates differing only in the nature of the leaving group may display much the same rates. This is expected when decomposition of the intermediates (I) greatly favours products rather than reagents and the rate coefficients for the formation of the intermediate, k_1, are not much different from one reaction to the other. The fact that this has been observed for several cases, often referred to as the lack of an element effect,[12] constitutes the second line of evidence in favour of the addition–elimination mechanism. Of course, when decomposition of the intermediate (I) is rate-limiting, differences in C—X bond energy, X polarisability, X^- solvation requirements *etc.*, may result in a large spread of rates for different substrates

---

[8] (*a*) J. F. Bunnett and R. H. Garst, *J. Amer. Chem. Soc.*, 1965, **87**, 3879; (*b*) A. J. Kirby and W. P. Jenks, *ibid.*, 1965, **87**, 3217; (*c*) F. Pietra, *Chimica e Industria*, 1965, **47**, 890; F. Pietra and D. Vitali, *J. Chem. Soc.* (*B*), 1968, 1200; (*d*) C. F. Bernasconi and H. Zollinger, *Helv. Chim. Acta*, 1967, **50**, 3; (*e*) C. F. Bernasconi, *J. Org. Chem.*, 1967, **32**, 2947; (*f*) C. F. Bernasconi and P. Schmid, *ibid.*, 1967, **32**, 2953.

[9] J. F. Bunnett and R. H. Garst, *J. Amer. Chem. Soc.*, 1965, **87**, 3875.

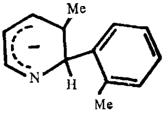
[10] J. F. Bunnett and C. Bernasconi, *J. Amer. Chem. Soc.*, 1965, **87**, 5209.

[11] E. Buncel, A. R. Morris, and K. E. Russell, *Quart. Rev.*, 1968, **22**, 123.

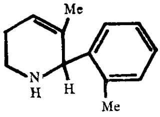
[12] J. F. Bunnett, E. W. Garbish jun., and K. M. Pruitt, *J. Amer. Chem. Soc.* 1957, **79**, 385.

differing in the nature of the leaving group.[13] However, the important point here is that a one-step mechanism in which C—X bond-breaking is more or less concerted with C—Y bond formation would require the presence of such an element effect[12] in every case, contrary to what has been observed. In this connection even more stringent evidence for the addition–elimination mechanism is provided again by a reaction of the type shown in equation (5). Thus, it has been found that in the reaction of 2,4-dinitrophenyl phenyl ether with piperidine the mere substitution of the ethereal ^{18}O for ^{16}O retards the reaction at low amine concentrations.[14] This isotope effect diminishes however at higher amine concentrations in full agreement with predictions from equation (6).[14]

The third important line of evidence for the addition–elimination mechanism concerns the direct observation of addition compounds of structure (Ia) often referred to as Meisenheimer complexes. Under particular circumstances, such as efficient delocalisation of the negative charge and high carbon basicity of both the leaving group and the nucleophile, stability is sufficient to allow isolation and structural investigation, even by diffraction methods,[15] of such complexes while other less stable complexes of this type have been identified and studied by means of their spectra in solution. There is now no doubt that these complexes are correctly represented by covalent structures such as (Ia).[11] Two lines of study are particularly relevant to the problem of the mechanism of nucleophilic aromatic substitution. The first concerns studies directed to prove that complexes of structure (Ia) really lie along the reaction path and are not simply found in side equilibria. One such study concerns the symmetrical exchange reaction of 2,4,6-trinitroanisole or of 2,4-dinitroanisole ([^{14}C]methyl) with sodium methoxide which is best described as proceeding through the corresponding Meisenheimer-type complexes, whose formation is fast for the trinitro-case but rate-limiting for the dinitro-case.[16a] Rate of formation and decomposition of 2,4-dinitrobenzene-1,1-dimethoxy sodium salt has also been directly followed by the temperature jump method.[16b] In the displacement of hydride from 3-methylpyridine by 2-tolyl-lithium there is evidence for the existence of the complex (II) along the reaction path as formation of (III) competes with formation of the products of hydride substitution and more



(II)



(III)

---

[13] F. Pietra and F. Del Cima, *Tetrahedron Letters*, 1967, 4573.

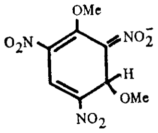
[14] C. R. Hart and A. N. Bourns, *Tetrahedron Letters*, 1966, 2995.

[15] (*a*) H. Ueda, N. Sakabe, J. Tanaka, and A. Furusaki, *Nature*, 1967, **215**, 956; (*b*) R. Destro, C. M. Gramaccioli, and M. Simonetta, *Acta Cryst.*, 1968, **B24**, 1369; G. C. Messmer and G. J. Palenik, *Chem. Comm.*, 1969, 470.

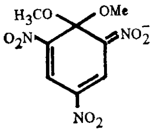
[16] (*a*) J. H. Fendler, *J. Amer. Chem. Soc.*, 1966, **88**, 1237; (*b*) C. F. Bernasconi, *ibid.*, 1968, **90**, 4982.

efficiently so in the presence of oxygen.[17a] It is thus believed that the only reasonable way to conceive formation of (III) is by disproportionation of (II).[17a] Structures like (II) are supported by ^{1}H n.m.r. spectra.[17b] On the other hand, more recent evidence[18] in support of the existence of intermediates of type (Ia) along the reaction path of aromatic nucleophilic substitution is questionable. The experimental evidence presented[18] seems in fact inadequate for the structural assignment.

The second line of studies concerns the interesting observation that (IV) and (V) are the kinetic and the thermodynamic products respectively of the interaction of methoxide with methyl picrate.[19] The structural assignments[19] were based on ^{1}H n.m.r. spectra for both products and correct a previous u.v. assignment[20] of charge-transfer structure for the kinetic product (IV). However, the idea[21] that the relative rates of formation of (IV) and (V) are governed mainly by steric compression in the transition states leading to such species is not substantiated by subsequent research.[22]



(IV)



(V)

B. The Nature of the Transition State.—Various efforts have been made to elucidate the transition-state structure for reactions in which formation of the addition intermediate is rate-determining. Thus, the finding that the Hammett ρ-values for the reactions of a series of substituted phenoxides with chloro-2,4-dinitrobenzene or the much slower 1,4-dichloro-2-nitrobenzene are comparable with those for protonation of phenoxides, where a full bond is formed, was taken as an indication that the rate-limiting transition state lies very near the addition intermediate along the reaction co-ordinate.[23] This conclusion is rendered uncertain by the likelihood that the two sets of reactions compared, protonation and aromatic substitution, may display a different sensitivity of ρ-values to temperature.[24]

---

[17] (*a*) R. A. Abramovitch and G. A. Poulton, *Chem. Comm.*, 1967, 274; (*b*) G. Fraenkel and J. C. Cooper, *Tetrahedron Letters*, 1968, 1825.

[18] P. Baudet, *Helv. Chim. Acta*, 1966, **49**, 545; R. Garboriaud and R. Schaal, *Compt. rend.*, 1967, **265**, *C*, 1376.

[19] K. L. Servis, *J. Amer. Chem. Soc.*, 1965, **87**, 5495; *ibid.*, 1967, **89**, 1508.

[20] J. B. Ainscough and E. F. Caldin, *J. Chem. Soc.*, 1956, 2528, 2540, 2546.

[21] M. R. Crampton and V. Gold, *J. Chem. Soc.* (*B*), 1966, 893.

[22] E. J. Fendler, C. E. Griffin, and J. H. Fendler, *Tetrahedron Letters*, 1968, 5631.

[23] J. R. Knowles, R. O. C. Norman, and J. H. Prosser, *Proc. Chem. Soc.*, 1961, 341.

[24] J. F. Bunnett, *Ann. Rev. Phys. Chem.*, 1963, **14**, 271.

The influence of hydrostatic pressure on reaction rates was also investigated. Brower studied the reaction of 2-chloroquinoline with piperidine and took care to separate the effects on the activation volumes due to differences in molecular dimensions between transition state and reactants from those due to degree of solvation.[25] The results indicate that the transition state lies about half-way between reagents and addition intermediate.[25] Other studies of this kind were also reported [25, 26] although inability to accomplish the above separation of effects renders the interpretation uncertain. Subject to these reservations, there is a tendency to interpret the results[25, 26] on the basis that the faster the reaction, the nearer lies the transition state to the reactants along the reaction co-ordinate, in accordance with the Ogg–Polanyi–Hammond postulate.[27]

A rather clear picture of the transition state for reactions of this class is afforded by another study. Thus, the reactivities of three amines of different steric bulk like piperidine, 2-methylpiperidine, and *trans*-2,6-dimethylpiperidine toward a series of substrates like fluoro-2- or fluoro-4-nitrobenzene and fluoro- or chloro-2,4-dinitrobenzene were examined in dimethyl sulphoxide where decomposition of the addition intermediate into products is fast.[28] The amine reactivity ratios are very large and independent of the substrate employed (*ca.* 1, 10^{-3}, and 10^{-5} for the three amines above, respectively), and the *ortho–para* activation ratio by the nitro group is *ca.* unity for all amines.[28] Consequently, steric inhibition of resonance of the *o*-nitro-group in the transition state is unimportant and the large drop in rate observed on changing amine must be attributed mainly to increased repulsive interactions between the nucleophile and the benzene ring carbons and hydrogens in the transition state.[28] The only reasonable way to rationalise this result is to assume a tetrahedral geometry around the reaction centre for the transition state, which must therefore be very close to the addition intermediate.[28] These results, together with closely related ones for reactions of anionic nucleophiles,[29] show also that the widespread belief that the *o*-nitro-group frequently undergoes steric inhibition of resonance in the transition state of aromatic nucleophilic substitution is not warranted.

A different model, analogous to Mulliken's pseudo-atom model for electrophilic aromatic substitution,[30] which does not involve rehybridisation at the reaction centre, has been suggested on the basis of Hückel MO calculations.[31] At the time of writing, however, the suggestion by the authors[31] that such a model of the transition state allows an acceptable one step mechanism for aromatic nucleophilic substitution is not supported by convincing experimental evidence.

These problems have been considered also for reactions where decomposition

---

[25] K. R. Brower, *J. Amer. Chem. Soc.*, 1963, **85**, 1401, and previous papers.

[26] J. Murto and M. Kiuttu, *Suomen Kem.*, 1966, **B39**, 14.

[27] R. A. Ogg jun., and M. Polanyi, *Trans. Faraday Soc.*, 1935, **31**, 1375; G. S. Hammond, *J. Amer. Chem. Soc.*, 1955, **77**, 334.

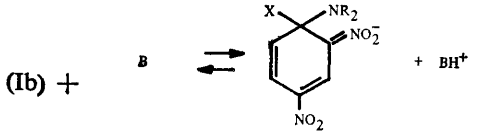
[28] F. Pietra and F. Del Cima, *J. Org. Chem.*, 1968, **33**, 1411.

[29] F. Pietra and F. Del Cima, *Chem. Comm.*, 1968, 216.

[30] N. Muller, L. W. Pickett, and R. S. Mulliken, *J. Amer. Chem. Soc.*, 1954, **76**, 4770.

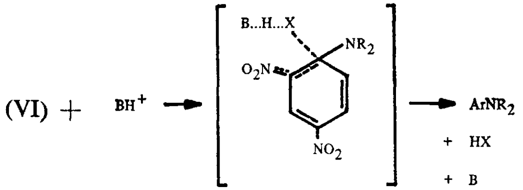
[31] P. Beltrame, P. L. Beltrame, and M. Simonetta, *Tetrahedron*, 1968, **24**, 3043, and preceding papers.

of the addition intermediate into products is rate-limiting. Thus, reversible transformation of (Ib) into its conjugate base (VI) (equation (7)) followed by general acid-catalysed loss of the leaving group (equation (8)) explains the kinetics observed for such reactions in protic solvents.[8a,b] When these reactions are carried out in non-polar non-protic solvents loss of the ammonium proton



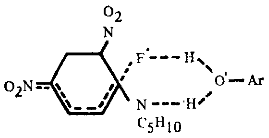
(VI)

(7)



(8)

and of the leaving group tends to occur simultaneously in order to avoid charge creation. This is shown by structure (VII) which depicts the proposed transition state for the phenol-catalysed reaction of fluoro-2,4-dinitrobenzene with piperidine in benzene.[32] This structure is indicated by the fact that the catalytic coefficients of free phenols are independent of their acid strength and typical bifunctional catalysts, like 2-pyridone, are extremely efficient.[32] In such solvents the *o*-nitro-group is also able to catalyse the removal of the ammonium proton from (Ib).[13] Such peculiar kinetic features are not manifested in protic solvents



(VII)

either because the formation of the intermediate is then rate-determining or because the protic solvent is able to catalyse the removal of the ammonium

---

[32] F. Pietra and D. Vitali, *J. Chem. Soc.* (*B*), 1968, 1318.

proton and fluoride ion from (Ib). This has to be accounted for when establishing leaving-group mobility orders.[13]

Some other related points of great mechanistic interest are much less understood *e.g.* the question of whether substitution of the *N*-deuteriated amine for the protic analogue as a nucleophile involves a primary isotope effect. The present position is that while, as expected, no primary isotope effect has been found for displacements of good leaving groups, displacement of very poor leaving groups, such as alkoxides, has thus far displayed small effects which might be primary ones.[14, 33, 34]

The problem of the position of the rate-limiting transition state along the reaction co-ordinate has also been approached on the basis of the addition–elimination mechanism through semiempirical calculations.[35] A number of experimental facts were thus consistently rationalised in terms of the shift of mechanism from fast to slow decomposition of the addition intermediate into products.[35] Among the facts correlated was the remarkable stability which allowed isolation of Meisenheimer adducts from picryl ethers;[35] the dependence of the $k_{\mathrm{ArF}}/k_{\mathrm{ArI}}$ reactivity ratios on the nature of the nucleophile;[36a] and the dependence of the nucleophilicity orders on the substrate nature.[35] In some cases, however, such predictions are not supported by experiments. Thus, Miller's calculations predict a very high $k_{\mathrm{ArF}}/k_{\mathrm{ArI}}$ rate ratio for the reactions of either methoxide or thiomethoxide with 1-X-4-nitrobenzenes.[35] While it was claimed that such prediction[35] was supported by experiments,[36b] a recent reinvestigation of the same reactions above shows[36c] that the $k_{\mathrm{ArF}}/k_{\mathrm{ArI}}$ rate ratio is much higher for methoxide than for thiomethoxide. This is in agreement with expectations from the principle of hard and soft acids and bases[37] as applied by Pearson[38] to the kinetics of nucleophilic substitutions. According to this principle,[37,38] in fact, transition states with several soft or several hard ligands on the attacked carbon should be more stable than transition states with a mixture of soft and hard ligands.[39]

3 Nucleophilic Aromatic Substitution with Rearrangement

Both acid- and base-induced title rearrangements are known and have been discussed recently in two monographs.[40, 41] Therefore, we have chosen to concentrate our attention on some recent aspects of these reactions which have great relevance to the problem of the competition among the various mechanisms available for nucleophilic aromatic substitution.

---

[33] F. Pietra, D. Vitali, and S. Frediani, *J. Chem. Soc.* (*B*), 1968, 1595.

[34] I. Giardi, G. Illuminati, and G. Sleiter, *Tetrahedron Letters*, 1968, 5505.

[35] J. Miller 'Aromatic Nucleophilic Substitution,' Elsevier, Amsterdam, 1968.

[36] (*a*) K. B. Lam and J. Miller, *Chem. Comm.*, 1966, 642. (*b*) J. Miller and K. W. Wong, *J. Chem. Soc.*, 1965, 5454; (*c*) L. Di Nunno and P. E. Todesco, *Tetrahedron Letters*, 1967, 2899.

[37] S. Ahrland, J. Chatt, and N. R. Davies, *Quart. Rev.*, 1958, **12**, 265; R. G. Pearson *J. Amer.*, *Chem. Soc.*, 1963, **85**, 3533.

[38] R. G. Pearson and J. Songstad, *J. Amer. Chem. Soc.*, 1967, **89**, 1827.

[39] K. C. Ho, J. Miller, and K. W. Wong, *J. Chem. Soc.* (*B*), 1966, 310.

[40] R. W. Hoffman, 'Dehydrobenzene and Cycloalkynes,' Academic Press, New York, 1967.

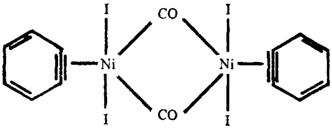
[41] H. J. Shine, 'Aromatic Rearrangements,' Elsevier, Amsterdam, 1967.

A. Base-promoted Rearrangements.—(i) *Cine-substitutions.* This term is used for those reactions in which the entering group occupies an *ortho*-position with respect to that vacated by the leaving group.[42] By far the best known such reactions are those proceeding through aryne intermediates as in the formation of equal amounts, after allowance for small isotope effects, of [1 — ^{14}C]aniline and [2 — ^{14}C]aniline from [1 — ^{14}C]chlorobenzene and potassamide in liquid ammonia.[43] This requires a symmetrical intermediate whose structure has been represented as dehydrobenzene (VIII) where the asterisk indicates the label.[43] Nucleophilic attack by amide at the triple bonded carbon of dehydrobenzene with subsequent protonation of the resulting carbanion will give the two 'isomeric' anilines.

(VIII)

Dehydrobenzene and similar aryne intermediates (usually called hetarynes when formed from heterocycles) may be generated in other ways such as metallation,[40] metal–halogen exchange,[40] or even under non-basic conditions as in the thermal decomposition of anthranilic acid.[40] The latter conditions are most favourable for attack on the aryne by a variety of materials in Diels–Alder type cyclisations.[40] Arynes from polyhalogenoarometics are particularly reactive in the latter type of reaction.[44]

The real nature of aryne intermediates, as distinct from transition states, is reasonably certain as arynes are able to discriminate among the reagents to be added. Moreover, arynes have been observed in flash-photolysis experiments and in mass spectrometry,[40] and recently dehydrobenzene has been trapped as a stable complex whose probable structure is (IX) from the reaction of *o*-di-iodobenzene with tetracarbonylnickel in pentane at 70°.[45] In this complex the C(6) groups retain their aromatic character as evidenced by ^{1}H n.m.r. measurements.[45] MO Calculations have been used to assign a structure with a triple bond, as in (VIII), to benzyne.[46]



(IX)

---

[42] J. F. Bunnett and R. E. Zahler, *Chem. Rev.*, 1951, **49**, 273.

[43] J. D. Roberts, H. E. Simmons jun., L. A. Carlsmith, and C. W. Vaughan, *J. Amer. Chem. Soc.*, 1953, **75**, 3290.

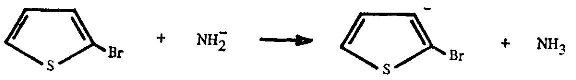
[44] See, for example, J. D. Cook, B. J. Wakefield, H. Heaney, and J. M. Jablonski, *J. Chem. Soc.* (*C*), 1968, 2727.

[45] E. W. Gowling, S. F. A. Kettle, and G. M. Sharples, *Chem. Comm.*, 1968, 21.

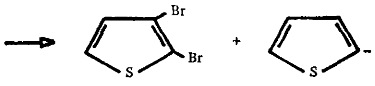
[46] C. A. Coulson, *Chem. Soc. Special Publ.*, No. 12, p. 85; H. E. Simmons, *J. Amer. Chem. Soc.*, 1961, **83**, 1657, and unpublished results cited in ref. 40, p. 267; T. Yonezawa, H. Konishi, and H. Kato, *Bull. Chem. Soc. Japan*, 1968, **41**, 1031.

Cine-substitutions not proceeding *via* arynes are also known. Such is the case of the von Richter rearrangement as exemplified by the transformation of *p*-chloronitrobenzene into *m*-chlorobenzoic acid in aqueous–alcoholic alkali metal cyanide solution. The mechanism of these rearrangements, whose starting step is cyanide attack at a nuclear position *ortho* to the nitro group, is well understood.[41] When dimethyl sulphoxide is used as a solvent a different reaction course is observed. Thus, *p*-chloronitrobenzene affords three disubstituted diphenylamines, 3-cyano-4-nitrophenol and 2,6-dicyano-4-chlorophenol.[47]

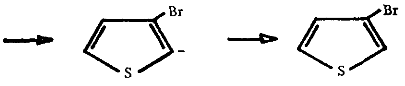
Another example is the reaction of 2-bromothiophene (X) with sodamide in liquid ammonia to give 3-aminothiophene (XVII) together with a small amount of 3-bromothiophene (XV).[48] Although such conditions are typical for aryne production, an aryne mechanism is ruled out by the observation that addition of potassium halides to the reagents does not alter the product distribution.[48] Moreover, under the above amination conditions, (*a*) 2-aminothiophene does not isomerise to its 3-isomer, and (*b*) 3-bromothiophene is aminated *ca.* 200 times more slowly than 2-bromothiophene. Observation (*a*) excludes a mechanism of direct displacement of 2-bromine by amide followed by isomerisation of 2- to 3-aminothiophene, while observation (*b*) refutes a mechanism of isomerisation of 2- to 3-bromothiophene followed by direct displacement of bromine by amide from 3-bromothiophene. A reasonable mechanism to account for all these facts is presented in equations (9)—(13) where isomers or compounds containing additional bromine atoms are equally probable for the intermediates marked with an asterisk.[48]



(X) (XI*) (9)

(XI*) + (X) 

(XII*) (XIII*) (10)

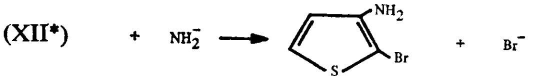
(XII*) + (XIII*) 

(XIV*) (XV) (11)

---

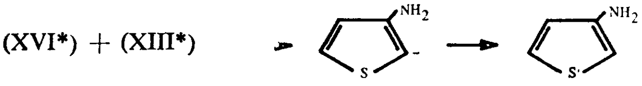
[47] G. T. Rogers and T. L. V. Ulbricht, *Tetrahedron Letters*, 1968, 1029.

[48] M. G. Reinecke and H. W. Adickes, *J. Amer. Chem. Soc.*, 1968, **90**, 511.



(XVI*)

(12)

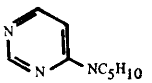


(XVII)

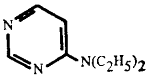
(13)

This mechanism involves proton abstraction from 2-bromothiophene [equation (9)] followed by a series of transbromination processes [equations (10), (11) and (13)] and a direct nucleophilic substitution at the ring carbon [equation (12)]. Polybromothiophenes have indeed been isolated from such reaction mixtures and they are quantitatively and rapidly transformed into 3-aminothiophene under the amination conditions.[48] Moreover, transhalogenations of this kind are involved in such processes as the isomerisation of 1,2,4- to 1,3,5-tribromobenzene in liquid ammonia in the presence of potassium anilide.[49]

It has also been shown that the hetaryne mechanism is unable to account for all of the cine-substitution products (XVIII) and (XIX) which are formed together with 5-dimethylamino- and (probably also) 5-piperidino-pyrimidine in the reaction of 5-chloro- or 5-bromo pyrimidine in a piperidine–diethylamine mixture in the absence of solvent.[50] The fact that addition of ethanol, a good protonating agent for carbanion precursors of arynes, inhibits the reactions of the bromo-, whereas it has no influence on those of the chloro-compound, suggests that a new mechanism is needed only for the reactions of the chloro-compound.[50] This is also suggested by the observation (which, however, should be substantiated by more experiments, as is apparent from examination of the Figure on p. 1182 of ref. 50) that the product molar ratio (XVIII) : (XIX) increases linearly for the bromo-compound and less than linearly for the chloro-compound with increase in the piperidine : diethylamine molar ratio.[50] This is inferred on the basis of the common finding in similar competition studies that such linear trends are observed only when a single mechanism is involved.[50] It is suggested that this new mechanism involves amine addition



(XVIII)



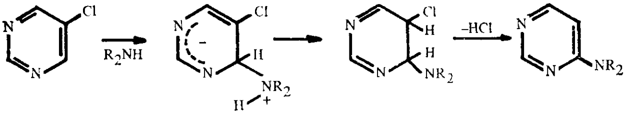
(XIX)

---

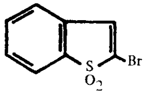
[49] J. F. Bunnett and D. J. McLennan, *J. Amer. Chem. Soc.*, 1968, **90**, 2190; J. F. Bunnett and G. Scorrano, Abstracts of Papers, Amer. Chem. Soc., 156th meeting, Sept., 1968, ORGN 105.

[50] T. Kauffmann, R. Nürnberg, and K. Udluft, *Chem. Ber.*, 1969, **102**, 1177.

at a nuclear position *ortho* to that occupied by the leaving group, followed by proton migration and elimination of hydrogen chloride (Scheme 1).[50] This mechanism has been termed anomalous addition–elimination mechanism[50] and was suggested years ago to account for the cine-substitution by piperidine on compound (XX) in ethanol.[51]



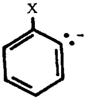
Scheme 1



(XX)

A number of the general factors which favour the above mechanisms in relation to the addition–elimination mechanism have been recognised. One such concerns the basicity of the attacking nucleophile. A nucleophile such as potassamide for which the basicity (towards hydrogen) is more marked than the nucleophilicity (towards carbon) favours the aryne mechanism. It seems also that the greater the steric bulk of the attacking base the less favoured is the addition–elimination mechanism while the less steric demanding aryne mechanism comes into play. This is borne out by the observed increasing proportion of substitution *via* hetaryne compared with that *via* direct displacement on 4-chloro- or 4-bromo-pyridine on changing from Li-piperidide to Li-diethylamide to Li-di-isopropylamide.[52]

Another factor is the nature of the leaving group. Thus, the fact that fluorobenzene only exchanges the *ortho*-hydrogens in KNH_2–liq.NH_3 whereas the other monohalobenzenes give aniline under these conditions is attributed to the slower heterolysis of the carbon–fluorine bond relative to the other carbon–halogen bonds in carbanions of structure (XXI); with $X = F$, the carbanion therefore undergoes preferential reprotonation.[40] We believe that a similar interpretation in terms of the poor leaving group ability of phenoxide can be offered for the recent report[53] that whereas the basic hydrolysis at high



(XXI)

---

[51] F. G. Bordwell, B. B. Lampert, and W. H. McKellin, *J. Amer. Chem. Soc.*, 1949, **71**, 1702.

[52] T. Kauffmann and R. Nürnberg, *Chem. Ber.*, 1967, **100**, 3427.

[53] G. W. Dalman and F. W. Neumann, *J. Amer. Chem. Soc.*, 1968, **90**, 1601.

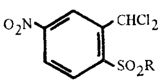
temperature of chlorobenzene gives phenol and diphenyl ether only *via* benzyne, that of diphenyl- or di-*p*-tolyl-ether gives under the same conditions phenol or *p*-cresol, respectively, only *via* direct substitution.

It has been suggested that the steric bulk of the leaving group also comes into play.[52] This is to rationalise the fact that the balance between occurrence of the addition–elimination mechanism and the hetaryne mechanism shifts regularly toward the latter with increasing weight of the halogen in the reactions of Li-piperidide with 4-chloro-, 4-bromo-, or 4-iodo-pyridine.[52] This shift is attributed to increasing steric compression in the transition state of the addition–elimination mechanism with increasing weight of the halogen.[52]

The nature of the radical from which the leaving group is to be displaced also seems to be an important factor. Thus, in the case of 2-bromothiophene,[48] the exceptional stability of *o*-halogenoanions and the high strain associated with five-membered hetarynes seem to contrast with the aryne mechanism.[48, 54]

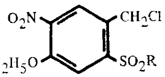
Finally, a further important factor is the nature of the solvent. Clearly a solvent capable of protonating (XXI) will effectively suppress the aryne mechanism. This has been observed for example in the reaction of (XX) with piperidine, which in benzene proceeds *via* both the hetaryne and the anomalous addition–elimination mechanism, whereas in ethanol only the latter mechanism operates.[55]

(ii) *Other rearrangements.* Both Smiles and Sommelet–Hauser rearrangements have been adequately reviewed.[41] Another interesting rearrangement is the reaction of (XXII) with ethoxide to give (XXIII).[1] That chloride expulsion must



R = *p*-tolyl

(XXII)



(XXIII)

be part of the driving force of the reaction is shown by the fact that when both chlorines of (XXII) are replaced by methoxy-groups, which are much poorer as leaving groups, only products of displacement of the nitro or of the *p*-tolyl group are observed.[1] To account also for the easy replacement of hydrogen, which, when displaced as hydride requires the presence of a good reducing agent, it is suggested[1] that hydrogen is expelled without its bonding electrons, as shown in equation (14). This type of rearrangement seems to be rather general.[56]

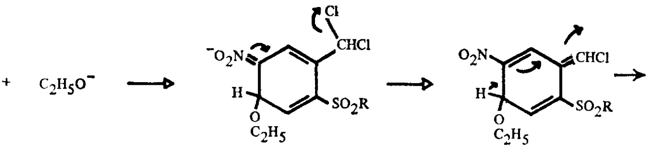
---

[54] T. Kauffmann, R. Nürnberg, J. Schulz, and R. Stabba, *Tetrahedron Letters*, 1967, 4273.

[55] T. Kauffmann, A. Risberg, J. Schulz, and R. Weber, *Tetrahedron Letters*, 1964, 3563.

[56] (*a*) A. Kliegl and W. Hölle, *Ber.*, 1926, **59**, 901; (*b*) K. Nagaraian and C. L. Kulkarni, *Tetrahedron Letters*, 1968, 2717; (*c*) E. J. J. Grabowski, E. W. Tristram, R. Tull, and P. I. Pollak, *Tetrahedron Letters*, 1968, 5931; (*d*) W. B. Dickinson, *J. Amer. Chem. Soc.*, 1964, **86**, 3580.

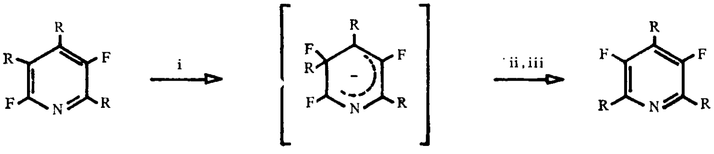
(XXII) + $C_2H_5O^-$



→ (XXIII)

(14)

Recently it has also been reported that (XXIV) rearranges to (XXV) in sulpholan–KF along the path indicated in Scheme 2.[57] R-Migration occurs intermolecularly, as shown when cross-over products were observed in the presence of perfluoroquinoline.[57]

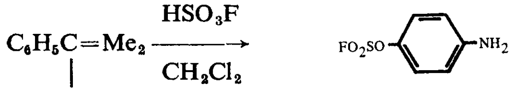


(XXIV) (XXV)

$R = CF(CF_3)_2$; i, KF ; ii, R-migration ; iii, $- F^-$.

Scheme 2

B. Acid-promoted Rearrangements.—It has been reported recently that organic fluoramines rearrange in fluorosulphonic acid as shown in equation (15). The



$$\underset{NF_2}{C_6H_5C}{=}Me_2 \xrightarrow[CH_2Cl_2]{HSO_3F} \qquad (15)$$

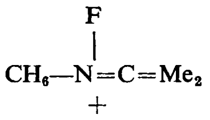
(XXVI)

key step is suggested to be the nucleophilic displacement by fluorosulphonic acid of fluoride and of a proton from the phenyl *p*-position of (XXVII) which should come from (XXVI) *via* aryl migration.[58] This suggestion[58] is based on the evidence that an authentic sample of the fluoborate of XXVII gives 4-(fluorosulphato)aniline with 68% yield on treatment with fluorosulphuric acid in methylene chloride followed by hydrolysis.[58] Resemblance with the Wallach rearrangement or the aromatic hydroxylamine–aminophenol rearrangement, which have been recently reviewed,[41] is apparent.

---

[57] R. D. Chambers, R. P. Corbally, J. A. Jackson, and W. K. R. Musgrave, *Chem. Comm.*, 1969, 127.

[58] T. E. Stevens, *J. Org. Chem.*, 1968, **33**, 2664.



$$CH_6-\overset{F}{\underset{+}{N}}=C=Me_2 \qquad \text{(XXVII)}$$

Another recent case which may be described as an acid-induced aromatic nucleophilic rearrangement is the formation of both *p*- and *o*-methoxy-*N*-t-butylaniline from *N*-chloro-*N*-t-butylaniline in methanolic silver perchlorate.[59]

4 Photonucleophilic Aromatic Substitution Reactions

Title reactions were not really discovered until 1956.[60] Since then several examples have been found where the hydroxy-group in aqueous alkali under u.v. irradiation more easily replaces a group located at the *meta*- than at the *ortho*- or *para*-position with respect to a ground-state* electron-withdrawing group. This is shown for example by the formation of 5-nitroguiacol from 4-nitroveratrole,[61] and by the fact that *m*-nitrophenol is easily obtained from *m*-nitrophenylphosphate whereas *o*- or *p*-nitrophenyl phosphate are hardly reactive.[62] This inversion of the usual ground-state order of chemical reactivity is the most interesting feature of these reactions.

Other newly discovered photoreactions include amination,[61-63] cyanation,[64] halogenation,[65] alkoxylation,[66] and alkylation with lithium alkyls.[67] Here, again, reaction courses are not usually predictable from ground-state chemistry though the reactivity orders observed for alkaline photohydrolysis do not always hold. Thus, methoxy-group replacement by methylamine is much easier with *p*- than with *m*-nitroanisole.[62, 63b] However, as in photohydrolysis, methylamine substitutes the *m*-methoxy-group of 4-nitroveratrole.[63c] Moreover, *ortho–para* orientation with respect to the nitro-group is observed in the photoamination of *m*- or *p*-chloronitrobenzene in liquid ammonia.[63a]

It has also been found that in some of these photoreactions the activating group of the ground state chemistry is replaced. This is the case for *p*-nitro-

---

* The term 'ground state' in this Review is used to indicate electronic ground state.

[59] P. G. Gassmann, G. Campbell, and R. Frederick, *J. Amer. Chem. Soc.*, 1968, **90**, 7377.

[60] E. Havinga, R. O. de Jongh, and W. Dorst, *Rec. Trav. chim.*, 1956, **75**, 378.

[61] E. Havinga, *Pure Appl. Chem.*, 1968, **16**, 137.

[62] E. Havinga and R. O. de Jongh, *Bull. Soc. chim. belges*, 1962, **71**, 803; R. O. de Jongh and E. Havinga, *Rec. Trav. chim.*, 1968, **87**, 1318; S. de Vries and E. Havinga, *ibid.*, 1965, **84**, 601.

[63] (*a*) A. van Vliet, M. E. Kronenberg, and E. Havinga, *Tetrahedron Letters*, 1966, 5957; (*b*) M. E. Kronenberg, A. van der Heyden, and E. Havinga, *Rec. Trav. chim.*, 1966, **85**, 56; (*c*) M. E. Kronenberg, A. van der Heyden, and E. Havinga, *Rec. Trav. chim.*, 1967, **86**, 254; (*d*) R. M. Johnson and C. W. Rees, *J. Chem. Soc.* (*B*), 1967, 15; (*e*) J. A. Barltrop, N. J. Bunce, and A. Thomson, *J. Chem. Soc.* (*C*), 1967, 1142.

[64] (*a*) R. L. Letsinger and J. H. McCain, *J. Amer. Chem. Soc.*, 1966, **88**, 2884; (*b*) C. M. Lock and M. E. Kronenberg, unpublished results quoted in ref. 61.

[65] (*a*) M. D. Johnson, *J. Chem. Soc.*, 1965, 805; (*b*) R. L. Letsinger and G. G. Wubbels, *J. Amer. Chem. Soc.*, 1966, **88**, 5041.

[66] J. T. Pinhey and R. D. G. Rigby, *Tetrahedron Letters*, 1969, 1271.

[67] R. H. Shapiro and K. Tomer, *Chem. Comm.*, 1968, 460.

phenylphosphate or *p*-nitroanisole where, under irradiation, the nitro-group substituted by pyridine.[2]

These altered reaction paths with respect to the ground-state chemistry have been attributed to the photoreactions going through an excited state whose electron distribution differs from that of the ground state.[61] Such a conclusion would require knowledge of the quantum yields for all possible processes, including fluorescence and quenching, which is not the case here. Thus, a lifetime of the excited state shorter for the *para* than for the *meta* isomer could be an alternative explanation for the greater product quantum yield for the latter. However, it is interesting that when identical displaceable groups occupy different positions in the same molecule, so that the lifetimes of intermediates are not involved, the *meta* group is replaced in preference to the *para*.[61]

In some papers [61] such an excited state is regarded as the first excited singlet of the substrate. The evidence suggests that chain mechanisms or free radicals are unlikely since product quantum yields are always below unity[61] and no typical products of radical reactions have been isolated.[63c] Moreover, triplet states are also believed to be unlikely, since addition of bromide ion, which is known to catalyse singlet-to-triplet transitions, depresses the *m*-nitrophenol quantum yield in the photohydrolysis of *m*-nitrophenol.[61, 68] The tentative mechanism shown in the Figure has thus been suggested[61] whereby a $\pi \rightarrow \pi^*$ transition gives the singlet, S_1, whose ring electron density is calculated[69] by the Hückel MO method to be as indicated in the Figure by an unconventional valence bond structure. The singlet has the alternatives of returning to the ground state by fluorescence (k_0), or quenching (k_q), or by attack by OH^- at the ring electron-deficient position may be transformed into the tetrahedral addition intermediate $S_0\ddagger$ which then partitions itself between reagents and products. Reactions of short-lived species such as S_1 with OH^- are also suggested by the need for a relatively high OH^- concentration in order to obtain a significant product quantum yield.[61] Moreover, as required by the mechanism in the Figure, the kinetics are first-order in light intensity and zero-order in *m*-nitroanisole and the reciprocal product quantum yield increases linearly with the reciprocal OH^- concentration.[61]

Recently, however, it has been discovered that the alkaline photohydrolysis of 4-nitroanisole to 4-nitrophenol is photosensitised by benzophenone.[70] It is suggested that 4-nitroanisole is raised to the triplet excited state by interaction with triplet benzophenone and that the triplet 4-nitroanisole lies along the reaction path.[70]

In other cases description of the intermediate species as an excited state of the substrate is not adequate. Thus, in the alkaline photohydrolysis of 1,3,5-trinitrobenzene to give 3,5-dinitrophenol the light-absorbing species is the

---

[68] R. O. de Jongh and E. Havinga, *Rec. Trav. chim.*, 1968, **87**, 1327.

[69] H. E. Zimmerman and V. R. Sandel, *J. Amer. Chem. Soc.*, 1963, **85**, 915; H. E. Zimmerman and S. Somasekhara, *ibid.*, 1963, **85**, 922.

[70] R. L. Letsinger and K. E. Steller, *Tetrahedron Letters*, 1969, 1401.

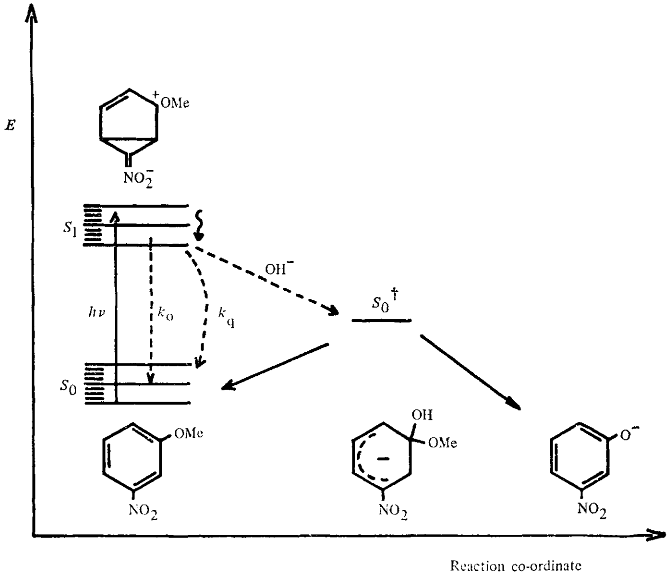


Figure 1 *Tentative energy relationships and reaction path for alkaline photohydrolysis of m-nitroanisole.*[61]

Meisenheimer-like complex of the substrate with OH^-.[71] This process is thought to be followed by nitro-group expulsion by another OH^-.[71] Another case is the photoreaction of *p*-nitrophenol with aqueous hydrogen chloride which affords 2,3,6-trichloro-4-aminophenol and tetrachlorohydroquinone.[65b] It has been suggested that the reaction proceeds by chloride-ion attack on an electronically excited protonated substrate molecule.[65b]

I thank Professor J. F. Bunnett for his assistance.

[71] V. Gold and C. H. Rochester, *J. Chem. Soc.*, 1964, 1717.