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MECHANISMS OF AROMATIC NUCLEOPHILIC SUBSTITUTION REACTIONS BY AMINES IN SOLVENTS OF LOW RELATIVE PERMITTIVITY

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The evidence for the mechanisms proposed for aromatic nucleophilic substitution reactions by primary and secondary amines in aprotic solvents of low relative permittivity is reviewed.

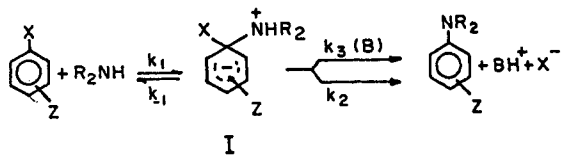
INTRODUCTION

The gross mechanism of aromatic nucleophilic substitution reactions in all solvents when either primary or secondary amines are the nucleophiles is usually represented by Scheme 1, although as long ago as 1954 Ross and Kuntz[1] demonstrated that the reaction of aniline with 1-chloro-2,4-dinitrobenzene in the solvents ethanol and ethanol–ethyl acetate (1 : 1), but not in ethyl acetate, could involve a complex between the two reactants. More recently Bacaloglu *et al.*,[2] for the closely related reaction of hydroxide ion with the same substrate in dimethyl sulphoxide (DMSO)–water mixtures, have produced evidence that the formation of Meisenheimer complexes is preceded by the formation of π and charge-transfer complexes. Application of the steady state hypothesis to Scheme 1 gives

$$k_A = \frac{k_1(k_2 + k_3[B])}{k_{-1} + k_2 + k_3[B]} \qquad (1)$$

where k_A is the observed second-order rate constant and B is either a second molecule of the nucleophile or an added base.

There is general agreement that in aprotic solvents such as cyclohexane and benzene, the uncatalysed decomposition of the intermediate to products takes



Scheme 1

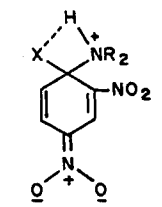
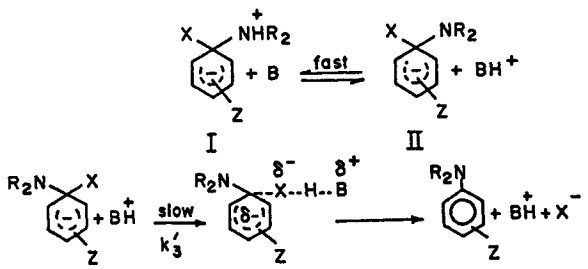


Figure 1. Hydrogen bonding in the uncatalysed decomposition of the intermediate products

place unimolecularly via the hydrogen-bonded intermediate shown in Figure 1, and in dipolar aprotic solvents such as DMSO and acetonitrile the mechanism of the base-catalysed path is that proposed by Bunnett and Davis[3] and given in Scheme 2, often referred to as the specific base–general acid (SB–GA) mechanism. In this mechanism there is a fast proton transfer between B and the first-formed intermediate to give its conjugate base, followed by the slow, electrophilically assisted expulsion of the leaving group. Capon and Rees[4] have proposed that in aprotic solvents the catalysed path



Scheme 2

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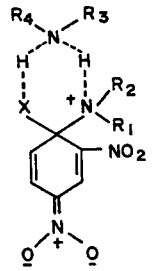


Figure 2. Cyclic intermediate for the base catalysed path in aprotic solvents

proceeds via cyclic intermediates such as that shown in Figure 2. Ayediran *et al.*[5] have discussed some difficulties associated with this proposal and suggested that because of the low relative permittivity of aprotic solvents and the consequent range of electrostatic forces, aggregates are formed within which mechanisms such as those proposed by Bunnett and Davies[3] can operate.

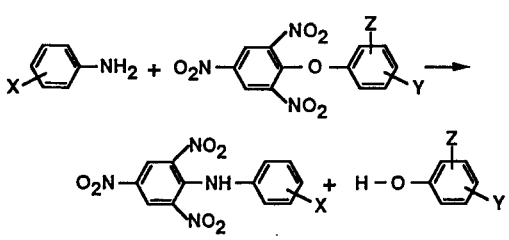
Equation (1) allows three kinetic forms. If $k_{-1} \ll k_2 + k_3[B]$, then $k_A = k_1$, and the reaction is not base catalysed. If $k_{-1} \gg k_2 + k_3[B]$, then the equation has the form

$$k_A = k' + k''[B] \qquad (2)$$

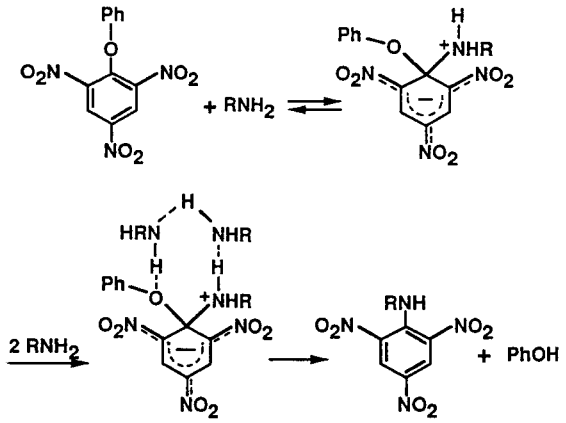
and if no simplification of the equation can be made, plots of k_A vs base concentration are curvilinear downwards. Frequently,[6-17] however, in aprotic solvents, a fourth kinetic form is observed in which plots of k_A vs base concentration have upward curvatures. Originally this was explained as a solvent effect, but more recently mechanistic explanations have been sought, three of which are based on Scheme 1.

REACTIONS THROUGH EIGHT-MEMBERED CYCLIC TRANSITION STATES

Banjoko and co-workers[13,18-20] have investigated the reactions of substituted anilines with picryl phenyl ethers in benzene as shown in Scheme 3. For Y = Z = H and X = H, 3- and 4-CH_3, 3- and 4-OCH_3 and 3- and 4-Cl and Z = H, Y = 2-, 3- and 4-NO_2, X = H, the measured second order-rate constant k_A has a linear dependence



Scheme 3



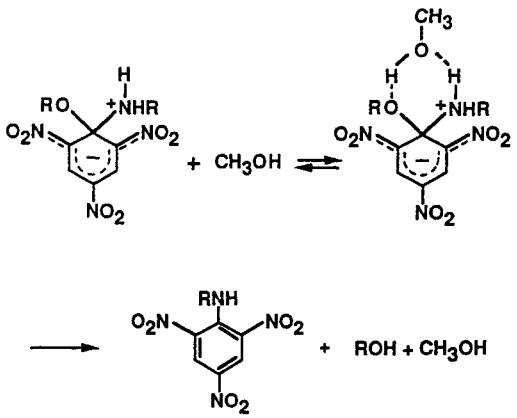
Scheme 4

on the square of the nucleophile concentration:

$$k_A = k'_M + k''_M\,[\text{nucleophile}]^2 \qquad (3)$$

Banjoko and co-workers interpreted the third-order term in nucleophile concentration as being due to reaction through an eight-membered ring formed through a network of inter-hydrogen-bonding between two aniline molecules and the zwitterionic intermediate as shown in Scheme 4.

They adduced support for the mechanism from the fact that the values of k_A for the reactions of substituted anilines with picryl phenyl ether[13] show little change over the temperature range 5–35 °C, k'_M is temperature invariant and for anilines containing electron-releasing substituents k''_M has a negative activation energy. Hammett plots give ρ values of $-4{\cdot}7$ and $-7{\cdot}7$ for k'_M and k''_M, respectively. The change in kinetic form of the reactions of aniline with ethers containing unsubstituted or mononitro-substituted leaving groups from a third-order dependence on the aniline concentration [equation (3)] to a second order dependence [equation (2)] for leaving groups containing 2,4-, 3,4- and 2,5-dinitro groups, to $k_A = k_1$ for the 2,6-dinitrophenoxy group, was ascribed to changes in the transition state for the decomposition of the intermediate from eight- to six- to four-membered rings (containing two, one and no moles of aniline, respectively, the last as in Figure 1) brought about by increases in the leaving group ability of the nucleofuge. Why an eight-membered transition state is more effective in removing the nucleofuge than a six-membered transition state was not explained. Addition of methanol to the reaction of aniline with picryl phenyl ether in benzene resulted in a continuous curvilinear increase in k_A over the entire range of solvent composition from pure benzene to pure methanol.[20] The order in aniline changes from three in pure benzene to two in pure methanol. Over the range 0–0·6% methanol, the



Scheme 5

expression

$$k_A = k_0 + k''_A[\text{aniline}]^2 + k''_{Me}[\text{MeOH}] \qquad (4)$$

holds and the cyclic mechanism in Scheme 5 was proposed for the methanol-catalysed decomposition of the intermediate to products. On the basis of this mechanism it is surprising that no catalysis by phenol was observed, especially as Pietra and Vitali[21] have shown that phenol catalyses the reaction of 1-fluoro-2,4-dinitrobenzene with piperidine in benzene.

The rate law of a reaction indicates the composition of the transition state but does not reveal the mechanism of assembly of the transition state. Negative values of the activation energy indicate the formation of one or more equilibria before the rate-determining step of the reaction, a feature common to most mechanisms of aromatic nucleophilic substitution reactions in solvents of low relative permittivity. When they are observed, the negative activation energies are accompanied by extremely low activation entropies, indicating that several initially kinetically independent species are bound together in the transition state. Similar sets of ρ values are also predicted by various mechanisms. Generally, neither negative activation energies nor ρ values can be used to distinguish between the mechanisms. Reactions of anilines as nucleophiles in hydrocarbon solvents are difficult to interpret. In cyclohexane the dimerization constant for aniline is more than six times greater than that of cyclohexylamine[22] and, as will be shown later, complexes which lie on the reaction path are formed between anilines and the substrates. Akinyele *et al.*[23] have also shown that, because of the greater acidity of the aminohydrogen atoms of anilines compared, say, with those of *n*-butylamine or piperidine, catalysis of the first step of the reaction can take place as depicted in Figure 3. Here Y is a base which can be the nucleophile or even chloride ion.

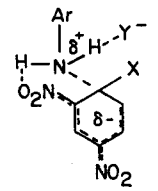


Figure 3. Transition state for base catalysis of the formation of the intermediate when anilines are the nucleophiles

'DIMER' MECHANISM

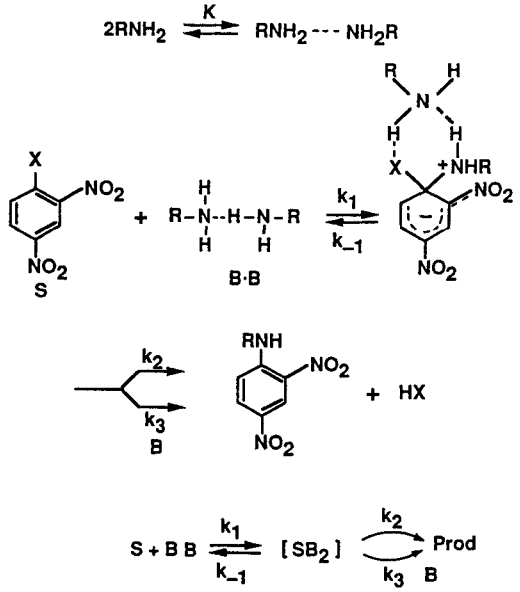
It is well known that in aprotic solvents of low relative permittivity, amines form aggregates of various degrees of complexity. The dominant species is the dimer, with typical formation constants for aliphatic amines in the range 0·02–0·1.[22,24] Nudelman and Palleros[25] assumed that the dimer is a stronger nucleophile than the monomer and proposed the 'dimer' mechanism given in Scheme 6.

In addition, attack by the free amine takes place simultaneously and a complete kinetic treatment involving both monomer and dimer mechanisms has been given.[15] For Scheme 6, the derived expression for k_A is

$$k_A = \frac{k_1k_2K[\text{B}] + k_1k_3K[\text{B}]^2}{k_{-1} + k_2 + k_3[\text{B}]} \qquad (5)$$

where $K = [\text{B}\cdot\text{B}]/[\text{B}]_0^2$.

Recently, Nudelman[26] has reviewed the evidence in favour of this mechanism. The salient features are as



Scheme 6

follows. For the condition $k_{-1} \sim (k_2 + k_3[B])$, at high [B] equation (5) reduces $k_A/[B] = k_1K$, and hence a plot of $k_A/[B]$ against [B] should give a plateau where $k_A/[B]$ is independent of [B]. This kinetic form has been observed for the reactions of 2,4-dinitroanisole with both *n*-butylamine[25] and cyclohexylamine[15] in benzene and for the latter nucleophile also in cyclohexane. The inverse temperature effect observed for the *n*-butylamine reaction and for that of cyclohexylamine in cyclohexane was explained[15] by the effect of temperature on the dimer equilibrium. Catalysis by tertiary amines, e.g. catalysis by pyridine (P) of the reaction of *o*-anisidine with 1-fluoro-2,4-dinitrobenzene (DNF)[16] in benzene, and the interpretation of the kinetic form of the catalysis by pyridine of the reaction of morpholine with DNF in benzene[6] as due to a second-order term in [P], were ascribed to attack by the mixed dimer B·P, followed by the pyridine-assisted decomposition of the intermediate so formed to products.[16] Similarly, the linear dependence of the rate of the reaction of 2,6-dinitroanisole with cyclohexylamine in toluene on DMSO concentration at low (<2%) DMSO concentrations was attributed to the reaction of the substrate with the mixed aggregate B–DMSO. The addition of small amounts of methanol to the reaction of 2,6-dinitroanisole with cyclohexylamine in benzene causes large decreases in reaction rate until a minimum is reached when approximately 25% of methanol is present, after which the rate increases with increasing methanol content.[27] This was rationalized as being due to competition between dimer formation and the formation of amine–methanol aggregates, ROH···NH_2R, the hydrogen atom donation to the amine decreasing its nucleophilicity. Plots of k_A against nucleophile concentration for the reactions in toluene of 1-fluoro-2,4-dinitrobenzene with cyclohexylamine have an upward curvature whereas those for both *cis*- and *trans*-1,2-diaminocyclohexane show the usual linear dependence on nucleophile concentration.[28] The change in form from curvilinear upwards to a linear dependence is said to be due to diaxial interactions preventing self-association in the case of the *trans*-diamine and to intramolecular hydrogen bonding in the *cis* isomer. This intramolecular hydrogen bonding is also responsible for the twofold increase in the rate for the *cis* over the *trans* isomer in spite of increased steric hindrance.

Nudelman's interpretation of the effect of methanol on the cyclohexylamine–dinitroanisole reaction has been criticized by Banjoko and Bayeroju,[20] who observed a different effect, already described when methanol was added to the reaction of aniline with picryl phenyl ether. (This criticism has recently been refuted by Nudelman *et al.*[28b] These authors showed that the cyclohexylamine–dinitroanisole reaction in toluene–octanol systems has a similar although smaller dependence on the protic solvent content to that observed in the toluene–methanol systems). The accelerations brought about by DMSO and pyridine, including a dependence on the square of the pyridine concentration, can be given despite Nudelman's assertation[26] to the contrary, and have been given,[29] an alternative explanation in the mechanism proposed by Hirst. None of the other mechanisms mentioned in this survey, however, can account for the plateau observed in some of the $k_A/[B]$ vs [B] plots.

HOMO-/HETEROCONJUGATE MECHANISM

As stated previously, because of conceptual difficulties associated with the concept of cyclic transition states, Ayediran *et al.*[5] have suggested that in solvents of low relative permittivity, reaction takes place within aggregates by SB–GA-like mechanisms. It was stressed,[29] however, that because of the range of electrostatic forces and the importance of hydrogen bonding in these solvents, several mechanisms can operate, the relative importance of which depends not only on the entities employed, but also on their concentrations. They explained[12] the upward-curving plots of k_A against nucleophile concentration as due to electrophilic catalysis by the homoconjugate of the conjugate acid of the nucleophile as shown in Scheme 7, where I and II refer to the intermediates in Schemes 1 and 2 and N is the nucleophile. (Banjoko and Ezeani[19] have called this the dimer mechanism. Nudelman,[26] although correctly stating that the mechanism involves electrophlic catalysis by the homoconjugate of the nucleophile, says that the proposal 'would require that the dimer of the nucleophile acts ... in the second step' and writes the mechanism as

$$S + B \underset{k_{-1}}{\overset{k_1}{\rightleftharpoons}} [SB] \xrightarrow[k_4B \cdot B]{k_3B} \text{products}$$

Although the second step of this mechanism which involves two molecules of B has the same stoichiometry as that given in Scheme 7, it is not the dimer of B but its homoconjugate which participates. This misapprehension leads to the erroneous conclusion[26,28a] that the mechanism cannot explain a catalytic term second order in pyridine 'since it is not possible to think about a pyridine dimer in the second step.')

Accelerations of the rate due to an additive P are explained by electrophilic catalysis by the heteroconjugate NH^+P, while a second-order term in the concentration of P can be obtained if the relative basicities of N and P are such that P can compete with N for

$$I + N \rightleftharpoons II + NH^+$$
$$NH^+ + N \rightleftharpoons NH^+N$$
$$II + NH^+N \rightarrow \text{products}$$

Scheme 7

removal of the proton from I followed by electrophilic catalysis by the homoconjugate PH^+P.

Support for this mechanism has been obtained from the study of the effect of twelve hydrogen-bond acceptors on the reactions of 1-chloro- and 1-fluoro-2,4-dinitrobenzene with morpholine in benzene.[29] The reaction of the chloro substrate is not base catalysed and the additives produced no accelerations at the concentrations employed. The reaction of the fluoro substrate is base catalysed and for ten of the additives there was a linear dependence of k_A on either their concentration ($k_A = k' + k''[P]$) or on the square of their concentration ($k_A = k' + k'''[P]^2$). An approximately linear correlation was found between the logarithms of the slopes (k'', k''') and the hydrogen-bonding parameter[30], pK_{HB}. The acceptors consisted of a variety of substances ranging from acetonitrile through nitrobenzene and pyridine *N*-oxide to hexamethylphosphoric triamide and covered a range of pK_{HB} values from 0·90 to 3·56. Anisole and dimethylaniline with the low pK_{HB} values of 0·02 and 0·45 did not produce any accelerations. The lack of effect of additives on the reaction of the chloro substrate was taken to imply that under the conditions employed, i.e. low concentrations, no significant pre-equilibria were established which resulted in the formation of entities participating in the transition state for the formation of the intermediate in Scheme 1, and for the homo/heteroconjugate mechanism of Scheme 7 kinetic equations are easily derived from which a linear dependence of the slopes k'' and k''' on pK_{HB} can be derived. (Regarding the former implication, this argument is not completely rigorous. If very low concentrations exist of a complex formed between the nucleophile and the additive which does not differ appreciably in nucleophilicity from that of the nucleophile, then if the formation of the intermediate in Scheme 1 is rate determining, the presence of the complex would not be detected kinetically. If the second step is rate determining and participation of the complexes is indicated, the above constraints imply that the catalytic effect of the complexes is very much greater than that of the nucleophile. Phenomenologically, relative catalytic powers are measured by the ratio of the slopes k''/k''_N, where k''_N is that of the nucleophile, and do not support this implication.)

In Nudelman's mechanism involving a cyclic intermediate given in Scheme 6, the exact role of the third amine molecule in the breakdown of the intermediate is not clear. Later,[27] however, the intermediate was recast as in Figure 4 (similar to that depicted in Figure 3) and it was stated that 'the third molecule of amine should form a homoconjugated acid BH^+B by proton transfer from the intermediate and the electrophilically catalysed departure of the nucleofuge could be at least partially due to BH^+B.' On this formulation the mechanisms of Hirst and Nudelman are essentially the same and together with the transition state depicted in

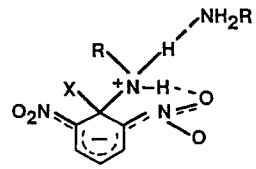


Figure 4. The recast intermediate in Nudelman's mechanism

Figure 3 reflect different parts of a spectrum of methods for the formation of II in Scheme 2. For a given nucleophile, dimer formation increases with increase in concentration, hence the relative importance of reaction via a dimer should increase with increasing nucleophile concentration.

Although there are conceptual difficulties associated with cyclic intermediates in S_NAr reactions, most of them pertain to catalyses by tertiary amines and reaction via these intermediates is not excluded under all circumstances. Akinyele *et al.*[31] have shown that in the solvents tetrahydrofuran and ethyl acetate, whereas the reactions of 1-fluoro-2,4-dinitrobenzene with secondary amines are strongly catalysed by both the nucleophiles and DABCO, the corresponding reactions of 1-phenoxy-2,4-dinitrobenzene, although strongly catalysed by the nucleophiles, either are not catalysed or show only mild catalysis by DABCO. The results were explained by a second molecule of the nucleophile, hydrogen bonded to the ethereal oxygen atom of the intermediate corresponding to I in Scheme 1, being most favourably situated for proton abstraction, possibly to the exclusion of all other catalysts. They pointed out that this should occur in aromatic nucleophilic substitution reactions of ethers in all solvents of low relative permittivity and gave a plausible mechanism for the formation of the cyclic transition states of Capon and Rees.[4] The concept has been developed[32] to rationalize reactions proceeding through cyclic transition states containing either two or three molecules of amine and to distinguish these reactions from those of ethers taking place by the SB–GA mechanism. A rationale is provided for the change in kinetic form observed by Banjoko and Ezeani[19] when a second nitro group is introduced into the leaving group in the reactions of aniline with substituted phenylpicryl ethers, which can also be applied to the changes in kinetic form which occurs with increased leaving group ability in the reactions of *O*-aryloximes with aliphatic primary and secondary amines in benzene.[33]

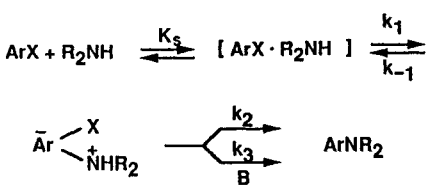
REACTIONS VIA COMPLEXES

Complexes formed by the substrate

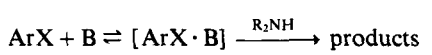
None of the above mechanisms take into account the complexes that are known to be formed by the

substrates with the nucleophiles and catalysts in solvents of low relative permittivity. These complexes can be either side-reactions or intermediates on the reaction path.[34] With electron donor–acceptor (EDA) complexes, concordance between values of the association constants obtained by spectroscopic and kinetic methods shows that at least an appreciable fraction of the reaction takes place via the complex. [Colter *et al.*[35] have shown that, strictly, agreement between kinetic and spectrophotometric association constants does not mean that the 1 : 1 complex (or complexes) responsible for the enhancement in optical density is the same complex (or complexes) producing the rate enhancement.] Catalysis involving the complex can be interpreted in two ways. As the first possibility, either the substrate and the nucleophile form a complex and reaction takes place in the complex to give an intermediate from which an amino proton is abstracted by the catalyst as shown in Scheme 8. The observation of base catalysis still indicates that the decomposition of the σ-complex to products is rate limiting and the only modification to the mechanistic interpretation of the kinetics of the reaction is that the normal concave-downward variation of k_A with base concentration can no longer be definitely associated with the condition $k_{-1} \sim k_2 + k_3[B]$. In the second possibility, the substrate and catalyst (nucleophile or added base) form a complex which is then attacked by a molecule of the nucleophile (Scheme 9). In this scheme catalysis need no longer be associated with proton removal. Thus, Forlani and Cimarelli[36] have shown that the formation of a Meisenheimer complex between 1,3,5-trinitrobenzene and 1,8 diazabicyclo[5.4.0]undec-7-ene in toluene takes place via an association complex and is second order in tertiary amine. Ryzhakov *et al.*[37] has shown that the *N*-oxides of 4-chloropyridine and 4-chloroquinoline act as π-donors toward tetracyanoethylene and that the reactions of these substrates with pyridine and quinoline are strongly catalysed by the π-acceptor.

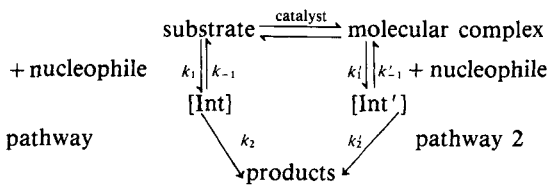
Since 1982, Forlani and Tortelli[38–40] have advocated the model in which the catalytic phenomenon is an



Scheme 8



Scheme 9



Scheme 10

effect of the substrate–nucleophile (or substrate–catalyst) interaction in a rapidly established equilibrium preceding the substitution process, as in Scheme 10. The catalyst can be either the nucleophile or an added base, and [Int] is the zwitterionic intermediate. In both pathways 1 and 2, base catalysis may be either present or absent.

In tetrahydrofuran, addition of substituted anilines to 1-fluoro-2,4-dinitrobenzene results in the observation[38] at zero reaction time of absorbances occurring at wavelengths in the UV spectrum where the reactants do not absorb. These absorbances were ascribed to the formation of molecular complexes. On the assumption that reaction takes place via these complexes, which are assumed to be more reactive than the free substrate, the variation of the second-order rate constant k_A with nucleophile concentration can be represented by

$$k_A(1 + K[N]) = k_2 + k_3[N] \qquad (6)$$

where K is the association constant for the formation of the complex and [N] the concentration of the nucleophile. The high (negative) ρ value of $-4{\cdot}88$ was deemed inappropriate for the usually accepted mechanism of the base-catalysed step (Scheme 1) and agreement within experimental error was obtained between the values of K obtained kinetically and spectroscopically. In both benzene and chloroform molecular complexes are also observed[40] to be formed between both 1-fluoro- and 1-chloro-2,4-dinitrobenzene and aniline and in the case of the fluoro substrate in benzene with *N*-methylaniline and the substituted anilines *p*-choroaniline, *m* and *p*-anisidines and toluidines also, giving a ρ value for log K of 2·76. Good agreement between the values of K for the fluoro compound–aniline complex in chloroform was obtained by UV and ^{1}H NMR spectroscopy. For the reactions of both substrates with aniline in both solvents, and for those of the fluoro substrate with substituted anilines and *N*-methylaniline in benzene, plots of k_A against nucleophile concentration had an upward curvature, but plots of $k_A/[N]$ against [N] were linear. The third-order term in nucleophile concentration was interpreted as arising from the decomposition of Int′ in pathway 2 in Scheme 10 taking place at least partially by a base-catalysed route.

DABCO forms a complex with 1-fluoro-2,4-dinitrobenzene in benzene[39] and reactions of this substrate with piperidine, *tert*-butylamine, aniline, *p*-toluidine and *m*-anisidine are catalysed by DABCO, obeying the equation

$$k_A = k_2 + k_3^{DABCO} \times 2[DABCO] \quad (7)$$

A kinetic analysis of the results based on Scheme 10 gives consistent values of the association constant K^{DABCO} from each nucleophile which agree with the value obtained from spectroscopic measurements. In these reactions the nucleophile also acts as a catalyst and the following relationship between these catalytic constants k_3^{amine} and k_3^{DABCO} was found to hold:

$$\log k_3^{DABCO} = 0{\cdot}32 + 1{\cdot}4 \log k_3^{amine} \quad (8)$$

For the aromatic amines a ρ value of -2.86 was found to hold for k_3^{DABCO}. These results were taken to imply that the transition state of the step catalysed by DABCO and the transition state of the step catalysed by the nucleophile have similar requirements and in both transition states the nucleophilic power (or basicity) of the nucleophiles is involved. This conclusion is not in accordance with the usual interpretation of the base-catalysed step (Scheme 1) but agrees with that given in Scheme 10.

In solvents of low relative permittivity, the order with respect to the nucleophile for the reactions of aromatic amines with 1-fluoro-2,4-dinitrobenzene changes from two in solvents of considerable donicity (tetrahydrofuran, dioxane) to three for those of low donicity[41] (benzene, carbon tetrachloride), and is explained as arising from competition between the solvent and amine for complex formation with the substrate. If this is the case then substances of low polarity but high donicity should decrease the order with respect to amine. In benzene, in the presence of a constant initial concentrate of triethylamine (TEA) of approximately the same magnitude as that of the nucleophile, the reactions of 1-fluoro-2,4-dinitrobenzene with both aniline and *p*-chloroaniline are no longer catalysed by the nucleophile, while catalysis is still observed when the reagent is *p*-anisidine. The association constant K^{TEA} for complex formation between 1-fluoro-2,4-dinitrobenzene and TEA (0·47) is high compared with those of aniline (0·062) and *p*-chloroaniline (0·02). Consequently, the substrate–nucleophile complexes are 'swamped' by that with TEA and no catalysis by the nucleophile is observed. The association constants of TEA and *p*-anisidine (0·67) are of the same order of magnitude and catalysis of the reaction by the nucleophile still takes place in the presence of TEA.

Substituted 2-aminothiazoles do not form complexes with 1-fluoro-2,4-dinitrobenzene in benzene[42] and their reactions with this substrate are not self-catalysed, although the range of basicities and nucleophilicities encompasses that of aromatic amines whose reactions exhibit this phenomenon. The reactions are, however, catalysed by DABCO, 2-hydroxypyridine and δ-valerolactam. The values of K^{DABCO} obtained kinetically agree with those obtained previously.[39] δ-Valerolactam was shown to form a hydrogen-bonded complex with the substrate and subsequently Forlani[43] showed that similar complexes are formed between 2-hydroxypyridine and aromatic nitro derivatives. The magnitude of k_A increases linearly with increasing nucleophile concentration for the reaction of picryl fluoride with 2-hydroxypyridine (Py) in chlorobenzene.[44] Usually only small isotope effects are observed in S_NAr reactions in apolar solvents, but monodeutero-2-hydroxypyridine gives a k_A^H/k_A^D value of 1·5. This is difficult to explain in terms of proton abstraction but can be accounted for by the value of 1·75 obtained for the ratio K_H/K_D for the association constants of the nucleophiles with the substrate. When the substrate is picryl chloride a slight linear increase in k_A with increasing nucleophile concentration is observed, which was interpreted in terms of Scheme 10, giving a value of K of 2·9 ± 1, identical with that for the fluoro substrate (3·0 ± 1). {Although the observation of strong catalysis in a system reacting according to Scheme 10 depends not only on the value of K but also on the relative reactivities of the complexed and 'free' substrates, it seems difficult to understand why these should differ so much for the chloro and fluoro substrates, giving values of the slope to intercept ratios [k''/k' equation (2)] differing from 6·6 to 182.}

Further evidence for reaction taking place via a complex can be obtained from some of Forlani's earlier work.[45] The values of k_A for the reactions of piperidine with 2-bromo- and 2-chloro-6-nitrobenzothiazole in benzene increase with increasing piperidine concentration according to equation (2), giving k''/k' values of 4·6 for both substrates. According to Bunnett and Garst's[46] criteria this low value of the ratio does not indicate base catalysis, and implies that the formation of the intermediate in Scheme 1 is rate limiting. In accordance with this interpretation, the reactions are not catalysed by triethylamine. An interpretation according to Scheme 10 would require only a small fraction of the reaction to proceed via a complex. Whatever the mechanism, though, the k_A^{Br}/k_A^{Cl} ratio of *ca* 1 shows that the breaking of the carbon–halogen bond is not involved in the rate-determining step. The reactions are strongly catalysed by 2-hydroxypyridine, the catalytic effect again obeying equation (2), giving k''_{Py}/k''_{am} ratios of 120 and 130 for the bromo and chloro substrates, respectively, where k''_{Py} and k''_{am} refer to the catalytic constant of equation (2) for 2-hydroxypyridine and piperidine. The results are in accordance with reaction proceeding through a substrate–2-hydroxypyridine complex.

On the basis that 1,2-dinitrobenzene forms stronger electron donor–acceptor (EDA) complexes with

aliphatic amines in hexane than 1,3- or 1,4-dinitrobenzene,[47] Singh and co-workers proposed that these complexes participate in the reactions of 1,2-dinitrobenzene (DNB) with aliphatic primary[48] and secondary[49] amines to give *N*-alkyl-2-nitroanilines in this solvent. The observed second-order rate constant k_A for the reaction of DNB with piperidine in hexane has the normal (concave downwards) dependence on piperidine concentration.[49] The authors stated that the mechanism can be either that of Scheme 1 with the condition $k_{-1} \sim k_2 + k_3$[amine] or that of Scheme 8, i.e. reaction taking place via a complex, but the catalysis referring to proton abstraction. The first possibility was rejected on the grounds that for the corresponding reaction with *n*-butylamine the authors had shown $k_{-1} \gg k_3^{BA}$ (Scheme 1) and S_NAr reactions with secondary amines are more prone to base catalysis than analogous reactions with primary amines of similar pK_a values. A kinetic analysis based on Scheme 8 gives values of the association complex K_S for the EDA complex between DNB and piperidine at various temperatures, in agreement with those obtained spectroscopically. When the nucleophile is changed to a primary aliphatic amine (*n*-butyl-, *sec*-butyl-, isobutyl-, *n*-propyl- and isopropylamine), a linear dependence of k_A on nucleophile concentration is observed at all temperatures[48] [equation (2)]. With the exception of isopropylamine, large values of the k''/k' ratio are observed (e.g. for *n*-butylamine the ratio is infinity), and this is taken as demonstrating base catalysis of the reaction. In the case of propylamine, catalysis is inferred from its reactions in the presence of pyridine (see below). Again, the kinetics can be interpreted either in terms of Scheme 1 ($k_{-1} \gg k_2 + k_3$[N]) or Scheme 8 ($1 \gg K_S$[N]). Preference is given to Scheme 8 based on the observation of absorbances attributed to EDA complexes between substrate and reactants at zero reaction time. The difference in kinetic form between piperidine and primary aliphatic amines is attributed to the greater K_S value of the former, e.g. at 27 °C K_S for piperidine is 0·55 and for isopropylamine 0·16. The reaction of *n*-butylamine is slightly inhibited by both triethylamine and tributylamine, the lack of catalysis being attributed to steric effects. The reactions of both *n*-butylamine and isobutylamine are catalysed by pyridine, k_A increasing linearly with increasing pyridine concentration. Although pyridine and DNB are known to form a complex ($K_S = 0·3$), the catalysis is explained as being due to electrophilic assistance of the leaving group by the heteroconjugate formed from pyridine and the conjugate acid of the nucleophile.

When the solvent is changed to benzene,[50] the second-order rate constants for the reactions of DNB with *n*-butylamine and *sec*-butylamine still have a linear dependence on nucleophile concentration. The values of the k''/k' ratio [equation (2)] are very much reduced (Bu^nNH_2 2·8; Bu^sNH_2 1·5) compared with those in hexane, and according to Bunnett and Garst's criteria[46] do not indicate base catalysis. From a comparison of the kinetic parameters of the two nucleophiles in benzene with those in hexane and other S_NAr reactions in benzene, it was concluded, however, that the mild accelerations did arise from the decomposition of the intermediate in Scheme 1. Triethylamine has no effect on the reaction of DNB with *n*-butylamine, but 2-hydroxypyridine, DABCO, DMSO and pyridine all give very mild accelerations, the magnitude of which qualitatively correlates with Taft's[51] hydrogen-bonding acceptor parameter β rather than with their basicities. It is known that benzene forms molecular complexes with aromatic nitro compounds; thus the stability constant of the molecular complex of benzene with 1-fluoro-2,4-dinitrobenzene in deuterochloroform is 0·018.[40]

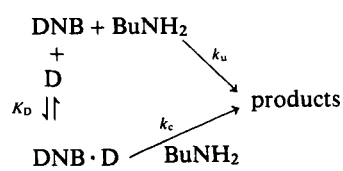
The authors suggested that in pure benzene DNB is preferentially solvated by the solvent through EDA complexation. Proximity effects of either additives or nucleophiles will be different from those in hexane and the preferential solvation by benzene explains the poor catalytic powers of added bases in these reactions. As a test of this hypothesis, they proposed that in hexane–benzene solvent mixtures two parallel reactions could take place, one through the free substrate with a pseudo-first-order rate constant k_u and the other through a 1:1 EDA complex of benzene, D, with the substrate, with a pseudo-first-order rate constant k_c as in Scheme 11. The observed rate constant, k_ψ, is given by

$$k_\psi = \frac{k_u + k_c K_D[D]}{1 + K_D[D]} \tag{9}$$

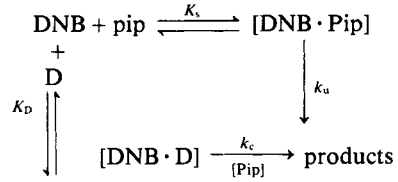
or

$$\frac{k_u}{k_\psi} = \frac{1 + K_D[D]}{1 + (k_c K_D/k_u)[D]} \tag{10}$$

The reaction of DNB with *n*-butylamine is slower in benzene than in hexane and when the reaction is carried out in hexane–benzene mixtures the ratio k_u/k_ψ has the curvilinear, concave-downward dependence on the benzene concentration demanded by equation (10), giving a K_D value of 0·55. When the reactions of DNB with piperidine and *n*-butylamine are carried out in toluene, chlorobenzene and diisopropyl ether,[52] the observed second-order rate constant k_A increases linearly with increasing amine concentration according to



Scheme 11



Scheme 12

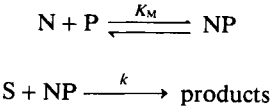
equation (2) and in all cases the k''/k' ratios are small, in the range 0·5–5·5. Mesitylene is a better EDA donor than benzene and k_ψ falls off more rapidly in hexane–donor solvent mixtures with mesitylene than benzene, giving a K_D value for mesitylene of 0·90. DNB is believed to be preferentially solvated also by all the other solvents in the set. The reaction of piperidine differs from that of *n*-butylamine in that it is faster in benzene than in hexane, but slower in diisopropyl ether. k_ψ increases with increase in donor solvent concentration in hexane–donor solvent mixtures for benzene, but decreases for mesitylene and diisopropyl ether, the inhibition being greatest for diisopropyl ether. The difference between the two nucleophiles is explained by the proposal that because the association constant K_s for substrate–nucleophile complex formation is greater for piperidine than for primary amines, the formation of this complex is important for the reactions of piperidine but not for primary amines, and competition between nucleophile and donor solvent is established as in Scheme 12. The expression for k_ψ is given by

$$k_\psi = \frac{k_c K_s [\text{Pip}] + k_c K_D [\text{D}]\,[\text{Pip}]}{1 + K_s [\text{Pip}] + K_D [\text{D}]} \qquad (11)$$

Hence in this system inhibition will be observed only if $K_D > K_S$. Equation (11) accurately represents the variation of k_ψ with mesitylene concentration, using values of K_S and K_D obtained from other systems.

Complexes formed by the nucleophile

The reactions of 1-fluoro-2,4-dinitrobenzene with *n*-butylamine in benzene[53] and 1,2-dinitrobenzene with piperidine in *n*-hexane[49] are catalysed by pyridine and have a curvilinear (concave-downwards) dependence on the pyridine concentration at constant nucleophile concentration. For both systems pyridine is a better catalyst at low than high nucleophile concentrations and Cattana *et al.*[49] have suggested that this is due to an association between pyridine and the nucleophile. In support of this, values of the second-order rate constant k_A at constant pyridine concentration tend to zero as the piperidine concentration decreases. Hirst *et al.*[54] have shown that for the reactions of picryl phenyl ether with aniline in benzene, at constant aniline concentration k_A increases linearly with increasing DABCO concentration. Over the concentration ranges



Scheme 13

0·08–0·3 M aniline and 0·001–0·02 M DABCO, the slopes of the plots of k_A vs [DABCO] decrease with increasing aniline concentration. None of the reaction mechanisms considered so far can accommodate this. They require that the slopes either be independent of, or increase with increasing, nucleophile concentration.

In Scheme 13, where N, P and S are the nucleophile, catalyst and substrate, respectively, for the condition [N] and [P] $\gg$ [S] and k_A is the measured second-order rate constant,

$$k_A = \frac{kK_M [\text{P}]}{1 + K_M [\text{P}]} \qquad (12)$$

where $[\text{P}] = [\text{P}]_{st}/(1 + K_M[\text{N}])$ and $[\text{P}]_{st}$ is the stoichiometric concentration of P. For $1 \gg K_M[\text{P}]$,

$$k_A = \frac{kK_M [\text{P}]_{st}}{1 + K_M [\text{N}]} \qquad (13)$$

Hence, provided [N] > [P], it is possible to obtain linear plots of k_A against the stoichiometric concentration of the catalyst and for the slopes of the plots to decrease with increasing nucleophile concentration. The essential difference between the complexes postulated here and those associated with Nudelman's[16] dimer mechanism is that here K_M is large enough for a significant proportion of the catalyst to be associated with the nucleophile, whereas in Nudelman's case the approximation $[\text{P}] \sim [\text{P}]_{st}$ can be made. In this respect the kinetic form of the picryl phenyl ether–aniline–DABCO reaction can be regarded as an extreme manifestation of the dimer mechanism.

CONCLUSIONS

There is little doubt that in solvents at low permittivity, the gross mechanism of aromatic nucleophilic substitution is that shown in Scheme 14, with the possibility of the formation of a complex prior to that of the intermediate I occurring. For a more detailed consideration of the mechanism of a particular reaction, the first point to be established is whether the formation or decomposition of the intermediate is rate limiting. Generally this has been done by a search for catalysis, and if this is established it has been assumed that there is base catalysis and except in special circumstances is taken as indicating that the decomposition of the intermediate to products is rate limiting. If a complex is established on the reaction path prior to the formation of the intermediate, this assumption is not necessarily

true. This establishment of a complex cannot be achieved by solely kinetic means; other data have to be utilized in conjunction with those obtained from kinetics.

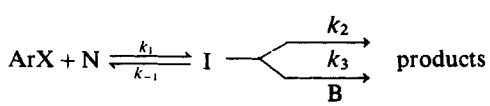
Once complex formation and commitant catalysis have been established, a choice still has to be made in the interpretation of the data between the mechanisms given in Schemes 8 and 9. The observation of catalysis by both nucleophile and an additive, e.g. DABCO, does not differentiate between the two but the observation of catalysis by one of the entities but not the other[31,42] can help in the mechanistic determination. With amines of appreciably greater basicity than *p*-anisidine (e.g. benzylamine, morpholine, piperidine) a term third order in nucleopile concentration indicates a rate-limiting decomposition of the intermediate I, but for aromatic amines the possibility exists of catalysis of the formation of I as in Figure 3, only attack taking place on the complex, not the free substrate.

As indicated earlier for the reactions of 2-halo-6-nitrobenzothiazoles with piperidine, k^{Br}/k^{Cl} ratios can be used diagnostically, low values indicating that the carbon–halogen bond is not broken in the rate-limiting step. This criterion has wider applications; thus, Arnone *et al.*[55] have shown that the second-order rate constant k_A for the reactions of 2-bromo-3,5-dinitrothiophene with *meta*- and *para*-substituted anilines in benzene obey equation (2). Although the k''/k' ratios are low (4·6–11), the accelerations are interpreted as being due to base catalysis on the grounds that there is an excellent linear correlation between k'' and k' and both give Hammett-type relationships. Alternative explanations can be given and k^{Br}/k^{Cl} values could be used to eliminate some of the possible mechanisms.

In solvents of low relative permittivity, whether or not the reaction proceeds via a complex is a function of the type of complex formed, the solvent and the nucleophile. If the putative complex is an EDA type, the substrate–nucleophile complex formation will depend on the relative electron-donating power of the nucleophile and the solvent. The relevant solvent property is its donicity, and reaction via a complex is more likely in solvents of low rather than high donicity. Aromatic amines are better donors than aliphatic amines, hence whereas the reactions of aliphatic amines in hexane appear to take place exclusively via a complex, this is not the case in benzene, but aromatic amines do react via complex formation in aromatic solvents. If complex formation takes place via hydrogen bonding, the relevant solvent property is its ability as a hydrogen-bond acceptor, reaction via complexes with the nucleophile being more likely in poor acceptors. Again, as the amino hydrogen atoms of aromatic amines are more acidic than those of aliphatic amines, in any given solvent there is a greater propensity for aromatic amines to react via complex formation. If the hydrogen-bond attachment is located at the leaving group,[43] there is little difference between this mechanism and that advocated by Hirst and co-workers[31,32] for the reaction of ethers. The essential difference is that in the latter, hydrogen bonding takes place on the intermediate formed within an aggregate and therefore should be less sensitive to changes in solvent and concentration. Irrespective of the nature of the complexes, reactions via complexes should be more prevalent at high rather than low concentrations of reactants and catalysts.

Whether a reaction proceeds via either the free substrate or a complex, the decomposition of the first-formed intermediate by the base-catalysed path when either the nucleophiles or primary or secondary amines are the catalysts can take place either through a cyclic transition state or by the homo/heteroconjugate mechanism. If reaction is via a hydrogen-bonded complex the cyclic mechanism will be preferred. A more detailed discussion of the factors affecting the two has been given by Emokpae *et al.*[32] Originally, one of the difficulties associated with the concept of cyclic transition states was that in many situations 'three-coordinate hydrogen' has to be assumed.[5] The existence of three-centred hydrogen bonds in crystals is now well established,[56] and if the formation of hydrogen bonds of weak to moderate strength is an electrostatic phenomenon, they should also exist in solutions of solutes in solvents of low relative permittivity. If the concept of reactions in these solvents taking place within aggregates is retained and three-centred hydrogen bonding is allowed, the distinction between cyclic and homo-heteroconjugate mechanisms becomes blurred.

In the homo-/heteroconjugate mechanism given in Scheme 7, II and NH^+ are probably present as an ion pair rather than free kinetic entities. The formation of homo- or heteroconjugates does not necessarily imply the existence of 'free' NH^+ (PH^+) as they can be



Scheme 14

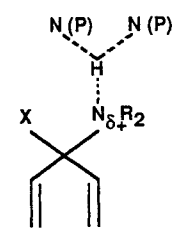


Figure 5. Three-centred hydrogen-bond formation of homo- and heteroconjugates

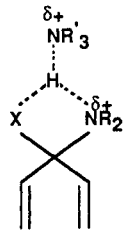


Figure 6. Transition state for catalysis of the decomposition of the intermediate by tertiary amines taking place via a cyclic mechanism

formed via the three-centred hydrogen-bonded entities represented in Figure 5.

For cyclic mechanisms, catalysis by tertiary amines can be represented by the bifurcated hydrogen-bonding structure in Figure 6. The two extreme cases of this structure are (i) there is little X—H bonding and the catalyst—H—NR_2 bonding is relatively strong, which corresponds to the ion pair of the homo-/heteroconjugate mechanism; and (ii) the catalyst—H—X bonding is relatively strong and the H—NR_2 bonding weak, corresponding to electrophilic catalysis of the nucleofuge in the homoconjugate mechanism. Case (i) is mostly likely to occur with fluoro substrates as C—F—H—Y hydrogen bonding has been reported to be either very weak[56] or undetectable[57], and case (ii) when the leaving group is alkoxy.

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