Mechanism of the Uncatalysed Path of Aromatic Nucleophilic Substitution in Dipolar Aprotic Solvents when Primary and Secondary Amines are the Nucleophiles; a Search for Electrophilic Catalysis of these Reactions

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The kinetics of the reactions of 1-chloro- and 1-fluoro-2,4-dinitrobenzene with morpholine have been studied in dimethyl sulphoxide, dimethylformamide, and nitromethane. The results confirm that the decomposition of the intermediate to products by the uncatalysed path takes place by a unimolecular mechanism. The kinetics of the reactions of 2,4-dinitroanisole with n-butylamine and piperidine in dipolar aprotic solvents have been determined. They show that when primary amines are the nucleophiles, reaction by the uncatalysed path does not occur by the unimolecular mechanism, but by the specific base–general acid (SB–GA) route. The reactions in dimethyl sulphoxide give another example of secondary amines reacting by a base catalysis mechanism whereas the corresponding reaction of a primary amine of the same basicity is not base-catalysed.

In a search for electrophilic catalysis the effects of lithium, trialkylammonium, and tetraalkylammonium ions on the reactions of piperidine with 2,4-dinitroanisole and of morpholine with 2,4-dinitrophenyl phenyl ether in dimethyl sulphoxide were investigated. No catalysis was found and a tentative reason is given. When aniline reacts with 2,4,6-trinitrophenyl methyl ether in dimethyl sulphoxide, 82% of the reaction occurs at the methyl carbon atom, and when the substrate is 2,4,6-trinitrophenyl phenyl ether the reaction is not base-catalysed. The first two observations of the change from base-catalysed to uncatalysed aromatic nucleophilic substitution reactions brought about by a change from protic to dipolar aprotic solvent are recorded.

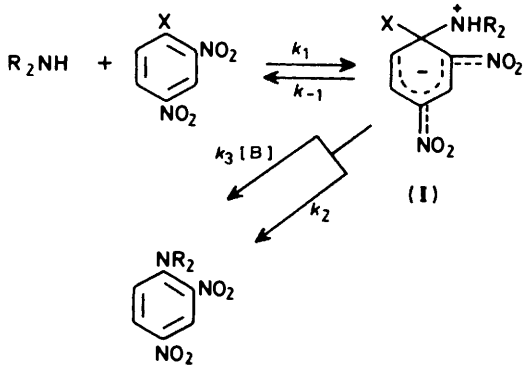
The mechanism of aromatic bimolecular nucleophilic substitution reactions when primary or secondary amines are the nucleophiles is now well established (Scheme 1). Application of the steady-state hypothesis gives equation (1), where k_A is the

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

observed second-order rate constant and 'B' can be either a second molecule of the nucleophile or an added base. Either the formation of the intermediate (I) or its decomposition to products can be rate-limiting. If $k_{-1} \ll (k_2 + k_3\{B\})$, then $k_A = k_1$, the reaction is not base catalysed, and the formation of (I) is the rate-limiting step. If this condition does not hold, the decomposition to products is rate-limiting and the reaction is base-catalysed. Two forms of base catalysis have been observed in protic and dipolar aprotic solvents: (a) when equation (1) cannot be simplified further, there is a curvilinear, concave-downward dependence of k_A on the concentration of the base; (b) when the condition $k_{-1} \gg (k_2 + k_3\{B\})$ holds equation (1) reduces to equation (2) and there is a linear dependence of k_A

$$k_A = k' + k''\{B\} \qquad (2)$$

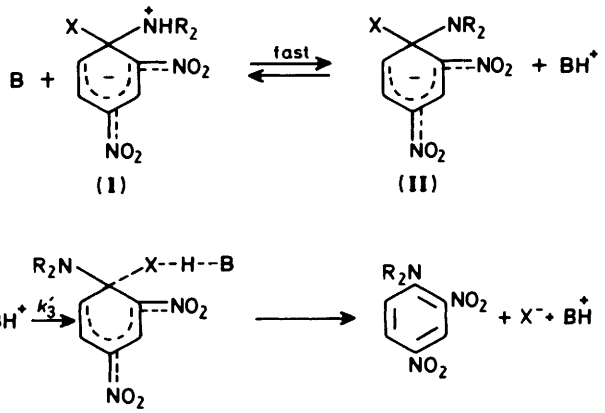
on catalyst concentration. In many aromatic bimolecular substitution reactions small, linear increases of k_A with increasing nucleophile (or more generally, added base) concentration are observed. The values of k''/k' are small, and the accelerating effect of the bases bears no relationship to their base strength. According to Bunnett[1] this does not represent true base catalysis, the formation of the intermediate is rate-determining in these reactions, and the small increases are due to some unspecified effect. In other reactions increase in base concentration has a powerful accelerating effect, the value of k''/k' is high (>50), and the catalytic effect increases with



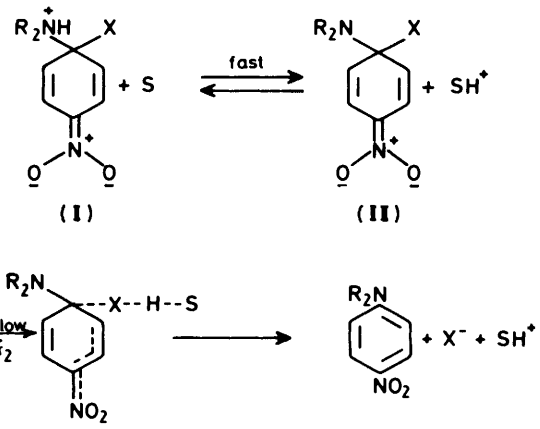
Scheme 1.

increase in strength of the base. These reactions are regarded as base-catalysed and the decomposition of the intermediate is rate-limiting.

Subsequent research has been directed towards the nature of both catalysed and uncatalysed decomposition of the intermediate (I). For reactions in dipolar aprotic solvents of high dielectric constant, *e.g.* dimethyl sulphoxide, the generally accepted mechanism for the catalysed route is that proposed by Bunnett and Davies.[2] This is the rapid transformation of the first formed intermediate into its conjugate base, followed by the slow, electrophilically catalysed expulsion of the leaving group as shown in Scheme 2. On this interpretation k_3 {equation (1)} = $\bar{k}_3 K_B$, where $K_B = [(II)][RNH_3^+]/[(I)][RNH_2]$. This mechanism, sometimes referred to as the SB–GA (specific base–general acid) mechanism, was believed originally to operate also in protic solvents, but this has been challenged by Bernasconi.[3]

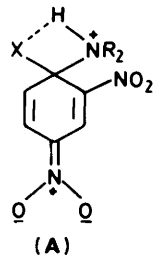


Scheme 2.



Scheme 3.

In dipolar aprotic solvents the mechanism of the uncatalysed route is usually discussed in terms of either a unimolecular decomposition *via* the internally hydrogen-bonded transition state (A) or by a mechanism similar to that of the catalysed pathway with a solvent molecule acting as a base as shown in Scheme 3. This latter mechanism requires k_2 {equation (1)} = $\bar{k}_2 K_s$, where $K_s = [(II)][SH^+]/[(I)]$. We have shown that this



(A)

mechanism does not apply when a secondary amine is the nucleophile. Our demonstration was based on the fact that K_S defines the strength of the conjugate acid of an amine and it is known that this can vary enormously depending on the basicity of the solvent in which it is measured (the ratio of acid strengths of the tri-n-butylammonium ion in dimethyl sulphoxide and acetonitrile[4] is 5×10^9:1). Hence if the Bunnett mechanism applies to both the catalysed and uncatalysed paths there should be a large difference in the value of k_3/k_2 ($=\bar{k}_3 K_B/\bar{k}_2 K_S$) in solvents of widely differing basicity. For the reactions of 2,4-dinitrophenyl phenyl ether with morpholine[5] and piperidine[6] there was little change in this ratio when the solvent was changed from dimethyl sulphoxide to acetonitrile; hence we concluded that the uncatalysed path did not proceed by this mechanism. One of the objectives of this work was to provide further evidence by studying the reaction of 1-fluoro- and 1-chloro-2,4-dinitrobenzenes with morpholine in a series of dipolar aprotic solvents.

In Scheme 1, when the substrate contains an *ortho*-nitro group, hydrogen bonding occurs in intermediate (I) between the ammonium hydrogen atoms and the oxygen atoms of the nitro group. When the nucleophile is a secondary amine this has to be broken before reaction can take place by either the Bunnett or the unimolecular mechanism. When the nucleophile is a primary amine a second hydrogen atom is available for reaction by either mechanism without prior breaking of the hydrogen bond, hence the mechanism of the uncatalysed path could be different for primary and secondary amines. In the reaction of 1-fluoro-2,4-dinitrobenzene with aniline[7] not only is there a large change in k_3/k_2 with change of solvent basicity but there is a gradual change from the condition $k_{-1} \ll k_2$ to $k_{-1} \gg k_2$ in the solvent series dimethyl sulphoxide, dimethylformamide, acetonitrile, nitromethane. Both these changes are explicable on the Bunnett, but not on the unimolecular, mechanism of decomposition of the intermediate. In this system there is a possibility[7]

Table 1. Rate constants (l mol^{-1} s^{-1}) for the reactions of 1-fluoro- and 1-chloro-2,4-dinitrobenzene with morpholine in some dipolar aprotic solvents

Solvent	Substrate*	t/°C							
Dimethyl sulphoxide	Chloro[a]	30.0	10^4[amine]/M	8	10	20	40	50		
			10 k_A	3.99	3.91	4.02	4.10	4.18		
	Fluoro[b]	30.0	10^4[amine]/M	3.20	4.40	5.60	6.40	9.60	12.8	16.0
			k_A	21.6	21.9	22.2	21.9	21.1	21.3	23.8
Dimethyl-formamide	Chloro[a]	30.4	10^4[amine]/M	5	10	30	50	80	100	
			10 k_A	2.14	2.00	2.08	2.18	1.98	2.02	
	Fluoro[a]	30.0	10^4[amine]/M	4	5	6	8	10	20	
			k_A	2.53	2.70	2.88	3.24	3.58	4.10	
Nitromethane	Chloro[c]	30.4	10^3[amine]/M	1.0	1.60	2.00	3.0	4.0		
			$10^2 k_A$	1.89	2.74	3.20	3.78	4.24		
	Chloro[d] in presence of 0.05M-morpholine hydrochloride	30.4	10^3[amine]/M	2.0	4.0	5.0	8.0	10.0		
			$10^2 k_A$	4.39	4.50	4.34	4.63	4.32		
	Fluoro[a]	30.4	10^4[amine]/M	4	8	10	16	20	32	40	50
			10 k_A	2.88	5.40	7.33	11.25	13.0	16.0	17.3	17.8

*[substrate]/M [a] 5×10^{-5}, [b] 2.98×10^{-5}, [c] 2.5×10^{-4}, [d] 1.25—2.5×10^{-4}

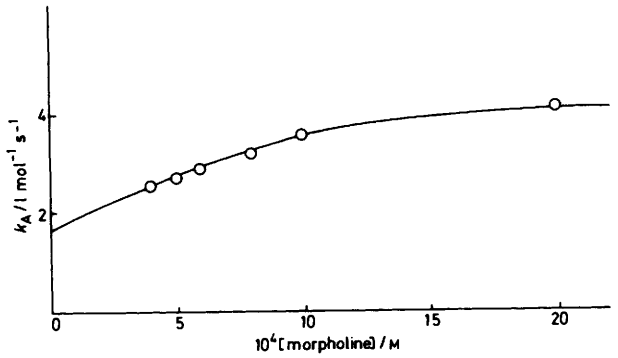


Figure 1. Plot of k_A against 10^4[morpholine]/M for the reaction of 1-fluoro-2,4-dinitrobenzene with morpholine in dimethylformamide at 30.0 °C

that the rate-limiting step is the abstraction of the proton from (I) in Scheme 2; hence it is desirable to examine a system with a primary–secondary amine pair of much greater basicity than aniline. The reactions of piperidine and n-butylamine with 2,4-dinitroanisole appeared appropriate as both reactions are known[3,8] to be base-catalysed in protic solvents. Finally it was hoped that both the fluoro and anisole systems would be suitable to demonstrate the electrophilic catalysis which Scheme 2 demands.

(i) *Reaction of Morpholine with 1-Fluoro- and 1-Chloro-2,4-dinitrobenzene.*—Reliable kinetic results were obtained for the reactions of both substrates in all the solvents investigated, and the experimental values of the absorbances at infinity agreed with the theoretical ones. The results are give in Table 1.

The second-order rate constant, k_A, for the reaction of the chloro substrate is independent of the morpholine concentration in all solvents, except nitromethane for which a curvilinear dependence on the nucleophile concentration occurs. Chloride ion is an extremely good leaving group, and as only one example[9] of an apparently base-catalysed aromatic nucleophilic substitution reaction is known which involves the expulsion of chloride, an alternative explanation was sought. In the presence of 0.05M-morpholine hydrochloride, k_A is constant over at least a five-fold range of morpholine concentration; thus the original variation is attributed to the equilibrium: morpholine + $CH_3NO_2 \rightleftharpoons$ morpholine $H^+ + {}^-CH_2NO_2$. The sequence of relative reactivities in dimethyl sulphoxide, dimethylformamide, acetonitrile,[10] and nitromethane (8.5:4.3:1:0.94) is similar to that obtained for this substrate with aniline[7] (63.6:19.5:1:0.4). In both cases the biggest change occurs between dimethylformamide and acetonitrile, which as already discussed[7] is in agreement with the solvating power of the solvents. The span of the reactivities however is greater for aniline. As the substrate contains an *ortho*-nitro group, built-in solvation[11] will occur in both reactions, but as aniline has two amino hydrogen atoms and morpholine only one, the solvent levelling effect of this phenomenon will be greatest for morpholine.[12]

The reactions of the fluoro-substrate are not base-catalysed in dimethyl sulphoxide, but in dimethylformamide there is a curvilinear dependence of k_A on the morpholine concentration (Figure 1), similar to that observed for this reaction in acetonitrile.[10] Because of the complications observed in the reactions of the chloro-substrate in nitromethane, the results in this solvent are treated separately.

Application of standard methods of analysis[1] to the results in dimethylformamide and acetonitrile gives values of k_1 5.13 l mol^{-1}s^{-1}; k_2/k_{-1} 0.13; k_3/k_{-1} 1.96×10^3 l mol^{-1} in dimethylformamide; and k_1 2.06 l mol^{-1} s^{-1}; k_2/k_{-1} 0.53; k_3/k_{-1} 262 l mol^{-1} in acetonitrile. These values of k_1 give relative values in dimethyl sulphoxide, dimethylformamide, and acetonitrile of 10.6:2.5:1, similar to those obtained for the chloro-substrate. There is a factor of *ca.* 30 between the derived values of k_3/k_2 (1.51×10^4 for dimethylformamide; 494 for acetonitrile) but apart from this being small as compared with the solvent variation of K_S, both these values and those of k_2/k_{-1} are in the opposite direction from that expected for the effect of solvent basicity on a Bunnett-type mechanism.

The values of k_2/k_{-1} and k_3/k_{-1} show that the reaction in dimethylformamide is on the border between the condition $k_{-1} \sim (k_2 + k_3[B])$ and $k_{-1} \ll (k_2 + k_3[B])$, and only a slight variation in the relative values of the rate constants is required to bring about the change. This is presumably what occurs in dimethyl sulphoxide; as dimethyl sulphoxide has either the same basicity or is *ca.* one pK unit more basic than dimethylformamide,[13] the change in kinetic form which occurs in this solvent cannot be ascribed to the effect of change of solvent basicity.

Analysis of the results in nitromethane gives k_1 2.78 l mol^{-1} s^{-1}; k_2/k_{-1} 0.09; k_3/k_{-1} 388 l mol^{-1}; whence k_3/k_2 4.3×10^3 l mol^{-1}. The value of k_1 is greater than that obtained in acetonitrile, which is contrary to all previous experience and confirms the deductions made from the behaviour of the chloro-substrate that there are complications in the reaction in this solvent, presumably because of interaction between the nucleophile and the solvent.

The values of the derived ratios must therefore at the best be very approximate. Even so there is only a factor of 2—6 between k_2/k_{-1} values in this and the other two solvents and the k_3/k_2 value is intermediate between that of acetonitrile and dimethylformamide. Hence no dramatic change in the magnitude of these ratios occurs in nitromethane, in agreement with the uncatalysed path following the unimolecular mechanism.

(ii) *Reactions of 2,4-Dinitroanisole with Piperidine and n-Butylamine.*—The reactions of 2,4-dinitroanisole with piperidine in dimethyl sulphoxide and acetonitrile gave values of the absorbance at infinite time which were less than the calculated ones at low piperidine concentrations, but good agreement between the two values was obtained at higher concentrations. This behaviour is due to the S_N2 attack of piperidine on the methyl group, forming *N*-methylpiperidine and 2,4-dinitrophenol. Formation of these products has been observed when the reaction is carried out in methanol[8] and in benzene.[14] The results at low piperidine concentrations gave values of the rate constant for the S_N2 reaction of *ca.* 6.2×10^{-6} l mol^{-1} s^{-1} in dimethyl sulphoxide and *ca.* 2.7×10^{-6} l mol^{-1} s^{-1} in acetonitrile, independent of the piperidine concentration. The effect of solvent change is similar to that on the reaction of triethylamine with ethyl iodide[15] (10^4k_2 8.73 in dimethyl sulphoxide; 2.27 in acetonitrile) and the relative values of the rate constants for attack at aromatic (given in Table 2) and aliphatic carbon atoms explains the increasing preponderance of attack at the aromatic centre with increasing piperidine concentration.

The plot of k_A against piperidine concentration is linear through the origin in both dimethyl sulphoxide (slope 9.67×10^{-4} l^2 mol^{-2} s^{-1}) and acetonitrile (slope 5.25×10^{-5} l^2 mol^{-2} s^{-1}). The kinetic form corresponds to the condition $k_{-1} \gg k_3\{B\} \gg k_2$, giving the slope $= k_1k_3/k_{-1}$. If, as believed, the mechanism of the base-catalysed step is the same for primary and secondary amines, the effect of solvent change on k_3/k_{-1} should be the same for both types of amine. For the reaction of 1-fluoro-2,4-dinitrobenzene with aniline,[7] k_3/k_{-1} decreases from 2.0 l mol^{-1} in dimethylformamide to 0.4 l mol^{-1} in acetonitrile. As the value of k_1 is greater in dimethyl

Table 2. Rate constants (l mol^{-1} s^{-1}) for the reactions of 2,4-dinitroanisole with piperidine and n-butylamine in some dipolar aprotic solvents at 30.0 °C

Solvent	Amine						
Dimethyl sulphoxide	Piperidine[a]	10^2[amine]/M	5	10	20	25	30	
		10^5k_A	4.58	9.51	19.6	23.4	28.9	
	n-Butylamine[a]	10^3[amine]/M	5	10	20	30	40	50
		10^2k_A	1.81	2.16	2.18	2.22	1.99	2.14
Dimethyl-formamide	n-Butylamine[a]	10^2[amine]/M		1.0	2.0	4.0	5.0	
		10^3k_A		7.75	7.75	8.03	7.92	
Acetonitrile	Piperidine[a]	10^2[amine]/M	5	10	20	40	50	70
		10^6k_A	2.62	4.84	9.84	20.5	27.1	37.9
	n-Butylamine[a]	10^3[amine]/M	5	10	20	30	40	50
		10^4k_A	6.50	7.81	8.75	9.03	9.20	9.30
	DABCO[a,b]	10^3[amine]/M	0	4.08	8.16	12.24	24.48	
		10^4k_A	6.50	7.28	7.94	8.66	8.66	

[a] Substrate concentration 3×10^{-4}M. [b] [n-butylamine] 5×10^{-3}M.

sulphoxide than in acetonitrile, the change in the magnitude of the slope is in the expected direction.

Because of the kinetic form of the reaction, no deductions can be made about the mechanism of the uncatalysed path in these reactions. At present there is a controversy over the mechanism of the base-catalysed step of piperidinodemethoxy aromatic substitutions in protic solvents,[3,16] but whatever the mechanism, in all cases the amount of product formed *via* the uncatalysed pathway is negligible as is the case in dipolar aprotic solvents.

The reaction of 2,4-dinitroanisole with n-butylamine went smoothly to completion in all solvents and no evidence for the formation of side products was obtained. This is similar to the results of Palleros and Nudelman[17] who found no evidence for an S_N2 component in the reaction of cyclohexylamine with 2,4- and 2,6-dinitroanisole in benzene and in hexane. The reaction in dimethyl sulphoxide and in dimethylformamide is not base-catalysed, and the ratio of the second-order rate constants $k_1(Me_2SO)/k_1(Me_2NCHO)$ of 2.6 is close to the value of 3.3 obtained for the reactions of 1-chloro-2,4-dinitrobenzene with aniline.[7] A comparison with the corresponding reaction of 2,4-dinitrophenyl phenyl ether in dimethyl sulphoxide[6] gives a value of $k_1(OPh)/k_1(OMe)$ of 2.7. The difference in kinetic form in dimethyl sulphoxide between the reactions of n-butylamine and piperidine provides another example of primary and secondary amines of the same basicity reacting by different mechanisms.[6,18]

In acetonitrile, k_A has a curvilinear dependence on both n-butylamine and 1,4-diazabicyclo[2.2.2]octane (DABCO) concentrations (Figure 2). The base-catalysed path of the reaction of 2,4-dinitro-1-naphthyl ethyl ether with n-butylamine in dimethyl sulphoxide has been shown[19] to occur by the SB–GA mechanism, and by analogy this is the mechanism for the present reaction. Thus the change of kinetic form with solvent basicity shows that the uncatalysed route proceeds by a Bunnett-type mechanism with solvent acting as a base, and the element of doubt which was present in the interpretation of the results of the aniline–1-fluoro-2,4-dinitrobenzene reaction[7] is not there. The similarity in behaviour of the two systens reinforces the belief that this mechanism also operates in the aniline system.

A similar type of kinetic form to that in acetonitrile has been observed for the reaction in 60% aqueous dioxane.[3] If this represents genuine base catalysis, then the results in dimethyl sulphoxide record the first observation of a change from catalysed to uncatalysed reaction brought about by a change from protic to dipolar aprotic solvent. The usual influence of solvent is to effect a change from non-catalysed to catalysed when the solvent is changed from protic or dipolar aprotic to aprotic. Thus the reaction of 4-fluoronitrobenzene with piperidine is not catalysed in methanol,[20] dimethyl sulphoxide,[20] dimethylformamide,[20] acetone,[20] or acetonitrile,[20] but in benzene the reaction is second-order in piperidine.[21] It would be imprudent however to draw mechanistic conclusions concerning the uncatalysed step in dipolar aprotic solvents in view of the uncertainty of the mechanism of the catalysed path in protic solvents[3] and the difference in hydrogen-bonding properties of the two types of solvent.

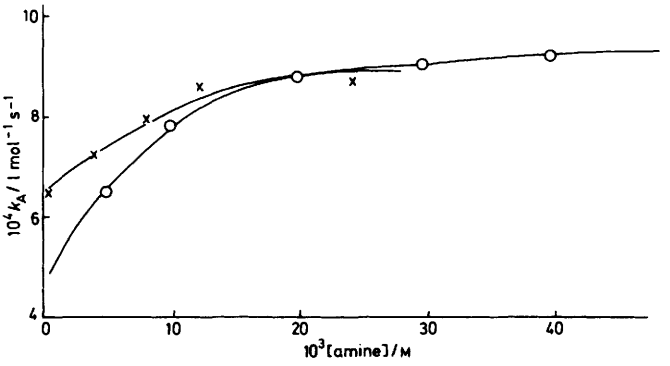


Figure 2. Plots of 10^4k_A against 10^3[amine]/M for the reaction of 2,4-dinitroanisole with n-butylamine in acetonitrile at 30.0 °C: ○, n-butylamine; × DABCO

(iii) *A Search for Electrophilic Catalysis.*—In dipolar aprotic solvents the evidence for the SB–GA mechanism for the base-catalysed decomposition of the intermediate to products given in Scheme 2 is supported by two pieces of evidence. Orvick and Bunnett[19] were able to measure separately the rates of formation and decomposition to products of the intermediate [the conjugate base corresponding to (II) in Scheme 2] formed in the reaction of 2,4-dinitro-1-naphthyl ethyl ether with n-butylamine in dimethyl sulphoxide. The decomposition of the intermediate was found to be first-order in n-butylammonium ion, but independent of free amine concentration. Ayediran, Bamkole, and Hirst[22] showed that the reaction between 1-fluoro-4-nitrobenzene and trimethylamine in dimethylsulphoxide is catalysed by trimethylammonium and lithium ions.

These demonstrations of electrophilic catalysis occur in systems which have characteristics somewhat unusual in aromatic nucleophilic substitution reactions. In the first, the intermediate formed is sufficiently stable (long lived) to be observed spectrally, and in the second no amino hydrogen atoms are present. Thus there is a dearth of evidence for the electrophilic catalysis of 'normal' nucleophilic substitution

Table 3. Effect of various additives on the rate constants (l mol s^{-1}) for the reactions of 2,4-dinitroanisole[a] with piperidine[b] and of 2,4-dinitrophenyl phenyl ether[a] with morpholine in dimethyl sulphoxide at 30.0 °C

2,4-Dinitroanisole with piperidine							
In the presence of methanol							
10^3[methanol]/M	0	6	10	20	30	40	50
10^4k_A	1.80	1.61	1.60	1.60	1.65	1.67	1.60
In the presence of triethylammonium perchlorate							
10^3[Et_3NHClO_4]/M	0	6	10	20	30	40	50
10^4k_A	1.80	1.58	1.54	1.43	1.23	1.12	0.96
In the presence of lithium perchlorate							
10^3[$LiClO_4$]/M	0	5	10	20	30	40	50
10^4k_A	1.80	1.72	1.81	1.87	1.94	2.07	2.19
In the presence of tetraethylammonium perchlorate							
10^3[Et_4NClO_4]/M	0	3	5	10	15	20	25
10^4k_A	1.80	1.77	1.75	1.80	1.79	1.83	1.81
Dinitrophenyl phenyl ether with morpholine							
In the presence of triethylammonium perchlorate[c]							
10^2[Et_3NHClO_4]/M	0	1.33	2.66	3.99	5.32	7.92	
10^5k_A	97.2	23.0	10.3	6.80	5.00	3.83	
In the presence of tetraethylammonium perchlorate[d]							
10^3[Et_4NClO_4]/M	0	5	10	30	60		
10^3k_A	1.48	1.47	1.49	1.48	1.49		
In the presence of lithium perchlorate[d]							
10^3[$LiClO_4$]/M	0	1.0	2.0	3.0	4.0	6.0	
10^3k_A	1.49	1.49	1.49	1.51	1.50	1.50	

[a] Substrate concentration 2.5—3.0 × 10^{-4}M. [b] [piperidine] 1.80 × 10^{-1}M. [c] [morpholine] 2.5 × 10^{-2}M. [d] [morpholine] 5.0 × 10^{-2}M.

reactions of primary and secondary amines with aromatic substrates.

As it has been shown[22] that in dimethyl sulphoxide the removal of fluoride ion is catalysed by alkylammonium and lithium ions, it was proposed to study the reaction of 1-fluoro-2,4-dinitrobenzene with morpholine, but as shown in section (i) the formation of the intermediate is rate-limiting in this solvent. As Bunnett[19] has demonstrated that the removal of ethoxide in dimethyl sulphoxide is subject to electrophilic catalysis, and the results discussed in section (ii) show that in this solvent the base-catalysed breakdown to products of the intermediate formed in the reaction of piperidine with 2,4-dinitroanisole is wholely rate-determining, this system was chosen for investigation. The effect of electrophilic catalysts on the rate was studied using a constant concentration of 0.18M in piperidine. In the presence of methanol the values of the absorbance at infinite time decreased slightly with increasing methanol concentration, indicating a small amount of methanolysis arising from the equilibrium $R_2NH + MeOH \rightleftharpoons R_2NH_2^+ + {}^-OMe$. For all the other additives good agreement was observed between calculated and experimental values of the absorbance at infinite time, hence for this piperidine concentration no complications due to side reactions occur. The results are given in Table 3.

The addition of 6—50 × 10^{-3}M-methanol has very little effect; the value of k_A remains constant at about 89% of its original value throughout the range of methanol concentrations investigated. This slight reduction in rate could be a manifestation of the stabilisation of the ground state by hydrogen bonding: $R_2HN \cdots H\text{–}OMe$.

Reliable rate constants for individual runs were obtained in the presence of triethylamine perchlorate,* but the value of k_A decreased with increasing concentration of perchlorate. This decrease was greater than could be accounted for even by assuming the equilibrium piperidine + $Et_3NH^+ \rightleftharpoons$ piperidine $H^+ + Et_3N$ was completely over to the right, and indicates stabilisation of the ground state by hydrogen bonding to piperidine by piperidinium ions.

The addition of lithium perchlorate gave a slight linear increase of k_A with increasing concentration of the salt. Apart from the very strong catalysis by lithium ions of the reaction of triethylamine with 1-fluoro-4-nitrobenzene in dimethyl sulphoxide,[22] the effect of lithium perchlorate on aromatic nucleophilic substitution reactions involving amines is usually small and difficult to rationalise. For the reaction of 1-chloro-2,4-dinitrobenzene with aniline in water[23] and for 2,4-dinitrophenyl phenyl ether with piperidine in acetonitrile,[24] the second-order rate constant decreases linearly with increasing perchlorate concentration. Addition of the salt however has no effect on the rate of reaction of 1-fluoro-2,4-dinitrobenzene with aniline in acetonitrile.[24] These differences are probably due to the fact that all these reactions exhibit different kinetic forms. For the present results, although the addition of tetraethylammonium perchlorate has no effect on the rate constant, the value of k''/k' (*ca.* 5) is much too small to indicate true base catalysis and is best regarded either as a salt effect or an example of Bunnett and Garst's[1] 'mild accelerations of unclear origin.' If it is due to catalysis the effect is extremely weak.

* Electrophilic catalysis cannot be demonstrated by using alkylammonium salts derived from the nucleophile. From Scheme 2:

$$d\{\text{products}\}/dt = k_3'[(II)][BH^+] = k_3'K[(I)][B]$$

where $K = [(II)][BH^+]/[(I)][B]$

Trialkylammonium salts have been used, as the parent amines are comparatively very unreactive as nucleophiles in aromatic nucleophilic substitution reactions.

As the kinetic form of the reaction with piperidine shows that $k_A = k_1k_3$ [piperidine]$/k_{-1}$, the results show that there is no significant electrophilic catalysis of the base-catalysed path by methanol or lithium ions.

In the foregoing reaction it possible that catalysis by triethylammonium ions may have been obscured by the equilibrium between them and piperidine. As morpholine is a much weaker base than piperidine it was thought that the use of this base as a nucleophile would be more conducive to the demonstration of electrophilic catalysis by triethylammonium ions, as the equilibrium between nucleophile and catalyst would be much more in favour of the triethylammonium ions. As the reaction of 2,4-dinitroanisole would be slow and possibly complicated by attack on the methyl group, the substrate used was the phenyl ether. The reaction has already been studied in dimethyl sulphoxide,[5] but before the effect of the addition of salts, given in Table 3, was investigated, the linear dependence of k_A on morpholine concentration was confirmed. The addition of lithium and tetraethylammonium perchlorates has no effect on the second-order rate constant, but with triethylammonium perchlorate, k_A decreases asymptotically with increasing salt concentration. If the rate constants are corrected for the equilibrium between the nucleophile and the salt, assuming pK_a values of morpholine in dimethyl sulphoxide of either 8.8 or 9.4,* k_A still decreases with increasing concentration of perchlorate.

The pK_a of aniline in dimethyl sulphoxide is 3.6,[4] and that of triethylamine is 9.0.[13] As the reaction in acetonitrile of aniline with 1-fluoro-2,4-dinitrobenzene is not adversely affected by the addition of trimethylammonium ions,[25] it was hoped that the system aniline–trimethylammonium ion would be suitable for the investigation of catalysis by trialkylammonium ions. The reaction of aniline with 1-fluoro-2,4-dinitrobenzene in dimethyl sulphoxide is not base-catalysed,[7] and hence a substrate with a much poorer leaving group is required, such as methoxy. As aniline is a much weaker nucleophile than piperidine (in acetonitrile, piperidine is 9×10^4 times as reactive towards 1-chloro-2,4-dinitrobenzene as is aniline) reaction with 2,4-dinitroanisole would be much too slow to be investigated; hence the more activated 2,4,6-trinitrophenyl methyl ether was used. Analysis of the products of the reaction (see Experimental section) showed that they consisted of 82% picric acid and only 18% of the product of aromatic nucleophilic substitution; hence the system is not suitable for the investigation of electrophilic catalysis. Cahn[26] has reported that this substrate is converted quantitatively into picric acid after 1 min reflux in either neat pyridine or piperidine, and the dramatic increase in the S_N2 rate relative to that of aromatic substitution when the system is changed from n-butylamine–2,4-dinitroanisole to aniline–2,4,6-trinitroanisole is in accord with the increase observed by Nudelman and Palleros[14] for the reactions of piperidine with 2,4- and 2,6-dinitroanisole in benzene.

Banjoko and Otiono[27] have shown that the reaction of 2,4,6-trinitrophenyl phenyl ether with aniline in methanol is base-catalysed; hence this appeared to be a suitable system to study electrophilic catalysis free from side reactions. In dimethyl sulphoxide reliable kinetics were obtained, the experimental absorbance at infinity agreeing with the calculated one. The results in Table 4 however show that the reaction is not base-catalysed, as k_A remains constant over a five-fold range of aniline concentration and the reaction is not catalysed by DABCO. The slight linear increase in the rate constant with increasing DABCO concentration gives a k''/k' value of *ca.* 11, too small to be regarded as indicative of authentic base catalysis; this may be due to the reaction of DABCO with the substrate. The absorbance of a solution containing only the ether and 1.6 10^{-2}M-DABCO (the highest concentration used in these reactions) was followed at 375 nm, the wavelength used in all these measurements. When the results were used to calculate an apparent rate constant using the same infinity value as for k_A, a value of 1.31×10^{-4} l mol^{-1} s^{-1} was obtained. The reaction of aniline with the ether is the second example of the change from catalysed to uncatalysed reaction brought about by a change from protic to dipolar aprotic solvent. Again it would be unwise to draw any mechanistic conclusions from this, as Bernasconi[3] has shown that in aqueous dioxane when the leaving group is phenoxy, the slow step of the reaction is most probably the abstraction of a proton from (I) (Scheme 2), and that there is considerable uncertainty about the mechanism of the uncatalysed path.

Table 4. Effect of aniline and 1,4-diazabicyclo[2.2.2]octane (DABCO) on the rate constants (l mol^{-1} s^{-1}) for the reaction of 2,4,6-trinitrophenyl phenyl ether[a] with aniline in dimethyl sulphoxide at 30.0 °C

10^3[aniline]/M	1.0	2.0	4.0	5.0	
10^2k_A	5.83	5.85	5.76	5.70	
10^3[DABCO][b]/M	0	4	8	12	16
10^2k_A	5.83	6.01	6.26	6.63	6.88

[a] Substrate concentration 3×10^{-4}M. [b] [aniline] 1×10^{-3}M.

The present investigation has produced no evidence for the catalysis of aromatic nucleophilic substitution reactions by lithium or trialkylammonium ions. In the case of lithium ions the evidence is unambiguous, but no definite conclusions can be drawn from this as there is no experimental evidence that the expulsion of methoxy or phenoxy groups in these reactions is capable of being catalysed by this ion: catalysis by lithium ion has only been demonstrated for the expulsion of fluoride ion. When the putative catalysts are trialkylammonium ions, the lack of catalysis of the expulsion of methoxide ion could be due to an unfavourable equilibrium between the triethylammonium ions and piperidine, but in the phenyl ether–morpholine system this is not the case, and although catalysis of the ejection of phenoxy has never been demonstrated experimentally, the premise that it does occur is the basis of the SB–GA mechanism.

The lack of catalysis is not likely to be due entirely to steric effects,† as with the substrate 2,4-dinitro-1-naphthyl ethyl ether, catalysis of the removal of the ethoxy group is observed[19] when the nucleophile and catalyst are the bulky t-butylamine and its ammonium ion. It may be that in these reactions the catalytic effect of an added electrophile is at the best small due to a 'proximity effect.' The second intermediate formed in the Bunnett mechanism is a highly reactive species. The conjugate acid of the base that removes the proton from the first intermediate is generated in the immediate vicinity of the leaving group and hence has an advantage over other catalysts in solution. In the case of the 2,4-dinitro-1-naphthyl ether, the intermediate has a much longer kinetic life, enabling it to build up sufficient concentration to be observed spectroscopically and to be attacked by other species in solution. If this interpretation

* The pK_A of morpholine in dimethyl sulphoxide is not known. The values of pK_a of morpholine differ from those of n-butylamine by 2.3 and 1.7 units in water and acetonitrile, respectively. The pK_a values cited for dimethyl sulphoxide solution were obtained by subtracting these values from that of n-butylamine in dimethyl sulphoxide.

† Since this manuscript was completed we have had access to the paper by Crampton and Routledge, *J. Chem. Soc., Perkin Trans. 2*, 1984, 573, who have shown that steric effects operate in the ejection of the leaving group when the nucleophile is piperidine and the catalyst its conjugate acid. Similarly, reductions in the rate constants for proton transfers from the zwitterionic intermediates to amines below that expected for diffusion-controlled reactions have been attributed to steric effects.

is correct it is unlikely that strong electrophilic catalysis will be observed in 'normal' aromatic nucleophilic substitution reactions. Experiments are in hand to assess the relative contributions of steric and proximity effects (if any) to the observed lack of electrophilic catalysis.

Experimental

The purifications of 1-chloro- and 1-fluoro-2,4-dinitrobenzene,[28] dimethyl sulphoxide,[22] dimethylformamide,[7] acetonitrile,[29] nitromethane,[7] aniline,[30] n-butylamine,[10] piperidine,[10] morpholine,[10] lithium perchlorate,[22] tetra-n-butylammonium perchlorate,[22] and DABCO[31] have been described previously. 2,4,6-Trinitroanisole, m.p. 68 °C(lit.,[32] 67.5—68 °C), and 2,4,6-trinitrophenyl phenyl ether, m.p. 155 °C (lit.,[33] 155—156 °C), were made from picryl chloride, and 2,4-dinitroanisole (m.p. 95—96 °C; lit.,[34] 95 °C) from 1-chloro-2,4-dinitrobenzene.

Kinetic Procedure.—All reactions were followed by the spectrophotometric determination of the products. The rates of the fast reactions were measured with either a Gilford 2400 or a Beckman DU 8 recording spectrometer; the other reactions were followed using the pipette technique already described.[28] When concurrent reactions reduced the experimental value of the absorbance at infinite time below the theoretical one, the rate constants were calculated by standard procedures.[35] It is known[29] that picryl chloride reacts with dimethyl sulphoxide, and both the methyl and phenyl ethers of picric acid gave yellow solutions in this solvent. The colour was discharged on addition to methanolic 2M-sulphuric acid and the reaction of the phenyl ether with aniline gave reliable kinetics with excellent agreement between the experimental and theoretical values of the absorbance at infinite time.

Products of the Reaction between 2,4,6-Trinitrophenyl Methyl Ether and Aniline in Dimethyl Sulphoxide.—The reaction between a 3×10^{-4}M-solution of the ether and 1×10^{-2}M-aniline was allowed to go to completion, and the products were analysed by paper chromatography. The two yellow rings obtained were very similar to the chromatogram obtained from a solution of *N*-picrylaniline and picric acid in the approximate ratio 1:4. The precise value of the ratio of products was calculated from measurements of the absorbance of the solution at 331 and 375 nm and the extinction coefficients of the two products which had been determined at these wavelengths.

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