Mechanism of Aromatic Nucleophilic Substitution in Aprotic Solvents

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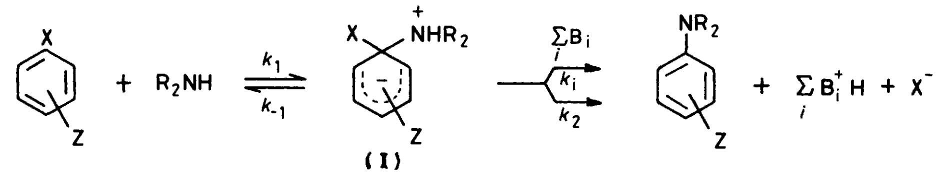
The effect of various hydrogen-bond acceptors on the reactions of 1-chloro- and 1-fluoro-2,4-dinitrobenzenes with morpholine in benzene at 30 °C has been investigated. The reaction of the chloro substrate is not base-catalysed and the additives produced no acceleration in the concentrations employed. The reaction of the fluoro substrate is base-catalysed. The addition of hydrogen-bond acceptors frequently leads to accelerations which vary linearly with the concentration of the acceptor. An approximately linear relationship exists between the logarithm of the slope of these correlations and the hydrogen-bonding parameter pk_{HB}. These effects are interpreted as electrophilic catalysis, by the heteroconjugates of the acceptors with the conjugate acid of morpholine, of the rate-determining decomposition of the intermediate in these reactions.

The S_NAr mechanism of aromatic nucleophilic substitution when either primary or secondary amines are the nucleophiles is given in equation (1).



(1)

Application of the steady-state hypothesis gives equation (2),

$$k_A = k_1(k_2 + \sum_i k_i[B_i])/(k_{-1} + k_2 + \sum_i k_i[B_i]) \quad (2)$$

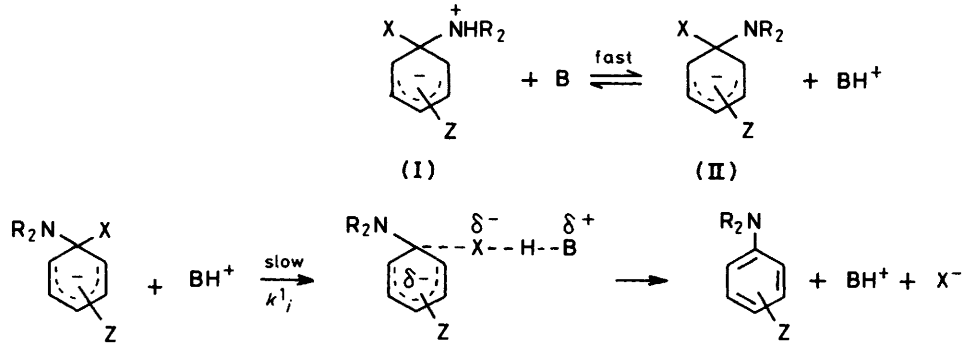
where k_A is the observed second-order rate constant and B is either an added base or a second molecule of the nucleophile.

According to equation (2), one of three kinetic forms should be observed:

(i) When $k_{-1} \ll k_2 + \sum_i k_i[B_i]$, $k_A = k_1$ and there is no base catalysis.

(ii) When $k_{-1} \gg k_2 + \sum_i k_i[B_i]$, $k_A = k_1(k_2 + \sum_i k_i[B_i])/k_{-1}$ and k_A has a linear dependence on the concentration of base.

(iii) No simplification is possible and k_A has a curvilinear (downward) dependence on base concentration. In aprotic solvents of low dielectric constant (benzene, toluene, cyclohexane, *etc.*), however, many examples are known[1–9] in which plots of k_A against base concentration have upward curvatures. Several explanations of this abnormal behaviour have been given, *e.g.* solvent effects,[1] association of the nucleophile with the base,[7] and electrophilic catalysis of the expulsion of the leaving group by homo- and hetero-conjugates of the conjugate acid of the nucleophile.[6] †



(3)

In dipolar aprotic solvents of modest to high dielectric constant the mechanism of the base-catalysed decomposition of the intermediate (I) [equation (1)] is believed to be that proposed by Bunnett and Davies[11] and given in equation (3).

Capon and Rees[12] suggested that in aprotic solvents the catalysed reaction proceeded *via* a cyclic intermediate such as is shown as (III). Initially there was no experimental evidence for a difference in mechanism between aprotic and dipolar aprotic solvents, but this has now been established.[6] Ayediran, Bamkole, Hirst, and Onyido[13] have proposed that in benzene, because of its low dielectric constant and the consequent range of electrostatic forces, aggregates are formed within which mechanisms such as those proposed by Bunnett can operate. We wish to emphasise at the outset that because of the range of these forces and the importance of hydrogen bonding in these

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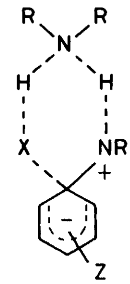
† Recently Banjoko and Ezeani[10] have severely criticised our proposals. The criticism seems to arise from a misunderstanding as it is based on reactions of the dimer of the nucleophile. We have never postulated such a reaction; our mechanism postulates electrophilic catalysis of the homo- and hetero-conjugates of the conjugate acid of the nucleophile.

Table 1. Rate constants (l mol^{-1} s^{-1} for the reactions of 1-chloro- and 1-fluoro-2,4-dinitrobenzene with morpholine in benzene at 30 °C and in the presence of various additives

(A) 1-Chloro-2,4-dinitrobenzene[a]							
10^3 [morpholine]/M	2.50	5.0	15.0	30.0	40.0	50.0	
10^3 k_A	5.39	5.49	5.47	5.21	5.35	5.34	
In the presence of 1,4-diazabicyclo[2.2.2]octane							
10^2 [DABCO]/M		0.75	1.0	4.0	8.0	12.0	
10^3 k_A	5.46	5.40	5.62	5.37	5.69	5.70	
In the presence of dimethyl sulphoxide							
10^3 [Me_2SO]/M		1.0	2.0	3.0	4.0	5.0	
10^3 k_A	5.58	5.45	5.58	5.58	5.53	5.55	
In the presence of hexamethylphosphoric triamide							
10^3 [HMPA]/M		1.0	2.0	3.0	4.0	5.0	
10^3 k_A	5.36	5.32	5.39	5.43	5.46	5.36	
In the presence of pyridine							
10^2 [pyridine]/M		1.0	2.0	4.0	5.0		
10^3 k_A	5.24	5.36	5.36	5.34	5.62		
In the presence of pyridine *N*-oxide							
10^3 [PNO]/M		1.0	2.0	3.0	4.0	5.0	
10^3 k_A	5.58	5.43	5.59	5.55	5.54	5.45	
In the presence of 4-methylpyridine							
10^2 [4-Mepy]/M		1.0	2.0	3.0	4.0	5.0	
10^3 k_A	5.58	5.67	5.60	5.48	5.47	5.56	
In the presence of cyclohexanone							
10[cyclohexanone]/M		1.0	2.0	3.0	4.0	5.0	
10^3 k_A	5.58	5.41	5.44	5.46	5.48	5.60	
In the presence of nitrobenzene							
10^3 [nitrobenzene]/M		1.0	2.0	5.0	10.0	20.0	
10^3 k_A	5.58	5.45	5.55	5.53	5.52	5.65	
(B) 1-Fluoro-2,4-dinitrobenzene[a]							
10^3 [morpholine]/M	1.0	2.0	2.5	5.0	10.0	20.0	
10^2 k_A	1.08	1.81	2.08	2.95	5.28	10.1	
10^3 [morpholine]/M	30.0	40.0					
10^2 k_A	13.3	18.4					
In the presence of 1,4-diazabicyclo[2.2.2]octane							
10^2 [DABCO]/M		0.5	1.0	4.0	6.0	8.0	12.0
10^2 k_A	1.99	3.70	5.98	14.1	23.3	27.6	41.5
In the presence of pyridine							
10^2 [pyridine]/M		1.0	4.0	8.0	10.0	15.0	20.0
10^2 k_A	1.95	2.20	2.84	3.59	3.91	4.77	6.61
10^2 [pyridine]/M	30.0	35.0	40.0	50.0			
10^2 k_A	8.80	11.5	14.7	21.6			
In the presence of dimethyl sulphoxide							
10^3 [Me_2SO]/M		1.0	2.0	3.0	4.0	5.0	
10^2 k_A	1.95	2.17	2.64	3.05	3.45	3.82	
In the presence of nitrobenzene							
10^3 [nitrobenzene]/M		1.0	2.0	5.0	10.0	20.0	
10^2 k_A	1.95	1.96	2.01	2.03	2.09	2.18	
In the presence of 4-methylpyridine							
10^3 [4-Mepy]/M		5.0	10.0	20.0	30.0	40.0	50.0
10^2 k_A	1.95	2.29	2.53	3.39	4.38	5.77	6.96
In the presence of acetonitrile							
10 [acetonitrile]/M		1.0	2.0	3.0	4.0	5.0	
10^2 k_A	1.95	2.33	2.63	3.00	3.19	3.52	
In the presence of tetrahydrofuran							
10^2 [THF]/M		2.0	4.0	6.0	10.0		
10^2 k_A	1.99	2.04	2.08	2.15	2.27		
In the presence of cyclohexanone							
10^2 [cyclohexanone]/M		2.0	4.0	6.0	10.0		
10^2 k_A	1.99	2.19	2.30	2.43	2.72		
In the presence of pyridine *N*-oxide							
10^4 [PNO]/M		5.0	10.0	15.0	20.0	25.0	
10^2 k_A	1.95	2.41	2.52	2.95	3.45	3.67	
In the presence of hexamethylphosphoric triamide							
10^4 [HMPA]/M		2.50	5.0	7.50	10.0	12.5	
10^2 k_A	1.95	2.48	2.98	3.66	4.31	5.11	
In the presence of anisole							
10^2 [anisole]/M		2.5	5.0	20.0	40.0	50.0	60.0
10^2 k_A	1.95	2.03	2.09	2.20	2.05	2.10	2.27
In the presence of *N*,*N*-dimethylaniline							
10 [DMA]/M		1.0	2.0	3.0	4.0	5.0	
10^2 k_A	1.95	1.93	2.01	2.04	2.04	2.02	

[a] Substrate concentration 2.47—2.93 × 10^{-4}M. The effect of additives was studied at a constant morpholine concentration of 2.50 × 10^{-3}M.



(III)

solvents, we believe that several mechanisms and solvent effects can operate, the relative importance of which depends not only on the entities employed, but on their concentrations as well. The following results and discussion are concerned principally with concentrations in the range 10^{-3}—10^{-2}M.

The effects of the addition of various substances on the second-order rate constants for the reactions of morpholine with 1-chloro- and 1-fluoro-2,4-dinitrobenzenes in benzene are given in Table 1.

The reaction of the chloro substrate is not catalysed by either morpholine or 1,4-diazabicyclo[2.2.2]octane (DABCO), *i.e.* $k_A = k_1$ and the first stage of the reaction is rate-determining. The various additives have no effect on the rate constant. Bernasconi *et al.*[14] have observed that the rate of reaction of 1-chloro-2,4-dinitrobenzene with piperidine in benzene increases with increase of dimethyl sulphoxide in the medium, but the concentrations of Me_2SO employed were much greater than in the present case. The main conclusion to be drawn from the study of the effect of these additives on the rate of reaction of the chloro substrate is that under the conditions employed, *i.e.* low concentrations, no significant pre-equilibria are established which result in the formation of entities participating in the transition state for the formation of the intermediate in equation (1).

The value of k_A for the fluoro substrate has a linear dependence on the concentrations of both morpholine and DABCO {equation (4), *i.e.* the kinetic form predicted by

$$k_A = k' + k''[B] \qquad (4)$$

equation (1) for the condition $k_{-1} \gg k_2 + k_3[B]$}. The addition of anisole and *N*,*N*-dimethylaniline has no effect on k_A; the effects of added nitrobenzene, acetonitrile, tetrahydrofuran, cyclohexanone, DABCO, dimethyl sulphoxide, pyridine *N*-oxide, or hexamethylphosphotriamide are in accord with equation (4), as is that of pyridine at low concentrations. Values of k'' and other relevant data are given in Table 2. At higher concentrations of pyridine and for 4-methylpyridine throughout the range of concentrations investigated there is a curvilinear upwards dependence of k_A on the concentration of the additive.

The results for morpholine, DABCO, and high concentrations

Table 2. Effect of some additives P on the reaction of 1-fluoro-2,4-dinitrobenzene with morpholine in benzene at 30 °C. Values of k'' (mol^2 l^{-2} s^{-1}) in the equation $k_A = k' + k''[P]$ and other relevant data

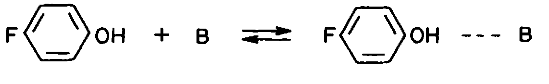
P	Anisole	DMA	MeCN	THF	Cyclohexanone	Nitrobenzene	Pyridine	4-Mepy	DABCO	Me_2SO	pyNO	HMPA
k''			3.09×10^{-2}	2.94×10^{-2}	6.69×10^{-2}	1.07×10^{-1}	1.87×10^{-1}	5.61×10^{-1}	3.26	3.89	6.94	25.1
pk_{HB}	0.02[a]	0.45[b]	0.90[b]	1.26[a]	1.32[b]	0.73[a]	1.88[a]	2.03[a]	2.20[b]	2.53[a]	2.76[a]	3.56[a]
$pk_a^{25}(H_2O)$[c]	−6.51	5.07[d]	−10.13[e]	−2.1[e]	−6.8	−11.26	5.22	6.00	8.60	0[e]	0.79	
E_{25}[f]	4.33		37.5	7.58	18.3[g]	34.8	12.4[h]			46.7		30.0[g]

[a] Ref. 18. [b] L. Jores, J. Mitsky, and R. W. Taft, *J. Am. Chem. Soc.*, 1972, **94**, 3438. [c] D. D. Perrin, 'Dissociation Constants of Organic Bases in Aqueous Solution,' I.U.P.A.C.–Butterworths, London, 1965. [d] M. M. Fickling, A. Fischer, B. R. Munn, J. Packer, and J. Vaughan, *J. Am. Chem. Soc.*, 1959, **81**, 4226. [e] E. M. Arnett, *Prog. Phys. Org. Chem.*, 1963, **1**, 223. [f] Dielectric constant; see 'Organic Solvents', ed. J. A. Riddich and W. B. Bunger, in 'Techniques of Organic Chemistry,' vol. II, 3rd edn., Wiley–Interscience, New York, 1970. [g] At 20 °C. [h] At 21 °C.

of pyridine are in agreement with those of Becker *et al.*[15] Similar results for DABCO and Me_2SO, and a linear dependence on the concentration of pyridine, were obtained by Bernasconi and Zollinger[16] and Bernasconi, Kaufmann, and Zollinger[14] when the nucleophile was changed to piperidine. The effect of Me_2SO and the upward curvature of the pyridine plots were interpreted as solvent effects. The effect of Me_2SO on base-catalysed aromatic nucleophilic substitution reactions in hydrocarbon solvents has also been studied by Suhr[17] and by Palleros and Nudelman.[9] Suhr attributed the large acceleration observed on the addition of 11—75% of Me_2SO to the reaction of 4-fluoronitrobenzene with piperidine in benzene to base catalysis by Me_2SO. Palleros and Nudelman investigated the reactions of cyclohexylamine with 2,6-dinitroanisole in toluene–Me_2SO mixtures ranging from 0 to 100% Me_2SO, using high (>0.2M) concentrations of cyclohexylamine in solvents low in Me_2SO content. The accelerations observed in the solvent composition range 0.4—2% were interpreted as due to nucleophilic attack by the complex formed by hydrogen-bonding of the amine with Me_2SO.

For the present results, the accelerations produced by the additives on the rate of reaction of the fluoro compound cannot be due to either a solvent effect or the formation of a more reactive species increasing the rate of the formation of the intermediate, as similar accelerations are not observed for the chloro substrate. Nor can they be due to a solvent effect increasing the rate of decomposition of the intermediate as there is no correlation between the magnitudes of the accelerations (as measured by k'' values) and the dielectric constants of the additives. Nitrobenzene and cyclohexanone, which have widely differing dielectric constants, cause accelerations of the same order of magnitude, while the effect of pyridine, with a smaller dielectric constant than either, is larger. Similarly there is no correlation between the magnitude of the accelerations and the basicity of the additives. Thus Me_2SO, a much weaker base than DABCO in water and 3×10^3 times weaker than pyridine in benzene,[14] is a more effective catalyst than either.

Taft[18] has introduced the parameter pk_{HB} as a measure of the strength of a hydrogen bond acceptor;* pk_{HB} is defined as $pk_{HB} = \log K_f$ where K_f is the equilibrium constant for reaction (5) in carbon tetrachloride at 25 °C, and Taft has shown that in



(5)

other solvents linear free energy relationships of the form $\log K'_f = mpk_{HB} + c$ are valid. Values of pk_{HB} are given in Table 2.

By visual inspection there is at least a rough correlation between the catalytic powers of the additives and their pk_{HB} values. Those with low pk_{HB} values either do not catalyse the reaction or else the magnitude of k'' is small; those with high values are much more effective catalysts.

If, for the mechanism given in equation (3), for additives P which are much less basic than the nucleophile N, electrophilic catalysis also occurs both with the heteroconjugate N^+HP formed between the conjugate acid of N and P and with the homoconjugate $N\overset{+}{H}N$ then for the condition (6), equation (7)

$$k_{-1} \gg k_2 + k_N K_N[N] + k_D{}^N K_D{}^N K_N[N]^2 + k_M K_M K_N[N][P] \quad (6)$$

$$k_A = \{k_1(k_2 + k_N K_N[N] + k_D{}^N K_D{}^N K_N[N]^2 + k_M K_M K_N[N][P])\}/k_{-1} \quad (7)$$

where $K_N =$

$$\frac{[(II)][NH^+]}{[(I)][N]};\ K_D{}^N = \frac{[NH^+N]}{[NH^+][N]};\ K_M = \frac{[NH^+P]}{[NH^+][P]}$$

applies and (**I**) and (**II**) are defined in equation (3); k_N, $k_D{}^N$, and k_M are the rate constants for electrophilic catalysis by NH^+, NH^+N, and NH^+P.

Hence at constant concentrations of the nucleophile a plot of k_A against $[P]$ should be linear as is observed, and of slope $k_1 k_M K_M K_N[N]/k_{-1}$. Assuming that the relationship $\log K_M = mpk_{HB} + c$ holds, then we have equation (8). If the value of log

$$\log(\text{slope}) = \log(k_1 K_N/k_{-1}) + \log k_M + mpk_{HB} + c \quad (8)$$

k_M is not very sensitive to the nature of the component P of the heteroconjugate then an approximately linear relationship should exist between the log of the slope and pk_{HB}.† A plot of $\log k''$ against pk_{HB} (Figure) obeys this relationship; hence we conclude that the accelerations observed are due to electrophilic catalysis of the decomposition of the intermediate (**II**) by the heteroconjugate formed between the additive and the conjugate acid of the nucleophile.

Equation (7) was obtained for additives which were much less basic than the nucleophile. For more basic additives, electrophilic catalysis is possible by the species PH^+ and its homoconjugate PHP^+. Under these conditions equation (7) becomes (9), where k_P and $k_D{}^P$ are the rate constants for catalysis by PH^+ and PHP^+. When the concentration of the nucleophile is kept constant, equation (9) is of the form (10), which gives (11).

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* Subsequently Taft has adopted the parameter β as a measure of hydrogen-bond acceptor ability and has shown[19] that towards donor Bu_3NH^+ $\log K_f = 9.79\beta - 3.14$.

† A referee has pointed out that the same kind of correlation would be obtained if k_M and K_M were linearly related.

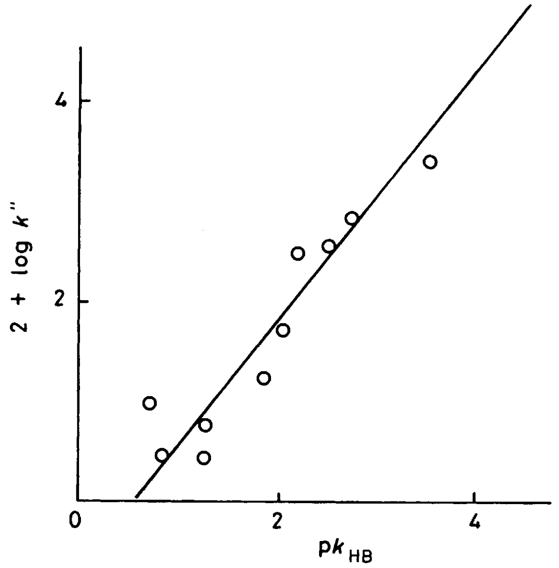

Figure. Plot of 2 + log k'' against pk_{HB} for the effect of additives on the reaction of 1-fluoro-2,4-dinitrobenzene with morpholine in benzene at 30 °C

$$k_A = \{k_1(k_2 + k_NK_N[N] + k_D{}^NK_D{}^NK_N[N]^2 + k_PK_P[P] + k_MK_MK_N[N][P] + k_D{}^PK_D{}^PK_P[P]^2)\}/k_{-1} \quad (9)$$

$$K_P = \frac{[PH^+][(\mathbf{II})]}{[P][(\mathbf{I})]};\ K_D{}^P = \frac{[PH^+P]}{[PH^+][P]}\ (K_N,\ K_N{}^D,\ K_M \text{ as before})$$

$$k_A = \mathrm{a} + k''[P] + k'''[P]^2 \quad (10)$$

$$(k_A - \mathrm{a})/[P] = k'' + k'''[P] \quad (11)$$

The rate constants for high concentrations of pyridine (*i.e.* the portion of the k_A *vs.* (pyridine] plot which is curvilinear) obey equation (11) and so do the values for 4-methylpyridine over the whole range of concentrations investigated.

Equation (9) yields (12). It is easily shown that $K_MK_N \gg K_P$;

$$k'' = \{k_1(k_pK_p + k_MK_MK_N[N])\}/k_{-1} \quad (12)$$

hence if $k_P \sim k_M$ then as before a plot of log k'' *vs.* pk_{HB} should be roughly linear.

Experimental

Pyridine *N*-oxide was prepared by oxidising pyridine with 1.7 equiv. of 30 vol. % hydrogen peroxide in glacial acetic acid. The amine oxide was distilled under reduced pressure and on solidification gave crystals, m.p. 63—65 °C (lit.,[20] 62—65 °C). All other materials were commercial samples purified by standard procedures.

The reaction was followed by the spectrophotometric determination of the products using the pipette technique already described.[21]

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