Some Salt Effects on the Reactions of 4-Fluoro- and Chloro-nitrobenzenes with Trimethylamine in Dimethyl Sulphoxide

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The influence of lithium, potassium, and tetra-n-butylammonium perchlorates and of lithium and trimethylammonium chlorides on the title reactions has been studied. Increasing concentrations of all the salts have little effect on the rate of reaction of the chloro-substrate, but the rate for 4-fluoronitrobenzene shows a strong, curvilinear dependence on the concentration of lithium and trimethylammonium ions. The results are interpreted in terms of a rate-determining electrophilically catalysed decomposition of the reaction intermediate formed by the fluoro-substrate.

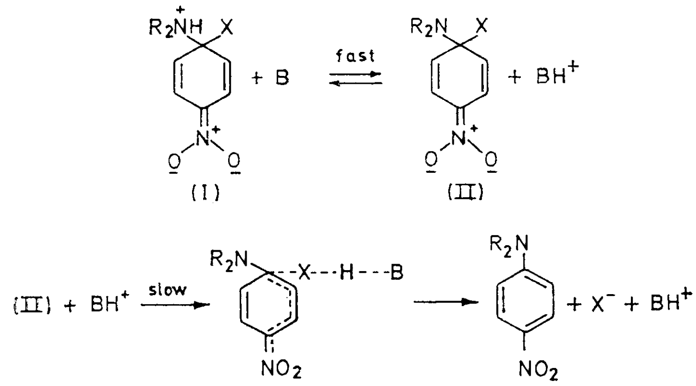
In aromatic bimolecular nucleophilic substitution reactions either the formation or the decomposition of the intermediate complex can be rate-determining. When the nucleophile is either a primary or a secondary amine, the two possibilities can be distinguished kinetically. Applying the steady state hypothesis to the mechanism [equation (i)], we obtain equation (ii) for the observed second order rate constant, k_A. When $(k_2 + k_3[R_2NH]) \gg k_{-1}$, equation (ii) simplifies to $k_A = k_1$ and the formation of the intermediate is rate-determining.

$$\begin{tikzcd}[column sep=large] & & \text{products} \\ R_2NH + \text{substrate} \arrow[r, shift left, "k_1"] & {[I]} \arrow[l, shift left, "k_{-1}"] \arrow[ur, "R_2NH", "k_3"'] \arrow[dr, "k_2"'] & & \text{(i)} \\ & & \text{products} \end{tikzcd}$$

$$k_A = (k_1k_2 + k_1k_3[R_2NH])/(k_{-1} + k_2 + k_3[R_2NH]) \quad \text{(ii)}$$

When $k_{-1} \gg (k_2 + k_3[R_2NH])$, equation (ii) has the form $k_A = k' + k''[R_2NH]$ and the observed second-order rate constant is linearly dependent on the initial amine concentration. If neither of these simplifying conditions holds, then k_A has a curvilinear dependence on the amine concentration. Hence the presence or absence of catalysis by amine (or more generally by a base) can be used to distinguish between rate-limiting formation and rate-limiting decomposition of the intermediate. When the substrates are activated aromatic halides another criterion is often applied. If the rate sequence $F > Cl \sim Br \sim I$ is observed, then breaking of the arene–halogen bond does not occur in the rate-determining step.[1]

For the reactions with amines, several mechanisms have been put forward to account for the base-catalysed reactions.[2] The most acceptable of these is the rapid, reversible transformation of the intermediate complex into its conjugate base followed by the slow electrophilically catalysed removal of the leaving group[3] (Scheme 1).



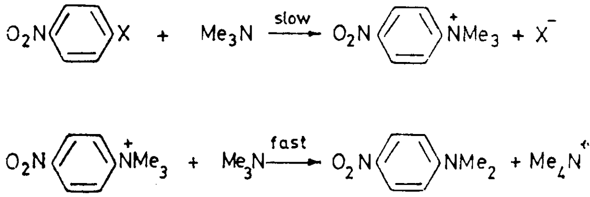
SCHEME 1

Several attempts have been made to demonstrate electrophilic catalysis in aromatic nucleophilic substitution reactions. Orvik and Bunnett[4] were able to measure separately the rates of formation and decomposition to products of the intermediate [the conjugate base corresponding to (II) in Scheme 1] formed in the reaction of 2,4-dinitro-1-naphthylethyl 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 the free amine concentration. Lam and Miller[5] in a preliminary communication claimed for the substrate 1-fluoro-2,4-dinitrobenzene in methanol that (*a*) replacement of potassium iodide as the nucleophile by hydroiodic acid increased the rate of halogen exchange by *ca.* 5×10^5 and (*b*) the rate of reaction with thiocyanate ions was increased *ca.* 2×10^3 times on addition of an equimolar amount of thorium ion. Subsequently Giles and Parker[6] showed that the reaction of 1-fluoro-2,4-dinitrobenzene with thiocyanate ion is not a simple aromatic substitution, nor is it catalysed by thorium ion.

Banjoko, Bevan, and Hirst[7] attempted a demonstration of electrophilic catalysis from the effects of added salts on the reactions of 1-fluoro- and 1-chloro-2,4-dinitrobenzenes with aniline in acetone. Some evidence for electrophilic catalysis was obtained but the interpretation of the results was complicated by the high sensitivity of the reactions to the ionic strength of the medium and by ion pair formation.

Suhr[8] has reported that 4-fluoronitrobenzene reacts slower than 4-chloronitrobenzene with trimethylamine in dimethyl sulphoxide, which, according to the criterion given above, indicates that, for the fluoro-compound at least, the decomposition of the intermediate is kinetically significant. As dimethyl sulphoxide is a good ionising, dipolar aprotic solvent of moderately high dielectric constant, this appeared to be a good system for demonstrating electrophilic catalysis in aromatic nucleophilic substitution.

We have investigated the effects of added salts on the reactions of trimethylamine with 4-fluoro- and 4-chloronitrobenzenes in dimethyl sulphoxide at 120 °C. Suhr[8] has shown that the reaction sequence is as illustrated in Scheme 2. In agreement with this we have shown that 4-chloronitrobenzene under first- or second-order conditions gives good rate constants, the same values being obtained by following the rate of liberation of chloride ion potentiometrically and the rate of formation of the product, *NN*-dimethyl-4-nitroaniline spectrophotometrically; the amounts of chloride ion liberated and product formed at infinity agreed with the theoretical values. When the substrate was 4-fluoronitrobenzene only 70% of the theoretical amount of product was formed. In the presence of trimethylamine hydrochloride the amount of product increased with increasing concentration of the salt, and at 0·1M-trimethylamine hydrochloride the theoretical amount of *NN*-dimethyl-4-nitroaniline was formed. We have assumed that these results are due to some unidentified reaction of the fluoride ion liberated during the course of the reaction. Fluoride ions are very strong nucleophiles in dimethyl sulphoxide, but in the presence of trimethylamine hydrochloride they can become hydrogen bonded and their nucleophilic power is thus reduced. This hypo-



SCHEME 2

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

[2] J. F. Bunnett and R. H. Garst, *J. Amer. Chem. Soc.*, 1965, **87**, 3879.

[3] J. F. Bunnett and G. T. Davies, *J. Amer. Chem. Soc.*, 1960, **82**, 665.

[4] J. A. Orvik and J. F. Bunnett, *J. Amer. Chem. Soc.*, 1970, **92**, 2417.

[5] K. B. Lam and J. Miller, *Chem. Comm.*, 1966, 642.

[6] D. E. Giles and A. J. Parker, *Austral. J. Chem.*, 1970, **23**, 1581.

[7] O. Banjoko, C. W. L. Bevan, and J. Hirst, *Nigerian J. Sci.*, 1969, **3**, 153.

[8] H. Suhr, *Annalen*, 1967, **701**, 101.

thesis could not be tested by studying the effect of added fluoride ion on the reaction as the fluorides of lithium, sodium, and potassium were too insoluble, and quaternary ammonium fluorides are known to decompose in dimethyl sulphoxide [9] above 60 °C. In the presence of lithium, potassium, and tetrabutylammonium perchlorates both fluoro- and chloro-substrates gave only *ca.* 83% of product. As both substrates and *NN*-dimethyl-4-nitroaniline are stable in the presence of these salts, we are unable to rationalise these results (see Experimental section).

TABLE 1

Rate constants [a] (l mol^{-1} s^{-1}) for the reactions of 4-X-nitrobenzenes with trimethylamine in dimethyl sulphoxide at 120 °C

X	10^2[amine]/M:	7·69	10·8	14·0	16·2	17·9	21·2	27·0	30·0	40·0
Cl	10^5k_2:	9·90 (9·90) [b]	10·1 (10·1) [b]	10·3	10·3 (10·1) [b]		10·0		10·1	
F	10^5k_2:	7·60				7·70		7·70		7·52

[a] Not corrected for thermal expansion of the solvent. [b] Values obtained by estimation of chloride ion.

With the exception of a few runs with 4-chloronitrobenzene, all the reactions were studied spectrophotometrically under first-order conditions with trimethylamine in large excess. As some of the reactions did not proceed to completion, and the reasons for this are not known, there is no obvious way of deciding which infinity value (the experimental or the calculated one) should be used in the calculation of the rate constants. The arguments presented in this paper depend on the kinetic form of the reactions, *i.e.* the variation of the second-order rate constants with the concentration of added salts, and the same form is obtained by using rate constants calculated on the basis of either experimental or calculated infinities. All the results reported have been calculated by using the theoretical values of the infinities.

TABLE 2

Effect of added salts on the reactions of 4-chloro- and 4-fluoro-nitrobenzenes with trimethylamine in dimethyl sulphoxide at 120 °C. Rate constants in l mol^{-1} s^{-1}

Salt	10^2[salt]/M:		5	10·0	20·0	30·0	40·0
Me_3NHCl	10^5k_2	Cl		10·1	11·1	11·5	12·1
		F	18·2	22·0	26·9	29·8	
$LiClO_4$	10^5k_2	Cl		9·70	10·3	10·3	
		F	21·2	23·3	24·9	26·4	
LiCl	10^5k_2	F		22·8	27·6	28·9	
$KClO_4$	10^5k_2	Cl		10·0	11·2	11·8	
		F		11·3	14·1	18·7	
$Bu^n_4NClO_4$	10^5k_2	Cl		10·4	10·3	11·2	
		F		9·70	10·5	13·4	

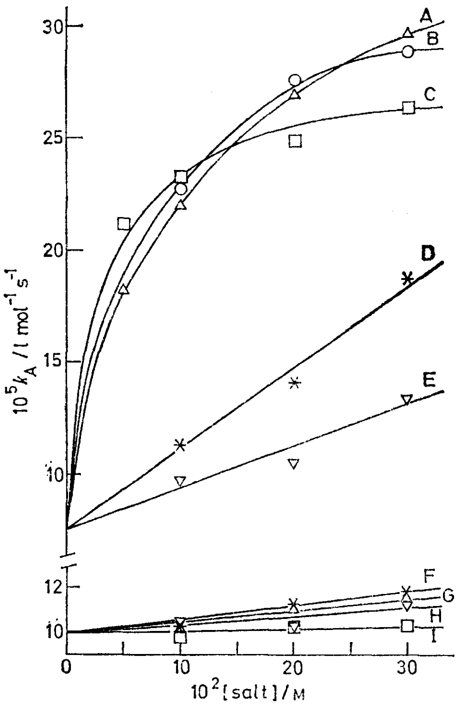

FIGURE 1 Plots illustrating the influence of added salts on the reactions of trimethylamine with 4-X-nitrobenzenes in dimethyl sulphoxide at 120 °C; curves A—E X = F; curves F—I X = Cl; A and G, Me_3NHCl; C and I, $LiClO_4$; D and F, $KClO_4$; E and H, $Bu^n_4NClO_4$; B, LiCl

The results in Table 1 confirm the sequence F < Cl reported by Suhr [8] and show that the second-order rate constants for the reactions of both substrates are independent of the amine concentration. The results in Table 2, illustrated graphically in Figure 1, show that the effect of added salts is much greater when the substrate is 4-fluoronitrobenzene than when it is 4-chloronitrobenzene. This difference could be due either to a greater sensitivity of the reaction of the fluoro-compound to ionic strength effects, or, at least in some cases, to electrophilic catalysis. If the rate-determining stage for both compounds is the formation of intermediate in equation (i) then there is no reason for them to differ markedly in their sensitivity to salt effects. If, as indicated by the rate sequence F < Cl,* the formation of the intermediate is rate-determining for the chloro-substrate, and decomposition is rate-determining for the fluoro-substrate, then a positive salt effect would be expected for the chloro-compound as the transition state of the rate-determining step is more polar than the initial state. On this hypothesis the rate determining sequence for 4-fluoronitrobenzene can be written as in Scheme 3. The transition state for the decomposition

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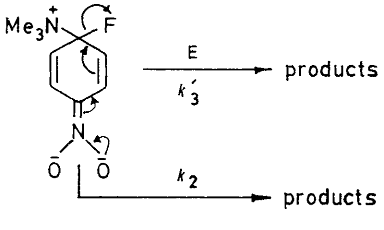
* The sequence F < Cl is compatible with the decomposition of the intermediate being rate-determining in both cases. This interpretation will still require a specific effect for the lithium and trimethylammonium cations when the substrate is 4-fluoronitrobenzene.

[9] J. Hayami, N. Uno, and A. Kaji, *Tetrahedron Letters*, 1968, 1385.

of the intermediate is again more polar than the ground state. It is difficult to assess the relative stabilising effect of salts on the transition state for the formation of



SCHEME 3

the intermediate and on that for its decomposition, but they would not be expected to differ greatly in their sensitivity to salt effects.

The effects of lithium and trimethylammonium cations on the reaction of 4-fluoronitrobenzene differ not only in magnitude but also in their form from their effects on the reaction of 4-chloronitrobenzene. The shapes of the curves are typical of many base-catalysed aromatic nucleophilic substitution reactions of primary and secondary amines. When trimethylamine is the nucleophile ' base ' catalysis in the sense of proton abstraction from the intermediate is not possible, but electrophilic catalysis of its decomposition can take place. If it is assumed that these ions electrophilically catalyse the rate-determining decomposition of the intermediate as in Scheme 3, the overall rate for the reaction is given by equation (iii). This equation has exactly the same

$$k_A = (k_1k_2 + k_1k'_3[E])/(k_{-1} + k_2 + k'_3[E]) \qquad \text{(iii)}$$

mathematical form as equation (ii), and if neither of the limiting cases discussed for that equation apply, then k_A should have a curvilinear dependence on salt concentration as is shown in Figure 1.

If equation (iii) is inverted, equation (iv) is obtained,

$$1/k_A = 1/k_1 + k_{-1}/k_1(k_2 + k_3'[E]) \qquad \text{(iv)}$$

and if the assumption is made that $k_3'[E] \gg k_2$, this reduces to equation (v). A plot of $1/k_A$ *vs.* $1/[E]$ should

$$1/k_A = 1/k_1 + k_{-1}/k_1k_3'[E] \qquad \text{(v)}$$

be linear, except when conditions which allow simplification to equation (v) are not fulfilled. This would be expected to occur at low salt concentrations; hence the plots should be initially linear, but deviating towards the $1/[E]$ axis at low salt concentrations. Rearrangement of equation (iv) gives equation (vi). The value of

$$k_A/(k_1 - k_A) = k_2/k_{-1} + k_3'[E]/k_{-1} \qquad \text{(vi)}$$

k_1 can be obtained by application of equation (v) and a plot of $k_A/(k_1 - k_A)$ constructed. As no simplifying assumptions have been made in deriving equation (vi), this plot should be linear over the whole range of salt concentrations used.

The data for the lithium and trimethylammonium cations give the type of plots described; typical plots are shown in Figures 2 and 3. This does not, however, constitute a unique proof of the mechanism, as once the curvilinear dependence of k_A on any variable is established, the forms of the $1/k_A$ and the $k_A/(k_1 - k_A)$ plots follow automatically as a property of this type of curve. The identification of the curvature as a consequence of a particular mechanism does allow certain constants associated with the mechanism to be calculated.

In principle, the values of k_1 and ratios of the various rate constants can be obtained from equations (v) and (vi). Of the ratios, the values of k'_3/k_2 are of particular interest. As k_2, the rate constant for the uncatalysed decomposition of the intermediate, is independent of the electrophile, these values give the relative catalytic powers of the cations. Because of the uncertainty in the method of calculating k_A, the figures obtained have no absolute numerical significance, but can be taken as indicating trends. Values of k_1 and k'_3/k_2 are given in Table 3. The k_1 values derived from

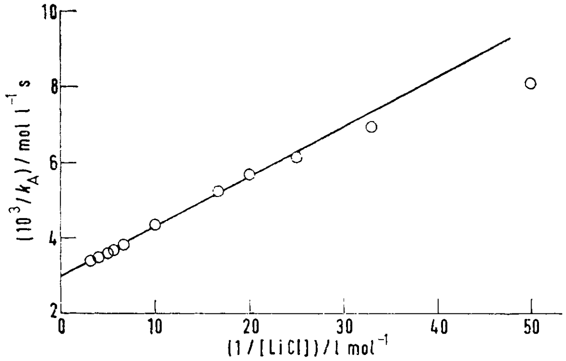


FIGURE 2 Plot of $10^3/k_A$ *vs.* $1/[LiCl]$ for the reaction of 4-fluoronitrobenzene with trimethylamine in dimethyl sulphoxide at 120 °C

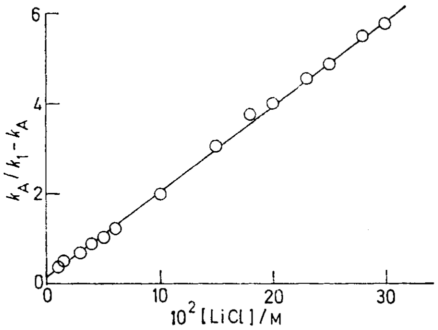


FIGURE 3 Plot of $k_A/(k_1 - k_A)$ against $10^2[LiCl]$ for the reaction of 4-fluoronitrobenzene with trimethylamine in dimethyl sulphoxide at 120 °C

TABLE 3

Values of k_1 (l mol^{-1} s^{-1}) and k_3'/k_2 derived from salt effects for the reaction of 4-fluoronitrobenzene with trimethylamine in dimethyl sulphoxide at 120 °C

Salt	10^4k_1	k_3'/k_2
$LiClO_4$	2·8	100
LiCl	3·5	95
Me_3NHCl	3·6	48
$KClO_4$		5
$Bu^n_4NClO_4$		2

the three salts are approximately the same, as must be the case if the identification of the kinetic form of the reaction with the proposed mechanism is correct, and the results for lithium chloride and lithium perchlorate give the same value for the catalytic power of the lithium cation. The k'_3/k_2 values also indicate that the lithium ion is a better electrophilic catalyst than the trimethylammonium ion.*

The effect of added potassium and tetra-n-butylammonium salts when the substrate is 4-fluoronitrobenzene can be represented by equation (vii). As

$$k_A = k_0 + k_s[\text{salt}] \qquad \text{(vii)}$$

already pointed out these salt effects are greater in magnitude than those encountered with 4-chloronitrobenzene. If it is assumed that they are due to electrophilic catalysis, then for the condition $k_{-1} \gg (k_2 + k'_3[\text{E}])$, equation (iii) reduces to $k_A = k_1(k_2 + k'_3[\text{E}])/k_{-1}$ and $k_s/k_0 = k'_3/k_2$. On this basis the order of electrophilic catalytic activity $\text{Li}^+ > \text{K}^+ > \text{Bu}^n{}_4\text{N}^+$ is obtained. This is similar to the sequence, $\text{Li}^+ > \text{Na}^+ > \text{Bu}^n{}_4\text{N}^+$, obtained by Winstein *et al.*[10] for the electrophilically assisted ionisations of *p*-methoxy-ββ-dimethylphenethyl toluene-*p*-sulphonate and the *p*-nitrobenzoate of spiro-[4,5]deca-6,9-dien-8-ol in acetone.

EXPERIMENTAL

Materials.—4-Chloronitrobenzene, m.p. 83°, 4-fluoronitrobenzene, m.p. 26·5°, and trimethylamine hydrochloride, m.p. 277°, were recrystallised commercial samples. Lithium and potassium perchlorates were dried at 110 °C for 48 h. Lithium chloride was dissolved in water and the dioxan solvate was precipitated by addition of an excess of dioxan. This was strongly heated to 150 °C under reduced pressure. Karl Fischer titration of solutions of these salts in dimethyl sulphoxide showed that the water content of the solvent was not increased. Dimethyl sulphoxide was distilled under reduced pressure, the distillate was refluxed with calcium hydride for 16 h and then vacuum distilled. It contained 0·01% of water (Karl Fischer titration).

Tetra-n-butylammonium perchlorate. Tetra-n-butylammonium iodide, m.p. 144—145°, was prepared from tri-n-butylamine and n-butyl iodide in acetone solution. The iodide was dissolved in water and the perchlorate precipitated with perchloric acid. Repeated crystallisation from conductivity water gave crystals of m.p. 212° (lit.,[11] 212—212·5°. *NN*-Dimethyl-4-nitroaniline, m.p. 165—166° (lit.,[12] 163—166°), was prepared by the method of Senaer *et al.*[12]

Trimethylamine in dimethyl sulphoxide. Trimethylamine, prepared from purified trimethylamine hydrochloride and sodium hydroxide, and dried over solid potassium hydroxide, was dissolved in dimethyl sulphoxide under nitrogen. The concentration was estimated by acid–alkali titration and adjusted to the required value by dilution with dimethyl sulphoxide, and the solution was then standardised.

Kinetic Procedure.—Sealed ampoules containing aliquot portions of the reaction mixture were removed from the thermostat at known times and plunged into iced water. For spectroscopic determinations, the contents of the ampoule were diluted with acetone and optical densities were measured at 390 nm. Chloride ion was determined by potentiometric titration with silver nitrate.

Reactions with Lithium Perchlorate.—Although Karl Fischer titration indicated that dissolution of the salt does not increase the water content of the solvent, the possibility of hydrolysis occurring to produce 4-nitrophenol was checked by monitoring at 400 nm, the wavelength at which 4-nitrophenol has an absorption maximum. 4-Nitrofluorobenzene and *NN*-dimethyl-4-nitroaniline were found to be stable in the presence of lithium perchlorate, and no absorbance was detected at 400 nm. A 4 : 1 mixture of *NN*-dimethyl-4-nitroaniline and 4-nitrofluorobenzene of the same concentrations as obtained in a kinetic run, in the presence of 0·1M-lithium perchlorate, was monitored at 390 and at 400 nm. No change in absorbance at these wavelengths took place in 120 h at 120 °C.

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* The rate constants for 4-fluoronitrobenzene in the presence of 0·2M- and 0·3M-trimethylamine hydrochloride exceed those for the reactions of this substrate in the presence of corresponding concentrations of lithium perchlorate. For these reactions k_{-1}/k_2 is *ca.* 5, and for this value the observed rate constant k_A is very sensitive to the value of k_1. The value of k_1 in the presence of perchlorate ions is slightly less than the value in the presence of chloride ions (Table 3), but this is sufficient to account for the above sequence. Similar relative effects of perchlorate and chloride ions have been obtained in other systems (Bamkole and Hirst, unpublished results).

[10] S. Winstein, E. C. Friedrick, and S. Smith, *J. Amer. Chem. Soc.*, 1964, **86**, 305.

[11] S. Winstein, P. E. Klinedinst, and G. C. Robinson, *J. Amer. Chem. Soc.*, 1961, **83**, 895.

[12] A. E. Senear, M. M. Rapport, J. F. Mead, J. T. Maynard, and J. B. Koepfli, *J. Org. Chem.*, 1946, **11**, 378.