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INFLUENCE OF SOME STERIC AND ELECTRONIC EFFECTS ON THE MECHANISM OF S_NAr REACTIONS IN DIMETHYL SULPHOXIDE

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The reactions of 1-chloro- and 1-fluoro-2,4-dinitrobenzenes with aniline and 4-methylaniline in dimethyl sulphoxide are not base catalysed. When the nucleophile is 2-methylaniline, the reaction of the fluoro compound is base catalysed whereas that of the chloro compound is not. The reactions of 1-bromo-2-fluoro- and 1-bromo-2-chloro-3,5-dinitrobenzenes with both aniline and 2-methylaniline are not base catalysed. These results indicate that, in certain cases, the incidence or absence of base catalysis in aromatic nucleophilic substitution (S_NAr) reactions in dipolar aprotic solvents results from an interplay of steric and electronic factors as they affect the magnitude of the $(k_2 + k_3[B])/k_{-1}$ ratio.

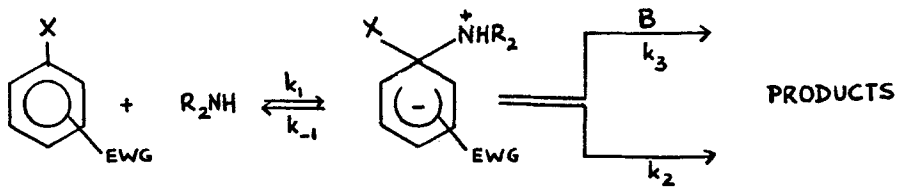
INTRODUCTION

The mechanism of nucleophilic aromatic substitution (S_NAr) reactions has been a subject of discussion and there is general agreement regarding the gross mechanism when primary or secondary amines are the nucleophiles. This mechanism is given in Scheme 1. Equation (1) is the steady-state rate expression for the observed second-order rate constant, k_A, expressed in terms of the component steps in Scheme 1. For the condition $k_{-1} \ll k_2 + k_3[B]$, $k_A = k_1$,

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

the formation of **I** is rate limiting and the reaction is not base catalysed. When this condition does not hold, decomposition of **I** into products is rate limiting and the reaction is base catalysed, the kinetic form depending on the relative magnitudes of k_{-1} and $k_2 + k_3[B]$. When $k_{-1} \approx k_2 + k_3[B]$, k_A has a curvilinear dependence on base concentration.

Bernasconi[1] has discussed the various factors responsible for the incidence of base catalysis and in most cases they are well substantiated experimentally. However, in the case of steric effects, although they have been invoked to explain differences in the behaviour of primary and secondary amines, more satisfactory rationalizations are available[1,2] and there is no unambiguous example of a steric effect influencing the occurrence of base catalysis. There are at least three ways in which this could occur. For bulky nucleophiles, steric strain in **I** can be relieved by reversion to reactants



(I)

Scheme 1

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leading to an increase in k_{-1}. As the transition state for the decomposition to reactants of **I** is the same as its formation, and its position on the reaction coordinate is close to that of the intermediate,[3] steric compressions would be expected in the transition state and these should be manifested in a reduction in k_1. A second is due to the fact that when the group X leaves the intermediate, the incoming group must move from the 'tetrahedral' position to a position in the plane of the benzene ring. Any interference with this motion by other groups in the molecule will lead to a reduction in k_2 and k_2. A related effect that causes the attenuation of k_2 and k_3 has been described by Bernasconi and de Rossi.[4]

RESULTS AND DISCUSSION

We have shown[5] that a 2-methyl substituent in the nucleophile has a substantial steric effect on the reaction of picryl chloride with aniline. As it is known[6] that mechanistically the reaction of 1-fluoro-2,4-dinitrobenzene with aniline is close to the borderline and is not catalysed in dimethyl sulphoxide, we thought that the introduction of a 2-methyl group into the aniline nucleus might be sufficient to tip the balance and give a catalysed reaction. The results and other pertinent data are given in Table 1.

The reactions of both 2- and 4-methylaniline with 1-chloro-2,4-dinitrobenzene are not base catalysed. A comparison of their rate constants with that of aniline under the same conditions[6] for which $k_A = 4{\cdot}40 \times 10^{-4}$ l mol^{-1} s^{-1} shows that whereas a 4-methyl group increases the rate constant by a factor of 3·2, a 2-methyl group gives a 12·3-fold reduction. The deactivating effect of a 2-methyl group when this reaction is carried out in ethanol has also been reported by Van Opstall[7] and Singh and Peacock.[8] Hence appreciable steric effects are present in this reaction.

When the substrate is picryl chloride, a rate enhancement of 3·8-fold for a 4-methyl group[9a] and a reduction of over 30-fold for a 2-methyl group[5] have been reported for reactions with aniline in acetonitrile. Thus, whereas the activating effect of a 4-methyl group is independent of the substrate, the deactivating effect of a 2-methyl group is greater for picryl chloride, in agreement with the greater steric requirements of the transition state of its reaction.

The reaction of 1-fluoro-2,4-dinitrobenzene is not base catalysed and comparison of its rate constant with the value of $k_A = 2{\cdot}25 \times 10^{-2}$ l mol^{-1} s^{-1} reported[6] for the reaction of the same substrate with aniline gives a value of $k_{4\text{-Me}}/k_H$ of 5·2, of the same order of magnitude as for the chloro substrate. In contrast, the reaction with 2-methylaniline shows a small but definite curvilinear dependence on the concentration of the nucleophile, as shown in Figure 1, and the approximately 38-fold reduction in the rate constant due to the introduction of a 2-methyl group is much greater than that observed when 1-chloro-2,4-dinitrobenzene is the substrate. In view of the small increase in k_A for this reaction, it could be argued that the small changes in k_A represent a medium effect. However, analysis of data according to standard procedures[9b] gives a value of 308 for the k_3/k_2 ratio (Scheme 1). This ratio measures the catalytic efficiency of the base-catalysed pathway over the uncatalysed mode of decomposition of **I**. Its magnitude, in the present case, according to Bunnett's criterion,[9b] is unambiguous evidence that (i) decompo-

Table 1. Rate constants (l mol^{-1} s^{-1}) for the reactions of 1-X-2,4-dinitrobenzene (X = F, Cl) and their 6-bromo derivatives with some aromatic amines in dimethyl sulphoxide at 30 °C

Substrate	X	Amine	Parameter	Values					
Unsubstituted	Cl[a]	2-Methylaniline	10^2[amine] (M)	2·32	6·31	14·1	23·5		
			$10^5 k_A$	3·53	3·65	3·65	3·45		
		4-Methylaniline	10^2[amine] (M)	3·28	10·2	19·2			
			$10^3 k_A$	1·36	1·46	1·37			
	F[b]	2-Methylaniline	10^3[amine] (M)	4·66	11·6	16·3	23·3	37·7	46·6
			$10^4 k_A$	5·87	6·80	7·01	7·47	7·54	7·93
		4-Methylaniline	10^3[amine] (M)	4·82	9·79	16·9			
			$10 k_A$	1.16	1·19	1·12			
6-Bromo	Cl[c]	Aniline	10^2[amine] (M)	3·31	6·61	13·2	33·1		
			$10^4 k_A$	8·01	8·15	7·97	8·08		
	F[d]	Aniline	10^3[amine] (M)	3·04	5·87	9·11	11·6	15·2	32·6
			$10 k_A$	1·27	1·11	1·16	1·27	1·20	1·22
		2-Methylaniline	10^3[amine] (M)	6·50	13·0	32·5			
			$10^3 k_A$	7·77	7·89	7·67			

[a] [Chloro]$_0 = 2{\cdot}83 \times 10^{-4}$ M.
[b] [Fluoro]$_0 = (2{\cdot}76–3{\cdot}13) \times 10^{-4}$ M.
[c] [Chloro]$_0 = 3{\cdot}08 \times 10^{-4}$ M.
[d] [Fluoro]$_0$ = (i) with aniline $6{\cdot}05 \times 10^{-5}$ M, (ii) with 2-methylaniline $3{\cdot}17 \times 10^{-4}$ M.

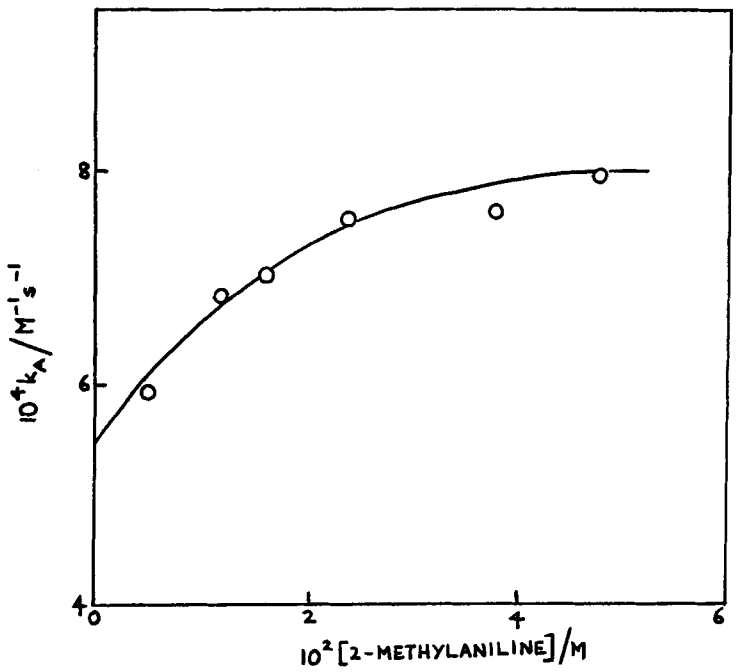


Figure 1. Plot of the second-order rate constant k_A against 2-methylaniline concentration for the reaction of 1-fluoro-2,4-dinitrobenzene with 2-methylaniline in dimethyl sulphoxide at 30 °C

sition of **I** is rate limiting at low base concentration and (ii) the kinetic condition $k_{-1} \approx k_2 + k_3[B]$ holds. The value of k_F/k_{Cl}, where k_F and k_{Cl} are the rate constants for the fluoro and chloro substrates, is reduced from 83 for 4-methylaniline to 16. This latter value is comparable to the value of 11 obtained[10] for the reaction of these substrates with *N*-methylaniline in acetonitrile, systems for which the formation of the intermediate is rate determining for the chloro substrate and its decomposition to products is rate determining for the fluoro substrate. The catalytic effect of the much stronger base 1,4-diazabicyclo[2.2.2]octane (DABCO) could not be observed as it reacts with the substrate at a rate comparable to that of 2-methylaniline (see Experimental).

As steric effects are the same in the fluoro and chloro substrates,[11] the data indicate that there is an appreciable steric effect in the formation of the intermediate, hence the most likely explanation for the change from a rate-limiting formation to a rate-limiting decomposition of the intermediate on the introduction of a 2-methyl group in the anilinodefluorination reaction is that it is due to an increase in k_{-1}, resulting from release of steric compressions when the intermediate reverts to reactants.

Congestion at the reaction centre can be increased by introducing a substituent at the 6-position of the substrate. As we have already shown[3] that picryl chloride reacts with dimethyl sulphoxide, a less reactive substrate was required, hence the kinetics of the 6-bromo derivatives of 1-fluoro- and 1-chloro-2,4-dinitrobenzenes were investigated. The effect of a 6-bromine atom will be the resultant of an activating electronic effect and any rate-reducing steric effects.

The reactions of the 6-bromo derivatives of both the fluoro and chloro substrates with aniline are not base catalysed. The net effect of the bromo substituent is mildly activating, giving $k_{2\text{-Br}}/k_H$ values of 1·8 and 5·4 for the chloro and fluoro compounds, respectively, where $k_{2\text{-Br}}$ and k_H are the rate constants for the substituted and unsubstituted substrates, respectively. The electronic effect of a 2- or 4-bromine substituent is the resultant of electron withdrawal by an inductive mechanism and a deactivating conjugative electron release. As conjugative effects are more effective from the 4-position and inductive effects greater from the 2-position,[12] the activating effect of a bromo substitution would be expected to be greater when it is in the 2- than in the 4-position. The effect of a 4-bromo substituent has been determined in several aromatic nucleophilic substitution reactions. For the 2-nitrochlorobenzene systems $k_{4\text{-Br}}/k_H$ values of 9·6 and 15·4 are obtained for the nucleophiles piperidine[13] and methoxide ion,[14] respectively, and in the 2,6-dinitrochlorobenzene–methoxide ion system[13] the value of the ratio is 13·6. These values are substantially greater than the present values, hence we conclude that greater steric effects are

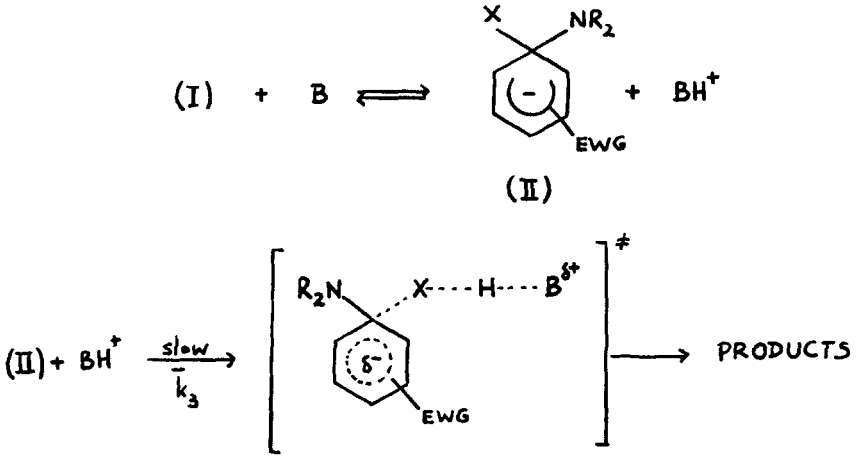
present in the reactions of the 6-substituted substrates than in the unsubstituted substrates. These additional compressions, however, have not led to any change of mechanism.

The reaction of 1-bromo-2-fluoro-3,5-dinitrobenzene with 2-methylaniline, resulting in the displacement of the fluorine atom, is not base catalysed. The introduction of a 2-methyl group into the aniline nucleus reduces the rate constant by a factor of 15·6, similar to the value of 12·3 obtained for substrate 1-chloro-2,4-dinitrobenzene where both aniline and the substituted aniline react by the same mechanism. Thus the introduction of a 6-bromo substituent into 1-fluoro-2,4-dinitrobenzene has caused the mechanism of its reaction with 2-methylaniline to revert to a rate-determining formation of the intermediate. As we have shown that increasing the steric requirements of the intermediate favours its rate-limiting decomposition to products, the present results therefore suggest the probable existence of an additional factor due to the electronic effect of the bromine atom, which overcomes the steric effect in this reaction and possibly also in that of aniline.

Little is known about electronic effects exerted by substituents in the substrate on the $(k_2 + k_3[B])/k_{-1}$ ratio. From the data of Kavalek and Sterba[15] for the reaction of 4-X-2-nitrofluorobenzene with piperidine in 50% acetonitrile–benzene solvent, k_2/k_{-1} values of 3·74, 1·73 and 1·24 can be calculated for X = CH_3CO, $C_6H_5N_2$ and NO_2, respectively. The figures show that the ratio is relatively insensitive to changes in the 4-substituent, since there is no obvious correlation between its magnitude and the activating effects of the groups. The reaction of piperidine in benzene with 4-nitro-[16] and 2,4-dinitrofluorobenzene[17,18] is base catalysed but that of 2-nitrofluorobenzene[16] is not. These results are probably due to hydrogen bonding and not to changes in activation. When a nitro group is moved from the 4- to the 2-position, hydrogen bonding occurs in the intermediate between the amino hydrogen atoms and the oxygen atoms of the 2-nitro group. This reduces both k_2 and k_{-1} but the effect is greater for k_{-1}, and the condition $k_2 \gg k_{-1}$ holds.[1] When a second nitro group is introduced at the 4-position, a large proportion of the negative charge on the intermediate is accommodated on this group, as it is well known[19] that a nitro group has a greater stabilizing effect on Meisenheimer complexes in the 4- than in the 2-position. The strength of the hydrogen bond is reduced and the condition $k_{-1} \gg k_2$ holds once again.

The mechanism[20] of the base-catalysed pathway in dipolar aprotic solvents is given in Scheme 2. A rapid reversible removal of a proton by a base is followed by the slow expulsion of the leaving group electrophilically catalysed by the conjugate acid of the base. In this mechanism, k_3 [equation (1)] = k_3K_B, where $K_B = [\mathbf{II}][R_2\overset{+}{N}H_2]/[\mathbf{I}][R_2NH]$.

The uncatalysed step when the nucleophile is a secondary amine can proceed by a unimolecular mechanism involving intramolecular catalysis of nucleofuge expulsion, shown in Figure 2, mentioned as a possibility by Kirby and Jencks.[21] A variant of this mechanism could involve the incorporation of one or more solvent molecules, particularly when the reaction is carried out in hydroxylic solvents.[1] When the nucleophile is a primary amine it is possible[6] that the mechanism is the same as for the catalysed path, with a molecule of solvent replacing that of the base. Bernasconi and de Rossi[4] pointed out that electron-withdrawing substituents increase the acidity of the



Scheme 2

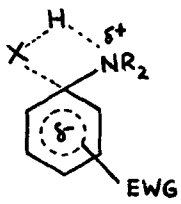


Figure 2. Intramolecular catalysis of nucleofuge expulsion

ammonio proton in the intermediate **I** and hence make it a better catalyst for leaving group departure by both pathways. As already stated, hydrogen bonding occurs in the intermediate between the amino hydrogen atoms and the 2-nitro group and an increase in the acidity of the hydrogen atoms will strengthen the hydrogen bond, resulting in a reduction in k_{-1}. Hence the introduction of a 6-bromo substituent into the substrate will increase the magnitude of $(k_2 + k_3[B])/k_{-1}$. In the borderline system investigated, this increase is probably sufficient to re-establish the condition $k_{-1} \ll k_2 + k_3[B]$ and the reaction is not base catalysed. We believe that this is the first time this effect has been clearly elucidated.

EXPERIMENTAL

The purification of dimethyl sulphoxide,[22], DABCO,[23] 1-fluoro- and 1-chloro-2-,4-dinitrobenzene[24] and aniline[25] and the procedure for the determination of the rate constants by the spectrophotometric measurement of the concentrations of the products of the reactions[24] at 400 nm have been described previously. 2-Methyl and 4-methylaniline were commercial samples purified by successive distillations from zinc dust and potassium hydroxide pellets (3-methylaniline) and recrystallization from ethanol (4-methylaniline). 1-Bromo-2-X-3-,5-dinitrobenzene (X = F, Cl) were prepared by the method of Hirst and Udosen[26] for the bromination of deactivated benzene rings using 1-X-2,4-dinitrobenzenes (X = F, Cl) as starting materials; m.p.:X = F, 70–71 °C (lit.[27] 68 °C); X = Cl, 58 °C (lit.[27] 58–59 °C).

Reaction of 1-fluoro-2-4-dinitrobenzene with DABCO. A solution containing 1-fluoro-2,4-dinitrobenzene ($3{\cdot}35 \times 10^{-3}$ M) and DABCO ($5{\cdot}31 \times 10^{-2}$ M) only was monitored at 400 nm, and left until no further increase in absorbance occurred. When this maximum value of the absorbance was used as an 'infinity' reading, a value of $2{\cdot}54 \times 10^{-4}$ l mol^{-1} s^{-1} was obtained for the 'rate constant'.

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