The Effect of *ortho* Substituents on the Mechanism of Aromatic Nucleophilic Substitution Reactions in Dipolar Aprotic Solvents

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The reactions of 2,6-dinitrophenyl phenyl ether and of 6-methyl-2,4-dinitrophenyl phenyl ether with piperidine, morpholine, butylamine and benzylamine are base catalysed in both dimethyl sulfoxide and acetonitrile. The reaction of 2-phenoxy-3,5-dinitropyridine with aniline is base catalysed in acetonitrile, but not in dimethyl sulfoxide, and its reactions with piperidine, morpholine, butylamine and benzylamine in acetonitrile are also base catalysed. The results are discussed in terms of the prevailing theories of aromatic nucleophilic substitution reactions. Increase in activation of the substrate increases the k_2/k_{-1} and k_3/k_{-1} ratios. For *ortho* substituents, steric/steroelectronic effects in the transition state reduce both k_{-1}, the rate constant for the decomposition of the zwitterionic intermediate to reactants, and k_2 and k_3, the rate constants for its decomposition to products. When the substrate has two *ortho* groups the different behaviour of primary and secondary amines found with substrates containing only one *ortho*-nitro group is not observed.

The mechanism of aromatic nucleophilic substitution reactions when primary and secondary amines are the nucleophiles is given in Scheme 1. Application of the steady state hypothesis gives eqn. (1) where k_A is the observed second-order rate con-

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

stant and B is either a second molecule of the nucleophile or an added base. For the condition $k_{-1} \ll k_2 + k_3[B]$, eqn. (1) reduces to $k_A = k_1$, the formation of the intermediate is rate limiting and the reaction is not base catalysed. If this condition is not satisfied then the decomposition of the intermediate to products is rate limiting and the reaction is base catalysed. If eqn. (1) cannot be simplified further, k_A has a curvilinear (concave downwards) dependence on base concentration, but when $k_{-1} \gg k_2 + k_3[B]$, eqn. (1) has the form $k_A = k' + k''[B]$ (when B = nucleophile, $k''/k' = k_3/k_2$). In many reactions, small linear increases of k_A with increasing base concentration are observed. The values of k''/k' are small and the accelerating effect of the bases bears no relationship to their base strengths. According to Bunnett[1] this does not represent true base catalysis, the formation of the intermediate is rate limiting and the accelerations are due to some unspecified effect. In other reactions, the addition of base has a powerful accelerating effect and k''/k' is high (>50). These reactions are regarded as base catalysed and the decomposition of the intermediate is rate limiting.

While the factors affecting the incidence of base catalysis are broadly understood, the effects of an *ortho* substituent on the substrate are complex and in order to obtain a better understanding of them we wished to compare the effects of *ortho*-methyl, -aza and nitro groups with hydrogen. Capon and Chapman[2] have shown that while the polar effect of a methyl group is small, the steric effect of an *ortho*-methyl group is appreciable. Thus in 99.8% ethanol the introduction of a 6-methyl group into 1-chloro-2,4-dinitrobenzene reduces the rate constant for the reaction with piperidine by a factor of 276 and for aniline by 16. An ortho-aza group is powerfully activating, and Eggimann, Schmid and Zollinger[3] have shown that its introduction into 1-chloro-2,4-dinitrobenzene increases the rate constant for the reaction with aniline in acetonitrile by a factor of 5.87×10^3. Moreover, from a consideration of the relative reactivities of aniline and *N*-methylaniline they conclude that the lone electron pair on the nitrogen atom is less bulky than a hydrogen substituent. The activating power of a nitro group in aromatic nucleophilic substitution is known[4] to be greater than that of an aza group and its bulk is comparable with that of a methyl group.[5] It was hoped to utilise the known[6,7] difference in steric and hydrogen-bonding effects between primary and secondary amines and their differing behaviour in dipolar aprotic solvents of similar relative permittivity, but widely differing basicity,[8] to distinguish the factors causing the effects of the *ortho* groups. For these reasons we had hoped to compare the reactions of 2,4-dinitro-6-methylphenyl, 3,5-dinitropyridin-2-yl and 2,4,6-trinitrophenyl phenyl ethers with butylamine and piperidine, and benzylamine and morpholine, two sets of amine pairs where the primary and secondary amines have similar basicities[9] in dimethyl sulfoxide and acetonitrile, with the corresponding reactions of 2,4-dinitrophenyl phenyl ether. The reactions of the dinitropyridinyl and trinitrophenyl ethers in dimethyl sulfoxide were too fast to be measured by the techniques available to us, so the 2,6-dinitrophenyl phenyl ether, where the congestion at the reaction site is the same as in the 2,4,6-trinitrophenyl phenyl ether, was studied instead. In an attempt to get a direct comparison of the substrates with the same reagent, the reactions with aniline were studied, but that of the 6-methyl substrate was too slow to be followed. The results are given in Tables 1 and 2.

The reaction of 6-methyl-2,4-dinitrophenyl phenyl ether with butylamine in acetonitrile has a k''/k' ratio of 41, very close to the lower limit recognised by Bunnett[1] as representing true base catalysis, and as the tendency towards base catalysis increases with decrease of basicity of the nucleophile,[6,10] both this and the corresponding reaction with benzylamine were investigated in more detail. The rate constants for both reactions showed a linear dependence on the concentration of added 1,4-diazabicyclo[2.2.2]octane (DABCO), the k''/k' ratios being 125 for butylamine and 122 for benzylamine. At 100 °C, the rate constants of both reactions had a linear dependence on the concentration of the nucleophiles, but although the values of the k''/k' ratios increased to 167 (butylamine) and 108 (benzylamine), the values of the second-order rate constants k_A only increased by a factor of *ca.* 1.8 for butylamine and 3.5 for benzylamine. These very small increases for a 70 °C rise in temperature indicate a multi-step mechanism. We conclude

Table 1 Rate constants/$dm^3\ mol^{-1}\ s^{-1}$ for the reactions of some phenyl ethers with amines in acetonitrile at 30 °C

Substrate[a]	Nucleophile/base	Concentration/mol dm^{-3}	k_a	k''/k'[b]
2,6-Dinitrophenyl phenyl ether	Piperidine	4.0×10^{-2}	0.56×10^{-4}	335
		6.0×10^{-2}	0.82×10^{-4}	
		8.0×10^{-2}	1.10×10^{-4}	
		10.0×10^{-2}	1.36×10^{-4}	
		14.0×10^{-2}	1.90×10^{-4}	
		20.0×10^{-2}	2.66×10^{-4}	
	Morpholine	4.0×10^{-2}	2.15×10^{-6}	
		6.0×10^{-2}	3.00×10^{-6}	
		8.0×10^{-2}	3.80×10^{-6}	
		10.0×10^{-2}	4.65×10^{-6}	
		14.0×10^{-2}	4.90×10^{-6}	
		20.0×10^{-2}	5.00×10^{-6}	
		30.0×10^{-2}	5.10×10^{-6}	
	Butylamine	2.0×10^{-3}	2.20×10^{-2}	153
		4.0×10^{-3}	2.65×10^{-2}	
		6.0×10^{-3}	3.13×10^{-2}	
		8.0×10^{-3}	3.64×10^{-2}	
		10.0×10^{-3}	4.16×10^{-2}	
		12.0×10^{-3}	4.73×10^{-2}	
	Benzylamine	4.0×10^{-3}	5.10×10^{-3}	66.5
		6.0×10^{-3}	5.65×10^{-3}	
		8.0×10^{-3}	6.15×10^{-3}	
		10.0×10^{-3}	6.75×10^{-3}	
		12.0×10^{-3}	7.24×10^{-3}	
		14.0×10^{-3}	7.78×10^{-3}	
2,4-Dinitrophenyl phenyl ether	Piperidine	4.0×10^{-2}	2.84×10^{-2}	
		5.0×10^{-2}	3.01×10^{-2}	
		7.0×10^{-2}	3.16×10^{-2}	
		8.0×10^{-2}	3.20×10^{-2}	
		9.0×10^{-2}	3.18×10^{-2}	
	Morpholine	0.16	1.19×10^{-3}	
		0.20	1.34×10^{-3}	
		0.22	1.38×10^{-3}	
		0.26	1.43×10^{-3}	
2-Phenoxy-3,5-dinitropyridine	Aniline	2.0×10^{-2}	0.70×10^{-5}	70.2
		4.0×10^{-2}	1.13×10^{-5}	
		6.0×10^{-2}	1.50×10^{-5}	
		8.0×10^{-2}	1.93×10^{-5}	
		10.0×10^{-2}	2.35×10^{-5}	
	Piperidine	4.0×10^{-4}	0.83	∞
		6.0×10^{-4}	1.24	
		8.0×10^{-4}	1.69	
		10.0×10^{-4}	2.18	
	Morpholine	4.0×10^{-3}	0.080	∞
		6.0×10^{-3}	0.120	
		8.0×10^{-3}	0.153	
		10.0×10^{-3}	0.204	
	Butylamine	4.0×10^{-4}	0.76	1077
		6.0×10^{-4}	0.917	
		8.0×10^{-4}	1.01	
		10.0×10^{-4}	1.12	
	Benzylamine	1.0×10^{-3}	0.154	163
		2.0×10^{-3}	0.175	
		3.0×10^{-3}	0.195	
		4.0×10^{-3}	0.218	
		5.0×10^{-3}	0.240	
6-Methyl-2,4-dinitrophenyl phenyl ether	Piperidine	2.0×10^{-2}	0.75×10^{-4}	
		4.0×10^{-2}	1.40×10^{-4}	
		6.0×10^{-2}	2.03×10^{-4}	
		8.0×10^{-2}	2.65×10^{-4}	
		10.0×10^{-2}	3.25×10^{-4}	
		20.0×10^{-2}	5.50×10^{-4}	
		30.0×10^{-2}	7.83×10^{-4}	

Table 1 (*continued*)

Substrate[a]	Nucleophile/base	Concentration/mol dm^{-3}	k_a	k''/k'[b]
	Morpholine	4.0×10^{-2}	4.55×10^{-6}	
		6.0×10^{-2}	6.60×10^{-6}	
		8.0×10^{-2}	8.55×10^{-6}	
		10.0×10^{-2}	10.5×10^{-6}	
		20.0×10^{-2}	13.2×10^{-6}	
		30.0×10^{-2}	14.0×10^{-6}	
	Butylamine	1.0×10^{-2}	5.40×10^{-3}	40.5
		1.5×10^{-2}	6.10×10^{-3}	
		2.0×10^{-2}	6.80×10^{-3}	
		2.5×10^{-2}	7.50×10^{-3}	
		3.0×10^{-2}	8.55×10^{-3}	
	Butylamine[c]	5.0×10^{-3}	9.50×10^{-3}	167
		6.0×10^{-3}	10.30×10^{-3}	
		7.0×10^{-3}	11.2×10^{-3}	
		8.0×10^{-3}	12.0×10^{-3}	
		10.0×10^{-3}	13.8×10^{-3}	
	DABCO[d]	0	5.30×10^{-3}	124.5
		4.0×10^{-3}	8.0×10^{-3}	
		6.0×10^{-3}	9.50×10^{-3}	
		10.0×10^{-3}	12.1×10^{-3}	
		14.0×10^{-3}	14.8×10^{-3}	
		20.0×10^{-3}	18.7×10^{-3}	
	Benzylamine	2.0×10^{-2}	5.80×10^{-4}	20.4
		4.0×10^{-2}	9.40×10^{-4}	
		6.0×10^{-2}	11.0×10^{-4}	
		8.0×10^{-2}	12.5×10^{-4}	
		10.0×10^{-2}	13.9×10^{-4}	
	Benzylamine[c]	1.0×10^{-2}	1.60×10^{-3}	108
		2.0×10^{-2}	2.42×10^{-3}	
		3.0×10^{-2}	3.25×10^{-3}	
		4.0×10^{-2}	4.10×10^{-3}	
		5.0×10^{-2}	4.90×10^{-3}	
	DABCO[e]	0	5.60×10^{-4}	122
		4.0×10^{-3}	8.50×10^{-4}	
		8.0×10^{-3}	11.4×10^{-4}	
		10.0×10^{-3}	12.8×10^{-4}	
		14.0×10^{-3}	15.7×10^{-4}	
		20.0×10^{-3}	20.1×10^{-4}	

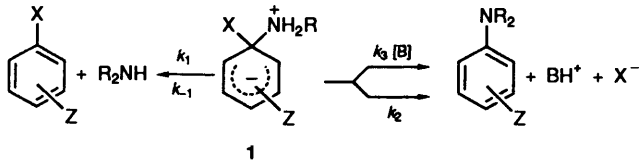
[a] Substrate concentration = 1.0–35 $\times 10^{-5}$ mol dm^{-3}. [b] See text. [c] At 100 °C. [d] [Butylamine] = 1.00×10^{-2} mol dm^{-3}. [e] [Benzylamine] = 2.00×10^{-2} mol dm^{-3}.

that, for both reactions in acetonitrile, the decomposition of the intermediate to products is rate limiting.

Although the k_3/k_2 values of these reactions in dimethyl sulfoxide at 30 °C are lower (butylamine, 26; benzylamine, 17) than in acetonitrile, they are quite appreciable, and the results obtained in acetonitrile warranted further investigation in DMSO. Both reactions were found to be linearly catalysed by DABCO (k''/k' 107 for the reaction with butylamine and 61 for the benzylamine reaction) and we conclude that in this solvent too, the decomposition to products is rate limiting.

Discussion

In dipolar aprotic solvents the mechanism of the base-catalysed path in Scheme 1 is believed to be that proposed by Bunnett and Davies[11] and often referred to as the SB–GA mechanism. 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.



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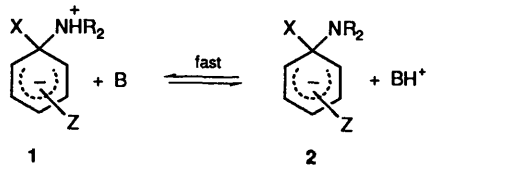
Scheme 1



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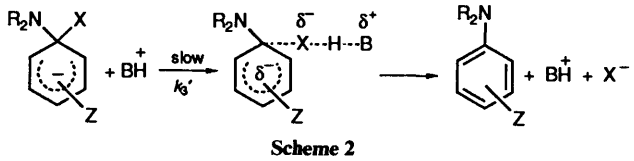


Scheme 2

For secondary amines the uncatalysed path takes place unimolecularly *via* the internally hydrogen-bonded intermediate in Fig. 1; while for primary amines an alternative mechanism is available, similar to that of the catalysed route with a solvent

Table 2 Rate constants/dm^3 mol^{-1} s^{-1} for the reactions of some phenyl ethers with amines in dimethyl sulfoxide at 30 °C

Substrate[a]	Nucleophile/base	Concentration/mol dm^{-3}	k_a	k''/k'[b]
2,6-Dinitrophenyl phenyl ether	Piperidine	2.0×10^{-2}	0.33×10^{-3}	128
		4.0×10^{-2}	0.56×10^{-3}	
		6.0×10^{-2}	0.78×10^{-3}	
		8.0×10^{-2}	1.03×10^{-3}	
		10.0×10^{-2}	1.25×10^{-3}	
		12.0×10^{-2}	1.50×10^{-3}	
	Morpholine	4.0×10^{-2}	0.48×10^{-5}	107
		6.0×10^{-2}	0.66×10^{-5}	
		8.0×10^{-2}	0.87×10^{-5}	
		10.0×10^{-2}	1.08×10^{-5}	
		20.0×10^{-2}	2.03×10^{-5}	
	Butylamine	2.0×10^{-3}	5.60×10^{-2}	112
		4.0×10^{-3}	7.13×10^{-2}	
		6.0×10^{-3}	8.10×10^{-2}	
		8.0×10^{-3}	9.00×10^{-2}	
		10.0×10^{-3}	10.0×10^{-2}	
	Benzylamine	4.0×10^{-3}	1.37×10^{-2}	106
		6.0×10^{-3}	1.58×10^{-2}	
		8.0×10^{-3}	1.77×10^{-2}	
		10.0×10^{-3}	1.96×10^{-2}	
		20.0×10^{-3}	3.00×10^{-2}	
2-Phenoxy-3,5-dinitropyridine	Aniline	2.0×10^{-2}	0.85×10^{-3}	27.5
		4.0×10^{-2}	1.15×10^{-3}	
		6.0×10^{-2}	1.43×10^{-3}	
		8.0×10^{-2}	1.75×10^{-3}	
		10.0×10^{-2}	2.05×10^{-3}	
	Aniline[c]	4.0×10^{-2}	2.10×10^{-2}	5.7
		6.0×10^{-2}	2.30×10^{-2}	
		8.0×10^{-2}	2.55×10^{-2}	
		10.0×10^{-2}	2.67×10^{-2}	
6-Methyl-2,4-dinitrophenyl phenyl ether	Piperidine	4.0×10^{-2}	1.95×10^{-4}	572
		6.0×10^{-2}	2.90×10^{-4}	
		8.0×10^{-2}	3.85×10^{-4}	
		10.0×10^{-2}	4.76×10^{-4}	
	Morpholine	6.0×10^{-2}	0.55×10^{-4}	84.6
		8.0×10^{-2}	0.705×10^{-4}	
		10.0×10^{-2}	0.81×10^{-4}	
		20.0×10^{-2}	1.60×10^{-4}	
	Butylamine	4.0×10^{-3}	1.18×10^{-1}	25.7
		6.0×10^{-3}	1.24×10^{-1}	
		8.0×10^{-3}	1.28×10^{-1}	
		10.0×10^{-3}	1.35×10^{-1}	
	DABCO[d]	0	0.118	107
		2.0×10^{-3}	0.140	
		4.0×10^{-3}	0.165	
		6.0×10^{-3}	0.191	
		8.0×10^{-3}	0.200	
		10.0×10^{-3}	0.250	
	Benzylamine	1.0×10^{-2}	1.28×10^{-2}	17
		2.0×10^{-2}	1.68×10^{-2}	
		3.0×10^{-2}	1.80×10^{-2}	
		4.0×10^{-2}	1.94×10^{-2}	
		5.0×10^{-2}	2.14×10^{-2}	
	DABCO[e]	0	1.28×10^{-2}	61
		2.0×10^{-3}	1.43×10^{-2}	
		4.0×10^{-3}	1.58×10^{-2}	
		6.0×10^{-3}	1.76×10^{-2}	
		8.0×10^{-3}	1.89×10^{-2}	
		10.0×10^{-3}	2.06×10^{-2}	

[a] Substrate concentration = $1.0–3.5 \times 10^{-4}$ mol dm^{-3}. [b] See text. [c] At 100 °C. [d] [Butylamine] = 4.0×10^{-3} mol dm^{-3}. [e] [Benzylamine] = 1.0×10^{-2} mol dm^{-3}.

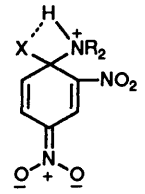


Fig. 1 Internally hydrogen-bonded intermediate for the reaction of secondary amines with 2,4-dinitrophenyl phenyl ether

molecule acting as the base. The evidence[8] for the latter is based on the changes in kinetic form which occur when a reaction is performed in dipolar aprotic solvents of approximately the same relative permittivity but widely differing basicities and implies either that this mechanism takes place in all solvents investigated or that in the less basic solvent a change takes place to a unimolecular mechanism if this becomes energetically more feasible. The present results are rationalised in accordance with the above ideas.

With three exceptions, all the reactions reported are either not base catalysed or the catalysis has a linear dependence on the nucleophile concentration. In the case of the reactions of piperidine and morpholine with 2-phenoxy-3,5-dinitropyridine in acetonitrile, plots of k_A against nucleophile concentration are linear through the origin, that is they are third-order reactions. The three exceptions are the reactions in acetonitrile of piperidine and morpholine with 6-methyl-2,4-dinitrophenyl phenyl ether and of 2,6-dinitrophenyl phenyl ether with morpholine. With all three reactions the rate constants have a linear dependence on the nucleophile concentration in dimethyl sulfoxide, but a curvilinear one in acetonitrile, *i.e.* there is a change in the conditions of eqn. (1) from $k_{-1} \gg k_2 + k_3[B]$, to $k_{-1} \sim k_2 + k_3[B]$. The greater tendency of a substrate containing an *ortho*-nitro group to undergo base catalysed reactions with secondary amines than with primary amines of the same basicity has been explained[6,7] in terms of the ammonio proton in the intermediate **1** hydrogen bonding to the oxygen atoms of the nitro group. The effect on k_{-1} will be approximately the same for both primary and secondary amines, but the effect on the expulsion of the leaving group will be different, as the hydrogen bond must be broken when the nucleophile is a secondary amine, but not when it is a primary one. This will result in a greater reduction of the $(k_2 + k_3[B])/k_{-1}$ ratio for secondary amines compared to primary ones. Bernasconi[6] has also shown that the effect of this hydrogen bond is greater on k_{-1} than k_2 and the discrepancy between the two is magnified when the hydrogen bond is strong. Dimethyl sulfoxide is much more basic than acetonitrile and can form a quite strong hydrogen bond with the ammonio proton. Thus intramolecular hydrogen bonding is much more effective in acetonitrile giving an increase in k_2/k_{-1} compared to dimethyl sulfoxide.

The reaction of pyrrolidine with 6-methyl-2,4-dinitrophenyl phenyl ether follows the same pattern[12] and although previously the reactions of 2,4-dinitrophenyl phenyl ether with morpholine[13] and piperidine[7] were reported to have a k_A linearly dependent on the nucleophile concentration in acetonitrile, when the range of nucleophile concentration was increased to that used for the 6-methyl substrate, a curvilinear dependence of k_A on nucleophile concentration has been found at higher nucleophile concentrations in this solvent.

Comparisons involving 2,6-Dinitrophenyl Phenyl Ether.—In dimethyl sulfoxide the reactions of both 2,4,6-trinitrophenyl phenyl ether[14] and 2-phenoxy-3,5-dinitropyridine with aniline, together with those of 2,4-dinitrophenyl phenyl ether[7] with butylamine and benzylamine are not base catalysed, whereas those of butylamine and benzylamine with 2,6-dinitrophenyl phenyl ether are catalysed.

Although the 2,6-dinitro substrate is not as activated as the 2,4,6-trinitro one, the congestion around the reaction centres is identical and any effects arising from the increased bulk or greater leaving group ability[6,10] of aniline compared to butylamine should mitigate towards catalysis. Hence the difference in kinetic form of the two systems is not due to steric effects.

If, for primary amines, the uncatalysed path takes place by a mechanism similar to that given in Scheme 2 with a molecule of solvent, S, replacing the base B, then k_2 [eqn. (1)] = $\bar{k}_2 K_s$, where $K_s = [\mathbf{2}][SH^+]/[\mathbf{1}]$, is the acidity constant of the intermediate and $\bar{k}_2$ is the rate constant for the reaction of **2** with SH^+. Bernasconi[15] has shown that when a series of nucleophiles form σ-complexes with the same substrate, the ratio of the acidity constants of the complexes to that of the nucleophiles is approximately constant (500 for the system 1,3,5-trinitrobenzene–butylamine–DMSO).[16] The pKa's[17] of butylamine and aniline in dimethyl sulfoxide are 11.1 and 3.6, hence k_2 (aniline) should be much greater than k_2 (butylamine). The condition $(k_2 + k_3[B]) > k_{-1}$ will also be promoted by the 4-nitro group in the trinitrophenyl–aniline system. Kaválek and Stêrba[18] have shown for the reactions of 4-substituted 2-nitrofluorobenzenes with piperidine in acetonitrile–benzene mixtures that although k_2/k_{-1} ratios are relatively insensitive to the 4-substituent, the k_3/k_{-1} ratios increase strongly with increased activation of the substrates and Bernasconi and de Rossi[19] state that increase in the acidity of the ammonio proton in the intermediate **1** increases both k_2 and k_3, but the increase is greater for k_3. These two effects combine to overcome the greater tendency towards base catalysis when the basicity of the nucleophile is decreased,[6,11] and the reactions of the 2,4,6-trinitrophenyl and 3,5-dinitropyridin-2-yl substrates with aniline are not base catalysed.

There is little difference in the gross activation of the 2,4- and 2,6-dinitro substrates. In methanol where the reactions of both substrates with butylamine are not catalysed[7,12] the $k_{2,6}/k_{2,4}$ ratio is approximately six, comparable with the value of *ca.* 10 obtained by Nudelman and Palleros[20] for the ratio of the first-order rate constants of the substrates in neat cyclohexylamine. The origins of the difference in kinetic form of the reactions of the two substrates with both butylamine and benzylamine is therefore steric. There are various sources of this effect. Steric compressions in the σ-complex would be relieved by expulsion of the nucleophile giving an increase in k_{-1}. Bernasconi[19] has pointed out that hindrance by an *ortho* substituent to the development of resonance in the product (Fig. 2) would reduce both k_2 and k_3, and Bunnett[21] has ascribed the 11 000-fold difference in rates of decomposition to products of the complexes corresponding to **2** formed between 2,4-dinitro-1-naphthyl ethyl ether and pyrrolidine and piperidine in dimethyl sulfoxide, to stereoelectronic effects in the transition state, forced by differences of conformation between the two amino groups in the adducts as they release the nucleofuge. By the same token, steric and stereoelectronic effects involving the leaving group, especially when it is an ether, in the transition state of the decomposition to reactants of the first-formed intermediate **1**, should reduce k_{-1}, and it appears that this dominates any acceleration due to relief of steric compressions arising from the ejection of the nucleophile from the complex. Thus for the complexes **3a** and **3b** (Fig. 3), formed from 2,4,6-trinitrophenetole (X = OEt) in dimethyl sulfoxide, when the nucleophiles are butylamine and benzylamine, Crampton[22] has stated that k_{-1} [rate constant for the reversion of (*a*) to reactants] will be several orders of magnitude less than k_{-3} [rate constant for the reversion of (*b*) to reactants]. For the corresponding complexes formed by the same two nucleophiles with 2,4,6-trinitrobenzyl chloride (X = CH_2Cl),[23] the k_{-3} values are 2.3×10^4 (butylamine) and 6×10^4 (benzylamine)

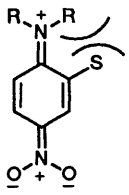
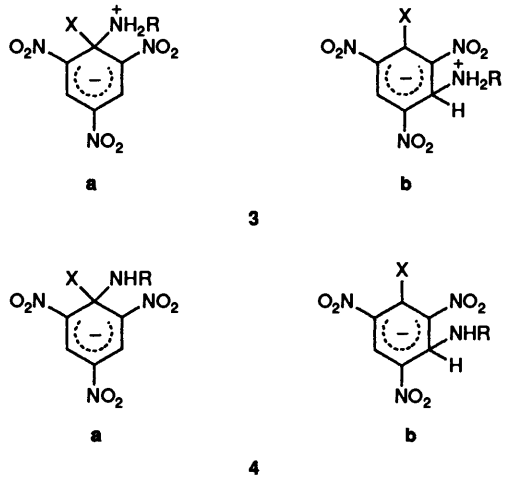


Fig. 2 Resonance form of the product. Development of this form is hindered by the steric effect of an *ortho* substituent.

but the corresponding k_{-1} values are reduced to 13 and 110 s^{-1}.

Steric hindrance to the approach of the conjugate acid of the nucleophile (base) would retard electrophilic catalysis of the removal of the nucleofuge. If it is assumed that the sensitivities to steric effects involving the same acid are approximately the same for electrophilic catalysis of leaving group departure and the reprotonation of **2** (Scheme 2) then there is evidence for steric retardation of the expulsion of the leaving group. The rate constants for the reprotonation of **4** (X = H) by RNH_3 where RNH_2 is butylamine or benzylamine[16] are $>4 \times 10^4$ dm^3 mol^{-1} s^{-1}, but for the complexes formed from trinitrophenetole (**4a**, X = OEt) the corresponding values are[22] >50 (butylamine) and >60 (benzylamine). Similarly for the same two nucleophiles and 2,4,6-trinitrobenzyl chloride[23] (X = CH_2 – Cl) the rate constants for reprotonation of the σ-1 (**4a**) and σ-3 complexes (**4b**) by the conjugate acids are *ca.* 10^3 times less for the σ-1 complex compared to the σ-3. We conclude that the origin of the change in kinetic form between the 2,4- and 2,6-dinitro substrates arises from a combination of steric inhibition of the approach of the electrophilic catalyst to the nucleofuge and any steric/stereoelectronic effect reducing k_2 and k_3, which outweighs any reduction in k_{-1} brought about by an increase in steric/stereoelectronic effects on the ejection of the nucleophile from the zwitterionic complex due to the change in the substrate.

The presence of two *ortho*-nitro groups in the 2,6-dinitro substrate allows the possibility of hydrogen bonding of both ammonio hydrogen atoms in the complex formed by reaction with a primary amine. Although this will not increase the susceptibility of the system to base catalysis, because as already stated Bernasconi[6] has shown that hydrogen bonding of the ammonio hydrogen atom to an *ortho*-nitro group in the σ-complex reduces k_{-1} more than k_2, it does have an effect on the mechanism of the uncatalysed path of decomposition to products. We have already mentioned that there is evidence that, in dipolar aprotic solvents, the mechanism of this path differs when primary and secondary amines are the nucleophiles. For the unimolecular mechanism, a decrease in solvent basicity, particularly from dimethyl sulfoxide to acetonitrile, should have little effect on the k_{-1}/k_2 and k_3/k_2 ratios, but for the SB–GA-like mechanism, the change should be accompanied by large increases in their values. In the present series the values of k_3/k_2 for the reactions of 2,4-dinitro-6-methylphenyl phenyl ether with piperidine * and morpholine only change by a factor of *ca.* two when the solvent is changed from dimethylsulfoxide to acetonitrile. Similar changes in k_3/k_2 values are observed for the reactions of 2,6-dinitrophenyl phenyl ether with piperidine and morpholine and have already been recorded for the reactions of these two nucleophiles with 2,4-dinitrophenyl phenyl ether.[7] The reaction of 2-phenoxy-3,5-dinitropyridine with aniline is not catalysed in dimethyl sulfoxide, but is catalysed in acetonitrile. Similar behaviour has been observed in the reaction of 2,4-dinitroanisole with butylamine,[14] 2,4,6-trinitrophenyl phenyl ether with aniline[14,24] and 1-fluoro-2,4-dinitrobenzene with aniline.[8] In all cases these changes when primary amines are the nucleophiles correspond to a change in the condition $k_{-1}/k_2 \ll 1$ in dimethyl sulfoxide to $k_{-1}/k_2 \gg 1$ in acetonitrile. In the case of the fluorodinitrobenzene–aniline system, values of k_3/k_2 increase from 36 in dimethylformamide to infinity in acetonitrile and nitromethane. The pattern observed for the reactions of 2,6-dinitrophenyl phenyl ether and of 6-methyl-2,4-dinitrophenyl phenyl ether with butylamine and benzylamine resembles that of secondary amines rather than that of primary ones. Catalysis is observed in both dimethyl sulfoxide and acetonitrile and there is only a small change in the k_3/k_2 values with change of solvent (for the change dimethyl sulfoxide to acetonitrile with the 2,6-dinitro substrate, the changes in k_3/k_2 are butylamine, 112 to 153; benzylamine, 106 to 67. With the 6-methyl substrate the values are: butylamine 26 to 41; benzylamine 17 to 20).



3

4

Fig. 3 Meisenheimer complexes used to demonstrate steric effects

When two *ortho* groups are present, congestion at the reaction centre inhibits the bimolecular SB–GA-like mechanism of the uncatalysed mode of decomposition of the intermediate when primary amines are the nucleophiles, and favours unimolecular decomposition *via* an internally hydrogen-bonded transition state. Evidence for steric inhibition of the bimolecular abstraction of a proton from the intermediate is provided by the application of the principle of microscopic reversibility to the rate of reprotonation of intermediate **2** discussed earlier, and Nudelman's[26] demonstration of strong retardation of the isopropylamine-catalysed decomposition of the intermediate formed from *p*-nitrofluorobenzene and isopropylamine in toluene. Furthermore, hydrogen-bonding of both ammonio hydrogen atoms to the two *ortho*-nitro groups in the zwitterionic σ-complex formed for the 2,6-dinitro substrate would give a situation analogous to that of the hydrogen bonding of the ammonio proton in the complex formed by a secondary amine with a substrate containing *one* nitro group. Hence when two *ortho* groups are present, particularly if they are nitro groups, primary and secondary amines will tend to behave in a similar fashion.

The amino hydrogen atoms of aniline are sufficiently acidic that they hydrogen bond with dimethyl sulfoxide to form a 1:1 complex.[27] When aniline is the nucleophile these already strong hydrogen bonds will increase in strength on Meisenhiemer complex formation as the nitrogen atom becomes more positively charged, and will strongly dispose the uncatalysed decomposition of the σ-complex **1** to take place by a SB–GA-like mechanism. When this nucleophile reacts with 2,4,6-trinitrophenyl phenyl ether the bulk of the aniline moiety probably hinders the σ-complex assuming the highly specific conformation required for both ammonio hydrogen atoms to

* Values of k_3/k_2 of 429 for piperidine and 171 for morpholine in acetonitrile were obtained by standard procedures.[25]

hydrogen bond to the two *ortho*-nitro groups. These two factors combine to give the normal pattern of solvent change found in this reaction.*

The Effects of ortho-*Methyl, Aza and Nitro Groups.*—(*a*) *Secondary amines.* Previously[7] we have reported that over the concentration ranges 5–30 $\times 10^{-3}$ mol dm^{-3} (piperidine) and 4–16 $\times 10^{-2}$ mol dm^{-3} (morpholine), k_A for the reactions of these nucleophiles with 2,4-dinitrophenyl ether in acetonitrile increased linearly with increasing nucleophile concentration. When these concentrations are extended to cover the range used in the investigation of the 6-methyl derivative (up to 90 $\times 10^{-3}$ mol dm^{-3}, piperidine, and 26 $\times 10^{-2}$ mol dm^{-3} morpholine) a curvilinear dependence on nucleophile concentration was found at high nucleophile concentrations. Hence, provided comparisons are made over the same range of nucleophile concentration, both substrates have the same kinetic form and there is no drastic change in the $(k_2 + k_3[B]/k_{-1}$ ratio. It would appear that any steric/stereoelectronic effect of the methyl group on k_2 and k_3 is balanced by an effect of similar magnitude on k_{-1}.

The introduction of an *ortho*-methyl group has little effect on the k_3/k_2 ratios for both nucleophiles in the two solvents. The values are: 2,4-dinitro;[7] piperidine 461, morpholine 86: 6-methyl; piperidine 572, morpholine 85 (dimethyl sulfoxide) and 2,4-dinitro;[7] piperidine 542, morpholine 185: 6-methyl; piperidine 429, morpholine 171 (acetonitrile). As the methyl group is only mildly deactivating electronically, its differential effect on k_2 and k_3 will be small and obscured by steric effects when it is in the *ortho* position.

The plots of the rate constants for the reactions of 2-phenoxy-3,5-dinitropyridine with both piperidine and morpholine in acetonitrile are linear through the origin. Hence, as no steric effects are involved in these reactions, the increased activation brought about by the introduction of an *ortho*-aza group into the 2,4-dinitro substrate while not sufficient to increase k_2/k_{-1} and k_3/k_{-1} to bring about a change in the condition $k_{-1} \gg k_2 + k_3[B]$, does result in the expected increase in the k_3/k_2 ratio. The reaction with primary amines reveals an additional effect which actually decreases the k_2/k_{-1} and k_3/k_{-1} ratios.

(*b*) *Primary amines.* In both dimethyl sulfoxide and acetonitrile, for both butylamine and benzylamine, the introduction of a 6-methyl group changes the kinetic form of the reactions from an uncatalysed one[7] to one in which there is a linear dependence of the rate constant on the nucleophile concentration. The effect of the methyl group in bringing about the change in the condition from $k_{-1} \ll k_2 + k_3[B]$ to $k_{-1} \gg k_2 + k_3[B]$ is in the same direction as that observed for changing the position of a nitro group from the 4- to the 2-position for the reactions of the same two nucleophiles with 2,4- and 2,6-dinitrophenyl phenyl ethers in dimethyl sulfoxide.

The reactions of both nucleophiles with 2-phenoxy-3,5-dinitropyridine in acetonitrile have second-order rate constants whose magnitude increases linearly with nucleophile concentration. Thus the introduction of an *ortho*-aza group, an activating group with no steric implications, has had the unusual effect of increasing k_{-1} relative to $k_2 + k_3[B]$. This is probably due to the aza group introducing additional possibilities for resonance and thus lowering the electron density on the oxygen atoms of the *ortho*-nitro group and consequently reducing the strength of the hydrogen bond they form with an ammonio proton in the zwitterionic complex. As mentioned earlier, the effect of this will be greatest on k_{-1}, thus increasing its relative magnitude. The effect is similar to that observed for 2-nitrofluorobenzene where the reaction with piperidine in benzene, which is not base catalysed,[28] is turned into a base-catalysed one by the introduction of a 4-nitro group.[29] A similar explanation can be made for the observation that, while a 4-nitro group is more activating than a 4-bromo one, the reaction of 4-bromo-2-nitroanisole with piperidine in dimethyl sulfoxide is not base catalysed,[20] but that of 2,4-dinitroanisole is.[14]

As the reactions of 2,4-dinitrophenyl phenyl ether with butylamine and benzylamine in acetonitrile are not base catalysed, the effects of *ortho*-methyl and aza groups on the k_3/k_2 ratio could not be determined. However, the increases in the values for the change *ortho*-methyl to *ortho*-aza [40 to 1077 (butylamine) and 20 to 163 (benzylamine)] are in the direction predicted by Bernasconi. His argument though is based on the uncatalysed path taking place *via* the unimolecular mechanism. If both the uncatalysed and catalysed paths occur by the same SB–GA mechanism in both solvents then increase in activation would not be expected to have a substantial effect on the ratio. We have already seen that when the substrate contains two *ortho* groups, there is evidence that when the Meisenheimer complexes formed from primary amines as nucleophiles decompose *via* an uncatalysed path, they do so by the unimolecular mechanism. The evidence for the SB–GA-like mechanism for the uncatalysed path when primary amines react with mono-*ortho*-substituted substrates rests on the variation of k_2/k_{-1} and k_3/k_2 values with changes in basicity of solvents of high relative permittivity. The evidence is consistent with reaction by the SB–GA-like mechanism in DMSO, but owing to the large decrease in basicity when the solvent is changed to acetonitrile, for the reaction to occur by the unimolecular path, or for the two mechanisms to coexist, in this solvent. The reactions of aniline dispose towards this hypothesis. In acetonitrile the rate constants for the reactions of this nucleophile with both 2-phenoxy-3,5-dinitropyridine and 2,4,6-trinitrophenyl phenyl ether have a linear dependence on the aniline concentration. For the 3,5-dinitropyridine substrate k''/k' has a value of 70 at 30 °C and for the 2,4,6-trinitrophenyl ether Banjoko[24] gives a figure of 16 390 at 25 °C for this ratio (the assumption that the reaction is second-order in aniline, *i.e.* $k_3/k_2 = \infty$, gives good third-order rate constants). This very large increase in the ratio with increased activation is more commensurate with the uncatalysed path proceeding by a unimolecular mechanism in acetonitrile than the alternative SB–GA-like one.

Experimental

The preparation of the substrates and products of reaction, together with the analytical data for new compounds and details of the spectrophotometric determination of the rate constants, have already been given.[30,31]

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* The explanation given on page 129 for the difference in kinetic form between the trinitrophenyl–aniline and 2,6-dinitrophenyl–butylamine systems in DMSO is based on the uncatalysed path of the latter system taking place by an unrestrained SB–GA-like mechanism. As, in practise, this is inhibited sufficiently to allow reaction by the unimolecular mechanism, the conclusions k_2 (trinitrophenyl–aniline system) $\gg k_2$ (2,6-dinitrophenyl–butylamine system) is still valid.

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