Relative Reactivity and Kinetic Pattern of Aniline and *N*-Methylaniline as Nucleophiles in Aromatic Substitution (S_NAr) Reactions

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ABSTRACT: Kinetic results are reported for the reactions of 4-nitrophenyl-2,4,6-trinitrophenyl ether **3** with aniline and *N*-methylaniline in dimethyl sulphoxide, acetonitrile, methanol, and benzene. The reactions gave the expected 2,4,6-trinitrodiphenylamine and were base catalyzed in all the solvents. Both nucleophiles showed the same kinetic pattern under the same reaction conditions but aniline was found to be considerably more reactive than *N*-methylaniline. The greater catalytic efficiency of aniline over *N*-methylaniline is consistent with the proton transfer mechanism of the base-catalyzed step. Dichotomy of amine effects in aromatic substitution (S_NAr) reactions is discussed. © 2004 Wiley Periodicals, Inc. Int J Chem Kinet 36: 188–196, 2004

INTRODUCTION

The general mechanism of aromatic nucleophilic substitution reactions when either primary or secondary amines are the nucleophiles is given in Scheme 1. Equation (1) is the steady-state expression for the observed second-order rate constant k_A expressed in terms of the component steps in Scheme 1.

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

A salient feature of this mechanism is that the intermediate **1** can proceed to the product spontaneously (k_2) or through general base catalysis (k_BB). If no catalysis is observed, the inference can be made that the formation of the intermediate **1** is rate-limiting and the condition $k_2 + k_B\,[B] \gg k_{-1}$ prevails. In this case, the measured overall constant k_A is equal to k_1. When this condition does not hold, decomposition of **1** into product is rate limiting and the reaction is base-catalyzed; the kinetic form then depends on the relative magnitude of k_{-1} and $k_2 + k_B[B]$. Provided that $k_{-1} \gg k_2$, Eq. (1) describes generally a dependence of k_A on [B], which is linear in low nucleophile concentrations but changes to a plateau as the base concentration is increased. At low [B] values, $k_{-1} \gg k_2 + k_B\,[B]$ and k_A responds linearly to base concentration. The second-order rate

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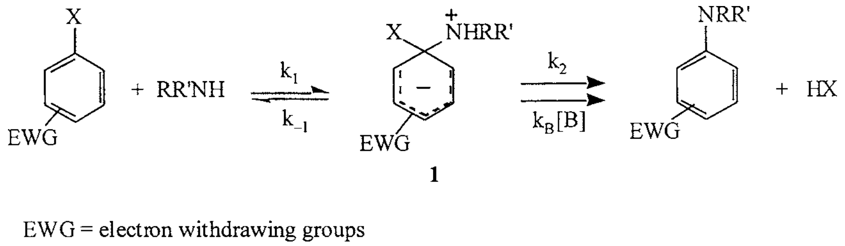


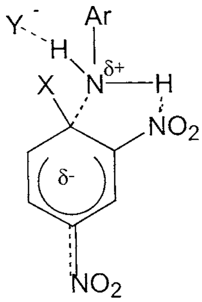
Scheme 1

constant then obeys an equation such as (2)

$$k_A = k' + k'' \,[\mathrm{B}] \qquad (2)$$

If $k_{-1} \approx k_B$ [B] within the experimental range of base concentrations, k_A depends hyperbolically on base concentration.

In aromatic substitution (S_NAr) reactions, when a substrate containing an ortho-nitro group reacts with primary and secondary aliphatic amines of the same basicity, quite often, the reactions with secondary amines are base-catalyzed whereas the corresponding reactions with primary amines are not. The situation with primary and secondary aromatic amines is not so clear cut since it has been found that some aromatic nucleophilic substitution reactions involving aniline as nucleophile are base-catalyzed while the corresponding reactions of *N*-methylaniline are not. Kavalek et al. [1] have reported that the reaction of *N*-methylaniline with 1-fluoro-2,4-dinitrobenzene in acetonitrile is not based-catalyzed by *N*-methylaniline whereas the same reaction with aniline exhibits base catalyses by the amine. On the basis of the observed order of halogen mobility (Cl > F) for the reactions with *N*-methylaniline, these workers concluded that the decomposition of zwitterionic intermediate to product constitutes the rate-limiting step of the reaction. Hirst et al. [2] reexamined the same reaction and came to the conclusion that there was mild catalysis by *N*-methylaniline. The reaction was also strongly catalyzed by 1,4-diazabicyclo-[2.2.2]-octane (Dabco). When the nucleophile was changed to aniline, the plot of k_A against aniline concentration was curvilinear and passed through the origin; hence the uncatalyzed pathway was negligible. On the contrary, the reaction of 2,4-dinifluorobenzene with *N*-methylaniline in ethanol was catalyzed by acetate ion, whereas no catalysis was observed in the reaction of the same substrate with aniline [3,4]. Hirst [5] has indicated that catalysis by anilines as nucleophile is difficult to interpret. Akinyele et al. [6] have shown that because of the greater acidity of the amino hydrogen atoms of aniline, compared with that of *n*-butylamine or piperidine, catalysis of the first step of the reaction can take place as in structure **2**. Here Y is a base which may be the nucleophile or even chloride ion



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To circumvent this problem, we decided to use a system devoid of such complication. In an earlier investigation of steric and electronic effect on the mechanism of nucleophilic reactions of some phenyl-2,4,6-trinitrophenyl ethers [7] we made a preliminary comparison of the reactivity of aniline and *N*-methylamine in dimethyl sulfoxide (DMSO) and acetonitrile. Here in we report detailed kinetic studies of the reactions of these two nucleophiles with 4-nitrophenyl-2,4,6-trinitrophenyl in various solvents. Our aim was to determine whether the dichotomy of amine effects prevalent in the reactions of aliphatic and alicylic amines exist in S_NAr reactions involving aromatic amines.

EXPERIMENTAL

The substrate 4-nitrophenyl-2,4,6-trinitrophenyl ether was prepared by the reaction of picryl chloride with 1 equiv of base in the presence of an excess of 4-nitrophenol in aqueous ethanol. The reaction product 2,4,6-trinitrodiphenylamine and it *N*-methyl derivative were prepared by reaction of picryl chloride with fourfold excess of the appropriate amine in ethanol. Recrystallization was from ethanol. ^{1}NMR data, melting points, and C,H,N analysis are given in Tables I and II. The purification of solvents, aniline, and

Table I ^{1}H NMR Shifts in CD_3CN and Melting Points for Reactant and Products

	^{1}H NMR Shifts[b]					mp (°C)	
Compound[a]	H3,5	H2′	H3′	H4′	Other	Found	Lit[7]
3	9.11	7.15	8.26	–	–	158	157
7a	8.96	7.15	7.33	7.25	9.96NH	179	178
7b	8.85	6.86	7.26	7.00	3.27(Me)	127	108

[a] Compound **3** is 4′-nitrophenyl-2,4,6-trinitrophenyl ethers, **7a** is 2,4,6-trinitrodiphenylamine, and **7b** its *N*-methyl derivative.

[b] Ortho coupling, *J* 7–8 Hz is observed.

N-methylaniline has been described previously [7]. ^{1}H NMR spectra were measured with Varian Mercury 200 MHz or Varian Unity 300 MHz. The details of spectrophotometric determination of the rate constants have already been given [7].

RESULTS AND DISCUSSION

Reactions of the substrate with aniline in all the solvents proceeded without the observation of intermediates to give the expected 2,4,6-trinitrodiphenylamine in quantitative yield. UV and NMR spectra at the completion of the reaction were identical with that of the expected substitution product in the reaction medium. Kinetic measurements in acetonitrile and DMSO were made with aniline and with solutions containing aniline and Dabco. Reactions in methanol were carried out in the presence of the amine and with amine containing amine hydrochloride. With these concentrations in large excess of the substrate concentration, first-order kinetics was observed.

Reactions in Acetonitrile

Plots of second-order rate constants vs aniline concentration pass through the origin and curve with decreasing slope as aniline concentration is increased Fig. 1. This implies that the uncatalyzed pathway k_2 in Scheme 2 is relatively unimportant. Hence, Eq. (1) reduces to Eq. (3), where k_{AN} represents the pathway catalyzed by aniline.

Table II CHN Analysis of the Reactant and Products

		Calculated (%)			Found (%)		
Compound	M_{w}	C	H	N	C	H	N
3	350.20	41.12	1.73	15.99	40.97	1.67	15.88
7a	304.22	47.33	2.65	14.41	47.23	2.65	18.37
7b	318.25	49.02	3.17	17.60	48.95	3.14	17.57

$$k_{\mathrm{A}} = \frac{k_{\mathrm{obs}}}{[\mathrm{Aniline}]} = \frac{k_1 k_{\mathrm{AN}}[\mathrm{Aniline}]}{k_{-1} + k_{\mathrm{AN}}[\mathrm{Aniline}]} \tag{3}$$

An equivalent form is Eq. (4)

$$k_{\mathrm{A}} = \frac{K_1 k_{\mathrm{AN}}[\mathrm{Aniline}]}{1 + \frac{k_{\mathrm{AN}}}{k_{-1}}[\mathrm{Aniline}]} \tag{4}$$

Provided $k_{-1} \gg k_{\mathrm{AN}}$ [Aniline], values of k_{A} data in Table III allow the calculation of k_1 0.26 ± 0.08 dm^3 mol^{-1} s^{-1}, $\frac{k_{\mathrm{AN}}}{k_{-1}}$ 4 ± 1 dm^3 mol^{-1}, and $K_1 k_{\mathrm{AN}}$ 1.03 ± 0.03 dm^6 mol^{-2} s^{-1}. At a constant aniline concentration, values of the second-order rate constant k_{A} increased linearly with Dabco concentration as shown in Fig. 2. The slope of this plot allows the calculation of a value for $K_1 k_{\mathrm{Dabco}}$ of 3.4 dm^6 mol^{-2} s^{-1}. Values are summarized in Table IV.

With *N*-methylaniline, we found that studies by UV–vis spectroscopy of the reaction of 3 (5×10^{-5} mol dm^{-3}) with excess nucleophile in acetonitrile was miserably slow and did not yield the expected substitution product. This may be due to trace quantities of impurities in the solvent or the amine which was redistilled. However, a ^{1}HNMR study in CD_3CN using substrate concentration (0.04 mol dm^{-3}) with *N*-methylaniline in large excess showed the development of bands over several days attributable to the expected reaction product. Integration of the bands due to the reactant and the product allowed the progress of the reaction to be monitored. Values of the first-order rate coefficient k_{obs} were calculated to be 1.1×10^{-6} s^{-1} and 1.0×10^{-5} s^{-1} when the concentrations of the nucleophile were 0.25 and 0.85 mol dm^{-3}, respectively. These results indicate that the value of the second–order rate constant k_{A} is linearly dependent on the concentration of the amine. The value k'' ($K_1 k_{\mathrm{N\text{-}MeAN}}$) calculated from the slope of such a plot is 1.6 ± 0.2 10^{-5} dm^6 mol^{-2} s^{-1}. The corresponding value for aniline is ca 10^5 higher than that of *N*-methylaniline.

Reactions in Dimethyl Sulphoxide

A plot (not shown) of the second-order rate constant k_{A} vs aniline concentration was linear with positive intercept. The intercept of such a plot represents the product of the equilibrium constant K_1 for the formation of **4** and the rate constant for its uncatalyzed decomposition to product k_2. The positive slope indicates the presence of a base-catalyzed route. At a constant aniline concentration however value of k_{A} increased linearly with Dabco concentrations. The results are best analyzed in

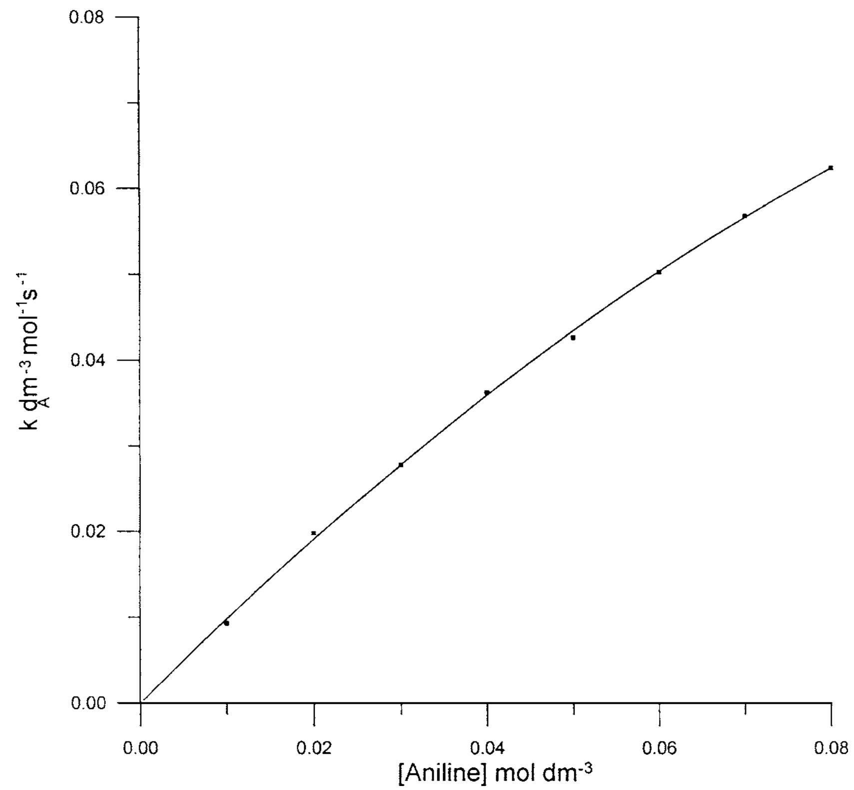
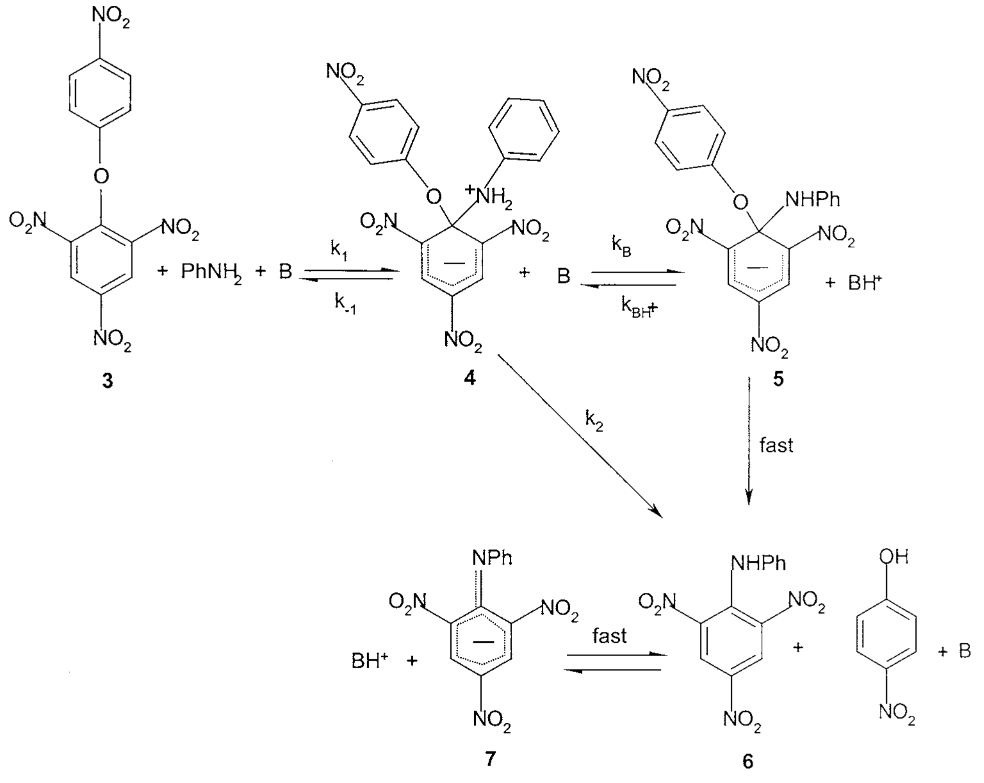


Figure 1 Plot of k_A vs [Aniline] in acetonitrile at 25°C for the reaction of 4-nitrophenyl-2,4,6-trinitrophenyl ether **3** with aniline. Experimental values are denoted by ■, and the curve is generated by $k_A = 1.03[\text{aniline}]/(1 + 4[\text{aniline}])$.



Scheme 2

Table III Kinetic Results for the Reactions of **3** with Amines in Various Solvents at 25°C

Acetonitrile								
[Aniline] (mol dm^{-3})	0.01	0.02	0.03	0.04	0.05	0.06	0.07	0.08
k_A (10^{-2} dm^3 mol^{-1} s^{-1})	0.93	1.98	2.78	3.62	4.26	5.02	5.68	6.24
[Dabco] (mol dm^{-3})	0.01	0.02	0.03	0.04	0.05	0.06		
k_A^a (10^{-2} dm^3 mol^{-1} s^{-1})	3.81	6.84	10.00	13.50	17.80	20.10		
Methanol								
[Aniline] (mol dm^{-3})	0.005	0.01	0.02	0.03	0.04	0.05	0.06	
k_A (10^{-2} dm^3 mol^{-1} s^{-1})	2.60	3.00	3.81	4.55	5.30	–	–	
k_A^b (10^{-2} dm^3 mol^{-1} s^{-1})	–	0.75	1.30	1.85	2.40	2.95	3.60	
[*N*-Methylaniline] (mol dm^{-3})	0.04	0.06	0.08	0.10				
k_A (10^{-4} dm^3 mol^{-1} s^{-1})	2.15	2.74	3.35	3.93				
k_A^c (10^{-4} dm^3 mol^{-1} s^{-1})	1.15	1.68	2.19	2.70				
Benzene								
[Aniline] (10^{-3} mol dm^{-3})	0.5	1.0	1.2	1.5	1.8	2.0		
k_A (10^{-3} dm^3 mol^{-1} s^{-1})	0.5	1.8	2.5	3.9	5.5	6.8		
[*N*-Methylaniline] (10^{-2} mol dm^{-3})	2.0	3.0	4.0	5.0				
k_A (10^{-4} dm^3 mol^{-1} s^{-1})	0.53	0.90	1.36	2.08				
Dimethyl sulfoxide								
[Aniline] (mol dm^{-3})	0.06	0.08	0.1	0.15	0.2			
k_A (10^{-1} dm^3 mol^{-1} s^{-1})	3.6	3.6	3.7	4.1	4.5			

[a] Kinetic results for the reactions with aniline (0.01 mol dm^{-3}) and various concentrations of Dabco.

[b] Contains 0.1 mol dm^{-3} aniline.

[c] Contains 0.1 mol dm^{-3}*N*-methylaniline hydrochloride.

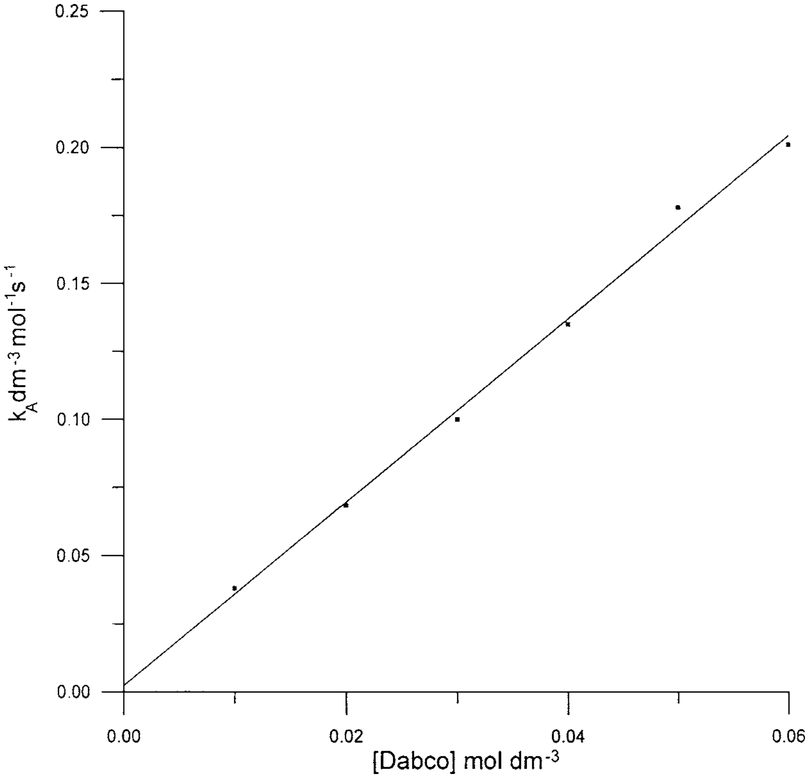


Figure 2 Plot of k_A vs [Dabco] in acetonitrile at 25°C for the reaction of 4-nitrophenyl-2,4,6-trinitrophenyl ether **3** with increasing concentration of Dabco at constant 0.01 mol dm^{-3} [Aniline] ($r = 0.996$).

Table IV Summary of Rate Data[a] for the Reaction of **3** with Aniline and *N*-Methylaniline

Amine	Solvent	K_1k_2 ($dm^3\ mol^{-1}\ s^{-1}$)	K_1k_{An} ($dm^6\ mol^{-2}\ s^{-1}$)	K_1k_{Dabco} ($dm^6\ mol^{-2}\ s^{-1}$)	k_{An}/k_{Dabco}	k_{An}/k_2 ($dm^3\ mol^{-1}$)
Aniline	DMSO	3.2×10	0.65	0.9	0.72	2.0
	Acetonitrile	–	1.03	3.4	0.30	–
	Methanol	2.23×1	0.77	–	–	34.6
	Methanol[b]	1.67×1	0.564			338
N-Methylaniline	DMSO	3.0×10	9.0×10^{-6}	–	–	3.0
	Acetonitrile	–	1.6×10^{-5}	–	–	–
	Methanol	9.60×1	2.98×10^{-3}	–	–	31
	Methanol[c]	1.24×1	2.58×10^{-3}	–	–	208

[a] Values quoted are ±10%.

[b] Obtained with addition of 0.1 mol dm^{-3} aniline.

[c] Obtained with addition of 0.1 mol dm^{-3} *N*-methylaniline hydrochloride.

terms of the processes shown in Scheme 2. Making the assumption that the zwitterion can be treated as a steady state intermediate leads to the rate expression of Eq. (5), where k_{AN} and k_{Dabco} represent $k_3[B]$ for the respective bases.

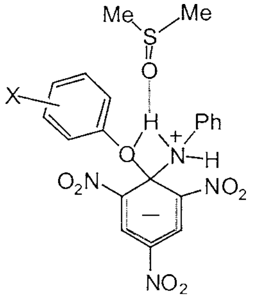
$$k_{obs} = \frac{k_1[AN][k_2 + k_{AN}[AN] + k_{Dabco}[Dabco]]}{k_{-1} + k_2 + k_{AN}[AN] + k_{Dabco}[Dabco]} \quad (5)$$

If $k_{-1} \gg k_2 + k_{AN}[AN] + k_{Dabco}[Dabco]$, then Eq. (6) applies

$$k_A = \frac{k_{obs}}{[Aniline]} = K_1(k_2 + k_{AN}[AN] + k_{Dabco}[Dabco]) \quad (6)$$

The value obtained for K_1k_2 is 0.32 $dm^3\ mol^{-1}\ s^{-1}$ while the values for K_1k_{An} and K_1k_{Dabco} are 0.65 $dm^6\ mol^{-2}\ s^{-1}$ and 0.9 $dm^6\ mol^{-2}\ s^{-1}$, respectively. Based on the acceleration produced by added Dabco, we conclude that at high aniline concentrations, there was some evidence of weak base catalysis. Similar observation has been made by Crampton and Robotham [8].

The greater susceptibility of an amine nucleophile to base catalysis in acetonitrile than in DMSO may be traceable to the nature of the solvent. The first step in adduct formation (Scheme 1) is the formation of the zwitterion and this involves the production of charges. DMSO is much better than acetonitrile at solvating charged polarizable species, such as the zwitterion. The values of overall equilibrium constants for adduct formation are 10^4 higher in DMSO than acetonitrile [9]. However, DMSO is also a good hydrogen bond acceptor so that $-NH_2^+$ protons will be strongly hydrogen-bonded to the solvent. This will reduce values of rate constants for proton transfer from zwitterions to base. There is evidence that values of the rate constants for such proton transfer are ca 10^4 lower in DMSO than in acetonitrile [9]. Hence the increases observed in k' and k'' on going from acetonitrile to DMSO are a combination of increases in K_1 values and the reduction in k_2 and k_{AN} values. The low ratio of k''/k' in DMSO may reflect solvent-assisted intramolecular proton transfer as depicted in **8**.



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Interestingly the numerical values of K_1k_{AN} are close in the two solvents. However, this similarity is likely to be due to the compensation of large increase in the value of K_1 and correspondingly large decrease in the value of k_{AN} as the solvent is changed from acetonitrile to DMSO.

The reaction of the substrate with *N*-methylaniline in [$^2H_6$] DMSO (Table V) shows a similar pattern to that obtained with aniline with both the uncatalyzed and the base-catalyzed pathways contributing to the reaction flux. The result conforms to Eq. (2) with values of K_1k_2 of 3×10^{-6} $dm^6\ mol^{-1}\ s^{-2}$ and $K_1k_{N\text{-}MeAN}$ of 9×10^{-6} $dm^3\ mol^{-1}\ s^{-1}$. Comparisons with the results for reaction with aniline indicate a factor of ca 10^5. This is exactly the same aniline/*N*-methylaniline reactivity ratio found in acetonitrile. The lower value of K_1k_{AN} for *N*-methylaniline is likely to be the result of decrease in both K_1 and in k_{AN}. In the zwitterion,

Table V Rate Data[a] for the Reaction of **3** with *N*-Methylaniline in [$^2H_6$] DMSO at 25°C

[*N*-Methylaniline] (mol dm^{-3})	k_{obs}[b] (10^{-6} s^{-1})	k_A (10^{-6} dm^3 ml^{-1} s^{-1})
0.4	2.7	6.7
0.6	4.7	7.8
0.8	7.8	9.8

[a] Measured by integration of ^{1}H NMR bands, with substrate 0.04 mol dm^{-3}.

[b] Values ±10%.

there will be considerable steric crowding at the reaction center resulting in a reduction of the value of K_1. Release of the steric strain would enhance k_{-1} for *N*-methylaniline.

Buncel [10] has estimated in the Dabco-induced Meisenheimer complex formation between 1,3,5-trinitrobenzene [TNB] and *N*-methylaniline or aniline that with *N*-methylaniline as the nucleophile, k_{-1} is an order of magnitude greater than in the case of aniline, reflecting the effect of release of steric compression in the zwitteronic intermediate on reversion to reactants in the former case. An additional factor may be the role of hydrogen bonding known to occur between the ammonio hydrogen atoms of the intermediate complex and the oxygen atoms of the ortho-nitro group. This hydrogen bonding stabilizes the intermediate so that k_{-1} is reduced, because reversion to reactants involves the breaking of the hydrogen bond in addition to the C—N bond. This effect will be about the same for aniline and *N*-methylaniline, but the effect on the expulsion of nitrophenoxide ion will be different, as the hydrogen bond will have to be broken when the nucleophile is *N*-methylaniline but not when it is aniline because of the availability of a free transferable proton in aniline. The ratio $k_2 + k_3$ [B]/k_{-1} will definitely be smaller for *N*-methylaniline than aniline, and as such aniline may be less prone to base catalysis in DMSO. Recently, such intramolecular interactions have been shown not to contribute much to the lowering of the K_1k_{An} value for *N*-methylaniline [7].

Reactions in Methanol

The second-order rate constants k_A for the reactions of the nucleophiles with 3 increases linearly with increasing concentration of the nucleophile, i.e. $k_A = k' + k''$ [Nucleophile]. Thus, for the reactions of both nucleophiles in methanol the decomposition of the intermediate to product is rate limiting. The reactions with aniline and *N*-methylaniline have low values of k''/k', 35 ± 0.5 and 31 ± 0.5, respectively. The addition of 0.1 mol dm^{-3} of the hydrochloride of the nucleophile, while decreasing substantially the rate constants of the reactions of the substrate with aniline and *N*-methylaniline, results in a large increase in the k''/k' to 338 ± 60 and 208 ± 22, respectively. Inspection of the individual values of k' and k'' in Table IV shows that the addition of amine hydrochloride has little effects on k''; the variation is entirely on k'. In terms of Scheme 1, k' $(=K_1k_2)$ and k'' $(=K_1k_B)$; hence, the addition amine hydrochloride has little effects on the base-catalyzed step k_B, consistent with the operation of proton transfer mechanism, but gives a reduction in the values of k' of approximately 13-fold and eight fold for the reactions with aniline and *N*-methylaniline, respectively. This was attributed to increased steric/stereoelectronic effects as a result of added anilinium ion [11]. The relatively low values of k''/k' ratios might reflect some solvent assistance by methanol in the intramolecular proton transfer involved in the k_2 step.*

Reaction in Benzene

Benzene is an aprotic, apolar, and scarcely polarizable solvent, which represents an ideal medium to promote the need for base catalysis for the decomposition of the intermediate. Aromatic nucleophilic substitution reactions are therefore more prone to base catalysis in aprotic solvents of low relative permittivity than in dipolar solvents [12]. In benzene, the values of the second-order rate constants k_A for the two nucleophile increased rapidly with amine concentration; the plots (not shown) exhibit a curvilinear response, which are concave toward the rate constant axis. The curved response shows that the order with respect to [Amine] is >2. Further the plots of the quotient k_A/[Amine] against [Amine] gave straight lines. In these systems, aniline is more efficient than *N*-methyaniline in catalyzing the reaction. In DMSO, we have shown that the reaction is mildly catalyzed by aniline, while the plot of k_A against aniline concentration is curvilinear downward with negligible intercept in acetonitrile and curvilinear upward in benzene. With *N*-methylaniline as nucleophile, the change in the kinetic form is from one in which the plot is linear with definite intercept in acetonitrile and DMSO to one which is again curvilinear upward in benzene, a kinetic form that is observed quite frequently in S_NAr reactions in solvents

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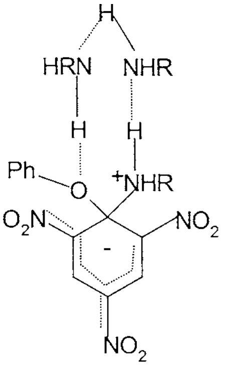
*A referee has suggested that another possibility for the observed decrease in the values of k' in the presence of amine hydrochloride may results from a reduction in methoxide concentration (present in equilibrium with the amine) acting as a general base in the deprotonation of the zwitterions.

of low permittivity. At present, there is controversy as to the origin of the curvature. It is however usually attributed to a term third order in the nucleophile concentration. The mechanistic interpretation of this term is still a subject of active discussion. Banjoko and coworkers [13] have explained the third-order term as being due to reaction occurring through a cyclic transition state containing an eight-member ring formed through a network of inter-hydrogen bonding between two aniline molecules and zwitterionic intermediate as shown in **9**. Akinyele et al. [14] gave a plausible mechanism for the formation of the cyclic transition state originally proposed by Capon and Rees [15]. The concept has been developed by Emokpae et al. [16] to rationalize reactions proceeding through cyclic transition states containing either two or three molecules of amine and to distinguish these reactions from those taking place by the specific base-general acid (SB-GA) mechanism. Hirst et al. [6] has, however, explained the upward curvature obtained by Bernasconi and Zollinger [17] in the reaction of *p*-anisidine with 1-fluoro-2,4-dinitrobenzene in benzene as due to electrophilic catalysis of the departure of the leaving group by the homo-conjugate of the conjugate acid of the nucleophile. Recently, Hirst [18] however advanced convincing reasons to show that there is only a thin dividing line between the cyclic transition state and the homo/hetero-conjugate mechanism. For the present reaction, we prefer to interpret the results along the lines suggested by Banjoko.



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Mechanism of Substitution

The greater catalytic efficiency of aniline over *N*-methylaniline may not be unconnected with the greater bulk of *N*-methylaniline as it affects the mechanism of the base-catalyzed step. Catalysis by Dabco in the system under investigation is an indication of general base catalysis so that the removal of the ammonium proton from the zwitterionic intermediate is rate-limiting. In dipolar aprotic solvents this can occur substantially either by a slow, rate-limiting proton abstraction from the zwitterionic intermediate **4** by the base to form the deprotonated intermediate **5**, from which the leaving group breaks off rapidly or by rapid deprotonation equilibrium followed by a slow detachment of the leaving group from **5**, which is general acid-catalyzed by the conjugate acid of the amine. The latter pathway, the SB-GA mechanism, has been widely accepted for reactions occurring in DMSO and has been shown to apply in substitutions of several other ring activated alkyl aryl ethers [19]. There is now strong evidence that with phenyl ether and phenyl sulfides rate-limiting proton transfer is from the zwitterion. One argument against the SB-GA mechanism is the failure to observe anionic intermediates such as **5** on the reaction pathway. For the reaction of 1-ethoxy-2,4-dinitro naphthalene with aliphatic amines in DMSO, which is widely recognized as a model for the SB-GA mechanism, Bunnett and Orvik [20] were able to observe in separate steps the formation of intermediate of structure of type **5** and their acid-catalyzed conversion into substitution products. Related intermediates have been observed during the reactions of several other ring-activated alkyl aryl ethers with amines [21] and there is no doubt that the SB-GA mechanism applies in this system.

As Bernasconi et al. [22] have noted that in protic solvents there is evidence that catalysis of alkoxide ion expulsion from Meisenheimer complex is weak or occurs only with acids considerably stronger than $R_2\overset{+}{N}H_2$. In water, the pK_a of phenol, anilinium, and *N*-methylanilinium ions are 9.95, 4.62, and 4.84, respectively. These values are unlikely to be reduced on transfer to DMSO or acetonitrile. Since the pK_a of 4-nitrophenol in water is 7.14, the equilibrium $NO_2PhO^- + R_2\overset{+}{N}H_2 \leftrightharpoons NO_2PhOH + R_2NH$ is only favored in the thermodynamic sense by 2.3 pK units for the leaving group to be lost in a slow general acid-catalyzed step. This may not constitute enough driving force to compensate for the expense in entropy in incorporating an addition molecule into the transition state [22]. There is already severe steric congestion around the zwitterionic intermediate **5** which will make it harder for another molecule to approach the reaction center.

The case against the SB-GA mechanism in our system is further supported [7] by the effects of substituents on the base-catalyzed pathway in the reactions of aniline with X-phenyl, 2,4,6-trinitrophenyl ethers [$X = 4\text{-}(H, CH_3, NO_2, Br, Cl), 3\text{-}NO_2$]. If the base-catalyzed pathway involves rate-limiting proton transfer from the zwitterion to base (the k_B step), then there should be little dependence on the nature of X. Values of $K_1 k_{\mathrm{An}}$ obtained in the series vary only by a factor of <3 between the more activating NO_2 and the least activating CH_3 group consistent with a rate limiting proton transfer mechanism. The results from previous investigation suggest that steric rather than electronic factors determine the rate constant for such proton transfer, which may be slower than the diffusion limit [19,20]. The $k_{\mathrm{An}}/k_{\mathrm{Dabco}}$ ratio of 0.3 shows that despite the large difference by 7 pK units in the basicities of aniline and Dabco their ability to effect the proton transfer from **4** is similar. That the ratio is <1 indicates that Dabco is less sterically demanding than aniline so that it is easier for it to approach the reaction center in the zwitterion. The alternative SB-GA mechanism will require that proton transfer from an ammonium ion to the anionic adduct **5** to be rate determining. The k_{B} step is therefore a product of the equilibrium constant for the conversion of the zwitterionic intermediate to the anionic adduct and the rate constant for the general acid-catalyzed expulsion of the nucleofuge ($K_1 k_{\mathrm{fast}}$). Since the latter term involves loss of the nucleofuge, then a strong dependence on the nature of X would be expected. The failure to observe such dependence argues against the SB-GA mechanism in our system.

Our conclusion is that in the present system as in related phenyl ethers base catalysis reflects rate-limiting proton transfer from zwitterionic intermediates. The weaker ability of N-methylaniline than aniline to catalyze the reactions of **3** in acetonitrile may therefore be reconciled on the basis that N-methylaniline is less effective in abstracting the proton from **4** because of its greater steric requirement relative to aniline. In all the solvents, both nucleophiles show the same kinetic pattern under the same experimental condition. The dichotomy of amine effects often found in the reactions of aliphatic amine does not exist in our system.

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