Anilinolysis of Nitro-Substituted Diphenyl Ethers in Acetonitrile: The Effect of Some Ortho-Substituents on the Mechanism of S_NAr Reactions

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ABSTRACT: Rate data are reported for the reactions of a series of X-phenyl 2,4,6-trinitrophenyl ethers **1a–e** [X = H, 4-NO_2, 2-NO_2, 2,4-$(NO_2)_2$, or 2,6-$(NO_2)_2$] with substituted anilines **2a–e** [Y = H, 2-CH_3, 2,4-$(CH_3)_2$, 2,6-$(CH_3)_2$, or N-CH_3] in acetonitrile as solvent. For individual amine, kinetic data show that there is little steric hindrance to attack at the 1-position of the parent molecules, even in the presence of di-ortho substitution. With each substrate, however, there is evidence for significant steric interactions; such effects leading to rate retardation were very severe for 2,6-dimethylaniline **2d** (2,6-$(CH_3)_2$) and N-methylaniline **2e** (Y = N-CH_3), the deactivating effect of N-CH_3 in most cases is slightly higher than that of 2,6-$(CH_3)_2$. However, the reactions with **2e** are base catalyzed whereas those of **2d** are not. The corresponding reactions with aniline **2a** (Y = H) and mono-ortho methyl-substituted aniline **2b** (Y = CH_3) are wholly base catalyzed. Only with the dinitro substrates, an uncatalyzed reaction is observed and when X = 2,6-$(NO_2)_2$ this pathway takes all the reaction flux. A rationale is provided for the dichotomy of amine effects observed in this investigation. © 2009 Wiley Periodicals, Inc. Int J Chem Kinet 42: 37–49, 2010

INTRODUCTION

In activated aromatic nucleophilic substitution reactions (S_NAr), considerable attention has been attached to the observation of base catalysis by primary and secondary amines and its significance [1–4]. The presence or absence of base catalysis, exerted by the nucleophile itself or by an externally added base,

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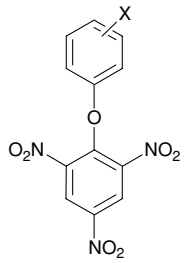
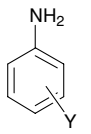
Supporting Information related to values of k_{obs} for the reactions of **2d** with the diphenyl ethers **1e** and for the reactions of **2c** with **1f** (Tables S1 and S2, respectively) is available in the online issue at www.interscience.wiley.com.

has played an important role in deciding whether formation or decomposition of the intermediate complex is rate limiting [5]. While the factors affecting the incidence of base catalysis have been extensively discussed and in most cases substantiated experimentally, only meagre attention has been given to the effects of ortho-substitution in the nucleophile. This may be due to complications arising from the ortho-effect of most substituents. Apart from the simple steric effect owing to a bulky substituent [6], other factors have been considered, such as the steric inhibition of resonance [7], the field effect [8], and the intramolecular hydrogen bonds [9,10]. It has been shown generally that steric effects are not linearly dependent in various reactions [11] but rather vary nonlinearly with the substituent, becoming suddenly appreciable at its certain size. The universal scales of steric effect, therefore, have no physical applicability and little practicability only in combination with other parameters. In this respect, the steric effect differs from inductive and also from resonance effects [12].

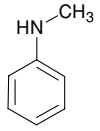
We found recently that in the reactions of ring-substituted anilines with 2,4-dinitrophenyl phenyl ether **1d** in acetonitrile, conversion of the zwitterionic intermediate to the products was rate limiting and involved both uncatalyzed k_2 and base-catalyzed k_{An} pathways. Alkyl substituents at the 2-position resulted in considerable reduction in reactivity. These effects were more pronounced for the base-catalyzed pathway, and in 2,6-dimethylaniline the uncatalyzed pathway took all the reaction flux [13]. Similarly, in the reactions with aniline in acetonitrile of a series of substituted phenyl 2,4,6-trinitrophenyl ethers, there was evidence of base catalysis, interpreted as rate-limiting deprotonation of the zwitterionic intermediate. Only with the dinitro-derivatives was an uncatalyzed reaction involving intramolecular proton transfer observed, and when the substituent was the 2,6-dinitro group (**1e**), the reaction was not amine catalyzed [14]. These studies were independently limited to investigation of the effect of substituent on the phenolic-leaving group or in attacking nucleophile. In the present study, we have employed not only the substituents X in the leaving group in **1** but also substituents Y in the attacking aniline nucleophile **2**. To deal with an effect that can be classified as purely steric, we restricted the investigation to methyl-substituent in the nucleophile. The ortho-methyl group has been shown to have weak polar effect and appreciable steric effect in S_NAr reactions [15]. Herein we report the results of detailed kinetic studies in acetonitrile of the reactions of a series of nitro-activated aryl phenyl ethers **1a–e** and with anilines carrying methyl substituent at the ortho position(s) **2a–d** and with *N*-methylamine **2e.**



1a–e
1a X=H
1b X=4-NO_2,
1c X=2-NO_2
1d X=2,4-$(NO_2)_2$
1e X=2,6-$(NO_2)_2$
1f X=Cl.



2a–d (Y=CH_3)
2a Y=H
2b Y=2-CH_3
2c Y=2,4-$(CH_3)_2$
2d Y=2,6-$(CH_3)_2$



2e

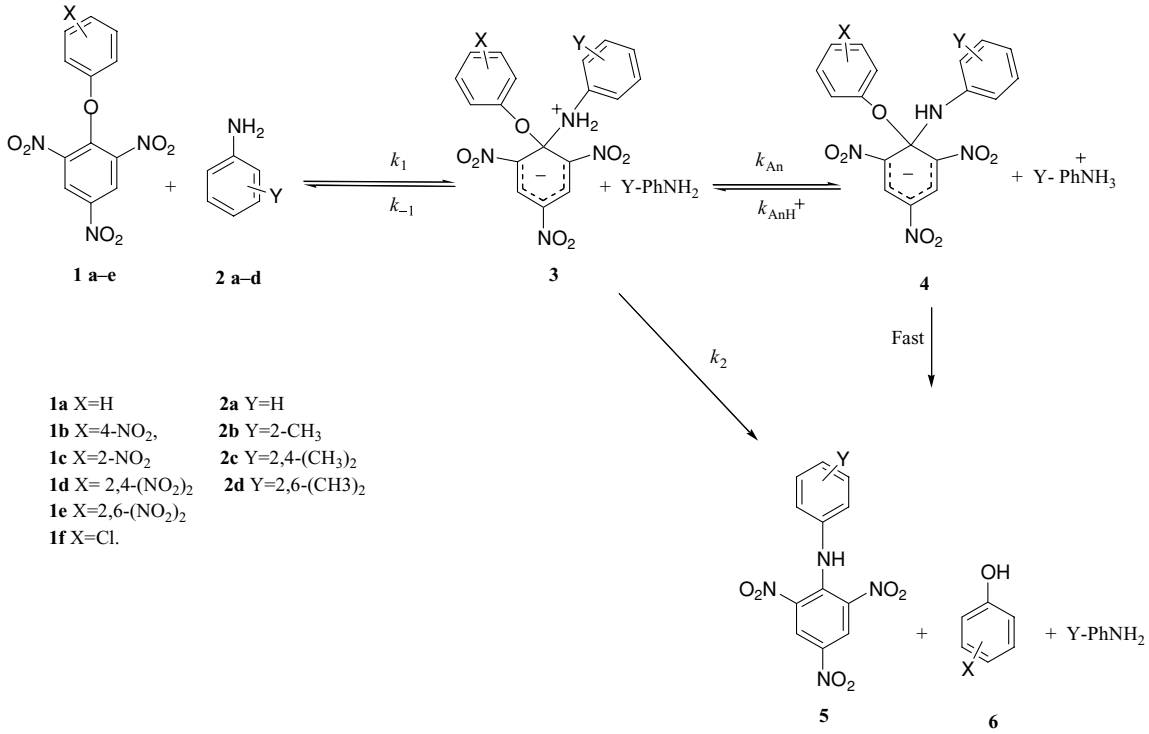
Our goal was to (i) determine the effect of steric crowding at the reaction center on the individual step depicted in Scheme 1 and (ii) compare the kinetic parameters for the reactions of **2e**, *N*-methylaniline with those for other sterically hindered anilines carrying methyl group(s) close to the reaction center **2a–d**. Kinetic data for the reactions of **2a**, **2e**, with **1b** together with those of **2a–d** with **1d** have been reported elsewhere [13,14,16].

EXPERIMENTAL

The diphenyl ethers **1a–e** and 1-chloro-2,4,6-trinitrobenzene **1f** were available from the previous work [13,14,16]. Anilines and acetonitrile were the purest available commercial samples. ^{1}H NMR spectra in CD_3CN were recorded with Varian Mercury 400 MHz or a Bruker Avance-400 MHz instruments. UV–vis spectra and kinetic measurements were made at 25°C using a Perkin–Elmer Lambda 2, Varian Cary 100, or a Shimadzu UV PC spectrophotometer. First-order rate constants were measured with the aniline concentration in large excess of substrate concentration, 5×10^{-5} mol dm^{-3}, and were evaluated using standard methods. Values are precise to ±3%. Kinetic measurements with *N*-methylaniline were made using ^{1}H NMR spectroscopy in deuterated solvents and are precise to ±5%.

RESULTS AND DISCUSSION

The reactions of individual diphenyl ether **1a–e** with the anilines **2a–d** in acetonitrile gave the expected products of substitution of the phenoxide in quantitative yield. Spectroscopic data are collected in Table I. Visible spectra at the completion of the measured process were in all identical to those of the independently



Scheme 1

prepared products **5** in the solution of the same amine concentration. There was no evidence either from the spectra or the kinetics for the accumulation of intermediate such as **3** or **4** on the reaction pathway. Kinetic measurements were made spectrophotometrically by monitoring the increase of the absorption maximum due to product as a function of time. With concentrations of anilines 0.01–0.8 mol dm^{-3} in large excess of the concentration of diphenyl ethers 5.0×10^{-5} mol dm^{-3}, first-order kinetics were observed and rate constants, k_{obs}, were evaluated by standard methods. Values are precise to ±3%. Division by the concentration of anilines of values of k_{obs} gave second-rate constants, k_A, collected in Tables II and III.

Previous studies of the reactions of aliphatic amines with strongly activated compounds such as **1a** in acetonitrile and in DMSO have shown that substitutions may be preceded by formation under kinetic control

Table I ^{1}H NMR Shifts in CD_3CN for Reactants and Products

	^{1}H NMR Shifts[a]				
Compound	H3,5	H2′	H3′	H4′	Other
1a, X = H	9.03	7.00	7.40	7.25	–
1b, X = 4-NO_2	9.11	7.15	8.26	–	–
1c, X = 2-NO_2	9.01	–	8.16	7.68	7.41(H5′), 7.24 (H6′)
1d, X = 2,4-$(NO_2)_2$	9.18	–	8.43	7.36	–
1e, X = 2,6-$(NO_2)_2$	8.92	–	8.34	7.66	8.34 (H5′)
5a, Y = H	8.99	7.18	7.39	7.29	10.02 (NH)
5b, Y = 2-CH_3	8.78	–	6.82	7.04	2.20 (2′ Me), 6.95 (H5′), 7.17 (H6′), 9.70 (NH)
5c, Y = 2,4-$(CH_3)_2$	9.04	–	6.72	–	2.16 (2′Me), 2.38 (4′Me), 7.17 (H5′), 7.26 (H6′), 9.72 (NH)
5d, Y = 2,6-$(CH_3)_2$	8.92	–	7.12	7.20	2.16 (Me), 10.10 (Me)
10, Y = *N*-CH_3	8.85	6.86	7.26	7.00	3.27 (Me)

[a]Compounds **1** are X-substituted phenyl 2,4,6-trinitrophenyl ethers. **5** and **10** are 2,4,6-trinitrodiphenylamine, and its *N*-methyl derivative, respectively. Ortho coupling, J = 7–8 Hz, is observed.

Table II Kinetic Results[a] for the Reactions of X-Phenyl-2,4,6-trinitrophenyl Ether **1a–e** with 2-Methylaniline **2b** in Acetonitrile at 25°C

	$k_A(10^{-4}$ dm^3 mol^{-1} s$^{-1})$				
[2-Methylaniline] (mol dm^{-3})	**1a**, X = H	**1c**, X = 2-NO_2	**1b**, X = 4-NO_2	**1d**, X = 2,4-$(NO_2)_2$[b]	**1e**, X = 2,6-$(NO_2)_2$
0.005					566
0.01	0.7		2.07	48	550
0.015				50	
0.02	1.55	4.33	3.78	53	550
0.025				55	
0.03	2.35	5.67		56	544
0.04	2.88	7.0	6.42		542
0.05	3.60	8.67	8.03		533
0.06				70	
0.08	5.58	13.0	12.30	79	520
0.1	7.07	1.63	14.93	83	483

[a] Second-order rate constant (values are precise to ±3%).
[b] Values are from [13].

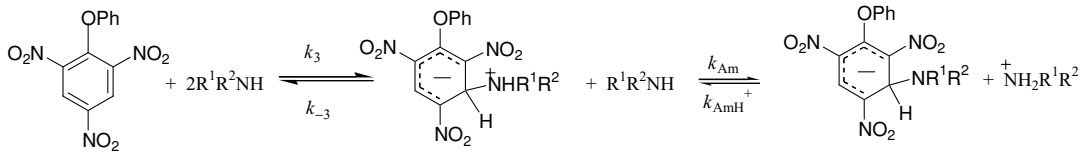
Table III Kinetic Results[a] for the Reactions of X-Phenyl-2,4,6-trinitrophenyl Ether **1a–e** with 2,4-Dimethylaniline (DMA) **2c** in Acetonitrile at 25°C

	$k_A(10^{-3}$ dm^3 mol^{-1} s$^{-1})$				
[2,4-DMA] (mol dm^{-3})	**1a**, X = H	**1c**, X = 2-NO_2	**1b**, X = 4-NO_2	**1d**, X = 2,4-$(NO_2)_2$[b]	**1e**, X = 2,6-$(NO_2)_2$
0.002					258
0.005				25	256
0.01				26	237
0.015				27	
0.02	0.81	2.17	1.83	28	243
0.025					243
0.03	1.17	2.83	2.68	29	234
0.04	1.55	3.67	3.25		229
0.05		4.33			
0.06	2.28	5.17	5.03		

[a] Second-order rate constant (values are precise to ±3%).
[b] Values are from [13].

of adducts **7** or **8** resulting from the unsubstituted C-3 position followed by isomerization to give the thermodynamically most stable substitution product at C-1 (Scheme 2). The values of the equilibrium constant for such process depend on the degree of ring activation, the strength of the amine, and also on the solvent. In acetonitrile, values are ca. 10^4 less than in DMSO and this was attributed to the greater ability of DMSO than of acetonitrile to solvate the ionic species [17]. However, with weaker aromatic amines used in this investigation, such adducts were not observed.

The results are best analyzed in terms of the process in Scheme 1. Base catalysis is attributed to rate-limiting proton transfer from **3** to base followed by rapid



1a **7** **8**

Scheme 2

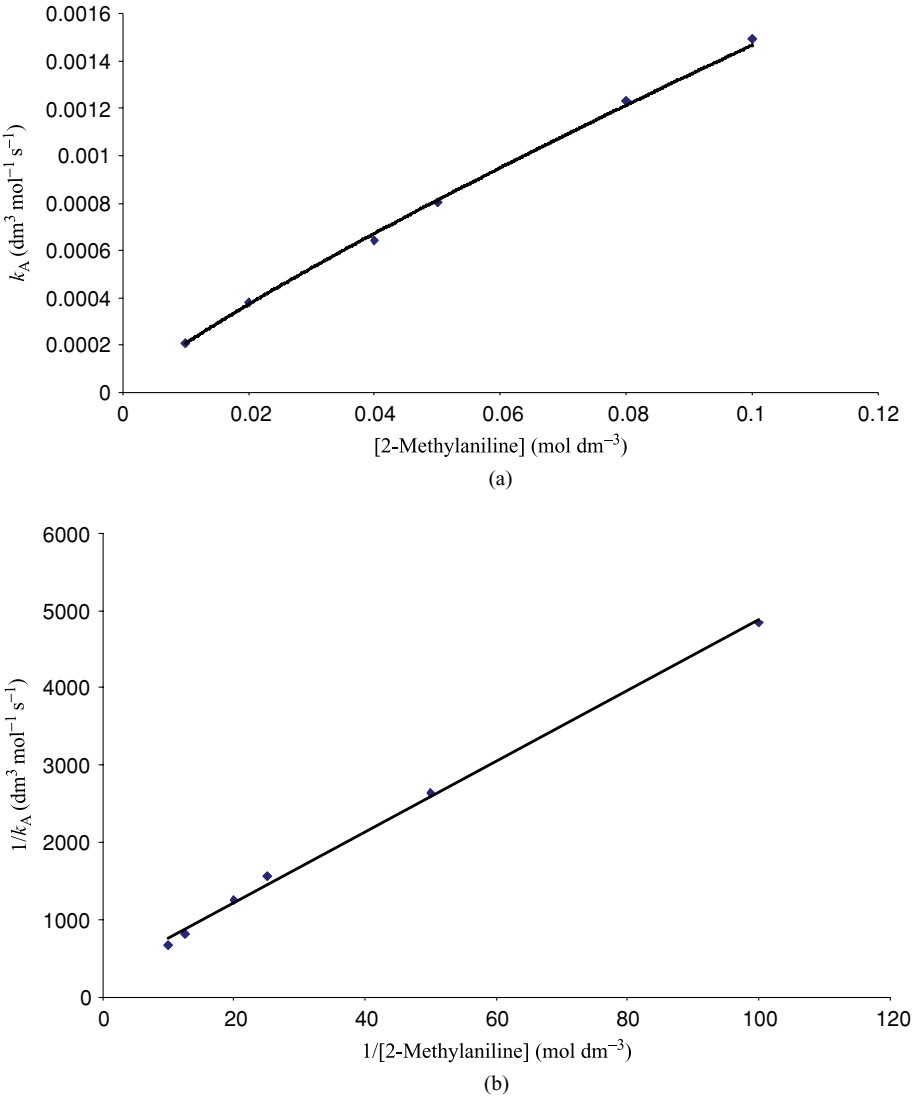


Figure 1 (a) Plot of k_A versus the amine concentration and (b) plot of $1/k_A$ versus 1/[An] for the reaction of 4-nitrophenyl-2,4-6-trinitrophenyl ether **1b** with 2-methylaniline **2b** in acetonitrile at 25°C.

expulsion of the phenoxide. The treatment of the zwitterion **3** as steady-state intermediates leads to Eq. (1), where [An] represents the concentration of substituted anilines.

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

An alternative form of this equation is Eq. (2), where $K_1 = k_1/k_{-1}$ is the equilibrium constant for the formation of the zwitterionic intermediate.

$$k_A = \frac{K_1 k_2 + K_1 k_{An}[An]}{1 + \frac{k_2}{k_{-1}} + \frac{k_{An}[An]}{k_{-1}}} \quad (2)$$

Reaction with Aniline and Ortho-Substituted Anilines

For the reactions of the individual diphenyl ethers **1a–c** with **2a–c**, plots of k_A versus the amine concentration pass through the origin, indicating that the uncatalyzed pathway (k_2 in Scheme 1) is unimportant and curves with decreasing slope as the aniline concentration is increased (a representative plot for the reaction of **1a** with **2b** is shown in Fig. 1a). Hence, Eq. (1) reduces to Eq. (3). This in turn may be written as Eq. (4).

$$k_A = \frac{k_{obs}}{[Aniline]} = \frac{k_1 k_{An}[Aniline]}{k_{-1} + k_{An}[Aniline]} \quad (3)$$

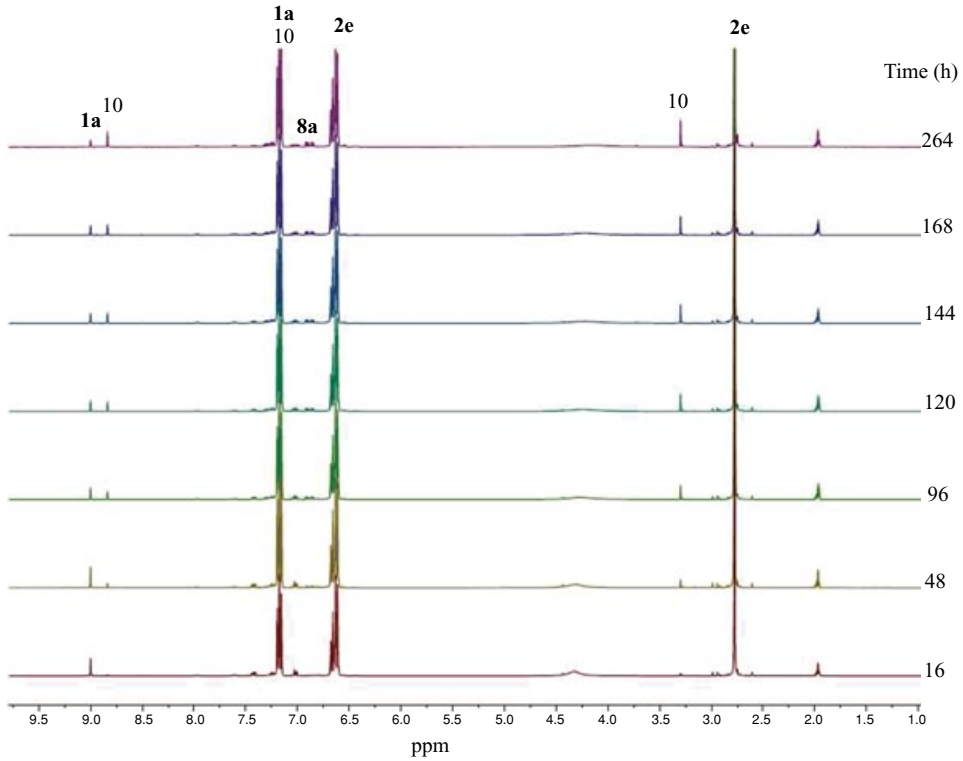


Figure 2 ^{1}H NMR spectrum of the reaction of phenyl-2,4,6-trinitrophenyl ether **1a**, 0.04 mol dm^{-3}, with *N*-methylaniline **2e**, 0.8 mol dm^{-3}, in CD_3CN taken over 11 days at 25°C. [Color figure can be viewed in the online issue, which is available at www.interscience.wiley.com.]

$$k_A = \frac{K_1 k_{An}}{1 + \dfrac{k_{An}[\text{Aniline}]}{k_{-1}}} \tag{4}$$

Values of k_1, K_1k_{An}, and k_{An}/k_{-1} obtained by standard methods from the reciprocal plots of k_A versus [An] (a typical plot for the reactions of **1a** with **2b** is shown in Fig. 1b) are assembled later in Table VI. However, the plots (not shown) of k_A versus the amine concentration for **1d**, the 2,4-dinitro derivative, are linear with distinct intercepts ($R^2 = 0.998$–0.999), indicating the contribution of the uncatalyzed pathway. Hence Eq. (5) applies; values of K_1k_{An} and K_1k_2 in Table VI later in the paper are extracted from the intercepts and slopes of the plots.

$$k_A = K_1k_2 + K_1k_{An}[An] \tag{5}$$

Kinetic measurements for the reactions of **1a–e** with **2d** (2,6-$(CH_3)_2$) show precise first-order dependence on the amine concentration. This indicates in terms of Scheme 1 that nucleophilic attack is rate limiting. The results yielded values of k_1 collected along with those previously obtained for the 1-chloro-derivative **1f** [18–22] in Table VII later in the paper. Values of k_{obs} for the reactions of **2d** with the diphenyl ethers **1e** and for the reactions of **2c** with **1f** are available as Supporting Information in Tables S1 and S2, respectively.

Reactions with N-Methylaniline

As observed in the previous investigation, reactions with excess **2e** were inconveniently slow that studies by conventional UV–visible spectroscopy were not successful. However, ^{1}H NMR measurements with high concentration of reagents in CD_3CN show the development of bands over several days attributable to the expected products. A representative ^{1}H NMR spectrum of the reaction of phenyl-2,4,6-trinitrophenyl ether **1a**, 0.04 mol dm^{-3}, with *N*-methylaniline, 0.8 mol dm^{-3}, in CD_3CN taken over 11 days at 25°C is shown in Fig. 2.

The increase in the intensity of the band at δ 8.85 due to the product **10** was used for kinetic measurements; with *N*-methylaniline **2e** in large excess of the concentration of the substrates **1a–e**, a first-order process was observed whose rate constant, $k_{obs'}$, was evaluated by standard methods. Typical data for the reaction of 2,4-dinitrophenyl-2,4,6-trinitrophenyl ether **1d**, 0.04 mol dm^{-3}, with *N*-methylaniline **2e**, 0.4 mol dm^{-3}, are presented in Table IV. Division of k_{obs} by

Table IV Kinetics of Reaction of 2,4-Dinitrophenyl-2,4,6-trinitrophenyl Ether **1d**, 0.04 mol dm^{-3}, with N-Methylaniline **2e**, 0.4 mol dm^{-3}, in CD_3CN at 25°C

	Relative Concentrations[a]		
Time (10^4 s)	**A**	**C**	$k_{obs}(\times 10^{-5}\ s^{-1})$[b]
0.07	98.9	1.1	1.4
0.66	91.5	8.5	1.4
1.38	83.4	16.6	1.3
1.98	77.0	23.0	1.3
5.50	46.0	54.0	1.4
7.98	31.8	68.2	1.4
8.92	27.8	72.2	1.4
9.94	24.0	76.0	1.4
16.70	8.7	91.3	1.5

[a]Determined by ^{1}H NMR integration of bands at δ 9.18 due to **A**, 2,4-dinitrophenyl 2,4,6-trinitrophenyl ether, and at δ 8.85 due to **C**, *N*-methyl 2,4,6-trinitrodiphenylamine.
[b]Calculated as $k_{obs} = (1/t)\ln(100/\mathbf{A})$.

the *N*-methylaniline concentration leads to values of k_A assembled in Table V. As in the case with aniline, the plot of the second-order rate constants k_A for the reaction of **1a** with **2e** varies linearly with the amine concentration exhibiting null intercept. Data are interpreted in a manner similar to that given for aniline so that Scheme 3 is applicable. Hence, the condition $k_{-1} \gg k_{An}$ [An] holds and Eq. (1) reduces to Eq. (6), where k_{An} represents the pathway catalyzed by aniline. This is the same kinetic pattern observed in the previous work for the reaction of **2e** with **1b** [16]. The only parameter which can be determined is K_1k_{An}. Values for this parameter are summarized in Table VI.

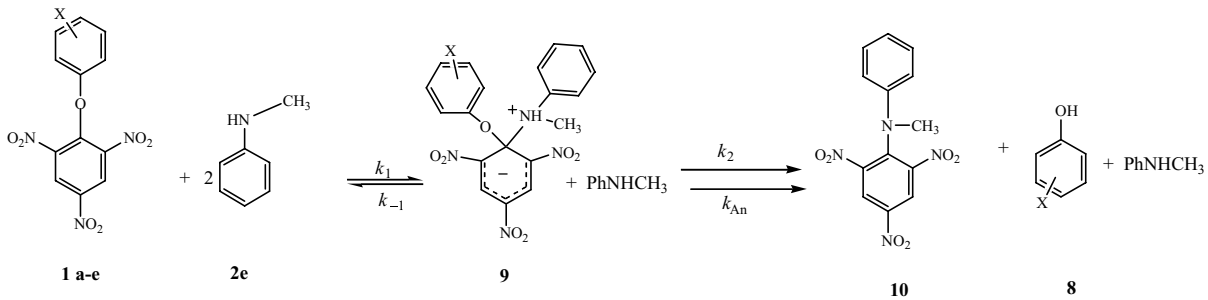
$$k_A = K_1k_{An}[An] \quad (6)$$

However, the plots of k_A versus the *N*-methylaniline concentration for **1c** and **1d**, the 2-nitro- and 2,4-dinitro derivatives, had definite intercepts representing the contribution of the uncatalyzed pathway. Equation (2) applies, and the values of K_1k_{An}, and K_1k_2, and k_{An}/k_{-1} are collected in Table VI. For **1e**, the 2,6-dinitro derivative, the values of k_A are independent of the aniline concentration, indicating that either the condition $k_2 + k_{An} \gg k_{-1}$ holds so that $k_A = k_1$ and/or the condition $k_2 \gg k_{An}$ [An] applies so that $k_A = k_1k_2/(k_{-1} + k_2)$. Values of the first-order rate constants (k_{obs}) increase linearly with the amine concentration (0.001–0.04) and allow the determination of values of k_1 assembled in Table VI.

Table V Kinetic Results[a] for the Reactions of X-Phenyl-2,4,6-trinitrophenyl Ether **1a–e** with N-Methylaniline **2e** in CD_3CN at 25°C

	$k_A(10^{-5}\ dm^3\ mol^{-1}\ s^{-1})$				
[*N*-Methylaniline](mol dm^{-3})	**1a**, X = H	**1c**, X = 2-NO_2	**1b**, X = 4-NO_2[b]	**1d**, X = 2,4-$(NO_2)_2$	**1e**, X = 2,6-$(NO_2)_2$
0.2		0.3			
0.25			0.46		
0.4		0.49		3.5	0.1
0.6	0.11	0.63		5.2	0.09
0.8	0.15	0.79		6.9	
0.85			1.18		
1.0					0.1

[a]Measured by integration of ^{1}H NMR bands, with substrate 0.04 mol dm^{-3}. Values are precise to ±10%.
[b]Data are from [16].



Scheme 3

Table VI Summary of Rate Data for Reaction of X-Phenyl-2,4,6-trinitrophenyl Ethers **1a–e**, with Aniline **2a–e** in Acetonitrile at 25°C

Nucleophile	Substrate, X	k_1 (dm^3 mol^{-1} s^{-1})	K_1k_2 ($\times 10^{-2}$ dm^3 mol^{-1} s^{-1})	K_1k_{An} (dm^6 mol^{-2} s^{-1})	k_{An}/k_{-1} (dm^3 mol^{-1})
2a, Y = H[a]	**1a**, H	0.24 ± 0.10[c]		0.48 ± 0.02	2 ± 1
	1b, 4-NO_2	0.26 ± 0.08		1.03 ± 0.03	4 ± 1
	1c, 2-NO_2	0.32 ± 0.10		0.95 ± 0.03	3 ± 1
	1d, 2,4-$(NO_2)_2$	0.8 ± 0.3	0.08 ± 0.01	2.2 ± 0.20	2.8 ± 0.5
	1e, 2,6-$(NO_2)_2$	1.5 ± 0.2	Large		
2b, Y = 2-CH_3	**1a**, H	$4.11 \pm 0.4 \times 10^{-3}$		$8.07 \pm 0.2 \times 10^{-3}$	
		1.96 ± 0.5			
	1b, 4-NO_2	$3.32 \pm 0.3 \times 10^{-3}$		$2.2 \pm 0.1 \times 10^{-2}$	6.61 ± 1
	1c, 2-NO_2	$3.67 \pm 0.3 \times 10^{-3}$		$1.5 \pm 0.1 \times 10^{-2}$	6.4 ± 1
	1d, 2,4-$(NO_2)_2$[b]		4.5×10^{-3}	$4.0 \pm 0.2 \times 10^{-2}$	<1
	1e, 2,6-$(NO_2)_2$	$4.9 \pm 0.5 \times 10^{-2}$			
2c, Y = 2,4-$(CH_3)_2$	**1a**, H	$2.3 \pm 0.2 \times 10^{-2}$		$4.0 \pm 0.2 \times 10^{-2}$	1.81 ± 0.5
	1b, 4-NO_2	$2.7 \pm 0.5 \times 10^{-2}$		$9.8 \pm 0.6 \times 10^{-2}$	3.69 ± 1
	1c, 2-NO_2	$1.4 \pm 0.3 \times 10^{-2}$		0.13 ± 0.003	8.8 ± 1
	1d, 2,4-$(NO_2)_2$[b]		$2.0 \pm 0.3 \times 10^{-2}$	0.2 ± 0.01	<1
	1e, 2,6-$(NO_2)_2$	0.23 ± 0.1			
2d, Y = 2,6-$(CH_3)_2$	**1a**, H				
	1b, 4-NO_2	$2.0 \pm 0.1 \times 10^{-5}$			
	1c, 2-NO_2	$2.0 \pm 0.1 \times 10^{-5}$			
	1d, 2,4-$(NO_2)_2$[b]	$6.0 \pm 0.5 \times 10^{-5}$			
	1e, 2,6-$(NO_2)_2$	$1.6 \pm 0.1 \times 10^{-4}$			
2e, *N*-CH_3	**1a**, H	–		$1.85 \pm 0.1 \times 10^{-6}$	
	1b, 4-NO_2			$1.60 \pm 0.1 \times 10^{-5}$	
	1c, 2-NO_2		$2.0 \pm 0.1 \times 10^{-6}$	$8.0 \pm 0.4 \times 10^{-6}$	
	1d, 2,4-$(NO_2)_2$		$1.0 \pm 0.05 \times 10^{-6}$	$9.0 \pm 0.5 \times 10^{-5}$	
	1e, 2,6-$(NO_2)_2$	$1.0 \pm 0.05 \times 10^{-6}$			

[a]Data are from [14, 16].
[b]Data are from [13].
[c]Error limits are standard deviations.

COMPARISON

Rate Constants for Nucleophilic Attack

It is evident from the data in Table VI that values of k_1, the rate constant for nucleophilic attack by individual aniline, increase slightly with increasing electron withdrawal by the X-substituent in the leaving group. Previous results [16] for the reaction with aniline and derivatives of **1** gave a linear Hammett plot, with a small ρ value of 0.5, which indicates that the bulk of the negative charge is delocalized conjugatively into the trinitrophenyl ring. Substituents in the incipient leaving group will, therefore, have only a small increase on charge delocalization. This is compatible with an "early" transition state for nucleophilic attack with relatively little bond formation. For such reactions, steric hindrance will be insignificant in determining the value of k_1. The magnitude of ρ_x for the reaction in this and previous studies contrasts sharply with that of ρ_x determined for the aminolyses of X-substituted phenyl benzoates. The Hammett correlation with σ-constants exhibits good linearity with large slope ($\rho_x = 3.54$) for the reaction with piperidine, implying that the leaving group departure occurs at the rate-determining step [23].

For the reactions of individual substrate with aniline and ortho-substituted anilines (**2a–c**), there was evidence of significant steric interactions. Values of k_1 listed in Table VII show a strong dependence on the nature of the substituent Y in the nucleophile. This indicates a product-like transition state for nucleophilic attack where bonding between the nucleophile and the ring is well developed. Specifically, the substitution of a 2-methyl group into aniline reduces the values of rate constants k_1 by factors of between 30 and 80. Interestingly, the factor of 30 obtained in the reaction with **1e**, the 2,6-dinitro derivative, is the same as that observed with **1f**, the 1-chloro derivative [18]. The corresponding factors for the reactions with **2d** are between

Table VII Summary of Values of k_1/dm^3 mol^{-1} s^{-1} for the Reactions of Diphenyl ether **1a–d** and 1-chloro-2,4,6-trinitrobenzene **1f** with Substituted Anilines **2a–e** in Acetonitrile at 25°C

	Substrate **1a–f**, k_1 (dm^3 mol^{-1} s^{-1})					
Nucleophile	**1a**, H	**1b**, 4-NO_2	**1c**, 2-NO_2	**1d**, 2,4-$(NO_2)_2$[a]	**1e**, 2,6-$(NO_2)_2$	**1f**[b]
2a, H[c]	0.24	0.26	0.32	0.8	1.5	0.2
2b, 2-CH_3	4.11×10^{-3}	3.32×10^{-3}	3.67×10^{-3}		0.049	6.9×10^{-3}
2c, 2,4-$(CH_3)_2$	0.023	0.027	0.014		0.23	$3.5 \pm 0.1 \times 10^{-2}$
2d, 2,6-$(CH_3)_2$		2.0×10^{-5}	2.0×10^{-5}	6.0×10^{-5}	1.6×10^{-4}	4.66×10^{-5}
2e, *N*-CH_3			1.5×10^{-5}		1.0×10^{-6}	5.32×10^{-6}

[a] Data from [13].

[b] Data for reaction of **2a**,**b** and **2d** are obtained from [18]. Data for reaction with **2c** are from the present work. Data for reaction with **2e** are calculated using values of $k_1 = 2.91$ dm^3 mol^{-1} s^{-1}, $E_a = 54$ kJ mol^{-1}, and $\Delta H^{\ddagger} = 51.0$ kJ mol^{-1} obtained at 50°C from [50].

[c] Data from [14].

1.3×10^4 and 1.6×10^4. The relative reactivity ratio drops to 4.3×10^3 for the reaction of **2d** with **1f**, the 1-chloro analogue [19]. The huge deactivating effect exhibited by **2d** was previously analyzed in terms of primary steric effect, steric occlusion of solvation of the transition state, and secondary steric effect. Two methyl groups, located at the 2- and 6-positions of aniline, may prevent coplanarity and hence conjugation between the amino group and the aromatic ring. The secondary steric effect of a 2-methyl group was found to be insignificant, but that of the 2,6-dimethyl group was enormous [20–22].

As can be seen in Tables VI and VII, **2e** exerts a dramatic decrease in reactivity with respect to **2a** with a **2a**/**2e** reactivity ratio of ca. 1×10^5. The superior reactivity of **2a** when compared with **2e** can be reasonably attributed to the greater steric requirement of the secondary amine. Furthermore, steric hindrance to nucleophilic attack in most cases is slightly more severe with **2e** than with **2d**. On the whole, for reactions with individual substrate, the values of k_1 decrease in the order **2a** > **2c**> **2b** > **2d** > **2e** reflecting the order of steric hindrance exerted by the methyl group(s).

Base Catalysis

Base catalysis in the reactions of nitro aryl phenyl ethers **1a–e** depends on the values of k_{An}/k_{-1}; a lower value of this ratio, leading to the condition $k_1 \gg k_{An}$, results in the reactions showing susceptibility to base catalysis. It has been argued previously [24–26] that, with strongly activated substrates such as **1a–d**, the zwitterions are considerably stronger acids than the corresponding ammonium ions so that the proton transfer process, k_{An}, is thermodynamically favored in the direction **3** → **4**. However, the values of k_{An} may approach the diffusion limit but are known to be reduced by increasing steric congestion at the reaction center, greater with secondary than with primary amines [27,28] and the presence of a group that is bulkier than hydrogen at the site of nucleophilic attack [29]. The decrease in the value of k_{An} is thought to reflect increasing steric hindrance to the approach of the reagents. Hence, steric rather than electronic factors determine the rate constant for such proton transfer. The reactions between **2a–e** and **1e** and those of **2d** with **1a–e** show first-order dependence on the concentration of the amine. This corresponds to the condition $k_{An} \gg k_{-1}$ so that $k_A = k_1$. The reactions of **2a–c** and of **2e** with **1a–d** were, however, base catalyzed. In general, the data displayed in Table VI show that, for the reactions of individual aniline, the values of $K_1 k_{An}$ increase regularly as X substituent becomes more electron withdrawing; the increases are relatively small and reasonably attributed to increases in K_1 as the electron withdrawal at the 1-position increases. Similarly, increases in k_{An}/k_{-1} will reflect decreases in k_{-1}. As argued previously [13,16], the results are consistent with a reactant-like transition state in which the bond formation between the nucleophile and the substrate is not greatly advanced in the transition state. Steric hindrance would, therefore, be insignificant in determining reactivity. It may, as observed in the 2,6-disubstituted compounds, decrease the rate of intermolecular proton transfer (k_{An}) to a catalyzing base but may not be severe enough to cause a change in the reaction order in $PhNH_2$ without the assistance of electronic effects. This is borne out by the similarity in the kinetic behavior observed previously for compounds in the methyl series [X = H, 2-CH_3, 3-CH_3, 4-CH_3 2,4-$(CH_3)_2$, or 2,6-$(CH_3)_2$]. Substitutions in this series are wholly amine catalyzed even in the presence of di-ortho methyl groups [14]. On the other hand, the appearance of the k_2 step in the reaction of **1c**, **1d**, and **1e** depends on the electronic nature of the substituent X in the leaving group, which increases with decreasing pKa of the conjugate acid. With **1e**, the 2,6-dinitro derivative, the steric hindrance

to intermolecular transfer to base is sufficient to make the base-catalyzed pathway insignificant relative to the k_2 pathway [14].

The change in the mechanistic pathway was more magnified when the reactions were conducted in benzene. For X = H, 2-CH_3, 3-CH_3, and 4-CH_3, 2,4-$(CH_3)_2$ and 2,6-$(CH_3)_2$, the plots of the second-order rate constant versus [An] had upward curvatures, which corresponds to a parabolic dependence of k_A versus [An] and a fourth-order kinetic law. For the nitro series, the change in the kinetic form for the reactions of aniline with ethers containing unsubstituted or mononitro-substituted leaving groups is from a third-order dependence on the aniline concentration to a second-order dependence for the leaving group containing 2, 4-, 3,4-, and 2,5-dinitro groups, to $k_A = k_1$ for the 2,6-dinitrophenoxy group. The trend was rationalized by the cyclic transition state mechanism and ascribed to changes in the transition state for the decomposition of the intermediate from eight- to six- to four-member rings (containing two, one, and no moles in aniline, respectively), brought about by increases in the leaving group ability of the nucleofuge [30,31].

The reactions of 2-substituted anilines with substrates **1a–c** are wholly base catalyzed, but the reactions with **1d** involved both the catalyzed and the uncatalyzed pathways. For these reactions, there is, as in the case of k_1, evidence for unfavorable steric interaction, which is known to be of greater magnitude the later the transition state. Thus, the 2-methyl group introduced into aniline reduces the values of K_1k_{An} by factors of between 30 and 80. These results accord better with a "late" transition state for nucleophilic attack with considerable charge development. Sterically hindered anilines for such reactions can decrease not only the reaction rate but also the reaction orders in $PhNH_2$. This reduction is slightly lower for the K_1k_2 value, indicating that steric effects in anilines retard the catalyzed step a little more than the spontaneous decomposition of the zwitterionic intermediate [32–34]. Substituents in the ortho-position(s) of aniline decrease k_2/k_{-1} values probably by increasing k_{-1} due to relief of strain, and reactivity is decreased despite favorable electronic effect of the methyl group. On the other hand, ortho-substitution in aniline reduces k_{An}/k_{-1} by reducing the rate of proton transfer, k_{An}; although it may be argued that there is also an increase in the rate of decomposition of the intermediate to reactants, k_{-1}, because of the steric congestion, the influence of steric effect is more pronounced for K_1k_{An} than for K_1k_2 [35]. Thus, for all reactions of **2d**, hindrance of approach to the reaction center is so severe as to make the k_{An} coefficient vanishingly small compared to k_2 and so the catalytic pathway cannot be detected experimentally. This reflects the condition $k_{-1} \gg k_2 \gg k_{An}$ [An] so that $k_A = k_1k_2/k_{-1}$. It is worth noting that values of K_1k_{An} decrease in the order **2a** > **2c** > **2b** > **2e**, the same trend as was observed for the rate constant for nucleophilic attack. This could be taken as an indication that steric effects are related to the values of the rate constant for proton transfer, which diminish with the bulk of the amine. On the contrary, since k_2 involves an intramolecular proton transfer, the steric effect should be small. Hence, the major steric effect on K_1k_2 values is likely to be on the equilibrium formation of the zwitterionic intermediate, yielding reduced values of K_1. The slight increase in the values of K_1k_2 for **2c** as compared to **2b** is reasonably attributed to electronic effect.

THE DICHOTOMY OF AMINE EFFECTS

The absence of intercepts in the linear plots of k_A versus [An] in the reactions of **2a–c** and **2e** with nitro phenyl aryl ether **1a,1c** shows that the reactions are catalyzed wholly by the nucleophiles in a linear fashion indicating that the value of k_{An}/k_{-1} is relatively low (<5 dm^3 mol^{-1}); deprotonation of the zwitterionic intermediate **3** formed along reaction coordinate is therefore rate limiting.

The values of the parameter K_1k_{An} are lowered by a factor of ca. 10^5 for **2e** relative to **2a**. The dramatic reduction, as discussed previously, is attributed to increased steric hindrance both in the formation of the zwitterionic intermediate and in the proton transfer process [16]. An alternative but quite unlikely explanation to be considered is the role of hydrogen bonding known to occur [7,16] between ammonio hydrogen atoms of **3** and the oxygen atoms of the ortho-nitro group. Such intramolecular hydrogen bonding that affects the hydrogen to be transferred has been invoked to explain the dichotomy of the amine effect usually observed in the reactions of aliphatic primary and secondary amines of similar basicity. The influence 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, however, be different as the hydrogen bond must be broken when the nucleophile is a secondary amine but not when it is a primary amine. In the case of primary amines, there will always be a free transferable proton, thus reducing the susceptibility to base catalysis. While this may be a plausible explanation for the dichotomy of the amine effect between **2d** and **2e**, the fact that the corresponding reactions with **2a**, a primary aromatic amine, are base catalyzed vitiates the hydrogen bond theory. Furthermore, our recent observation of base catalysis in the reactions of piperidine with 2-trifluoromethyl

4-nitro- (involving a bulky trifluoromethyl group with negligible hydrogen-bonding acceptor properties) but not with 2-nitro-4-trifluoromethyl phenyl ethers adds to the growing body of evidence that in acetonitrile such hydrogen bonding at least in strongly activated substrates is not a major factor [36,37].

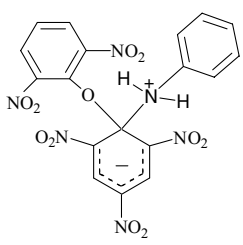
It is curious that in the present system, while the reactions of **1a–d** with **2a** and **2e** are base catalyzed, no base catalysis was observed with 2,6-dimethylaniline **2d**. In terms of the mechanism depicted in Scheme 1, these changes are equivalent to a shift from the kinetic condition $k_{-1} \gg k_{An}$ to $k_{-1} \ll k_{An}$ as the nucleophile is changed from **2a** or **2e** to **2d** (a relatively weaker nucleophile [38]). This does not appear to be reasonable. Usually when amines of the same type and under the same conditions react by different mechanisms, there is a considerable difference in their basicities; the change is ascribed to a decrease in the strength of C–N bond with a decrease in amine basicity leading to an increase in k_{-1} [39]. This implies that reactions of **2d** should be more prone to base catalysis than those of **2a** or **2e**. Experimental results obtained in this investigation, however, indicate the reverse. It is interesting to note that similar effects have been observed recently by Crampton and co-workers [40,41] in σ-complex formation reactions involving 1,3,5-trinitrobenzene (TNB), Dabco, and the same set of substituted anilines in DMSO. For this system, Buncel and Eggimann [42] reported that the proton transfer stage was solely catalyzed by Dabco, i.e., catalysis by **2a** or **2e** and the solvent dimethyl sulfoxide was not significant. However, it has been shown in a related system that even though aniline is a much weaker base, it might also contribute to the proton transfer equilibrium [43]. Thus, it is known that the trinitrocyclohexadienate group in **3**, even though negatively charged, is electron withdrawing relative to hydrogen [44–47]. Hence, **3** will be more acidic than the corresponding anilinium ion so that the proton transfer step **3** → **4** will be thermodynamically favored even when the reaction involves aniline as the base and the corresponding anilinium ion as BH^+.

The overall equilibrium constant for this process (1.7×10^{-5}) is, however, very small due the loss in resonance of **2a** in formation of the conjugate acid

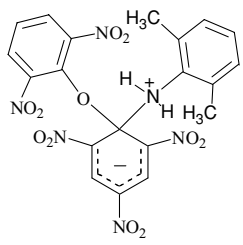
$$TBN.NH_2Ph^+ + PhNH_2 \rightarrow TNB.NH\,Ph^- + PhNH_3^+$$

Hence a much stronger base such as Dabco is needed to displace the equilibrium in the direction of the products. The equilibrium transformation of the zwitterionic complex to the anionic σ-complex, being directly related to the basicity of the abstracting base, is favored in the Dabco system by ca. 10^4 [48]. It is, therefore, likely that, due to severe steric requirement, the deprotonation process involving 2,6-dimethylaniline acting both as a nucleophile and a proton-accepting base will be more kinetically disfavored. If this is the explanation in the TNB/$PhNH_2$/Dabco system, then the change in the kinetic form observed in our system can be reconciled on the basis that **2d** may not be particularly effective in abstracting the proton from the zwitterionic intermediate **3** because of greater loss of resonance due to severe steric requirement relative to aniline. There is, therefore, a pronounced reduction in the rate constant for the proton transfer step involving **2d**; under such circumstances, decomposition of the adduct **3** would occur largely by the uncatalyzed pathway.

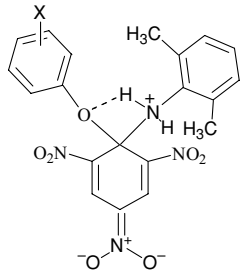
Another factor that may contribute to the change of mechanism is the relative magnitude of k_{-1}, the rate constant for the reversion of **3** to reactants for the three anilines **2a, 2d**, and **2e**. With **2e** as nucleophile in the TBN/$PhNH_2$/Dabco system, k_{-1} is an order of magnitude higher than in the case of **2a**, reflecting the release of strain in the zwitterionic intermediate as it reverts to the reactants. The k_{-1} is likely to be larger for **2a** than **2d** probably due to stabilization of the transition state for the decomposition of zwitterionic adduct to reactants for aniline by interaction of the partially liberated lone pair of electrons on the nitrogen atom with the aromatic ring of the amine as shown in **11**. Such stabilization may be reduced in the case of **12** for the reaction with **2d** because of the presence of two methyl groups in the 2- and 6-positions of the aniline.



11



12



13

The uncatalyzed step (k_2) is likely to proceed by a unimolecular mechanism involving the intramolecular catalysis of the nucleofuge expulsion (depicted in **13**), mentioned as a possibility by Kirby and Jencks [2]. In a reasonable good donor solvent like acetonitrile (DN = 14.1 kcal/mol) [49], the presence of the methyl group in the 2- and 6-positions of aniline prevents amine association or effective solvation. It also reduces the nucleophilicity of the amine with a concomitant increase in acidity of the ammonio proton in the intermediate **3d** as compared to that of **3a**. Bernasconi and de Rossi [6] have stated that the increase in the acidity of the ammonio proton in the intermediate **3** increases both k_2 and k_{An}, but the increase is greater for k_{An}. Besides a bulkier tetrahedral intermediate (**3d** or **4d**) collapses faster to products because of steric acceleration. These effects combine to overcome the greater tendency toward base catalysis when the basicity of the nucleophile is decreased, and all the reactions of 2,6-dimethylaniline are not based catalyzed. By thus shifting the rate-determining step, sterically hindered amines decrease the rate of aminolysis and the reaction order in $PhNH_2$.

In conclusion, our kinetic data show that, for the reactions of individual aniline, increasing substitution does not sterically inhibit nucleophilic attack and an "early" transition state is likely. For such reactions, steric hindrance may decrease the rate of intermolecular proton transfer, the k_{An} step, but may not be severe enough to reduce the reaction order in amine without the aid of electronic effect. The involvement of spontaneous decomposition of the zwitterionic intermediate, the k_2 step, was brought about by increases in the leaving group ability of the nucleofuge. With each substrate, however, there is strong evidence for significant interactions consistent with "late" transition state. Such effects leading to rate retardation were very severe for *N*-methylaniline **2e** and 2,6-dimethylaniline **2d**. Steric hindrance for such reactions can decrease not only reactivity but also the reaction order in the nucleophile. Deactivation in most cases is slightly lower for 2,6-dimethylaniline than *N*-methylaniline. This notwithstanding, the reactions with 2,6-dimethylaniline of all the substrates are not base catalyzed whereas those with *N*-methylaniline show a gradation in behavior from the kinetic conditions $k_{-1} \gg k_{An}$ for X = H, 4-NO_2 to $k_{-1} \gg k_{An} + k_2$ for X = 2-NO_2, 2,4-(NO_2) to $k_{-1} \ll k_2 + k_{An}$ for X = 2,6-(NO_2). This gradation is less pronounced in the reactions with aniline and mono ortho-methyl substituted anilines **2a–c**. With these anilines, the main reactions flux occur through the base-catalyzed pathway. Only for the reaction of the dinitro derivatives are the uncatalyzed pathways observed, and when X = 2,6-(NO_2)$_2$ this pathway takes the reaction flux. With *N*-methyl aniline, the uncatalyzed pathway becomes significant when the nucleofuge contains an ortho nitro group. Our findings, therefore, provide an interesting example of how gradual increase of crowding in the transition state may give rise to a change in the nature of the rate-determining step in the substitution pathway. The difference in the kinetic behavior of **2a** and **2d** may be a strong evidence for some unusual steric interactions in zwitterion **3**.

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