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Kinetics of S_NAr reactions of 1-phenoxy-nitrobenzenes with aliphatic amines in toluene: ring substituent and solvent effects on reaction pathways

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Rate constants are reported for the reactions of a series of 4-substituted-1-phenoxy-2,6-dinitrobenzenes 1 and 6-substituted-1-phenoxy-2,4-dinitrobenzenes 2 activated by CF_3, $COOCH_3$, CN, NO_2 groups or by ring-nitrogen with *n*-butylamine, pyrrolidine or piperidine in toluene. The results are compared with those reported previously for reactions of the same substrates and nucleophiles in acetonitrile [Crampton *et al*., *Eur. J. Org. Chem*., 2006, 1222–1230]. Plots of the overall second-order rate constant, k_A *versus* [Am] for the reactions with *n*-butylamine and pyrrolidine followed a similar kinetic pattern to that obtained for the same reactions in acetonitrile whereas for reactions with piperidine, an upward (convex) curvature is observed, an indication that a small third order term in amine may be present. Overall reactivity is lower in toluene than in acetonitrile. Mechanisms for the overall substitution process have been rationalised in terms of the proton transfer mechanism and cyclic transition mechanism, for reactions involving third-order kinetics. Copyright © 2009 John Wiley & Sons, Ltd.

Supporting information may be found in the online version of this article.

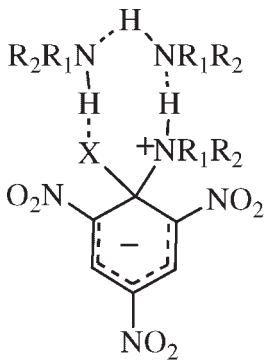
Keywords: aliphatic amines; nucleophilic aromatic substitution; solvent effects; substituent effects

INTRODUCTION

The study of mechanisms and reactivity of aromatic nucleophilic substitution reactions in protic, aprotic solvents and more recently in ionic liquids has been of keen interest to chemists.[1–4] The medium in which the reaction is carried out may have a large effect on the stability of the reaction intermediates and on the mechanistic pathway. Nucleophilic substitution in the reactions of activated aromatic compounds with amines usually involves the S_NAr mechanism[1,2] as shown in Scheme 1 (where X is the nucleofugal group). When the second step is rate limiting then general base catalysis may be observed.

The nature of the rate determining step in such reactions involving nitro-activated aromatic ethers and some heterocyclic analogues with amines has been found to be dependent on the interplay of electronic, steric and solvent effects.[5] Extensive studies to improve the understanding of the mechanism of the base catalysed step in protic as well as in dipolar aprotic solvents have been reported.[6] In contrast, the mechanisms and reactivity in similar systems in non-polar aprotic solvents like benzene and toluene have been found to be sometimes more complex due to the inability of these solvents to stabilise ionic species such as **Z**.[7,8] Of particular interest is the observation of an upward curvature in the plot of second-order rate constant, k_A *versus* [B]. This corresponds to a *parabolic* dependence of k_A on [B], a fourth-order overall kinetic law on changing from dipolar aprotic to non-polar aprotic solvents.[9] These 'anomalous' kinetics have intrigued chemists in the last two decades and inspired much work aimed at the mechanistic rationalisation of the observed solvent effect in S_NAr reactions carried out in 'inert' solvents.[10,11]

Most proposals assume that the decomposition of the zwitterionic intermediate proceeds via a cyclic transition state like **I**.[12–16] Another possibility in these solvents is the dimer mechanism, which involves initial attack of a dimer of the amine to give first the cyclic intermediate **II**.[17–19] Mechanisms involving bifunctional catalysis have been suggested in some specific instances.[20–27]



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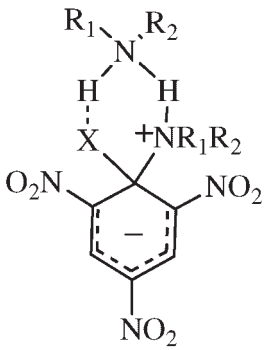

II

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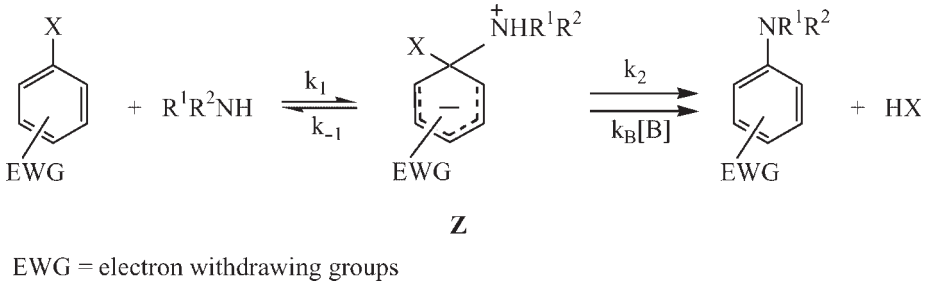
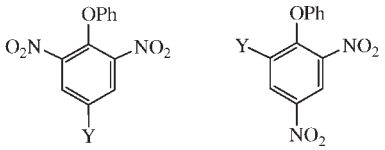


Scheme 1.

Recently, kinetic study of the reactions of 1-chloro-, 1-fluoro- and 1-phenoxy-nitrobenzenes and 4-substituted-1-chloro-2,6-dinitrobenzenes, 6-substituted-1-chloro-2,4-dinitrobenzenes activated by CF_3, $COOCH_3$, CN, NO_2 groups or by ring-nitrogen and some of the corresponding 1-phenoxy derivatives with *n*-butylamine, pyrrolidine and piperidine in acetonitrile as solvent has been reported.[28,29] The observation of base catalysis, dependent on the value of the ratio $k_B[B]/k_{-1}$, was interpreted in terms of rate limiting proton transfer from the zwitterionic intermediate, **Z**, to the base.

We thought that it would be of interest to carry out similar studies in toluene, a typical aprotic, apolar and scarcely polarisable solvent, which represents an ideal medium to promote the need for base catalysis for the decomposition of the zwitterionic intermediate. Herein, we report kinetic studies of the reactions in toluene of a series of 4-substituted-1-phenoxy-2,6-dinitrobenzenes, **1**, 6-substituted-1-phenoxy-2,4-dinitrobenzenes **2**, with *n*-butylamine, pyrrolidine and piperidine.



1 **2**

1 or 2 Y = H (**a**), CF_3 (**b**), CO_2Me (**c**), Y = CN (**d**), ring N (**e**), NO_2 (**f**)

There has not been such a comprehensive study of the effect of ring activation on S_NAr reactions involving aliphatic amines with highly activated benzenes bearing a phenoxy nucleofugal group in non-polar aprotic solvents. Previous studies of S_NAr reactions in non-polar aprotic solvents involved mostly 1-halogeno or alkoxy dinitro-activated benzene substrates.[10–26] Our aims were to (i) examine the effect, on the overall reactivity, due to a change in the solvent medium from acetonitrile to toluene, (ii) determine the kinetic order of the reactions and hence the mechanism in this medium (iii) compare quantitatively the values of rate constants for the individual steps in the reaction pathway with results obtained in acetonitrile.

RESULTS AND DISCUSSION

The reactions of **1a–d** and **2a**, **2b**, **2e** and **2f** with the amines studied in toluene gave the expected products of substitution of phenoxide in >95% yield. Kinetic measurements were made spectrophotometrically with the concentration of amine in large excess of the parent concentration, *ca.* $5 \times 10^{-5} - 1 \times 10^{-4}$ mol/dm^3, and first-order kinetics were observed. Substitution on all substrates proceeded without the formation of transient species in spectroscopically observable concentrations on the substitution pathway. Previous studies[30,31] with more strongly activated compounds **1f** and **2e** in acetonitrile and in DMSO have shown the possibility of the initial formation of σ-adducts **3** resulting from attack at unsubstituted ring-positions (Scheme 2). The equilibrium constants for this adduct formation in acetonitrile are 10^4 times smaller than in DMSO, and this was attributed to the greater ability of the latter than the former to solvate the adducts. It is therefore not surprising that adducts such as **3** are not observed even at high amine concentration for similar reactions in toluene, an inert solvent with poor solvating properties for ionic species.[32]

The general substitution processes are interpreted by Scheme 3. Making the same assumption as in previous studies[28,29] that the zwitterionic adduct **4** may be treated as a steady-state intermediate leads to Eqn (1), when the amine acts both as the nucleophile and as the catalysing base

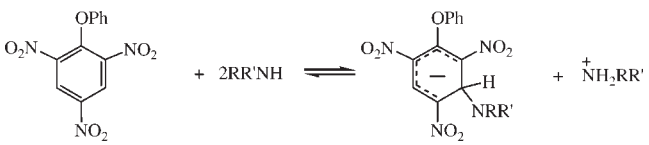
$$k_A = \frac{k_{obs}}{[Am]} = \frac{k_1(k_2 + k_{Am}[Am])}{k_{-1} + k_2 + k_{Am}[Am]} \quad (1)$$

When the condition $k_{-1} >> k_2 + k_{Am}[Am]$ holds, Eqn (2) applies where $K_1 = k_1/k_{-1}$,

$$k_A = K_1 k_{Am}[Am] + K_1 k_2 \quad (2)$$

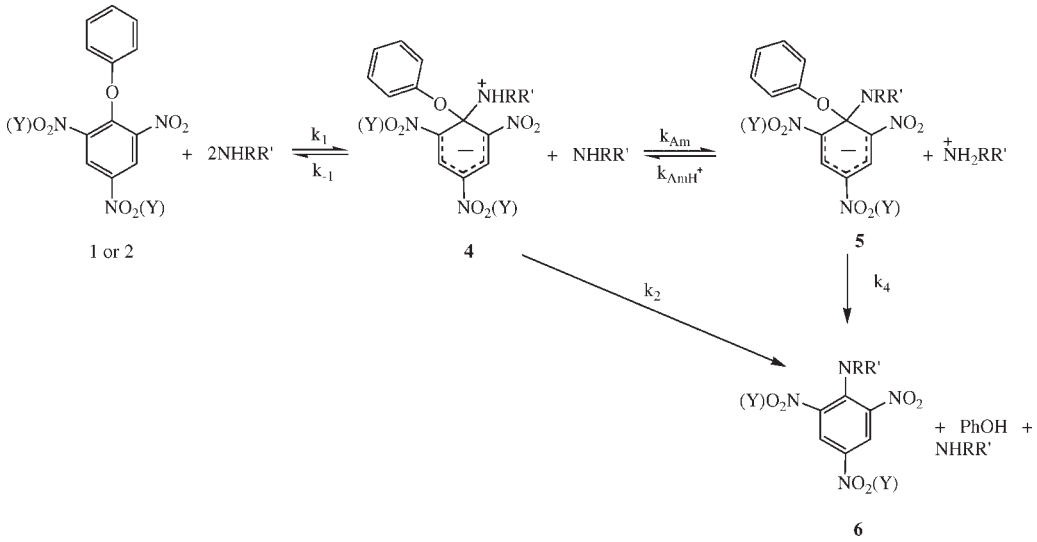
Reactions of *n*-butylamine with **1a–f** and **2e** gave the first-order rate constant k_{obs} with values which increased linearly with the amine concentration. Hence, values of the second-order rate constant, k_A, were independent of the amine concentration. This corresponds to the condition $k_2 + k_{Am}[Am] >> k_{-1}$ so that $k_A = k_1$. Values of rate constants for the reactions of **1a–f** with *n*-butylamine are given as Supporting Information in Table S1 and values for **2a–f** are in Table 1. For **2a** and **2b** plots, not shown, of k_A *versus* [*n*-butylamine] showed concave curvature and passed through the origin. The condition $k_{Am}[Am] \sim k_{-1}$ holds and hence Eqn (3) applies. Values of k_A in Table 2 gave a good fit with Eqn (3):

$$k_A = \frac{K_1 k_{Am}[Am]}{1 + \frac{k_{Am}}{k_{-1}}[Am]} \quad (3)$$



1f **3**

Scheme 2.



Scheme 3.

Interestingly, a similar kinetic pattern has been found for reactions of **2b**, carrying an *ortho*-CF_3 substituent, with *n*-butylamine in acetonitrile.[28] In this solvent the curvature was shown to be indicative of general base catalysis, observed also in the presence of added Dabco. Evidence from the X-ray crystal structure of **2b** suggests that there is some steric crowding around the reaction site which is comparatively as severe as in **1b** and **1f**.[28] Hence, base catalysis observed in the reactions with **2b** may result from the large 'steric' effect of the *ortho*-trifluoromethyl substituent, probably due to electrostatic repulsion between the negative charge on the CF_3 group and the incoming base catalyst. This has the effect of reducing the value of k_{Am}.

Plots of k_A *versus* [amine], with values in Tables S2, for all the reactions with pyrrolidine except for **2e** are essentially linear with excellent correlation coefficients ($R^2 = 0.995–0.999$). In some cases small negative intercepts were observed. Linear regression analysis, however, shows that the standard deviation of the intercept is more than 10 times its estimated value and the assumption that the reaction is second order in nucleophile concentration gives good fits with data. The lack of intercept in the linear plot implies that the uncatalysed pathway k_2 in Scheme 3 is relatively unimportant. Hence, the condition $k_{-1} >> k_{Am}[Am]$ applies and Eqn (1) reduces to Eqn (4), where k_{Am} represents the pathway catalysed by amine. The only parameter which can be determined is K_1k_{Am}.

$$k_A = K_1k_{Am}[Am] \quad (4)$$

Table 1. Kinetic results for reaction of **2a–f** with *n*-butylamine in toluene at 25 °C

	k_A[a] ($\times 10^{-4}$ dm^3 mol^{-1} s^{-1})	k_A[a] ($\times 10^{-3}$ dm^3 mol^{-1} s^{-1})	k_{obs}[b] ($\times 10^{-4}$ s^{-1})	k_{obs}[b] ($\times 10^{-2}$ s^{-1})
[*n*-butylamine] (mol dm^{-3})	2a(Y = H)	2b(Y = CF_3)	2e(Y = ring N)	2f(1f) (Y = NO_2)
0.0005				2.6
0.0008				4.2
0.001				6.4
0.002		9.25 (9.23)	1.28	
0.004		17.50 (17.87)	3.22	
0.006		26.10(25.99)	5.58	
0.008		34.80(33.62)	7.92	
0.01		39.70(40.80)	9.50	
0.02	0.25(0.25)	72.30(71.31)		
0.04	0.49(0.47)			
0.2	1.5(1.7)			
0.4	2.3(2.5)			
0.6	2.9(2.9)			
1.0	4.1(3.5)			

[a] Second-order rate constant k_A. Values of k_{calc} in parentheses were calculated using Eqn (3) with the values collected in Table 5.
[b] First-order rate constants, k_{obs}.

Table 2. Kinetic results for reaction of **2a–f** with pyrrolidine in toluene at 25 °C

	k_A ($\times 10^{-2}$ dm^3 mol^{-1} s^{-1})	k_A ($\times 10^{-2}$ dm^3 mol^{-1} s^{-1})	k_A[a] (dm^3 mol^{-1} s^{-1})	k_A (dm^3 mol^{-1} s^{-1})
[Pyrrolidine] (mol dm^{-3})	2a(Y = H)	2b(Y = CF_3)	2e(Y = ring N)	2f(1f)(Y = NO_2)
0.001		0.14	3.0(3.0)	4.3
0.002			5.7(5.5)	7.41
0.003			7.5(7.6)	
0.004		0.30	8.9(9.4)	18.04
0.005	0.10		11.0(11.0)	20.57
0.008		0.52		
0.01	0.21	0.63		
0.015		0.93		
0.016	0.34			
0.0.02	0.43	1.43		
0.03	0.64	2.15		
0.04		2.72		
0.05		3.55		
0.1	1.88			

[a] Values in parenthesis were calculated using Eqn (3) with K_1k_{Am} 3.3 $\times$ 10^3 dm^6 mol^{-2} s^{-1} and k_{Am}/k_{-1} 100 dm^3 mol^{-1}.

However, for the reactions of pyrrolidine with **2e** carrying a ring nitrogen there is a definite downward (concave) curvature in the plot of k_{Am} *versus* [Am], indicating that the condition k_{Am}[Am] $\sim k_{-1}$, hence Eqn (3) applies, allowing the values of k_1, 33 dm^3 mol^{-1}, K_1k_{Am}, 3.3 $\times$ 10^3 dm^6 mol^{-2} s^{-1} and k_{Am}/k_{-1}, 100 dm^3 mol^{-1} to be calculated. We note that the value of k_1 obtained in the reaction of **2e** with pyrrolidine is, as expected,[28] much higher than that obtained for the same reaction with *n*-butylamine. The reactions with piperidine gave evidence for base catalysis by either one or two molecules of the amine nucleophile. Plots, not shown, with values in Tables 3 and 4 of k_A *versus* amine concentration are generally linear with small negative intercepts. This corresponds to the condition $k_{-1} >> k_{Am}$[Am] as observed in the reactions with pyrrolidine. The small upward curvature observed in some cases in the plot of k_A *versus* [Am] indicates the presence of a small third-order term. Values of the rate constant k_A/[Am] are constant within experimental error for the reactions of **1a**, **2a**, **2b** and **2e**, hence Eqn (4) applies and allows for the calculation of only the parameter K_1k_{Am} assembled in Table 5. For the reactions of **1b–f**,

Table 3. Kinetic results for reaction of **1a–d** with piperidine in toluene at 25 °C

	k_A ($\times 10^{-2}$ dm^3 mol^{-1} s^{-1})	k_A[a] ($\times 10^{-2}$ dm^3 mol^{-1} s^{-1})	k_A[a] ($\times 10^{-2}$ dm^3 mol^{-1} s^{-1})	k_A[a] ($\times 10^{-2}$ dm^3 mol^{-1} s^{-1})
[Piperidine] (mol dm^{-3})	1a(Y = H)	1b(Y = CF_3)	1c(Y = $COOCH_3$)	1d(Y = CN)
0.004				2.2(2.2)
0.006				3.5(3.5)
0.008				4.97(4.9)
0.01		0.45(0.46)	0.32(0.39)	
0.015		0.70(0.71)	0.68(0.63)	10.0(10.1)
0.025		1.27(1.22)		19.0(19.0)
0.04		2.10(2.0)	2.53(2.3)	
0.05			3.13(3.1)	
0.06		3.12(3.2)	4.17(3.9)	
0.08		4.35(4.4)	5.77(6.2)	
0.1		5.67(5.7)		
0.3	0.0088			
0.4	0.0104			
0.6	0.015			
0.8	0.019			
1.0	0.024			

[a] Values in parentheses were calculated from Eqn (6) using the values given in Table 5.

Table 4. Kinetic results for reaction of **2a–d** with piperidine in toluene at 25 °C

	k_A ($\times 10^{-2}$ dm^3 mol^{-1} s^{-1})	k_A ($\times 10^{-2}$ dm^3 mol^{-1} s^{-1})	k_A ($\times 10^{-2}$ dm^3 mol^{-1} s^{-1})	k_A[a] ($\times 10^{-2}$ dm^3 mol^{-1} s^{-1})
[Piperidine] (mol dm^{-3})	2a(Y = H)	2b(Y = CF_3)	2e(Y = ring N)	2f(1f)(Y = NO_2)
0.002			17.6	26.8(27.1)
0.004			33.5	57.1(56.7)
0.005			43.6	78.0(72.3)
0.006			50.2	
0.008			65.2	127.9(123)
0.01			79.6	166.2(160)
0.015				261.7(261)
0.025			171.8	
0.04		0.036		
0.05	0.045			
0.06		0.053		
0.08		0.070		
0.1	0.094	0.087		
0.15		0.126		
0.2	0.198	0.178		
0.3	0.293	0.265		
0.4	0.397			
0.6	0.622			

[a] Values in parenthesis calculated from Eqn (6) using the values given in Table 5.

the upward curvature is more pronounced and Eqn (5) holds. When the condition $k_{Am}[Am] + k'_{Am}[Am]^2 << k_{-1}$ applies, Eqn (5) can be simplified to Eqn (6). Plots of k_A/[Am] *versus* [Am] for

$$k_A = \frac{k_1(k_{Am}[Am] + k'_{Am}[Am]^2)}{k_{-1} + k_{Am}[Am] + k'Am[Am]^2} \quad (5)$$

$$k_A = K_1 k_{Am}[Am] + K_1 k'_{Am}[Am]^2 \quad (6)$$

the reactions of **1b–f** with piperidine gave good fits with Eqn (6), and values of K_1k_{Am} and $K_1k'_{Am}$ were obtained from the intercepts and slopes. We noted that the values of K_1k_{Am} and $K_1k'_{Am}$ increase with an increase in the ring activation. The presence of a term which is third order in amine is well known in S_NAr reactions in benzene.[12–16,26] The change in kinetic form is more noticeable with the more reactive substrates carrying two *ortho* nitro groups and may possibly be attributed to an increase in the strength of the intermolecular hydrogen bond formed in the cyclic transition state structure which increases the likelihood of the participation of a third molecule of the nucleophile.

COMPARISONS

The various rate coefficients obtained in the present study together with literature data determined in acetonitrile[28] are summarised in Table 5.

Rate constants, k_1, for nucleophilic attack

The observed kinetic pattern for the reactions with pyrrolidine and piperidine did not allow a complete determination of k_1 values, the rate constants for the nucleophilic attack at the ring carbon for the series of compounds studied. However, k_1 values obtained for the reaction of **2e** with pyrrolidine are *ca.* 330 greater than the value obtained for the corresponding reaction with *n*-butylamine. In acetonitrile, the reactivity order of pyrrolidine > piperidine > *n*-butylamine was generally observed except where steric factors were dominant. This is the order commonly found in nucleophilic substitution reactions[1,2] and reflects the relative basicities of the amines in acetonitrile; pK_a values,[33] for the protonated amines are pyrrolidine 19.58, piperidine 18.92, *n*-butylamine 18.26. The superior reactivity of the secondary amines has also been attributed to favourable ion-induced dipole interactions in the transition state between the partially positively charged nitrogen moiety and the polarisable alkyl substituents attached to it.[34]

Ring activation

For compounds **1a–f** the steric situation at the reaction centre is similar, and the data in Table 5 show that each amine values of k_1 increases regularly with increased electron withdrawal of the 4-substituent. A Hammett plot, not shown, with k_1 values for the reactions with *n*-butylamine *versus* σ^- is reasonably linear with slope, ρ, of *ca.* 2.5 indicating that bond formation is fairly well developed in the transition state for nucleophilic attack. However, there is some evidence for downward curvature in the Hammett plot as electron-withdrawal by the 4-substituents increases, and this may be indicative (as observed for the same reactions in acetonitrile) of a shift towards an 'earlier' transition state. Also Hammett plots using K_1k_{Am} for the reactions with pyrrolidine or piperidine gave ρ of *ca.* 4.7, reflecting the increase in the value of K_1 with increasing ring activation. The reactions with the 6-substituted-1-phenoxy-2,4-dinitrobenzenes **2**, with *n*-butylamine, pyrrolidine and piperidine generally show a reactivity order NO_2 > ring N > CF_3 > H which parallels the

Table 5. Summary of results[a] for reaction of **1** and **2** with aliphatic amines in toluene at 25 °C

Substrate, Y			*n*-butylamine	Pyrrolidine	Piperidine
1a	4-H	k_1 ($dm^3\,mol^{-1}\,s^{-1}$)	0.046(0.047)	(0.024)	—
		K_1k_{Am} ($dm^6\,mol^{-2}\,s^{-1}$)	—	0.0067 (0.083)	0.00025(0.0011)
1b	4-CF_3	k_1 ($dm^3\,mol^{-1}\,s^{-1}$)	4.6(5.6)	(12)	—
		K_1k_{Am} ($dm^6\,mol^{-2}\,s^{-1}$)	—	19.1(120)	0.46(3.3)
		$K_1k'_{Am}$ ($dm^6\,mol^{-2}\,s^{-1}$)	—	—	1.12
1c	4-CO_2Me	k_1 ($dm^3\,mol^{-1}\,s^{-1}$)	6.35(9.3)	(17.5)	—
		K_1k_{Am} ($dm^6\,mol^{-2}\,s^{-1}$)	—	22.0(350)	0.34(10.2)
		$K_1k'_{Am}$ ($dm^6\,mol^{-2}\,s^{-1}$)	—	—	5.4
1d	4-CN	k_1 ($dm^3\,mol^{-1}\,s^{-1}$)	19.3(45)	(450)	—
		K_1k_{Am} ($dm^6\,mol^{-2}\,s^{-1}$)	—	240.2(3200)	5.35(112)
		$K_1k'_{Am}$ ($dm^6\,mol^{-2}\,s^{-1}$)	—	—	94
2a	6-H	k_1 ($dm^3\,mol^{-1}\,s^{-1}$	4.7×10^{-4} (4.9×10^{-3})	(0.37)	−(0.16)
		k_{Am} (k_{-1} $dm^3\,mol^{-1}$)	2.7		—
		K_1k_{Am} ($dm^6\,mol^{-2}\,s^{-1}$)	1.3×10^{-3}	0.20(26)	0.011(0.80)
2b	6-CF_3	k_1 ($dm^3\,mol^{-1}\,s^{-1}$)	0.28(2.0)	(>2)	—
		k_{Am}/k_{-1} ($dm^3\,mol^{-1}$)	16.9(220)	(<5)	—
		K_1k_{Am} ($dm^6\,mol^{-2}\,s^{-1}$)	4.8(450)	0.71(11.3)	0.009(0.30)
2e	Ring N[b]	k_1 ($dm^3\,mol^{-1}\,s^{-1}$)	0.10(0.95))	33(85)	(24)
		k_{Am}/k_{-1} ($dm^3\,mol^{-1}$)	—	100(1300)	(100)
		K_1k_{Am} ($dm^6\,mol^{-2}\,s^{-1}$)	—	$3.3\times10^3(1.1\times10^5)$	66(2440)
2f	6-NO_2	k_1 ($dm^3\,mol^{-1}\,s^{-1}$)	53.3(183)	(2400)	(650)
		K_1k_{Am} ($dm^6\,mol^{-2}\,s^{-1}$)	—	$4.35\times10^3(1.3\times10^5)$	130(5200)
		$K_1k'_{Am}$ ($dm^6\,mol^{-2}\,s^{-1}$)			2950

[a] Values in parentheses are the values obtained in acetonitrile.

activating power of the substituent. In acetonitrile, the various factors responsible for the trend in the microscopic rate constants have already been considered. It should be noted that as observed in the corresponding reactions in acetonitrile that for all three amines the increase in the values of k_1, the rate constant for nucleophilic attack at the 1-position of the substrates, with increased ring-activation may be reduced by steric repulsion at the reaction centre. Specific steric effects, leading to rate-retardation, are noted for the *ortho*-CF_3 group. We have reported[28] earlier that X-ray crystal structures of phenyl 4-trifluoromethyl-2,6-dinitrophenyl ether **1b**, phenyl 6-trifluoromethyl-2,4-dinitrophenyl ether **2b** and phenyl,2,4,6-trinitrophenyl ether **1e** provide evidence that these ethers are sterically strained molecules, kinetic data also suggest that steric effects due to the *ortho*-CF_3 substituent is greater than that of a nitro group on nucleophilic attack.[28,29] In the reactions of 4-substituted-1-phenoxy-2,6-dinitrobenzenes, **1**, a change in the substituents Y has no influence on the steric conditions at C(1), the reaction centre. To a first approximation we would, therefore, expect a substituent effect of very similar magnitude on the reactions *n*-butylamine, pyrrolidine and piperidine. The K_1k_{Am} pyrrolidine/piperidine reactivity ratio for all the compounds **1a–f** in Table 5 gave a fairly constant value of *ca*. 30 which reflects the constancy in the steric requirement at the reaction centre. However, the K_1k_{Am} pyrrolidine/piperidine reactivity ratios varied from 18, 50 and 78 for the corresponding reactions with **2a**, **2e** and **2b**, respectively. Although piperidine is generally more sterically disadvantaged relative to pyrrolidine in the reactions of compounds **1** and **2**, the increase in the value of pyrrolidine/piperidine reactivity ratio to 78 obtained in the reactions with **1b**, is also a reflection of the increased steric hindrance due to the CF_3 group, being more severe for the reactions with piperidine.

Solvent effect

The values of k_1 in Table 6 for the reaction with *n*-butylamine show that the rate of nucleophilic attack is not greatly reduced on transfer from acetonitrile to toluene. Values of the k_1 MeCN/toluene ratio increase from unity for the reactions with **1a** to *ca*. 10 for the reactions of *n*-butylamine with **2a** and **2e**. We have also found that the reactivity ratio of K_1k_{Am} MeCN/toluene for reactions in acetonitrile compared to toluene increases from

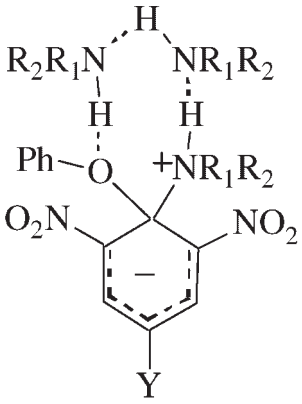
Table 6. Comparison of reactivities in toluene and acetonitrile

Substrate, Y		k_1(acetonitrile/toluene)	K_1k_{Am}(acetonitrile/toluene)	
		n-butylamine	Pyrrolidine	Piperidine
1a	4-H	1.0	12.4	4.4
1b	4-CF_3	1.2	6.3	7.2
1c	4-CO_2Me	1.5	16	30
1d	4-CN	2.3	13.3	21
2a	6-H	10.4	130	72.7
2b	6-CF_3	7.1	16	33.3
2e	Ring N	9.5	33.3	37
2f	6-NO_2	3.4	30	40

ca. 6 for the reactions of pyrrolidine with **1b** to 130 when the substrate is **2a** in the reaction series. Values of the ratio in piperidine are in the same range as those in pyrrolidine. These changes are likely to be largely due to the decrease in the values of K_1, the equilibrium constant for zwitterion formation, as the solvent is changed from acetonitrile to toluene. As the relative permittivity of the solvent is decreased, the intermediate will have lower stability; values of k_1 will decrease and values of k_{-1} will increase. Interestingly, the reactivity difference found in the present investigation (reactions in acetonitrile compared to toluene) is not very large compared with the large variation in the dielectric constant. This might result from some stabilisation in toluene of the zwiterrionic intermediate **4** by solvent molecules arising from π–π stacking interaction between the ring plane of the zwitterion and solvent molecules. The strength of these interactions is known to vary uniformly with solvent polarity and correlates well with the empirical $E_T(30)$ parameter.[35] The association constant for such arene–arene interactions between cyclophanes and aromatic compounds is only a factor that is 10 times larger in *N,N*-dimethylformamide than in benzene, whereas it is up to 10^6 times larger in polar solvents like water than in benzene. $E_T(30)$ values at 25 °C[36] are for water 63.1, acetonitrile 46, *N,N*-dimethylformamide 43.8, benzene 34.5 and toluene 33.9. Though the values of such association constants were not reported for acetonitrile and toluene, we estimate the difference to be less than a factor of 100 when acetonitrile is compared to toluene which accounts for the small difference in the microscopic rate constants in the present study.

Base catalysis

The incidence of base catalysis depends on the values of the k_{Am}/k_{-1} ratio. In toluene base, catalysis is observed with all compounds studied in their reactions with pyrrolidine and piperidine. The results in Table 5 show that for **2a** and **2b**, base catalysis is also observed with *n*-butylamine. For comparison, the reaction of **2b** with *n*-butylamine is also base catalysed in acetonitrile, as are reactions of all substrates with pyrrolidine and piperidine. Where comparison is possible, i.e in reactions of **2b** with *n*-butylamine and **2e** with pyrrolidine, values of k_{Am}/k_{-1} are *ca*. 10 times lower in toluene than in acetonitrile. This is likely to be due to an increase in the value of k_{-1} in the less polar solvent. It seems likely that the values of k_{Am}, the rate constant for proton transfer, will not differ greatly between the two solvents. There is strong evidence [28–31] that in strongly activated compounds, the zwitterionic intermediates, **4**, are more acidic than the corresponding ammonium ions $R^1R^2NH_2^+$ so that the proton transfer process, k_{Am}, is in the thermodynamically 'downhill' direction. Hence, the values of k_{Am} may approach the diffusion limit but are reduced by steric factors which have been shown to decrease in the order *n*-butylamine > pyrrolidine > piperidine. However, in the less activated compounds studied in the present work, the electron withdrawing power of the ring in the zwitterions will be reduced so that the proton transfer process, k_{Am}, may not be thermodynamically favoured. This may account for the observation of base catalysis in the reactions of **2a** with *n*-butylamine, where the low value for k_{Am}/k_{-1} of 2.7 reflects the relatively low value for k_{Am} and high value for k_{-1}. As mentioned previously, steric effects at the reaction centre in **2b** are likely to reduce the value for k_{Am}. It is also of interest to note that in addition to k_{Am}, the third-order term k'_{Am} is observed for reactions with piperidine, the more sterically hindered amine. This is an indication that the values of the base catalysed step are strongly influenced by steric factors.



III

Y= CF_3, COOMe, CN, NO_2.

The observation of the upward curvature in the plot of k_A *versus* [Am] concentration has been explained in terms of solvent effects, association of the nucleophile of the base and electrophilic catalysis of the expulsion of the leaving group by homo- and hetero-conjugate acid of the nucleophiles. For this investigation, we prefer to explain our results by the cyclic transition state mechanism depicted in **III**. The concept was developed by Banjoko[12–16] and Emokpae[26,37] to rationalise reactions proceeding through the cyclic transition state containing two or three molecules of the nucleophile and to distinguish these reactions from those of ethers taking place by the specific base-general acid mechanism (SB-GA mechanism).

EXPERIMENTAL

The compounds, **1a–f** and **2a–f** and the corresponding amine substitution products were available from previous work.[28,29] Amines and toluene were the purest available commercial samples. Kinetic measurements were made spectrophotometrically at the absorption maxima of the products using Varian Cary 50 or 100 UV–Vis spectrophotometers. Rate constants were measured at 25 °C under pseudo-first-order conditions with substrate concentrations of $1 \times 10^{-4} - 1 \times 10^{-5}$ mol dm^{-3} and were calculated by standard methods. Values are precise to ±3%.

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