Nucleophilic Heteroaromatic Substitution: Kinetics of the Reactions of Nitropyridines with Aliphatic Amines in Dipolar Aprotic Solvents

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ABSTRACT: Rate data are reported for the reactions of 2-chloro-5-nitropyridine **2a**, 2-chloro-3-nitropyridine **2b**, and the corresponding 2-phenoxy derivatives **2c** with *n*-butylamine, pyrrolidine and piperidine and **2d** with *n*-butylamine and pyrrolidine in dimethyl sulfoxide (DMSO) as solvent. The same reactions in acetonitrile had been reported earlier (Crampton et al., *Eur J Org Chem* 2007, 1378–1383). Values in these solvents are compared with those of 2,4-dinitrochlorobenzene **3a**, 2,6-dinitrochlorobenzene **3b**, and the corresponding nitroactivated diphenyl ethers **3c** and **3d**. Reactions with *n*-butylamine in both solvents gave values of k_{obs}, which increase linearly with amine concentration indicating that nucleophilic attack is rate limiting. The only exception is the reactions in acetonitrile with **2c** where base catalysis was observed. Values of k_1, the rate constant for the nucleophilic attack, decrease in the order pyrrolidine > piperidine > *n*-butylamine. In acetonitrile, kinetic data show that $k_1^{3\text{-}NO_2}/k_1^{5\text{-}NO_2}$ ratios are more than unity while the inverse is the case in DMSO. With the phenoxy derivatives, substitution was the only process observed. Base catalysis detected in the reactions of the 1-phenoxy derivatives is attributed to rate-limiting deprotonation of the initially formed zwitterionic intermediate. Our results shed more light on fundamental aspects of activation, hydrogen bonding, and steric effects associated with an aza or a nitro group in the molecules investigated as it affects the nucleophilic aromatic substitution (S_NAr) reaction pathways.
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INTRODUCTION

It is now well documented that pyridine and other fully aromatic nitrogen heterocycles often considered to be ring aza-substituted arenes are electron deficient due to the presence of an electronegative nitrogen atom in

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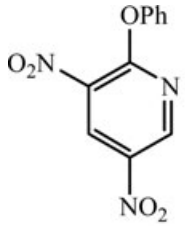
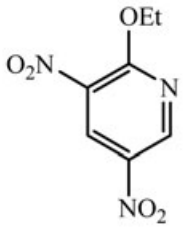


1a



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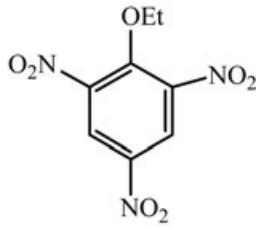
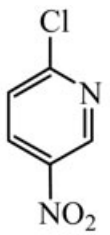


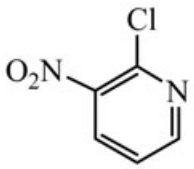
1c

the aromatic ring [1,2]. The deficiency makes these heterocycles more susceptible to nucleophilic substitution of suitable leaving group especially at the 2- and 4 positions to the heteroatom than the corresponding benzenes. So far little attention has been given to these heterocyles, despite the fact that they are known to exhibit specific reactivity toward nucleophiles being kinetically more susceptible to nucleophilic attack at the unsubstituted carbon C-6 relative to attack at the carbon atom C-2 carrying the leaving group. It is only recently that we presented a detailed and a comprehensive analysis of the competitive behavior of σ-adduct formation versus nucleophilic substitution in the reactions of the three aliphatic amines with 2-ethoxy- and 2-phenoxy-3,5-dinitropyridine in dimethyl sulfoxide (DMSO) [3]; the ratio of the rate constants for attack by *n*-butylamine at the unsubstituted 6-position (k_6) and 2-postion (k_2) is 2000 for 2-phenoxy-3,5-dintropyridine **1a** and 8000 for 2-ethoxy-3,5-dintropyridine **1b**. This contrasts with the behavior of 1-ethoxy-2,4,6-trinitrobenzene **1c**, where there are considerable steric interactions around that position [4]. Here, the ratio of the rate constants, k_3:k_1, for attack by *n*-butylamine at the unsubstituted 3-position and the 1-position, is only 13.

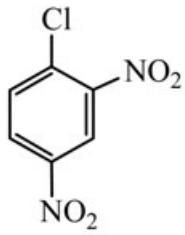
There have been reports of the reactions with aliphatic amines in DMSO and in acetonitrile, of 2,4- and 2,6-dinitrochlorobenzenes and the corresponding 1-phenoxy derivatives [5]. However, only a few studies involving substitutions in the analogous pyridine compounds have been carried out in the same solvents. In continuation of our previous studies [3,6,7] of the effect of ring-nitrogen on reactivity, we report the kinetics of the reactions in DMSO of 2-chloro-5-nitropyridine **2a**, 2-chloro-3-nitropyridine **2b**, and the corresponding 2-phenoxy derivatives **2c** with *n*-butylamine, pyrrolidine, and piperidine and **2d** with *n*-butylamine and pyrrolidine. Their kinetic forms are compared with those



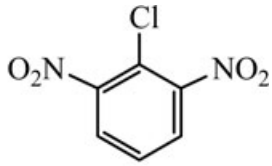
2a



2b



3a



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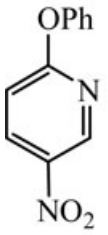
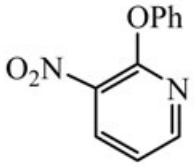


2c



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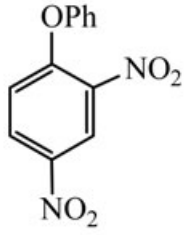
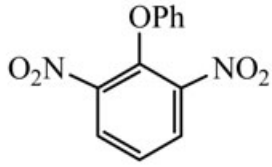


3c



3d

of the reactions of 2,4- and 2,6-dinitrochlorobenzenes **3a**, **3b** and phenyl-2,-4-, and phenyl-2,6-dinitrophenyl ethers **3c** and **3d** [4,5a,6,8]. We are particularly interested in the (i) relative reactivity of an aza and a nitro function and their effects on the mechanism of substitution and (ii) ortho versus para activation in the pyridines series in dipolar aprotic solvents irrespective of which step is rate limiting in the well-established two-step mechanism of S_NAr reactions.

EXPERIMENTAL

The 2-halogeno compounds were the purest available commercial samples. The 2-phenoxy compounds **2c** and **2d** were prepared by reaction at 45°C for 2 h of the appropriate 2-chloro compound (1 equiv.) with potassium hydroxide (1 equiv.) in an excess of phenol in aqueous ethanol. On completion, water was added and the solid formed recrystallized from ethanol. Analytical data for **2c** and **2d** were in agreement with the expected structures. **2c**: m.p. 92°C (lit. [6]. 93°C). **2d**: m.p. 88°C (lit. [6]. 89°C).

Amines and DMSO were the purest available commercial samples. Kinetic measurements were made spectrophotometrically at the absorption maxima of the products using Perkin-Elmer Lambda 2 or Shimadzu UV PC spectrophotometers. Rate constants were determined at 25°C under first-order conditions with substrate concentrations of ca. 1×10^{-4} mol dm^{-3} and were evaluated by standard methods. Values are precise to ±3%.

RESULTS AND DISCUSSION

The Chloro Compounds

The reactions of the 2-chloro-substituted compounds gave the expected 2-amino derivatives in quantitative yield in a single stage without the observation of intermediates. Kinetic measurements were made with the concentration of the amine in large excess of the parent concentration ca. 1×10^{-4} mol dm^{-3} and first-order kinetics were observed. Values of k_{obs}, the first-order rate constants, increase linearly with amine concentration (Tables S1–S3[1]), indicating that nucleophilic attack is rate limiting, and the reactions are not subject to catalysis by the amines. Here the breakdown of the intermediate complex is kinetically insignificant. Division of the pseudo-first-order coefficient by the appropriate concentration of the amine gave the second-order rate coefficient k_A presented in Table IV.

The Phenoxy Compounds

Previous studies have shown that substitution may be preceded by formation under kinetic control of adduct resulting from attack at the unsubstituted ring position followed by isomerization to give the thermodynamically most stable substitution product [3,4,8–13]. The UV–visible spectra of **1a** or **1b** in DMSO containing *n*-butylamine, pyrrolidine, or piperidine show that the reactions produced species that absorb strongly at 490–495 nm. The absorption faded rapidly to give spectra that are identical with those of the authentic samples of the products dissolved in the same reaction medium [3]. Values of the equilibrium constants for such processes have been shown to depend on the degree of ring activation and also on the solvent [4,8–15]. Thus, the values for the reactions in DMSO are ca. 10^4 larger than in acetonitrile. The dominant factor here is likely to be the greater ability of DMSO than acetonitrile to solvate the ionic products. It is, therefore, not surprising that for **2c** and **2d**, substrates that are less activated than **1**, substitutions proceed in both acetonitrile and DMSO smoothly to give first-order kinetics without the observation in spectroscopically measurable concentration of transient species on the reaction pathway. A typical UV–visible spectra scan in DMSO of the reaction of **2c** with pyrrolidine displayed in Fig. 1 showed a neat conversion of the reactant to product. Isobestic point was observed at 330 nm and the product absorbed strongly at 390 nm.

Kinetic results of the reactions of 2-phenoxy compounds are best analyzed in terms of Scheme 1 in which base catalysis is attributed to rate-limiting proton transfer (RLPT) from zwitterionic intermediate **4** to base followed by rapid expulsion of the phenoxide. On the assumption that the zwitterionic intermediate **4** may be treated as a steady state, when the amine acts both as the nucleophile and as the catalyzing base, leads to Eq. (1).

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

For the condition $k_{-1} \ll k_2 + k_{Am}[Am]$, Eq. (1) reduces to Eq. (2),

$$k_A = k_1 \qquad (2)$$

the formation of the intermediate is rate limiting and the reaction is not catalyzed by the amine. If this condition is not satisfied, then the decomposition of the

[1]Additional chemical kinetic data in tabular form (Tables S1–S3) are available as Supplementary Material at http://www.interscience.wiley.com/jpages/0538-8066/suppmat/.

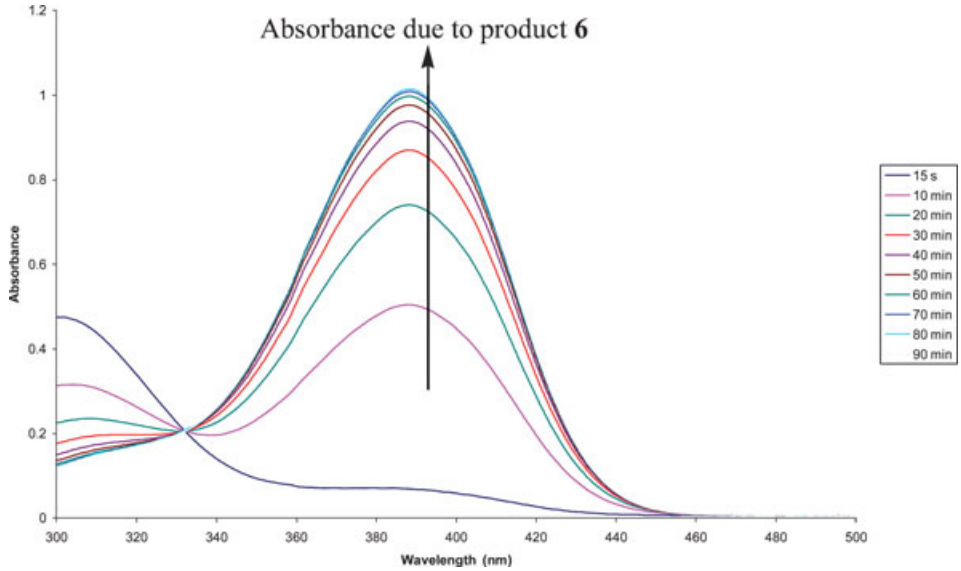
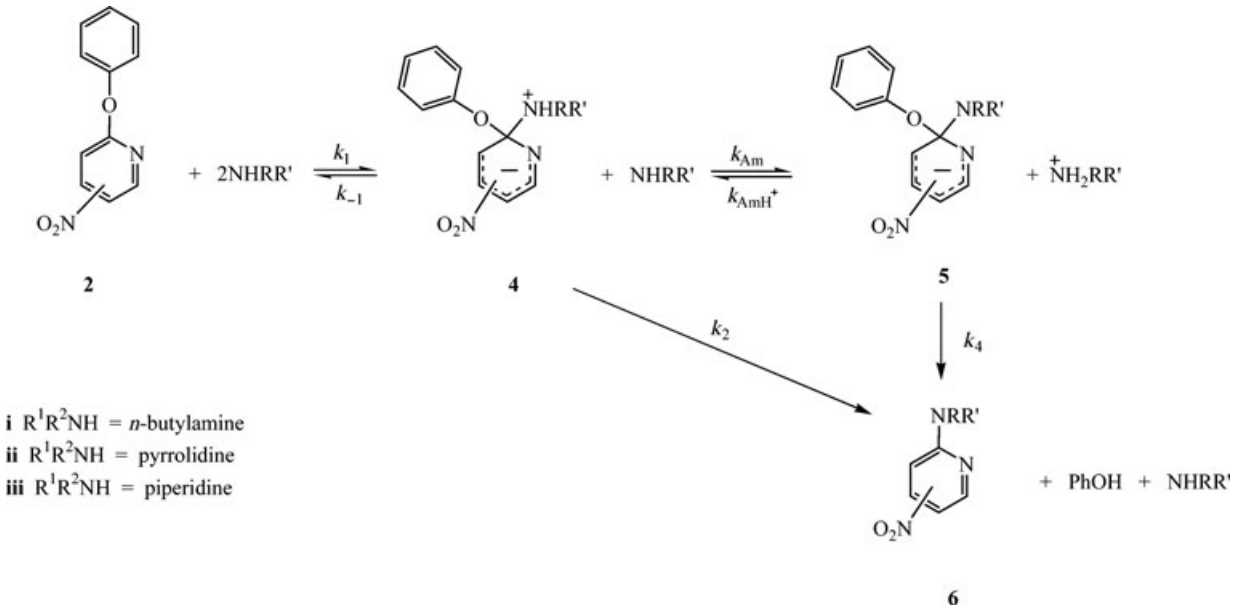


Figure 1 UV–vis rapid scan of the reaction mixtures of 5.0×10^{-5}M, 2-phenoxy-5-nitropyridine with 0.2 M pyrrolidine in DMSO. [Color figure can be viewed in the online issue, which is available at www.interscience.wiley.com.]



Scheme 1

intermediate to products is rate limiting and the reaction is amine catalyzed. When the condition $k_{-1} \gg k_2 + k_{Am}[Am]$ applies, Eq. (1) reduces to Eq. (3)

$$k_A = K_1 k_2 + K_1 k_{Am}[Am], \text{ where } K_1 = \frac{k_1}{k_{-1}} \quad (3)$$

and the plot of k_{Am} versus [Am] is linear. If Eq. (1) cannot be simplified further, then k_A has a curvilinear (concave downward) dependence on amine concentration. The assumption that the expulsion of the leaving group (the k_4 step) is not rate determining leads to Eq. (4).

$$k_A = \frac{k_{obs}}{[Am]} = \frac{k_1 k_{Am}[Am]}{k_{-1} + k_{Am}[Am]} \quad (4)$$

An equivalent form is Eq. (5).

$$k_A = \frac{K k_{Am}[Am]}{1 + \frac{k_{Am}}{k_{-1}}[Am]} \quad (5)$$

Table I Kinetic Results for Reaction of **2c** with *n*-Butylamine in DMSO at 25°C

[*n*-Butylamine]/ (mol dm^{-3})	k_{obs}/ (10^{-3} s^{-1})	k_A/ (10^{-3} dm^3 mol^{-1} s^{-1})
0.012	0.0045	0.38
0.016	0.0065	0.41
0.02	0.0081	0.41
0.04	0.018	0.45
0.08	0.034	0.43
0.1	0.04	0.40

Table III Kinetic Results for Reaction of **2c** with Piperidine in DMSO at 25°C

[Piperidine]/ (mol dm^{-3})	k_{obs}/ (10^{-3} s^{-1})	k_A/ (10^{-3} dm^3 mol^{-1} s^{-1})
0.008	0.0039	0.49
0.06	0.031	0.52
0.08	0.042	0.53
0.1	0.054	0.54
0.2	0.12	0.60
0.4	0.29	0.73

These three limiting types of catalysis were observed in this investigation.

The results for the reaction in DMSO for **2c**, with *n*-butylamine and with pyrrolidine in Tables I and II show that values of k_{obs} increase linearly with amine concentration. This indicates that the condition $k_{Am} \gg k_{-1}$ applies so that Eq. (1) reduces to Eq. (2). Values of k_1 calculated from Eq. (2) are presented in Table IV. The situation with pyrrolidine as nucleophile in the reaction of **3c** is more complex. The plot (not shown) of k_A versus amine concentration is curved with intercept indistinguishable from zero; this indicates that the uncatalyzed pathway, the k_2 step in Scheme 1, is unimportant. The curvature of the plot shows that the proton transfer step, k_{Am} is partially rate limiting so that Eq. (5) applies. For the reaction with piperidine, such a plot has a small positive intercept.

In the reactions of **2c** and **2d**, measurements with piperidine indicate a squared dependence of k_{obs} on amine concentration reflecting the condition $k_{-1} \gg k_{Am}$ so that proton transfer is rate limiting. Plots of k_A versus piperidine concentration are linear with positive intercept indicating that the uncatalyzed decomposition of the intermediate, the k_2 step contributes significantly to the reaction flux so that Eq. (2) applies. Values of Kk_2 and Kk_{Am} obtained from the intercepts and the slope of the plot gave good fit with experimental data. For the reactions of **2c** in acetonitrile [6] with *n*-butylamine, pyrrolidine, and piperidine and those of **2d** with pyrrolidine and piperidine, the behavior was shown to be qualitatively similar to that of **3c** with pyrrolidine in DMSO [4,8]; values of $k_2$are negligibly small and the data in Table III conform to Eq. (5) with the values summarized in Table IV. However, the plot of k_A versus piperidine concentration for **3d** is linear and has a distinct intercept reflecting the contribution of the uncatalyzed pathway. Hence, Eq. (3) applies.

Table II Kinetic Results for Reaction of **2c** with Pyrrolidine in DMSO at 25°C

[Pyrrolidine]/ (mol dm^{-3})	k_{obs}/ (10^{-3} s^{-1})	k_A/ (10^{-3} dm^3 mol^{-1} s^{-1})
0.01	0.036	3.6
0.02	0.076	3.8
0.04	0.17	4.3
0.08	0.34	4.3
0.1	0.40	4.0

COMPARISON

Relative Activation of a Ring Nitrogen and 6-Nitro Group in Acetonitrile and DMSO

Kinetic data for the reactions of the nucleophiles with **2a** and **3a** allow an assessment of the relative activation of a ring nitrogen and a 6-nitro group expressed in terms of $k_1^{6\text{-}NO_2}/k_1^N$ ratio. Values in acetonitrile are 23.2 (*n*-butylamine), 17.8 (pyrrolidine), and 15.8 (piperidine), respectively. In DMSO, the ratios are also >1. With the phenoxy derivative, **3c** is ca. 40–250 times more reactive than **2c** in the rates of nucleophilic attack. Hence, in the absence of steric encumbrance, the activating power of a 6-nitro group is greater than that of a ring nitrogen. This was attributed to the more efficient delocalization of the negative charge with a nitro group than with a ring nitrogen in the transition state [2,16].

However, when similar evaluations were carried out for the reactions in acetonitrile of **2b** and **3b**, a different pattern emerged. For *n*-butylamine, where steric effects are likely to be unimportant, the 6-nitro group was found to be more activating than the ring nitrogen while the order was reversed for the secondary amines. Similar sequence was observed recently in the reactions in acetonitrile of 2-chloro-3,5-dinitropyridine and 1-chloro-2,4,6-trinitrobenzene [7]. This may be attributed to the steric effect of the 6-nitro group, which is more severe in the reactions with secondary amines. Previous results [17–20] have

Table IV Summary of Results[a] for Reaction of **2** and **3** with Aliphatic Amines in DMSO at 25°C

Substrate, R		*n*-Butylamine	Piperidine	Pyrrolidine
2a	k_1/ (dm^3 mol^{-1} s^{-1})	0.011(1)	0.29(26)	0.62(56)
2b	k_1/ (dm^3 mol^{-1} s^{-1})	5.9×10^{-3}(1)	0.09(15)	0.52(88)
2c	k_1/ (dm^3 mol^{-1} s^{-1})	4.1×10^{-4}(1)	–	4.1×10^{-3}(10)
	K_1k_{Am}/ (dm^6 mol^{-2} s^{-1})	–	6.4×10^{-4}	–
	K_1k_2/ (dm^3 mol^{-1} s^{-1})	–	4.7×10^{-4}	–
3a[b]	K_1/ (dm^3 mol^{-1} s^{-1})	–	1.9	–
3c[b]	K_1/ (dm^3 mol^{-1} s^{-1})	4.2×10^{-2}(1)	0.6(14)	1.15(27)
	k_{Am}/k_{-1} (dm^3 mol^{-1})	–	1.3	37
	K_1k_{Am}/ (dm^6 mol^{-2} s^{-1})	–	0.8	43
	K_1k_2/ (dm^3 mol^{-1} s^{-1})	–	5.0×10^{-3}	–
3d[c]	K_1k_{Am}/ (dm^6 mol^{-2} s^{-1})	5.34	0.012	–
	K_1k_2/ (dm^3 mol^{-1} s^{-1})	0.05	1.0×10^{-4}	–

[a] Values in parentheses are the reactivities for a given compound relative to that for *n*-butylamine; i.e. k_1(pyrrolidine)/k_1(*n*-butylamine) and k_1(piperidine)/k_1(*n*-butylamine).

[b] Values from [4, 8].

[c] Values from [5a].

shown that the value of the ratio decreases dramatically from 3.5 when these substrates reacted with aniline in acetonitrile to 1.05×10^{-4} for similar reactions with *N*-methylaniline. In this system, like other reactions with secondary amines, the ring nitrogen is more activated than a nitro group, an observation that is characteristic of the operation of some kind of steric effect. In 2-chloro-3–5-dinitropyridine, the ring nitrogen occupies one of the ortho position and its lone electron pair takes the place of the 6-nitro group in 1-chloro-2,4,6-trinitrobenzene. This lone electron pair is less bulky than even a hydrogen substituent [2,16,18].

The Ortho/Para Ratio

It is worth considering the ortho/para ratio expressed as $k_1^{3\text{-}NO_2}/k_1^{5\text{-}NO_2}$ in the reactions of nitropyridines with aliphatic amines in dipolar solvents. Examination of the data in Table V shows that in acetonitrile **2b** is more reactive in nucleophilic attack (k_1 step) than **2a**. Values of the reactivity ratio $k_1^{3\text{-}NO_2}/k_1^{5\text{-}NO_2}$ are 1.6 (*n*-butylamine), 2.40 pyrrolidine, and 1.06 (piperidine). With the phenoxy derivatives **2c** and **2d**, kinetic data also follow the same pattern. The ratios are 2.17, 3.40, and 1.08 for *n*-butylamine, pyrrolidine, and piperidine, respectively. It is only in the case of the bulky nucleophile, piperidine, that the reactivity is nearly the same. The situation is slightly different in the reactions of **3a** and **3b**. With *n*-butylamine, the $k_1^{3\text{-}NO_2}/k_1^{5\text{-}NO_2}$ ratio is >1. Para substitutions were, however, dominant in the reactions with secondary amines. Values of reactivity ratios $k_1^{3\text{-}NO_2}/k_1^{5\text{-}NO_2}$ are 0.042 (pyrrolidine) and 0.044 (piperidine). This may again be attributed to the steric effect of the 6-NO_2 group, which is more severe in reactions with secondary amines [1,2,7].

In DMSO, the order of reactivity was, however, reversed in the reactions of **2a** and **2b**. With the three nucleophiles, the reactions of **2a** were faster than those of **2b**. Values of the reactivity ratios $k_1^{3\text{-}NO_2}/k_1^{5\text{-}NO_2}$ are 0.54 (*n*-butylamine), 0.83 (pyrrolidine), and 0.45 (piperidine).

The reactivity sequence **2b** > **2a** and **2d** > **2c** observed in acetonitrile is in agreement with previous reports that for amine nucleophiles, the ortho/para ratio was usually found to be >1 [21,22]. This was attributed to a combination of reduced nonbonding interactions (NBI) due to the nucleophile being uncharged and a stabilizing effect of intramolecular hydrogen bonding involving a hydrogen atom attached to nitrogen in the attacking nucleophile and the oxygen atom of the ortho-nitro group. This effect outweighs the NBI effect [23]. The inversion in order of reactivity observed in DMSO in the reactions of **2a** and **2b** is possibly related to the differences in the properties of the two dipolar aprotic solvents [24]. The relative permittivity of acetonitrile is comparable with that of DMSO; the values are 36 and 46.6, respectively. However, acetonitrile is much less basic solvent and the pK_a values of aliphatic ammonium ions are ca. 8 units larger than in DMSO. This solvent is known to be a good hydrogen-bond acceptor [24,25], and this is reflected in the greater relative stabilization through hydrogen-bonding interactions, of the primary ammonium ions than of secondary ammonium ions in the solvent.

The need for stabilization of the substituted ammonium ions in acetonitrile is evidenced by the

Table V Summary of Results[a,b] for Reaction of **2** and **3** with Aliphatic Amines in Acetonitrile at 25°C

Substrate, R		*n*-Butylamine	Piperidine	Pyrrolidine
2a	K_1/ (dm^3 mol^{-1} s^{-1})	3.84×10^{-4}(1)	0.033(87)	0.073(190)
2b	K_1/ (dm^3 mol^{-1} s^{-1})	6.12×10^{-4}(1)	0.035(57)	0.175(286)
2c	K_1/ (dm^3 mol^{-1} s^{-1})	2.3×10^{-5}(1)	5.3×10^{-4}(23)	1.47×10^{-3}(64)
	$K_1/k_{-1}{}^-$ (dm^3 mol^{-1})	3.1(1)	1.0(0.31)	2.6(0.84)
	K_1k_{Am}/ (dm^6 mol^{-2} s^{-1})	7.2×10^{-5}(1)	5.4×10^{-4}(7.5)	3.8×10^{-3}(52)
2d	K_1/ (dm^3 mol^{-1} s^{-1})	5.0×10^{-5}(1)	5.7×10^{-4}(11)	5.0×10^{-3}(100)
	$k_{Am}/k_{-1}{}^-$ (dm^3 mol^{-1})	20	0.86 (0.043)	5.4 (0.27)
	K_1k_{Am}/ (dm^6 mol^{-2} s^{-1})	1.0×10^{-3}	4.9×10^{-4} (0.49)	2.7×10^{-2} (27)
3a	K_1/ (dm^3 mol^{-1} s^{-1})	8.9×10^{-3}(1)	0.52(58)	1.3(146)
3b	K_1/ (dm^3 mol^{-1} s^{-1})	1.53×10^{-2}(1)	2.3×10^{-2}(1.5)	5.5×10^{-2}(3.4)
3c	K_1/ (dm^3 mol^{-1} s^{-1})	4.9×10^{-3}(1)	0.16(33)	0.37(76)
	$k_{Am}/k_{-1}{}^-$ (dm^3 mol^{-1})	–	5.0	70
	K_1k_{Am}/ (dm^6 mol^{-2} s^{-1})	–	0.8	26
3d	k_1/ (dm^3 mol^{-1} s^{-1})	4.7×10^{-2}(1)	–	0.024(0.51)
	$k_{Am}/k_{-1}{}^-$ ($dm^3 mol^{-1}$)	–	–	3.5
	K_1k_{Am}/ (dm^6 mol^{-2} s^{-1})	–	1.1×10^{-3}	0.083
	K_1k_2/ (dm^3 mol^{-1} s^{-1})	–	5.7×10^{-3}	–

[a] Values in parentheses are the reactivities for a given compound relative to that for *n*-butylamine; i.e. k_1 (pyrrolidine)/k_1(*n*-butylamine) and k_1(piperidine)/k_1(*n*-butylamine).

[b] Values from [6].

observation of their homoconjugation with the parent amines.

$$R^1R^2\overset{+}{N}H_2 + R^1R^2NH_2 \rightleftharpoons R^1R^2\overset{+}{N}H_2 \cdots\cdots NHR^1R^2$$

Such interaction is not observed in DMSO.

The first step in adduct formation from neutral molecules is zwitterionic formation, and this involves the production of charges. It has long been recognized that the rates of reactions involving the formation of extensively ionic transition state from uncharged molecules are strongly solvent dependent [26]. DMSO is much better than acetonitrile at solvating charged polarizable species such as the zwitterions. For any adduct-forming reaction a 4-nitro group in **2a(c)** has been shown to be more stabilizing than a 2-nitro group in **2b(d)** by ca. 6 kJ. Previous kinetic results have confirmed that the transition state for ortho substitution is less extensively solvated than the transition for para substitution [2,16].

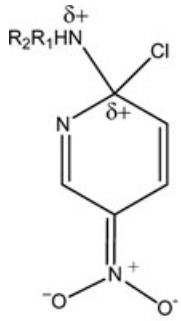
The higher reactivity of **2a** over **2b** in DMSO may have arisen from the absence of steric hindrance in **2a** and the greater solvation of the para-like than the ortho-like quinoniod structures **7** and **8**, respectively. Intramolecular hydrogen bonding to the o-nitro group or ring nitrogen is less significant since the -NH_2^+ proton will be strongly hydrogen bonded to the solvent as depicted in structures **9** and **10**.

Similar reactivity pattern (**2a** > **2b**) observed in methanol [2c] for the reactions of piperidine and of morpholine with these substrates was interpreted along similar lines. In methanol, a polar hydroxylic solvent, hydrogen bond is relatively weak, and the intermediates, because they are zwitterionic in character, are extensively solvated; the para-like quinoniod structure **7** being more solvated than the ortho-like quinonoid structure **8**.

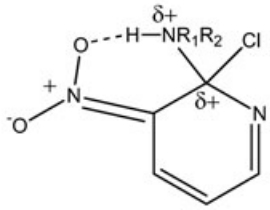
The reversed order **2b** > **2a** observed in benzene in the reactions of piperidine and morpholine was rationalized in terms of strong intramolecular hydrogen bonding between the ammonium hydrogen, and the *ortho*-nitro group in the intermediate. Benzene is a nonpolar solvent, quite incapable of solvating charged species like the zwitterionic intermediate. With a smaller number of electron-withdrawing groups to share the negative charge in the molecule, the intrahydrogen bond may be strong enough to overwhelm the steric effect of the nitro group and, therefore, reverse the order of reactivity.

Base Catalysis

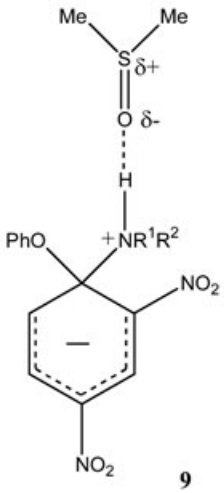
Base catalysis, as argued previously in the reactions with aliphatic amines of some phenyl aryl ethers in DMSO and in acetonitrile, is indicative of RLPT from the zwitterionic intermediate to the base in contrast to general acid catalysis by BH^+ of the leaving group departure. The latter, the SB–GA mechanism, has been shown to apply to substrates such as alkyl ethers carrying poor leaving groups [11,27–29]. There



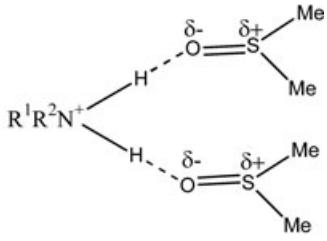
7



8



9



10

is now good evidence that in trinitro-activated substrates the ratio of k_{Am}/k_{Am+H} will have a value of ca. 500, reflecting the higher acidities of the zwitterionic adducts than of the corresponding ammonium ions [4,13]. The ratio is not expected to vary greatly with the nature of the substrate or the amine. Hence, k_{Am} represents a thermodynamically favorable proton transfer between nitrogen atoms and its value may approach the diffusion limit, but is known to be strongly influenced by steric constraints rather than basicity considerations [30–33]. Values are, therefore, considerably decreased by steric considerations around the 1-position and have been found to decrease in the order *n*-butylamine (3×10^7 dm^3 mol^{-1} s^{-1}) > pyrrolidine (1.5×10^6 dm^3 mol^{-1} s^{-1}) > piperidine (1.4×10^5 dm^3 mol^{-1} s^{-1}). These reductions have the effect of changing the nature of the rate-limiting step in S_NAr reactions. The susceptibility of such reactions to base catalysis depends on the value of k_{Am}/k_{-1}. If at a given amine concentration $k_{Am} \gg k_{-1}$, then base catalysis is not observed. This is the situation that applies to our measurements with *n*-butylamine as the nucleophile in acetonitrile. This is likely to be a consequence of the relative high values of k_{Am} (the rate constant for proton transfer) and low values of k_{-1}. The only exception is the reaction with **2c**, where base catalysis was observed. Interestingly no catalysis was detected by this amine in its reaction with **2d**, reminiscent of the drastic increase observed in the value of k_2/k_{-1} ratio on moving the nitro group to the 2-position in the reaction with piperidine in benzene of 4- and 2-nitrofluorobenzene [21]. This has been rationalized by Bernasconi [34,35] by assuming that in general hydrogen bonding decreases k_{-1} more effectively than it does k_2 and the discrepancy between the two is magnified when the hydrogen bond is strong. This is likely to be the case in acetonitrile where there are only a few electron-withdrawing groups in the molecule to delocalize the negative charge. There is, therefore, a shift from the condition $k_{Am} \ll k_{-1}$ to $k_{Am} \gg k_{-1}$ as the substrate is changed from **2c** to **2d**.

The reactions of the phenoxy compounds in acetonitrile with secondary amines, pyrrolidine and piperidine, gave evidence for base catalysis. Rate constants in Table V show rate dependence between first and second order on the amine concentration. This is consistent with the proton transfer step being partially rate limiting. As noted earlier [6], the only system in acetonitrile where the uncatalyzed decomposition pathway makes significant contribution to the reaction flux is the reaction of **3d** with piperidine. Here the plot of k_A against piperidine concentration is linear with definite intercept. The k_2 step is likely to involve intramolecular proton transfer within the zwitterionic adduct **4** coupled with the movement of electrons away from the anionic ring. This, in addition to the relative low value expected for k_{Am} for reactions involving piperidine (as compared with pyrrolidine) allows

Table VI Summary of Kinetic Pattern for Reaction of **2** and **3** with Aliphatic Amines in Acetonitrile at 25°C

Subtrate/ Amine	2c	2d	3c	3d
Pyrrolidine	Catalyzed, curvilinear, no intercept	Catalyzed, curvilinear, no intercept	Catalyzed, curvilinear, no intercept	Catalyzed, curvilinear, no intercept
Piperidine	Catalyzed, curvilinear, no intercept	Catalyzed, curvilinear, no intercept	Catalyzed, curvilinear, no intercept	Catalyzed, linear with intercept

competition of the uncatalyzed with the catalyzed pathway. An additional factor that may be considered is the intramolecular hydrogen bonding in the zwitterionic intermediate **4** between the ammonio proton and the oxygen atom of the nitro group. The presence of such hydrogen bonding, affecting the proton to be transferred, is often used as an argument to explain the differences in reactivity between primary and secondary amines. In the case of primary amine, there will be one nonhydrogen-bonded proton available for transfer, resulting in greater reduction in k_{Am}/k_{-1} ratio for secondary compared to primary amine. However, previous studies [3,7,12] involving strongly activated substrates with severe steric congestion at the reaction centers have not found evidence for such hydrogen bonding. In those systems, the bulk of the negative charge is delocalized into the trinitro-substituted ring, thus lowering the electron density on the oxygen atoms of the nitro group. Consequently, the strength of the hydrogen bond they form with an ammonio proton in the zwitterionic complex is drastically reduced. Steric factors alone that lead to the decreases in the values of k_{Am} in the series *n*-butylamine, pyrrolidine, and piperidine were invoked to explain the observed reactivity pattern.

For the system studied in the present investigation, the hydrogen bond formed between the N–H proton and the *ortho*-nitro group is expected to be strong due to the relatively higher electron density on the oxygen of the *ortho*-nitro group since there are a few electron-withdrawing groups to carry the negative charge in the molecule. This factor may be potent enough to be used as an argument to explain the dichotomy in the behavior of primary and secondary amines.

In DMSO, the reactions of **2c**, **3c**, and **3d** with *n*-butylamine together with the reactions of **2c** with pyrrolidine are not base catalyzed, whereas their reactions with piperidine are catalyzed. The kinetic forms of the base-catalyzed reactions in both DMSO and acetonitrile are displayed in Tables VI and VII. For the reaction in DMSO of **3c** with pyrrolidine, the plot of the second-order rate constants k_A against nucleophile concentration has a curvilinear dependence on nucleophile concentration and pass through the origin. With piperidine as nucleophile, such plot has a small intercept indicating that, the uncatalyzed conversion of the zwitterion to product, the k_2 step, contributes significantly to the reaction flux. In the case of the reactions of piperidine with **2c** and **3d**, the plot of k_A against piperidine concentration is linear with definite intercept.

The reaction between **2c** and pyrrolidine in acetonitrile is subject to base catalysis, whereas in DMSO, catalysis is not detected. Hence in these systems, there is a change of mechanism from deprotonation of the zwitterionic intermediate being the rate-limiting step to its formation constituting the rate-limiting step of the reaction induced by a change of solvent. In terms of mechanism of Scheme 1, the change is equivalent to a change from the kinetic form condition $k_{-1} \gg k_{Am}$ to $k_{-1} \ll k_{Am}$. This result can be understood, if in DMSO the catalyzed pathway involves the deprotonation of the intermediate by solvent molecule. This pathway will not be favored in the less basic solvent, acetonitrile, as there is ca. 10^8-fold difference in the basicities of DMSO and acetonitrile. In addition, k_{-1} would be expected to be greater in acetonitrile than in DMSO because of the former inability to solvate cations [24,25].

Table VII Summary of Kinetic Pattern for Reaction of **2** and **3** with Aliphatic Amines in DMSO at 25°C

Subtrate/ Amine	2c	2d	3c	3d
Pyrrolidine	Not base catalyzed	–	Curvilinear, no intercept	–
Piperidine	Catalyzed, linear with intercept	–	Catalyzed, curvilinear with intercept	Catalyzed, linear with intercept

CONCLUSION

Our study reveals that in reactions in which steric effects are likely to be unimportant a 6-nitro group is more activating than an aza function. The order is, however, reversed if there is severe congestion around the reaction center. Despite the differences in the electron-withdrawing ability and the steric requirements of these substituents, the mechanism of the reaction of the pair **2c**, **3c,** and the pair **2b**, **3d** is not dramatically altered. In acetonitrile, reactions with *n*-butylamine are not base catalyzed. The only exception is the reaction with **2c** where proton transfer is partially rate limiting. This mechanism was also observed in the reactions with pyrrolidine and piperidine. It is only in the reaction of **3d** with piperidine that a plot of k_A versus amine concentration is linear with intercept.

For all the reactions with *n*-butylamine in DMSO, nucleophilic attack is rate limiting. The reaction of pyrrolidine with **2c** in acetonitrile is not base catalyzed whereas that in DMSO is catalyzed, an example of a change in the rate-limiting step of an S_NAr reaction induced by a change of solvent. With piperidine, there is a shift from condition $k_{-1} \gg k_2 + k_3[B]$ to $k_{-1} \approx k_2 + k_3[B]$ as the substrate is changed from **2c** to **3c**.

In acetonitrile, the $k_1^{3-NO_2}/k_1^{5-NO_2}$ is greater than unity, due to intramolecular hydrogen bonding between the ammonium hydrogen and the *ortho*-nitro group. The sequence is reversed in DMSO due to extensive solvation of the zwitterionic intermediate, the para-like quinonoid structure being more solvated than the ortho-like structure.

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