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Kinetic and equilibrium studies of σ-adduct formation and nucleophilic substitution in the reactions of 2-phenoxy-3,5-dinitropyridine and 2-ethoxy-3,5-dinitropyridine with aliphatic amines in dipolar aprotic solvents †

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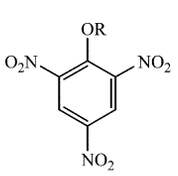
Received 29th November 2002, Accepted 28th January 2003
First published as an Advance Article on the web 20th February 2003

The reactions of aliphatic amines with 2-phenoxy-3,5-dinitropyridine, **4**, and 2-ethoxy-3,5-dinitropyridine, **5**, in DMSO result in the rapid reversible formation of anionic σ-adducts at the 6-position. Kinetic studies show that proton transfer from the initially formed zwitterions to base may be rate-limiting. Slower reactions result, except in the case of **5** and piperidine, in displacement of the 2-substitutent *via* intermediates which have lower thermodynamic stabilities than their 6-isomers.

Base catalysis of the substitution process is attributed in the case of **4** to rate-limiting proton transfer from zwitterionic intermediates, but in **5** to acid catalysis of ethoxide departure (SB-GA mechanism). X-Ray crystallography of **5** shows a planar non-strained structure although the structure of 2-piperidino-3,5-dinitropyridine, **10c**, shows distortion resulting from steric interactions of the 2- and 3-substituents. Kinetic and equilibrium results are compared with those for related reactions of the more sterically strained 2,4,6-trinitrobenzene derivatives.

Results for the reactions of **4** and **5** with pyrrolidine in three dipolar aprotic solvents are compared. Values of equilibrium constants for σ-adduct formation decrease in the order DMSO > DMF ≫ Acetonitrile, while values of rate constants for proton transfer are in the reverse order.

The reactions of alkyl 2,4,6-trinitrophenyl ethers **1** with nucleophiles to give σ-adducts are well documented.[1–3] The usual pattern is the initial formation of adducts at the 3-position under kinetic control followed by isomerisation to give the thermodynamically more stable adducts at the 1-position. That the relative stabilities of 1-adducts may be *ca.* 10^4 times that of the corresponding 3-adducts has been attributed to the relief of steric strain in **1** accompanying reaction at the 1-position, together with the stabilising effects of di-alkoxy substitution at an sp^3-hybridised carbon atom. That attack at the 3-position is faster is thought to be due to the lower F-strain associated with attack at an unsubstituted position relative to attack at a substituted position, and to the possibility of partially conserving the resonance interaction present in **1** between the alkoxy group and the nitro-groups in the transition state for attack at the 3-position but not at the 1-position.[1–4]



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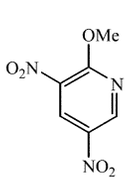

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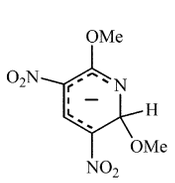

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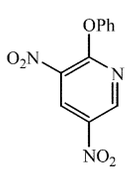
There have been few studies involving the reactions of 2-alkoxy-3,5-dinitropyridines, but intriguingly it has been reported that reaction of the 2-methoxy compound, **2**, with methoxide yields the σ-adduct, **3**, as the kinetically and thermodynamically preferred product.[5–7] Consequently the adduct at the 2-position has not been observed. This switch in reactivity pattern compared to **1** confirms the importance of steric effects, and their relief, in directing the course of σ-adduct formation.

Here we report on the reactions of 2-phenoxy-3,5-dinitropyridine **4** and of 2-ethoxy-3,5-dinitropyridine **5** with aliphatic amines in dipolar aprotic solvents. Most results refer to dimethyl sulfoxide (DMSO) but comparison is made with results in acetonitrile and in dimethylformamide. As with methoxide initial attack is at the 6-position, however, the use of amine nucleophiles allows the slower attack at the 2-position, leading to irreversible substitution, to be investigated. There have been no previous reports of the reactions of the alkyl ethers **2** or **5** with amines but kinetic studies have reported base catalysis in the amino-dephenoxylations of **4** in acetonitrile,[8] benzene,[9] and methanol.[10] There is current interest in the mechanism of such catalysis. Studies with trinitro-activated substrates have established that base catalysis may indicate rate-limiting proton-transfer from a zwitterionic intermediate to yield an anionic intermediate. Alternatively it may indicate general acid catalysis of leaving group departure in the SB-GA mechanism of substitution.[3,11–14] Our results provide evidence of both these pathways in reactions of the dinitropyridyl ethers.



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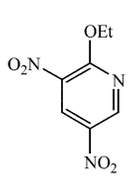

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Results and discussion

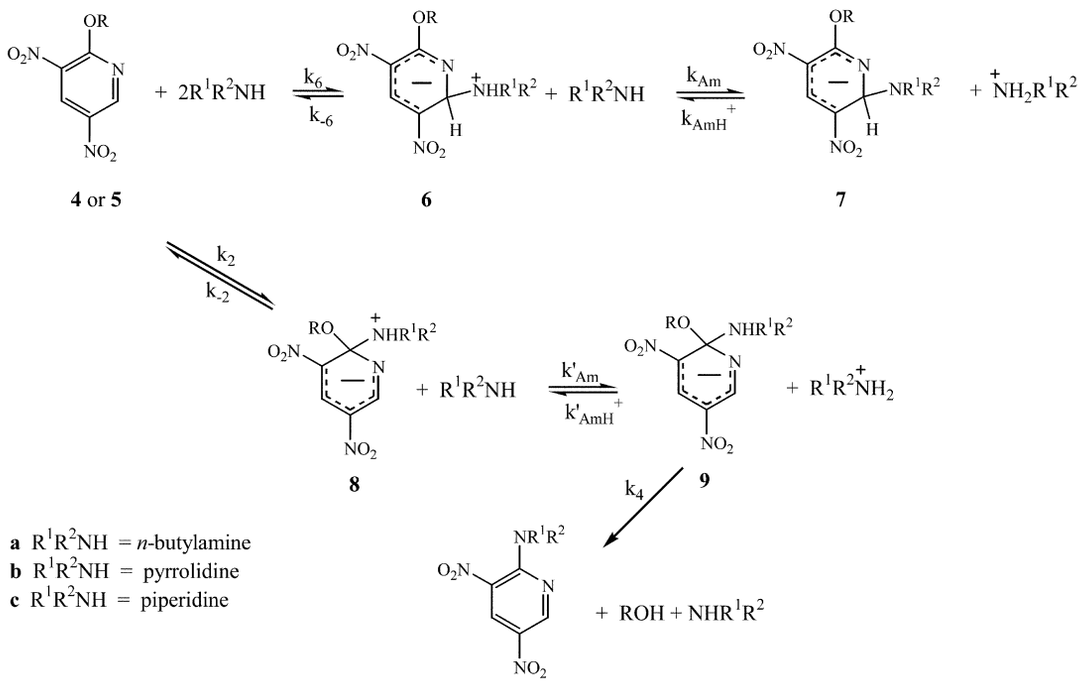
The UV–visible spectra of the phenoxy ether, **4**, in DMSO containing *n*-butylamine, pyrrolidine or piperidine showed that the initial reactions produced species absorbing strongly at 490–495 nm. This absorption rapidly faded to give spectra which were

† Electronic supplementary information (ESI) available: Tables 10–15. See http://www.rsc.org/suppdata/ob/b2/b211639c/

DOI: 10.1039/b211639c

Table 1 Spectroscopic data for reactants, products and intermediates in DMSO

	δ			UV absorbance	
	H4	H6	2-substituent	λ_{max}/nm	$\varepsilon/10^4$ dm^3 mol^{-1} cm^{-1}
4	9.14	9.14	7.2–7.6(5H)	290	1.05
5	9.34	9.11	4.63(OCH_2), 1.38(CH_3)	290	1.1
10a	9.27	8.94	9.3(NH), 3.65, 1.60 1.33(CH_2), 0.88(CH_3)	345	1.3
10b	9.08	8.83	3.58(4H), 1.70(4H)	363	1.8
10c	9.11	8.82	3.54(4H), 1.62(6H)	368	1.9
7b, R=Et	8.45	5.69	4.1(OCH_2), 1.2(CH_3)	498	2.4
7c, R=Et	8.52	5.50	4.1(OCH_2), 1.2(CH_3)	495	2.4



a R^1R^2NH = *n*-butylamine
b R^1R^2NH = pyrrolidine
c R^1R^2NH = piperidine

Scheme 1

identical to those of the expected substitution products, **10a**–**c**, in the same medium. The reactions of the ethoxy ether, **5**, with *n*-butylamine and with pyrrolidine were similar to those of **4**, although the initial products, λ_{max} 495–498 nm, were much longer lived. However, in the reaction of **5** with piperidine the initial product, λ_{max} 495 nm, was stable for several hours and the slow fading process did not yield **10c**.

Spectroscopic data for reactants and products are in Table 1. In the case of the reactions of **5** with piperidine and pyrrolidine it was possible to record ^{1}H NMR spectra for the initially produced species. These show resonances at *ca.* δ 5.6 and 8.5 due to ring hydrogens consistent with nucleophilic attack at the unsubstituted 6-position to yield adducts of type **7**. The large shift to lower frequency of H6 is consistent with the change to sp^3 hybridisation associated with reaction at this position.[1–3] The observed spectra are not consistent with the observation of adducts **9** formed by reaction at the 2-position, but might be compatible with adducts formed by attack at the 4-position. However, this possibility is rendered unlikely both by analogy with methoxide attack on **2** which is known,[5,6] from the use of the 6-deuterio labelled derivative, to give **3**, and by the knowledge[1–3] that a *para*-aza function is far less stabilising in σ-adduct forming reactions than a *para*-nitro group. Hence our results are interpreted in terms of Scheme 1.

Kinetic study of these reactions showed the presence of two processes well separated in time. The more rapid process, observable by stopped-flow spectrophotometry, is attributed to equilibration of reactants with **7**, while the slower process yields the substitution product, **10**. In the presence of high amine concentrations the products, **10**, were themselves found, as mentioned later, to be in rapid equilibrium with their 6-amino adducts. It is worth noting that adducts **9**, with lower thermodynamic stabilities than their isomers **7**, will not be observable in the substitution process even though they may be reaction intermediates.

Rate constants were measured under first order conditions. For reactions with buffers (amine plus amine salt) the buffer components were in large excess of the substrate concentration, which was usually 5×10^{-5} mol dm^{-3}. For adduct formation in the absence of added salt, sufficient excess of amine was used to ensure that >95% conversion was achieved, thus isolating the forward reaction. Making the assumption that the zwitterionic form **6** may be treated as a steady state intermediate leads[12,14,15] to eqn. (1) for the general rate expression for equilibration between reactants and **7**. When $k_{Am}[Am] \gg k_{-6}$, corresponding to rapid proton transfer, eqn. (1) reduces to eqn. (2). The

$$k_{fast} = \frac{k_6 k_{Am}[Am]^2}{k_{-6} + k_{Am}[Am]} + \frac{k_{-6} k_{AmH^+}[AmH^+]}{k_{-6} + k_{Am}[Am]} \quad (1)$$

$$k_{fast} = k_6[Am] + \frac{k_{-6} k_{AmH^+}}{k_{Am}} \frac{[AmH^+]}{[Am]} \quad (2)$$

Table 2 Kinetic results for reaction of **4** with *n*-butylamine in DMSO at 25 °C

[*n*-Butylamine]/mol dm^{-3}	[*n*-Butylammonium perchlorate]/mol dm^{-3}	k_{fast} [a]/s^{-1}	k_{slow} [b]/s^{-1}	k_{calc} [c]/s^{-1}
0.006	0	91	—	—
0.008	0	110	—	—
0.010	0	130	—	—
0.002	0.001	—	0.017	0.016
0.005	0.001	—	0.038	0.033
0.010	0.001	—	0.049	0.044
0.020	0.001	—	0.036	0.038
0.003	0.010	—	0.023	0.024
0.005	0.010	—	0.038	0.039
0.010	0.010	—	0.073	0.074
0.020	0.010	—	0.123	0.121
0.040	0.010	—	0.137	0.140

[a] Measured as a colour forming reaction at 495 nm. [b] Measurement as a colour forming reaction at 345 nm or 405 nm gave identical results. [c] Calculated from eqn. (7) with k_2 8 dm^3 mol^{-1} s^{-1} and $K_{c,6}$ 8 dm^3 mol^{-1}.

other limiting form, when $k_{-6} \gg k_{Am}$ [Am], corresponds to rate limiting proton transfer and is given by eqn. (3), where $K_6 = k_6/k_{-6}$. The stoichiometric equilibrium constant for formation of the 6-adducts, **7**, is defined by eqn. (4).

$$k_{fast} = k_6 k_{Am}[Am]^2 + k_{AmH^+}[AmH^+] \quad (3)$$

$$K_{c,6} = \frac{[7][AmH^+]}{[Parent][Am]^2} = \frac{k_6}{k_{-6}} \times \frac{k_{Am}}{k_{AmH^+}} \quad (4)$$

The rate expression for the irreversible substitution reaction is eqn. (5), which may be written as eqn. (6) where $K_2 = k_2/k_{-2}$. The limiting forms are eqn. (7) when $k_B[Am] \gg k_{-2}$, and eqn. (8) when $k_{-2} \gg k_B[Am]$. Here k_B is the rate constant representing the base catalysed conversion of the zwitterion **8** to product. The significance of k_B depends on the mechanism of base catalysis. When proton transfer from **8** to give **9** is rate limiting then $k_B \equiv k'_{Am}$, while in the case of rate limiting acid-catalysed loss of alkoxide (SB-GA mechanism) $k_B = k'_{Am} k_4/k'_{AmH^+}$. It should be noted that values of rate constants for proton transfer will vary depending on the ring position at which attack has occurred. Hence $k_{Am} \neq k'_{Am}$ and $k_{AmH^+} \neq k'_{AmH^+}$.

$$k_{slow} = \frac{k_2 k_B[Am]^2}{k_{-2} + k_B[Am]}\left(\frac{1}{1+\frac{K_{c,6}[Am]^2}{[AmH^+]}}\right) \quad (5)$$

$$k_{slow} = \frac{K_2 k_B[Am]^2}{1+\frac{k_B}{k_{-2}}[Am]}\left(\frac{1}{1+\frac{K_{c,6}[Am]^2}{[AmH^+]}}\right) \quad (6)$$

$$k_{slow} = k_2[Am]\left(\frac{1}{1+\frac{K_{c,6}[Am]^2}{[AmH^+]}}\right) \quad (7)$$

$$k_{slow} = K_2 k_B[Am]^2\left(\frac{1}{1+\frac{K_{c,6}[Am]^2}{[AmH^+]}}\right) \quad (8)$$

Results in DMSO

The kinetic data in Table 2 indicate that in the reaction of **4** with *n*-butylamine nucleophilic attack is rate limiting in both the formation of adduct **7a** and in nucleophilic substitution. In the absence of added salt values of k_{fast} increase linearly with *n*-butylamine concentration giving, from eqn. (2), a value for k_6 of 1.5 × 10^4 dm^3 mol^{-1} s^{-1}. Values of k_{slow} for the substitution process accord with eqn. (7) with k_2 8 dm^3 mol^{-1} s^{-1} and $K_{c,6}$ 8 dm^3 mol^{-1}. The same values were obtained for these parameters at both 10^{-3} and 10^{-2} mol dm^{-3} salt concentration, indicating the absence of major salt effects.

In contrast the results in Table 3 for the formation of **7c** from **4** and piperidine show that proton transfer is rate-limiting so that the data are fitted by eqn. (3) with K_6k_{Am} 6.6 × 10^5 dm^6 mol^{-2} s^{-1} and k_{AmH^+} 2.5 × 10^4 dm^3 mol^{-1} s^{-1}. Combination of these values gives $K_{c,6}$ 26 dm^3 mol^{-1}. Proton transfer is partially rate limiting in the substitution reaction and the data require the use of eqn. (6) with K_2k_B 1200 dm^6 mol^{-1} s^{-1}, k_B/k_{-2} 12 dm^3 mol^{-1} and $K_{c,6}$ 26 dm^3 mol^{-1}. Combination of the former two values yields k_2 100 dm^3 mol^{-1} s^{-1}.

A situation intermediate between *n*-butylamine and piperidine is encountered in reaction of **4** with pyrrolidine. Here proton transfer is rate limiting in the formation of **7b**, with K_6k_{Am} 1.4 × 10^7 dm^6 mol^{-1} s^{-1} and k_{AmH^+} 4 × 10^5 dm^3 mol^{-1} s^{-1}, and nucleophilic attack is rate limiting in the substitution reaction, with k_2 146 dm^3 mol^{-1} s^{-1}. Data here are given in Table 10 as supplementary information.†

Results for reaction of **5**, the ethyl ether, with *n*-butylamine are in Table 4. The rapid reaction forming **7a**, is at the limit of measurement by the stopped-flow method. Data are consistent with rate limiting nucleophilic attack, eqn. (2), and yield approximate values for k_6 7000 dm^3 mol^{-1} s^{-1} and k_{-6} k_{AmH^+}/k_{Am} 8000 s^{-1}. Combination of these values gives $K_{c,6}$ 0.9 dm^3 mol^{-1}. The substitution reaction differs from the corresponding reaction of **4** in that base catalysis is observed and the data are fitted by eqn. (6). The values required for optimum fit are given at the foot of Table 4. They vary slightly with salt concentration, but yield a value of k_2 of 5 ± 1 dm^3 mol^{-1} s^{-1}.

The results (Table 11, supplementary information†) for the reaction of **5** with pyrrolidine show that in the formation of **7b** proton transfer is rate limiting. The value of K_6k_{Am} is 5 × 10^6 dm^6 mol^{-1} s^{-1} and equilibrium constant $K_{c,6}$ has the value 2.4 dm^3 mol^{-1}. Combination of these values gives k_{AmH^+} 2 × 10^6 dm^3 mol^{-1} s^{-1}. Proton transfer is also rate limiting in the substitution reaction with K_2k_B 3.3 dm^6 mol^{-2} s^{-1}.

The formation of **7c** from **5** and piperidine follows the pattern of the reaction with pyrrolidine. The results (Table 12, supplementary in formation†) yield K_6k_{Am} 2 × 10^5 dm^3 mol^{-1} s^{-1} and $K_{c,6}$ 1.6 dm^{3}mol^{-1}. Combination of these values gives k_{AmH^+} 1.2 × 10^5 dm^3 mol^{-1} s^{-1}. However, the fading reaction is

Table 3 Kinetic results for the reaction of **4** with piperidine in DMSO at 25 °C

[piperidine]/mol dm^{-3}	[piperidine perchlorate]/mol dm^{-3}	k_{fast} [a]/s^{-1}	k_{calc} [b]/s^{-1}	k_{slow} [c]/ 10^{-2} s^{-1}	k_{calc} [d]/ 10^{-2} s^{-1}
0.008	0	46	42	—	—
0.010	0	65	66	—	—
0.020	0	260	260	—	—
0.030	0	600	600	—	—
0.004	0.01	—	—	1.6	1.7
0.005	0.01	—	—	2.6	2.6
0.008	0.01	—	—	6.1	6.0
0.010	0.01	330	320	9.4	8.5
0.020	0.01	520	510	20	19
0.030	0.01	(840)	(850)	24	24
0.040	0.01	—	—	24	25

[a] Colour forming process at 495 nm. [b] Calculated from eqn. (3) with K_6k_{Am} 6.6 × 10^5 dm^6 mol^{-2} s^{-1} and k_{AmH^+} 2.5 × 10^4 dm^3 mol^{-1} s^{-1}. [c] Colour forming process at 368 nm. [d] Calculated from eqn. (6) with K_2k_B 1200 dm^6 mol^{-2} s^{-1}, k_B/k_{-2} 12 dm^3 mol^{-1} and $K_{c,6}$ 26 dm^3 mol^{-1}.

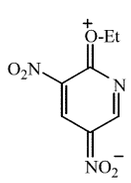
Table 4 Kinetic results for reaction of **5** with *n*-butylamine in DMSO at 25 °C

[*n*-Butylamine]/ mol dm^{-3}	[*n*-Butylammonium perchlorate]/mol dm^{-3}	k_{fast} [a]/s^{-1}	k_{calc} [b]	k_{slow} [c]/10^{-2} s^{-1}	k_{calc} [d]/10^{-2} s^{-1}
0.020	—	150	140	—	—
0.050	—	300	350	—	—
0.10	—	500	700	—	—
0.001	0.001	—	—	0.13	0.13
0.002	0.001	—	—	0.42	0.41
0.005	0.001	—	—	1.6	1.6
0.010	0.001	(820)	(820)	3.4	3.9
0.020	0.001	600	550	6.6	7.3
0.040	0.001	600	500	8.8	9.2
0.10	0.001	700	800	7.1	6.1
0.001	0.01	—	—	0.098	0.095
0.002	0.01	—	—	0.31	0.31
0.005	0.01	—	—	1.3	1.3
0.010	0.01	—	—	3.0	3.1
0.020	0.01	—	—	6.8	7.0
0.040	0.01	—	—	14	14

[a] Colour forming reaction at 495 nm. [b] Calculated from eqn. (2) with k_6 7000 dm^3 mol^{-1} s^{-1} and $k_{-6}k_{AmH^+}/k_{Am}$ 8000 s^{-1}. [c] Colour forming process at 345 nm. [d] Results at 0.001 mol dm^{-3} salt calculated from eqn. (6) with K_2k_B 1600 dm^6 mol^{-2} s^{-1}, k_B/k_{-2} 280 dm^3 mol^{-1} and $K_{c,6}$ 0.8 dm^3 mol^{-1}; results at 0.01 mol dm^{-3} salt with K_2k_B 1200 dm^6 mol^{-2} s^{-1}, k_B/k_{-2} 280 dm^3 mol^{-1} and $K_{c,6}$ 1.0 dm^3 mol^{-1}.

extremely slow, and does not, from the NMR evidence, yield the expected substitution product.

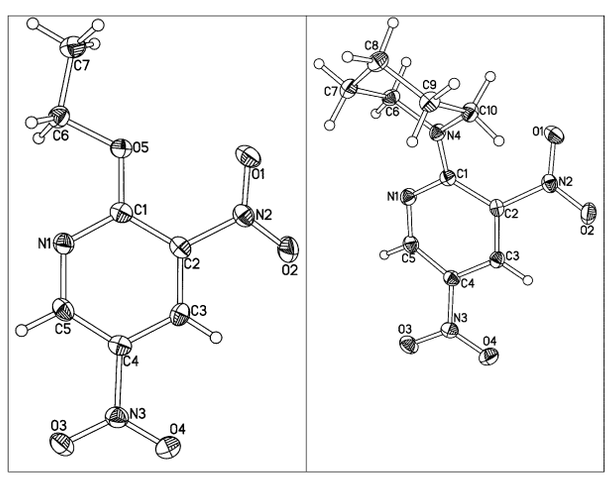
Before discussing the kinetic data it is useful to consider X-ray crystal structures, which have been determined for the reactant **5** and the substitution product with piperidine, **10c**. The structure of **5**, shown in Fig. 1a, indicates a nearly planar molecule with the ethoxy group *syn* to the ring nitrogen. The nitro-group at the *ortho* position shows only a small degree of twisting, 13°, from the ring plane and there is evidence from the shortened 05–C1 (1.319Å) and C2–C3 (1.375Å) bond lengths for conjugation between ethoxy and nitro groups as shown in **11**. There is similarly evidence for a relatively unstrained molecule in the corresponding methyl ether.[16]



11

In contrast the structure of **10c**, shown in Fig. 1b, indicates considerable deformation of the ring, with deviations from planarity of *ca* 20°. The *ortho*-nitro group is twisted by 30° indicating considerable steric interaction with the adjacent piperidyl group.

In all cases attack by amine at the unsubstituted 6-position



a b

Fig. 1 X-Ray crystallographic structures of a) **5** and b) **10c**.‡

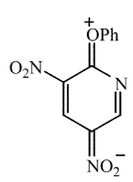
was a faster process than at the substituted 2- position. The kinetic results obtained in DMSO are summarised in Table 5. In the case of n-butylamine the ratio of rate constants k_6/k_2 is 2000 for **4** and 8000 for **5**. An important factor here is likely to be the stabilisation of reactants by cross-conjugation between

‡ CCDC reference numbers 198285–198286. See http://www.rsc.org/suppdata/ob/b2/b211639c/ for crystallographic data in .cif or other electronic format.

Table 5 Summary of rate and equilibrium data for reaction of **4** and **5** with amines in DMSO at 25 °C

Amine	**4**	**5**
n-Butylamine		
k_6/dm^3 mol^{-1} s^{-1}	1.5×10^4	7×10^3
$K_{c,6}$/dm^3 mol^{-1}	8	0.9
k_2/dm^3 mol^{-1} s^{-1}	8	5
K_2k_B/dm^6 mol^{-2} s^{-1}	—	1400
k_B/k_{-2} dm^3 mol^{-1}	—	280
Pyrrolidine		
$K_{c,6}$/dm^3 mol^{-1}	40	2.4
K_6k_{Am}/dm^6 mol^{-2} s^{-1}	1.4×10^7	5×10^6
k_{AmH^+}/dm^3 mol^{-1} s^{-1}	4×10^5	2×10^6
k_2/dm^3 mol^{-1} s^{-1}	146	—
K_2k_B/dm^6 mol^{-2} s^{-1}	—	3.3
Piperidine		
$K_{c,6}$/dm^3 mol^{-1}	26	1.6
K_6k_{Am}/dm^6 mol^{-2} s^{-1}	6.6×10^5	2×10^5
k_{AmH^+}/dm^3 mol^{-1} s^{-1}	2.5×10^4	1.2×10^5
k_2/dm^3 mol^{-1} s^{-1}	100	—
K_2k_B/dm^6 mol^{-2} s^{-1}	1200	—
k_B/k_{-2} dm^3 mol^{-1}	12	—

the ethoxy- and nitro-group[4,17] as shown in **11**, or phenoxy- and nitro-group as shown in **12**. Such stabilisation will be lost on attack at the 2-position but may be partially conserved when attack occurs at the 6-position. The higher reactivity ratio for **5** than for **4** is consistent with somewhat greater stabilisation expected[17] in **11** than in **12**.



12

A further factor favouring attack at the 6-position is the lower F-strain associated with nucleophilic attack at an unsubstituted ring position relative to attack at an atom carrying an electronegative substituent.[18,19] Also, the absence of steric strain around the 2-position in the reactant molecules **4** and **5** means that there is little energy to be gained from its relief. All these factors result in the 6-adducts being preferred, both kinetically and thermodynamically, to the 2-adducts. This contrasts with the behaviour of 1-ethoxy-2,4,6-trinitrobenzene, **1**, R = Et, where there are considerable steric interactions around the 1-position.[20] Here the ratio of k_3 : k_1 of rate constants for attack by *n*-butylamine at the unsubstituted 3-position and the 1-position is only 13, while the relief of steric strain resulting from adduct formation at the 1-position results[12] in a value for the ratio of equilibrium constants $K_{c,1}$: $K_{c,3}$ of 3×10^4.

Values of $K_{c,6}$ for formation of adducts **7a**,**b**,**c** are between 15 and 30 times lower than values for $K_{c,3}$ corresponding to reaction of the three amines at the unsubstituted 3-position of 1-ethoxy-2,4,6-trinitrobenzene.[12,14] This indicates that here the *ortho*-aza function is rather less activating than on *ortho*-nitro group, although the difference is not large. Similar values have been reported[7] for equilibrium constants for the reactions of methoxide in methanol at unsubstituted ring positions in **2** and in **1**, R = Me.

The results in Table 5 show that the ratio of $K_{c,6}$ values for **4** and **5** varies between 9 and 16 for the three amines studied. That the values for **5** are lower than for **4** is attributed to the greater ground state stabilisation in the ethyl ether, referred to earlier, which is progressively lost on passage to the transition state and to the anionic adduct. Comparison of data for the three amines shows that values of $K_{c,6}$ and also of k_2 fall in the order pyrrolidine > piperidine > *n*-butylamine which is the usual order in reactions involving nucleophilic attack.[12–15]

Base catalysis

In the reactions forming the σ-adducts **7**, R = Ph and **7**, R = Et, from **4** and **5** respectively, nucleophilic attack is rate limiting when the amine is *n*-butylamine but proton transfer is rate limiting with pyrrolidine and piperidine. A similar situation applies[12,13] in reactions of the corresponding trinitro-compounds **1** R = Ph, and **1**, R = Et. In these reactions, involving strongly activated substrates, the proton-transfer process **6** ⇌ **7**, is expected to be thermodynamically favoured as discussed previously.[12–15,21] Hence rate constants for proton-transfer will be largely determined by steric factors. Since proton-transfer involves approach of an amine molecule to the zwitterion, **6**, steric hindrance is likely to be higher for pyrrolidine and piperidine than for *n*-butylamine. This explains the difference in rate-determining step in the reactions involving secondary and primary amines. The argument has been used that intramolecular hydrogen-bonding between an amino proton and an *ortho*-nitro group plays an important role in differentiating the behaviour of primary and secondary amines.[3,22] However, we have argued previously that in DMSO the acidic protons in **6** will be hydrogen-bonded to the solvent, a good hydrogen-bond acceptor, rather than to an adjacent nitro-group.[12–15]

It is interesting that values of k_{AmH^+} are *ca.* one hundred times greater for reactions involving **4** and **5** than for the corresponding reactions involving **1**, R = Ph and **1**, R = Et, respectively. For example in reactions with pyrrolidine values are **4** 4×10^5 dm^3 mol^{-1} s^{-1} **1**, R = Ph 3×10^3 dm^3 mol^{-1} s^{-1} and **5** 2×10^6 dm^3 mol^{-1} s^{-1}, **1**, R = Et 1×10^4 dm^3 mol^{-1} s^{-1}. These factors which are likely also to reflect k_{Am} values are attributable to the lower steric hindrance to the approach of the amine to **6** relative to the approach to the corresponding zwitterions from **1**. All values of k_{AmH^+} are about ten times lower for piperidine than for pyrrolidine reflecting the higher steric requirements of this amine.[12–15]

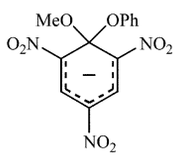
The reactions of amines at unsubstituted ring positions of **4** and **5**, to give adducts **7**, show similar susceptibility to base catalysis. Nevertheless, the substitution reactions of **5**, to give **10**, are far more likely to be base catalysed than the corresponding reactions of **4**. Thus the reaction of **5** with pyrrolidine is wholly base catalysed while in the reaction with **4** nucleophilic attack is rate-limiting. Also substitutions of **5** are considerably slower than those of **4**. This difference in behaviour is attributable to a change in the nature of the rate-limiting step. Phenoxide is known to be a considerably better leaving group than alkoxides;[3] for example phenoxide departure is 10^6 times faster[23] than methoxide departure from **13**. Also it is known[13] that in the substitution reactions of **1**, R = Ph, the trinitro-analogue of **4**, with amines base catalysis is due to rate-limiting proton transfer from the zwitterionic intermediates. Hence we similarly attribute the base catalysis observed in the reaction of **4** with piperidine. In the reactions with *n*-butylamine and pyrrolidine nucleophilic attack, the k_2 step, is rate-limiting, probably as a consequence of the relatively rapid deprotonation of the zwitterionic intermediates. Although a value of K_2k_B ($\equiv K_2k'_{Am}$) is not directly measurable in the reaction of **4** with pyrrolidine, the value is likely to be higher than that for the corresponding reaction with piperidine, and we may estimate a value of *ca* 10^4 dm^6 mol^{-1} s^{-1}. This value is considerably higher than the value of 3.3 dm^6 mol^{-2} s^{-1} observed (Table 5) for reaction of **5** with pyrrolidine, indicating a different rate-limiting

Table 6 Kinetic results for reaction of **4** with pyrrolidine in DMF at 25 °C

[Pyrrolidine]/mol dm^{-3}	[Pyrrolidinium perchlorate]/mol dm^{-3}	k_{fast} [a]/s^{-1}	k_{slow} [b]/s^{-1}	k_{calc} [c]/s^{-1}
0.005	—	450	—	—
0.010	—	840	—	—
0.002	0.001	—	0.18	0.19
0.005	0.001	—	0.49	0.48
0.010	0.001	—	0.86	0.86
0.020	0.001	—	1.3	1.3
0.030	0.001	—	1.3	1.3
0.040	0.001	—	1.2	1.2
0.050	0.001	—	1.1	1.1
0.050	0.005	—	2.5	2.8

[a] Colour forming at 490 nm. [b] Measured at 360 nm. [c] Calculated from eqn. (7) with k_2 98 ± 5 dm^3 mol^{-1} s^{-1} and $K_{c,6}$ 1.4 ± 0.2 dm^3 mol^{-1}.

step. In the case of **5** general base catalysis is attributed to acid-catalysis of ethoxide departure from **9**, the k_4 step in Scheme 1. Hence the values of K_2k_B in Table 5 correspond to $K_{c,2}k_4$, where $K_{c,2}$ is the equilibrium constant for formation of the anionic intermediates, **9**. The lower value of $K_{c,2}k_4$ obtained for pyrrolidine compared with *n*-butylamine, 3.3 *vs* 1400 dm^6 mol^{-1} s^{-1}, probably reflects lower values for both $K_{c,2}$ and k_4 resulting from the greater steric requirements of the secondary amine.



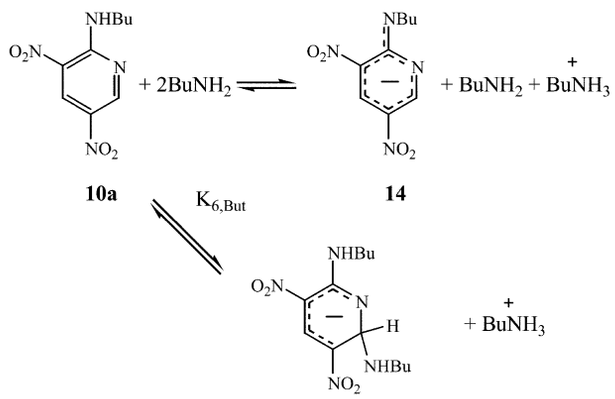
13

Interestingly reaction of **5** with piperidine does not yield **10c** the product of nucleophilic substitution. It is known both from studies of the reaction of **1**, R = alkyl [3,12,14,24] and also 1-alkoxy-2,4-dinitronaphthalenes [25,26] that when reaction occurs by the SB-GA mechanism substitutions involving piperidine are several orders of magnitude slower than the corresponding reactions of pyrrolidine. This has been attributed to the difficulty in obtaining the required anti-periplanar arrangement of entering and leaving groups in the transition state for acid catalysed leaving group expulsion.[25,26] The X-ray structure, Fig. 1b, of 2-piperidino-3,5-dinitropyridine shows that unfavourable steric interactions between the 2- and 3-substituents remain in the substitution product also contributing to the slowness of its formation. The consequence is that **9c**, decomposes by an alternative pathway. We have not investigated this, but it is likely to involve cleavage of a ring carbon-nitrogen bond. There is precedent for this possibility from studies [27] of the hydrolysis of 2-chloro-3,5-dinitropyridine which show that reaction occurs by an S_N(ANRORC) ring-opening mechanism.

Reactions of 2-amino-3,5-dinitropyridines with amines

In the presence of amine the reaction products **10** were found to be in rapid equilibrium with amine-adducts. In the case of **10a**, reaction with *n*-butylamine resulted in a shift in wavelength from 345 nm to 470 nm. Absorbance values are given in Table 13 (supplementary information †). By analogy with previous work [28,29] on 1-butylamino-2,4,6-trisubstituted benzenes, the reaction of **10a**, is expected to yield the anion **14** formed by proton loss at low amine concentrations, and the σ-adduct **15** at higher amine concentrations, as shown in Scheme 2. The results in Table 13 show that at the concentrations used there is a squared dependence on the amine concentration indicating that formation of the σ-adduct is dominant and yielding a value for $K_{6,But}$ of 0.015 dm^3 mol^{-1}.

Spectroscopic changes were also observed for **10b** and **10c** in the presence of high amine concentrations and are attributed to σ-adduct formation. Since these processes occur after the rate determining step they do not affect the kinetics of the substitution reactions of **4** or **5**



Scheme 2

Reactions in *N*,*N*-dimethylformamide (DMF)

It is known that σ-adduct formation may occur in DMF [30] although there have been few quantitative studies. To allow comparison of solvent effects we examined the reactions of **4** and **5** with one amine, pyrrolidine, in DMF. The results are qualitatively similar to those obtained in DMSO, and are similarly interpreted. Thus with both **4** and **5** there was a fast reaction resulting in increased absorbance at 490–495 nm attributed to the formation of adducts **7b**; this was followed by a slower reaction giving increased absorbance at 360 nm corresponding to substitution to give **10b**.

Data for reaction of **4** are in Table 6. Values of k_{fast} are only just within the limits of measurement but indicate that nucleophilic attack is rate limiting so that eqn. (2) applies with k_6 *ca.* 9 × 10^4 dm^3 mol^{-1} s^{-1}. Values for k_{slow} accord nicely with eqn. (7) with k_2 98 ± 5 dm^3 mol^{-1} s^{-1} and $K_{c,6}$ 1.4 ± 0.2 dm^3 mol^{-1} This indicates that nucleophilic attack is rate limiting in the displacement of phenoxide.

Results for reaction of **5** (Table 14, supplementary information †) show that formation of the adduct **7b** is too rapid for measurement. Absorbance values at completion of this reaction yield a value for $K_{c,6}$ of 0.15 ± 0.02 dm^3 mol^{-1}. Values of k_{slow} give a precise fit with eqn. (8) with $K_{c,6}$ 0.15 ± 0.02 dm^3 mol^{-1} and with K_2k_B 1.15 ± 0.05 dm^6 mol^{-2} s^{-1}. The interpretation, as when the solvent is DMSO, is that the SB-GA mechanism operates here so that K_2k_B corresponds to $K_{c,2}k_4$.

Reactions in acetonitrile

For comparison purposes data were obtained for reactions of **4** and **5** with pyrrolidine in acetonitrile. It is known [14] that the formation of anionic σ-adducts is much less thermodynamically favourable in acetonitrile than in DMSO. Hence reaction of

Table 7 Kinetic and equilibrium results for the reaction of **5** with pyrrolidine in acetonitrile at 25 °C

[Pyrrolidine]/ mol dm^{-3}	[Pyrrolidine perchlorate]/ mol dm^{-3}	Abs[a] (495 nm)	$K_{c,6}$[b]/10^{-4} dm^3 mol^{-1}	$K^{o}_{c,6}$/10^{-4} dm^3 mol^{-1}	k_{slow}[d]/10^{-3} s^{-1}	k_{calc}[e]/10^{-3} s^{-1}
0.05	0.001	—	—		0.44	0.50
0.075	0.001	—	—		1.0	1.1
0.1	0.001	0.02	17	5[c]	1.9	2.0
0.15	0.001	—	—	—	4.4	4.4
0.2	0.001	0.10	23	4[c]	7.8	7.4
0.3	0.001	0.30	37	5[c]	15	14
0.3	0	1.2	—		—	—

[a] At completion of rapid reaction. [b] Calculated as $K_{c,6} = \left(\frac{\text{Abs}}{1.2 - \text{Abs}}\right)\frac{[\text{AmH}^+]}{[\text{Am}]^2}$. [c] It is known that in acetonitrile pyrrolidinium ions are stabilised by homoconjugation with free pyrrolidine, K_h = 23 dm^3 mol^{-1} (see ref. 14). $K^{o}_{c,6}$ is the value of $K_{c,6}$ extrapolated to zero amine concentration, where pyrrolidinium ions will be unassociated. $K_{c,6} = K^{o}_{c,6}(1 + K_h[\text{pyrrolidine}])$. [d] Measured at 360 nm. [e] Calculated from eqn. (8) with K_2k_B 0.20 dm^6 mol^{-2} s^{-1} and $K_{c,6} = 4 \times 10^{-4}(1 + 23[\text{pyrrolidine}])$.

Table 8 Comparison of data for reactions of **4** and **5** with pyrrolidine in DMSO, DMF and acetonitrile at 25 °C

	DMSO	DMF	Acetonitrile
Substrate **4**			
$K_{c,6}$/dm^3 mol^{-1}	40	1.4	<10^{-2}
Reaction at 6-position	Rate limiting proton transfer	Rate limiting nucleophilic attack	Not observed
k_2/dm3 mol^{-1} s^{-1}	146	98	85
k'_{Am}/k_{-2} dm^3 mol^{-1}	≥1000	≥5000	1300
Substrate **5**			
$K_{c,6}$/dm^3 mol^{-1}	2.4	0.15	5×10^{-4}
$K_{c,2}.k_4$/dm^6 mol^{-2} s^{-1}	3.3	1.15	0.20

4 with low concentrations, ≤5×10^{-3} mol dm^{-3}, of pyrrolidine resulted in formation of the substitution product **10b** without the formation of transient species, such as **7**, at observable concentrations. The data, Table 15 supplementary information, † are fitted by eqn. (6) with $K_{c,6} < 10^{-2}$ dm^3 mol^{-1}, K_2k_B 1.1 × 10^5 dm^6 mol^{-2} s^{-1} and k_B/k_{-2} 1300 dm^3 mol^{-1}. Combination of these values allows the calculation of a value for k_2 of 85 dm^3 mol^{-1} s^{-1}.

In the case of **5**, the substitution reaction was considerably slower and at the higher concentrations of pyrrolidine used a transient absorption band was observed at 495 nm attributed to **7**, R=Et. Absorbance values, in Table 7, lead to a value for $K^{o}_{c,6}$ of (4 ± 1) × 10^{-4} dm^3 mol^{-1}. Values of k_{slow} are accommodated by eqn. (8) with K_2k_B 0.2 ± 0.02 dm^6 mol^{-2} s^{-1} and $K^{o}_{c,6}$ 4 × 10^{-4} dm^3 mol^{-1}. This value of K_2k_B is nearly 10^6 times lower than the value obtained for reaction of **4** indicative of a change in the nature of the rate determining step. With **4** the rate limiting proton transfer is from the zwitterionic intermediate **8** to base so that K_2k_B corresponds to $K_2k'_{Am}$. With the ethoxy derivative, **5**, the SB-GA mechanism applies so that K_2k_B corresponds to $K^{o}_{c,2}k_4$.

Comparison of solvent effects

Data for reactions of **4** and **5** with pyrrolidine are compared in Table 8. Values of $K_{c,6}$ fall in the order DMSO > DMF ⩾ acetonitrile. The major factor is likely to be the greater ability of DMSO than of acetonitrile [14,31,32] to solvate the charged species which are the products of reaction at the 6-position. Values in DMF are closer to those in DMSO than in acetonitrile.

Previous work [14] has shown that rate constants for proton transfers between nitrogen atoms may be considerably lower, by a factor of 10^4, in DMSO than in acetonitrile. This has been attributed to the excellent hydrogen-bond acceptor properties of DMSO [33,34] so that acidic ammonium protons, in –NHR^{1}R^{2+} groups, will be H-bonded to the solvent thus reducing rate constants for their transfer. This will be expected to reduce values for k_{Am}, k_{AmH^+}, k'_{Am}, k'_{AmH^+} and k_4 in DMSO relative to acetonitrile. Although our measurements do not lead to the direct evaluation of rate constants for proton transfer in DMF, the results suggest that values are higher than in DMSO. Thus in the formation of **7b** from **4** and pyrrolidine proton transfer, k_{Am}, is rate limiting in DMSO while nucleophilic attack, k_6, is rate limiting in DMF. Also in the corresponding reaction of **5** proton transfer is again rate limiting in DMSO, while the reaction is too fast to measure in DMF.

In each solvent the results for the displacement of phenoxide from **4** indicate that the rate limiting step is either nucleophilic attack, k_2, or proton transfer, k'_{Am}, from the zwitterion **8** to base. The values of k_2 in Table 8 show small variations from DMSO to acetonitrile compatible with an early transition state involving little charge development. In contrast the substitution reaction of **5** involves rate limiting general-acid-catalysed expulsion of ethoxide from **9b**. Values of the parameter $K_{c,2}k_4$ again show relatively small variation with solvent. However this is attributed to large decreases in the value of the equilibrium constant $K_{c,2}$ on going from DMSO to acetonitrile which are compensated for by large increases in value of k_4. In the case of DMF, if it may be assumed that the solvent effect on $K_{c,2}$ is similar to that on $K_{c,6}$ so that $K_{c,2}$(DMF) : $K_{c,2}$(DMSO) = 2.4 : 0.15, then the ratio of k_4(DMF) : k_4(DMSO) may be calculated as *ca.* 6. This again indicates that proton transfers are likely to be somewhat faster in DMF than in DMSO although the effect is not large. Overall the results suggest that values of rate and equilibrium constants for σ-adduct formation and for nucleophilic substitution reactions in DMF are likely to be closer to those in DMSO than those in acetonitrile.

Experimental

Compound **4** was prepared by reaction of 2-chloro-3,5-dinitropyridine with one equivalent of base in the presence of 1.3

Table 9 Summary of data collection, structure solution and refinement details

	10c	**5**
Empirical formula	$C_{10}H_{12}N_4O_4$	$C_7H_7N_3O_5$
M	252.24	213.16
Crystal size/mm	0.38 × 0.34 × 0.08 mm³	0.52 × 0.24 × 0.08
Crystal system	Triclinic	Monoclinic
a/Å	5.9847(12)	6.4904(4)
b/Å	7.3833(15)	16.7850(11)
c/Å	12.375(3)	8.2216(5)
α/°	94.29(3)	90.0
β/°	95.28(3)	102.454(1)
γ/°	91.80(3)	90.0
V/ Å³	542.5(2)	874.60(9)
Space group	$P\bar{1}$	$P2_1/n$
Z	2	4
$F(000)$	264	440
D_{calc}/g cm^{-3}	1.544	1.619
μ/mm^{-1}	0.12	0.14
T/K	120	120
ω-scan; max 2θ/°	55	58
Unique reflections	2484	2316
Data/restraints/parameters	2484 / 0 / 211	2316 / 0 / 164
R	0.033	0.038
wR_2	0.094	0.096

equiv of phenol in aqueous ethanol, mp 158 °C (lit.,[35] 159 °C). Found, % C 50.1; H 2.7; N 16.1, Calcd, % C 50.5; H 2.7; N 15.8. **5** was prepared by reaction of 2-chloro-3,5-dinitropyridine with one equivalent of sodium ethoxide in ethanol, mp 64 °C (lit.,[36] 69 °C). Found, % C 39.2; H 3.3; N 19.5. Calcd, % C 39.4; H 3.3; N 19.7. Reaction products **10a**,**b**,**c** were prepared as before[9] by reaction of the 2-chloro compound with a 4 fold excess of the appropriate amine in ethanol. Recrystallisation was from ethanol. Spectroscopic data are in Table 1.

^{1}H NMR spectra were measured with Varian Mercury 200 MHz or Varian Unity 300 MHz instruments. UV/visible spectra and kinetic measurements were made at 25 °C with an Applied Photophysics SX-17 MV stopped-flow instrument, or with Perkin-Elmer Lambda 2, or Shimadzu UV PC spectrometers. Rate constants were measured under first order conditions with substrate concentrations of 5–10 × 10^{-5} mol dm^{-3}, and were evaluated by standard methods. Values are precise to ±5%.

The X-ray diffraction experiments for **10c** and **5** were carried out on a SMART 3-circle diffractometer with 1K and 6K CCD area detectors respectively (graphite monochromated Mo–Kα radiation; hemispheres of reciprocal space were covered by a combination of 4 sets of ω scans, each set at different φ and 2θ angles). Crystals were cooled using a Cyrostream (Oxford Cyrosystems) open-flow N_2 gas cyrostat. For **10c**, absorption correction was performed by ψ scans. The structures were solved by direct methods and refined by full-matrix least squares against F^2 of all data, using SHELXTL software. Data are in Table 9.

Acknowledgements

We thank ICSC-World Laboratory, Lausanne for a scholarship to enable C. I. to visit Durham, U.K.

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