Mechanism of base catalysis in the reactions of phenyl aryl ethers with aliphatic amines in dimethyl sulfoxide

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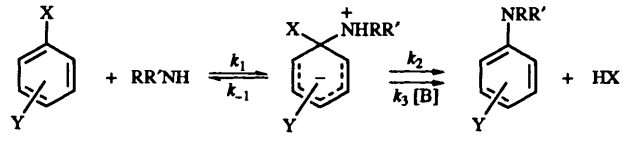
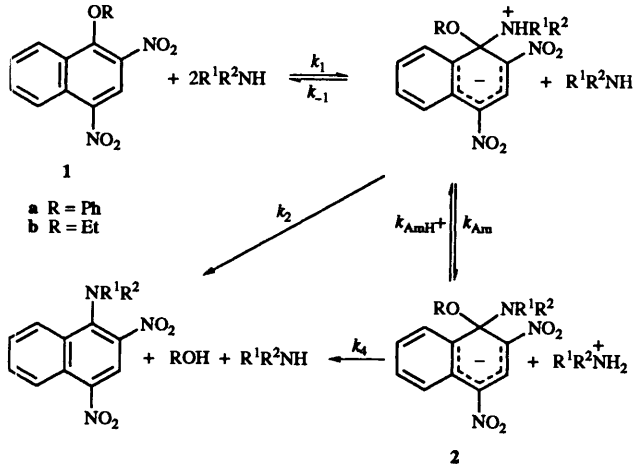
The reactions of n-butylamine, pyrrolidine and piperidine with phenyl 2,4,6-trinitrophenyl ether, **3**, in DMSO result in the rapid reversible formation of adducts by reaction at the 3-position followed by attack at the 1-position leading to substitution of the phenoxy group. With phenyl 2,4-dinitronaphthyl ether, **1a**, and phenyl 2,4-dinitrophenyl ether, **8**, substitution is the only process observed. For each substrate reactions with n-butylamine show a first order dependence on the amine concentration indicating that nucleophilic attack is rate-limiting. However, the reactions with pyrrolidine and with piperidine are subject to general base catalysis and it is argued that here the deprotonation of the initially formed zwitterionic intermediates is rate determining. The results are compared and contrasted with those of the corresponding ethyl ethers, where base catalysis involves the SB-GA mechanism, and with phenyl sulfides.

Many aromatic substitutions by amine nucleophiles have been found to be subject to general base catalysis.[1,2] The overall pathway is shown in Scheme 1, and there is continuing interest in the mechanism of catalysis.[3-5]



Scheme 1

In a classic study of the reactions of ethyl 2,4-dinitronaphthyl ether **1b** with amines in dimethyl sulfoxide Bunnett and Orvik[6] were able to observe anionic intermediates **2b** and follow their general acid catalysed conversion to products (Scheme 2).



Scheme 2

When the k_4 step is rate-determining this pathway is the SB-GA mechanism. It has gained wide acceptance for reactions in DMSO, and has been shown to apply in substitutions of several other ring-activated alkyl aryl ethers.[7-13]

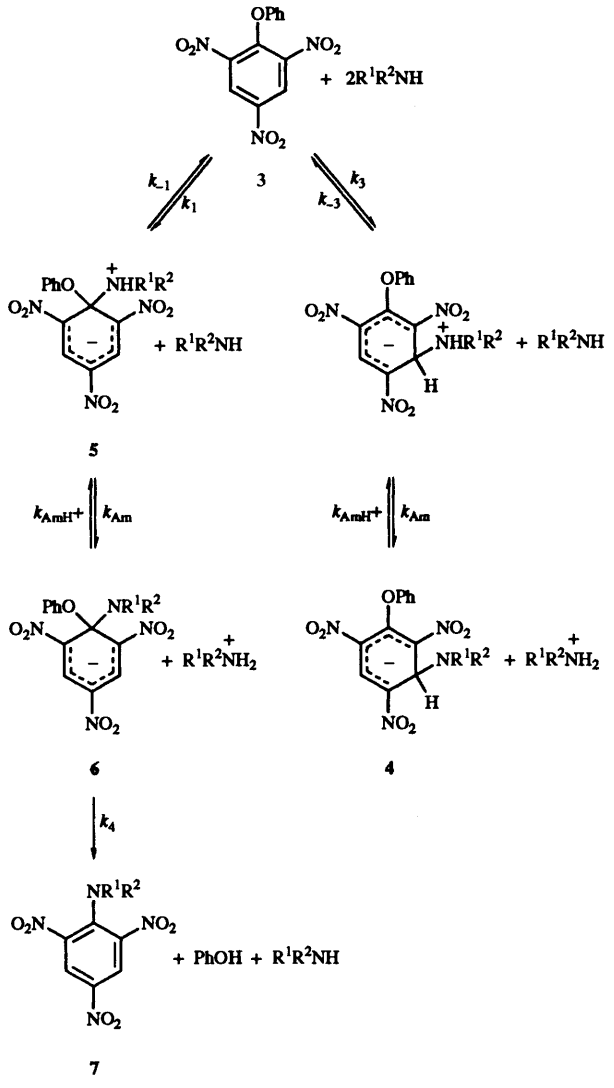
However, we have shown recently that general base catalysis in the reactions with aliphatic amines of ethyl thiopicrate[14] and of some phenyl aryl sulfides[15] is likely to involve rate limiting deprotonation of the zwitterionic intermediate followed by rapid loss of the ethylthio or phenylthio leaving groups. Sekiguchi and co-workers have produced evidence that base catalysis in the substitution reaction of 1-pyrrolidino-2,4-dinitronaphthalene with n-butylamine also involves rate limiting proton transfer between nitrogen atoms.[16] It is known that in DMSO the values of rate constants for such proton transfers, in the thermodynamically downhill direction, may be considerably lower than the diffusion controlled limit.[17,18]

In this paper we are concerned with substitutions involving phenoxy leaving groups. It is worth noting the current interest in the regiospecificity of σ-adduct forming reactions involving phenoxide ions as nucleophiles and in the contrast between the behaviour of phenoxide and alkoxide ions.[19,20] There have been several previous studies involving substitutions of phenyl aryl ethers with amines. Bernasconi and co-workers provided convincing evidence that in aqueous media base catalysis in the reactions of nitroaryl ethers with aliphatic amines is the result of rate limiting proton transfer from the zwitterionic intermediate.[21] One argument against the SB-GA mechanism was that acid catalysed expulsion of phenoxide was unlikely since it would involve a proton transfer from a weaker acid (the substituted ammonium ion) to a stronger one. Nevertheless differences in the susceptibility to base catalysis of the reactions in aqueous media of pyrrolidine and piperidine with 2,4-dinitrophenyl phenyl ether were attributed to rate-limiting expulsion of the phenoxy leaving group.[22] Observations of base catalysis in dimethyl sulfoxide solvent have, following the work of Bunnett and Orvik,[6] generally been interpreted in terms of the SB-GA mechanism. There have been reports of reactions with aliphatic amines in DMSO of 2,4-dinitrophenyl phenyl ether,[23,24] 2,6-dinitrophenyl phenyl ether[25] and 6-methyl-2,4-dinitrophenyl phenyl ether.[25]

We report here kinetic studies of the reactions of 2,4,6-trinitrophenyl phenyl ether, 2,4-dinitronaphthyl phenyl ether and 2,4-dinitrophenyl phenyl ether with n-butylamine, pyrrolidine and piperidine in DMSO. Our results are compared with those for reactions of the corresponding alkyl ethers and also with those for phenyl sulfides. It is argued that base catalysis in substitutions of the phenoxy groups reflects rate limiting proton transfer from the zwitterionic intermediates rather than acid catalysis of leaving group departure.

Experimental

Phenyl 2,4,6-trinitrophenyl ether, **3**, was prepared by reaction at 40 °C for 30 min of picryl chloride (1 equiv.) with sodium hydroxide (1 equiv.) in an excess of phenol containing a little



Scheme 3

water. On completion of the reaction water was added to remove any picric acid produced and the solid residue was recrystallised from an ethanol–toluene mixture, mp 150 °C (lit.,[26] 153 °C). The ^{1}H NMR spectrum in [$^2H_6$]DMSO showed bands at δ 9.25 (s, nitro-substituted ring) and 7.19 (t), 7.39 (t) and 7.40 (d, phenyl ring). Phenyl 2,4-dinitronaphthyl ether, **1a**, was prepared in a similar manner from 1-chloro-2,4-dinitronaphthalene. Recrystallisation from ethanol gave a solid, mp 180 °C (lit.,[27] 183 °C). The ^{1}H NMR spectrum in [$^2H_6$]DMSO showed bands at δ 8.99 (s), 8.57 (d), 8.26 (d), 8.07 (t) and 6.88 (t, naphthyl ring) and 7.14 (t), 7.37 (t) and 7.00 (d, phenyl ring). Phenyl 2,4-dinitrophenyl ether (**8**) was the purest available commercial specimen. The expected substitution products from reactions with n-butylamine, pyrrolidine or piperidine were available from previous work.[15] Solvent, amines and amine salts were prepared and/or purified as described previously.[14]

^{1}H NMR spectra were recorded using Varian-200XL or Bruker 250 MHz instruments with [$^2H_6$]DMSO as solvent. UV–VIS spectra and kinetic measurements were made with Beckman Lambda 2, or Hi-Tech SF 3L stopped-flow spectrophotometers at 25 °C. Reported rate coefficients are the means of several determinations and are precise to ±5%. Rate constants were measured under first order conditions. Hence for reactions in buffers (amine plus amine salt) the buffer components were in large excess of the substrate concentration ($1–5 \times 10^{-5}$ mol dm^{-3}). For reactions with amines in the absence of added amine salts a large excess of amine was used, sufficient in the case of σ-adduct forming reactions to achieve >95% conversion into adduct at equilibrium. Under these conditions eqn. (1) applies and was used to calculate rate constants.

$$\ln\left[\frac{A_\infty}{A_\infty - A}\right] = k_{obs}\, t \qquad (1)$$

Results

Phenyl 2,4,6-trinitrophenyl ether, 3

UV–VIS measurements of **3** in DMSO containing amines (0.001–0.05 mol dm^{-3}) showed the presence of two processes well separated in time which are interpreted[9,15] by Scheme 3. With each amine a rapid reaction was observed leading to the 3-adduct **4** with λ_{max} 430–435 nm and 505 nm. A second much slower reaction resulted in the formation of *N*-substituted picramide derivatives, **7**. The final spectra were identical to those of the independently prepared products, **7**, in solutions of the same amine concentration.[18] There was no evidence from the spectra or from the kinetics for the accumulation of spectroscopically observable concentrations of intermediates **6** on the substitution pathway. NMR spectra confirmed the eventual substitution products. Thus the spectrum of **3** (0.03 mol dm^{-3}) after reaction with piperidine (0.2 mol dm^{-3}) and piperidine hydrochloride (0.03 mol dm^{-3}) showed bands at δ 5.65 and 8.45 consistent[18] with the formation of the 3-piperidino adduct of **7** together with multiplets at δ 6.77 and 7.14 attributable to the displaced phenol.

It is assumed that zwitterionic forms may be treated as steady state intermediates, so that the general rate expression for reaction at the 3-position to produce adducts **4** is eqn. (2).

$$k_{fast} = \frac{k_3 k_{Am}[Am]^2 + k_{-3}k_{AmH^+}[AmH^+]}{k_{-3} + k_{Am}[Am]} \qquad (2)$$

The overall equilibrium constant, $K_{c.3}$, for conversion of substrate to **4** is defined by eqn. (3) and is related to rate constants by eqn. (4).

$$K_{c.3} = \frac{[\mathbf{4}][AmH^+]}{[\mathbf{3}][Am]^2} \qquad (3)$$

$$K_{c.3} = \frac{k_3}{k_{-3}} \times \frac{k_{Am}}{k_{AmH^+}} \qquad (4)$$

We will make the assumption, justified later, that leaving group expulsion (the k_4 step in Scheme 3) is not rate limiting. In that case, taking account of the rapid reversible reaction at the 3-position, the rate expression for product formation is eqn. (5).

$$k_{slow} = \frac{k_1 k_{Am}[Am]^2}{(k_{-1} + k_{Am}[Am])} \times \left(1 + K_{c.3}\frac{[Am]^2}{[AmH^+]}\right)^{-1} \qquad (5)$$

It is convenient to define a modified rate constant, k'_{slow}, by eqn. (6), so that eqn. (5) may be written as eqn. (7).

$$k'_{slow} = k_{slow}\left(1 + K_{c.3}\frac{[Am]^2}{[AmH^+]}\right) \qquad (6)$$

$$k'_{slow} = \frac{k_1 k_{Am}[Am]^2}{k_{-1} + k_{Am}[Am]} \qquad (7)$$

Table 1 Kinetic data for reaction of **3** with n-butylamine in DMSO at 25 °C

$[BuNH_2]$/ mol dm^{-3}	$[BuNH_3^+ClO_4^-]$/ mol dm^{-3}	k_{fast}[a]/s^{-1}	k_{calc}[b]	k_{slow}[a]/s^{-1}	k_{calc}[c]
0.006	—	45	48	—	
0.008	—	63	64	—	
0.010	—	76	80	—	
0.015	—	120	120	—	
0.020	—	160	160	—	
0.003	0.01	149	151	1.12	1.04
0.004	0.005	83	80	1.03	0.98
0.006	0.01	108	110	1.40	1.40
0.010	0.01	120	118	1.33	1.32
0.020	0.01	200	180	0.86	0.86
0.030	0.01	—	—	0.61	0.62
0.040	0.01	—	—	0.44	0.47
0.050	0.01	—	—	0.39	0.38

[a] Measured at 430 nm, with **3** 2.5 × 10^{-5} mol dm^{-3}. [b] Calculated from eqn. (8) with k_3 8000 dm^3 mol^{-1} s^{-1} and ($k_{-3}k_{AmH^+}/k_{Am}$) 38 s^{-1}. [c] Calculated as $k_1[Am] \times (1 + K_{c.3}[Am]^2/[AmH^+])^{-1}$ with k_1 410 dm^3 mol^{-1} s^{-1} and $K_{c.3}$ 210 dm^3 mol^{-1}.

Table 2 Kinetic data for reaction of **3** with pyrrolidine in DMSO at 25 °C

[Pyrrolidine]/ mol dm^{-3}	[Pyrrolidinium perchlorate]/ mol dm^{-3}	k_{fast}[a]/s^{-1}	k_{calc}[b]	k_{slow}[a]/s^{-1}	k'_{slow}/s^{-1}	k_{calc}[c]
0.0015	—	8.6	8.5	—		
0.0020	—	15.1	14.8	—		
0.0030	—	32.2	32.1	—		
0.0040	—	55	55	—		
0.0050	—	84	83	—		
0.0060	—	116	116	—		
0.0010	0.01	31.3	32.7	—		
0.0020	0.01	43.2	42.6	—		
0.0030	0.01	58	59	—		
0.0040	0.01	85	81	0.94	2.6	1.10
0.0050	0.01	109	108	1.13	4.2	1.27
0.010	0.01	—	—	1.40	17	1.45
0.020	0.01	—	—	1.49	67	1.34
0.030	0.01	—	—	1.24	124	1.18
0.040	0.01	—	—	1.07	190	1.06
0.050	0.01	—	—	0.97	207	0.95

[a] Measured at 430 nm, with **3** 2.5 × 10^{-5} mol dm^{-3}. [b] Calculated from eqn. (2) with k_3k_{Am}/k_{-3} 4 × 10^6 dm^6 mol^{-2} s^{-1}, k_{Am}/k_{-3} 40 dm^3 mol^{-1} and k_{AmH^+} 3000 dm^3 mol^{-1}. [c] Calculated from eqn. (5) with k_1k_{Am}/k_{-1} 2.1 × 10^5 dm^6 mol^{-2} s^{-1}, k_{Am}/k_{-1} 20 dm^3 mol^{-1} and $K_{c.3}$ 1100 dm^3 mol^{-1}.

Data for reaction with n-butylamine are in Table 1. In the absence of added amine salt values of k_{fast}, representing reaction at the 3-position to give **4**, increase linearly with amine concentration. This shows that the condition $k_{Am}[Am] \gg k_{-3}$ applies so that eqn. (2) reduces to eqn. (8). Values calculated

$$k_{fast} = k_3[Am] + \frac{k_{-3}k_{AmH^+}}{k_{Am}}\frac{[AmH^+]}{[Am]} \qquad (8)$$

with k_3 8000 dm^3 mol^{-1} s^{-1} and $k_{-3}k_{AmH^+}/k_{Am}$ 38 s^{-1} give excellent agreement with experimental values. Combination of these values leads *via* eqn. (4) to a value for $K_{c.3}$ of 210 dm^3 mol^{-1}. Values of k_{slow}, for reaction at the 1-position, are also in Table 1. Values of k'_{slow} (not shown) were calculated from eqn. (6) using the known value of $K_{c.3}$ and increase linearly with amine concentration. This indicates that the condition $k_{Am}[Am] \gg k_{-1}$ applies and allows the calculation of a value for k_1 of 410 dm^3 mol^{-1} s^{-1}.

Values of rate constants for reactions with pyrrolidine are in Table 2. The results for the rapid reaction indicate that proton transfer is partly rate limiting in the formation of the 3-adduct. Values calculated from eqn. (2) with k_3k_{Am}/k_{-3} 4 × 10^6 dm^6 mol^{-2} s^{-1}, k_{Am}/k_{-3} 40 dm^3 mol^{-1} and k_{AmH^+} 3000 dm^3 mol^{-1} s^{-1} give excellent agreement with experimental data. They allow the evaluation of k_3 as 1 × 10^5 dm^3 mol^{-1} s^{-1}. Values of k_{slow} are also compatible with proton transfer being partially rate limiting in the substitution process. They give a satisfactory fit with eqn. (5) with k_1k_{Am}/k_{-1} 2 × 10^5 dm^6 mol^{-2} s^{-1}, k_{Am}/k_{-1} 20 dm^3 mol^{-1} and $K_{c.3}$ 1100 dm^3 mol^{-1}. The value calculated for k_1 is 1 × 10^4 dm^3 mol^{-1} s^{-1}.

Visible spectra of **3** in the presence of piperidine showed the rapid initial formation of the adduct at the 3-position with λ_{max} 430 and 500 nm followed by the slower conversion to 1-piperidino-2,4,6-trinitrobenzene. Spectra at completion of the reactions were identical to those of the separately prepared substitution product in solutions of the same amine composition. Thus with piperidine 0.004 mol dm^{-3} and piperidinium chloride 0.01 mol dm^{-3} λ_{max} was 395 nm. We make this point since the corresponding reaction with piperidine of alkyl 2,4,6-trinitrophenyl ethers yields 1-adducts which are stable for several hours.[9] Kinetic data are in Table 3. The results indicate that in the formation of the 3-adduct, **4**, proton transfer is rate limiting, $k_{-3} \gg k_{Am}[Am]$. Hence eqn. (2) simplifies to give eqn. (9). Values calculated with k_3k_{Am}/k_{-3}

$$k_{fast} = \frac{k_3k_{Am}}{k_{-3}}[Am]^2 + k_{AmH^+}[AmH^+] \qquad (9)$$

1.7 × 10^5 dm^6 mol^{-2} s^{-1} and k_{AmH^+} 400 dm^3 mol^{-1} s^{-1} gave

Table 3 Kinetic data for reaction of **3** with piperidine in DMSO at 25 °C

[Piperidine]/ mol dm^{-3}	[Piperidinium chloride]/ mol dm^{-3}	k_{fast} [a]/s^{-1}	k_{calc} [b]	k_{slow} [a]/s^{-1}	k'_{slow} [c]	$k'_{slow}[Am]^{-2}$/ dm^6 mol^{-2} s^{-1}
0.006	—	6.2	6.1	—		
0.008	—	12	11	—		
0.010	—	16	17	—		
0.020	—	61	68	—		
0.030	—	150	150	—		
0.002	0.01	—		0.012	0.014	3400
0.003	0.01	—		0.021	0.029	3200
0.004	0.01	6.5	6.7	0.025	0.041	2600
0.006	0.01	8.6	10	0.037	0.090	2500
0.008	0.01	15	15	0.062	0.22	3400
0.01	0.01	20	21	0.058	0.29	2900
0.02	0.01	67	72	0.070	1.19	3000

[a] Measured at 430 nm with **3** 2.5 × 10^{-5} mol dm^{-3}. [b] Calculated from eqn. (9) with k_3k_{Am}/k_{-3} 1.7 × 10^5 dm^6 mol^{-2} s^{-1}, k_{AmH^+} 400 dm^3 mol^{-1} s^{-1}. [c] Calculated from eqn. (6) with $K_{c.3}$ 400 dm^3 mol^{-1}.

excellent agreement with experimental data. Proton transfer is also rate limiting in the substitution process, $k_{-1} \gg k_{Am}[Am]$, so that values of k'_{slow} increase linearly with the square of the amine concentration. The value of k_1k_{Am}/k_{-1} is 3000 dm^6 mol^{-2} s^{-1}.

There is current interest in the regiospecificity of σ-adduct formation.[19,20] Previous work on related systems has shown that attack by amines at the 3-position of 1-substituted 2,4,6-trinitrobenzenes is a faster process than attack at the 1-position.[9,10,14,15] Hence the initially formed adducts are the 3-adducts. Confirmation of this in the present work can be found in the dependence of k_{slow} on amine concentration. The data in Tables 1 and 2 show that with increasing amine concentration, at constant salt concentration, values of k_{slow} increase to a maximum value and then decrease. This behaviour is consistent with the observed adducts having structure **4** so that eqn. (5) applies. However, it is not compatible with the observed adducts having structure **6** since values of k_{slow} would then be predicted to reach a plateau.

Phenyl 2,4-dinitronaphthyl ether

UV–VIS measurement of **1a** with amines in DMSO showed in each case a single process. Spectra at completion of the reactions were identical to those of authentic samples of the product dissolved in the reaction medium. No intermediates were observed during the substitution process. We interpret the results in terms of Scheme 2, and the assumption that expulsion of the leaving group (the k_4 step) is not rate determining, leads to the general rate expression given in eqn. (10).

$$k_{obs} = \frac{k_1k_{Am}[Am]^2}{k_{-1} + k_{Am}[Am]} \quad (10)$$

In the reaction with n-butylamine values of the first order rate constant, k_{obs}, increased linearly with amine concentration (0.001 to 0.05 mol dm^{-3}). This indicates that nucleophilic attack is rate limiting, $k_{Am}[Am] \gg k_{-1}$, and allowed the determination of a value of 31 dm^3 mol^{-1} s^{-1} for k_1.

Rate constants for reaction with pyrrolidine, Table 4, showed a dependence between first and second order on amine concentration. This is consistent with the proton transfer step, k_{Am}, being partially rate limiting. Values calculated with $k_1/k_{Am}/k_{-1}$ 2.4 × 10^4 dm^3 mol^{-1} s^{-1} and k_{Am}/k_{-1} 41 dm^3 mol^{-1} gave a good fit with experimental data. These values allow the calculation of a value for k_1 of 590 dm^3 mol^{-1} s^{-1}.

Measurements with piperidine, in Table 5, indicate a squared dependence of k_{obs} on amine concentration. This indicates that $k_{-1} \gg k_{Am}[Am]$ so that proton transfer is rate determining and leads to a value for k_1k_{Am}/k_{-1} of 550 dm^6 mol^{-2} s^{-1}. Rate constants were, as expected, unaffected by the presence of piperidinium chloride but increased in the presence of DABCO. Here a good fit is obtained with eqn. (11) with k_1k_{DABCO}/k_{-1} 85 dm^6 mol^{-2} s^{-1}.

$$k_{obs} = \frac{k_1}{k_{-1}}[Am](k_{Am}[Am] + k_{DABCO}[DABCO]) \quad (11)$$

Table 4 Kinetic data for reaction of **1a** with pyrrolidine in DMSO at 25 °C

[Pyrrolidine]/ mol dm^{-3}	k_{obs} [a]/s^{-1}	k_{calc} [b]
0.004	0.33	0.33
0.006	0.68	0.69
0.01	1.84	1.70
0.02	5.39	5.27
0.03	10.0	9.7
0.04	14.6	14.5
0.05	19.7	19.6
0.07	28	30
0.10	43	47

[a] Measured at 440 nm with **1a** 2.5 × 10^{-5} mol dm^{-3}. [b] Calculated from eqn. (10) with k_1k_{Am}/k_{-1} 2.4 × 10^4 dm^6 mol^{-2} s^{-1}, and k_{Am}/k_{-1} 41 dm^3 mol^{-1}.

Table 5 Kinetic data for reaction of **1a** with piperidine in DMSO at 25 °C

[Piperidine]/ mol dm^{-3}	[Piperidinium chloride]/ mol dm^{-3}	[DABCO]/ mol dm^{-3}	k_{obs} [a]/s^{-1}	k_{calc} [b]/s^{-1}
0.01	—	—	0.060	0.055
0.02	—	—	0.23	0.22
0.03	—	—	0.52	0.50
0.04	—	—	0.94	0.88
0.05	—	—	1.45	1.38
0.02	0.01	—	0.22	0.22
0.03	0.01	—	0.50	0.50
0.04	0.01	—	0.84	0.89
0.02	—	0.05	0.28	0.29
0.02	—	0.10	0.35	0.39
0.02	—	0.15	0.48	0.48
0.02	—	0.20	0.54	0.56

[a] Measured at 420 nm with **1a** 2.5 × 10^{-5} mol dm^{-3}. [b] Calculated from eqn. (10) or eqn. (11) with k_1k_{Am}/k_{-1} 550 dm^6 mol^{-2} s^{-1} and k_1k_{DABCO}/k_{-1} 85 dm^6 mol^{-2} s^{-1}.

Table 6 Kinetic data for reaction of **8** with pyrrolidine in DMSO at 25 °C

[Pyrrolidine]/mol dm^{-3}	k_{obs}[a]/10^3 s^{-1}	k_{calc}/10^3 s^{-1}
0.0020	0.20	0.18
0.0025	0.30	0.28
0.0050	1.1	1.0
0.0075	2.4	2.1
0.010	3.6	3.5
0.020	10	10
0.030	19	19
0.040	28	29
0.050	37	38

[a] Measured at 383 nm with **8** 5 × 10^{-5} mol dm^{-3}. [b] Calculated from eqn. (10) with k_1k_{Am}/k_{-1} 50 dm^6 mol^{-2} s^{-1} and k_{Am}/k_{-1} 45 dm^3 mol^{-1}.

Table 7 Kinetic data for reaction of **8** with piperidine in DMSO at 25 °C

[Piperidine]/ mol dm^{-3}	[DABCO]/ mol dm^{-3}	k_{obs}[a]/10^3 s^{-1}	k_{calc}[b]/10^3 s^{-1}
0.010	—	0.13	0.13
0.020	—	0.42	0.41
0.030	—	0.81	0.83
0.040	—	1.5	1.4
0.050	—	2.2	2.1
0.10	—	7.5	7.5
0.020	0.05	0.56	0.53
0.020	0.10	0.65	0.65
0.020	0.15	0.76	0.76
0.020	0.20	0.87	0.87

[a] Measured at 392 nm with **8** 2.5 × 10^{-5} mol dm^{-3}. [b] Calculated from eqn. (12), after rearrangement, with k_1k_{Am}/k_{-1} 0.8 dm^6 mol^{-2} s^{-1}, k_1k_{DABCO}/k_{-1} 0.13 dm^6 mol^{-2} s^{-1}, k_1k_2/k_{-1} 0.005 dm^3 mol^{-1} s^{-1}, k_{Am}/k_{-1} 1.3 dm^3 mol^{-1}, k_{DABCO}/k_{-1} 0.21 dm^3 mol^{-1} and k_2/k_{-1} 8.1 × 10^{-3} dm^3 mol^{-1}.

Phenyl 2,4-dinitrophenyl ether (8)

With each amine a single process was observed leading to the expected substitution product. Data are interpreted in a manner similar to that given for the naphthyl ether (**1**) so that Scheme 2 is applicable and eqn. (10) will apply.

Values of k_{obs}, the first order rate constant for reaction with n-butylamine were precisely linear in amine concentration indicating that k_{Am}[Am] ≫ k_{-1} and yielding a value for k_1 of 0.042 dm^3 mol^{-1} s^{-1}. This compares with a previously calculated value[24] at 30.2 °C of 0.055 dm^3 mol^{-1} s^{-1}.

A plot, not shown, of k_{obs}/[Amine] *vs.* [Amine] for the values obtained with pyrrolidine was curved with an intercept indistinguishable from zero. This indicates that the uncatalysed pathway, the k_2 step, is unimportant and that proton transfer is partially rate limiting in the base catalysed pathway. Values given in Table 6 calculated using eqn. (10) with k_1k_{Am}/k_{-1} 50 dm^6 mol^{-2} s^{-1} and k_{Am}/k_{-1} 45 dm^3 mol^{-1} gave an excellent fit with experimental data. Combination of these values gives k_1 1.1 dm^3 mol^{-1} s^{-1}.

Rate constants for reaction with piperidine, with and without added DABCO are in Table 7. A plot, not shown, of k_{obs}/[piperidine] *vs.* [piperidine] had a small positive intercept indicating that the uncatalysed pathway, the k_2 step, makes a contribution to the reaction flux. The plot showed, at the higher amine concentrations, some downward curvature indicating that here the condition k_{-1} ≫ k_{Am}[Am] does not strictly hold. Previous measurements at 30.2 °C and at lower amine concentrations[24] did not reveal this curvature. Here eqn. (12), is required, and values calculated with k_1k_{Am}/k_{-1} 0.8 dm^6 mol^{-2} s^{-1}, k_1k_{DABCO}/k_{-1} 0.13 dm^6 mol^{-2} s^{-1}, k_1k_2/k_{-1} 0.005 dm^3 mol^{-1} s^{-1} and k_{Am}/k_{-1} 1.3 dm^3 mol^{-1} gave an excellent fit with experimental data. These values allow the calculation of k_1 0.6 dm^3 mol^{-1} s^{-1}.

$$k_{obs} = \frac{k_1[Am](k_2 + k_{Am}[Am] + k_{DABCO}[DABCO])}{k_{-1} + k_2 + k_{Am}[Am] + k_{DABCO}[DABCO]} \quad (12)$$

Discussion

Reaction at the unsubstituted 3-position of 3 to give 4

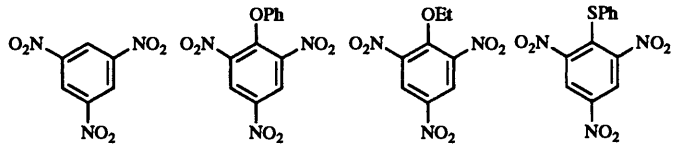
With each of the three amines used, n-butylamine, pyrrolidine and piperidine the most rapid reaction of **3** results in formation of the 3-adduct, **4**. Kinetic and equilibrium data are compared in Table 8 with corresponding values for reactions with 1,3,5-trinitrobenzene, **9**, ethyl 2,4,6-trinitrophenyl ether, **10**, and phenyl 2,4,6-trinitrophenyl sulfide, **11**. The values of the overall equilibrium constant, $K_{c.3}$, decrease in the order H > OPh > SPh > OEt providing evidence for both the electronic and steric effects of the 1-substituent on reaction at the 3-position. It is known[3,28] that the presence of a bulky group at the 1-position may result in rotation of the nitro-groups at the 2- and 6-positions from the ring-plane. Since nitro-groups exert their maximum electron withdrawing influence when they are coplanar with the aromatic ring this is expected to result in a decrease in values of $K_{c.3}$. This effect is responsible for the decrease in values of 1-substituted 2,4,6-trinitrobenzenes relative to **9**.

The σ_{meta} values for phenoxy and ethoxy groups are reported[29] as 0.25 and 0.10 so that both have a favourable electronic effect for reaction at the 3-position. The much larger values of $K_{c.3}$ for reaction of **3** than of **10** indicate that the adverse steric effects of the phenoxy group are smaller than those of the ethoxy group. The electronic effect of the phenylthio group is expected[30] to be similar to that of the phenoxy group so that the smaller value for $K_{c.3}$, reflects its greater disruptive effect on the planarity of the *ortho* nitro-groups.

Values of k_3, the rate constant for nucleophilic attack, largely parallel the values of $K_{c.3}$ although the values for **10** and **11** are inverted. For reaction with pyrrolidine values of the ratio k_{Am}/k_{-3} are available and show little dependence on the nature of the substrate. Similarly values of k_{AmH^+}, the rate constant for proton transfer to the 3-adduct, are for a given amine independent of the nature of the 1-substituent. This is expected since the steric situation at the 3-position itself, which will largely affect proton transfer rates, will be similar in all the compounds.

For each compound listed the values of $K_{c.3}$ and of k_3 decrease with amine in the order pyrrolidine > piperidine > n-butylamine. This order reflects the relative basicities of the amines[17] and indicates that there is little steric hindrance to attack at the unsubstituted 3-position. Values of k_{AmH^+} are observed to decrease by an order of magnitude from n-butylamine to pyrrolidine and by a further order of magnitude from pyrrolidine to piperidine. It has been argued previously[17,31] that in trinitro-activated substrates the ratio of k_{Am}/k_{AmH^+} will have a value of *ca.* 500, reflecting the higher acidities of zwitterionic adducts than of the corresponding ammonium ions. This ratio is not expected[17,31] to vary greatly with the nature of the substrate or the amine. Hence values of k_{Am} will also decrease in the order n-butylamine > pyrrolidine > piperidine. These reductions have the effect of changing the nature of the rate determining step in adduct formation. Thus with n-butylamine nucleophilic attack is rate-determining (k_{Am}[Am] > k_{-3}) and with piperidine proton transfer is rate-determining (k_{Am}[Am] < k_{-3}). Pyrrolidine gives the intermediate case where proton transfer is partially rate determining (k_{Am}[Am] ~ k_{-3}).

Table 8 Kinetic and equilibrium data[a] for formation of 3-adducts in DMSO at 25 °C



	9[b]	**3**	**10**[c]	**11**[d]
Reaction with n-butylamine				
$K_{c.3}$/dm^3 mol^{-1}	1000	210	15	33
k_3/dm^3 mol^{-1} s^{-1}	4.5 × 10^4	8000	3200	1500
$k_{-3}k_{AmH^+}/k_{Am}$ s^{-1}	45	38	210	45
k_{AmH^+}/dm^3 mol^{-1} s^{-1}	6 × 10^4	—	>4 × 10^4	—
Reaction with pyrrolidine				
$K_{c.3}$/dm^3 mol^{-1}	3500	1300	70	108
k_3/dm^3 mol^{-1} s^{-1}	7.5 × 10^5	1.0 × 10^5	5.0 × 10^4	1.3 × 10^4
k_{Am}/k_{-3} dm^3 mol^{-1}	14	40	15	22
k_{AmH^+}/dm^3 mol^{-1} s^{-1}	3000	3000	1 × 10^4	2600
Reaction with piperidine				
$K_{c.3}$/dm^3 mol^{-1}	2140	400	27	48
k_3k_{Am}/k_{-3} dm^6 mol^{-2} s^{-1}	6 × 10^5	1.7 × 10^5	4.3 × 10^4	1.5 × 10^4
k_{AmH^+}/dm^3 mol^{-1} s^{-1}	280	400	1600	500

[a] Statistical corrections have not been applied. [b] Data from ref. 17 and 32 for reaction at an unsubstituted ring-position. [c] Data from ref. 9 and 10. [d] Data from ref. 15.

Table 9 Kinetic and equilibrium data for reaction at the 1-position in DMSO at 25 °C

	3	**10**[a]	**1a**	**1b**[b]	**8**
Reaction with n-butylamine					
k_1/dm^3 mol^{-1} s^{-1}	410	250	31	32	0.042
$K_{c.1}$/dm^3 mol^{-1}	—	5 × 10^4		540	—
Reaction with pyrrolidine					
k_1/dm^3 mol^{-1} s^{-1}	1 × 10^4	4 × 10^3	590	650	1.1
k_{Am}/k_{-1} dm^3 mol^{-1}	20	30	41	—	45
K_1k_{Am}/dm^6 mol^{-2} s^{-1}	2 × 10^5	1.2 × 10^5	2.4 × 10^4	—	50
$k_4K_{c.1}$/dm^6 mol^{-2} s^{-1}	—	500	—	54	—
k_{AmH^+}/dm^3 mol^{-1} s^{-1}	—	60	—	—	—
Reaction with piperidine[c]					
k_1/dm^3 mol^{-1} s^{-1}	(5000)	(2000)	(300)	240	0.6
K_1k_{Am}/dm^6 mol^{-2} s^{-1}	3000	5600	550	—	0.8
k_{Am}/k_{-1} dm^3 mol^{-1}	(0.6)	(3)	(2)	—	1.3
k_{Am}/k_{DABCO}	—	—	6.5	—	6.2
$k_4K_{c.1}$/dm^6 mol^{-2} s^{-1}	—	(< 1)	—	0.0022	—

[a] Data from refs. 9, 10. [b] Data from refs. 6, 7, 8. [c] Figures in parentheses were calculated assuming that the value of k_1 for reaction with piperidine is half the value for reaction with pyrrolidine.

The substitution reaction

Substitution of the phenoxy group in **3** was observed as a slow reaction following rapid equilibration of the substrate with adducts, **4**, formed by reaction at the 3-position. In the case of **1a**, and of **8**, attack at the 1-position was the only process observed. In all cases substitution occurred without the appearance in spectroscopically observable concentrations of intermediates on the reaction pathway. Data are collected in Table 9 where they are compared with values for the corresponding ethyl ethers **10** and **1b**.

A noteworthy difference in behaviour of the phenyl and ethyl ethers is that, with the latter, anionic intermediates on the reaction pathway are directly observable. Thus in the reactions of **1b** and **10** with amines measurements may be made both on the formation of intermediates, such as **2b** and on their general acid catalysed conversion to products. Hence in these cases values are available for both the parameters $K_1k_{Am}(k_1k_{Am}/k_{-1})$ relating to formation of the intermediates and for $k_4K_{c.1}$ relating to their conversion to products.

Reactions of the phenyl ethers with n-butylamine are first order in amine indicating that nucleophilic attack is rate-limiting. With pyrrolidine and piperidine base catalysis is observed. Catalysis by DABCO indicates that this is general base catalysis so that proton transfer is rate-limiting or partially rate-limiting. Is this proton transfer from zwitterionic intermediates, such as **5**, to amine, or from ammonium ions to 1-adducts such as **6**? Although the SB-GA mechanism, the latter case, operates with alkyl ethers the evidence suggests that with phenyl ethers the rate-limiting proton transfer is from the zwitterion.

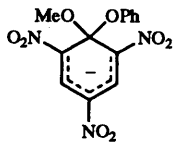
One factor arguing against the SB-GA mechanism is the failure to observe adducts **2a** or **6** on the reaction pathway with phenyl ethers. It might be argued that such adducts are not observed due to their low thermodynamic stability relative to the reactant so that they are present in very low concentrations. Nevertheless use of the data in Table 9 indicates that values of $K_{c.1}$ for the phenyl ethers should be greater than those for the ethyl ethers. For example comparison of the data for reaction of

pyrrolidine with **3** and **10** gives a ratio for k_1 values of 2.5:1 and a ratio for k_{Am}/k_1 of 0.7:1, since values of k_{AmH^+} are unlikely to be significantly different for the two substrates we obtain a ratio for values of $K_{c.1}$ ($=k_1k_{Am}/k_{-1}k_{AmH^+}$) of 2:1. Similarly in reactions with n-butylamine and piperidine the similar or higher values of k_1 for reaction with phenyl ethers compared to corresponding ethyl ethers are in accord with the significantly greater electron withdrawing effect of the phenoxy group relative to the ethoxy group. The inference is that sterically the phenoxy group is no worse than the ethoxy group for reaction at the 1-position. The SB-GA mechanism requires proton transfer from an ammonium ion to the anionic adduct to be rate limiting. Thus the failure to observe such intermediates in cases where they are thermodynamically favoured relative to the reactants is a strong argument against the mechanism. This argument holds for reaction of all amines with the naphthyl ether **1a**, where there is no alternative site for amine attack and for reactions of n-butylamine with **3**, where attack at the 1-position is thermodynamically preferred to attack at the 3-position. It is less strong for reaction of **3** with piperidine and pyrrolidine where the values of $K_{c.3}$ and $K_{c.1}$ are comparable. (The regiospecificity of attack is considered later.)

A further convincing argument against the SB-GA mechanisms comes from comparison of pyrrolidine:piperidine reactivity ratios. It is well documented[7,8,33] that, for stereoelectronic reasons, reactions which involve rate determining leaving group expulsion are very much more rapid when pyrrolidine is the nucleophile than for reactions involving piperidine. Thus values of $k_4K_{c.1}$ for reaction of **1b** with pyrrolidine and piperidine are 54 and 0.0022 $dm^6\ mol^{-2}\ s^{-1}$ respectively,[7] giving a ratio of 2.5×10^4. We have interpreted base catalysis in the reactions of **1a** in terms of rate limiting proton transfer from the zwitterionic intermediate leading to values for K_1k_{Am} of $2.4 \times 10^4\ dm^6\ mol^{-2}\ s^{-1}$ for pyrrolidine and 550 $dm^6\ mol^{-2}\ s^{-1}$ for piperidine. If the data were interpreted in terms of the SB-GA mechanism then these values would correspond to values of $k_4K_{c.1}$. The observed ratio for pyrrolidine:piperidine of 44:1 is too small to be compatible with rate limiting departure of the nucleofuge. However it is readily interpretable in terms of the K_1k_{Am} values since for reaction with pyrrolidine the value of K_1 is expected to be 2–3 times larger than for reaction with piperidine, and the value of k_{Am} is expected to be about 10–20 times larger.[32]

For reaction of **10** values of both K_1k_{Am} and $k_4K_{c.1}$ are available. For reaction with pyrrolidine these values are 1.2×10^5 and 500 $dm^6\ mol^{-2}\ s^{-1}$ respectively. For the phenyl ether, **3**, the observed value of $2 \times 10^5\ dm^6\ mol^{-2}\ s^{-1}$ corresponds precisely to that expected for K_1k_{Am}. Thus the value of K_1 is expected to be *ca.* twice as large for **3** as for **10** while values of k_{Am} will be similar. This is further evidence that the parameter we are measuring is K_1k_{Am} corresponding to rate determining proton transfer from the zwitterionic intermediates.

As Bernasconi[21] has pointed out there should be no thermodynamic driving force for acid catalysis of the k_4 step since this would involve proton transfer from a weaker acid, the substituted ammonium ion, to a stronger acid, the phenolic leaving group. Our conclusion is that in DMSO, as in water,[21] for the phenyl ethers base catalysis reflects rate-limiting proton transfer from zwitterionic intermediates. The anionic intermediates, once formed, rapidly decompose by uncatalysed loss of phenoxide to give the substitution products. The difference in behaviour between alkyl and phenyl ethers derives from the different leaving group abilities of alkoxide and phenoxide ions. Thus it is known[34] that phenoxide departure is 10^6 times faster than methoxide departure from the adduct **12**.



12

Our results show that base catalysis is observed in reactions of the phenyl ethers with pyrrolidine and with piperidine but not with n-butylamine. The observation of base catalysis depends on the value of the ratio k_{Am}/k_{-1}. Results from this and previous work[9,17,32] show that values of k_{Am} decrease in the order n-butylamine > pyrrolidine > piperidine reflecting increasing steric hindrance to approach of the amine to the zwitterionic intermediate. Further, values of k_{-1} are expected to increase for secondary amines compared to primary amines due to increased steric congestion in zwitterions, such as **5**. Both these factors will lead to decreases in the value of k_{Am}/k_{-1} in the series n-butylamine, pyrrolidine, piperidine and hence to the observation of rate-limiting proton transfer with the latter amines. Our results, Table 9, show that DABCO is a somewhat less efficient catalyst than piperidine, $k_{piperidine}/k_{DABCO} = 6$; this is in accord with data from related systems[16,17,32] involving rate-limiting proton transfer where values of k_{Amine}/k_{DABCO} are in the range 3–6.

The results in Table 9 show that for a particular amine the values of k_{Am}/k_{-1} do not show a marked dependence on the nature of the substrate. Values of k_{Am} will be sensitive to the steric situation at the 1-position, so that the presence of *ortho* substituents will result in their reduction. Values of k_{-1} will tend to increase as ring activation decreases, and the zwitterionic intermediates become less stable. In the series 2,4,6-trinitrophenyl, 2,4-dinitronaphthyl, 2,4-dinitrophenyl values of k_{Am} will increase (as the steric interference decreases) but values of k_{-1} will also increase (as the ring activation decreases). Hence the factors compensate each other. Hirst and co-workers[25] have shown that reactions of phenyl 2,6-dinitrophenyl ether with amines are susceptible to base catalysis, and here even the reaction with n-butylamine is catalysed. This may be attributed to the high value for k_{-1}, associated with low ring activation, and low value for k_{Am} due to steric interference at the reaction centre.

Regiospecificity of amine attack

There is current interest in the kinetic and thermodynamic preferences shown by 1-substituted 2,4,6-trinitrobenzenes in their reactions with nucleophiles.[19,20] Comparison of data in Tables 8 and 9 show that for both **3** and **10** values of k_3 are, for a given amine, larger than values of k_1 by at least an order of magnitude. Hence there is a kinetic preference for attack at the 3-position. For **10** values of $K_{c.1}$ are larger than for $K_{c.3}$ although the ratio $K_{c.1}:K_{c.3}$ decreases from 3000 for n-butylamine to 28 for pyrrolidine and 22 for piperidine.[9,10] This behaviour may be described as K3 T1 in Buncel's nomenclature;[19,20] kinetic preference for reaction at the 3-position but thermodynamic preference for formation of the adduct at the 1-position.

Adducts **6** resulting from attack at the 1-position of **3** are not observed since they spontaneously decompose to substitution products. Nevertheless it is possible, as described previously in this paper, to estimate values for $K_{c.1}$ which are *ca.* twice as large as corresponding values for formation of adducts from **10**. This approach leads to ratios of $K_{c.1}:K_{c.3}$ of 480 for n-butylamine, 3 for pyrrolidine and 3 for piperidine. Hence the behaviour is also K3 T1 although with the secondary amines there is no strong thermodynamic preference for attack at the 1-position.

The smaller values of the ratio $K_{c.1}:K_{c.3}$ observed for secondary amines than for n-butylamine may reflect steric interactions in adducts, **6**, between the bulky substituents at the 1-position and the *ortho*-substituents.

For the phenyl sulfide, **11**, 3-adducts are initially formed indicating kinetic preference for attack at the 3-position, and values of $K_{c.3}$ are available (Table 8). The value for reaction with pyrrolidine is 108 dm^3 mol^{-1}. For reaction with this amine a value for K_1k_{Am} of 250 dm^6 mol^{-2} s^{-1} has been reported.[15] If we assume a value for k_{AmH^+} of 60 dm^3 mol^{-1} s^{-1}, similar to that for other 1-substituted trinitrobenzenes then we may calculate a value for $K_{c.1}$ of 4 dm^3 mol^{-1}. Hence here the 3-adduct is favoured both kinetically and thermodynamically, K3 T3 behaviour. Similar behaviour may be predicted for the secondary amine, piperidine. However by analogy with the phenyl ethers the $K_{c.1}:K_{c.3}$ ratio should be at least one hundred times greater for n-butylamine than for reaction with the secondary amines. Hence with the primary amine K3 T1 behaviour is predicted. The lower propensity for reaction at the 1-position of phenyl sulfides relative to phenyl ethers may be attributed to the lower electronegativity of sulfur relative to oxygen and to its greater steric requirement leading to greater unfavourable congestion in the 1-adducts.[35]

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Paper 5/03538D
Received 2nd *June* 1995
Accepted 29th *June* 1995