The reactions of 4-nitrobenzofuroxan with amines in DMSO; kinetic and equilibrium studies

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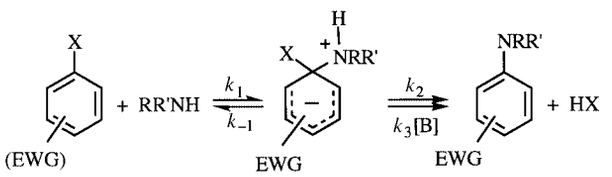
Kinetic and equilibrium studies are reported for the reactions of six aliphatic amines with 4-nitrobenzofuroxan, **3**, in dimethyl sulfoxide. Rapid reaction at the 5-position to yield σ-adducts is followed by slower formation of the thermodynamically more stable adducts at the 7-position. ^{1}H NMR spectra are reported. The results are compared with those for reaction of the amines with 1,3,5-trinitrobenzene, **2**. These reactions involve the initial formation of zwitterionic intermediates which transfer an amino proton to a second molecule of amine. It is found that the proton-transfer step is less likely to be rate determining in the reactions of **3** than of **2**; this may be due to the lower steric requirements of **3**.

Kinetic studies of the reactions of aromatic substrates with amine nucleophiles have provided important evidence for the S_NAr mechanism of substitution[1–3] (Scheme 1). It has been



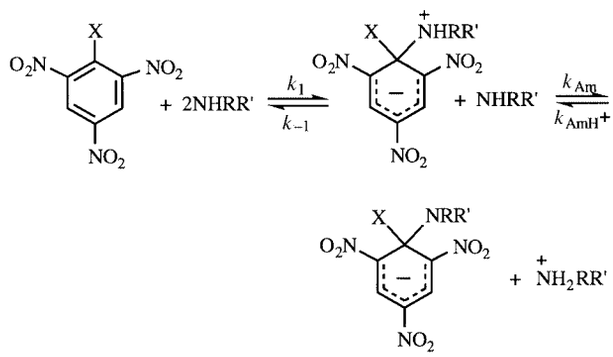
1

EWG = electron withdrawing group(s)

Scheme 1

shown that base catalysis in such reactions may result from rate-limiting proton transfer[4–6] from the zwitterionic intermediate, **1**, or, alternatively, may involve rapid interconversion of **1** with its deprotonated form followed by general acid catalysis of leaving group departure[1,7–9] (the SB-GA mechanism). In dimethyl sulfoxide (DMSO) as solvent the latter possibility becomes more likely with decreasing nucleofugality of the leaving group.

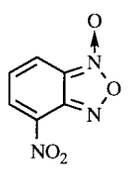
Useful information about the values of rate constants for proton transfer between nitrogen atoms in these systems has come from studies involving substrates such as 1,3,5-trinitrobenzene, **2**, where stable σ-adducts are formed. These studies have shown that in DMSO the proton transfer step in Scheme 2 may be rate-limiting, with values of k_{Am} considerably



Scheme 2 1,3,5-Trinitrobenzene, **2**, X = H.

lower than the diffusion-controlled limit.[10–14] There is evidence that steric congestion at the reaction centre may decrease the value of k_{Am}, so that lower values are obtained with secondary than with primary amines, and also when the size of the X group is increased.[15]

In the present study we report kinetic and equilibrium results for reaction of six aliphatic amines with 4-nitrobenzofuroxan, **3**, in DMSO. One of the aims of this work was to examine



3

σ-adduct forming reactions with amine nucleophiles in an activated system where steric effects are likely to be less pronounced than in a trinitro-activated benzene ring.

3 is also of interest since it has been shown that its action as an *in vitro* inhibitor of nucleic acid and protein biosynthesis in animal cells probably involves σ-adduct formation.[16–18] There have been previous studies of its reactions with oxygen nucleophiles. NMR studies have shown that reaction with methoxide ions results in rapid attack at the 5-position followed by slower isomerisation to the thermodynamically more stable 7-methoxy σ-adduct.[19,20] Kinetic and equilibrium data have been reported for these reactions in methanol,[21] and also for similar reactions of 4-nitrobenzofurazan derivatives.[22] NMR studies[23] of the reaction of **3** with aryloxides have shown that reaction occurs *via* the oxygen centre of these potentially ambident nucleophiles; in contrast with methoxide addition the 7-aryloxy adducts are preferred both kinetically and thermodynamically to the 5-adducts. There have been several reports[20,24] showing that, following initial σ-adduct formation, reaction of **3** with nucleophiles may result in slow irreversible reactions yielding 4-nitrobenzofurazan derivatives.

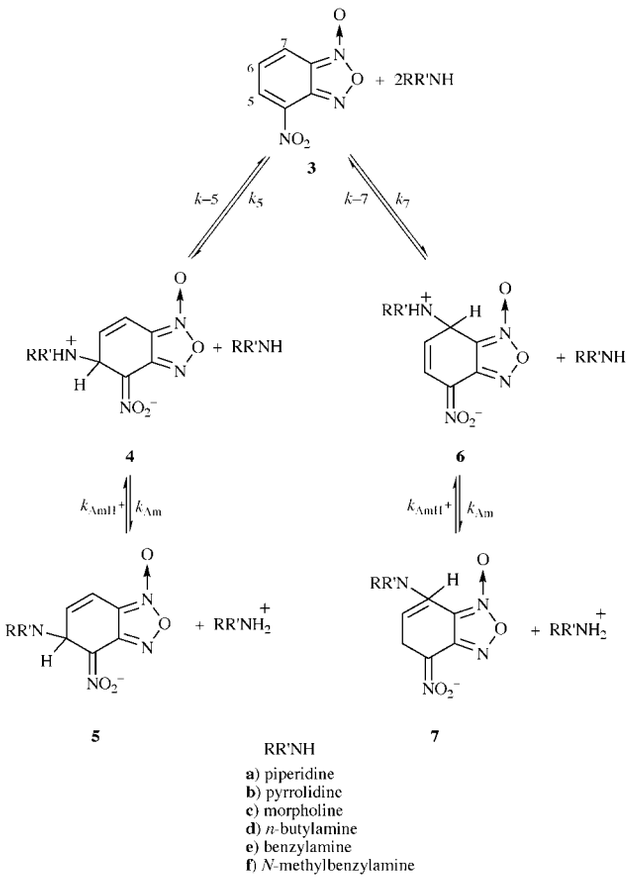
Results and discussion

Our results for the reactions of **3** with six aliphatic amines in DMSO provide evidence for the σ-adduct forming reactions shown in Scheme 3. The ^{1}H NMR spectra, recorded immedi-

Table 1 ^{1}H NMR data[a] for **3** and adducts, **7**, in [$^2H_6$]-DMSO

	^{1}H NMR Shifts					
	H5	H6	H7	J_{56}	J_{67}	Other[b]
3	8.61	7.53	8.13	7.3	8.9	
7a	6.94	4.92	4.47	10.2	4.4	2.5(2H), 2.2(2H), 1.3(6H)
7b	6.99	5.03	4.73	10.4	4.6	2.6(2H), 2.4(2H), 1.6(4H)
7c	7.04	5.00	4.61	10.4	4.4	3.48(4H), 2.60(2H), 2.35(2H)
7d	6.93	4.94	4.62	10.4	4.4	2.35(1H), 2.15(1H), 1.40(2H), 0.82(3H)
7e	6.99	5.00	4.71	10.2	4.2	4.95(NH), 3.61(1H), 3.41(1H)
7f	7.09	5.14	4.73	10.4	4.4	3.59(2H), 2.05(NMe)

[a] *J* values in Hz. [b] Non-equivalence is observed for hydrogen atoms on the carbon atom(s) α to nitrogen in the adducts.

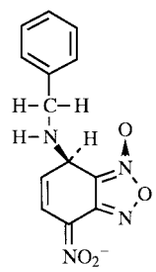


Scheme 3

ately after mixing, of **3** in the presence of a four-fold excess of amine in [$^2H_6$]-DMSO indicate that the thermodynamically stable adducts result from reaction at the 7-position to give **7**. The data summarised in Table 1 show that in the adducts, **7**, spin-coupled bands are observed for H7 at *ca.* δ 4.6, for H6 at *ca.* 5.0 and for H5 at *ca.* 7.0. Interestingly the spectra show that in the adducts rotation is slow about the nitrogen to α-carbon bond in the added amine. For example in **7e**, the adduct from benzylamine, the methylene hydrogens give an AB quartet with δ 3.41 and 3.61 and *J* 13.4 Hz. In a related manner in the piperidine adduct, **7a**, the two methylene groups adjacent to nitrogen give distinct multiplets at δ 2.2 and δ 2.5. The NMR spectra show that the initial formation of σ-adducts is followed by slow irreversible decomposition reactions which were not investigated.

Comparison with data for the isomeric methoxide adducts[19] shows that the spectra obtained are not compatible with formation of **5**, where H6 is expected to be considerably less shielded than is observed.

Kinetic measurements by stopped flow spectrophotometry generally showed two rate processes associated with σ-adduct



7e

formation. These are reasonably attributed to the rapid formation of adducts **5** followed by slower formation of the thermodynamically more stable adducts, **7**. The UV absorption spectrum of **3** shows a band at 414 nm, ε 8×10^3 dm^3 mol^{-1} cm^{-1}; on adduct formation the maximum shifts to 350 nm, ε 1.5×10^4 dm^3 mol^{-1} cm^{-1} with a shoulder at 400 nm. Kinetic measurements were made at 350 nm under first order conditions. Thus for reactions in buffers (amine plus amine salt) the buffer components were in large excess of the substrate concentration (2–4 $\times$ 10^{-5} mol dm^{-3}). For reactions with amines in the absence of added amine salts a sufficient excess of amine was used to ensure >95% conversion to adduct at equilibrium. Under these conditions eqn. (1) applies and was used to calculate rate constants.

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

It is assumed that the zwitterionic forms **4** and **6** may be treated as steady state intermediates, so that the general rate expression for reaction at the 5-position to give **5** is eqn. (2).

$$k_{fast} = \frac{k_5 k_{Am}[Am]^2 + k_{-5}k_{AmH^+}[AmH^+]}{k_{-5} + k_{Am}[Am]} \qquad (2)$$

The overall equilibrium constant for formation of the 5-adduct is defined in eqn. (3). Values of k_{fast} were, in most cases, high

$$K_{c,5} = \frac{[\mathbf{5}][AmH^+]}{[\mathbf{3}][Am]^2} = \frac{k_5 \cdot k_{Am}}{k_{-5} \cdot k_{AmH^+}} \qquad (3)$$

and towards the limit of detection by the stopped-flow method. In addition, particularly in the presence of amine salts, amplitudes were low. Hence only limited measurements of k_{fast} were possible.

The general rate equation for the equilibration of **3** and **7**, in the presence of **5**, is eqn. (4). If, in the formation of **7**, the proton transfer equilibrium between **6** and **7** is rapid (corresponding to the condition $k_{Am}[Am] \gg k_{-7}$) then eqn. (4) reduces to eqn. (5). The overall equilibrium constant for formation of **7**

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

Item	[Piperidine]/ mol dm^{-3}	[Piperidine H$^+$Cl$^-$]/ mol dm^{-3}	k_{fast} [a]/s^{-1}	k_{calc} [b]/s^{-1}	k_{slow}/s^{-1}	k_{calc} [c]/s^{-1}
1	0.002	0	62	57	—	—
2	0.004	0	200	190	—	—
3	0.006	0	380	380	—	—
4	0.008	0	620	600	—	—
5	0.010	0	800	850	—	—
6	0.001	0.10	—	—	9.8	9.6
7	0.002	0.10	—	—	9.1	8.7
8	0.004	0.10	—	—	12.1	12.1
9	0.007	0.10	—	—	19.4	19.2
10	0.010	0.10	—	—	26.6	26.7
11	0.001	0.06 [d]	—	—	5.7	5.8
12	0.001	0.04 [d]	—	—	4.3	5.2
13	0.001	0.02 [d]	—	—	3.1	4.0
14	0.002	0.02 [d]	—	—	5.5	5.9
15	0.001	0.06	—	—	8.0	—
16	0.001	0.04	—	—	6.7	—
17	0.001	0.02	—	—	5.2	—
18	0.002	0.02	—	—	6.6	—
19	0.002	0.005	—	—	6.0	6.1
20	0.003	0.005	—	—	8.6	8.6
21	0.004	0.005	—	—	11.1	10.9
22	0.006	0.005	—	—	14.4	14.5
23	0.008	0.005	—	—	17.1	17.1
24	0.010	0.005	—	—	18.9	18.9

[a] Where no value is given, rate constants were too high for measurement. [b] Calculated from eqn. (8) with K_5k_{Am} 1.7 × 10^7 dm^6 mol^{-2} s^{-1} and k_{Am}/k_{-5} 100 dm^3 mol^{-1}. [c] Calculated from eqn. (5) or (9), with values given in the text. [d] Salt concentration maintained at 0.10 mol dm^{-3} using tetra-*n*-butylammonium chloride.

$$k_{slow} = \frac{k_7k_{Am}[Am]^2}{(k_{-7} + k_{Am}[Am])\left(1 + \frac{K_{c,5}[Am]^2}{[AmH^+]}\right)} + \frac{k_{-7}k_{AmH^+}[AmH^+]}{k_{-7} + k_{Am}[Am]} \quad (4)$$

$$k_{slow} = \frac{k_7[Am]}{\left(1 + \frac{K_{c,5}[Am]^2}{[AmH^+]}\right)} + \frac{k_{-7}k_{AmH^+}}{k_{Am}}\frac{[AmH^+]}{[Am]} \quad (5)$$

is given in eqn. (6). It should be noted that, in general, the

$$K_{c,7} = \frac{[\mathbf{7}][AmH^+]}{[\mathbf{3}][Am]^2} = \frac{k_7{\cdot}k_{Am}}{k_{-7}{\cdot}k_{AmH^+}} \quad (6)$$

values of k_{Am} in formation of **5** and **7** will have different values; similarly values of k_{AmH^+}.

In order to obtain the maximum kinetic information it was necessary to make rate measurements at different concentrations of amine salt. Measurements were made at low, ≤0.01 mol dm^{-3}, salt concentration and also at higher, 0.10 mol dm^{-3}, concentrations using perchlorate and/or chloride salts. It was found that values of the equilibrium constant $K_{c,5}$ and $K_{c,7}$ were slightly higher at the higher salt concentration. This is attributable to a general salt effect expected for the formation of ionic products from neutral reactants. In agreement with previous work,[7,12,15] a specific effect of chloride ions was also observed. Thus it is known that stabilisation of substituted ammonium ions occurs by association with chloride ions. The values of K_{Cl^-} defined in eqn. (7) are *ca.* 10 dm^3 mol^{-1}. The expected effect of

$$RR'NH_2^+ + Cl^- \xrightarrow{K_{Cl^-}} RR'NH_2^+ \cdots Cl^- \quad (7)$$

a 0.1 mol dm^{-3} chloride concentration[7,12,15] is to increase values of $K_{c,5}$ and $K_{c,7}$ by a factor of *ca.* 2.0. The main effect on rate constants is expected to be a *ca.* two-fold lowering in values of k_{AmH^+}.

Reactions of piperidine

Data are in Table 2. In the absence of added salt it was possible to measure rate constants for the rapid process corresponding to the formation of **5a**. Since no amine salt is present the reverse reaction makes a negligible contribution to the rate expression. Hence eqn. (2) commutes to eqn. (8) where $K_5 = k_5/k_{-5}$. The

$$k_{fast} = \frac{K_5k_{Am}[Am]^2}{1 + \frac{k_{Am}[Am]}{k_{-5}}} \quad (8)$$

results, items 1–5, show that k_{fast} shows a dependence between first and second order on the amine concentration. Values calculated with K_5k_{Am} 1.7 × 10^7 dm^6 mol^{-2} s^{-1} and k_{Am}/k_{-5} 100 dm^3 mol^{-1} give a good fit with the experimental data. These values lead to a value for k_5 of 1.7 × 10^5 dm^3 mol^{-1} s^{-1}. Since a value of 27 dm^3 mol^{-1} is calculated later for the value of $K_{c,5}$ at low salt concentration it is possible to calculate using eqn. (3) a value for k_{AmH^+} of 6 × 10^5 dm^3 mol^{-1} s^{-1}.

It was found that values of k_{slow}, measured in the presence of piperidine hydrochloride, are correlated by eqn. (5). This indicates that the proton transfer equilibrium **6a**⇌**7a** is rapid with $k_{Am}/k_{-7} > 1000$ dm^3 mol^{-1}. The results also show that when [amine salt] ≥ 0.01 mol dm^{-3} the initial formation of **5a** was sufficiently inhibited that eqn. (5) reduces to eqn. (9).

$$k_{slow} = k_7[Am] + \frac{k_{-7}{\cdot}k_{AmH^+}}{k_{Am}}\frac{[AmH^+]}{[Am]} \quad (9)$$

Items 6–10 in Table 2 give an excellent fit with this equation with values of k_7 2600 ± 200 dm^3 mol^{-1} s^{-1} and $k_{-7}{\cdot}k_{AmH^+}/k_{Am}$ 0.07 ± 0.01 s^{-1}. Combination of these values, using eqn. (6), gives a value for $K_{c,7}$ of (3.7 ± 0.5) × 10^4 dm^3 mol^{-1}. Items 11–14 obtained with varying concentrations of piperidine hydrochloride but with the ionic strength maintained also gave an acceptable fit with the above parameters. Items 15–18 were used to calculate the variation of $k_{AmH^+}k_{-7}/k_{Am}$ with piperidine hydrochloride concentration. Values calculated for this par-

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

Item	[Pyrrolidine]/ mol dm^{-3}	[Pyrrolidine $H^+ClO_4^-$]/ mol dm^{-3}	k_{slow}/s^{-1}	k_{calc} [a]/s^{-1}
1	0.001	0.01	9.4	9.4
2	0.002	0.01	12.4	12.8
3	0.003	0.01	17.1	17.1
4	0.005	0.01	25.6	25.4
5	0.01	0.01	38	38
6	0.02	0.01	38	38
7	0.03	0.01	34	32
8	0.04	0.01	29	26
		[Pyrrolidine H^+Cl^-]/mol dm^{-3}		
9	0.001	0.01	8.5	8.5
10	0.002	0.01	12.1	11.9
11	0.003	0.01	16.9	16.0
12	0.005	0.01	25	24
13	0.01	0.01	33	33
14	0.02	0.01	32	32
15	0.03	0.01	27	26
16	0.04	0.01	21	21
17	0.002	0.10	16	16
18	0.003	0.10	17	19
19	0.005	0.10	25	26
20	0.01	0.10	46	46
21	0.0125	0.10	54	54

[a] Calculated using eqn. (5) with the following values: items 1–8, k_7 (5500 ± 500) dm^3 mol^{-1} s^{-1}, $k_{-7}k_{AmH^+}/k_{Am}$ (0.39 ± 0.05) s^{-1} and $K_{c,5}$ (47 ± 5) dm^3 mol^{-1}; items 9–16, k_7 (5200 ± 500) dm^3 mol^{-1} s^{-1}, $k_{-7}k_{AmH^+}/k_{Am}$ (0.33 ± 0.05) s^{-1} and $K_{c,5}$ (57 ± 5) dm^3 mol^{-1}; items 17–21, k_7 (4900 ± 500) dm^3 mol^{-1} s^{-1}, $k_{-7}k_{AmH^+}/k_{Am}$ (0.12 ± 0.03) s^{-1} and $K_{c,5}$ (100 ± 50) dm^3 mol^{-1}.

ameter from eqn. (9), on the assumption that k_{Am} is constant, increased from 0.07 to 0.14 s^{-1} as the concentration of amine salt was decreased from 0.1 to 0.02 mol dm^{-3}. This allowed the estimation of a value for $k_{AmH^+}k_{-7}/k_{Am}$ of 0.16 s^{-1} at a salt concentration of 0.005 mol dm^{-3}. Use of this value in eqn. (5) together with values of k_7 2900 ± 300 dm^3 mol^{-1} s^{-1}, and $K_{c,5}$ 27 ± 5 dm^3 mol^{-1} gave an excellent fit for items 19–24. Combination of these values of k_7 and $k_{AmH^+}k_{-7}/k_{Am}$ using eqn. (6) leads to a value at low salt concentration of (1.8 ± 0.4) × 10^4 for $K_{c,7}$.

Reactions with pyrrolidine

Two reactions were observed, the faster of which was inconveniently rapid for measurement. Data for the slower reaction, corresponding to equilibration with adduct **7b**, are in Table 3. Values of k_{slow} measured in the presence of 0.01 mol dm^{-3} pyrrolidine perchlorate or hydrochloride go through a maximum with increasing pyrrolidine concentration as predicted by eqn. (5). Combination of values using eqn. (6) gives values of $K_{c,7}$ (1.4 ± 0.2) × 10^4 and (1.6 ± 0.3) × 10^4 dm^3 mol^{-1} respectively. In the presence of 0.1 mol dm^{-3} pyrrolidine hydrochloride the value of $K_{c,7}$ is increased to (4 ± 1) × 10^4 dm^3 mol^{-1}.

Reactions with morpholine

Morpholine is considerably less basic than piperidine or pyrrolidine and the presence of 0.001 mol dm^{-3} amine salt was sufficient to inhibit formation of the adduct **5c**. A limit for $K_{c,5}$ < 1 dm^3 mol^{-1} may be calculated. Values of k_{slow} in Table 4 measured in the presence of 0.1 mol dm^{-3} morpholine hydrochloride give an excellent fit with eqn. (9), and lead to a value of $K_{c,7}$ of (550 ± 100) dm^3 mol^{-1}. We may predict a value at 0.01 mol dm^{-3} amine salt for $K_{c,7}$ of 280 dm^3 mol^{-1}. In the presence of 0.001 mol dm^{-3} amine salt the final term in eqn. (9) becomes

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

Item	[Morpholine]/ mol dm^{-3}	[Morpholine hydrochloride]/ mol dm^{-3}	k_{slow}/s^{-1}	k_{calc} [a]/s^{-1}
1	0.006	0.10	12.7	13.1
2	0.008	0.10	11.3	11.1
3	0.010	0.10	10.2	10.2
4	0.012	0.10	10.0	9.8
5	0.014	0.10	9.8	9.7
6	0.016	0.10	10.0	9.9
7	0.018	0.10	10.1	10.2
8	0.020	0.10	10.5	10.5
9	0.006	0.001	1.47	1.5
10	0.010	0.001	2.42	2.5
11	0.014	0.001	3.44	3.5
12	0.018	0.001	4.40	4.5
13	0.020	0.001	4.96	5.0

[a] Calculated from eqn. (9) with values as follows: items 1–8, k_7 360 ± 60 dm^3 mol^{-1} s^{-1}, $k_{AmH^+}\cdot k_{-7}/k_{Am}$ 0.66 ± 0.06 s^{-1}; items 9–13, k_7 250 ± 30 dm^3 mol^{-1} s^{-1}, $k_{AmH^+}k_{-7}/k_{Am}$ 0 s^{-1}.

negligible so that a linear dependence of k_{slow} on amine concentration is observed (Table 4) with a value for k_7 of 250 ± 30 dm^3 mol^{-1} s^{-1}.

Reactions with *n*-butylamine

Both processes, involving formation of the adducts **5d** and **7d**, were measurable. Analysis of the data in Table 5 indicates that the proton transfer equilibria between zwitterionic intermediates and anionic adducts are rapid, and limits may be set at k_{Am}/k_{-5} > 2000 dm^3 mol^{-1} and k_{Am}/k_{-7} > 1000 dm^3 mol^{-1}. Hence eqn. (2) reduces to eqn. (10). Values of k_{fast} calculated with k_5

$$k_{fast} = k_5[Am] + \frac{k_{-5}\cdot k_{AmH^+}}{k_{Am}}\frac{[AmH^+]}{[Am]} \qquad (10)$$

(1.7 ± 0.2) × 10^4 dm^3 mol^{-1} s^{-1} and $k_{-5}\cdot k_{AmH^+}/k_{Am}$ (155 ± 15) s^{-1} gave a good fit with this equation and lead to a value for $K_{c,5}$ of (110 ± 20) dm^3 mol^{-1}.

The values of k_{slow} measured at 0.01 mol dm^{-3} salt concentration correspond to eqn. (5) with k_7 (140 ± 20) dm^3 mol^{-1} s^{-1}, $k_{-7}\cdot k_{AmH^+}/k_{Am}$ (0.025 ± 0.005) s^{-1} and $K_{c,5}$ (90 ± 10) dm^3 mol^{-1}. Combination of these values leads to $K_{c,7}$ (5.6 ± 1) × 10^3 dm^3 mol^{-1}. In the presence of amine hydrochloride, 0.1 mol dm^{-3}, the values of best fit to eqn. (5) are k_7 (115 ± 10) dm^3 mol^{-1} s^{-1}, $k_{-7}\cdot k_{AmH^+}/k_{Am}$ (0.0088 ± 0.0010) s^{-1} and $K_{c,5}$ (205 ± 20) dm^3 mol^{-1}. These allow the calculation of $K_{c,7}$ (1.3 ± 0.2) × 10^4 dm^3 mol^{-1}. As expected values of $K_{c,5}$ and $K_{c,7}$ are increased by a factor of *ca.* 2 in the presence of 0.1 molar amine hydrochloride.

Reactions with benzylamine

Data for the slow reaction are in Table 6. They indicate that the proton transfer equilibrium **6e**⇌**7e** is rapid with k_{Am}/k_{-7} > 500 dm^3 mol^{-1}. Values of rate constants give a good fit with eqn. (5) with the parameters appending the Table.

Reactions with *N*-methylbenzylamine

In contrast with the results obtained for benzylamine the data in Table 7 indicate that with *N*-methylbenzylamine proton transfer is partially rate limiting in the formation of both **5f** and **7f**. It was possible to follow the formation of the 5-adduct in the absence of amine salt. Items 1–3 in the Table show an approximately squared dependence on the amine concentration consistent with eqn. (11) which is the form of eqn. (8) when

Table 5 Kinetic data for reaction of **3** with *n*-butylamine in DMSO at 25 °C

Item	[*n*-Butylamine]/ mol dm^{-3}	[*n*-Butylamine hydrochloride]/ mol dm^{-3}	k_{fast}/s^{-1}	k_{calc}[a]/s^{-1}	k_{slow}/s^{-1}	k_{calc}[b]/s^{-1}
1	0.004	0.001	118	114	—	—
2	0.006	0.001	136	136	—	—
3	0.008	0.001	164	165	—	—
4	0.010	0.001	195	198	—	—
5	0.002	0.010	—	—	0.39	0.41
6	0.004	0.010	—	—	0.59	0.57
7	0.006	0.010	340	340	0.75	0.70
8	0.008	0.010	280	310	0.77	0.77
9	0.010	0.010	300	300	0.78	0.79
10	0.020	0.010	460	390	0.64	0.64
11	0.040	0.010	740	660	0.38	0.38
12	0.050	0.010	810	810	0.33	0.31
13	0.002	0.10	—	—	0.67	0.67
14	0.003	0.10	—	—	0.61	0.63
15	0.004	0.10	—	—	0.66	0.67
16	0.006	0.10	—	—	0.83	0.79
17	0.008	0.10	—	—	0.98	0.92
18	0.010	0.10	—	—	1.09	1.04
19	0.012	0.10	—	—	1.13	1.14
20	0.014	0.10	—	—	1.17	1.21
21	0.016	0.10	—	—	1.22	1.26

[a] Calculated using eqn. (10) with the following values: items 1–4, k_5 1.8×10^4 dm^3 mol^{-1} s^{-1}, k_{-5}·k_{AmH^+}/k_{Am} 166 s^{-1}; items 7–12, k_5 1.6×10^4 dm^3 mol^{-1} s^{-1}, k_{-5}·k_{AmH^+}/k_{Am} 145 s^{-1}. [b] Calculated using eqn. (5) with the values: items 5–12, k_7 146 dm^3 mol^{-1} s^{-1}; $k_{-7}k_{AmH^+}/k_{Am}$ 0.025 s^{-1} and $K_{c,5}$ 91 dm^3 mol^{-1}; items 13–21, k_7 115 dm^3 mol^{-1} s^{-1}, k_{-7}·k_{AmH^+}/k_{Am} 0.0088 s^{-1}, and $K_{c,5}$ 205 dm^3 mol^{-1}.

Table 6 Kinetic data for reaction of **3** with benzylamine in DMSO at 25 °C

Item	[Benzylamine]/ mol dm^{-3}	[Benzylamine H^+, ClO_4^-]/ mol dm^{-3}	k_{slow}/s^{-1}	k_{calc}[a]/s^{-1}
1	0.002	0.01	0.82	0.72
2	0.003	0.01	0.55	0.55
3	0.005	0.01	0.45	0.45
4	0.01	0.01	0.50	0.51
5	0.02	0.01	0.77	0.75
6	0.03	0.01	0.92	0.92
7	0.04	0.01	0.99	0.99
8	0.06	0.01	0.98	0.99
9	0.01	0.10	1.12	1.22
10	0.02	0.10	1.04	1.10
11	0.03	0.10	1.24	1.25
12	0.04	0.10	1.46	1.45
13	0.06	0.10	1.81	1.83

[a] Calculated from eqn. (5) with the following values: items 1–8, k_7 (40 ± 5) dm^3 mol^{-1} s^{-1}, k_{-7}·k_{AmH^+}/k_{Am} (0.13 ± 0.02) s^{-1} and $K_{c,5}$ (4.1 ± 1) dm^3 mol^{-1}. Items 9–13, k_7 (33 ± 5) dm^3 mol^{-1} s^{-1}, k_{-7}·k_{AmH^+}/k_{Am} (0.09 ± 0.02) s^{-1} and $K_{c,5}$ (5 ±1) dm^3 mol^{-1}.

$$k_{fast} = K_5 k_{Am}[Am]^2 \quad (11)$$

$k_{-5} \gg k_{Am}[Am]$. A value for K_5k_{Am} of $(1.6 \pm 0.4) \times 10^5$ dm^6 mol^{-2} s^{-1} is obtained.

$$k_{slow} = \frac{K_7 k_{Am}[Am]^2 + k_{AmH^+}[AmH^+]}{1 + k_{Am}[Am]/k_{-7}} \quad (12)$$

The presence of 0.01 mol dm^{-3} amine salt is sufficient to inhibit formation of **5f** and the data are fitted by eqn. (12) which is a form of eqn. (4) when $K_{c,5} \ll 1$. Items 4–10 in Table 7 yield values for K_7k_{Am} 8600 ± 2000 dm^6 mol^{-2} s^{-1}, k_{Am}/k_{-7} 25 ± 10 dm^3 mol^{-1} and k_{AmH^+} 170 ± 10 dm^3 mol^{-1} s^{-1}. Combination of these values gives k_7 340 ± 100 dm^3 mol^{-1} s^{-1} and $K_{c,7}$ 50 ± 10 dm^3 mol^{-1}. The only changes in these parameters in the presence of 0.1 mol dm^{-3} salt, items 11–16, are a reduction in the value of k_{AmH^+} to 75 dm^3 mol^{-1} s^{-1} leading to a value for $K_{c,7}$ of 110 ± 20 dm^3 mol^{-1}.

Comparisons

Results are summarised in Table 8, where they are compared with corresponding values for reactions of 1,3,5-trinitrobenzene, **2**.

The data show, in agreement with NMR results, that the 7-adducts from **3** are considerably more stable thermodynamically than the isomeric 5-adducts. Thus values of $K_{c,7}$ are *ca.* 100 times larger than values of $K_{c,5}$. The actual value of the ratio $K_{c,7}/K_{c,5}$ depends slightly on the nature of the amine, and increases from 50 for *n*-butylamine and 73 for benzylamine to 300 for pyrrolidine and 600 for piperidine. These increases may indicate some unfavourable steric interactions with the *ortho*-nitro group in the adducts **5a** and **5b** formed by addition of the bulkier secondary amines.

Nevertheless the 5-adducts are formed more rapidly than the 7-adducts and for some amines the kinetics of the faster reaction were too fast for measurement by the stopped-flow method. For the reactions of piperidine and *n*-butylamine k_5/k_7 has a value of *ca.* 100. Although a precise value of k_5 is not obtainable for reaction of *N*-methylbenzylamine the value of k_5k_{Am}/k_{-5} is considerably higher than that of k_7k_{Am}/k_{-7}, again implying a higher value for k_5 than for k_7. It is also significant that, where measurable, the value of $k_{-5}k_{AmH^+}/k_{Am}$ is *ca.* 10^4 times larger than the value of $k_{-7}k_{AmH^+}/k_{Am}$ for the corresponding amine. The value of k_{Am}/k_{AmH^+}, which reflects the acidity of the adduct relative to that of the parent ammonium ion, will not be expected to vary greatly with the position of attack. Hence the implication is that $k_{-5} \gg k_{-7}$.

The kinetic preference for 5-attack, but the thermodynamic preference for 7-attack, may be explicable in terms of the extent of charge delocalisation possible in the adducts. Thus comparison of the resonance forms available, Scheme 4, indicates the possibility of greater charge delocalisation in the 7-adducts. This will result in greater stability of the 7-adducts coupled with the higher kinetic barrier to their formation. Thus Bernasconi has argued that increase in charge delocalisation generally results in a higher intrinsic barrier to reaction.[26]

pK_a values, measured in DMSO, for the conjugate acids of the amines are given in Table 8. For the three cyclic secondary amines, piperidine, pyrrolidine and morpholine, there is a reasonably good correlation of values of $K_{c,5}$ and $K_{c,7}$ with bas-

Table 7 Kinetic data for reaction of **3** with *N*-methylbenzylamine in DMSO at 25 °C

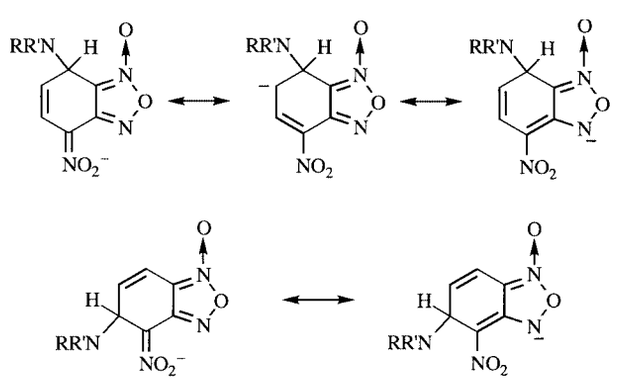
Item	[*N*-Me benzylamine]/ mol dm^{-3}	[*N*-Me benzylamine $H^+ClO_4^-$]/mol dm^{-3}	k_{fast}/s^{-1}	k_{fast} [a]/[Am]^2 dm^6 mol^{-2} s^{-1}	k_{slow}/s^{-1}	k_{calc} [b]/s^{-1}
1	0.0125	0	32	2×10^5	—	—
2	0.0175	0	41	1.3×10^5	—	—
3	0.025	0	90	1.5×10^5	—	—
4	0.003	0.01	—	—	1.64	1.65
5	0.005	0.01	—	—	1.71	1.70
6	0.01	0.01	—	—	2.00	2.05
7	0.02	0.01	—	—	3.2	3.4
8	0.03	0.01	—	—	5.3	5.4
9	0.04	0.01	—	—	7.8	7.7
10	0.05	0.01	—	—	10.3	10.3
11	0.001	0.10	—	—	7.4	7.3
12	0.002	0.10	—	—	7.3	7.2
13	0.003	0.10	—	—	6.9	7.0
14	0.005	0.10	—	—	6.8	6.8
15	0.010	0.10	—	—	6.6	6.7
16	0.0125	0.10	—	—	6.6	6.7

[a] Corresponds to K_5k_{Am}, from eqn. (11). [b] Calculated from eqn. (12) with K_7k_{Am} 8600 dm^6 mol^{-2} s^{-1}, k_{Am}/k_{-7} 25 dm^3 mol^{-1}, and with k_{AmH^+} 170 dm^3 mol^{-1} s^{-1} at 0.01 mol dm^{-3} salt and 75 dm^3 mol^{-1} s^{-1} at 0.1 mol dm^{-3} salt.

Table 8 Summary of results in DMSO at 25 °C

	Piperidine	Pyrrolidine	Morpholine	*n*-Butylamine	Benzylamine	*N*-Methylbenzylamine [b]
pK_a [a]	10.85	11.06	9.15	11.12	10.16	9.30 [c]
Reaction with ***3*** [d]						
k_5/dm^3 mol^{-1} s^{-1}	1.7×10^5	—	—	1.7×10^4	—	—
$\frac{k_{-5} \cdot k_{AmH^+}}{k_{Am}}$/s^{-1}	6.3×10^3	—	—	155	—	—
$K_{c,5}$/dm^3 mol^{-1}	27	52	<1	110	4.1	<1
k_{AmH^+}/dm^3 mol^{-1} s^{-1}	6×10^5	—	—	—	—	—
k_7/dm^3 mol^{-1} s^{-1}	2900	5300	300	140	40	340
$\frac{k_{-7} \cdot k_{AmH^+}}{k_{Am}}$/s^{-1}	0.16	0.36	1.1	0.025	0.13	6.8
$K_{c,7}$/dm^3 mol^{-1}	1.8×10^4	1.5×10^4	280	5.6×10^3	300	50
k_{AmH^+}/dm^3 mol^{-1} s^{-1}	—	—	—		—	170
Reaction with ***2*** [e]						
k_1/dm^3 mol^{-1} s^{-1}	$>2 \times 10^5$	7.5×10^5	>100	4.5×10^4	1.3×10^4	—
$\frac{k_{-1} \cdot k_{AmH^+}}{k_{Am}}$/s^{-1}	>100	210	>2.5	45	120	—
$K_{c,1}$/dm^3 mol^{-1}	2.1×10^3	3.5×10^3	34	1×10^3	105	—
k_{AmH^+}/dm^3 mol^{-1} s^{-1}	280	3×10^3	250	6×10^4	1.5×10^4	—

[a] Values for corresponding ammonium ions, from ref. 25. [b] For *N*-methylbenzylamine the value of k_5k_{Am}/k_{-5} is 1.5×10^5 dm^6 mol^{-2} s^{-1}, and the value of k_7k_{Am}/k_{-7} is 8.6×10^3 dm^6 mol^{-2} s^{-1}. [c] M. R. Crampton and L. C. Rabbitt, unpublished observation. [d] Values at 0.01 mol dm^{-3} salt concentration. [e] Refer to Scheme 2. $K_{c,1} = k_1 \cdot k_{Am}/k_{-1} \cdot k_{AmH^+}$. Data from refs. 11–13, with 0.1 mol dm^{-3} salt concentration. A statistical correction has not been applied.



Scheme 4

icity. Thus values for morpholine, the least basic amine, are considerably lower than those for piperidine. Also nucleophilicity, as measured by values of k_7, follows the same pattern. Similarly comparison of the data for the two primary amines, *n*-butylamine and benzylamine, indicates that the higher basicity of *n*-butylamine is reflected in higher values of $K_{c,5}$, $K_{c,7}$ and k_7. Nevertheless when comparing the data for the secondary amines with those for the primary amines, the relatively high nucleophilicities of the secondary amines are noteworthy. For example the value of k_7 for reaction with pyrrolidine is larger by a factor of *ca*. 40 than that for reaction with *n*-butylamine, an amine with a similar pK_a value. Likewise the value for k_7 for *N*-methylbenzylamine is almost tenfold higher than that for benzylamine, despite the higher proton basicity of the latter. It should, however, be remembered that while nucleophilicity is measured here by rate constants for attack at a carbon atom, the pK_a values refer to equilibrium protonation. It has been argued [25] that primary ammonium ions are particularly well stabilised in DMSO by hydrogen bonding of the NH^+ protons to the solvent. Such stabilisation may be less effective in the transition states for nucleophilic attack, where charge development is only partial. The variation with the nature of

the amine of values of k_7 and $K_{c,7}$ indicates that steric hindrance either to nucleophilic attack at the 7-position, or in the adducts **7**, is not an important factor. The one exception may be in the adduct **7f** formed from *N*-methylbenzylamine where the value of $K_{c,7}$ is unexpectedly low.

Comparison with 1,3,5-trinitrobenzene

1,3,5-Trinitrobenzene, **2**, is the bench-mark for comparisons of reactivity in σ-adduct forming reactions.[3] The results in Table 8 show that values of $K_{c,7}$ for reaction at the 7-position of **3** are between three and eight times larger, for corresponding amines, than the values of $K_{c,1}$ for reaction at an unsubstituted position of 1,3,5-trinitrobenzene. (The values of ratios would be three times larger if a statistical correction were to be applied to account for the equivalent positions in **2**.) This confirms the excellent ability, reported previously[21,22,27] in reactions with alkoxides, of the 4-nitrobenzofuroxan system in delocalising negative charge. Despite the higher thermodynamic stabilities of adducts from **3**, the values of k_7 for nucleophilic attack are considerably lower than values of k_1 for reaction with **2**. This may be a consequence of the possibility, referred to earlier, of the extensive charge delocalisation in the benzofuroxan system which leads to higher intrinsic barriers to reaction.

A further difference in the reactions of **3** and **2** with amines is in the nature of the rate determining step. With **3** the proton transfer equilibria between zwitterions and anions **6**⇌**7**, are generally rapid so that nucleophilic attack, the k_7 step, is rate-limiting in the forward direction. The only exception is in the reaction with the sterically hindered amine *N*-methylbenzylamine where proton transfer becomes partially rate determining. By contrast in the reaction of 1,3,5-trinitrobenzene with amines the proton transfer step is generally rate limiting with secondary amines and may be partially rate-limiting with primary amines.[11] It should be noted that the zwitterionic intermediates for both **2** and **3** are expected to be considerably more acidic than the corresponding ammonium ions. In the case of **2** a value for k_{Am}/k_{AmH^+} of *ca*. 500 has been estimated,[11] and the failure to observe zwitterionic intermediates in reactions of **3** indicates that $k_{Am}/k_{AmH^+} \gg 1$. Hence the proton transfers from zwitterions to amines, k_{Am}, are thermodynamically favourable processes. Nevertheless in the reactions of **2** values of k_{Am} are considerably below the diffusion limit. For example k_{Am} has the value 5×10^4 dm^3 mol^{-1} s^{-1} for the reaction involving piperidine.[11] It has been argued that steric hindrance at the reaction centre is responsible, and that this is more severe with secondary than with primary amines.[11,15] It should be noted that this is steric hindrance to proton transfer between the zwitterion and amine as distinct from steric hindrance to nucleophilic attack. The latter is thought to be unimportant when reaction occurs at a ring carbon atom carrying hydrogen.

The results for adduct formation from **3** show that the proton transfer equilibria are generally rapid and are not rate-limiting. This suggests that rate constants for proton transfer may be faster in the 4-nitrobenzofuroxan system than in the 1,3,5-trinitrobenzene system. This would be reasonable since **3** is a considerably less sterically demanding reactant than is **2**, where reaction must occur *ortho* to two nitro-groups. There is evidence that this conclusion is valid in formation of the 5-adducts, **5**. Thus in the reaction with piperidine k_{AmH^+} has a value of 6×10^5 dm^3 mol^{-1} s^{-1} compared with a corresponding value of 280 dm^3 mol^{-1} s^{-1} in the 1,3,5-trinitrobenzene system. Although these values refer to the reverse proton transfers, from piperidinium ions to the anionic adducts, they will largely reflect the steric situation at the reaction centre. The factor of 2000 is consistent with less steric hindrance in the reaction involving **3**. Nevertheless for reaction at the 7-position of **3** we must add the caveat that the nature of the rate determining step depends on the value of the ratio k_{Am}/k_{-7} rather than on the value of k_{Am} alone. The results in Table 8 show that values of the parameter $k_{-7}k_{AmH^+}/k_{Am}$ for reaction of **3** are considerably lower than the corresponding values of $k_{-1}k_{AmH^+}/k_{Am}$ for reaction of **2**. This indicates that values of k_{-7} are likely to be considerably lower than values of k_{-1}. Thus the difference in the nature of the rate determining step in the reactions of **3** and **2** with amines is likely to be a consequence both of higher rate constants for proton transfer with **3** and also a reduction in the value of k_{-7} relative to k_{-1}.

The interesting exception is the reaction of **3** with *N*-methylbenzylamine. Here proton transfer is partially rate-limiting in formation of both the 5-adduct and the 7-adduct. Since these proton transfers must occur from the respective zwitterions **4f** and **6f** to *N*-methylbenzylamine, large steric effects are likely. Hence values of k_{Am} and k_{AmH^+} will be reduced.

Experimental

4-Nitrobenzofuroxan was prepared, as previously described,[28] by nitration of benzofuroxan: mp 143 °C (lit.[28] mp 143 °C). Amines and solvents were the purest available commercial products. Amine salts were prepared as solutions in DMSO by accurate neutralisation of amines, with the appropriate acid.

^{1}H NMR spectra were recorded in [$^2H_6$]-DMSO with a Varian Mercury 200 MHz spectrometer. UV–vis spectra and kinetic measurements were made at 25 °C with a Perkin-Elmer Lambda 2 spectrophotometer, a Shimadzu UV-2101 PC spectrometer or an Applied Photophysics SX-17 MV stopped-flow spectrometer. Reported rate constants are the means of several determinations and are precise ±5%.

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