The Stabilities of Meisenheimer Complexes. Part 32.[1] Rate-limiting Proton Transfer in the Reactions of 1,3,5-Trinitrobenzene with Pyrrolidine and Piperidine

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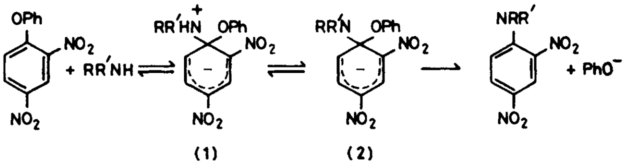
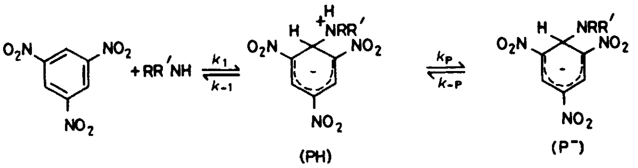
Rate and equilibrium measurements are reported for the reactions of 1,3,5-trinitrobenzene with pyrrolidine and with piperidine in dimethyl sulphoxide (DMSO) and in a DMSO–water mixture. These reactions lead to the formation of anionic σ-adducts *via* zwitterionic intermediates and it is shown that proton transfer is rate-limiting or partially rate-limiting. In DMSO the rate of proton transfer is an order of magnitude faster for the reaction with pyrrolidine than for the reaction with piperidine. However, the addition of water reduces this difference. Implications for the mechanism of base catalysis in nucleophilic aromatic substitution reactions are discussed.

The reaction of 1,3,5-trinitrobenzene (TNB) with aliphatic amines in dimethyl sulphoxide (DMSO) leads [2] to the formation of anionic σ-adducts *via* zwitterionic intermediates as shown in Scheme 1. Kinetic studies of the reaction in DMSO [3] and in mixed aqueous solvents [4] have shown that the proton transfer step may be rate-determining. For reactions in DMSO with the primary amines n-butylamine, benzylamine, and isopropylamine values [3] of the rate constants, k_{Am}, for proton transfer from PH to amine are *ca.* 1×10^7 l mol^{-1} s^{-1}. That these values are lower than that expected for a diffusion controlled reaction has been attributed to steric effects.[3,4] For reaction with the secondary amine, piperidine, where steric effects will be more severe, k_{Am} has the value 5×10^4 l mol^{-1} s^{-1} in DMSO.



Scheme 1.



Scheme 2.

Bunnett and Cartano [5] have recently reported kinetic data for the nucleophilic substitution reactions by the S_N Ar mechanism of 2,4-dinitrophenyl phenyl ether with piperidine and with pyrrolidine catalysed by hydroxide ions in dioxane–water (Scheme 2). They showed that breakdown of the intermediate (1) to products was *ca.* 14 times faster for the reaction with pyrrolidine than for the reaction with piperidine. Two mechanistic possibilities for this difference are (i) rate limiting proton transfer from (1) to base with proton transfer from the piperidino-intermediate being much slower than from the pyrrolidino-intermediate, or (ii) rapid proton transfer from (1) to base and rate limiting detachment of phenoxide from the anionic intermediate (2). Since there is evidence [6] that change of nucleophile from pyrrolidine to piperidine may slow nucleofuge departure, they preferred the latter alternative.

Relevant to these studies we report here an extension of our previous work [3] to include data for the reaction of TNB with pyrrolidine in DMSO and for the reactions of TNB with pyrrolidine and with piperidine in a DMSO–water mixture.

Experimental

G.P.R. grade DMSO was dried by refluxing over calcium hydride, fractionally distilled under reduced pressure, and subsequently protected from moisture. DMSO–water mixtures were prepared from the above by the addition of boiled distilled water. 1,3,5-Trinitrobenzene was a recrystallised commercial specimen, m.p. 123 °C. A commercial sample of 1,4-diazabicyclo[2.2.2]octane (DABCO) was used as supplied. Piperidine and pyrrolidine were AnalaR grade reagents used as supplied. Tetraethylammonium perchlorate was prepared by mixing equivalent quantities of aqueous perchloric acid and tetraethylammonium hydroxide; the white precipitate was washed with water and methanol and dried under vacuum. Piperidinium perchlorate and pyrrolidinium perchlorate were prepared in solution in DMSO from weighed amounts of amine and perchloric acid; to check for neutrality small samples of these solutions were taken and the pH was measured after dilution with water.

Kinetic measurements were made with freshly prepared solutions of reagents using a Hi-Tech SF3L stopped-flow spectrophotometer. Rate coefficients at 25 °C are the mean of five separate determinations and are precise to ±5%. Optical densities were measured with a Pye-Unicam SP8-100 spectrophotometer.

Results

Mixing dilute solutions of TNB and either pyrrolidine or piperidine in DMSO or DMSO–water resulted in rapid formation of the σ-adduct (P^-) with visible maxima at 450 and 530 nm.[2,3]

Our kinetic analysis follows that given previously.[3] Proton transfer from (PH) in Scheme 1 may involve either the amine (Am), or any general base such as DABCO (B), or the solvent, while proton transfer to (P^-) will involve the protonated amine (AmH^+), protonated base (BH^+), or protonated solvent (SH^+). Hence we obtain equations (1) and (2).

$$k_P = k_{Am}[Am] + k_B[B] + k_S \quad (1)$$

$$k_{-P} = k_{AmH^+}[AmH^+] + k_{BH^+}[BH^+] + k_{SH^+}[SH^+] \quad (2)$$

Table 1. Rate data for the colour-forming reaction of TNB (6×10^{-6}M) with pyrrolidine in DMSO at 25 °C

	10^4[Pyrrolidine]/ M	[DABCO]/ M	$(k_f)_1$/ s^{-1}	$(k_f)_2$/ l mol^{-1} s^{-1}	$(k_f)_{1(calc)}$ [a]/ s^{-1}
1	5.1		2.8	5 500	2.6
2	7.7		6.1	7 900	6.1
3	10.2		10.8	10 600	10.7
4	15.3		24.2	15 800	24
5	20.4		40	19 500	42
6	30.7		86	28 000	94
7	3.0	0.01	12	40 000	11
8	3.0	0.02	22	73 000	20
9	3.0	0.04	37	123 000	36
10	3.0	0.07	55	183 000	56
11	3.0	0.10	76	253 000	73
12	3.0	0.20	113	377 000	110

[a] Calculated from equation (3) with k_1 7.5×10^5 l mol^{-1} s^{-1}, k_{Am}/k_{-1} 14 l mol^{-1}, k_{DABCO}/k_{-1} 4.8 l mol^{-1}, and k_S zero.

Colour-forming Reaction.—Rates of colour formation were measured by stopped-flow spectrophotometry with amine and base (if present) in large excess of TNB, but with no protonated amine initially present. Under these conditions conversion of TNB into adduct (P^-) was nearly complete (>95%) so that first-order kinetics were observed. Treating (PH) as a steady-state intermediate[7,8] leads to equation (3) where $(k_f)_1$ is the observed rate coefficient. The second-order rate coefficient for the forward reaction is given by equation (4).

$$(k_f)_1 = \frac{k_1[\mathrm{Am}](k_{Am}[\mathrm{Am}] + k_B[\mathrm{B}] + k_S)}{k_{-1} + k_{Am}[\mathrm{Am}] + k_B[\mathrm{B}] + k_S} \tag{3}$$

$$(k_f)_2 = (k_f)_1/[\mathrm{Am}] \tag{4}$$

Fading Reaction.—Mixing, in the stopped-flow spectrophotometer, solutions of the pre-formed σ-adduct (P^-) with solutions of the appropriate substituted ammonium salt resulted in fading of colour. With concentrations of amine and salt in large excess of the stoicheiometric TNB concentration both forward and reverse reactions are first order and equations (5) and (6) will apply.

$$k_{obs} = (k_f)_1 + (k_r)_1 \tag{5}$$

$$(k_r)_1 = \frac{k_{-1}(k_{AmH^+}[\mathrm{AmH^+}] + k_{SH^+}[\mathrm{SH^+}])}{k_{-1} + k_{Am}[\mathrm{Am}] + k_S} \tag{6}$$

Equilibrium Constants.—An equilibrium constant K for conversion of TNB into (P^-) is defined by equation (7). This is related by equation (8) to the equilibrium constant K_1 for formation of the zwitterionic intermediate (PH), and to the acid dissociation constants of (PH) and of the protonated amine, AmH^+. Equation (9) relates the equilibrium constant K to the rate constants associated with the formation of (PH) and its amine catalysed conversion into (P^-).

$$K = \frac{[\mathrm{P^-}][\mathrm{AmH^+}]}{[\mathrm{TNB}][\mathrm{Am}]^2} \tag{7}$$

$$K = K_1 K_a^{\mathrm{PH}}/K_a^{\mathrm{AmH^+}} \tag{8}$$

$$K = \frac{k_1\, k_{Am}}{k_{-1} k_{AmH^+}} \tag{9}$$

Table 2. Rate data for the colour-forming reaction of TNB (5×10^{-6}M) with pyrrolidine in 90 : 10 DMSO-water at 25 °C

10^4[Pyrrolidine]/M	$(k_f)_1$/s^{-1}	$(k_f)_2$/l mol^{-1} s^{-1}
6.2	1.9	3 100
9.3	4.5	4 900
12.4	9.7	7 800
18.6	17	9 100
24.8	32	12 900
31.0	46	15 000
37.2	58	15 500
49.6	106	21 000

Table 3. Rate data for the fading reaction of the TNB–pyrrolidine adduct on mixing with pyrrolidinium perchlorate [a] at 25 °C

Solvent	10^4[Pyrrolidine]/ M	[Pyrrolidinium perchlorate]/M	k_{obs}/ s^{-1}	k_{calc}/ s^{-1}
DMSO	5.0	0.0055	23	20 [c]
DMSO	5.0	0.011	35	36 [c]
DMSO	5.0	0.0165	49	52 [c]
DMSO	5.0	0.025	70	78 [c]
DMSO–H_2O [b]	10.0	0.0023	23	20 [d]
DMSO–H_2O [b]	10.0	0.0045	36	33 [d]
DMSO–H_2O [b]	10.0	0.0090	55	60 [d]

[a] Ionic strength 0.10M with tetraethylammonium perchlorate. [b] Solvent composition is 90 : 10 (v/v). [c] Calculated from equation (11) with $(k_f)_1$ 3 s^{-1}, k_{AmH^+} 3 000 l mol^{-1} s^{-1}. [d] Calculated from equation (11) with $(k_f)_1$ 6 s^{-1}, k_{AmH^+} 6 000 l mol^{-1} s^{-1}.

Reaction with Pyrrolidine.—Data for reaction in DMSO are in Table 1. Rates measured in the presence of 0.1M tetraethylammonium perchlorate were within experimental error of those reported. For items 1—6 a plot of $(k_f)_2$ *vs.* amine concentration had an intercept close to zero showing that under our conditions $k_s \ll k_{Am}[\mathrm{Am}]$. Also in the absence of DABCO catalysis equation (3) may be inverted to yield equation (10). From the slope of the linear plot of $1/(k_f)_2$ *vs.* 1/[Am] we obtain a value for $K_1 k_{Am}$ of $(1.05 \pm 0.05) \times 10^7$

$$\frac{1}{(k_f)_2} = \frac{1}{k_1} + \frac{1}{K_1 k_{Am}[\mathrm{Am}]} \tag{10}$$

l^2 mol^{-2} s^{-1}. However the intercept of this plot is small and of high uncertainty so that we are able only to set a limit of $>1 \times 10^5$ l mol^{-1} s^{-1} on the value of k_1.

However for items 7—12 a reciprocal plot of $1/(k_f)_2$ *vs.* 1/[DABCO] gave values of $K_1 k_{DABCO}$, $(3.6 \pm 0.2) \times 10^6$ l^2 mol^{-2} s^{-1} and k_1, $(7.5 \pm 2.5) \times 10^5$ l mol^{-1} s^{-1}. Hence it is possible to calculate values for the ratios k_{DABCO}/k_{-1} 4.8, and k_{Am}/k_{-1} 14 l mol^{-1}. Using these values acceptable agreement between calculated and observed values of $(k_f)_1$ were obtained.

Data for the colour-forming reaction in 90 : 10 (v/v) DMSO–water are in Table 2. A reciprocal plot of $1/(k_f)_2$ *vs.* 1/[Am] gave a value for $K_1 k_{Am}$ of $(5.3 \pm 0.5) \times 10^6$ l^2 mol^{-2} s^{-1} and allowed a limit of $>1 \times 10^5$ l mol^{-1} s^{-1} to be set on the value of k_1.

Rate measurements for the fading reaction in DMSO and in 90 : 10 DMSO–water are in Table 3. We have shown that the contribution to the forward reaction of the term involving solvent, k_S, is small. Similarly for the reverse reaction the contribution from the terms involving protonated solvent $k_{SH^+}[\mathrm{SH^+}]$ will be small compared with that involving protonated amine. Also, since at the amine concentrations

Table 4. Equilibrium measurements for reaction of TNB (2.63×10^{-5}M) with pyrrolidine in DMSO at 25 °C

[Pyrrolidine]/M	[Pyrrolidinium perchlorate] [a]/M	OD(449 nm)	K/l mol^{-1}
0.0019	0.010	0.30	2 300
0.0019	0.020	0.21	2 600
0.0047	0.050	0.40	3 400
0.0047	0.025	0.47	2 800
0.0095	0.050	0.57	3 500
0.0019	0	0.66	
0.005	0	0.67	

[a] I = 0.10M with tetraethylammonium perchlorate.

Table 5. Equilibrium measurements for reaction of TNB (2.46×10^{-5}M) with pyrrolidine in 90 : 10 DMSO-water at 25 °C

[Pyrrolidine]/M	[Pyrrolidinium perchlorate] [a]/M	OD(449 nm)	K/l mol^{-1}
0.0020	0.020	0.065	670
0.0049	0.050	0.14	680
0.0049	0.025	0.24	730
0.0099	0.050	0.35	830
0.0049	0	0.56	

[a] I = 0.10M with tetraethylammonium perchlorate.

Table 6. Rate data for the colour-forming reaction of TNB (5×10^{-6}M) with piperidine in 90 : 10 DMSO-water at 25 °C

10^3[Piperidine]/M	$(k_f)_1$/s^{-1}	$(k_f)_2$/l mol^{-1} s^{-1}
1.92	2.71	1 400
4.96	14.1	2 900
6.71	26.2	3 900
7.93	39.5	5 000
9.59	58.2	6 100

Table 7. Rate data for the fading reaction of the TNB–piperidine adduct on mixing with piperidinium perchlorate [a] at 25 °C

Solvent	10^3[Piperidine]/M	[Piperidinium perchlorate]/M	k_{obs}/s^{-1}	k_{calc}/s^{-1}
DMSO	2.0	0.0093	5.6	4.9 [c]
DMSO	2.0	0.028	10.9	10.1
DMSO	2.0	0.037	12.9	12.7
DMSO	2.0	0.056	18.1	18.0
DMSO	2.0	0.093	26.1	28.3
DMSO–H_2O [b]	2.0	0.005	8.7	8.7 [d]
DMSO–H_2O	2.0	0.010	15.7	14.7
DMSO–H_2O	2.0	0.020	25.5	26.7
DMSO–H_2O	2.0	0.030	36	39
DMSO–H_2O	2.0	0.040	44	50
DMSO–H_2O	2.0	0.060	81	75
DMSO–H_2O	2.0	0.080	98	99
DMSO–H_2O	2.0	0.10	120	123

[a] Ionic strength, 0.1M with tetraethylammonium perchlorate. [b] Solvent composition is 90 : 10 (v/v). [c] Calculated from equation (11) with $(k_f)_1$ 2.3 s^{-1} and k_{AmH^+} 280 l mol^{-1} s^{-1}. [d] Calculated from equation (11) with $(k_f)_1$ 2.7 s^{-1} and k_{AmH^+} 1 200 l mol^{-1} s^{-1}.

used $k_{-1} \gg k_{Am}[Am]$ equations (5) and (6) can be simplified to yield equation (11). Linear plots of k_{obs} *vs.* concentration of

$$k_{obs} = (k_f)_1 + k_{AmH^+}[AmH^+] \qquad (11)$$

pyrrolidinium ions allowed the calculations of values of k_{AmH^+} in the two-solvent systems.

Combination of the observed values of K_1k_{Am} with values of k_{AmH^+} yields values for the equilibrium constant K of 3 500 l mol^{-1} in DMSO and 880 l mol^{-1} in 90 : 10 DMSO–water. These are in reasonable agreement with values calculated from equilibrium optical densities (OD) in Tables 4 and 5.

Reaction with Piperidine.—Rate data for the colour-forming reaction, with and without DABCO, have been reported previously.[3] Recalculation of these data give values of K_1k_{Am} 6×10^5 l^2 mol^{-2} s^{-1}, K_1k_{DABCO} 1.3×10^5 l^2 mol^{-2} s^{-1}, and $k_1 > 2 \times 10^5$ l mol^{-1} s^{-1}.

Data for the reaction in 90 : 10 DMSO–water are given in Table 6. A reciprocal plot according to equation (10) gave values of K_1k_{Am} 7×10^5 l^2 mol^{-2} s^{-1} and $k_1 > 2 \times 10^4$ l mol^{-1} s^{-1}.

Data for the fading reaction in DMSO and in 90 : 10 DMSO–water are in Table 7. They accord well with equation (11).

Combination of values of K_1k_{Am} and k_{AmH^+} gave values for K of 2 140 l mol^{-1} in DMSO and 600 l mol^{-1} in DMSO–water.

Discussion

Data for reaction in DMSO and in DMSO–water, 90 : 10, are collected in Table 8. Items in the first seven rows are experimentally determined quantities while items in lines eight and nine were calculated using an estimated value for the ratio $K_a^{PH} : K_a^{AmH^+}$. This ratio measures the acidity of zwitterionic adducts (PH) relative to the corresponding substituted ammonium ions (AmH^+). Since the trinitrocyclohexadienate group, although negatively charged, is electron-withdrawing relative to hydrogen [9,10] the ratio will have a value greater than unity, and a value of 500 independent of the amine and solvent has been justified previously.[3] However our main conclusions do not depend on the value taken.

In the present work we have throughout used perchlorate as the counter-ion. Previously measurements involving piperidine in DMSO were made using chloride salts.[3] There is evidence [11,12] for the association of chloride ions with substituted ammonium ions, in this case the piperidinium ion, to yield complexes, $RR'NH_2^+ \cdots Cl^-$, in which the activities of the ammonium ions are reduced. This accounts for the higher value for k_{AmH^+} found here than reported previously, 256 *vs.* 100 l mol^{-1} s^{-1} and the lower value found for K 2 140 *vs.* 4 500 l mol^{-1}.

Values reported for other amines in our previous report [3] are not affected since they were obtained in the absence of chloride ions or with very small chloride concentrations.

We consider first the data for reaction in DMSO. Values for the equilibrium constants K and K_1 for pyrrolidine are slightly greater than the corresponding values for piperidine. Similarly pyrrolidine has been found to show slightly greater nucleophilic reactivity than piperidine.[5,13] However the main differences are that k_{AmH^+} and k_{Am} are an order of magnitude larger in the reaction with pyrrolidine than with piperidine. For comparison it should be noted that the corresponding values

Table 8. Summary of rate and equilibrium constants for reaction of TNB with pyrrolidine and piperidine at 25 °C

	DMSO		DMSO–Water 90 : 10 (v/v)	
	Pyrrolidine	Piperidine	Pyrrolidine	Piperidine
k_1/l mol^{-1} s^{-1}	7.5×10^5	$>2 \times 10^5$	$>1 \times 10^5$	$>2 \times 10^4$
K_1k_{Am}/l^2 mol^{-2} s^{-1}	1.05×10^7	6×10^5	5.3×10^6	7×10^5
K_1k_{DABCO}/l^2 mol^{-2} s^{-1}	3.6×10^6	1.3×10^5		
k_{Am}/k_{-1} (l mol^{-1})	14	<10		
k_{DABCO}/k_{-1} (l mol^{-1})	4.8	<2.5		
k_{AmH^+}/l mol^{-1} s^{-1}	3 000	280	6 000	1 200
K/l mol^{-1}	3 500	2 140	880	600
K_1 [a]/l mol^{-1}	7	4.3	1.75	1.2
k_{Am} [b]/l mol^{-1} s^{-1}	1.5×10^6	1.4×10^5	3×10^6	6×10^5

[a] From equation (8), assuming $K_a^{PH}/K_a^{AmH^+}$ has the value 500. [b] K_1k_{Am}/K_1, line 2 divided by line 8.

in reactions with primary amines are again an order of magnitude higher than those for reaction with pyrrolidine.[3] Now k_{Am} refers to thermodynamically favourable proton transfer from the zwitterion (PH) to amine. That these reactions have rates which are considerably slower than those expected for diffusion-control may be attributed to steric factors.[3,4] It is reasonable that these should be more serious for secondary than for primary amines but the difference between piperidine and pyrrolidine is less easy to understand. Nevertheless recent work [6] also indicates the greater steric requirements of piperidine than of pyrrolidine.

We refer now to the nucleophilic substitution reaction of Scheme 2. Our results in DMSO show that proton transfer from a zwitterionic intermediate derived from pyrrolidine is an order of magnitude faster than from a similar intermediate derived from piperidine. This might be taken as evidence for rate limiting proton transfer in the mechanism of Scheme 2. However an important difference is that the nucleophilic substitution was carried out in a solvent containing water. Hence we examined the effects of added water on the TNB–amine reaction. Our data, Table 8, indicate that as expected [14] values of the equilibrium constants K and K_1 decrease when water is added to the solvent. They also show that values of the catalytic coefficients k_{Am} and k_{AmH^+} increase, and that the increase is larger for the reaction involving piperidine than for pyrrolidine. These increases probably result from the transfer of protons *via* interstitial water molecules. Hence as the solvent becomes more aqueous steric factors are less important. In 90 : 10 DMSO–water the ratio of values of k_{Am} in pyrrolidine and piperidine is reduced to five and there is evidence that in more aqueous media the ratio will be reduced further.[4] Hence we agree with Bunnett and Cartano [5] that in aqueous media rates of proton transfer from the intermediates (1) of Scheme 2 are likely to be similar for the piperidine and pyrrolidine reactions.

Acknowledgements

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