Acid–Base Properties of Highly Substituted Diaminonaphthalenes

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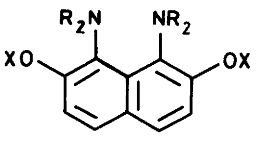
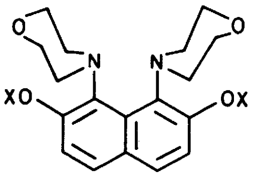
The kinetic and equilibrium acid–base behaviour of four new highly hindered diaminonaphthalenes has been studied in aqueous solution or in Me_2SO–H_2O mixtures containing hydroxide ion. In concentrated aqueous sodium hydroxide solutions, 1,8-bis(dimethylamino)-2,7-diethoxynaphthalene and 1,8-bis(diethylamino)-2,7-diethoxynaphthalene are almost fully protonated and aqueous pK_a values of 16.1 and 15.9, respectively, have been measured from comparative studies with other diaminonaphthalenes in 60% (v/v) Me_2SO–H_2O. Studies of the protonation of 1,8-dimorpholino-2,7-dimethoxynaphthalene (pK_a 13.0) and 1,8-dimorpholino-2,7-diethoxynaphthalene (pK_a 12.5) were made in aqueous sodium hydroxide. The reversible acid–base reactions of the diaminonaphthalenes in the presence of hydroxide ion occur slowly. For example the approach to an equilibrium mixture of the protonated and unprotonated forms of 1,8-bis(diethylamino)-2,7-diethoxynaphthalene in 60% (v/v) Me_2SO–H_2O with 0.01 mol dm^{-3} NaOH occurs with a half-life of 8 s. It is found that 2- and 7-substituents have large effects in increasing the basicity and decreasing the rates of proton transfer and this is due in part to an increase in strain in the amines and in the transition state for proton transfer.

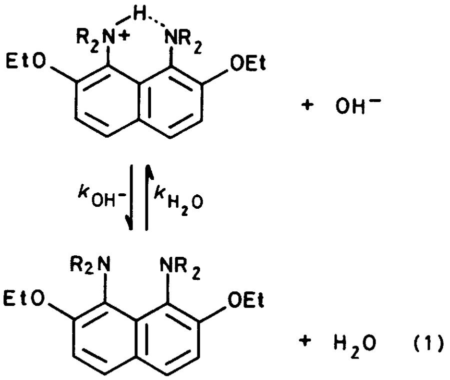
The unusual basicity[1–3] of substituted 1,8-bis(dialkylamino)naphthalenes (**I**) has been attributed to the relief of strain which occurs on protonation. Unfavourable interactions involving the nitrogen lone pairs and the alkyl groups (R) introduce severe strain into the amines. Strain is less severe in the protonated amines which can adopt a conformation, different from that of the free amines, with an intramolecular hydrogen bond. The rates of proton transfer involving the amines are exceptionally low[2,4,5] and the presence of the intramolecular hydrogen bond in the protonated amines and strain in the transition states are considered to be about equally responsible.[6] In the present work, two new compounds of type (**I**) with R = Me, X = Et and R = Et, X = Et have been studied and the results are compared with those for other compounds in this series. The properties of 1,8-dimorpholino-2,7-dimethoxy- and 1,8-dimorpholino-2,7-diethoxy-naphthalene (**II**; X = Me and Et) are compared with published data for 1,8-dimorpholinonaphthalene.[7] The aim is to find even more strongly basic amines than those already known.



(**I**)



(**II**)



(1)

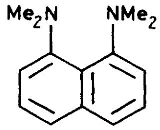
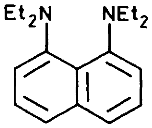
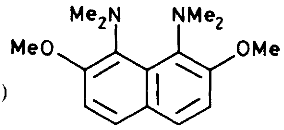
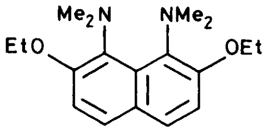
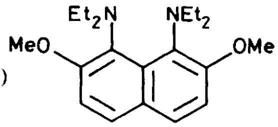
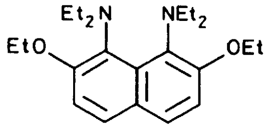
Experimental

Synthesis.—The preparations of 1,8-bis(dimethylamino)-2,7-diethoxy- (**4**) and 1,8-bis(diethylamino)-2,7-diethoxy-naphthalene (**6**) were achieved using procedures established for similar compounds.[8] Thus, 2,7-dihydroxynaphthalene was alkylated with diethyl sulphate and nitration of the product followed by reduction gave 1,8-diamino-2,7-diethoxynaphthalene. Complete *N*-alkylation was obtained by refluxing under nitrogen for 72 h with potassium hydride and excess of methyl or ethyl bromide in tetrahydrofuran. Sublimation gave 1,8-bis(dimethylamino)-2,7-diethoxynaphthalene as a solid, m.p. 60 °C, in 8% yield with $\delta(CDCl_3)$ 7.0—7.5 (m, 4 H, arom), 4.10 (q, 4 H, OCH_2CH_3), 2.91 (s, 12 H, NCH_3), and 1.47 (t, 6 H, OCH_2CH_3). 1,8-Bis(diethylamino)-2,7-diethoxynaphthalene was obtained as a yellow solid, m.p. 67 °C, in 6% yield and had $\delta(CDCl_3)$ 6.9—7.5 (m, 4 H, arom), 4.05 (q, 4 H, OCH_2CH_3), 3.25 (q, 8 H, NCH_2CH_3), 1.55 (t, 6 H, OCH_2CH_3), and 0.90 (t, 12 H, NCH_2CH_3).

Conversion of 1,8-diamino-2,7-dimethoxy- and 1,8-diamino-2,7-diethoxy-naphthalene, prepared as above, into the 1,8-dimorpholino derivatives was carried out by refluxing with a 10-fold molar excess of bis-2-chloroethyl ether in the presence of a 30-fold excess of sodium carbonate at 170 °C for 1.5 h. Aqueous extraction followed by ether extraction of the aqueous extract gave, after evaporation, 1,8-dimorpholino-2,7-dimethoxy- (**8**) and 1,8-dimorpholino-2,7-diethoxy-naphthalene (**9**) which were purified by recrystallisation from methylene dichloride–methanol. Pure compound (**8**) was solid, m.p. 229 °C, obtained in 3% yield with $\delta(CDCl_3)$ 7.00—7.65 (m, 4 H, arom), 3.95 (s, 6 H, OCH_3), 3.85 (m, 8 H, OCH_2CH_2N), and 3.30 (m, 8 H, OCH_2CH_2N) and (**9**) was obtained as a purple solid, m.p. 199 °C, in 15% yield with $\delta(CDCl_3)$ 7.03—7.57 (m, 4 H, arom), 4.19 (q, 4 H, OCH_2CH_3), 3.90 (m, 8 H, OCH_2CH_2N), 3.29 (m, 8 H, OCH_2CH_2N), and 1.53 (t, 6 H, OCH_2CH_3).

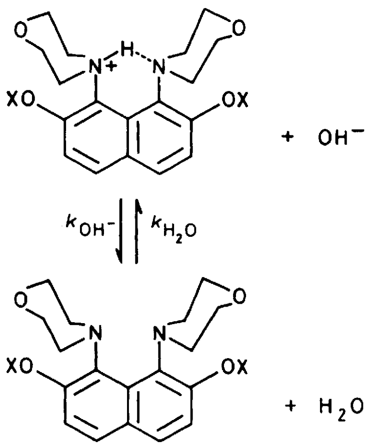
Equilibrium Measurements.—Equilibrium constants for reaction (1) were determined spectrophotometrically for 1,8-bis(dimethylamino)-2,7-diethoxy- (R = Me) and 1,8-bis(diethyl-

Table 1. Kinetic and equilibrium results for deprotonation of protonated 1,8-bis(dialkylamino)naphthalenes by hydroxide ion in Me_2SO-H_2O mixtures

	Solvent[a]	K/dm^3 mol^{-1}	k_{OH^-}/ dm^3 mol^{-1} s^{-1}	k_{H_2O}/s^{-1}	k_{OH^-}/k_{H_2O} (dm^3 mol^{-1})	pK	Ref.
(1) 	Aqueous[b]	52 ± 14	1.9 ± 0.4 × 10^5	3 900 ± 500	49 ± 15	12.1	2
	30% (v/v) Me_2SO-H_2O[c]	2 800 ± 200	6.1 ± 0.5 × 10^5	200 ± 30	3 100 ± 700		4
(2) 	30% (v/v) Me_2SO-H_2O[c]	380 ± 80	1.6 ± 0.2 × 10^4	47 ± 4	340 ± 70	13.0	4
(3) 	60% (v/v) Me_2SO-H_2O[b]	270 ± 30	640 ± 40	2.4 ± 0.5	270 ± 60	16.1	5
(4) 	60% (v/v) Me_2SO-H_2O[b]	248 ± 25	472 ± 40	2.0 ± 0.3	236 ± 70	16.1	*d*
(5) 	60% (v/v) Me_2SO-H_2O[b]	120 ± 20	3.7 ± 0.4	0.048 ± 0.005	87 ± 15	16.3	5
	70% (v/v) Me_2SO-H_2O[b]	2 500 ± 1 000	10.6 ± 0.5				
(6) 	60% (v/v) Me_2SO-H_2O[b]	362 ± 26	3.6 ± 0.3	0.010 ± 0.002	360 ± 100	15.9	*d*
	70% (v/v) Me_2SO-H_2O[b]		9.8 ± 0.5	*ca.* 0			*d*

[a] Ionic strength 0.1 mol dm^{-3}. [b] 25 °C. [c] 35 °C. [d] Present work.

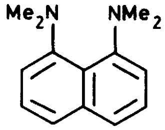
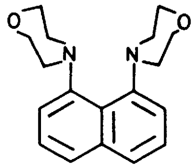
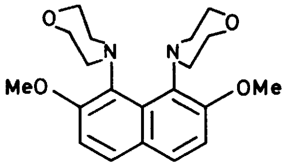
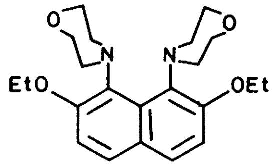
amino)-2,7-diethoxy-naphthalene (R = Et) in 60% (v/v) Me_2SO-H_2O at 25.0 °C. The ionic strength was maintained at 0.1 mol dm^{-3} by addition of potassium chloride. Absorbance readings for solutions of 1,8-bis(dimethylamino)-2,7-diethoxy- (6×10^{-5} mol dm^{-3}) or 1,8-bis(diethylamino)-2,7-diethoxy-naphthalene (2×10^{-5} mol dm^{-3}) in the presence of sodium hydroxide concentrations in the range 0.001—0.012 mol dm^{-3} were taken at 350 nm where the free amines absorb strongly. The spectra of the amine in the free base and protonated forms were obtained from measurements in the presence of 0.04 mol dm^{-3} and in the absence of sodium hydroxide, respectively. Values for the equilibrium constants for reaction (1; R = Me and Et) are given in Table 1.



(2)

The equilibrium in equation (2) with 1,8-dimorpholino-2,7-dimethoxy- (X = Me) or 1,8-dimorpholino-2,7-diethoxy-naphthalene (X = Et) was studied spectrophotometrically in aqueous solution at 25 °C and ionic strength 0.5 mol dm^{-3}. Absorbance readings (A) were taken at 240 nm, where the protonated amines absorb strongly, for solutions containing the amine (1.5×10^{-6} mol dm^{-3}) and sodium hydroxide (0.02—0.5 mol dm^{-3}). The absorbance due to the protonated amine (A_{BH^+}) was obtained in the absence of sodium hydroxide, but conditions could not be found where the amine was entirely in the base form, so that the absorbance (A_B) due to the base form could not be determined. Values for the equilibrium constants (K) for reaction (2) were therefore obtained as the gradients of

Table 2. Kinetic and equilibrium results for deprotonation of protonated 1,8-dimorpholinonaphthalenes by hydroxide ion in aqueous solution and Me_2SO-H_2O mixtures

		Solvent[a]	$K/\mathrm{dm^3\,mol^{-1}}$	$k_{OH^-}/\mathrm{dm^3\,mol^{-1}\,s^{-1}}$	$k_{H_2O}/\mathrm{s^{-1}}$	pK	Ref.
(**1**)		Aqueous[b,d]	52 ± 14	$1.9 \pm 0.4 \times 10^5$	3 900 ± 500	12.1	2
		20% (v/v) Me_2SO-H_2O[b,e]	660 ± 60	$2.9 \pm 0.2 \times 10^5$	350 ± 50		4
		30% (v/v) Me_2SO-H_2O[b,e]	2 800 ± 200	$6.1 \pm 0.5 \times 10^5$	200 ± 30		4
(**7**)		Aqueous	2.0×10^6	$5.4 \pm 0.4 \times 10^4$[c,d]	*ca.* 0	7.49[b,d]	*f*
(**8**)		Aqueous[d]	5.8 ± 0.8[c]	99.8 ± 8[c]	*ca.* 3[c]	13.0[b]	*f*
		20% (v/v) Me_2SO-H_2O[b,d]	72 ± 7	188 ± 20	*ca.* 1		
		30% (v/v) Me_2SO-H_2O[b,d]	334 ± 30	256 ± 30	*ca.* 0.3		
(**9**)		Aqueous[d]	19.1 ± 2[c]	79.2 ± 5[c]	5.5 ± 1.5[c]	12.5[b]	*f*
		20% (v/v) Me_2SO-H_2O[b,d]	*ca.* 150	159 ± 10	1.0 ± 0.1		
		30% (v/v) Me_2SO-H_2O[b,d]	*ca.* 1 000	233 ± 20	0.2 ± 0.1		

[a] Conditions: *b* and *c* refer to ionic strength 0.1 and 0.5 mol dm^{-3} respectively and *d* and *e* refer to 25 and 35 °C, respectively. [f] Present work.

plots of $(A_{BH^+} - A)/[OH^-]$ against A as in equation (3) and

$$(A_{BH^+} - A)/[OH^-] = KA - KA_B \qquad (3)$$

the results K 5.8 ± 0.8 and 19.1 ± 2 for the dimethoxy and diethoxy derivatives, respectively, were obtained. These were combined with the ionic product of water at ionic strength 0.5 mol dm^{-3} and 25 °C (K_w 1.87×10^{-14}) to give pK values of 13.0 and 12.5 for the two amines as shown in Table 2. The values at infinite dilution are likely to be *ca.* 0.2 units higher.[9]

For 1,8-dimorpholino-2,7-dimethoxynaphthalene, equilibrium studies were also made in 20 and 30% (v/v) Me_2SO-H_2O at 25 °C and ionic strength 0.1 mol dm^{-3} using similar procedures. Because of the absorbance by the solvent at 240 nm, measurements were made at 260 nm with solutions containing 9×10^{-6} mol dm^{-3} of the amine. The solubility of 1,8-dimorpholino-2,7-diethoxynaphthalene is too low to permit accurate measurements under these conditions. The results for 1,8-dimorpholino-2,7-dimethoxynaphthalene are given in Table 2.

Kinetic Measurements.—Rate coefficients k_{OH^-} and k_{H_2O} for proton transfer involving 1,8-bis(dimethylamino)-2,7-diethoxynaphthalene [equation (1)] were determined in 60% (v/v) Me_2SO-H_2O at 25 °C and ionic strength 0.1 mol dm^{-3} using the temperature-jump technique. Chemical relaxation of the equilibrium in equation (1) following a temperature jump of 3.5 °C was observed at 360 nm and relaxation times (τ) were measured at different hydroxide ion concentrations. The linear dependence of τ^{-1} on hydroxide ion concentration [equation (4)] gave the values of k_{OH^-} and k_{H_2O} shown in Table 1. The

$$\tau^{-1} = k_{OH^-}[OH^-] + k_{H_2O} \qquad (4)$$

ratio of these values is in good agreement with the result for the equilibrium constant of the reaction determined separately, from spectrophotometric equilibrium studies (see Table 1).

For proton transfer with 1,8-bis(diethylamino)-2,7-diethoxynaphthalene in 60% (v/v) Me_2SO-H_2O the stopped-flow technique with spectrophotometric detection was used to study the kinetics. In 70% (v/v) Me_2SO-H_2O under our experimental conditions the reaction was sufficiently slow with half-lives in the seconds range that a conventional spectrophotometer could be used. In 60% (v/v) Me_2SO-H_2O the reaction was studied with hydroxide ion concentrations in the range 0.01—0.1 mol dm^{-3} whereas in 70% Me_2SO-H_2O much lower concentrations (0.001—0.005 mol dm^{-3}) were used. The values of the rate coefficients k_{OH^-} and k_{H_2O} for reaction (1) with 1,8-bis(diethylamino)-2,7-diethoxynaphthalene are given in Table 1.

The kinetics of the proton-transfer reactions of 1,8-dimorpholinonaphthalene, 1,8-dimorpholino-2,7-dimethoxynaphthalene, and 1,8-dimorpholino-2,7-diethoxynaphthalene [equation (2)] were studied in aqueous sodium hydroxide at 25 °C and ionic strength 0.5 mol dm^{-3} using the stopped-flow method. The reactions which occurred when aqueous solutions of the protonated amines were mixed with aqueous sodium hydroxide were observed spectrophotometrically at 240 nm where the protonated amines absorb strongly. The reactions of the 2,7-dialkoxy derivatives were also studied in 20 and 30% (v/v) Me_2SO–H_2O. The kinetic and equilibrium results for the dimorpholinonaphthalenes are given in Table 2.

Discussion

The amines 1,8-bis(dimethylamino)-2,7-diethoxynaphthalene (**4**) and 1,8-bis(diethylamino)-2,7-diethoxynaphthalene (**6**) are too strongly basic to permit studies of their acid–base equilibria in aqueous solution. The equilibria were studied in 60% (v/v) Me_2SO–H_2O and the pK values in Table 1 were estimated by comparing the values of the equilibrium constants (K) referring to equation (1) for (**4**) and (**6**) with those for (**3**) and (**5**) under the same conditions. Aqueous pK values for (**3**) and (**5**) have been estimated previously[5] by comparing the acid–base equilibria of (**3**) and (**5**) in 35% (v/v) Me_2SO–H_2O with that for (**1**), for which the equilibrium could also be studied in aqueous solution. This stepwise procedure is likely to lead to somewhat approximate aqueous pK values. The results for (**4**) and (**6**), pK 16.1 and 15.9, respectively, make these amines slightly less strongly basic than (**5**), previously studied. An aqueous pK 16.0 means that the protonated amine is dissociated to the extent of $<0.5\%$ in 1 mol dm^{-3} sodium hydroxide. Along the series (**1**)–(**2**)–(**3**), the increase in pK values given in Table 1 shows the effect of increasing substitution and strain on the basicity of the amines, but the similar pK values for (**3**)—(**6**) suggest that an upper limit in basicity may have been reached for compounds of this type.

The reversible proton transfer involving the amine (**6**) and its protonated form in the presence of hydroxide ion occurs with half-lives in the seconds range. The reaction occurs much more slowly than the corresponding reaction of (**4**). The values of the rate coefficients k_{OH^-} in Table 1 show that the amine (**6**) is the most unreactive, kinetically, although (**5**) reacts almost as slowly. It has been found that proton transfer from the protonated amines (**3**) and (**5**) occurs through a non-hydrogen-bonded open form from which the proton is removed by base. The rates are low because reaction goes through a low-concentration intermediate and because attack of base on the open form is sterically hindered. Down the series of compounds (**1**)—(**6**), the rate coefficient (k_{OH^-}) decreases as the amine becomes more highly substituted. This arises because in going from (**1**) to (**6**) the equilibrium to give the non-hydrogen-bonded open form becomes increasingly unfavourable and because steric hindrance to attack of base on the open form increases. The changes in k_{OH^-} do not precisely follow the changes in pK values because they are controlled by different factors. In going from (**1**) to (**2**) a seven-fold reduction in K [equation (2)] is accompanied by a 40-fold reduction in k_{OH^-} and comparing (**4**) and (**5**), K is reduced two-fold as k_{OH^-} is reduced 100-fold. Between (**4**) and (**6**), K increases slightly as k_{OH^-} is reduced over 100-fold. For the amines (**1**)—(**6**) proton transfer from the protonated amines to hydroxide ion is thermodynamically favourable; the value of k_{OH} for a series of simple amines under these conditions would be constant at the diffusion limit. The changes in k_{OH^-} observed here reflect the unusual behaviour of these amines.

The rates of proton transfer and basicities (Table 2) of 1,8-dimorpholino-2,7-dimethoxy- and diethoxy-naphthalene (**8**) and (**9**), respectively, are less exceptional than the results obtained for (**6**). However, introduction of 2- and 7-alkoxy substituents into 1,8-dimorpholinonaphthalene has a considerable effect on the pK value, even larger than the effect of a similar substitution in 1,8-bis(dimethylamino)naphthalene. Thus 1,8-dimorpholinonaphthalene (pK 7.49) is 4 pK units more basic than *N*-phenylmorpholine and 1,8-dimorpholino-2,7-dimethoxynaphthalene is a further 5.5 units more basic still. Rates of proton transfer from protonated 1,8-dimorpholinonaphthalene to hydroxide ion have been measured previously[7] and the results are compatible with the values obtained here (Table 2). 1,8-Dimorpholino-2,7-dimethoxynaphthalene (**8**) and 1,8-dimorpholino-2,7-diethoxynaphthalene have not been studied previously and the results show that introduction of 2,7-dimethoxy substituents into 1,8-dimorpholinonaphthalene reduces the rate coefficient for proton transfer from the protonated amine to hydroxide ion in aqueous solution 500-fold compared with the 2 000-fold effect on the rate for 1,8-bis(dimethylamino)naphthalene in 35% (v/v) Me_2SO–H_2O.[4] In the morpholine series the lowest rates are *ca.* 30-fold above the lowest rates observed for 1,8-bis(dialkylamino)naphthalenes and the latter would have probably reacted even more slowly if studies could have been made in aqueous solution.

In the present work, a series of amines with quite exceptional acid–base properties are obtained by severe crowding of substituents around the amino groups at the 1- and 8-positions of naphthalene. The very high pK values mean that it is necessary to study the deprotonations in Me_2SO–H_2O mixtures. It has been found in preliminary experiments[10] that the basicities of the diaminonaphthalenes are less exceptional when studied in pure Me_2SO, presumably because Me_2SO weakens the intramolecular hydrogen bond and possibly because the product of proton transfer in a non-aqueous solvent is an ion pair or hydrogen-bonded complex whose stability is reduced by the hindered basic site in the diaminonaphthalenes.

Acknowledgements

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References

1 R. W. Alder, P. S. Bowman, W. R. S. Steele, and D. R. Winterman, *Chem. Commun.*, 1968, 723.
2 F. Hibbert, *J. Chem. Soc., Perkin Trans. 2*, 1974, 1862.
3 R. W. Alder, N. C. Goode, N. Miller, F. Hibbert, K. P. P. Hunte, and H. J. Robbins, *J. Chem. Soc., Chem. Commun.*, 1978, 89.
4 A. Awwal and F. Hibbert, *J. Chem. Soc., Perkin Trans. 2*, 1977, 1589.
5 F. Hibbert and K. P. P. Hunte, *J. Chem. Soc., Perkin Trans. 2*, 1983, 1895.
6 G. H. Barnett and F. Hibbert, *J. Am. Chem. Soc.*, 1984, **106**, 2080.
7 F. Hibbert and K. P. P. Hunte, *J. Chem. Soc., Perkin Trans. 2*, 1981, 1562; A. Awwal, R. Burt, and A. J. Kresge, *ibid.*, p. 1566.
8 R. W. Alder, M. R. Bryce, N. C. Goode, N. Miller, and J. Owen, *J. Chem. Soc., Perkin Trans. 1*, 1981, 2840.
9 M. C. Cox, D. H. Everett, D. A. Landsman, and R. J. Munn, *J. Chem. Soc. B*, 1968, 1373.
10 F. Hibbert, unpublished work.

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