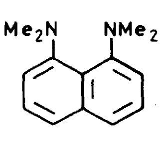
Effect of Ring Size on the Basicity and Kinetic Behaviour of 1,5-Dimethylnaphtho[1,8-*bc*]-1,5-diazacycloalkanes

Frank Hibbert* and Gareth R. Simpson
Department of Chemistry, King's College London, Strand, London WC2R 2LS

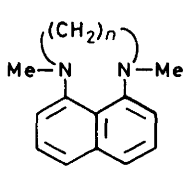
The basicities and rates of proton transfer for a series of 1,5-dimethylnaphtho[1,8-*bc*]-1,5-diazacycloalkanes (**2**)—(**5**) are compared with data for 1,8-bis(dimethylamino)naphthalene (**1**). For amines (**2**) and (**3**) with smaller rings, the rates of proton transfer are higher and the basicities are lower than for (**1**). For (**2**), the results are not very different from those expected for a simple aromatic amine. With larger rings, as in (**4**) and (**5**), the rates of proton transfer are lower and the basicities are higher than for (**1**). The results can be explained on the basis that with smaller and less flexible rings, the conformations of the amine and protonated amine are similar and there is little difference in strain between the two. For larger rings the protonated amine can adopt a conformation with an intramolecular hydrogen bond and in this conformation there is much less strain than in the amine. The basicity and rates for 1,8-dipyrrolidinonaphthalene (**6**) are also considered.

The pK_a value (12.1) of 1,8-bis(dimethylamino)naphthalene is exceptionally high for an aromatic amine.[1] One factor which is considered to be important is the difference in strain between the amine and protonated amine. In the amine, the nitrogen lone pair interaction and the crowding of methyl groups around the nitrogen atoms is relieved somewhat by a twist of the dimethylamino groups and a distortion of the naphthalene ring.[2] In the protonated amine the most stable conformation is one where the proton is in an intramolecular hydrogen bond between the nitrogen atoms.[3] With 2,7-substituents, as in 1,8-bis(diethylamino)-2,7-dimethoxynaphthalene (pK_a 16.3), a different distortion of the amine is required to avoid the additional interaction between the diethylamino groups and the methoxy substituents.[4]

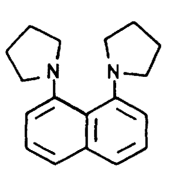
According to the foregoing arguments, the acid–base properties of the diaminonaphthalenes are dependent on the amine and the protonated amine being able to adopt conformations in which strain is reduced and, in the case of the protonated amine, in which an intramolecular hydrogen bond is formed. It is of interest to find out whether the acid–base properties of the molecules can be modified by controlling the conformational changes which can occur and in the present work the effect of introducing methylene bridges between the nitrogen atoms has been investigated. The basicities and rates of proton transfer for compounds (**2**)—(**6**) are considered in comparison with the results obtained for (**1**).



(1)



(2) n = 2
(3) n = 3
(4) n = 4
(5) n = 5



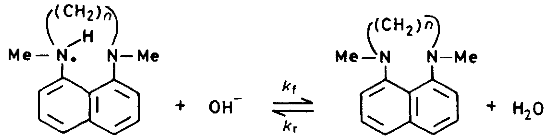
(6)

Experimental

Materials.—The diaminonaphthalenes used were prepared[5] and given to us by Dr. R. W. Alder.

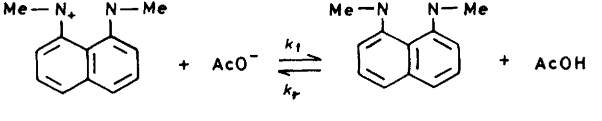
Equilibrium Measurements.—The pK_a values of the amines (**2**)—(**6**) were determined from spectrophotometric measurements under various conditions. For (**2**) measurements were made in aqueous acetate buffer solutions at 355 nm where the free amine absorbs strongly. For (**3**) and (**6**) aqueous borax buffer solutions were used. Measurements were made at 350 nm for (**3**) where the absorbance is due mainly to the free amine and at 225 nm for (**6**) where the protonated amine absorbs strongly. The resulting pK_a values (Table) refer to finite ionic strength, 0.1 mol dm^{-3} for (**2**) and *ca.* 0.03 mol dm^{-3} for (**3**) and (**6**).

The amines (**4**) and (**5**) are too strongly basic to permit equilibrium measurements to be made in aqueous solution at moderate concentrations of sodium hydroxide but in 30 and 40% (v/v) $Me_2SO–H_2O$ the equilibria between the amines and the protonated amines [equation (1)] can be studied with concentrations of sodium hydroxide in the range 0.001—0.1 mol dm^{-3}. Absorbance readings were taken at 340 nm for solutions containing *ca.* 1.0 × 10^{-5} mol dm^{-3} of the amines in the presence of different hydroxide ion concentrations at a constant ionic strength (0.1 mol dm^{-3}), maintained by addition of potassium chloride. The values of the equilibrium constant for reaction (1) involving (**4**) and (**5**) are given in the Table. These results can be compared with the value of the equilibrium constant for the reaction of (**1**) under similar conditions[6] and hence used to deduce approximate pK_a values for (**4**) and (**5**) from the pK_a value for (**1**) measured in aqueous solution. This procedure assumes that the change in solvent from aqueous solution to 30% (v/v) $Me_2SO–H_2O$ has the same effect on the value of the equilibrium constants for (**1**), (**4**), and (**5**).



(1)

Kinetic Measurements.—The acid–base equilibrium of 1,5-dimethylnaphtho[1,8-*bc*]-1,5-diazacycloheptane (**2**) in aqueous acetate buffers [equation (2)] occurred too rapidly to permit



(2)

Table. Equilibrium constants and rate coefficients for proton transfer involving diaminonaphthalenes[a]

Compound	Solvent	Base	K/dm^3 mol^{-1}	$10^{-5}k_f$/dm^3 mol^{-1} s^{-1}	k_r/s^{-1}	k_f/k_r/dm^3 mol^{-1}	pK_a	Reference
(1)	H_2O	OH^-	52 ± 14	1.9 ± 0.4	3 900 ± 500	49 ± 15	12.1 ± 0.1	*b*
	20% Me_2SO–H_2O	OH^-	660 ± 60	2.9 ± 0.2	350 ± 50	830 ± 150		
	30% Me_2SO–H_2O	OH^-	2 800 ± 200	6.1 ± 0.5	200 ± 30	3 100 ± 700		
(2)	H_2O	OAc^-	0.78	>500			4.62 ± 0.05	*c*
(3)	H_2O	Borax					10.27 ± 0.07	*c*
(4)	30% Me_2SO–H_2O	OH^-	99 ± 10	4.7 ± 0.5	4 800 ± 500	98 ± 20	13.6 ± 0.1	*c*
	40% Me_2SO–H_2O	OH^-	560 ± 30	7.0 ± 0.6	1 200 ± 200	609 ± 140		
(5)	30% Me_2SO–H_2O	OH^-	347 ± 40	0.52 ± 0.07	160 ± 20	316 ± 90	13.0 ± 0.1	*c*
	40% Me_2SO–H_2O	OH^-	2 170 ± 100	0.79 ± 0.06	Small			
(6)	H_2O	Borax					9.97 ± 0.08	*c*
	30% Me_2SO–H_2O	OH^-		0.73 ± 0.05	Small			
	40% Me_2SO–H_2O	OH^-		1.1 ± 0.1	Small			

[a] Temperature 25 °C, ionic strength 0.1 mol dm^{-3} except for (1) in 30% Me_2SO–H_2O which was studied at 35 °C. [b] Ref. 6. [c] Present work.

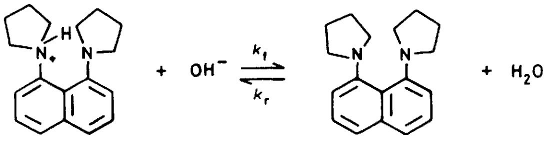
determination of the rate coefficients k_f and k_r by our temperature-jump apparatus, but we have been able to estimate lower limits for the rate coefficients. The change in absorbance for a solution of (2) in an aqueous acetate buffer following a rapid perturbation of 4.8 °C was complete within the heating time of our apparatus (*ca.* 5 μs) even at the lowest buffer concentrations which could be used and at several buffer ratios. The change in absorbance was identified as corresponding to a shift of the equilibrium between the protonated and unprotonated amine because the variation in the magnitude of the absorbance change with wavelength at various wavelengths in the range 270—380 nm was exactly paralleled by the variation in the difference of the values of the molar absorptivities of the amine and the protonated amine ($\varepsilon_B - \varepsilon_{BH^+}$). At 355 nm the value of $\varepsilon_B - \varepsilon_{BH^+}$ and the rapid change in absorbance following a temperature-jump pass through a maximum. The observed change in absorbance could involve reaction of (2) and its protonated form with the acid–base pair H_2O–H_3O^+ or AcO^-–AcOH. If the reaction involves AcO^-–AcOH, as in equation (2), the lower limits $k_f >$ *ca.* 5×10^7 dm^3 mol^{-1} s^{-1} and $k_r >$ *ca.* 7×10^7 dm^3 mol^{-1} s^{-1} are deduced from the time constant of the rapid change in absorbance. If the pair H_2O–H_3O^+ is involved, it is calculated that the rate coefficients in the forward and reverse directions have values greater than *ca.* 1×10^5 s^{-1} and *ca.* 4×10^9 dm^3 mol^{-1} s^{-1}, respectively. Therefore the conclusion is reached that for (2), proton transfer occurs rapidly. A similar conclusion was reached for (3) in aqueous solutions containing low concentrations of sodium hydroxide [equation (1) with $n = 3$]. The result $k_f >$ *ca.* 1×10^8 dm^3 mol^{-1} s^{-1} was deduced for proton removal by hydroxide ion.

Kinetic studies using the temperature-jump technique were possible for the larger ring compounds, 1,5-dimethylnaphtho-[1,8-*bc*]-1,5-diazacyclo-nonane (4) and -decane (5) because the reactions occurred more slowly. The reversible reactions of the protonated amines to the free amines in the presence of sodium hydroxide were observed in 30 and 40% (v/v) Me_2SO–H_2O at an ionic strength of 0.1 mol dm^{-3}. In 30% Me_2SO–H_2O temperature jumps of 3.6 and 9.9 °C respectively were used to disturb equilibrium (1) involving (4) and (5) and in 40% (v/v) Me_2SO–H_2O, the jumps were 3.8 and 10.5 °C. The solutions containing *ca.* 2×10^{-5} mol dm^{-3} of the amines were initially thermostatted at a temperature such that after the perturbation the reaction temperature was 25.0 °C. The chemical relaxation to a new equilibrium position at 25.0 °C was observed at 340 nm where an increase in absorbance accompanying an increase in concentration of the free amine occurred as a result of the shift in equilibrium (1) towards products. The dependence of the reciprocal relaxation time for the change in absorbance on hydroxide ion concentration was linear [equation (3)] from

$$\tau^{-1} = k_f[OH^-] + k_r \qquad (3)$$

which the values of k_f and k_r given in the Table were calculated. The ratios of k_f/k_r for (4) and (5) were compatible with the values of the separately measured equilibrium constants for the reaction (see Table).

The kinetics of proton transfer from protonated 1,8-dipyrrolidinonaphthalene [equation (4)] were studied in 30 and



(4)

40% (v/v) Me_2SO–H_2O at 25.0 °C and ionic strength 0.1 mol dm^{-3} using the stopped-flow technique. The reaction could not be studied in wholly aqueous solution because of the limited solubility of the amine. A solution of the protonated amine (1.6×10^{-5} mol dm^{-3}) in the partially aqueous solvent was mixed with an equal volume of the solvent containing hydroxide ion and the appropriate quantity of potassium chloride to maintain constant ionic strength. The increase in absorbance accompanying the deprotonation was observed at 250 nm. The values of k_f [equation (4)], are given in the Table but values of k_r and of the equilibrium constant for the reaction could not be obtained because even in the presence of low concentrations of hydroxide ion the equilibrium position lies almost entirely in favour of products.

Discussion

The pK_a values of the diamines (1)—(6) are given in the Table. The large difference in pK_a between (2) and (3) has been observed previously[*] and illustrates the remarkable change in pK_a with ring size along the series (2)—(5). The rates of proton transfer also vary considerably along the series (2)—(5). The variation in basicity and rates can largely be accounted for by considering the differences in strain between the protonated and unprotonated forms of the amines and whether an intramolecular hydrogen bond is present in the protonated amine. It is also necessary to assume that proton removal by hydroxide ion is sterically hindered.

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[*] For (2) and (3), previous measurements[7] gave pK_a 4.61 and 10.30 respectively, in good agreement with the present work.

For (**2**), the conformation imposed by the bridge means that there is little interaction between the nitrogen lone pairs in the amine and also that the protonated amine is unable to form an intramolecular hydrogen bond. Both forms are likely to have similar conformations. In contrast to (**1**), protonation is not accompanied by a relief of strain and the pK_a value and rates of proton transfer are similar to the values observed for a simple aromatic amine. The properties of (**3**) are intermediate between the properties of (**2**) and the larger ring compounds (**4**) and (**5**). Thus proton transfer is rapid and the pK_a value is higher than expected for a simple aromatic amine, but lower than the pK_a values of (**4**) and (**5**).

In the case of (**4**) and (**5**) the basicities are even higher than for (**1**). The rates of proton transfer for (**4**) are similar to the rates for (**1**), but (**5**) reacts about an order of magnitude more slowly. Low rates of reaction are also found for 1,8-dipyrrolidinonaphthalene (**6**). The equilibrium basicity is higher than expected for an aromatic amine but lower than for (**1**), (**4**), and (**5**). The high basicities of (**4**) and (**5**) are a result of the same factors which operate for (**1**). The preferred conformation of the protonated amines places the proton in an intramolecular hydrogen bond between the basic nitrogen atoms and in this conformation the protonated forms are much less strained than the free amines. The larger rings of (**4**) and (**5**) allow greater conformational flexibility than is permitted in (**2**) and (**3**). The low rates of proton transfer from other protonated diaminonaphthalenes have been explained by a mechanism in which reaction occurs through a non-hydrogen-bonded open form present in low concentration and on the assumption that attack of base on the open form is subject to steric hindrance.[8] For (**2**) and (**3**) with absent or weak hydrogen bonds in the protonated amines, rearrangement to an open non-hydrogen-bonded species does not introduce a strongly unfavourable equilibrium. Also, since proton transfer is fast, it is likely that attack of base is not strongly sterically hindered and the rates could be quite close to the diffusion-controlled values found for normal ammonium ions. With (**4**)—(**6**) for which the possibility of an intramolecular hydrogen bond in the protonated amines exists, the rates of proton removal are reduced. The values of the rate coefficients (k_f) are not very strongly dependent on the solvent, but if the reactions could have been studied in wholly aqueous solution it is probable, by comparison with the behaviour observed for (**1**),[6] that the values would have been slightly lower than the results in $Me_2SO–H_2O$. For (**4**)—(**6**), it can be assumed that the rates are low because reaction occurs through a low-concentration intermediate (open form) and because attack on the open form is subject to steric hindrance, but it is difficult to assess the relative importance of these two effects. If the difference in rates for (**4**) and (**5**) was due entirely to a stronger hydrogen bond in (**5**), leading to a lower concentration of the reactive open form, it would have been expected that the stronger hydrogen bond would also have led to an increased pK_a value for (**5**) compared with (**4**) and this is the reverse of what is found. It is necessary, therefore, in explaining the particularly low rates of proton transfer involving (**5**) and (**6**) to consider that strain in the transition state is also important. This effect together with differences in strain between the protonated and unprotonated amines and differences in hydrogen bond strength in the protonated amines will account for the changes in pK_a values and rates for amines (**1**)—(**6**).

Acknowledgements

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