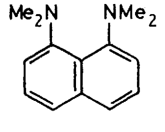
1,8-Dimorpholinonaphthalene: Proton Transfer Reactions

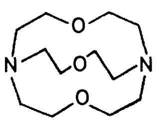
By **Abdul Awwal, Richard Burt,** and **A. Jenny Kresge,*** Department of Chemistry, University of Toronto, Scarborough College, West Hill, Ontario M1C 1A4, Canada

1,8-Dimorpholinonaphthalene is found to have an unusually high basicity [pK_a(BH$^+$) = 7.51 ± 0.01] and rate constants for downhill proton transfer from its conjugate acid which are substantially below (by factors of 10^5—10^7) the encounter-controlled limit. This is taken to indicate that this base, in forming its conjugate acid, receives a proton into a strong intramolecular hydrogen bond, thus relieving a considerable amount of steric strain. The isotope effect on deprotonation of the conjugate acid by hydroxide ion, as well as the appearance of the Brönsted plot for this reaction, are consistent with a two-step mechanism for proton transfer out of the intramolecular hydrogen bond.

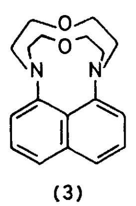
PROTON transfer between electronegative atoms in the direction of decreasing free energy is generally a very fast reaction. The process may be slowed down, however, by incorporating the proton undergoing transfer in an intramolecular hydrogen bond and also by providing steric hindrance to the approach of the proton acceptor.[1] Of particular interest in this respect are the reactions of 1,8-bis(dimethylamino)naphthalene (proton sponge) (1): downhill proton transfer from the conjugate acid of this substance to the hydroxide ion has a rate constant five orders of magnitude below the encounter-controlled limit.[2] Much slower yet is proton transfer from the conjugate acids of the bicyclic cryptand (2) in which the acidic protons are held in a small molecular cavity.[3] In an attempt to combine these interesting properties of (1) and (2) in a single molecule, we sought to synthesize the bridged analogue of proton sponge (3) but we obtained 1,8-dimorpholinonaphthalene (4), instead. This material proved to have noteworthy acid–base properties of its own, some of which we describe here.



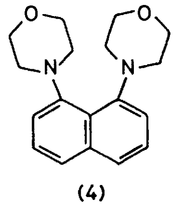
(1)



(2)



(3)



(4)

EXPERIMENTAL

Materials.—1,8-Dimorpholinonaphthalene was prepared by treating 1,8-diaminonaphthalene (Aldrich) with a tenfold molar excess of bis-(2-bromoethyl) ether in the presence of two equivalents of Na_2CO_3. This mixture was stirred at 150 °C for 75 min, cooled, and taken up in ether. The ether solution was washed with water, and the ether was then removed by rotary evaporation. The residue so obtained was dissolved in ethanol and enough dilute aqueous HCl was added to neutralize the amine. Excess of bromo-ether was then removed by extraction with hexane, the ethanol–water solution was made basic by adding aqueous NH_3, and the resulting mixture was extracted with $CHCl_3$; the extract was then concentrated and the residue was subjected to column chromatography on alumina. The remaining bromo-ether was first eluted using 15% diethyl ether–85% hexane as the solvent, and then 30% diethyl ether–70% hexane was used to elute the product, which, upon recrystallization from methanol was obtained as fine needles. The yield was low; no attempt was made to optimize it.

The ^1H and ^{13}C n.m.r. spectra of this material were consistent with the 1,8-dimorpholinonaphthalene structure, as was also the mass spectrum. These properties, however, did not serve to distinguish this substance from the isomeric bridged compound (3), and its structure was therefore proved by *X*-ray diffraction.[4]

Methylphosphonic acid was synthesized as described before;[5] all other reagents were best available commercial grades.

Solutions were prepared using deionized H_2O purified further by distillation from alkaline permanganate, or D_2O (99.7%; Merck, Sharp, and Dohme) as received.

pK_a *Determination*.—The concentrations of protonated and unprotonated 1,8-dimorpholinonaphthalene were determined spectroscopically at 236 nm using a Pye–Unicam 1800 spectrophotometer with thermostatted cell compartment operating at 25.0 ± 0.05 °C. The extinction coefficient of the free base, ε_B 4.23×10^4 dm^3 mol^{-1} cm^{-1}, was measured in 0.01M-NaOH solution, and the extinction coefficient of the conjugate acid, ε_{BH} 3.18×10^3 dm^3 mol^{-1} cm^{-1}, was measured in 0.01M-HCl solution. Apparent extinction coefficients ε_{app} were then measured in $H_2PO_4^-$–HPO_4^{2-} buffer solutions of pH 7.3—7.9 and ionic strength, *I* 0.01—0.14M. Concentration ratios were calculated using the formula $[BH^+]/[B] = (\varepsilon_B - \varepsilon_{app})/(\varepsilon_{app} - \varepsilon_{BH^+})$. Care was taken throughout not to exceed the rather low maximum solubility of 1,8-dimorpholinonaphthalene in water, *ca*. 6×10^{-6}M; solutions of concentration below this value were found to obey the Beer–Lambert law exactly. Measurements of pH were made with a Beckman model 1019 research pH meter.

Kinetics.—Reaction rates were measured spectroscopically at 236 nm using a Durrum–Gibson model D-110 stopped-flow spectrophotometer operating at 25.0 ± 0.1 °C. The substrate dissolved in very dilute hydrochloric acid solution was loaded into one syringe, sodium hydroxide or buffer solution of appropriate concentration was placed in the other, and these were mixed in equal proportions. Final concentrations of substrate in the reaction mixtures were 0.5—1.0 × 10^{-5}M. Rate constants were calculated by feeding the output from the spectrophotometer through a digitizing interface into a Textronix 4051 computer, which performed a linear least-squares fit to the first-order rate expression. Hydroxide ion or buffer base concentrations always exceeded the substrate concentration by at least a factor of 100, and the first-order rate law was obeyed within the experimental precision.

RESULTS

pK_a.—Two groups of measurements were made in series of $H_2PO_4^-$–HPO_4^{2-} buffer solutions of decreasing buffer concentration at two different buffer ratios. The data are summarized in Table 1. The pH values reported there were determined experimentally, but they were also calculated using pK_a 7.200 [6] and activity coefficients recommended by Bates.[7] Calculated and experimental values never differed from one another by more than 0.028, and the agreement was usually much better than that.

TABLE 1

Ionization of 1,8-dimorpholinonaphthalene in wholly aqueous hydrogenphosphate buffer solutions at 25 °C

pH	Ionic strength (M) [a]	$[BH^+]/[B]$
Series 1		
7.300	0.124	2.56, 2.20, 2.20
7.386	0.062	1.67, 1.58
7.442	0.0372	1.47, 1.42
7.492	0.0124	1.26, 1.24
Series 2		
7.700	0.132	0.941, 0.941
7.771	0.0692	0.666, 0.740
7.815	0.0415	0.598, 0.642
7.851	0.0277	0.496, 0.505

[a] Determined by buffer species alone.

The experimental data were extrapolated to zero ionic strength using the function given in equation (1) in which b

$$\log([BH^+]/[B]) + pH - 0.5115\sqrt{I}/(1 + \sqrt{I}) = pK_a - bI \qquad (1)$$

is the ionic interaction coefficient in the expression used for the activity coefficient of BH^+, $\log y_{BH} = -0.5115\sqrt{I}/(1 + \sqrt{I}) + bI$. Least-squares analysis gave pK_a 7.509 ± 0.010 and b −0.15 ± 0.13. These results were used to calculate a value for the concentration quotient, $K_c = [B][H^+]/[BH^+]$, at I 0.100M: K_c was 2.72 × 10^{-8} mol dm^{-3}, and this value was used in the kinetic analysis.

Kinetics.—Hydroxide ion solutions. Rate measurements were performed in sodium hydroxide solutions in H_2O and in D_2O; the data are summarized in Table 2. In both cases observed first-order rate constants, k_{obs}, proved to be accurately proportional to base concentration. Linear least-squares analysis of the relationship between k_{obs} and [Base] provided the bimolecular rate constants k_{HO^-} (8.75 ± 0.32) × 10^4 dm^3 mol^{-1} s^{-1} and k_{DO^-} (7.10 ± 0.12) × 10^4 dm^3 mol^{-1} s^{-1}; these give the isotope effect k_H/k_D of 1.23 ± 0.05. The intercepts in these analyses were not significantly different from zero, indicating that proton transfer to the solvent was negligible in these solutions.

Buffer Solutions.—Rate measurements were also made in buffer solutions of two amines, carbonate ion, and methylphosphonate ion; these data are summarized in Table 3.

TABLE 2

Rates of proton transfer from the conjugate acid of 1,8-dimorpholinonaphthalene to hydroxide ion in H_2O and D_2O solution at 25 °C [a]

10^3[Base]/M	$10^{-2}\ k_{obs}/s^{-1}$
H_2O	
1.00	0.875, 0.832, 0.879
1.50	1.16, 1.33, 1.08, 1.34, 1.33, 1.20, 1.30, 1.28
2.00	1.72, 1.90, 1.64, 1.62, 1.59, 1.55, 1.76, 1.79
2.50	2.00, 2.04, 2.35, 2.30, 2.06, 2.02
3.00	2.63, 2.34, 2.48, 2.59, 3.09
3.50	2.98, 2.94, 2.90, 3.31, 3.07, 2.80
$k = (-4.74 \pm 7.72) \pm (8.75 \pm 0.32) \times 10^4[HO^-]$	
D_2O	
0.79	0.512, 0.554, 0.529, 0.536, 0.530, 0.496, 0.494, 0.509
1.26	0.854, 0.863, 0.843, 0.883, 0.858, 0.791, 0.802, 0.778
1.74	1.27, 1.22, 1.18, 1.21, 1.23, 1.17, 1.19
2.22	1.48, 1.55, 1.50, 1.48, 1.53, 1.56, 1.56
$k = (-4.50 \pm 1.85) + (7.10 \pm 0.12) \times 10^4[DO^-]$	
$k_{HO}/k_{DO} = 1.23 \pm 0.05$	

[a] Ionic strength determined by sodium hydroxide.

TABLE 3

Rates of proton transfer from the conjugate acid of 1,8-dimorpholinonaphthalene in aqueous buffer solutions at 25 °C and I 0.10M

10^2[B]	$10^{-1}\ k_{obs}/s^{-1}$
Et_3N–Et_3NH^+	$[BH^+]/[B]$ 1.00
2.00	8.14, 8.27, 7.76, 8.05, 7.92, 7.88
4.00	8.54, 8.59, 8.54, 8.61, 8.54, 8.38
7.00	9.13, 8.82, 9.16, 9.32, 9.07, 9.01, 8.63, 9.02
$k_{adj} = (8.16 \pm 0.09) \times 10 + (1.25 \pm 0.18) \times 10^2[B]$	
Et_3N–Et_3NH^+	$[BH^+]/[B]$ 2.00
1.00	4.20, 4.22, 4.09, 4.05, 4.24, 4.10, 4.18, 4.14
2.00	4.16, 4.44, 4.46, 4.20, 4.29, 4.43, 4.43, 4.32
3.00	4.62, 4.63, 4.56, 4.56, 4.68, 4.58, 4.59, 4.51
4.00	4.82, 4.91, 4.68, 4.59, 4.69, 4.69, 4.80
$k_{adj} = (4.14 \pm 0.04) \times 10 + (1.52 \pm 0.15) \times 10^2[B]$	
$BuNH_2$–$BuNH_3^+$	$[BH^+]/[B]$ 1.20
1.00	5.63, 5.54, 5.51, 5.41, 5.72, 5.47, 5.48, 5.54
2.00	6.42, 6.53, 6.67, 6.32, 6.47, 6.41, 6.56, 6.53
3.00	7.58, 7.40, 7.48, 7.55, 7.44, 7.45
4.00	8.34, 8.34, 8.11, 8.21, 8.23, 8.17
5.00	8.68, 8.77, 8.71, 8.85, 8.60, 8.93, 8.94
$k_{adj} = (5.27 \pm 0.05) \times 10 + (7.34 \pm 0.16) \times 10^2[B]$	
$BuNH_2$–$BuNH_3^+$	$[BH^+]/[B]$ 2.00
1.00	3.83, 3.73, 3.83, 3.78, 3.70, 3.74, 3.63, 3.83
2.00	4.42, 4.53, 4.54, 4.46, 4.50, 4.37, 4.62, 4.40
3.00	5.33, 5.15, 5.19, 5.26, 5.31, 5.23, 5.28
4.00	5.72, 5.86, 5.81, 5.63, 5.74, 5.87, 5.83, 5.61
5.00	6.31, 6.30, 6.38, 6.29, 6.25, 6.43, 6.36, 6.34, 6.34, 6.36
$k_{adj} = (3.35 \pm 0.33) \times 10 + (6.13 \pm 0.10) \times 10^2[B]$	
$BuNH_2$–$BuNH_3^+$	$[BH^+]/[B]$ 1.20
1.00	5.69, 5.47, 5.34, 5.49, 5.60, 5.60, 5.50
2.00	6.71, 6.59, 6.75, 6.65, 6.78, 6.73, 6.65
3.00	7.75, 7.33, 7.37, 7.49, 7.48, 7.47, 7.65
4.00	8.13, 8.09, 8.23, 8.15, 8.38, 8.54, 8.35
$k_{adj} = (5.23 \pm 0.05) \times 10 + (7.77 \pm 0.20) \times 10^2[B]$	
CO_3^{2-}–HCO_3^-	$[BH^-]/[B^{2-}]$ 1.00
2.00	2.24, 2.37, 2.25, 2.26, 2.17, 2.18
4.00	4.19, 4.19, 4.36, 4.28, 4.33, 4.18
6.00	5.53, 5.50, 5.45, 5.62, 5.50
8.00	7.25, 7.92, 7.88, 7.18, 7.44, 7.90, 7.86, 7.75
$k_{adj} = (7.40 \pm 1.20) + (8.68 \pm 0.22) \times 10^3[B^{2-}]$	

TABLE 3 (*continued*)

CO_3^{2-}–HCO_3^-	$[BH^-]/[B^{2-}]$ 2.00
1.00	1.21, 1.22, 1.20, 1.17, 1.17, 1.14
2.00	2.22, 2.26, 2.21, 2.14, 2.15, 2.13, 2.24
3.00	3.11, 3.06, 2.97, 3.00, 2.97, 2.92
4.00	3.67, 3.71, 3.81, 3.67, 3.75, 3.92

$k_{adj} = (5.05 \pm 0.43) + (8.38 \pm 0.16) \times 10^3[B^{2-}]$

CO_3^{2-}–HCO_3^-	$[BH^-]/[B^{2-}]$ 4.00
1.00	1.15, 1.17, 1.17, 1.17, 1.14, 1.16
1.50	1.77, 1.71, 1.69, 1.72, 1.66, 1.66, 1.67
2.00	2.03, 2.02, 2.05, 1.97, 2.10, 2.10, 2.08

$k_{adj} = (3.61 \pm 0.51) + (8.70 \pm 0.34) \times 10^3[B^{2-}]$

$CH_3PO_3^{2-}$–$CH_3PO_3H^-$	$[BH^-]/[B^{2-}]$ 0.25
0.80	1.59, 1.58, 1.58, 1.60, 1.59, 1.62
1.20	2.45, 2.43, 2.46, 2.44, 2.46, 2.47, 2.48
1.60	3.30, 3.40, 3.33, 3.43, 3.33, 3.32, 3.35, 3.33
2.40	5.01, 5.04, 4.76, 4.86, 4.88, 4.90, 5.14

$k_{obs} = (-4.79 \pm 4.02) \times 10^{-1} + (2.09 \pm 0.02) \times 10^3[B^{2-}]$

$CH_3PO_3^{2-}$–$CH_3PO_3H^-$	$[BH^-]/[B^{2-}]$ 0.50
0.40	0.991, 0.995, 0.961, 0.976, 0.984, 0.983, 0.969, 0.954
0.60	1.45, 1.45, 1.47, 1.43, 1.46, 1.45
0.80	1.91, 1.93, 1.88, 1.95, 1.96, 1.93, 1.96

$k_{obs} = (1.28 \pm 1.54) \times 10^{-1} + (2.40 \pm 0.03) \times 10^3[B^{2-}]$

$CH_3PO_3^{2-}$–$CH_3PO_3H^-$	$[BH^-]/[B^{2-}]$ 1.00
0.100	0.314, 0.307, 0.322, 0.307, 0.311, 0.314, 0.320, 0.314, 0.320
0.200	0.613, 0.635, 0.611, 0.620, 0.612, 0.623, 0.627
0.300	0.909, 0.941, 0.904, 0.931, 0.914, 0.903, 0.916
0.400	1.22, 1.21, 1.27, 1.25, 1.25, 1.21, 1.21

$k_{obs} = (8.89 \pm 6.22) \times 10^{-2} + (3.05 \pm 0.02) \times 10^3[B^{2-}]$

$CH_3PO_3^{2-}$–$CH_3PO_3H^-$	$[BH^-]/[B^{2-}]$ 2.00
0.25	1.07, 1.12, 1.11, 1.11, 1.16, 1.14
0.50	2.00, 2.07, 2.18, 2.05, 2.06, 2.14
0.75	3.46, 3.45, 3.37, 3.38, 3.21, 3.33

$k_{obs} = (-1.11 \pm 0.75) + (4.58 \pm 0.13) \times 10^3[B^{2-}]$

TABLE 4

Summary of rate constants for proton transfer from the conjugate acid of 1,8-dimorpholinonaphthalene in aqueous solution at 25 °C

Base	pK_a (BH)	$\Delta G°$/kcal mol^{-1}	$10^3\ k_B$
HO^-	15.74	−11.2	87.5 ± 3.2
DO^-	15.74		71.0 ± 1.2
Et_3N	10.72 [a]	−4.37	0.139 ± 0.012
$BuNH_2$	10.64 [a]	−4.27	0.708 ± 0.009
CO_3^{2-}	10.33 [b]	−3.85	8.59 ± 0.14
$CH_3PO_3^{2-}$	8.00 [c]	−0.67	1.69 ± 0.05

[a] R. A. Robinson and R. H. Stokes, ' Electrolyte Solutions,' Butterworths, London, 1959, Appendix 12.1. [b] H. S. Harned and S. R. Scholes, *J. Am. Chem. Soc.*, 1941, **63**, 1706. [c] A. J. Kresge and Y. C. Tang, *J. Org. Chem.*, 1977, **42**, 757.

With each base, series of buffer solutions of constant stoicheiometric buffer ratio but changing buffer concentration were used. This technique served to hold hydroxide ion concentrations constant in methylphosphonate buffers. In the case of the significantly stronger amine bases and carbonate ion, however, appreciable hydrolysis occurred, and the extent of hydrolysis changed with buffer concentration; hydroxide ion concentrations were consequently not constant along series of these buffer solutions. Such ' buffer failure ' was corrected for by adjusting observed rate constants to constant hydroxide ion concentrations by a method we have described before for acid-catalysed reactions in acidic buffers.[8] Hydroxide ion concentrations needed for this purpose were calculated from thermodynamic pK_a values of the buffer constituents (Table 4) and activity coefficients recommended by Bates [7] for HO^-, HCO_3^-, and CO_3^{2-}, and calculated using the formula $\log y = -A\sqrt{I}/(1 + B\mathring{a}\sqrt{I})$ with $\mathring{a} = 6.0$ Å [9] for the amine cations; a ratio of the activity coefficients of $CH_3PO_3H^-$ and $CH_3PO_3^{2-}$ was calculated using data obtained in pK_a determinations.[5] This method of adjusting buffer base rate constants also requires knowledge of the hydroxide ion rate constant, and the value measured in sodium hydroxide solutions was used for this purpose. The method also produces hydroxide ion rate constants (see below) which are largely independent of the value put in, and the fact that the average of the results obtained for the eight series of buffer solutions to which the method was applied, k_{HO^-} $(8.97 \pm 0.56) \times 10^4$ dm^3 mol^{-1} s^{-1}, is in excellent agreement with the directly measured value, $k_{HO^-} = (8.75 \pm 0.32) \times 10^4$ dm^3 mol^{-1} s^{-1}, attests to the validity of the method.

First-order rate constants adjusted in this way were good linear functions of buffer base concentration. The data were therefore subjected to linear least-squares analysis, and second-order rate constants were obtained as the slopes of these relationships. These second-order rate constants showed only random variation with buffer ratio, and best values were therefore obtained as simple averages of all results for a given buffer system. These are listed in Table 4.

The intercepts of these least-squares relationships represent proton transfer to the hydroxide ion, and hydroxide-ion rate constants were therefore obtained by dividing these intercepts by hydroxide ion concentration; hydroxide ion concentrations calculated for the buffer failure adjustments were used for this purpose. As noted above, the hydroxide ion rate constants obtained in this way were in good agreement with the directly measured value.

No adjustment of the data was required in the case of methylphosphonate buffers and observed rate constants were therefore used directly for investigating the relationship between rate and buffer concentration. This was found to be accurately linear for each of the four series employed. Linear least-squares analysis gave intercepts which were within experimental uncertainty zero, consistent with the negligible contribution from reaction with hydroxide ion expected at the pH values of these solutions.

The slopes obtained were in this case not constant but showed systematic variation with buffer ratio (Figure 1). This again is as expected, for the pK_a difference between donor and acceptor is in this case near zero; the concentration equilibrium constant for the reaction under study [equation (2)] at the ionic strength used, *I* 0.10M, is in fact

$$SH^+ + CH_3PO_3^{3-} \underset{k_{BH}}{\overset{k_B}{\rightleftharpoons}} S + CH_3PO_3H^- \qquad (2)$$

K_c 1.03. The reverse reaction will consequently make a significant contribution to the observed rate, and this contribution will change systematically with buffer ratio.

The rate law which holds under these conditions is shown as equation (3). Since $[BH^+]/[B] = BR$ (buffer ratio)

$$k_{obs} = k_B[B] + k_{BH}[BH^+] \qquad (3)$$

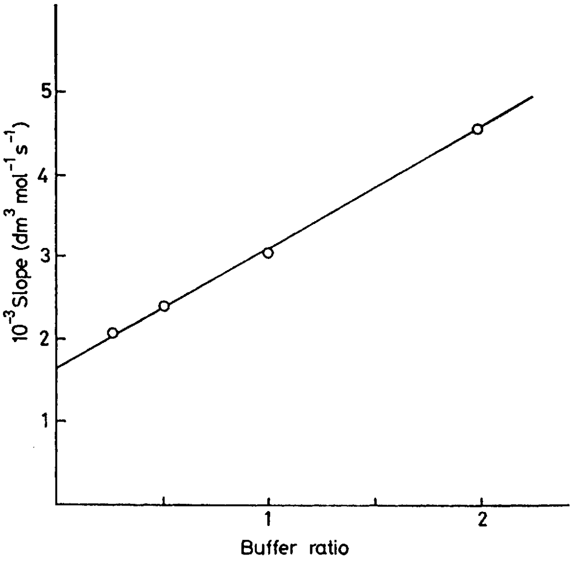


FIGURE 1 Relationship between buffer ratio and slopes of plots of k_{obs} *versus* buffer base concentrations for proton transfer from the conjugate acid of 1,8-dimorpholinonaphthalene in $CH_3PO_3H^-$–$CH_3PO_3^{2-}$ buffers at 25 °C

$[BH^+]$ in this expression may be replaced by $[B]\cdot BR$ giving equation (4).

$$k_{obs} = (k_B + k_{BH}BR)[B] \qquad (4)$$

Figure 1 shows that the present data adhere to this relationship well; least-squares analysis gives k_B $(1.69 \pm 0.05) \times 10^3$ dm^3 mol^{-1} s^{-1} and k_{BH} $(1.43 \pm 0.05) \times 10^3$ dm^3 mol^{-1} s^{-1}. The ratio of these two rate constants is equal to the equilibrium constant for the reaction, $k_B/k_{BH} = K_c$, and the value obtained, k_B/k_{BH} 1.18 ± 0.05, is in fact consistent with expectation: $K_c = 1.03$.

DISCUSSION

pK_a.—Placement of an amino-group on an aromatic ring generally lowers its basicity by a substantial amount: for the α-position of naphthalene, the effect ranges from 5 to 7 pK units. The pK_a determined here for 1,8-dimorpholinonaphthalene, 7.51, is therefore unusual, for it is only one pK unit less than the pK_a of the conjugate acid of morpholine itself, 8.49.[10] This is reminiscent of the situation for proton sponge, which is actually more basic than the related aliphatic amine, dimethylamine [pK_a(BH^+) 12.03 [11] and 10.77,[12] respectively], and it is likely that the explanation for this unusual behaviour which applies in the case of proton sponge holds for 1,8-dimorpholinonaphthalene as well.

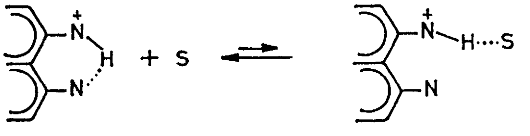
Proton sponge is a strained molecule. An *X*-ray determination of its structure [13] shows severe distortion of the naphthalene framework brought about by the bulk and lone pair–lone pair repulsion of the large *peri*-dimethylamino groups situated in a near face-to-face configuration. Protonation of the molecule relieves this strain in part, inasmuch as the proton is taken up into a position between the two nitrogen atoms,[14] placing a positive charge between the two lone pairs and forming a strong hydrogen bond. This relief of strain increases the energy difference between proton sponge and its conjugate acid, and that makes the conjugate acid a weaker acid and proton sponge a stronger base. An *X*-ray determination of the structure of 1,8-dimorpholinonaphthalene shows it to be strained in much the same way as proton sponge,[4] and it is reasonable to conclude, therefore, that its basicity is enhanced for the same reasons.

Kinetics.—Hydroxide ion. This conclusion is reinforced by the kinetics of protonation of 1,8-dimorpholinonaphthalene and of proton removal from its conjugate acid. Since the pK_a of protonated 1,8-dimorpholinonaphthalene is 7.51, it is a stronger acid than water (pK_a 15.74) and proton transfer to the hydroxide ion [equation (5)] is a reaction which is downhill in free energy. And yet the rate constant for this process is

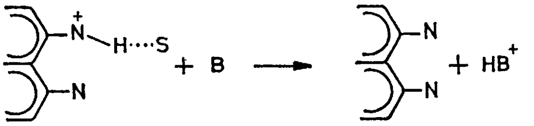
$$BH^+ + HO^- \longrightarrow B + H_2O \qquad (5)$$

only 8.75×10^4 dm^3 mol^{-1} s^{-1}, more than five orders of magnitude below the encounter-controlled limit. This is very similar to the rate constant determined for the analogous reaction of proton sponge, 2×10^5 dm^3 mol^{-1} s^{-1},[2] which suggests that here, just as there, the rate is slowed by steric hindrance and strong intramolecular hydrogen bonding.

There is an interesting question concerning the mechanism of proton transfer from an intramolecularly hydrogen-bonded acid.[15] It has been suggested that such reactions occur in two steps: the intramolecular hydrogen bond is first broken to give a species in which the acidic proton is hydrogen bonded externally to a solvent molecule [equation (6)]; this is then followed by a fast proton transfer similar to that between any normal acid-base pair [equation (7)] but the overall rate of reaction is slowed because the externally hydrogen-bonded acid is a low-concentration reaction intermediate.[1a] It has been pointed out, however, that a slow overall rate of reaction would also result from a mechanism in which the proton is transferred out of the intramolecular hydrogen bond directly in a single step, for the transition state of such a process would contain a trico-ordinated proton with an unfavourable non-linear arrangement of forming and breaking bonds [equation (8)].[16]

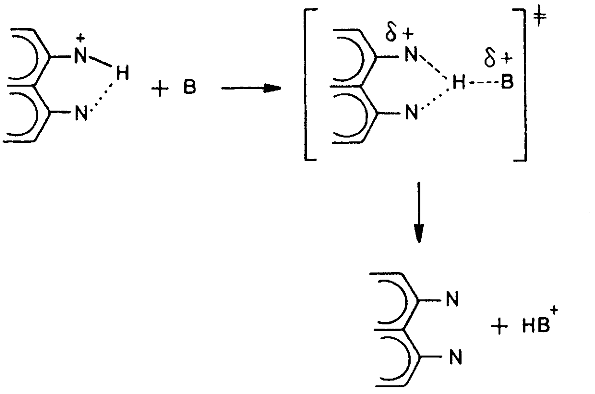


(6)



(7)

The linear dependence of rate on hydroxide ion concentration found here is consistent with this single-step mechanism and also with a two-step reaction scheme in which the change from intramolecularly to externally hydrogen-bonded acid is faster than the subsequent proton transfer. It is different, however, from the inverse relationship between hydroxide ion concentration and rate found for certain systems under conditions where the two-step mechanism with slow hydrogen bonding change and fast proton transfer is believed to operate.[17]



(8)

The isotope effect determined here for the hydroxide ion reaction [equation (5)], k_{HO^-}/k_{DO^-} 1.23 ± 0.05, is similar to other near-unity isotope effects measured for proton transfer from the conjugate acid of another derivative of proton sponge, 2,7-dimethoxy-1,8-bis-(dimethylamino)naphthalene, which is believed to occur by the two-step mechanism with fast hydrogen bonding change.[18] Small isotope effects can in fact be predicted for this reaction scheme. With B = HO^-, equation (7) will be a very strongly downhill process; its standard free energy change is even more negative than that of the overall reaction [equations (6) and (7)] for which $\Delta G°$ is 11 kcal mol^{-1}. Since kinetic isotope effects on proton transfer between nitrogen and oxygen atoms are known to describe narrow maxima and to have values appreciably greater than unity over a range only a few kcal to either side of $\Delta G°$ 0,[19] there will be no primary isotope effect on this reaction step; the only effect will be a decrease in the rate of encounter of the externally bound acid with the base, B, of *ca.* 20% brought about by the greater viscosity of the D_2O solvent.[20] This factor will be offset somewhat by the isotope effect on the hydrogen bonding change of equation (6). Recent fractionation factor measurements have shown that protons are held more loosely in strong hydrogen bonds than in weak ones,[21] but the difference between the internally and externally bound species of equation (6) is likely to be small because the fractionation factor of the internally hydrogen bonded proton in proton sponge is close to unity, ϕ 0.90.[11] An overall kinetic isotope effect of approximately unity is therefore to be expected for the two-step reaction mechanism.

It is more difficult to predict an isotope effect for the single-step mechanism of equation (8), and this renders the agreement between the experimental value and that expected for the two-step mechanism less diagnostic than it might otherwise be. There is reason to believe that kinetic isotope effects will vary in magnitude, passing through a maximum value near $\Delta G°$ 0, and that this maximum will be fairly broad for intrinsically slow reactions.[22] Since the unfavourable transition state of equation (8) makes this process a slow reaction, its isotope effect, despite the fact that $\Delta G°$ is 11 kcal mol^{-1} when B = HO^-, may still be close to a maximum value. This maximum value, however, could itself be quite low: it is believed that non-linear transition states such as that in equation (8) give lowered isotope effects,[23] and the additional bonding in the trico-ordinate configuration required here might lead to further reduction. A small isotope effect, k_H/k_D *ca.* 1.5, has in fact recently been found for an internally hydrogen-bonded acid believed to react with the hydroxide ion in this way.[24]

General bases. Further mechanistic information on proton transfer from intramolecularly hydrogen-bonded acids might be obtained from the appearance of their Brönsted plots Rapid proton transfer reactions between electronegative atoms show biphasic Brönsted relationships of the kind first observed by Eigen for normal acids and bases:[1a] linear arms of slope zero and one are joined by a fairly sharply curving region or break at $\Delta G°$ 0. The normal proton transfer part of the two-step mechanism [equation (7)] will give rise to such a biphasic Brönsted plot, but the break will be displaced to positive values of (overall) $\Delta G°$ by an amount corresponding to the equilibrium constant of the pre-equilibrium step [equation (6)]. The result will be rate constants k_B for the

$$SH^+ + B \underset{k_{BH}}{\overset{k_B}{\rightleftharpoons}} S + HB^+ \qquad (9)$$

deprotonation reaction (9) which are independent of the base strength of the proton acceptor for some distance on either side of $\Delta G° = 0$, and rate constants for protonation which continue to rise with increasing $\Delta G°$ through $\Delta G°$ 0. Such behaviour has been observed for proton

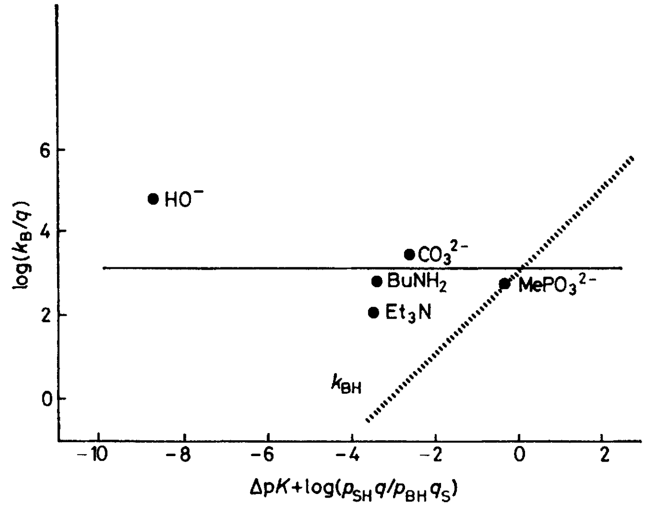


FIGURE 2 Brönsted plot for proton transfer from the conjugate acid of 1,8-dimorpholinonaphthalene to a group of proton acceptors in aqueous solution at 25 °C: solid line, forward reaction (k_B); broken line, reverse reaction (k_{BH})

transfer from a substituted salicylate ion to a series of amine bases[25] and also for proton transfer from 2,7-dimethoxy-1,8-bis(dimethylamino)naphthalene to several phenolate ions.[26] Very recently, moreover, a break in the Brönsted plot for the latter reaction has been found.[27] The conclusion has therefore been drawn that these reactions proceed *via* the two-step mechanism; this is reinforced by the fact that contrasting behaviour is reported for a system believed to react by the single-step mechanism.[25b]

In the present study we determined values of k_B for four bases (Table 4); these are displayed in the form of a Brönsted plot as Figure 2. It may be seen that these rate constants show no systematic variation with the base strength of the proton acceptor. The value for triethylamine is lower than the rest, but this might be expected on steric grounds. The remaining three bases show a constancy in k_B of the order of 10^3 dm^3 mol^{-1} s^{-1}. This behaviour is consistent with the two-step reaction mechanism.

We are grateful to the Natural Sciences and Engineering Research Council of Canada for its financial support of this research.

[1/701 *Received*, 1*st May*, 1981]

REFERENCES

[1] (*a*) M. Eigen, *Angew. Chem., Int. Ed. Engl.*, 1964, **3**, 1; for a recent example of steric retardation, see (*b*) C. F. Bernasconi and P. J. Carre, *J. Am. Chem. Soc.*, 1979, **101**, 2698, 2707.

[2] F. Hibbert, *J. Chem. Soc., Chem. Commun.*, 1973, 463; *J. Chem. Soc., Perkin Trans. 2*, 1974, 1862.

[3] J. Cheney and J. M. Lehn, *J. Chem. Soc., Chem. Commun.*, 1972, 487; J. Cheney, J. P. Kitzinger, and J. M. Lehn, *Nouv. J. Chim.*, 1978, **2**, 411.

[4] A. Awwal, R. Burt, A. J. Kresge, S. C. Nyburg, and W. W. Ng, *Acta Crystallogr.*, 1981, **B37**, in the press.

[5] A. J. Kresge and Y. C. Tang, *J. Org. Chem.*, 1977, **42**, 757.

[6] A. K. Grybowski, *J. Phys. Chem.*, 1958, **62**, 555.

[7] R. G. Bates, ' Determination of pH, Theory and Practice,' Wiley, New York, 1973, p. 49.

[8] A. J. Kresge, H. L. Chen, Y. Chiang, E. Murrill, M. A. Payne, and D. S. Sagatys, *J. Am. Chem. Soc.*, 1971, **93**, 413.

[9] R. N. Roy, R. A. Robinson, and R. G. Bates, *J. Am. Chem. Soc.*, 1973, **95**, 8231.

[10] H. B. Hetzer, R. G. Bates, and R. A. Robinson, *J. Phys. Chem.*, 1966, **70**, 2869.

[11] Y. Chiang, A. J. Kresge, and R. A. More O'Ferrall, *J. Chem. Soc., Perkin Trans. 2*, 1980, 1832.

[12] D. H. Everett and W. F. K. Wynne-Jones, *Proc. R. Soc. London, Ser. A*, 1941, **177**, 499.

[13] H. Einspahr, J. B. Robert, R. E. Marsh, and J. D. Roberts, *Acta Crystallogr.*, 1973, **B29**, 1611.

[14] M. R. Truter and B. L. Vickery, *J. Chem. Soc., Dalton Trans.*, 1972, 395.

[15] A. J. Kresge, *Chem. Soc. Rev.*, 1973, **2**, 475.

[16] J. L. Haslam and E. M. Eyring, *J. Phys. Chem.*, 1967, **71**, 4470 and previous references cited therein; T. Fueno, O. Kajimoto, Y. Nishigaki, and T. Yoshioka, *J. Chem. Soc., Perkin Trans. 2*, 1973, 738.

[17] B. Permutter-Hayman and R. Shinar, *Int. J. Chem. Kinet.*, 1975, **7**, 453, 798; B. Permutter-Hayman, R. Sarfaty, and R. Shinar, *ibid.*, 1976, **8**, 741.

[18] F. Hibbert and H. J. Robbins, *J. Chem. Soc., Chem. Commun.*, 1980, 141.

[19] N. A. Bergman, Y. Chiang, and A. J. Kresge, *J. Am. Chem. Soc.*, 1978, **100**, 5954; M. M. Cox and W. P. Jencks, *ibid.*, p. 5956; H. Fischer, F. X. DeCandis, S. D. Ogden, and W. P. Jencks, *ibid.*, 1980, **102**, 1340.

[20] W. J. Albery in ' Proton Transfer Reactions,' eds. E. F. Caldin and V. Gold, Chapman and Hall, London, 1975, p. 263.

[21] M. M. Kreevoy and T. M. Liang, *J. Am. Chem. Soc.*, 1980, **102**, 3315.

[22] A. J. Kresge in ' Isotope Effects on Enzyme-catalysed Reactions,' eds. W. W. Cleland, M. H. O'Leary, and D. B. Northrup, Univ. Park Press, Baltimore, 1977, ch. 2; A. J. Kresge, D. S. Sagatys, and H. L. Chen, *J. Am. Chem. Soc.*, 1977, **99**, 7228.

[23] R. A. More O'Ferrall, *J. Chem. Soc. B*, 1970, 785.

[24] B. Permutter-Hayman and R. Shinar, *Int. J. Chem. Kinet.*, 1978, **10**, 407.

[25] (*a*) F. Hibbert and A. Awwal, *J. Chem. Soc., Chem. Commun.*, 1976, 995; *J. Chem. Soc., Perkin Trans. 2*, 1978, 939; (*b*) B. Permutter-Hayman and R. Shinar, *Int. J. Chem. Kinet.*, 1977, **9**, 1.

[26] F. Hibbert and H. J. Robbins, *J. Am. Chem. Soc.*, 1978, **100**, 8239.

[27] A. J. Kresge and M. F. Powell, *J. Am. Chem. Soc.*, 1981, **103**, 972.