

Intramolecular Hemiacetals. The Acid–Base-Catalyzed Ring-Chain Interconversion of 2-Substituted 2-Hydroxy-4,4-dimethylmorpholinium Cations in Aqueous Solution*

Poul E. Sørensen,^{a,†} Robert A. McClelland^b and Richard D. Gandour^c

^aChemistry Department A, The Technical University of Denmark, DK-2800 Lyngby, Denmark, ^bDepartment of Chemistry, University of Toronto, Toronto, Ontario M5S 1A1, Canada and ^cDepartment of Chemistry, Louisiana State University, Baton Rouge, LA 70803-1804, USA

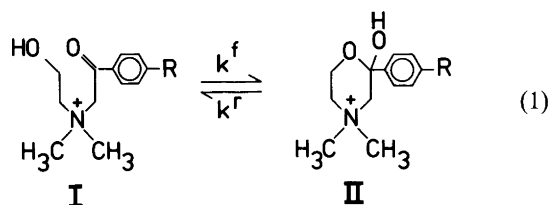
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The ring-chain tautomerism in aqueous solution of some aryl-substituted morpholinium salts (bromides), has been studied and equilibrium constants are reported. In the crystals the substrates exist entirely in their cyclic forms as hemiacetals, but in aqueous solution NMR measurements reveal that an equilibrium is established between the cyclic (hemiacetal) and the noncyclic (ketone) form, the degree of ring-opening being more pronounced with electron-donating aryl substituents at the carbonyl carbon.

The kinetics of the ring-chain interconversion in water has been investigated spectrophotometrically by a 'pH jump' stopped-flow technique. General base catalysis is observed with a Brønsted β value apparently independent of substituent and equal to 0.60. The Hammett ρ values for various base catalysts are close to those for very similar *intermolecular* reactions involving hemiacetal breakdown, leading to the suggestion of a 'normal' class n mechanism for base catalysis. For acid catalysis, however, a quite different situation is encountered, since no general acid but only (weak) catalysis by the hydronium ion can be detected. We believe this deviation from 'normal' general acid catalysis is caused by an electrostatic interaction, and we suggest that it might result from a change in the usual class e mechanism for general acid catalysis by a situation in which rate-limiting concerted proton transfer is replaced by rate-limiting preprotonation. This is supported by the observed drastic change in Hammett ρ value for catalysis by the hydronium ion, compared with the 'normal' case.

An interesting case is encountered for the 4-aminophenyl-substituted substrate, in which the amino group becomes protonated in acid solution, thus representing a new substituent. Despite this complication, the various equilibrium and rate constants may also be evaluated experimentally for this substrate.

Intramolecular reactivity constitutes an important and fascinating field in chemistry and biochemistry.^{1,2} In continuation of previous work³ we report here results from a thermodynamic and kinetic study of some 2-substituted 2-hydroxy-4,4-dimethylmorpholinium bromides [**II** in reaction (1)] in aqueous solution. The existence of ring-chain tautomerism of such compounds was demonstrated many years ago by Lutz and Jordan⁴ and by Cromwell and Tsou,⁵ but the dynamic and equilibrium aspects of the reaction were not investigated quantitatively.



In the solid state these compounds exist entirely in their cyclic (hemiacetal) form,^{4,6} whereas in aqueous solution the hemiacetal is reversibly converted into the chain form [**I** in reaction (1)], the degree of conversion depending on the substituent R in the phenyl ring.

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[†] To whom correspondence should be addressed.

The equilibrium shown in reaction (1) represents a classical example of a general acid–base-catalyzed reaction.⁷ However, in the present case the appearance of a positive charge in the substrate may lead to observable changes in the nature of the catalysis. Indeed, only a small component of catalysis by the hydronium ion, but no general acid catalysis, is observed. General base catalysis, however, is found to be ‘normal’ and much less sensitive to the presence of a charge in the substrate.

Experimental

Materials. Crystals of the title compounds [R = 4-H, 4-MeO and 4-NH₂ in reaction (1)] were prepared by condensation of the corresponding R-phenacyl bromides with *N,N*-dimethylethanolamine as described earlier.^{4,5} The solid products were recrystallized from methanol, and the following melting points were found: R = 4-H (185–187°C), R = 4-MeO (201–202°C), R = 4-NH₂ (207°C sharp).

Buffer substances were obtained and handled as described previously.⁸ We have recently found that 4-methyl-2-pentanone is an excellent solvent for recrystallization of phosphonic acids.

Equilibrium constants. *K* in reaction (1) was determined by the proton NMR technique (Bruker 500 MHz instrument) in 10⁻³ M D₂SO₄ in D₂O. A section of an NMR spectrum at 300 K is shown for the 4-methoxy compound (8 × 10⁻³ M solution) in Fig. 1. The peaks appearing in the range 7–8

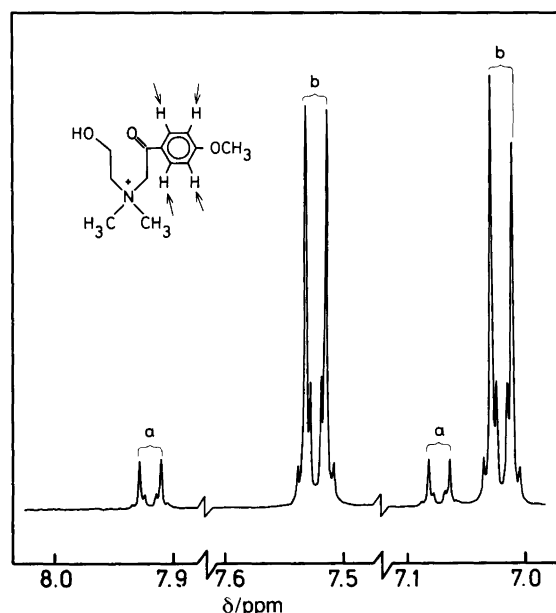


Fig. 1. The ¹H NMR spectrum of an 8 × 10⁻³ M solution of the 4-CH₃O-substituted morpholinium ion in 10⁻³ M D₂SO₄ in D₂O, 25°C, *I* = 1.0 (NaCl). (a) Peaks deriving from aromatic protons in the open form of the substrate [I in reaction (1)]. (b) Corresponding peaks from the closed form [II in reaction (1)].

ppm derive from the four protons in the benzene ring. The identification of the various peaks is also shown, integration and comparison of appropriate peaks leading to the equilibrium constant.

Kinetics. Rate constants for the tautomeric equilibrium in reaction (1) in various aqueous buffers were measured primarily by a ‘pH jump’ technique as described earlier.^{3a,b} This technique is based on the fact that the hydroxy group of the hemiacetal is more acidic than the hydroxy group of the open form, resulting in a shift of reaction (1) to the right in alkaline solution (0.01 M hydroxide). The UV spectral change associated with this shift (Fig. 2A) can be utilized to follow the reaction kinetically. Mixing of the alkaline solution of substrate in a stopped-flow apparatus

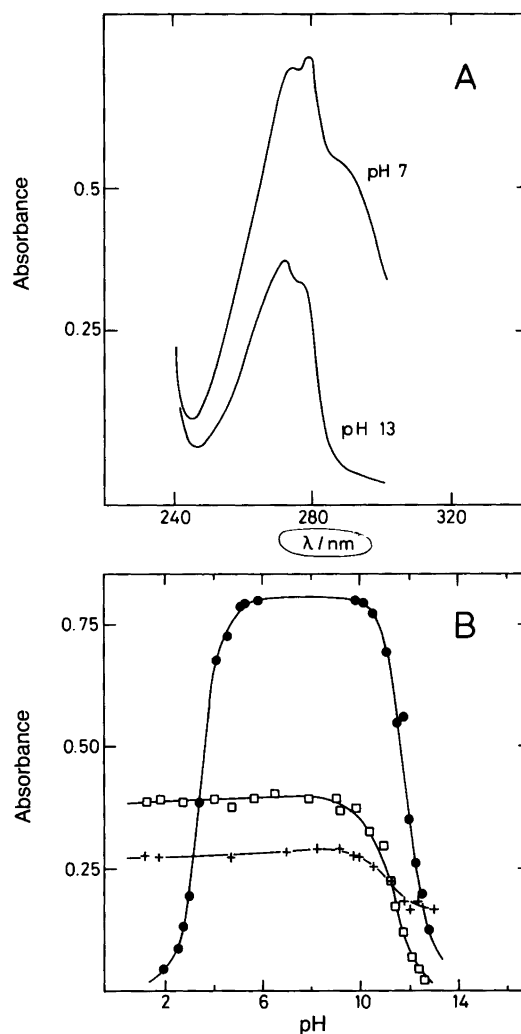


Fig. 2. The UV spectral behaviour of the substituted morpholinium ions in aqueous solution. (A) The spectral changes observed as a function of pH for the 4-CH₃O-substituted substrate (4 × 10⁻⁴ M in H₂O). (B) Dependence of absorbance on pH at selected wavelengths, (●) R = NH₂ (320 nm), (□) R = CH₃O (295 nm), (+) R = H (260 nm), 25°C, *I* = 1.0 (NaCl).

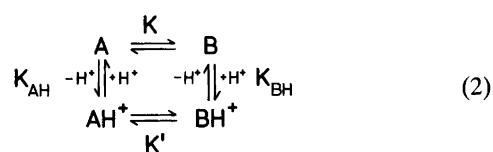
(Durrum) with a 'neutral' buffer or with acid (HCl) is accompanied by a pronounced increase in absorbance due to the regeneration of the open (keto) form of the substrate.

In one case ($R = 4\text{-NH}_2$) the complication appears that the substituent becomes protonated in the pH range below 4 (Fig. 2B), leading to ring closure as observed in basic solution and providing an alternative way of initiating the reaction. It is demonstrated that this behaviour is due to a difference in basicity of the amino group in the open and closed form, respectively, very similar in nature to the situation in basic solution.

A temperature-jump technique (using a Messanlagen instrument) was employed alternatively to study reaction rates in the pH range 7–8, where catalysis by the hydroxide ion becomes dominating. We had hoped to be able to follow the reaction rates by this method also at hydroxide ion concentrations high enough to cause partial dissociation of the hydroxyl group of the hemiacetal, leading to a 'saturation' effect in k_{obs} and a kinetic determination of its pK_a . However, all three substances investigated react so fast at pH 11–13 that the rates exceed the capacity of our equipment ($\tau^{-1} > 10^5 \text{ s}^{-1}$).

Results

Equilibrium and acidity constants. Values for K in reaction (1) as evaluated from the NMR spectra are presented in Table 1 together with the apparent acidity constants for the hemiacetal hydroxyl group, estimated from the inflection points of the 'titration' curves in Fig. 2B. Table 1 also lists the two acidity constants for the amino group in the 4-amino substituted substrate, the evaluation of which will be dealt with below. The protonation scheme for this substrate is presented in reaction (2), A and B denoting the open and closed form, respectively.



An *apparent* value of $pK_a = 3.7$ for this protonation reaction can be deduced from Fig. 2B (data reproduced in Fig. 3) as defined by the value of pH at 'half neutralization' ($\text{pH}_{1/2}$). If we assume that the titration curve in Fig. 2B (Fig. 3) represents the fraction of [A], expressed in terms of absorbance units at equilibrium, over the total concentration of substrate, the relationship between this value and the various equilibrium constants in reaction (2) is given by eqn. (3), where K and $K_{\text{AH}}(K_{\text{BH}})$ are equilibrium and acidity constants, respectively. Thus, unless either K_{AH} or K_{BH}

$$\log (K_{\text{AH}}^{-1} + K_{\text{BH}}^{-1}) = \text{pH}_{1/2} + \log (1 + K) \quad (3)$$

Table 1. Various equilibrium constants for some 2-substituted 2-hydroxy-4,4-dimethylmorpholinium salts [2-(4-R-C₆H₄)-MP] in aqueous solution at 298 K and ionic strength $I = 1.0$ (KCl).

Substrate	R = H	R = CH ₃ O	R = NH ₂	R = NH ₃ ⁺
K^a	≥ 20	8.6	1.40	176 ^d
K (corrected) ^b	≥ 21	9.2	1.49	187 ^d
pK_a (hemiacetal) ^c	≈ 10.8	11.3	≈ 12.0	—
pK_{AH} [reaction (2)]	—	—	—	2.0 ^e
pK_{BH} [reaction (2)]	—	—	—	4.1 ^f

^a K is defined from reaction (1) as $[\text{II}]/[\text{I}]$ at equilibrium (H_2O , 300 K). ^bThis is the value expected in H_2O solution as obtained from the relationship $K(\text{H}_2\text{O}) = K(\text{D}_2\text{O}) \Phi(\text{alcohol})/\Phi(\text{hemiacetal})$, where the fractionation factors $\Phi(\text{alcohol})$ and $\Phi(\text{hemiacetal})$ are taken as 0.99 and 0.93, respectively.^{9,10} ^cEstimated from Fig. 2B. ^e K' in reaction (2), calculated from $K' = K \times K_{\text{AH}}/K_{\text{BH}}$. ^fEstimated from Fig. 3. ^dCalculated from eqn. (3).

can be determined separately, or one constant can be ignored relative to the other, eqn. (3) does not permit a determination of the two individual acidity constants.

However, it became clear that an experimental value for K_{AH} in reaction (2) may be obtained from the stopped-flow kinetic studies of the hydronium ion catalyzed reaction, i.e. when a neutral solution of the substrate (consisting primarily of A and B under such conditions) is mixed (successively) with a range of hydrochloric acid solutions. As shown in Fig. 2B (Fig. 3) species A disappears in acid solutions, primarily ending up as BH^+ (*vide infra*), and according to reaction (2) this may happen in two ways: (a) via a route $\text{A} \rightarrow \text{B} \rightarrow \text{BH}^+$, where $\text{A} \rightarrow \text{B}$ is rate-limiting; (b) via a route $\text{A} \rightarrow \text{AH}^+ \rightarrow \text{BH}^+$, with the step $\text{AH}^+ \rightarrow \text{BH}^+$ being rate-limiting. Since route (b) involves a fast (diffusion-controlled) preprotonation of A, this step leads to a gradual 'quenching' of the 'slow' absorption change observed for the rate-limiting step as the concentration of acid is increased. The total absorbance change (ΔA) for the rate-limiting step is therefore a measure of the degree of protonation of A in the initial step $\text{A} \rightarrow \text{AH}^+$, and hence

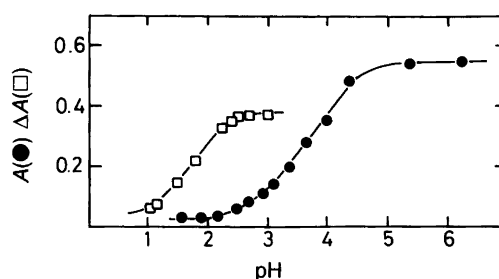


Fig. 3. The UV spectral behaviour of the 4-NH₂-substituted morpholinium ion in acidic solution. (●) Dependence of the absorbance, A, at 320 nm on pH for an equilibrated solution. (□) Dependence of the observed total change in absorbance, ΔA , at 320 nm on pH during a stopped-flow kinetic experiment, 25°C, $I = 1.0$ (NaCl).

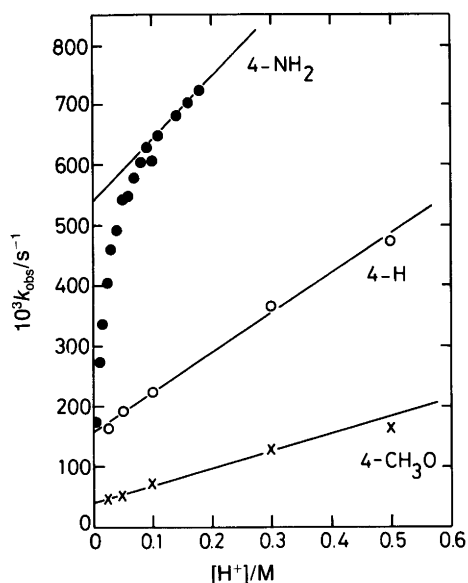


Fig. 4. Catalysis by the hydronium ion of the ring-chain interconversion of substituted morpholinium ions in water, 25 °C, $I = 1.0$ (NaCl), studied by stopped-flow spectrophotometry.

ΔA plotted against pH should lead to a sigmoid curve from which K_{AH} can be estimated. Such a plot is shown in Fig. 3 and leads to a value of $pK_{AH} = 2.0(1)$, and subsequently also to a value of pK_{BH} equal to 4.1(1) from eqn. (3). K' in reaction (2) can now be calculated as $K' = KK_{AH}/K_{BH} = 176$. This value explains the fact that the 4-amino substrate exists almost entirely as the closed form in acids.

Kinetics. In the following we report kinetic data for the acid–base-catalyzed equilibration of the reaction in reaction (1). First-order rate constants were always observed. We soon became aware of the fact that for acid catalysis only the hydronium ion has a measurable catalytic effect, which simplifies the investigation of the buffer catalysis greatly since only (in general) one buffer ratio is needed per catalyst for the evaluation of catalytic constants for general base catalysts. Fig. 4 shows results for catalysis by the hydronium ion (HCl), the detailed data being presented in Table S3.* As seen from Fig. 4 a ‘normal’ (although rather insensitive) linear dependence of k_{obs} on hydronium ion concentration is observed for the 4-H- and 4-CH₃O-substituted compounds. In the case of $R = 4-NH_2$, however, nonlinear behaviour is observed, the rather drastic initial acceleration with increasing hydronium ion concentration representing the transition from the unprotonated substrate system $A \rightleftharpoons B$ to the protonated system $AH^+ \rightleftharpoons BH^+$ in reaction (2) and with the latter being intrinsically faster. At high concentrations of H_3O^+ linearity is also observed for the 4- NH_2 -substrate, leading to a value of k_H of 1.0(1) $M^{-1} s^{-1}$ for the hydronium-ion-catalyzed

* Tables S1–S10 are available from the author as Supplementary material on request.

reaction of the protonated substrate. The intercept of this line provides us with a value of $k_{obs} = 5.4(2) \times 10^{-2} s^{-1}$ for the water-catalyzed reaction of the protonated substrate. It is not immediately possible to obtain the equivalent catalytic constants for the unprotonated system from the experimental data in Fig. 4, but as we shall see later these values may be estimated from extrapolations of Brønsted or Hammett plots.

Detailed experimental data for catalysis by a series of general bases are presented in Tables S4–S10, and the individual catalytic constants which can be extracted from this material are given in Table 2. The catalysis by acetate buffer (Table S7) was investigated for more than one buffer ratio per substrate. The results are plotted in the usual way in Fig. 5, where the insert depicts the slopes of the rate–buffer plots vs. fraction of buffer acid, and it is clear from this inset that within experimental error all three lines pass through zero at 100% acid, confirming that no general acid catalysis is observed for this buffer. The catalytic constants for catalysis by acetate ion of the three substrates can be read from the intercepts on the left-hand side of the inset in Fig. 5 (0% acid).

Since general acid catalysis by acetic acid could not be detected we have assumed this is also the case for the

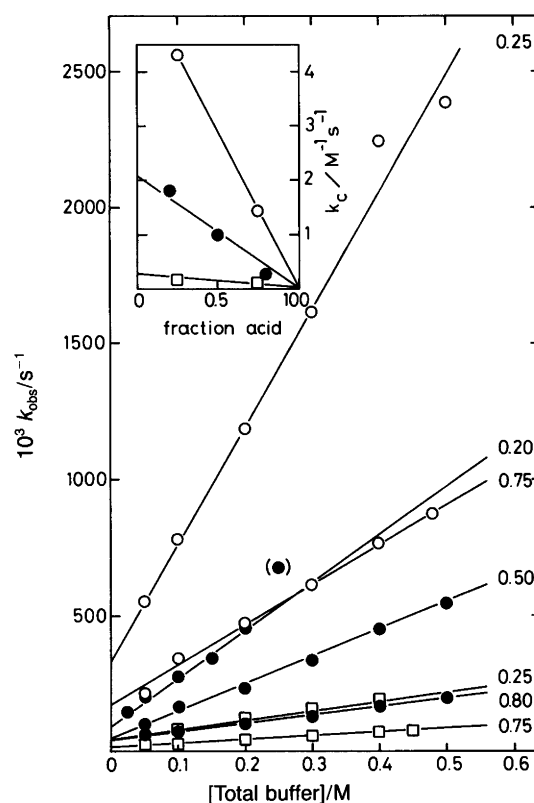


Fig. 5. Catalysis by acetate buffer (fraction of acid indicated) of the ring-chain interconversion of substituted morpholinium ions in aqueous solution, 25 °C, $I = 1.0$ (NaCl), studied by stopped-flow spectrophotometry. (○) $R=H$; (●) $R=CH_3O$; (□) $R=NH_2^-$. The inset shows the slopes, k_c , of the various lines as a function of the fraction of acetic acid in the buffer.

stronger general acids investigated, chloroacetic acid being the strongest ($pK_a = 2.70$). This is reasonable, since the catalytic constant for catalysis by the hydronium ion ($pK_a = -1.74$) is unusually small in the present reactions, and provided the Brønsted α values are not too close to zero. We do not know these coefficients in the present case, but low values are unlikely, since protonation of the substrates is presumably made very difficult by the presence of a positive charge in the molecule, leading to up-hill reactions and therefore higher α values.

Discussion

We can conclude that the substituted morpholinium cations studied in the present work exhibit ring-chain tautomerism in aqueous solution as suggested by earlier workers.^{4,5} In the following we will discuss quantitatively the various equilibrium and dynamic aspects of the reactions as well as possible reaction mechanisms.

Table 2. Collected catalytic constants for the general base-catalyzed ring-chain interconversion of some 2-substituted 2-hydroxy-4,4-dimethylmorpholinium salts [2-(4-R-C₆H₄)-MP] in aqueous solution at 298 K and ionic strength $I = 1.0$ (KCl). Data extracted from Tables S4–S10. Data for catalysis by H₃O⁺ are also presented.

Catalyst	pK_a^a	ρ, q^b	pH ^c	k_o/s^{-1}	$k_{cat}/M^{-1} s^{-1}$
R = H					
H ₂ O	-1.74	3,1	—	—	0.16(1)/55.5
ClCH ₂ CO ₂ ⁻	2.70	1,2	3.08	0.19(1)	0.39(8)
CH ₃ OCH ₂ CO ₂ ⁻	3.40	1,2	3.28	0.16(1)	1.7(1)
Cl(CH ₂) ₂ CO ₂ ⁻	3.93	1,2	3.79	0.21(1)	2.7(1)
CH ₃ CO ₂ ⁻	4.65	1,2	3.97	0.17(2)	5.7(2)
			4.92	0.33(2)	
(CH ₃) ₂ AsO ₂ ⁻	6.16	1,2	5.97	2.2(2)	92(2)
HPO ₄ ²⁻	6.49	2,3	6.37	3(1)	194(16)
CH ₃ PO ₃ ²⁻	7.3	1,3	7.07	25(2)	290(20)
HO ⁻	15.74	2,1	—	—	2.0(5) × 10 ⁸ ^d
H ₃ O ⁺	-1.74	3,1	—	0.16(1)	0.65(2) ^e
R = CH₃O					
H ₂ O	-1.74	3,1	—	—	0.040(5)/55.5
ClCH ₂ CO ₂ ⁻	2.70	1,2	2.70	0.035(5)	0.13(2)
CH ₃ OCH ₂ CO ₂ ⁻	3.40	1,2	3.41	0.035(5)	0.48(6)
Cl(CH ₂) ₂ CO ₂ ⁻	3.93	1,2	3.96	0.040(5)	0.82(2)
CH ₃ CO ₂ ⁻	4.65	1,2	4.01	0.044(5)	
			4.65	0.050(5)	2.1(2)
			5.23	0.08(2)	
(CH ₃) ₂ AsO ₂ ⁻	6.16	1,2	5.96	0.85(5)	28.8(8)
HPO ₄ ²⁻	6.49	2,3	6.48	1.9(1)	64(4)
CH ₃ PO ₃ ⁻	7.3	1,3	7.11	7.7(3)	144(10)
HO ⁻	15.74	2,1	—	—	7.0(5) × 10 ⁷ ^d
H ₃ O ⁺	-1.74	3,1	—	0.040(5)	0.29(1) ^e
R = NH₂					
H ₂ O	-1.74	3,1	—	—	—
ClCH ₂ CO ₂ ⁻	2.70	1,2	3.08	0.046	0.16(1)
CH ₃ OCH ₂ CO ₂ ⁻	3.40	1,2	3.27	0.0325(5)	0.28(1)
Cl(CH ₂) ₂ CO ₂ ⁻	3.93	1,2	3.80	0.020(2)	0.32(1)
CH ₃ CO ₂ ⁻	4.65	1,2	4.92	0.042(2)	0.46(1)
			3.97	0.0180(5)	
(CH ₃) ₂ AsO ₂ ⁻	6.16	1,2	5.95	0.39(1)	7.0(4)
HPO ₄ ²⁻	6.49	2,3	6.22	0.80(5)	19.0(5)
CH ₃ PO ₃ ²⁻	7.3	1,3	7.11	4.5(2)	(31.1)
HO ⁻	15.74	2,1	—	—	4.0(5) × 10 ⁷ ^d
H ₃ O ⁺	-1.74	3,1	—	—	—
R = NH₃⁺					
H ₂ O	-1.74	3,1	—	—	0.54(2)/55.5
H ₃ O ⁺	-1.74	3,1	—	0.54(2)/55.5	1.0(1) ^d

^aTaken from Ref. 8. ^bStatistical parameters. ^cAverage of pH measured in a buffer series. ^dBased on {HO⁻}. ^eBased on [H⁺].

Table 3. A comparison of experimental Hammett ρ values for the present cyclic (and charged) system [2-(4-R-C₆H₄)-MP] with those for similar, but non-cyclic, reactions.

R	NH ₂	CH ₃ O	H	NH ₃ ⁺	Hammett ρ			
					I ^a	II ^b	III ^c	IV ^d
K^e	1.49	9.2	≥ 21	187	1.5	—	1.8 ^h	1.71
σ^f	-0.66	-0.268	0	0.67 ^g				
K_H^i	1×10^{-1}	2.8×10^{-2}	3.0×10^{-2}	5.3×10^{-3}	-0.8	-2.2	-1.9	-2.0
$K_{H_2O}^i$	4.5×10^{-5}	7.1×10^{-5}	1.3×10^{-4}	5.2×10^{-5}	≈ 0	0.6	0.35	0.30
K_{HO}^i	1.6×10^7	6.9×10^6	9.1×10^6	4.4×10^6	-0.5	-0.4	-0.3	0.5
K_{Ac}^i	0.185	0.210	0.260	—	0.2	0.1	—	0.1

^aThis work. ^bDecomposition of methyl hemiacetals of substituted α -bromoacetophenones.¹¹ ^cDecomposition of ethyl hemiacetals of substituted benzaldehydes.¹² ^dDecomposition of substituted benzaldehyde hydrates.¹³ ^e K (corrected) from Table 1. ^fHammett's sigma values taken from Ref. 14. ^gTaken from Ref. 15. ^hFor methyl hemiacetals in methanol.¹⁶ ⁱ $M^{-1} s^{-1}$, calculated from $k' = k^{obs}/(1 + K)$, where k^{obs} is the experimentally observed catalytic constant. ^jEstimated from Hammett plot. ^kEstimated from Brønsted plot.

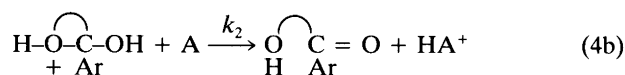
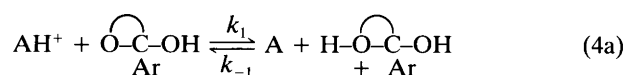
Aromatic substituent effects. Table 3 summarizes some results for the present work and from related studies of intermolecular systems. Despite the limited number of substituents in our case and the fact that the Hammett relation is not always well obeyed for substituents giving rise to large resonance effects (R = 4-NH₂ and 4-CH₃O),^{15a,17} the ρ values listed in column I of Table 3 are reasonably well-defined. We have chosen 'classical' σ values for the 4-NH₂ and 4-CH₃O substituents based on acidity constants for substituted benzoic acid,¹⁴ considering the resonance effects to be rather similar in benzoic acids and in our car-

bonyl systems (R-C₆H₄-C(=O)-OH vs. R-C₆H₄-C(=O)-R').

As seen from Table 3, there is generally good agreement between our ρ values and those of other (similar) reactions, which might be expected when similar reaction mechanisms are encountered. In the case of hydronium ion catalysis, however, there is a considerable difference in ρ , which might be explained in terms of a change in rate-limiting step, most likely to be imposed by the presence of the positive charge on nitrogen in the substrate. A discussion will be given in more detail below.

Acid catalysis. The amount of acid catalysis in our case is clearly drastically reduced compared with neutral, cyclic* and acyclic¹⁹ hemiacetals, presumably owing to the electrostatic effect caused by the positive charge on nitrogen. Further evidence for this comes from the ρ values for hydronium ion catalysis in Table 3, where ρ for the morpholine system is much less negative than for uncharged substrates. We think this charge may induce a change in rate-limiting step for this reaction. Thus, the 'normal' mechanism in operation for acid-catalyzed hemiacetal breakdown has been identified as belonging to class e, according to reaction (4).^{19,20}

* The mutarotation of glucose is a good example where 'normal' general acid catalysis is observed, e.g. Ref. 18.



The experimental value of $\rho \cong -2$ for the total reaction in reaction (4) can be regarded as a sum of $\rho_1 \cong -1$ for the fast pre-equilibrium step in reaction (4a) and $\rho_2 \cong -1$ for the rate-limiting step [reaction (4b)].¹³ However, the presence of a positive charge on nitrogen may destabilize the protonated species in reaction (4a) to such an extent that reaction (4a) becomes rate-limiting. Since this is an uphill reaction from left to right, it should lead to an experimental ρ value of approximately -1 , in agreement with our result of $\rho = -0.8$. If A in reaction (4) is water, K_a for the protonated substrate in reaction (4a) can be calculated from $K_a = k_{H_3O^+} k_{-1}/k_1 = 10^{11.9}$, where k_{-1} is taken as $10^{10} M^{-1} s^{-1}$ ¹⁹ and $k_1 = 0.65 M^{-1} s^{-1}$ is the experimentally determined catalytic constant for the parent substrate (Table 2). The pK_a of protonated morpholine is not known, but a value of -11.9 is not unlikely compared with pK_a values in the range -4.4 to -8.3 calculated for the neutral ethyl and trifluoroethyl hemiacetals of formaldehyde and acetaldehyde.¹⁹

The high sensitivity to 'extra' electrical charges of rate constants in the acid-catalyzed breakdown of hemiacetals and hydrates seems to be of a general nature. Thus, in the hydration/dehydration of substituted benzaldehydes, McClelland and Coe¹³ observed a considerable increase in the acid catalytic rate constants for phosphonate monoanions compared with neutral carboxylic acids. No such pronounced effects are noted in base catalysis, emphasizing the difference in mechanism from that for acid catalysis (*vide infra*).

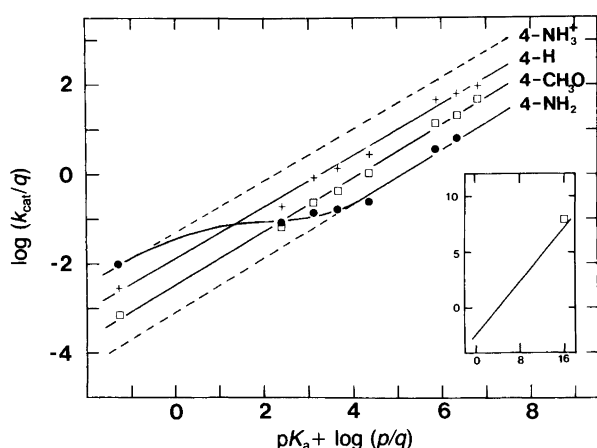
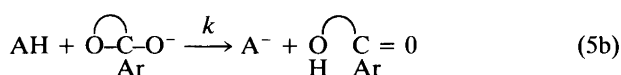
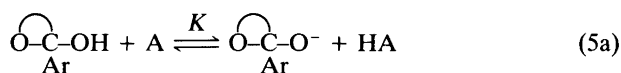


Fig. 6. Brønsted plots for general base catalysis of the ring-chain interconversion of substituted morpholinium ions. Four lines of slope $\beta = 0.60$ have been drawn through the four sets of points. The inset shows the line for $R = \text{CH}_3\text{O}$, including the point for catalysis by hydroxide ion.

Base catalysis. In striking contrast to acid catalysis, the base-catalyzed paths of reaction (1) seem to be relatively unaffected by the positive charge on nitrogen in morpholine, since 'normal' catalysis is observed for base catalysts ranging from water, *via* carboxylates, to hydroxide ion. Brønsted plots for these catalysts and the various substrates, based on the results in Table 2, are given in Fig. 6. Lines of common slope $\beta = 0.60$ have been drawn through the points. The unusual behaviour of the plot for $R = \text{NH}_2$ is a result of the conversion of this substituent into $R = \text{NH}_3^+$ in acid solution, leading to a new substrate with the (hypothetical) Brønsted plot indicated in Fig. 6. The location on the vertical axis of the points in the transition range for this substrate is rather arbitrary, since it depends to some extent on the buffer ratio chosen for the catalysts. The inset in Fig. 6 shows the Brønsted line for $R = \text{CH}_3\text{O}$ and the location of the point for hydroxide ion catalysis. The observed positive deviation for this point is a characteristic and generally observed feature in the decomposition of hemiacetals and hydrates.^{8,19} It may be taken as a sign that the molecular mechanism of the general base-catalyzed ring-opening of morpholine is of the usual class n concerted type, shown in reaction (5),^{13,19,20} with reaction (5b) being rate-limiting.



A value of $\beta = 0.60$ is not unlikely for such a mechanism, since values of $\beta > 0.5$ are usually observed for hemiacetals of low or medium stability in cases where the mechanism is known to be class n.^{19,21} The positive charge on nitrogen is

responsible for the fact that the acidities of the morpholines, as listed in Table 1, are greater than those for uncharged hemiacetals and hydrates,^{13,19} resulting in formation of a relatively large equilibrium proportion of the reactive anionic form of the substrate in reaction (5a) (K larger). Subsequently, this might be expected to lead to higher intrinsic rates of the base-catalyzed hemiacetal breakdown, parallel to the fact that lower intrinsic rates are observed in acid catalysis. However, this is not observed experimentally, the catalytic constants for base-catalyzed ring-chain conversion in the morpholines being largely identical with those for the breakdown of some neutral, unstable hemiketals, such as the substrates derived from α -bromoacetophenone.^{11,21} The explanation for this lack of charge effect in base catalysis may then be that the rate constant k of eqn. (5b) is decreased correspondingly for electrostatic reasons, to give a largely unchanged value for the observed overall rate constant of reaction (5), $k_{\text{obs}} = kK$. This situation is plausible, especially because no change in rate-limiting step is expected in general base catalysis, unlike the situation for acid catalysis.

It is interesting that electrostatic effects as discussed above also appear if the 'extra' electrical charge is placed on the catalyst. Again, acid-catalytic constants are sensitive to such charges, whereas rate constants for base catalysis are not.^{8,13}

Solvent catalysis. Data for catalysis by the solvent and solvent-derived species are conveniently presented as pH-profiles shown for various morpholines in Fig. 7, where k_{obs}° (taken as k_0 from Table 2) are plotted vs. pH.

In the simple cases (U-shaped plots) the solid curves drawn through the points are based on the expression $k_{\text{obs}}^{\circ} = k_{\text{H}_2\text{O}} + k_{\text{H}}(\text{H}^+) + k_{\text{HO}^-}\{\text{HO}^-\}$ with the catalytic constants also taken from Table 2. In the case of $R = \text{NH}_2$ irregularities are again observed owing to protonation of the amino group in acid solution. The question is whether this complication can be readily explained theoretically on the basis of the reaction scheme in reaction (2).

Strehlow has investigated the kinetics of the hydration of pyruvic acid by a pressure jump technique in the pH range where this substrate dissociates to the anionic form.²² His chemical system is identical in nature to our reaction scheme in reaction (2) in having two very fast protonation steps and two slower rate-limiting steps. Thus the interpretation of our data could be based on Strehlow's relaxation treatment.²² (The monograph by Bernasconi²³ is also helpful here.) Accordingly, eqn. (6) gives the observed reaction

$$-d(\Delta c_{\text{A}} + \Delta c_{\text{AH}})/dt = \frac{k_{\text{AB}}}{1 + \frac{\Delta c_{\text{AH}}}{\Delta c_{\text{A}}}} + \frac{k_{\text{BA}}}{1 + \frac{\Delta c_{\text{BH}}}{\Delta c_{\text{B}}}} + \frac{k_{\text{AHBH}}}{1 + \frac{\Delta c_{\text{B}}}{\Delta c_{\text{AH}}}} + \frac{k_{\text{BHAH}}}{1 + \frac{\Delta c_{\text{B}}}{\Delta c_{\text{BH}}}} (\Delta c_{\text{A}} + \Delta c_{\text{AH}}) \quad (6)$$

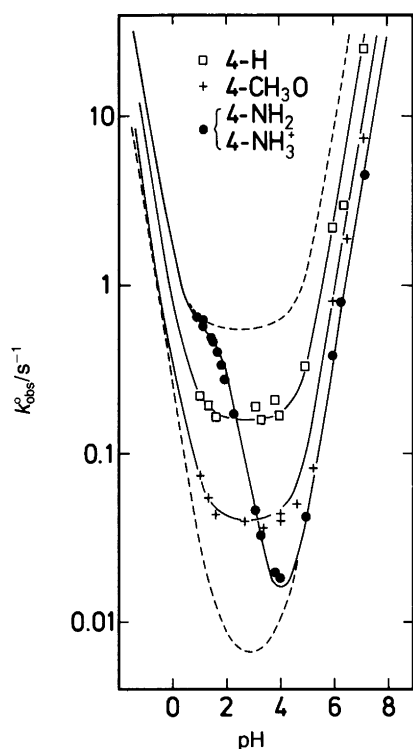


Fig. 7. Buffer-independent rate constants as a function of pH for the ring-chain interconversion of substituted morpholinium ions. The solid curves for R=H and R=CH₃O are drawn from $k_{\text{obs}}^{\circ} = k_{\text{H}_2\text{O}} + k_{\text{H}}\{\text{H}^+\} + K_{\text{HO}}\{\text{HO}^-\}$. The solid curve for R=NH₂ is drawn from eqn. (9). All catalytic constants and equilibrium constants needed for this figure are found in Tables 1–3. The broken curves are hypothetical constructions based on rate constants found by extrapolation of Brønsted and Hammett plots (Table 3).

rate where the various individual rate constants (k) and concentrations (c) refer to reaction (2). The linear nature of eqn. (6) implies that no restrictions need be put on the magnitude of the applied perturbation, which is usually substantial in stopped-flow experiments.

The fractions in the denominators of eqn. (6) may be expressed in terms of the equilibrium concentrations of the various reactants in using eqns. (7) and (8). Before eqns.

$$\frac{\Delta c_{\text{A}}}{\Delta c_{\text{AH}}} \approx \frac{c_{\text{A}}[c_{\text{B}}(c_{\text{AH}}+c_{\text{BH}})+c_{\text{H}}(c_{\text{BH}}+c_{\text{B}})]}{c_{\text{AH}}[c_{\text{B}}(c_{\text{BH}}+c_{\text{B}})+c_{\text{BH}}(c_{\text{A}}+c_{\text{H}})]} \quad (7)$$

$$\frac{\Delta c_{\text{BH}}}{\Delta c_{\text{B}}} \approx \frac{c_{\text{BH}}[c_{\text{AH}}(c_{\text{A}}+c_{\text{B}})+c_{\text{H}}(c_{\text{A}}+c_{\text{AH}})]}{c_{\text{B}}[c_{\text{A}}(c_{\text{BH}}+c_{\text{H}})+c_{\text{AH}}(c_{\text{A}}+c_{\text{H}})]} \quad (8)$$

(7) and (8) are inserted into eqn. (6) these equations may be reduced further by introducing the fact that c_{H} in the transition area in Fig. 7 is always considerably larger than the total concentration of the substrate (ca. 10^{-4} M). In that case eqns. (7) and (8) simply reduce to $\Delta c_{\text{A}}/\Delta c_{\text{AH}} \approx c_{\text{A}}/c_{\text{AH}}$ and $\Delta c_{\text{BH}}/\Delta c_{\text{B}} \approx c_{\text{BH}}/c_{\text{B}}$, respectively.

This leads to an observed rate constant in eqn. (6) as shown in eqn. (9), where K , K' , pK_{AH} and pK_{BH} refer to

$$\tau^{-1} = k_{\text{obs}}^{\circ} = \frac{k_{\text{obs}}^{\circ'}}{1+K} \frac{K}{1+10^{pK_{\text{AH}}-\text{pH}}} + \frac{1}{1+10^{pK_{\text{BH}}-\text{pH}}} + \frac{k_{\text{obs}}^{\circ''}}{1+K} \frac{K'}{1+10^{\text{pH}-pK_{\text{AH}}}} + \frac{1}{1+10^{\text{pH}-pK_{\text{BH}}}} \quad (9)$$

reaction (2) and are reported in Table 1; $k_{\text{obs}}^{\circ'}$ and $k_{\text{obs}}^{\circ''}$ are defined by the general equation $k_{\text{obs}}^{\circ} = k_{\text{H}_2\text{O}} + k_{\text{H}}\{\text{H}^+\} + k_{\text{HO}}\{\text{HO}^-\}$, where the various catalytic constants are for the neutral and protonated substrate form, respectively. These constants are either given in Table 2 or estimated (Table 3).

It is obvious from Fig. 7 that an excellent fit is obtained between eqn. (9) and the experimental points. The broken curves in Fig. 7 indicate the expected (extrapolated) kinetic behaviour for the 4-NH₂-substrate in the two pH ranges where either one or the other protolytic form is too unstable to exist.

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