Salt Effects on the Rates of Protonation of Amides

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The rates of protonation of three *NN*-dimethylamides have been measured in various electrolyte solutions using n.m.r. line broadening techniques. Activity coefficients of the amides in the electrolyte solutions have also been determined. The protonation rates increase rapidly with increasing electrolyte concentration. The results are discussed in relation to the behaviour of other acid catalysed reactions involving protonated intermediates. A comparison of the results in Li^+ solutions with those of the other alkali metals provides some evidence to support recent reports of strong interactions between Li^+ and various amides.

THE effect of electrolytes on the properties and rates of reaction of amides is of current interest because of their possible relevance to studies on the properties of macromolecules containing peptide [$-NHC(=O)-$] linkages.[1-4]

The investigation of medium effects on the hydrolysis rates of amides is difficult because of their relative stability towards hydrolysis compared with, for example, esters and acetals. Such studies have been limited to investigations of medium effects in concentrated acid solutions.[5-7] The rates of protonation of *NN*-dimethyl amides however, may be conveniently measured using n.m.r. line broadening techniques [8] and such techniques have been used to measure rates of protonation in both dilute and concentrated acid solutions.[9,10]

This paper describes the results of a study of the effects of concentrated electrolyte solutions on the rates of protonation of *NN*-dimethyl-acetamide, -isobutyramide, and -benzamide, together with measurements of the activity coefficients of the amides in the electrolyte solutions. The results are compared with earlier studies on ester [11] and acetal hydrolyses [12] and on the acid and base catalysed proton exchange reactions of *N*-methylamides.[2,3]

EXPERIMENTAL AND RESULTS

Materials.—Dimethyl-benzamide and -isobutyramide were prepared by the addition of dimethylamine to a solution of the appropriate acid chloride in ether.[13] Dimethylacetamide (L.R. grade) was purified by distillation. Isopentyl alcohol (3-methylbutan-1-ol), η_D^{20} 1.4075, b.p. 132°, was purified as previously described.[14,15] Cyclohexane (L.R. grade) was purified by distillation. Inorganic chemicals were of AnalaR grade and were used without further purification.

Rate Measurements.—Spectra were recorded on a JEOL 60 MHz n.m.r. spectrometer, with a probe temperature of 33 ± 0.5°. Rates of protonation (on the nitrogen atom) were obtained from the rates of rotation about the C–N bond of the amides and include a statistical factor of 2 to convert rates of rotation to rates of protonation.[10]

The *N*-methyl signals were not in fact simple doublets as there was in each case some broadening due to long range coupling. For dimethylacetamide it was possible to resolve the signals into two quartets (due to coupling with the *C*-methyl protons), the high field signal having a coupling constant of 0.54 (±0.04) and the low field signal 0.21 (±0.05) Hz. Nevertheless, equations for the exchange broadening of a doublet [16] were used to analyse the spectra as it has been shown that this procedure leads to significant errors only when the broadening of the multiplet components is less than the multiplet splitting.[8] Rotation rates were obtained from a comparison of calculated and observed spectra using standard procedures.[17]

Chemical shift differences for the *N*-methyl protons in the slow exchange limit in water for dimethyl-acetamide, -isobutyramide, and -benzamide were 9.25, 11.7, and 7.15 Hz respectively. Addition of electrolyte however, led to increases in these values of up to 15% and so for the kinetic analyses, they were redetermined in each of the salt solutions used.

Acid concentrations for the rate measurements were in the range $0.02 \leqslant [H^+] \leqslant 0.08$. In this region the observed rate law was as shown in equation (1), where τ^{-1} represents

$$2\tau^{-1} = \text{Rate}/[\text{amide}] = k_{H^+}[H^+] \qquad (1)$$

the rate constant for rotation about the C–N bond. Amide concentrations were *ca.* 0.2M.

The observed rates of protonation of the amides in the various electrolyte solutions are given in Table 1.

Activity Coefficient Measurements.—These were determined from the variation of the distribution coefficient for the partition of the amides between the aqueous electrolyte solutions and an immiscible organic phase.[18] For dimethylbenzamide and -isobutyramide, cyclohexane was used as the organic phase while for dimethylacetamide, isopentyl alcohol was used. The latter solvent was less satisfactory because of its relatively high solubility in water [*ca.* 2.7%

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[1] E. E. Schrier and E. B. Schrier, *J. Phys. Chem.*, 1967, **71**, 1851.

[2] T. Schleich, R. Gentzler, and P. H. von Hippel, *J. Amer. Chem. Soc.*, 1968, **90**, 5954.

[3] T. Schleich, B. Rollefson, and P. H. von Hippel, *J. Amer. Chem. Soc.*, 1971, **93**, 7070.

[4] R. S. Molday and R. G. Kallen, *J. Amer. Chem. Soc.*, 1972, **94**, 6739.

[5] C. O'Connor, *Quart. Rev.*, 1970, **24**, 553.

[6] C. A. Bunton, S. J. Farber, A. J. G. Milbank, C. J. O'Connor, and T. A. Turney, *J.C.S. Perkin II*, 1972, 1869.

[7] J. W. Barnett and C. J. O'Connor, *J.C.S. Perkin II*, 1973, 220.

[8] G. Fraenkel and C. Franconi, *J. Amer. Chem. Soc.*, 1960, **82**, 4478.

[9] C. A. Bunton, B. N. Figgis, and B. Nayak, Proc. 4th Internat. Meeting of Molecular Spectroscopy (1959), Bologna, 1962, vol. 3, p. 1209.

[10] B. G. Cox, *J. Chem. Soc.* (*B*), 1970, 1780.

[11] P. T. McTigue and A. R. Watkins, *Austral. J. Chem.*, 1965, **18**, 1943.

[12] F. A. Long and D. McIntyre, *J. Amer. Chem. Soc.*, 1954, **76**, 3243.

[13] S. Pinchas, D. Samuel, and M. Weiss-Broday, *J. Chem. Soc.*, 1961, 3063.

[14] C. A. Kraus and J. E. Bishop, *J. Amer. Chem. Soc.*, 1922, **44**, 2206.

[15] J. W. Williams and F. Daniels, *J. Amer. Chem. Soc.*, 1924, **46**, 903.

[16] J. A. Pople, W. G. Schneider, and H. J. Bernstein, 'High Resolution Nuclear Magnetic Resonance,' McGraw-Hill, 1959, ch. 10.

[17] A. Loewenstein and T. M. Connor, *Ber. Bunsengesellschaft Phys. Chem.*, 1963, **67**, 280.

[18] F. A. Long and W. F. McDevit, *Chem. Rev.*, 1952, **52**, 119.

TABLE 1

Effect of added salts upon the rates of protonation of *NN*-dimethyl-acetamide (DMA), -isobutyramide (DMI), and -benzamide (DMB) at 33°

		DMA		DMI		DMB	
	C_{salt}/mol dm^{-3}	$10^3k_{H^+}$ [a]	$\log k_{H^+}/k^0_{H^+}$ [b]	$10^3k_{H^+}$ [a]	$\log k_{H^+}/k^0_{H^+}$ [b]	$10^3k_{H^+}$ [a]	$\log k_{H^+}/k^0_{H^+}$ [b]
	0.000	0.972 [c]	0.000	1.00 [c]	0.000	0.356 [c]	0.000
LiCl	0.608	1.46	0.176				
	0.695					0.474	0.121
	0.904	1.70	0.243				
	1.31			1.88	0.274	0.600	0.223
	2.38	2.64	0.435	2.63	0.420	0.830	0.364
	3.35					1.28	0.549
	3.65	3.20	0.517	4.38	0.642		
	4.46	4.12	0.627			1.73	0.681
	5.20					2.12	0.771
	5.46	4.28	0.643	7.00	0.845		
LiBr	0.782	1.40	0.158				
	2.35	2.20	0.354				
	3.13	2.60	0.426				
	3.91	2.80	0.459				
	5.47	3.60	0.568				
NaCl	0.050	1.12	0.061				
	0.420			1.20	0.079	0.370	0.013
	0.841			1.38	0.137	0.490	0.134
	1.65	2.27	0.369	2.44	0.387	0.730	0.305
	2.60	3.40	0.549	3.33	0.521	1.03	0.455
	3.29	3.80	0.592	4.30	0.634	1.17	0.513
	3.96			5.45	0.736	1.42	0.596
	4.29	5.48	0.751				
NaBr	0.389	1.36	0.146				
	0.703	1.56	0.204				
	2.11	2.76	0.453				
	2.33	3.10	0.504				
	3.52	3.92	0.605				
	4.92	5.72	0.769				
$NaNO_3$	0.552					0.412	0.061
	0.770	1.76	0.258				
	1.10			1.75	0.234	0.564	0.196
	1.54	2.44	0.400				
	2.10	2.76	0.453	2.50	0.398	0.810	0.352
	2.81	3.60	0.568				
	3.08	4.00	0.641				
	3.33			3.63	0.560	1.24	0.537
	3.85	5.00	0.711				
	4.40					1.46	0.603
	5.10			6.50	0.813	1.79	0.696
$NaClO_4$	0.050	1.12	0.061				
	0.500	1.84	0.277				
	0.628			1.65	0.215	0.492	0.138
	1.00	2.30	0.375				
	1.26			2.46	0.391	0.596	0.220
	1.61	2.76	0.453				
	2.00	3.44	0.549				
	2.52			5.00	0.699	0.838	0.366
	2.80	3.92	0.605				
	3.85	5.72	0.769	9.00	0.989	1.55	0.634
	5.02			16.3	1.21	2.33	0.812
KCl	0.348	1.44	0.170				
	0.480					0.468	0.114
	0.740			1·25	0.097		
	0.990	1.80	0.267			0.481	0.127
	1.47			1.88	0.274		
	1.71	2·30	0.375			0.650	0.258
	2.15	2.60	0.427	2.75	0.439		
	2.41					0.794	0.382
	3.22	3.40	0.544	3.55	0.550	0.968	0.511
KBr	0.403	1.44	0.170				
	2.02	2.80	0.459				
	2.82	4.12	0.627				
	3.22	4.28	0.643				
CsCl	1.15	1.80	0.267				
	2.28	2.76	0.453				
	2.96	3.32	0.534				
CsI	0.523	1.68	0.238				
	1.04	1.84	0.276				
	1.57	2.36	0.386				
	2.09	2.56	0.420				

[a] k_{H^+}/mol^{-1} dm^3 s^{-1}. [b] $k^0_{H^+}$ is the value of k_{H^+} in the absence of added electrolyte. [c] $k^0_{H^+}$/mol^{-1} dm^3 s^{-1}.

(w/v) at 25° [19]] but was necessary because of the much higher solubility of dimethylacetamide in water than in cyclohexane. No corrections were made for any effects of mutual solubility of the two phases. Total amide concentrations were $\leqslant$ *ca.* 0.1M. The amide concentrations in the two layers were determined by g.l.c. analysis using a silicon SE 30 (10%) column at 150° for dimethylacetamide and an APL column at 120 and 180° respectively for dimethylisobutyramide and -benzamide.

TABLE 2

Effects of added salts upon the molar activity coefficients (y_s) of DMA, DMI, and DMB

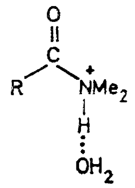
	C_{salt}/mol dm^{-3}	log y_{DMA} (33°)	log y_{DMI} (25°)	log y_{DMB} (25°)
LiCl	0.710		0.11	0.087
	0.892	0.15		
	1.42		0.20	0.15
	2.84		0.42	0.29
	3.57	0.23		
	4.25			0.36
	5.35	0.27		
	5.66		0.58	0.56
	7.14	0.34		
NaCl	0.540	0.10	0.14	0.06
	1.07	0.26	0.26	0.22
	2.15	0.37	0.57	0.48
	3.21	0.47	0.66	0.70
	4.29	0.52	0.97	0.93
NaBr	0.662	0.33		
	1.32	0.36		
	3.97	0.55		
	5.30	0.75		
$NaNO_3$	0.740		0.08	0.04
	1.47		0.22	0.14
	2.97	0.40	0.38	0.32
	3.21	0.49		
	4.42		0.68	0.56
	5.94	0.80	0.87	0.77
$NaClO_4$	0.250	−0.03		
	0.710		0.06	−0.05
	1.42		0.12	−0.05
	2.00	−0.03		
	2.85		0.25	0.07
	3.00	0.07		
	4.13	0.20	0.43	0.01
	5.70		0.60	0.14
KCl	0.366	0.24		
	0.452		0.15	
	0.730	0.28		
	0.905			0.13
	1.46	0.40		
	1.81		0.42	0.25
	2.20	0.45		
	2·82	0.61	0.57	0.48
	3.60		0.74	0.65

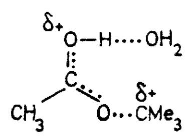
The measured activity coefficients are listed in Table 2. The activity coefficients of dimethylbenzamide have previously been measured in several different electrolyte solutions.[6] The agreement between these and the present results is good.

DISCUSSION

Kinetic salt effects on the rates of acid catalysed hydrolyses of esters and acetals have been extensively used as an aid in distinguishing between reactions involving nucleophilic participation of water in the rate-determining step (*A*2) and those without such participation (*A*1).[11,12,20,21] Typical *A*1 hydrolyses show large positive salt effects,[11,12] while addition of electrolyte to *A*2 hydrolyses has little effect on the hydrolysis rates. The different behaviour of reactions occurring by the two mechanisms may be readily explained in terms of the much greater involvement of water (the activity of which is decreased in the salt solutions) in the rate-determining step of the *A*2 reactions.

On this basis, the variation with salt concentration of the rates of protonation of amides is expected to be similar to that of the *A*1 hydrolyses. Water will not be involved directly as a reactant in either reaction and in particular, both the protonated amide (I) and the transition state for an *A*1 hydrolysis [*e.g.* t-butyl acetate (II) [11]] contain one acidic proton that is expected to interact strongly with water. The transition state for the protonation reaction is expected to resemble (I) closely, as values of the kinetic hydrogen isotope effects and the effect of concentrated acids on the rates suggest that the proton is almost completely transferred in the transition state.[10] The results in Table 1 show that for each of the amides studied, the rates of protonation do rise significantly with increasing salt concentrations (*e.g.* in 4M-electrolyte, the protonation rates are 4—10 fold faster than those in pure water). These effects are similar to but slightly smaller than those observed for typical *A*1 hydrolyses,[11,12] suggesting a slightly greater involvement of water in the protonation reactions. This is consistent with almost complete transfer of the proton in the transition state leading to (I).


(I)


(II)

It can be seen from the results in Table 2 that the activity coefficients of the amides increase significantly in the presence of added electrolyte (with the exception of $NaClO_4$). The general trends, including the behaviour in $NaClO_4$ solutions, are typical of behaviour previously observed for esters [11,18,20] and acetals.[12,18] In most cases, the increases in the activity coefficients are in fact sufficient to account for the observed increase in the rates of protonation of the amides. However, it is noticeable that in $NaClO_4$ solutions, even though the activity coefficients are considerably smaller than in other electrolyte solutions (and in some cases are even less than unity), the rate increases are as large or even larger than those for other electrolytes. This would suggest that the effects of the electrolytes on the activity coefficients of the amides may be largely cancelled by corresponding effects in the transition states. Some evidence to support this view comes from the results of a study of the acid catalysed proton exchange reactions of *N*-methylacetamide by Schleich *et al.*,[2,3] in which exchange rates at constant hydrogen ion activity in different

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[19] P. M. Ginnings and R. Baum, *J. Amer. Chem. Soc.*, 1937, **59**, 1111.

[20] R. F. Cross, Ph.D. Thesis, University of Melbourne, 1972.

electrolyte solutions were measured. Depending upon the assumption used to estimate the hydrogen ion activities (*i.e.* negligible liquid junction potential in the glass–calomel electrode system), they found only relatively small variations in the rates of proton exchange in different electrolyte solutions (generally $<\pm 40\%$).

Spectroscopic and electrochemical evidence suggests that alkali metal ions may interact strongly with amide molecules [21] and the presence of Li^+ ions have recently been shown to considerably increase the observed barrier height to torsion about the N–C(O) bond in *NN*-dimethylacetamide.[22] This latter study was carried out in dioxan as solvent, where interactions between Li^+ and dimethylacetamide would be expected to be considerably stronger than in water. Any strong interactions between the alkali metal ions and the amides might be important in determining the kinetic salt effects, and Schleich *et al.*[2,3] have interpreted their observed variations in proton exchange rates for *N*-methylacetamide in terms of specific interactions between the alkali metal ions and the transition states for the proton exchange reactions. In view of the large effects of salts on the activity coefficients of the amides observed here and elsewhere [1,6] (which will affect the proton exchange rates) such conclusions must only be tentative. The present results however, do show that the observed rate increases are in general smaller in LiCl (and LiBr) solutions, despite the fact that water activities are lower in LiCl solutions than in solutions containing similar concentrations of the other electrolytes.[23] This may be contrasted with salt effects on acetal hydrolyses where LiCl solutions lead to greater rate increases than those of either NaCl or KCl.[12] Any strong interaction between Li^+ and the carbonyl group of the amide would make protonation more difficult in agreement with the observed behaviour.

We thank Dr. P. T. McTigue of Melbourne University for discussion. One of us (P. D. M.) thanks the CNR (Rome) for financial support.

[4/2547 *Received, 7th December*, 1974]

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[21] *E.g.* J. N. Butler and J. C. Synnot, *J. Amer. Chem. Soc.*, 1970, **92**, 2602; C. Lassigne and P. Baine, *J. Phys. Chem.*, 1971, **75**, 3188.

[22] W. Egan, T. E. Bull, and S. Forsen, *J.C.S. Chem. Comm.*, 1972, 1099.

[23] R. A. Robinson and R. H. Stokes, ' Electrolyte Solutions,' Butterworths, London, 1959, 2nd edn.