culated based on the formation of an unreactive ion pair of **1** and perchlorate ion with an association constant of 2.5 M^{-1} and a Setschenow constant of $K_s = -0.09$ for the ratio log $(f_s/f_\pm)$. The line shows a satisfactory fit, but obviously does not represent a unique explanation of the data.[9] The effects could, of course, be attributed to salt-induced changes in water "structure", but we doubt that such an attribution has significant scientific usefulness at our present stage of understanding of salt effects and water structure.[10]

We do not wish to suggest that the practice of maintaining constant ionic strength with changing buffer concentration should be abandoned. However, these results serve to point up the fact that the neglect of specific salt effects can give rise to incorrect estimates of the magnitude, and even the existence, of terms in the rate law involving general acid or base catalysis in aqueous solution, as well as in mixed solvents,[3] especially when the catalysis is small. Downward curvature, such as was observed here when the ionic strength was maintained constant with tetramethylammonium chloride, could be mistaken for a change in the rate-determining step with increasing buffer concentration. It is desirable, therefore, to determine the sensitivity of reaction rates to both the concentration and the nature of salts when catalytic constants are determined in the presence of moderately concentrated salt solutions.

Experimental Section

N-*p*-Methoxybenzylidenepyrrolidinium perchlorate (**1**) was synthesized by the method of Leonard and Paukstelis.[11] The product had mp 117–118 °C, ir 1645 (>C=N<$^+$, in $CHCl_3$) or 1654 cm^{-1} (>C=N<$^+$, in Nujol),[12] and uv λ_{max} 315 nm (ϵ 14 200). Reagent grade inorganic salts, and acetic, formic, and trifluoroacetic acids were used without further purification. Glass-distilled water was used throughout.

First-order rate constants were determined spectrophotometrically by following the hydrolysis of **1** at 315 nm after the addition of 0.10 ml of a 7.5×10^{-4} M solution of the perchlorate salt of **1** in acetonitrile to 2.9 ml of buffer solution. The uv spectrum of the product was found to be identical with that of *p*-anisaldehyde.

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Dilute Acid-Catalyzed Amide Hydrolysis: Efficiency of the N-Protonation Mechanism[1]

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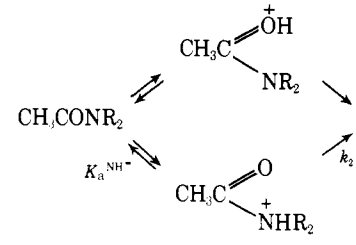
Abstract: The hydrolysis of some *N*-acetyltrialkylammonium tetrafluoroborate salts has been measured together with the acid-catalyzed hydrolysis of the parent *N,N*-dialkylacetamide; the pK_a of the corresponding N-protonated amide was estimated from the acid-catalyzed proton-exchange rate. We use the *N*-acetyltrialkylammonium salt as a nonprotonic model of the *N*-protonated amide to show that hydrolysis via the latter species is not sufficient to support the overall observed acid-hydrolysis rate constant for amides. The Hammett ρ observed for dilute acid-catalyzed hydrolysis is not consistent with the N-protonation path.

Introduction

The question of the site of major protonation of amides is an important problem which has attracted much discussion.[2] A related problem is the nature of the intermediate on the major path in acid-catalyzed hydrolysis of amides,[3] which is relevant to the discussion of the mode of activation of the peptide bond in the action of proteases.[4]

Recently, Kresge, Fitzgerald, and Chiang[5] showed that the relative rates for acid-catalyzed hydrolysis of *N*-acetylpiperidine and *N*-acetylpyrrolidine are not of the order expected for the formation of four-coordinated nitrogen from three-coordinated nitrogen in rings.[6] The existence of ^{18}O exchange in acid-catalyzed benzamide hydrolysis[7a] establishes that water attack on the protonated amide is the rate-limiting step provided proton transfer from the intermediate is not rate limiting; fast proton transfer would be expected for such a highly acidic intermediate. An earlier study by Edward and Meacock[7b] showed that the rate constant for imidate hydrolysis and the hydrolysis of protonated amide are essentially the same, providing both a necessary and sufficient criterion for the O-protonation mechanism. This work has been extended recently by Smith and Yates.[7c]

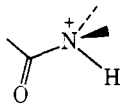
These experiments favor the O-protonation pathway, but give no indication as to the extent to which the (minor) N-



(1)

protonation path participates. It is the purpose of this work to estimate the contribution of the latter and to investigate the conditions where this path may predominate.

Bunton, O'Connor, and Turney[8] suggested tertiary *N*-acylammonium salts as models for the N-protonated amide I, but no kinetic data were available at that time except the knowledge that these derivatives were hydrolytically labile.[9a] Recently, the hydrolysis of *N*-acetylpyridinium salts[9b-d] and *N*-acetylimidazolium species[9e-i] has been studied, but in these compounds the formal positive charge is delocalized over a planar cyclic system II, whereas N-protonated amides have



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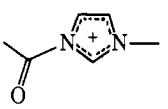


II

the charge localized on tetrahedral nitrogen. Paukstelis and Kim[10] have shown how tertiary *N*-acetylammonium salts may be prepared in good yield as thermally stable crystalline solids. We take advantage of this to study the hydrolytic lability of these compounds; moreover, perusal of the hydrolytic data for the *N*-acetylpyridinium salts (Figure 9 of ref 9b) indicates that the rate constants for the derivatives of the more basic tertiary amines should be well within the limits of conventional instruments. We may calculate the proportion of acid-catalyzed amide hydrolysis passing through the N-protonated intermediate from the hydrolytic rate constant for the model using the pK_a of the intermediate, which may be determined by an NMR technique.

Experimental Section

Material. *N,N*-Dimethylacetamide (bp 162 °C (760 Torr); lit. bp[11] 165 °C (765 Torr)) and *N*-methylacetamide (bp 204 °C (761 Torr); lit. bp[12] 206 °C (765 Torr)) were purchased from BDH and redistilled. Other acetamide derivatives were prepared from the corresponding secondary amines by refluxing with an equivalent amount of acetic anhydride in chloroform solvent. The solution was extracted with NaOH, dried, and evaporated to yield amide, which was vacuum distilled. Boiling points were obtained for comparison with literature values at atmospheric pressure. *N,N*-Diethylacetamide had bp 183 °C (765 Torr) [lit. bp[13] 185 °C (765 Torr)]; *N*-methyl-*N*-cyclohexylacetamide had bp 250 °C (761 Torr) [lit. bp[14] 249 °C (740 Torr)]; *N*-acetylpiperidine had bp 225 °C (750 Torr) [lit. bp[12] 227 °C (760 Torr)]; *N*-acetylpyrrolidine had bp 113 °C (763 Torr) [lit. bp[15] 114 °C (760 Torr)]. Acetyl chloride was purified by distillation from quinoline and tertiary amines were distilled from 4-toluenesulfonyl chloride; these materials (except the acetyl chloride) were kept over molecular sieves (4-Å pore size). Ether was distilled after being kept over sodium wire and acetic anhydride was redistilled before use. Tetrafluoroboric acid diethyl etherate was purchased from Aldrich and the bottle kept in a sealed polythene bag with silica gel in the refrigerator at 4 °C.

N-Acetyl-*N,N,N*-trialkylammonium tetrafluoroborates were prepared by the methods described by Paukstelis and Kim[10] with minor modifications. The reactions were carried out in a 150-ml Erlenmeyer flask with the neck sealed with a "Suba-Seal" rubber septum. To allow pressure equalization the seal was pierced with a syringe needle attached to a glass syringe (without the plunger) filled with calcium chloride granules. The reagents were added with syringes charged from stock solutions in a glove bag (made from a large, thin-guage, polythene bag fitted with regular rubber gloves) containing calcium chloride desiccant and dry nitrogen under slight pressure. To a solution of acetyl chloride (1.36 ml, 0.02 mol) in dry ether (25 ml) cooled in an acetone–dry ice bath was added dropwise (with magnetic stirring) a solution of the tertiary amine (0.01 mol) in dry ether (25 ml). The suspension was kept overnight in the acetone–dry ice bath (in a Dewar flask) in a deep freeze. Tetrafluoroboric acid diethyl etherate was then added dropwise with stirring. The suspension was allowed to come to room temperature in the glove bag, then the solid was filtered and washed with dry ether; in most cases a slight stickiness in the crystals was removed by rubbing the precipitate with a glass rod and washing with additional dry ether. These operations were carried out in a dry nitrogen atmosphere in the glove bag. The crystalline product was contaminated with a small amount of high-melting material, but this did not appear to alter the melting point of the main bulk, which fused at the temperatures reported by Paukstelis and Kim.[10] As judged from the infrared spectra this foreign material was probably the ammonium chloride; it proved difficult to remove this impurity, but we were able to estimate the purity of the *N*-acetylammonium salts by a technique which is described later. Infrared and NMR spectra agreed with those described.[10]

Other materials such as buffer components were of analytical reagent grade or were purified from bench-grade products by crystallization or distillation. Water, twice distilled from glass, was used throughout and deuterium oxide (99.8 atom %) and oxygen-18-enriched water (1.6 atom %) were obtained from Ryvan Chemical Co. and Prochem, respectively.

Methods. Infrared spectra were recorded with Unicam-SP200 or Perkin-Elmer Model 237 instruments using Nujol mulls. NMR spectra were obtained with a Perkin-Elmer R10 machine or with the help of Dr. D. O. Smith using a Jeol P.P. 100 Mc/s instrument equipped with Fourier transform apparatus. Mass spectra were recorded by Dr. R. B. Turner using an A.E.I. MS 902 high-resolution mass spectrograph. The measurement of pK_a's was carried out by titration with the appropriate reagent using a Radiometer pH-meter 25 machine.

Hydrolysis of the *N*-acetylammonium salts was followed at constant wavelength using a Beckman DBG spectrophotometer fitted with a linear logarithmic converter and servoscribe recorder with a back-off device. A Unicam-SP800 scanning machine was used to determine the most appropriate wavelength for kinetics. A typical experiment involved adding a solution (on the flattened tip of a glass rod) of the *N*-acetylammonium salt in acetonitrile (ca. 25 μl) to a buffer solution (2.5 ml) in a silica cuvette in the thermostated cell holder of the spectrophotometer. Two to three rapid vertical strokes of the glass rod in the solution effected complete stirring and the recorder was activated as the rod entered the buffer.

The hydrolyses were also followed using a pH stat assembly (Radiometer, Copenhagen) with a 0.5-ml buret charged with 0.1 M NaOH and a titration vessel of 5 ml. The rapidity of the hydrolysis made it difficult for the pH stat to attain the set pH at the initial stage of the reaction and the pH was adjusted by addition of NaOH with a Pasteur pipet. The loss of the first 0.5 min of the trace made it impossible to measure accurately the NaOH equivalent to complete hydrolysis. However, rough estimates, taking into account the pK_a of the products and the set pH, were within about 30% of the value expected from the known molarity of the substrate.

Amide hydrolysis was measured at elevated temperatures; a series of identical samples was held for varying times in a thermostated water bath and then frozen to stop the reaction. The composition of the samples was analyzed by proton NMR spectroscopy (at 33.5 °C) using the Perkin-Elmer R10 instrument. The appearance of the acetic acid absorption and the disappearance of the CH_3CO– absorption of the amides were estimated from the areas under the peaks by weighing. The sum of the weight of the acetic acid and acetyl peaks was used as an internal standard for the total material present.

The cis–trans isomerization of the amides was measured by an NMR technique (Perkin-Elmer of Jeol machines) using coalescence of peaks due to the acetyl protons in unsymmetrical amides and the atoms adjacent to the nitrogen in symmetrical amides. The isomerization rate at the acid concentration where the two peaks coalesce ($k = \pi\Delta\nu/\sqrt{2}$; the chemical shift difference between the nonexchanging absorptions is defined as $\Delta\nu$)[16] divided by the acid concentration yields the second-order rate constant for acid-catalyzed isomerization (see Results and Discussion). It was not convenient to use total line-shape analysis to estimate the exchange rate, which is as accurately given at coalescence by the simple equation. We employed a simple modification of the equation for conditions under coalescence devised by Grunwald, Loewenstein, and Meiboom[17] and tested by Rogers and Woodbrey,[18] since it was not always possible to choose the concentration of acid for accurate coalescence

$$k_c = \pi\Delta\nu(r + (r^2 - r))^{1/2}/\sqrt{2}$$

$$r = (a + a')/2c \qquad (2)$$

where a, a', and c represent peak heights and valley height, respectively. The rate constant from eq 2 was used to calculate the acidity for coalescence and the NMR experiment was then run at this con-

Table I. Acid-Catalyzed Amide Hydrolysis

	T, °C	$\Delta H^{\ddagger}$ [c,e]	$\Delta S^{\ddagger}$ [c,e]	$k \times 10^6$, $M^{-1}\ s^{-1}$ [b,f]
N,N-Diethylacetamide				
	90.8			6.23
	80.2			3.12
	84.3	15.1	−41.4	4.12
	25.0			0.029
N-Methyl-*N*-cyclohexylacetamide [d]				
	90.7			8.27
	80.2			3.63
	84.3	18.3	−32	5.02
	25.0			0.038
N-Acetylpiperidine [a]				
	84.3	16.3	−30.7	104
	70.0			42.5
	60.2			19.3
	90.8			178
	50.0			8.07
	25.0			0.81

[a] Molarity of HCl, 1 M. [b] Derived from pseudo-first-order rate constant by division by HCl molarity; each rate constant is an average of two experiments and the uncertainty is estimated not greater than ±5%. [c] Parameters refer to 84.3 °C and are in units of kcal/mol and entropy units/mol for $\Delta H^{\ddagger}$ and $\Delta S^{\ddagger}$, respectively. [d] The activation parameters for these compounds were inadvertently interchanged in the preliminary report.[1] [e] These values were obtained graphically and we estimate enthalpy and entropy to be accurate to 1 kcal/mol and 4 eu/mol, respectively. [f] Error limit on these parameters is not greater than ±10%.

centration to check the validity of the rate constant.

Estimates of the purity of the *N*-acetylammonium salts were made by adding aliquots of the stock solutions in acetonitrile to 1 M acetate buffers. A rapid increase in absorbance at 250 nm followed by a slow decrease (due to formation and decay of acetic anhydride) was observed. Extrapolation of the decay curve to zero time by use of a logarithmic first-order plot allowed estimation of the acetic anhydride ($\Delta\epsilon_{250}$ 45) produced and hence the molarity of the *N*-acetylammonium salt. The salts were never more than 70% pure as judged by this technique.

Results

Acid-Catalyzed Amide Hydrolysis. The bimolecular rate constant for acid-catalyzed hydrolysis of the amides (Table I) at 25 °C was estimated from results at higher temperatures (50–90 °C), assuming adherence to the Arrhenius equation in the extrapolated region. The Arrhenius plots show no evidence for curvature (Figure 1) and it is considered unlikely that a change in the rate-determining step will occur (e.g., from water attack to protonation), causing a deviation in the extrapolated region. Only one concentration of acid (1 M HCl) was employed, as there is considerable evidence that hydrolysis is linear up to this value for other amides.[19a] The data agree with values for similar hydrolyses reported in the literature.[19b] The values of $\Delta H^{\ddagger}$ and $\Delta S^{\ddagger}$ are estimated from[20]

$$k_{H^+} = (k'T/h)e^{\Delta S^{\ddagger}/R}e^{\Delta H^{\ddagger}/RT} \qquad (3)$$

for 84.3 °C and are given in Table I. No extraneous NMR peaks due to side reactions were observed in any of the amide hydrolyses.

Acid-Catalyzed Isomerization of Cis and Trans Amides. Proton and ^{13}C NMR spectroscopy indicated that the amides of Table II possessed absorptions which coalesced in the acidity range 0.01–2 M due to isomerization about the CN amide bond. In the case of *N*-methylacetamide (III) and *N*-methyl-*N*-cyclohexylacetamide (IV) a true isomerization was occurring, but the other amides only underwent a virtual

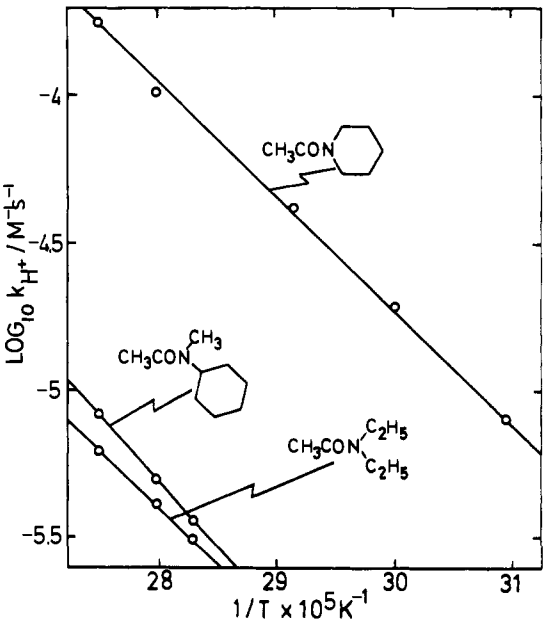
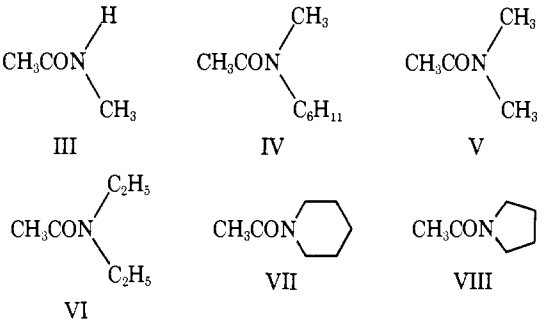
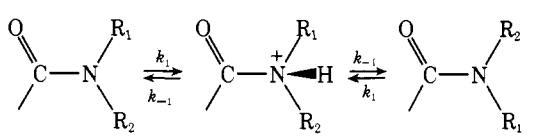


Figure 1. Temperature dependence of the hydrolysis of amides in 1 M HCl. Data from Table I; lines drawn from pseudothermodynamic parameters given in Table I.



isomerization. In the former case the equilibrium constant between the two forms is slightly larger than unity, probably reflecting van der Waals repulsion between the *N*-alkyl group and the methyl of the acetyl in the trans isomer; the "equilibrium constants" for the symmetrical derivatives are of course unity. The acidity at coalescence was used to obtain the acid-catalyzed isomerization rate constant from the coalescence exchange rate (see Methods). The work of Cox[21] shows that the rate of isomerization is proportional to acid up to 0.5 M for *N,N*-dimethylbenzamide and *N,N*-dimethylacetamide; moreover these results, obtained by the use of a curve-fitting technique, agree with ours and further validate the use of the simpler coalescence technique. We were able to check the method internally for *N*-methyl-*N*-cyclohexylacetamide, *N*-acetylpiperidine, and *N*-acetylpyrrolidine, where extra coalescences occurred at altered acidities due to different chemical-shift differences (see Table II). This check also gives an indication of the confidence limits to be placed on the results. In the case of the piperidine and pyrrolidine derivatives proton NMR studies are not possible even with decoupling and the simpler ^{13}C NMR with Fourier transform was employed.

The rate of proton transfer at the nitrogen of the amide may be estimated from the isomerization process if the following mechanism (eq 4)[22] is assumed. Provided the deprotonation



(4)

Table II. Specific Acid-Catalyzed Isomerization of Cis and Trans Forms of Acetamides[g,j]

	k_1, M^{-1} s^{-1}[d,f]	pK_a[a,f]	K[h]	a_{H^+}, M[b]	$\Delta\nu$, cps[c]	Calcd pK_a[t]
N-Methylacetamide	1070[n]	−7.27	1.04	0.023	5.5[l]	−7.56
N,N-Dimethylacetamide	280[r]	−7.85	1	0.175	11[l]	−7.53
N,N-Diethylacetamide	171	−8.07	1	0.901	3.5[l]	−7.18
N-Methyl-*N*-cyclohexylacetamide	79	−8.38[u]	1.05	0.45	8[l]	−7.16
	(89)			(0.015)	(3)[m]	
N-Acetylpyrrolidine	126	−8.2[u]	1	1.84	52[q]	−6.88
	(106)			(1.28)[s]	(31)[p]	
N-Acetylpiperidine[e]	1060	−7.22[u]	1	0.5	119[q]	−6.93
	(1340)			(0.05)	(15)[p]	

[a] This value is calculated from k_1 from the formula given in the Results (eq 5). [b] The acid concentration at coalescence (a_{H^+}) is calculated from the expression given in the Methods from data for k_1 derived from spectra close to and below coalescence using the approximate expression. Spectra at these derived concentrations were checked to demonstrate coalescence. Conditions are aqueous solvent at 1 M ionic concentration with NaCl. [c] The chemical shift difference between the two peaks ($\Delta\nu$) at zero acid concentration was shown not to vary significantly up to 0.01 M acid. [d] The rate constant (protonation of amide) is given by the equation $k_1 = 2k_{isom}$ (see text). [e] Carbon-13 NMR of the atoms adjacent to the nitrogen was used because the proton NMR of the hydrogens on these atoms is too complex for meaningful interpretation. [f] The temperatures for these parameters were limited by the NMR instruments: 22 ± 1 °C for the *N*-acetylpyrrolidine and *N*-acetylpiperidine (Jeol ^{13}C NMR) and 33.5 ± 0.1 °C for the other compounds (Perkin-Elmer R10). [g] Concentration of amide was in all cases 10% (v/v). [h] Equilibrium constant between cis and trans forms (K = cis/trans); these values were obtained from the NMR spectra at 1 M HCl using the two NCH_3 peaks assuming the cis form (NCH_3 cis to the carbonyl oxygen) has more shielding than the trans form, which is deshielded due to the magnetic anisotropy of the carbonyl and van der Waals coupling with the CH_3CO; the values of K greater than unity are probably due to van der Waals repulsion in the trans form. [j] We have a 20% confidence in the rate constants reported in this table. [l] NCH_2. [m] CH_3CO. [n] R. B. Martin, *J. Chem. Commun*, 793 (1972) finds 800 M^{-1} s^{-1} at 25 °C; 380 M^{-1} s^{-1} at 25 °C (A. Berger, A. Lowenstein, and S. Meiboom, *J. Am. Chem. Soc.*, 81, 62 (1959)); 833 M^{-1} s^{-1} (I. M. Klotz and B. H. Frank, *ibid.*, 87, 2721 (1965) for D_2O solvent); 360 M^{-1} s^{-1} (R. S. Molday and R. G. Kallen, *ibid.*, 94, 6739 (1972)). [p] NCH_2CH_2-. [q] NCH_2-. [r] 275 M^{-1} s^{-1} at 25 °C (B. G. Cox, *J. Chem. Soc., Perkin Trans. 2*, 1780 (1970)); 400 M^{-1} s^{-1} at 29 °C (G. Fraenkel and C. Franconi, *J. Am. Chem. Soc.*, 82, 4478 (1960)); 480 M^{-1} s^{-1} (C. A. Bunton, B. N. Figgis, and B. Nayak, *Proc. Int. Meet. Mol. Spectrosc. 4th*, 3, 1209, 1962 (1959)). [s] Since we were anxious, for purposes of comparison, to maintain the ionic strength at 1 M, we were not able to attain these values. These data were derived from spectra recorded at 1 M HCl via the equation given in the Methods. Check spectra at these higher concentrations did in fact show coalescence. [t] These values for pK_a are calculated using Fersht's equation (see Results). Values for pK_a's of the amines are from W. P. Jencks and J. Regenstein in "Handbook of Biochemistry", H. A. Sobers, Ed., Chemical Rubber Publishing Co., Cleveland, Ohio, 1968, p J150. *N*-Methylcyclohexylamine has a pK_a of 10.60. [u] From the average of the two k_1 values.

step is diffusion controlled the pK_a of the N-protonated amide may be estimated from[23]

$$k_1 = 2 \times 10^{10}/(1 + 10^{-(pK_{acceptor} - pK_{donor})}) \quad (5)$$

and the derived values are given in Table II. Since there is a probability of one-half that the N-protonated amide returns to its original configuration when it deprotonates, $k_1 = 2k_{isom}$.[24] The justification of the assumptions made here is given in the discussion. We utilize $pK_a = 0$ and 14 for the acids H_3O^+ and H_2O, respectively, to allow for the concentration of water (55.5 M) in the calculation of $pK_a^{NH^+}$.

The values obtained for pK_a (Table II) come as close as can be expected to the values predicted from the equation of Fersht[25a] (eq 6)

$$pK_a^{NH^+} = 1.04pK_{a(R_2NH_2^+)} - 18.6 \quad (6)$$

and given in the preliminary account[1] prior to our measurement of k_1.

Hydrolysis of *N*-Acetylammonium Tetrafluoroborates. The hydrolysis of *N*-acetylammonium salts in HCl/NaCl solutions showed good first-order kinetics up to about 90% of the reaction, as judged from the change in uv absorption at the wavelengths quoted in Table III. The pH dependence possessed a plateau up to about pH 5 (where acetate buffers were employed), but below pH 0 inhibition occurred (Figure 2).

In the presence of acetate buffers the *N*-acetylammonium salts (except that derived from triethylamine) give an initial rise in absorbance at 250 nm followed by a slow first-order decay (Figure 3). The decay-rate constant is identical with that for the hydrolysis of acetic anhydride under the same conditions (followed also at 250 nm; see caption to Figure 3) and the rise in absorbance with the *N*-acetylammonium salts is therefore almost certainly the formation of anhydride.

$$CH_3CO_2^- + CH_3CON^+\equiv \underset{k_{NR_3Ac_2O}}{\overset{k_{AcO^-}}{\rightleftharpoons}} CH_3COOCOCH_3 + N\equiv \quad (7)$$

Table III. Reaction of Acetate Ion and Water with *N*-Acetylammonium Salts[a]

Substrate		$k_{H_2O} \times 10^2$, s^{-1}[e,g]	k_{AcO^-}, M^{-1} s^{-1}[d]	$k_{NR_3Ac_2O}$, M^{-1} s^{-1}[b,f]
$CH_3CON^+(CH_3)_2$–⟨⟩	BF_4^-	3.1	0.37	3.79
CH_3CO-N^+⟨⟩ (Et)	BF_4^-	2.2	0.41	0.2
$CH_3CON^+(Et)_3$	BF_4^-	0.23	*c*	0.2

[a] Ionic strength made up to 1 M with NaCl, 25 °C. [b] This rate constant was measured using amine buffers at low base/acid ratio. The triethylamine and *N*-ethylpiperidine values are upper limits based on the probable errors in measuring slopes. [c] The existence of a strong absorption at 250 nm for this *N*-acetylammonium ion precluded the measurement of the acetate rate constant. [d] Measured by the increase in absorption at 250 nm. [e] See Figure 2 for details. [f] The equilibrium constant $[Ac_2O][N\equiv]/[AcN^+\equiv][AcO^-] = k_{AcO^-}/k_{NR_3Ac_2O} = 0.37/3.79 = 0.098$ and is approximately equal to those for the more basic pyridines (ref 9b,c); the calculation of the equilibrium constant assumes that the catalytic action of the tertiary amine with the acetic anhydride involves an acylammonium intermediate. [g] Extinction coefficients for hydrolysis at 235 nm: *N*-acetyl-*N,N*-dimethylcyclohexylammonium tetrafluoroborate, $\Delta\epsilon$40; *N*-acetyl-*N*-ethylpiperidinium tetrafluoroborate, $\Delta\epsilon$ 45; *N*-acetyl-*N,N,N*-triethylammonium tetrafluoroborate, $\Delta\epsilon$ 123.

It was possible to utilize the initial rise in absorbance to obtain a pseudo-first-order rate constant which, when plotted vs. acetate concentration (e.g., Figure 4), gave a slope (reaction of acetate with *N*-acetylammonium salt) and intercept (hydrolysis of the substrate in absence of buffer at the pH concerned). These parameters were practically the same for different base/acid ratios. The rate constants were obtained by extrapolating the acetic anhydride decay curve to zero time and using this line as the infinity; the reactions were rapid and the fastest had $t_{1/2} \sim 3$ s, which is easily measurable with the equipment at hand. The finite absorption at 250 nm of the

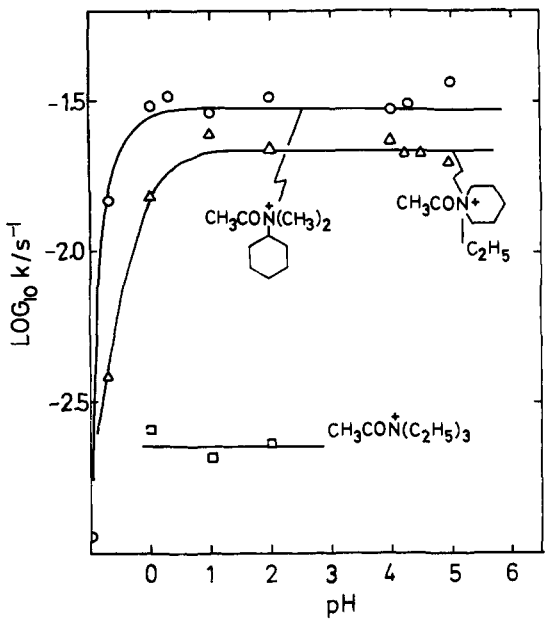


Figure 2. pH dependence of the hydrolysis of *N*-acetylammonium tetrafluoroborates in aqueous solvent at 25 °C; ionic strength made up to 1 M with NaCl. "Plateau" lines are drawn from data in Table III.

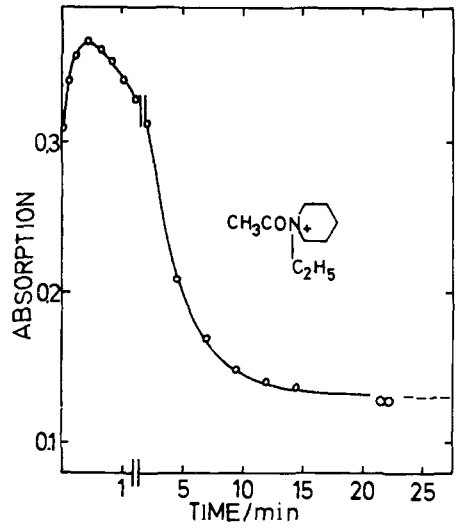


Figure 3. The reaction of *N*-acetyl-*N*-ethylpiperidinium tetrafluoroborate in sodium acetate buffer (1 M, acid/base = 1, 25 °C, ionic strength at 1 M, pH 4.5). The rate constant for the decay ($k = 2.51 \times 10^{-3}$ s^{-1}) is close to the decomposition of acetic anhydride in the same medium (2.48×10^{-3} s^{-1}).

N-acetylammonium salt from triethylamine precluded the measurement of a rate constant for this species. The data are collected in Table III; at 0.5 M sodium acetate the acetic anhydride path contributes approximately 90% of the reaction flux for both *N*-acetylammonium salts.

At pH's above 4.5 the hydrolysis yields acid

$$CH_3CON^+\equiv + H_2O \overset{k_{H2O}}{\rightleftharpoons} CH_3CO_2^- + HN^+\equiv \quad (8)$$

and a pH-stat method was used to follow the course of the reaction. This technique is capable of measuring rate constants of the magnitude given in Table III, but nonlinear logarithmic progress curves were obtained (Figure 5) although the machine was keeping the pH at the set value. The final part of the trace (Figure 5) is linear and corresponds to a rate constant close to that found for acetic anhydride hydrolysis measured in the same way (2.25×10^{-3} and 2.20×10^{-3} s^{-1}, respectively, at pH 4.25). The initial slope of the first part of the trace is close

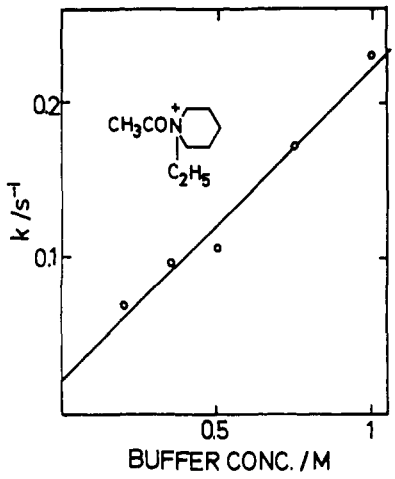


Figure 4. Plot of rate constant (measured at 250 nm) for reaction of *N*-acetyl-*N*-ethylpiperidinium tetrafluoroborate in acetate buffers at 25 °C (ionic strength made up to 1 M with NaCl). Line drawn from data in Table III.

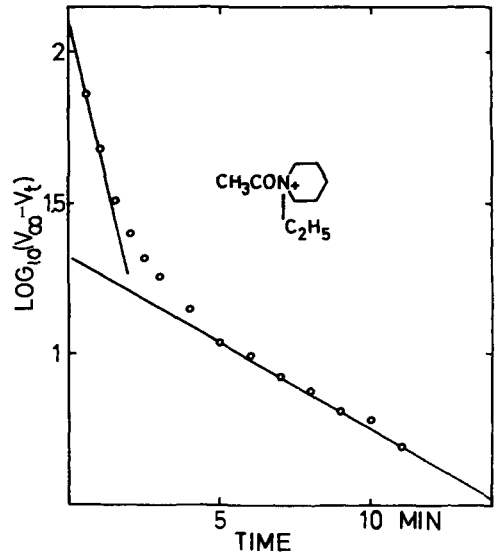


Figure 5. Hydrolysis of *N*-acetyl-*N*-ethylpiperidinium tetrafluoroborate at 25 °C, pH 4.95 in a pH stat (ionic concentration at 1 M with NaCl). Titrant is 0.1 M NaOH and 100 units of V are equivalent to 0.5 ml. Substrate concentration is 11 mM (5 ml) in the reaction vessel. Lines are taken from data in Table III.

to the rate constants obtained from the spectral studies for the hydrolysis of *N*-acetyl-*N*-ethylpiperidinium tetrafluoroborate. We believe that at the relatively high concentration of substrate ($\sim 10^{-2}$ M) necessary for the pH-stat experiment the acetate produced in the initial hydrolysis (eq 8) is sufficiently concentrated to form acetic anhydride with unchanged substrate (eq 7).

The possibility that the non-linear first-order plot was due to rapid formation of ketene

$$CH_3CON^+ \rightarrow CH_2CO \xrightarrow[2.\ H_2O\ \text{workup}]{1.\ D_2O} CH_2DCO_2H \quad (9)$$

followed by its slow hydrolysis was tested by carrying out the reaction in D_2O at pH 4 and in 0.1 M NaOD solution. The absence of deuterium incorporation in the product acetic acid excluded this path.

Discussion

Comparing the hydrolysis of *N*-acetylammonium salts with the rate constants for the protonated amides shows that the N-protonation pathway provides an insufficient rate constant

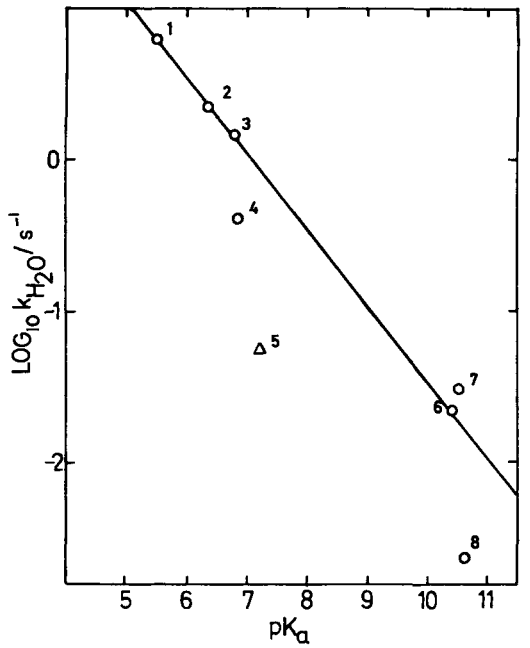


Figure 6. Hydrolysis of *N*-acetylammonium salts at 25 °C; (1) *N*-acetylpyridinium; (2) *N*-acetyl-4-methylpyridinium; (3) *N*-acetyl-3,4-lutidinium; (4) *N*-acetyl-4-methoxypyridinium, (5) *N*-acetylimidazolium; (6) *N*-acetyl-*N*-ethylpiperidinium; (7) *N*-acetyl-*N*,*N*-dimethylcyclohexylammonium, (8) *N*-acetyl-*N*,*N*,*N*-triethylammonium. Values for 1 to 5 are taken from ref 9b. Line has an arbitrary slope of $\beta_{LG} = 0.5$ and is not meant to represent a linear free-energy relationship. The *N*-acetyltrialkylammonium salts probably lie on the acyl pyridinium line due to steric depression of their intrinsically greater reactivity.

to account for the observed hydrolysis. Since the addition of water to the protonated substrate is the rate-limiting step in amide hydrolysis, it is certain that we are comparing similar rate steps. Even if proton transfer in amide hydrolysis were rate limiting the addition step would be faster than the observed rate constant, so that this would represent a lower limit to the former rate.

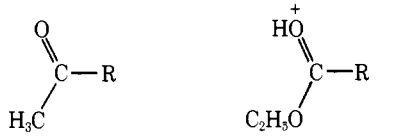
The spontaneous hydrolysis-rate constants for *N*-acetylammonium salts appear to be consistent with values predicted from *N*-acetylpyridinium hydrolysis (Figure 6). The overall rate constant for acid-catalyzed hydrolysis of amides via the N-protonated intermediate is given by

$$k_{H^+} = k_2/K_a^{NH^+} \qquad (10)$$

and provided k_2 (reaction of water with N-protonated amide) may be estimated, the pK_a of the N-protonated amide is then required. The only method for the latter is via the protonation rate constant,[25b] assuming the reverse deprotonation step is diffusion controlled.[23] This method is discussed by Kresge,[25b] who compares such pK_a's with those calculated from Fersht's equation, obtained via a thermodynamic cycle;[25a] the remarkable agreement found by us (Table II) and by Molday and Kallen[23] between calculated and estimated pK_a's seems to justify this assumption. All the presently known examples of slow deprotonation from NH^+ involve chelation of the proton in the conjugate acid; the presence of extensive delocalization in the conjugate base is not a sufficient criterion for slow rates. The measurement of acid-catalyzed inversion about the CN bond may be used to estimate proton addition rates, provided the rotation step is not rate limiting; the latter assumption has recently been challenged by Perrin,[26a] who showed that the lifetime of $RCONH_3^+$ is not long enough to attain rotational equilibrium and that the high rotation rate constants for single bonds (e.g., about the C–C bond in acetone $\sim 2 \times 10^{12}\ s^{-1}$)[26b] are reduced by solvation. The isomerization rate is therefore less than the protonation rate, leading to observed values of $K_a^{NH^+}$ larger than true. This effect can only be at the most a factor of possibly two and have a negligible effect for the purposes of this investigation on the fraction *F* (see Table IV).

Use of k_{H_2O} for *N*-acetyltrialkylammonium salts and $K_a^{NH^+}$ with eq 10 yields values of k_{H^+} (*A*, Table IV) well below the observed values for the corresponding secondary amides. Before a strict comparison is made between observed and calculated rate constants (*B* and *A* in Table IV, respectively), allowance must be made for (a) the steric effect of the *N*-alkyl group in the acetylammonium salt (substituting for the proton) on nucleophilic attack by water, (b) the effect of hydrogen bonding to the NH^+ by solvent not possible in the models,[26c] and (c) steric hindrance by the *N*-alkyl groups to solvation of ground and transition states.

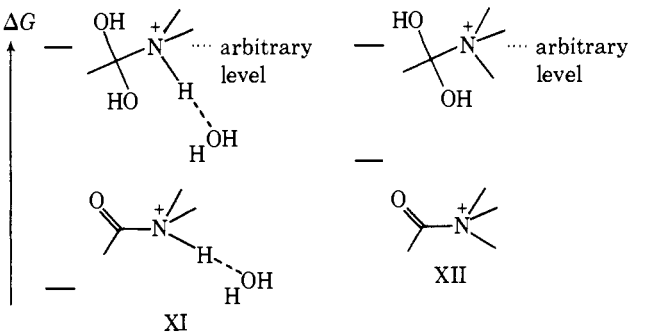
The first effect may be estimated by comparing E_s values for secondary alkyl (R_2CH–) with those for tertiary alkyl (R_2CR'–) for the difference between R_2NH^+– and R_2N^+R'–, respectively; the incursion of electrostriction in the ammonium species will have a slight effect. The available data indicate that replacing a hydrogen in a secondary alkyl by methyl or ethyl decreases E_s by a factor of one and two, respectively.[27] The addition of water to the *N*-acetylammonium carbonyl is sterically very similar to the addition of water to ethyl esters in acid-catalyzed hydrolysis and we would therefore expect a Taft δ of approximately unity to hold in our case; similar reactions



IX X

seem to possess δ values close to unity.[28a-d] The correction to be employed ($\log C = \delta \Delta E_s$) is given in Table IV. The values represented by *C* (the steric correction factor—see Table IV) are probably *upper* limits because there is evidence that the steric hindrance is not as pronounced as is to be expected from the δ values: for example, 2-methylpropionyl chloride is only fourfold more reactive than is pivaloyl chloride to water.[28e] It is also likely that water solvating the NH^+ group in the N-protonated amide exerts a steric effect at least as large as a methyl group (as in NCH_3^+), reducing the values represented by *C* well below the upper limits.

The effect of solvation is essentially to stabilize the N-protonated amide with respect to the transition state XI relative to the energy of the model with respect to its transition state XII. The Brønsted α for solvation (essentially hydrogen



XI XII

bonding) by water of NH^+ species must be less than unity (which represents a complete proton transfer) and a reasonable value seems to be close to 0.2.[29] If we assume the transition state approximates an N-protonated carbinolamine, then a ΔpK_a of about 15 (pK_a of N-protonated amide is ~ -7 and the pK_a of the protonated carbinolamine is ~ 8)[30] will correspond to a factor of 1000 in terms of the rate constant (*D* in Table IV). The values of *D* may be lower limits because the transition

Table IV. Estimation of the Bimolecular Rate Constant for Acid-Catalyzed Hydrolysis of Amides via the *N*-Protonated Intermediate

Acetamide	$k_{H_2O} \times 10^3$, s^{-1}	$pK_a^{NH^+}$ [b]	$k_{H^+} \times 10^9$ (A) [c]	$k_{H^+} \times 10^8$ (B) [b]	$A/B \times 10^4$	C [e]	Df	F, %g
N,N-Diethyl	2.3[a]	−8.07	0.0195	2.9	6.7	100	0.001	0.0067
N-Methyl-*N*-cyclohexyl	31[a]	−8.38	0.129	3.8	34	10	0.001	0.0034
N-Acetylpiperidine	22[a]	−7.22	1.33	81	16	100	0.001	0.016

[a] k_{H_2O} plateau rate constant for hydrolysis of the model *N*-acetylammonium salt (see Table III); 25 °C, ionic strength made up to 1 M with NaCl. [b] $pK_a^{NH^+}$ from Table II. [c] *A* units are M^{-1} s^{-1} and these values are *calculated* according to eq 10 from $K_a^{NH^+}$ and k_{H_2O}. [d] *B* values from Table I; units M^{-1} s^{-1}; from the Arrhenius plot for acid-catalyzed hydrolysis of the secondary acetamides (Figure 1, Table I). [e] *C* is the "steric" correction factor. [f] *D* is the correction factor for differential solvation. [g] Percentage of reaction path via the N-protonated amide.

state will not completely resemble the tetrahedral intermediate and may even be closer to the reactant; in any case the acidity will be intermediate between ground state and intermediate.

Steric inhibition of solvation by the substituted alkyl group is probably not important because the NH^+ group in the N-protonated amide is likely to be of similar size to ethyl or methyl due to solvation by water.

The Brønsted selectivity of the rate constant for the N-protonation mechanism to ammonium pK_a (β_{LG})

$$CH_3CONR_2 \overset{1.04^{25a}}{\rightleftharpoons} CH_3CON^+HR_2 \overset{-0.5^{9b}}{\rightleftharpoons} \text{product} \quad (11)$$

is estimated to be approximately 0.5 [32] from the Brønsted β for N-protonation of the amide (1.04)[25a] and for hydrolysis of *N*-acetylpyridinium salts (−0.5).[9b] We define a Brønsted selectivity as the slope (β) of a linear free-energy relationship against an appropriate pK_a. The observed selectivity for dilute acid-catalyzed hydrolysis of anilides is approximately zero,[31] consistent with a path not involving N-protonation and with an O-protonation mechanism where protonation on carbonyl oxygen and nucleophilic attack at carbonyl carbon would be expected to be influenced similarly by substituent change on the nitrogen. Work by Giffney and O'Connor[2,34] indicates that the selectivities for O-protonation (ρ = 1.4) and decomposition of intermediate (ρ = 1.2) in acetanilide hydrolysis do cancel out. Amides of highly basic amines would therefore be expected to favor the N-protonation pathway, but a changeover in mechanism is not possible because even the amide of one of the most basic amines appears to have only some 0.02% of hydrolysis via this path (see *F* for *N*-acetylpiperidine in Table IV).

The *N*-acetylammonium salts possibly hydrolyze via direct displacement (corresponding to the A_N^{D2} mechanism of Smith and Yates[7] for amide hydrolysis), via a tetrahedral intermediate (corresponding to A_N^{T2})[7] or an acylium ion (corresponding to A_N^{D1});[7] the latter could still give no deuterium incorporation in the product acetic acid if water attack at the RCO^+ were more effective than proton abstraction to give ketene. There is no evidence at present to distinguish between these possibilities, although at very high sulfuric acid concentrations acylium ion is the probable intermediate in amide hydrolysis.[35]

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