A Depressing Specific Salt Effect on the Hydrolysis of an Iminium Ion[1]

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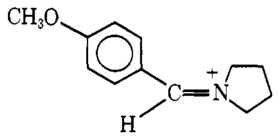
Abstract: The rate of hydrolysis of *N-p*-methoxybenzylidenepyrrolidinium ion at 25 °C shows a nonlinear increase with increasing concentration of acetate buffers when the ionic strength is maintained constant at 1.0 M. Upward curvature that could be mistaken for a term second-order in buffer concentration is found when the ionic strength is maintained constant with potassium chloride, potassium nitrate, potassium trifluoroacetate, and sodium perchlorate; downward curvature is found with tetramethylammonium chloride. The upward curvature is caused by a negative specific salt effect of potassium chloride and other alkali salts. Tetramethylammonium chloride exhibits a relatively small salt effect on the rate. Acetate ion itself has the smallest observed salt effect on the acetate-catalyzed reaction; consequently, the rate increases linearly with increasing buffer concentration if no salt is added to maintain constant ionic strength.

It is now generally accepted that catalytic constants for general acid and base catalysis in aqueous solution should be determined in the presence of a neutral salt to maintain constant ionic strength, in order that catalysis by the buffer may be distinguished from effects of changing ionic strength on the rate as the buffer concentration is increased. We (regretfully) report here a system in which anomalous results are obtained when the ionic strength is maintained constant with potassium chloride or other salts and a linear increase in rate with increasing buffer concentration is obtained only when the ionic strength is *not* maintained constant. The nonlinear catalysis is caused by a specific depressing effect of potassium chloride on the rate that is relieved when potassium chloride is substituted by potassium acetate.

Salomaa et al. have shown that specific-salt effects can, in mixed aqueous organic solvents, give rise to rate increases that may be mistaken for catalysis by buffers; these effects may be attributed to "solvent-sorting" brought about by the added salt.[3] The rate constants for the ionization of nitroethane in aqueous solution exhibit upward curvature as a function of increasing acetate buffer concentration because of a specific salt effect when the ionic strength is maintained constant with potassium nitrate. However, if the ionic strength is maintained constant with potassium trifluoroacetate the rate increases linearly with increasing acetate ion concentration up to 2 M buffer. The structures and salt effects of acetate and trifluoroacetate ions are sufficiently similar that substitution of one for the other does not cause a significant specific-salt effect on the rate of this reaction.[4]

The rate of hydrolysis of *N-p*-methoxybenzylidenepyrrolidinium ion (**1**) shows a greater than first-order dependence on the concentration of potassium acetate buffer, 80% ionized, when the ionic strength is maintained constant with potassium chloride (Figure 1, squares). In contrast to the acetate-catalyzed ionization of nitroethane, there is also significant curvature when the ionic strength is maintained constant with potassium trifluoroacetate (Figure 1, circles), although the curvature is less than with potassium chloride. The upward curvature of these lines could be taken as evidence for a third-order term involving two buffer molecules in the rate law. The curvature is, in fact, larger than that caused by the third-order term for the enolization of acetone under the same conditions.[5] However, rate constants obtained in 50 and 20% ionized acetate buffers exhibit less curvature with increasing (total) buffer concentration and the rate constants for all these buffers fall on the same curved line when plotted against the concentration of acetate ion (not shown). This shows that the upward curvature is associated with the ionized species rather than with a product term involving acetate and acetic acid.



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The upward curvature is similar when the ionic strength is maintained constant with potassium nitrate and considerably larger with sodium perchlorate (solid circles and diamonds, respectively, Figure 2). However, with tetramethylammonium chloride (triangles, Figure 2) there is a *downward* curvature. Catalysis by formate buffers was found to exhibit positive deviations from linearity of approximately 16% at 0.8 M formate ion when the ionic strength was maintained with chloride and trifluoroacetate salts.

The variation in the magnitude and direction of the curvature with different salts suggests that the upward curvature represents a specific salt effect caused by the replacement of a given salt by potassium acetate as the buffer concentration is increased. In fact, if no salt is added so that the ionic strength is not maintained constant, the rate increases linearly with increasing acetate buffer concentration (inset, Figure 2). The curvature is caused by an inhibitory effect of potassium chloride and most other salts on the rate, which is removed as the buffer concentration is increased and acetate is substituted for chloride ion.

The largest inhibition is exhibited by sodium perchlorate (Figure 3). This inhibition is similar to that for the hydrolysis of the cationic acyl compounds, acetylimidazolium and acetylpyridinium ions.[6] Plots of log k against [$NaClO_4$] for the hydrolysis of the acyl compounds is remarkably linear up to over 8 M salt concentration,[6] corresponding to a 500-700-fold rate decrease, but a similar plot for **1** exhibits upward curvature. Because of this nonlinearity it was not possible to determine Setschenow constants (K_s) for the inhibition according to

$$\log k_{\text{obsd}} = K_s[\text{salt}] \tag{1}$$

but a comparison of the effects of different salts was made from apparent Setschenow constants based on rate constants determined in the presence of 0 and 1.0 M added salt. The effect of added salt was determined in the presence of 0.03 and 0.83 M acetate buffer, 80% ionized, in order to examine the effects of salt on both the water and acetate-catalyzed reactions.

The results (Table I) show that the acetate-catalyzed reaction is inhibited somewhat less than the water reaction, but the inhibition is significant for both reactions with all salts except tetramethylammonium chloride. The inhibition of the

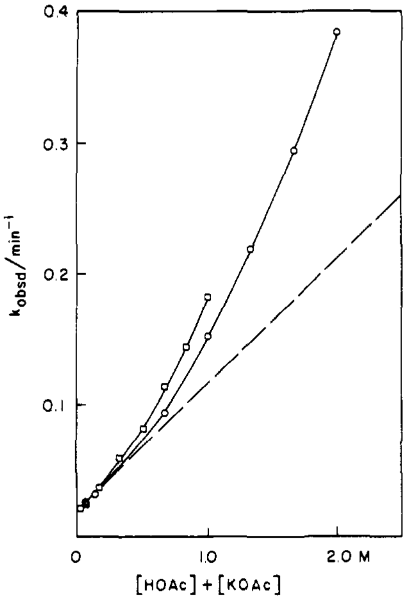

Figure 1. Catalysis of the hydrolysis of **1** by acetic acid-potassium acetate buffer, 80% anion, at 25 °C. The ionic strength was maintained at 1.0 M with potassium chloride (□) or at 2.0 M with potassium trifluoroacetate (○).

Table I. Effects of Salts on the Rate of Hydrolysis of **1** at 25 °C

	$-K_s$[a]	
Salt	0.03 M buffer[b]	0.83 M buffer[b]
$NaClO_4$	0.60	0.53
NaCl	0.33	0.23
KCl	0.31	0.20
KNO_3	0.34	0.15
KO_2CCF_3	0.21	0.12
$(CH_3)_4NCl$	0.10	−0.07

[a] $\log k_{obsd} = K_s$[salt], based on points at 0 and 1.0 M added salt. [b] Acetic acid buffer, 80% ionized.

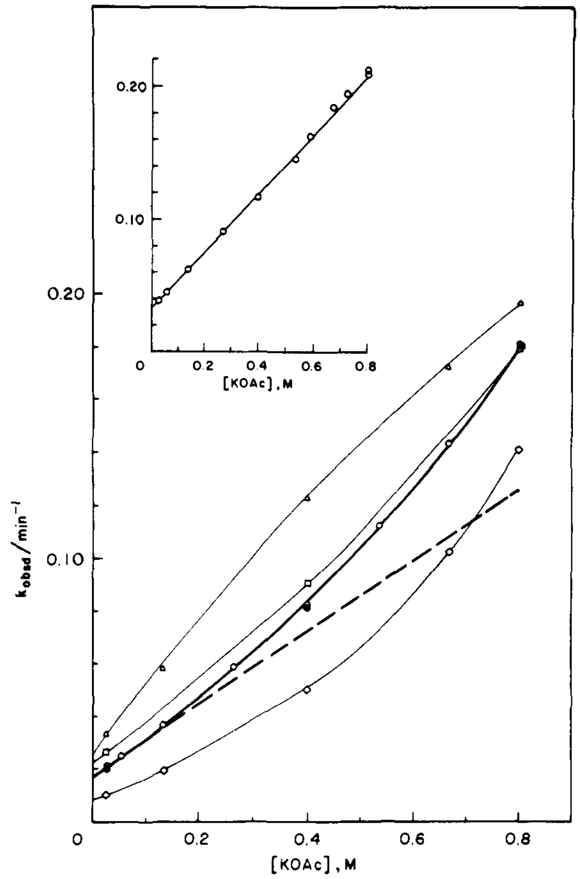

Figure 2. Catalysis of the hydrolysis of **1** by acetic acid-potassium acetate buffer, 80% anion, at 25 °C. The ionic strength was maintained at 1.0 M with potassium chloride (○), potassium nitrate (●), potassium trifluoroacetate (□), tetramethylammonium chloride (△), and sodium perchlorate (◇; with sodium acetate buffer). Inset: same, but without added salt to maintain constant ionic strength.

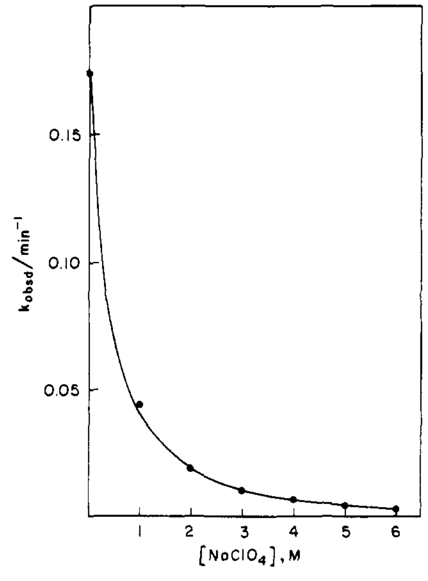

Figure 3. The effect of sodium perchlorate on the rate of hydrolysis of **1** in 0.8 M acetic acid-sodium acetate buffer, 80% anion, at 25 °C.

hydrolysis of **1** by 1 M sodium perchlorate is larger than that for the hydrolysis of acetylimidazolium and acetylpyridinium ions, as shown by an apparent Setschenow constant of −0.60 for **1** compared with values of −0.30 and −0.35 for the two acylammonium cations.[6] The order of inhibitory effectiveness for both the uncatalyzed and acetate-catalyzed reactions follows the Hofmeister series, with the largest effect from weakly basic, weakly hydrated anions and a compensating effect with tetramethylammonium cation; a similar order has been observed for the hydrolysis or hydration of acetylimidazolium and acetylpyridinium cations, triphenylmethylcarbonium ions, acid anhydrides, and esters.[6,7] The linear rate increase with acetate buffer in the absence of added salt shows that acetate ion has no detectable salt effect on the rate of the acetate-catalyzed reaction.

The inhibitory specific salt effect of sodium perchlorate and other salts on the rate could be caused by (a) a decrease in a_{H_2O} and a requirement for several water molecules in the transition state for hydrolysis, (b) the formation of an unreactive ion pair with the cationic substrate, or (c) an effect on the activity coefficient ratio $f_s/f_{\ddagger}$.[4,6-8] It is not caused by a salt-induced change in the rate-determining step because the same effect of potassium chloride was found in acetate buffers at pH 4.0-5.2 and the change to an acid-inhibited rate-determining step occurs only below pH 2.0. The inhibition cannot be accounted for quantitatively by a simple relationship based on any *one* of the factors a-c. An explanation based on a requirement for several water molecules for proton transfer is unlikely because the inhibition by sodium perchlorate is almost as large for the acetate-catalyzed reaction at high buffer concentration, in which only a single water molecule is presumably involved (Table I). The solid line in Figure 2 is calculated 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 $(f_s/f_{\ddagger})$. 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.

References and Notes

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

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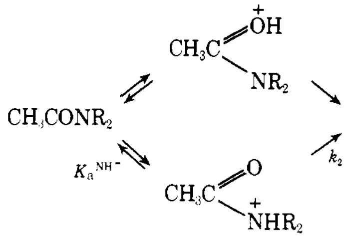
Abstract: The hydrolysis of some *N*-acetyltrialkylammonium tetrafluoroborate salts has been measured together with the acid-catalyzed hydrolysis of the parent *N*,*N*-dialkylacetamide; the pK_a of the corresponding N-protonated amide was estimated from the acid-catalyzed proton-exchange rate. We use 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-



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