$$\log (k/k_0) = -0.094[\sigma + 7.1(\sigma^+ - \sigma)]$$

The Yukawa–Tsuno equation is usually a flexible expression of situations intermediate between dependence on σ and on σ^+, the latter case being represented by a value of unity for the coefficient R (which is here 7.1). Values of R greater than 1, which are rare, correspond to dominance not by σ^+, which is itself a blend, but by that component of σ^+ which depends on a noninductive electron release mechanism. The effect of dominance by $(\sigma^+ - \sigma)$ rather than by σ^+ is (a) to make CH_3O 3.6 times as electron releasing as CH_3 instead of only 2.5 times, and (b) to transfer Cl from the electron-withdrawing to the electron-releasing groups, falling now between H and CH_3. One of the unusual cases of R greater than 1[26] is the brominolysis of benzeneboronic acids,[27] where a value of $R = 2.29$ is assigned.

Until we have longer substituent series and greater total rate effects, we postpone further speculation about the meaning of the unusual form of the substituent effects on the opening of tetramethyldioxetane. The data are alternatively fitted by the Swain–Lupton equation,[28] with $f = 0.116$ and $r = 0.833$. The ratio $r/f = 7.18$ has a similar meaning to the $R = 7.1$ of the Yukawa–Tsuno equation. The sensitivity to a single substituent in the present reaction is much less than in the direct reaction of triarylphosphines with molecular sulfur, which follows the Hammett σ and produces triarylphosphine sulfide as the final product.[24] By way of direct rate comparison, there is a free-energy ratio, $\log (k/k_0)_S/\log (k/k_0)_{TMD}$, of 10.3 between the effect of a methyl group in the sulfur reaction and that in the opening of TMD. This is at least in part a measure of the attenuation resulting from the intervention of a rhodium ion between the phosphorus and the site of the chemical change.

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(25) Hydrogen uptake by the rhodium complexes **8** and **10** has also been measured,[22] but the authors reporting this work remained unconvinced that the complexes themselves were adding hydrogen: no hydrogen-addition products could be isolated, a higher temperature was required to bring about the reaction than in the case of the iridium complexes, and the response to ligand change was small and irregular. Prior changes in the complexes may account for the fact that **8** and **10** fall in the opposite order from the corresponding iridium complexes toward hydrogen.
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Hydrolysis of 1-Benzyl-3-bromoacetylpyridinium Bromide. Evidence for Neighboring Group Participation

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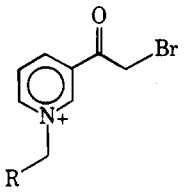
Abstract: The unusual solvolytic reactivity of 3-bromoacetylpyridinium ions has been investigated in a kinetic study of the hydrolysis of 1-benzyl-3-bromoacetylpyridinium bromide (**5**). The α-hydroxy ketone product of the hydrolysis was quantitatively determined by a novel application of the 2,6-dichlorophenol indophenol reagent. The progress of the hydrolysis reaction was followed by continuous titration of the hydrobromic acid which was formed (pH stat method). In addition to a direct dependence of the rate on the hydroxide ion concentration in the vicinity of neutrality, a primary solvent deuterium isotope effect as well as an inhibitory effect of added halide ions ($I^- > Br^- > Cl^-$) were observed. These findings were not consistent with a direct displacement mechanism for the reaction. The spectroscopic properties of **5** revealed that the carbonyl group exists in the hydrated form in aqueous solution. A mechanism for the hydrolysis involving ionization and cyclization of the hydrate to give an epoxide intermediate is proposed. The formation of epoxide intermediates in the solvolysis was confirmed by isolation of the α-hydroxyl dimethyl ketal, **6**, when the reaction was carried out in methanol solution.

We have initiated studies on the conversion of moderate molecular weight enzymes which are hydrolytic catalysts into modified enzymes capable of catalyzing a wide variety of synthetically important reactions such as oxidation–reduction, transamination, and decarboxylation. In the course of our studies we have focused our efforts on the preparation of coenzyme analogues containing reactive functional groups, permitting them to be attached at or near the periphery of the active sites of hydrolytic enzymes which are very available, easily purified, stable, and readily immobilized on solid supports. If suitable coenzyme analogues can be covalently attached to such relatively simple enzymes in a manner which permits the binding sites of the enzymes to remain accessible to organic substrates, it may be possible to catalyze many new

reactions with the modified enzymes.

The 3-bromoacetylpyridinium ions have been among the reactive coenzyme analogues with which we have begun the modification of hydrolytic enzymes along the lines outlined above. These ions have been studied previously[1a-c] for their ability to modify covalently nicotinamide adenine dinucleotide dependent oxidoreductases with a working model of the cofactor. The resulting species were used to probe both the physical properties and chemical reactivity of enzyme–cofactor combinations. One observation which received relatively little attention in these earlier studies was the remarkable hydrolytic reactivity of the modifying reagents. The 3-bromoacetylpyridinium ions (**1–4**) were readily hydrolyzed in neutral aqueous



No.	R
1	$(CH_2)_2CH_3$
2	$(CH_2)_3CH_3$
3	CH_2COOH
4	$(CH_2)_4COOH$
5	Ph

solution at 25 °C. and a distinct increase in rate was noted in going from pH 6.5 to 8.0. These findings were striking in light of the known solvolytic behavior of phenacyl halides.

A kinetic study of the solvolysis of a series of substituted phenacyl halides in mixtures of water and ethanol has been reported.[2] On the basis of solvent and substituent effects it was concluded that displacement occurred through a highly concerted S_N2 transition state. No evidence for participation of the carbonyl group through an addition or bridging intermediate[3] was obtained. Further, the rate showed no dependence on the acid concentration of the solutions. Experience in our own laboratories[4] indicated that direct displacement in phenacyl halides by hydroxide ion in aqueous solution becomes significant only at much higher values of pH when compared with the reactivity of 3-bromoacetylpyridinium ions. This disparity of effects suggested that the pyridinium ion hydrolysis was occurring through some unique mechanism, and it was this possibility that prompted the following kinetic study of the hydrolysis of 1-benzyl-3-bromoacetylpyridinium bromide (**5**).

Results

The synthesis of **5** was easily achieved by standard procedures. The compound, a crystalline solid which was stable when stored in a vacuum desiccator (P_2O_5), could be recovered unchanged after 12 h at room temperature in either methanol or dilute (10^{-3} M) aqueous hydrochloric acid solution. The material was, however, readily hydrolyzed in aqueous solution in the vicinity of neutrality. In every case, when a known quantity of **5** dissolved in a small volume of methanol was added to an aqueous solution with its pH maintained by means of a pH stat, a quantitative release of acid was observed.

Product Determination. The product of the hydrolysis was not readily isolated although ^1H NMR analysis of the reaction mixture showed that the 1,3-disubstituted pyridinium ion structure was maintained. It was necessary to resort to an indirect method for this determination. The expected product for the hydrolysis was the hydroxy ketone corresponding to displacement of the halide by hydroxide ion. The oxidation of hydroxy ketones to α-dicarbonyls using 2,6-dichlorophenol indophenol (DCI) has been reported.[5] This reaction occurs

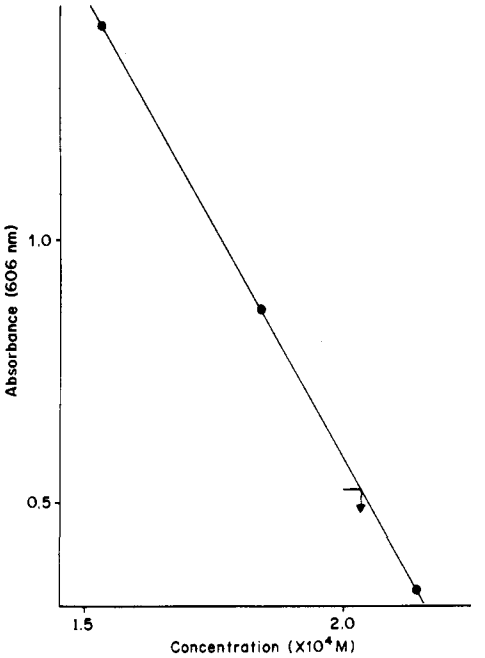


Figure 1. The determination of the hydrolysis product of **5** using 2.6-DCI. The closed circles represent the calibration of the 2.6-DCI solution with 1-benzyl-1,4-dihydronicotinamide. The arrow indicates the value obtained for the hydrolysis reaction. 2.00×10^{-4} M **5**, anaerobic, dark. 0.05 M phosphate. pH 7.5. 0.45 M sodium bromide. 25 °C.

with the complete loss of the absorbance maximum at 606 nm which is due to the oxidized form of DCI. It was reasoned that, if the hydrolysis was run in the presence of DCI, a loss of absorbance at 606 nm would be indicative of the formation of the hydroxy ketone and the extent of this loss would represent the yield. Strictly anaerobic conditions were required for the experiment to prevent reoxidation of the reduced DCI by molecular oxygen. Known quantities of 1-benzyl-1,4-dihydronicotinamide which rapidly reduces DCI were used as a standardization in the determination. A plot of the final absorbance at 606 nm against dihydronicotinamide concentration (Figure 1) gave a linear calibration of the DCI solution. When the hydrolysis reaction was carried out in the same solution, a gradual loss of absorbance was seen. The concentration of the product corresponding to the final absorbance value was obtained by interpolation of the standard curve. We concluded from these data that quantitative formation of the hydroxy ketone resulted from hydrolysis of the bromide.

Kinetics. The rate of the hydrolysis reaction was followed by the pH stat method. The plots which were obtained were found to be first order through at least 90% of the course of the reaction. The addition of a small aliquot of a freshly prepared stock solution of **5** in either methanol or 10^{-3} M HCl to the test solution in the pH stat was used to initiate the reaction. The rate was not affected by the solvent composition of the stock solution. In addition to a direct dependence on hydroxide ion concentration (Figure 2), the rate of hydrolysis was also influenced by solvent isotope differences and by the presence of added halide ions. Operating at constant acidity, the reaction was much slower in D_2O ($k_H/k_D = 4.0$). The rate was also lowered by increasing concentrations of halide ions (Table I). Surprisingly, the effect was greatest for iodide, a known[6] catalyst for the hydrolysis of alkyl bromides.

Evidence for a Hydrated Ketone in Aqueous Solution. The spectroscopic properties of **5** displayed distinct dissimilarities depending on the nature of the solvent employed. For example, a difference spectrum for equal concentrations of the compound in acetonitrile and 10^{-3} M HCl (Figure 3) revealed a clear absorbance maximum at 277 nm in the organic solvent

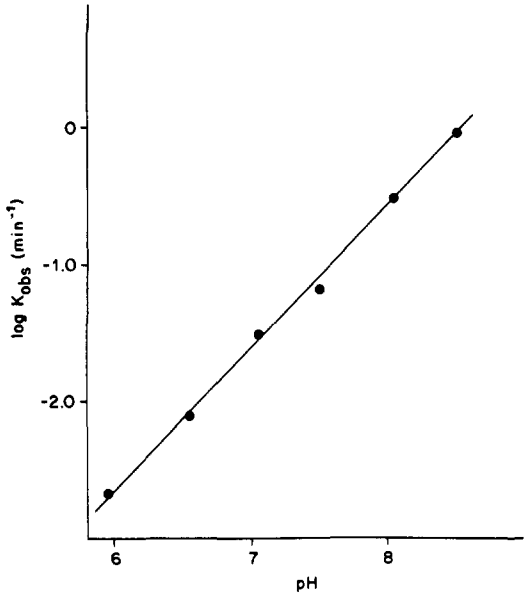


Figure 2. The effect of pH on the observed first-order rate constant for the hydrolysis of **5**. 2×10^{-4} M **5**, 0.25 M sodium chloride, 0.5% CH_3OH, 25.4 °C.

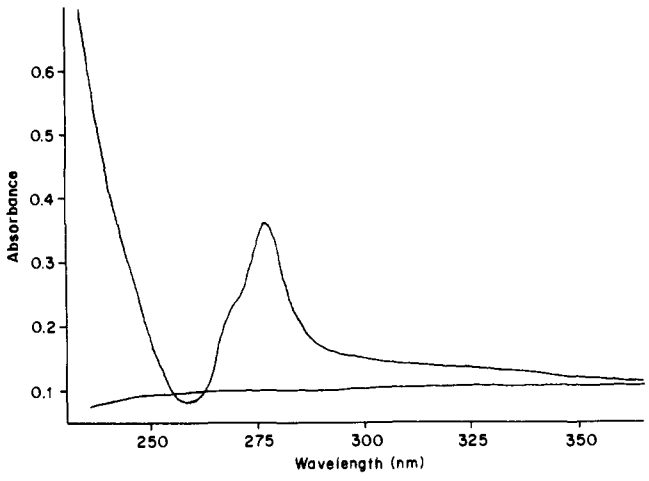


Figure 3. The difference spectrum for 1.48×10^{-4} M **5**, dissolved in CH_3CN (sample) and 10^{-3} M HCl (reference).

which was completely absent in aqueous solution. This finding was taken to indicate that the carbonyl absorbance seen in the organic solvent was lost in acidic aqueous solution due to hydration of the ketone. This hypothesis was supported by a comparison of the ^1H NMR spectrum of **5** dissolved in CD_3CN and in 10^{-3} M DCl in D_2O (Table II). The spectra were very nearly identical except for the position of the methylene protons α to the carbonyl which was shifted considerably downfield in the organic medium. This was a further indication that hydration of the ketone occurred in aqueous solution. A similar effect on the α protons was seen in CD_3OD solution (Table II), indicating that the compound was present in the hemiketal form.

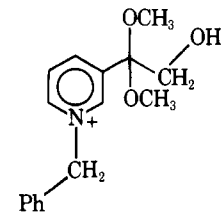
Methanolysis. In order to characterize the solvolysis further, a reaction of **5** with base in methanol solution was studied. When a solution containing 1 equiv of sodium hydroxide was slowly added to a dilute methanol solution of **5** at room temperature, the hydroxy dimethyl ketal, **6**, was obtained as the only product. This was easily distinguished from the isomeric methoxy hemiketal, **7**, on the basis of its ^1H NMR spectrum. A sharp six-proton singlet for the methoxy groups was observed. Also, a clear triplet was seen in dry Me_2SO-d_6 or $CDCl_3$ solution for the hydroxyl proton signal.

Table I. Variation in the Observed Rate Constant for the Hydrolysis of **5** in the Presence of Added Sodium Halide Salts. Initial Concentration of **5** 2.00×10^{-4} M, pH 7.05, 25.4 °C

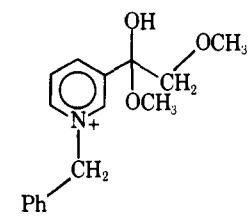
	$k_{obsd} \times 10^4$, s^{-1}		
$[X^-]$, M	X = Cl	Br	I
0.1	5.72	4.23	2.35
0.5	4.57	3.28	1.83

Table II. ^1H NMR Data for **5** in Various Solvents. Shifts Relative to DSS Internal Standard

		Chemical shift, ppm		
	H	CD_3CN	10^{-3} M DCl	CD_3OD
Ring	2	9.29	9.10	9.20
Ring	4	8.93	8.72	8.70
Ring	5	8.18	8.11	8.17
Ring	6	8.99	8.93	9.14
Ph		7.55	7.51	7.50
Benzyl		5.95	5.89	5.98
α		4.88	3.78	3.77



6



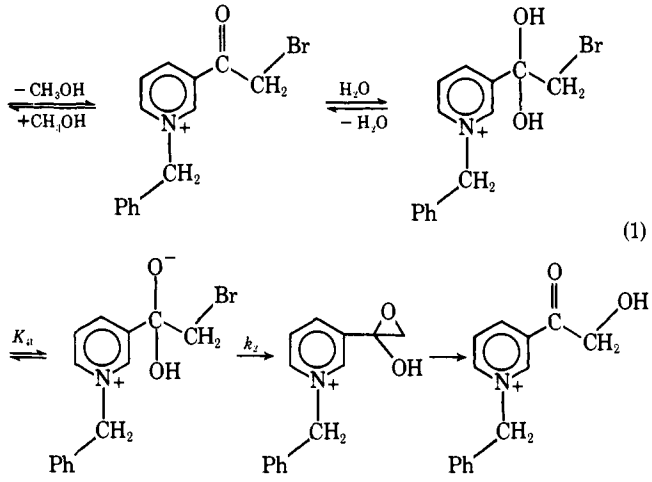
7

Discussion

Carbonyl compounds are activated with regard to hydration by the presence of electron-withdrawing substituents.[7] For example, polyhalogenated ketones exist in the hydrated form in aqueous solution.[8] Substitution of the pyridinium ring at a carbonyl position also leads to hydration in aqueous solution.[9] A rough comparison of the electron-withdrawing capacity of the pyridinium ring and the trifluoromethyl group can be obtained from ^1H NMR data. The α protons of 1-bromo-3,3,3-trifluoro-2-propanone absorb at 4.48 ppm in CD_3CN[10] compared to a value of 4.88 ppm for **5**. To the extent that the chemical shift represents the inductive influences of the groups, and considering that the pyridinium ring may exert some long range deshielding effects, it can be seen that the pyridinium ring of **5** causes at least as great an electron deficiency at the carbonyl position as the trifluoromethyl substitution. The observation of a hydrated species for **5** in aqueous solution was, therefore, not surprising.

In order to account for the unusual reactivity of the 3-bromoacetylpyridinium ions and at the same time to accommodate the observation of a hydrated species in aqueous solution, we propose the reaction sequence of eq 1 for the hydrolysis.

The mechanism of eq 1 is analogous to that for the alkaline cyclization of ethylene chlorohydrin.[11] An equilibrium dissociation precedes the rate-determining intramolecular displacement of bromide ion, giving an epoxide intermediate. This epoxide then rearranges by proton transfer to give the observed product. A similar mechanism[12] has been considered in the past[13] in an attempt to explain the difference in reactivity between α-halo ketones and alkyl halides in nucleophilic substitutions. While epoxide products have been observed in the



(1)

methanolysis of some α-halo ketones, searches for epoxide intermediates in cases where the product retains the carbonyl group have proved fruitless.[3,13,15]

The proposed scheme leads to the kinetic expression of eq 2 for the observed first-order rate constant.

$$k_{obsd} = \frac{k_2 K_a}{K_a + [H^+]} \tag{2}$$

This equation predicts that at low pH an inverse dependence for the observed rate constant on the acid concentration will be observed, while at high pH the rate will approach a limiting value depending on the pK_a of the ionizing species. The first of these expectations was clearly observed in the present case (Figure 2). However, the leveling effect on the rate anticipated at high pH was not seen due to experimental limitations on the determination of the faster rates. The hydrates of a series of substituted trifluoroacetophenones have been reported[16] and the pK_a values of these species range from 9.2 to 10.2. If the pK_a of the hydrate of **5** is 10, then the leveling effect would be at pH >9, just beyond the upper limit of the pH stat for determining hydrolysis rates.

Using a pK_a of 10.0 for ionization of the hydrate, an estimate of the cyclization rate constant (k_2) can be obtained from the slope of a plot of k_{obsd} against the hydroxide ion concentration. The value calculated was 0.58 s^{-1}. This was somewhat smaller than the rate constant for ethylene chlorohydrin cyclization.[17] An extrapolation of the data from the earlier work on ethylene chlorohydrin to the present case, however, was not possible because of the opposing effects of the substituent groups on the reaction rate. The electron-withdrawing pyridinium ring would have been expected to increase the rate, while the presence of the second hydroxyl group shuld have had just the opposite effect.

Variations in the rate of the alkaline cyclization of ethylene chlorohydrin with differences in solvent isotopes can be attributed exclusively to an effect on the equilibrium dissociation constant. Operating at constant base strength, it has been shown that the cyclization of ethylene chlorohydrin proceeds 1.54 times faster in D_2O than in H_2O.[18] The ratio for these rate constants is governed by

$$\frac{k_{obsd}^{D}}{k_{obsd}^{H}} = \frac{k_2^{D} K_a^{D} K_W^{H}}{k_2^{H} K_a^{H} K_W^{D}} \tag{3}$$

Using reported values (K_a^{D}/K_a^{H} = 4.9;[18] K_W^{H}/K_W^{D} = 7.5)[19] for the constants, it can be seen that the cyclization step is unaffected by the substitution of deuterium for hydrogen in the solvent (k_2^{D}/k_2^{H} = 1.01). An exactly analogous case can be made for the observed deuterium isotope effect in the hydrolysis of **5**. In this instance, operating at constant acidity, the ratio of rate constants will be given by

$$\frac{k_{obsd}^{H}}{k_{obsd}^{D}} = \frac{k_2^{H} K_a^{H}}{k_2^{D} K_a^{D}} \tag{4}$$

Typically, a shift of +0.6 pK unit would be expected[20] for an alcohol or phenol ionization in the appropriate pK region in going from H_2O to D_2O. This leads to a K_a^{H}/K_a^{D} value of 4.0, which is sufficient to account for the observed effect. Again, there is no influence on the slow cyclization step for solvent isotope differences.

The inhibitory effect of iodide ion can also be understood on the basis of the suggested scheme. Because of its tendency to form charge transfer complexes with pyridinium ions,[21] iodide will shift the hydration equilibrium toward the ketone form by reducing the electron-withdrawing capacity of the ring. The magnitude of this effect can be approximated by placing certain limitations on the kinetic scheme and by using literature values for some of the rate and equilibrium constants. Assuming that iodide displaces the bromide more rapidly than water and that hydrolysis does not occur for any species involved in a molecular complex, the kinetic expression of eq 5 for the observed rate constant, k_{obsd}, in the presence of excess iodide has been derived.

$$k_{obsd}' = \frac{k_2' K_a' K_{ct}}{[H^+][I^-] + K_{ct}[H^+] + K_{ct} K_a'} \tag{5}$$

In this equation the prime indicates that the reaction occurs through the iodide and K_{ct} is the equilibrium constant for dissociation of the charge transfer complex. The ratio of the rate constants obtained in the absence and presence of iodide can then be calculated as illustrated in eq 6.

$$\frac{k_{obsd}}{k_{obsd}'} = \frac{k_2 K_a}{k_2' K_a'} \left(\frac{[I^-]}{K_{ct}} + 1 \right) \tag{6}$$

The ratios for the cyclization rate constants and acid dissociation constants in the case of epoxide formation from 2-aryl-2-halogenoethanols have been determined to be 0.7 and 1.6, respectively.[17] Using these values to approximate the same behavior in the present case and a typical dissociation constant for a charge transfer complex of iodide and pyridinium ion, 0.55 M,[22] it can be shown that the hydrolysis rate should be some 2–3 times slower in the presence of 0.1–0.5 M iodide ion. This expectation was in excellent agreement with the observed effect.

The final step in the proposed reaction sequence is reminiscent of the epoxide carbonyl rearrangement,[23] observed, for example, in the peracid epoxidation of *trans*-α-chlorostilbene.[24] In that reaction, migration of the chloride occurs with ring opening to give the α-chloro ketone. The driving force for the reaction apparently is relief of strain in the three-membered ring. In the present reaction, the same objective can be achieved through a facile proton transfer.

Support for the proposed mechanism was obtained from the methanolysis experiment. It has been demonstrated[14] that epoxy ethers, obtained from the reaction of α-halo ketones with methoxide, give α-hydroxy ketals in alcohol solution. In some cases the ketal has been isolated directly from the initial reaction with the epoxy ether as a surmised intermediate.[25] Under the conditions of the present investigation, the ketal product could only have been derived from an epoxy ether. This means that the solvolysis proceeded as depicted in the scheme and not by direct displacement of the bromide by hydroxide or methoxide ion.

We conclude that in the presence of sufficiently electron-withdrawing substituents, the hydrolysis of an α-halo ketone proceeds through a hydrated carbonyl intermediate which accounts for the unusually high reactivity of these compounds in neutral and slightly basic solutions.

Experimental Section

Ultraviolet spectra were recorded on a Cary 15 spectrometer, and ^1H NMR spectra were obtained on a Bruker HS-270 spectrometer operating in the pulsed Fourier transform mode in conjunction with a Nicolet 1089 computer. The IR spectrum was recorded on a Perkin-Elmer 137 spectrometer. The elemental analyses were carried out by Microtech Laboratories, Skokie, Ill. Deuterated solvents were obtained from Aldrich. All other solvents were analytical reagent grade (Mallinckrodt). Methanol was stored over molecular sieves (Linde, 34) and was distilled through a column just prior to use.

1-Benzyl-3-bromoacetylpyridinium Bromide (5). 1-Benzyl-3-acetylpyridinium bromide (1.00 g, 3.42 mmol), prepared by a reported procedure,[27] was dissolved with magnetic stirring in 6 mL of glacial acetic acid. To this was added dropwise, over a period of 1 h, a brominating mixture consisting of 0.185 mL of bromine (0.575 g, 3.60 mmol) and 1 drop of hydrobromic acid (48%) dissolved in 3 mL of glacial acetic acid. Midway through the addition, a white solid precipitate of the product formed. The solid was collected on a filter, rinsed with ether, and dried (1.26 g, 3.39 mmol, 99%). Recrystallization from methanol-ethyl acetate provided fine white plates: mp 180–182 °C; IR (KBr) 1718 cm^{-1} (C=O); UV max (10^{-3} M HCl) 262 nm (ϵ 5050).

Anal. Calcd for $C_{14}H_{13}Br_2NO$: C, 45.31; H, 3.53; Br, 43.07; N, 3.77. Found: C, 45.32; H, 3.64; Br, 42.86; N, 3.76.

Hydrolysis Product Determination. Stock solutions of 1-benzyl-1,4-dihydronicotinamide[28] (13.0 mg, 6.16×10^{-2} mmol, 5.00 mL of CH_3OH) and 1-benzyl-3-bromoacetylpyridinium bromide (**5**) (29.6 mg, 7.98×10^{-2} mmol, 5.00 mL of CH_3OH) were prepared. The concentration of the reduced nicotinamide solution obtained by optical absorbance measurement was within 0.5% of the value determined by weight. A solution of DCl (7.0 mg, P and B Chemicals) in 100.0 mL of 0.05 M sodium phosphate buffer containing 0.45 M sodium bromide was rendered oxygen free by purging with a stream of nitrogen gas for 12 h at 4 °C. Aliquots of the standard nicotinamide solution (0.025, 0.030, 0.035 mL) were transferred by means of a gas-tight liquid syringe (Precision Sampling) into each of three 3.0-mL silica cuvettes equipped with ground glass stoppers. Into a fourth cuvette was placed 0.025 mL of the stock **5** solution. The methanol was removed from the cuvettes by using a stream of nitrogen. The cuvettes, four greased stoppers, and the DCl solution were all transferred into a glove box maintained with a nitrogen atmosphere. Into each of the cuvettes was transferred 2.00 mL of the DCl solution, noting the time of each addition. The cuvettes were carefully stoppered, removed from the glove box, and placed in the cell holder of the spectrophotometer. Recordings of the absorbance at 606 nm for each solution were made at regular intervals thereafter. The absorbance for the reduced nicotinamide solutions declined rapidly to a final, stable value. The decrease in absorbance for the solution of **5** was gradual but resulted in a stable infinity value. The concentrations of the standard solutions and the corresponding absorbances at 606 nm follow.

Concn ($\times 10^4$), M	Absorbance (606 nm)
1.53	1.413
1.84	0.873
2.14	0.336
(2.00)	0.546

Kinetics. All runs were carried out in a Radiometer pH stat (Titrator 11, Autoburette ABU 11, Titrigraph SBR2c, Assembly TTA31 with thermostated jacket, glass electrode, calomel reference). Constant temperature (±0.05 °C) was maintained by external circulation from a Lauda MGW constant temperature bath. Solutions were prepared using salts of analytical reagent grade (Mallinckrodt) and freshly distilled and deionized CO_2-free water. The pH of the solution was adjusted and maintained using 5 mM sodium hydroxide. In a typical experiment, 5.00 mL of a test solution was temperature equilibrated in a titration vessel equipped with a nitrogen atmosphere. The run was initiated by the introduction of 0.025 mL of a solution of **5** by means of a gas-tight liquid syringe. The pH was held constant by the automatic addition of base solution (0.200 mL, maximum). The first-order rate constant was evaluated from the resulting volume vs. time trace. Kinetic runs from solutions prepared on different days were reproducible to within 7%. The reported constants represent the average of at least two determinations.

The acidity of D_2O solutions was determined by adding 0.4 to the pH meter reading obtained with the glass electrode calibrated in buffers prepared with H_2O.[29] For the rates obtained in D_2O, 5 mM sodium deuterioxide in D_2O was used as titrant and the solutions of **5** were prepared either in 10^{-3} M DCl in D_2O or in CD_3OD.

Methanolysis. A methanol solution of sodium hydroxide (30.0 mL, 9.27 mM) was added dropwise at room temperature to a magnetically stirred solution of **5** (103.1 mg, 0.278 mmol) in 400 mL of methanol. The solvent was removed in vacuo, and the residue was triturated with chloroform to remove sodium bromide. When the solvent was removed in vacuo, an amorphous solid was obtained (109.1 mg, 1.11 × theoretical yield). NMR analysis revealed the presence of a single compound which contained the pyridinium ion structure. A small quantity of a highly colored impurity was removed by washing the solid twice with tetrahydrofuran, followed by recrystallization from chloroform and tetrahydrofuran: mp 167–168 °C dec; IR (KBr) 3334 (OH), 1087 cm^{-1} (OCH_3); NMR ($CDCl_3$) δ 9.27 (d, 1 H), 8.84 (s, 1 H), 8.33 (d, 1 H), 7.94 (t, 1 H), 7.51 (m, 2 H), 7.31 (m, 3 H), 5.99 (s, 2 H), 4.38 (t, 1 H), 3.73 (d, 2 H), 3.14 (s, 6 H).

Anal. Calcd for $C_{16}H_{20}BrNO_3$: C, 54.25; H, 5.69; Br, 22.55; N, 3.95. Found: C, 54.38; H, 5.41; Br, 22.22; N, 3.75.

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