Hydrolyses of 2- and 4-Fluoro N-Heterocycles. 3.[1] Nucleophilic Catalysis by Buffer Bases in the General Acid Catalyzed Hydrolysis of 4-Fluoroquinaldine

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Pseudo-first-order rate constants and catalytic rate constants are reported for the buffer-catalyzed hydrolysis of 4-fluoroquinaldine (1) in carboxylic acid and phosphoric acid buffers. The buffer catalysis is consistent with specific acid, general base catalysis. Hydrolyses in 99% ^{18}O-labeled water with 0.04 M unlabeled acetate, and complementary hydrolyses in unlabeled water with 90% ^{18}O-labeled acetate, indicate that the predominant catalytic mode for the acetic acid/acetate buffer system is nucleophilic catalysis by the acetate anion coupled with specific acid catalysis. The other buffers presumably react in a similar manner. A Brønsted-type plot of the catalytic rate constants for hydrolysis of protonated 1 has a slope of 0.57, with formate deviating positively from the line determined by acetate, chloroacetate, monohydrogen phosphate, and water. This Brønsted slope is less than that found for hydrolysis of the 2-fluoro-1-methylpyridinium ion, 2, but is still within the range expected for aromatic nucleophilic substitution. Rate constants and ^{18}O-labeling results for hydrolysis in acetate buffer are also reported for 4-acetoxyquinaldine (3), the proposed intermediate in the acetate-catalyzed hydrolysis of 1.

Nucleophilic addition and substitution reactions are commonly catalyzed by both acids and bases, particularly in reactions of carbonyl and activated aromatic substrates. Such catalysis may occur by a number of pathways, and much effort has gone into defining these.[2]

In particular, bases can participate in the rate-limiting step of a reaction either in a proton-transfer role (general base catalysis) or as a nucleophilic catalyst. These alternative modes of catalysis can be particularly difficult to distinguish.[3] In our previous paper[1] we presented evidence that the carboxylate buffer catalyzed hydrolysis of 2-fluoro-1-methylpyridinium iodide (2) proceeds by a nucleophilic catalysis pathway in which the carboxylate base first displaces the fluoride to give a 2-pyridyl ester intermediate, which then undergoes rapid hydrolysis. ^{18}O-Labeling experiments indicated that little or none of the reaction follows a general base catalyzed pathway in which water is the initial nucleophile, at least in acetate buffer.

We now report the results of a kinetic study of the hydrolysis of 4-fluoroquinaldine (1) in buffer solution. We have found this hydrolysis also to be buffer-catalyzed, with a buffer dependence typical of specific acid, general base catalysis. ^{18}O-Labeling experiments have shown the apparent general base catalysis to arise from nucleophilic reaction of the buffer base, as was the case for the hydrolysis of 2.

Results and Discussion

Kinetics of Buffer-Catalyzed Hydrolysis of 1. The rates of hydrolysis of 1 in carboxylic acid buffer solutions were determined either potentiometrically, by monitoring liberated fluoride with a fluoride-selective electrode (acetate), or spectrophotometrically, by following the increase in absorbance at 324 nm (acetate, formate, chloroacetate, phosphate). The wavelength monitored corresponds to an absorption maximum for the hydrolysis product, 4-hydroxyquinaldine (3). Comparable reaction rates were obtained for acetate buffers by these two methods.

The results of the kinetic runs in buffer solutions are summarized in Table I. The hydrolyses were found to be buffer-catalyzed, with rates increasing linearly with buffer concentration in all solutions except for the most acidic phosphate solution. In any given buffer system, such as acetic acid/acetate, in which rates were determined at more than one ratio of buffer acid to buffer base, rates were dependent upon pH as well as buffer concentration, particularly in the solutions of higher pH, such as in the acetate buffers (Figure 1). The rates were not strictly proportional to the concentration of buffer acid, but rather to the concentration of buffer base, when adjusted for the fraction of substrate converted to its conjugate acid form, as calculated from experimentally determined pH values and the acid dissociation constant for the protonated substrate (1.23×10^{-5}). This is the rate dependence expected from a reaction subject to specific acid, general base catalysis (k_{SHB}) as well as to specific acid catalysis alone (k_{SH}) (eq 1).

$$k_{obsd} = (k_{SH} + k_{SHB}[B^-])[SH^+]/S_T = (k_{SH} + k_{SHB}[B^-])[H^+]/([H^+] + K_{aSH}) \quad (1)$$

Although the kinetic expression for specific acid, general base catalysis (type n) can be rewritten and shown to be kinetically indistinguishable from the expression expected of general acid catalysis (type e),[4] this holds true only when a small fraction of the substrate is protonated.[2b] In the case at hand, the substrate was essentially completely protonated in solutions of pH below 3.5, while significant fractions of substrate existed in both protonated and unprotonated forms in the solutions of greater pH.

The catalytic rate constant for each of the buffer bases was determined as the slope of the pseudo-first-order rate constants divided by the factor ($[H^+]/(H^+) + K_{aSH}$)) to adjust for the fraction of substrate protonated at each pH plotted versus the buffer base concentration, [B^-]. There is some uncertainty in this analysis, because the acid dissociation constant for 1 (1.23×10^{-5}) was determined at 23.5 °C (room temperature), rather than at 50 °C, the temperature at which the hydrolyses were conducted. This was necessary because hydrolysis was too rapid at 50 °C for pK_a determination by the method used. That this

(1) For the previous paper, see: Muscio, O. J., Jr.; Rutherford, D. R. *J. Org. Chem.* **1987**, *52*, 5194-5198.

(2) For reviews of mechanisms of base catalysis, and discussions of nucleophilic vs general base catalysis, see: (a) Johnson, S. L. *Adv. Phys. Org. Chem.* **1967**, *5*, 237-330. (b) Jencks, W. P. *Catalysis in Chemistry and Enzymology*; McGraw-Hill: New York, **1969**. (c) Jencks, W. P. *Acc. Chem. Res.* **1980**, *13*, 161-169. (d) Bender, M. L.; Bergeron, R. J.; Komiyama, M. *The Bioorganic Chemistry of Enzymatic Catalysis*; Wiley-Interscience: New York, **1984**. (e) Jones, R. A. Y. *Physical and Mechanistic Organic Chemistry*, 2nd ed.; Cambridge University: Cambridge, **1984**.

(3) Hogg, J. L.; Gopalakrishnan, G. *J. Org. Chem.* **1981**, *46*, 4959-4964.

(4) Jencks, W. P. *Acc. Chem. Res.* **1976**, *9*, 425-432.

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Table I. Pseudo-First-Order Rate Constants ($\times 10^4$) for Buffer-Catalyzed Hydrolysis of 4-Fluoroquinaldine at 50 °C

acetate		formate		chloroacetate		phosphate	
M[a]	k, s^{-1}	M	k, s^{-1}	M	k, s^{-1}	M[b]	k, s^{-1}
pH 5.1		pH4.5		pH 3.6		pH 4.3	
0.19	4.7	0.25	24	0.50	5.1	3.0×10^{-3}	3.2
0.14	3.7	0.20	18	0.35	3.5	1.5×10^{-3}	1.6
0.094	2.3	0.15	14	0.25	3.2	0.6×10^{-3}	0.96
0.047	1.3	0.10	10	0.10	2.0	0.3×10^{-3}	0.82
0.012	0.42	0.05	5.7				
pH 4.1		pH 3.5		pH 2.5		pH 2.1	
0.063	3.6	0.167	21	0.50	4.4	0.50	1.2
0.047	2.7	0.125	16	0.35	3.4	0.25	1.1
0.031	2.0	0.083	11	0.25	2.7	0.10	1.2
0.016	1.3	0.042	7.9	0.10	1.5	0.05	1.1
		0.025	3.8				

[a] Concentration of buffer base. [b] Concentrations of monohydrogen phosphate at pH 4.3 and dihydrogen phosphate at pH 2.1.

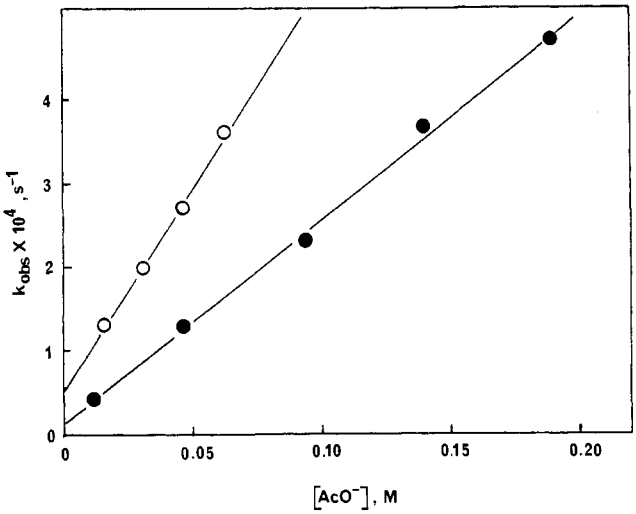


Figure 1. Pseudo-first-order rate constants vs concentration of acetate for the hydrolysis of 1 in acetate buffer solution at 50 °C: (○) pH 4.1; (●) pH 5.1.

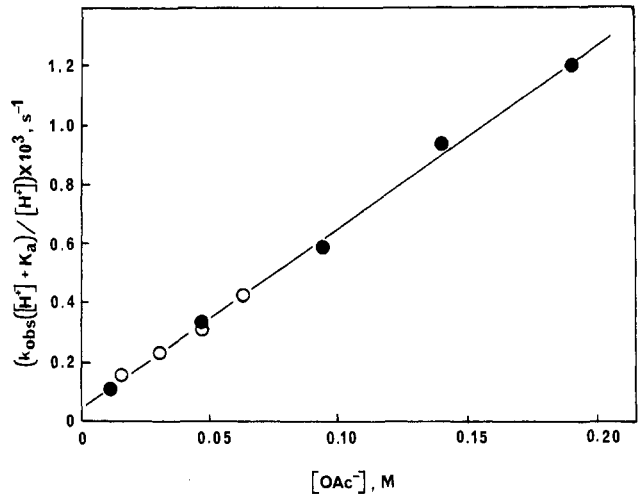


Figure 2. Catalysis by acetate of the reaction of 1 in acetate buffer solutions at 50 °C. Rate constants are adjusted for the proportion of 1 protonated at each pH: (○) pH 4.1; (●) pH 5.1.

value for K_a is not too much in error under reaction conditions is suggested by the agreement for results in two series of acetate buffers of different pH. The resulting plot is shown in Figure 2. Kinetic analysis in the acetate system is especially sensitive to the pK_a value because it is near the buffer pH. Analyses of the results for hydrolysis in buffers of lower pH are not as sensitive to the value for the pK_a of 1 because the substrate is nearly entirely protonated.

The results for all buffers are summarized in Table II. The value for the non-buffer-catalyzed water reaction was derived from the average of the intercepts at zero buffer concentration in the above plots of the other buffers. The variation among these values was rather large ($0.3–1.8 \times 10^{-4}$), but the average is consistent with the results of a kinetic study in dilute mineral acid.[5] The resulting rate constant for the water reaction was divided by the molarity of water to obtain the second-order rate constant.

The phosphate system requires special consideration, since more than one basic species will be present. Some catalytic activity was observed in the pH 4.3 phosphate system, which consisted of a solution of $H_2PO_4^-/HPO_4^{2-}$ in a ratio of 166:1. Although catalysis might be due to either species, or both, we observed no buffer catalysis at pH 2.1 in a solution consisting of dihydrogen phosphate and phosphoric acid. For this reason, it seems probable that the catalysis at pH 4.3 is due to the more basic monohydrogen phosphate, even though it is at much lower concentration. The catalytic rate constant for the phosphate buffer in Table II is based upon the concentrations of this species.

Table II. Second-Order Rate Constants for Buffer-Base-Catalyzed Hydrolysis of Protonated 4-Fluoroquinaldine at 50 °C

buffer base	pK_a	k_{SHB},[a] M^{-1} s^{-1}
HPO_4^{2-}	6.81[b]	1.1×10^{-1}
acetae	4.55[b]	6.2×10^{-3}
formate	3.66[b]	1.2×10^{-2}
chloroacetate	2.92[b]	7.6×10^{-4}
water	−1.74	1.6×10^{-6} [c]

[a] Second-order catalytic rate constants determined as the slopes of plots of pseudo-first-order rate constants divided by $[H^+]/([H^+] + K_{aSH})$ versus buffer base concentration. [b] Obtained at k0 °C under reaction conditions. [c] Determined as the average of the intercepts of plots such as Figure 2, divided by the molarity of water, 55.5 M.

A plot of the logarithmic catalytic constants vs the pK_a values of the buffers (those of the carboxylic acids were determined at 50 °C under the same reaction conditions as the hydrolyses) is shown in Figure 3. A good correlation is obtained, with the exception of formate, which deviates positively. We have found, as will be shown below, that catalysis by acetate is nucleophilic (Scheme I), as was also the case for the hydrolysis of 2. Since the other buffer bases may be expected to act similarly, the slope of this Brønsted-type plot, 0.57, is β_{Nu}. This slope is based on the Brønsted correlation of all bases excluding formate, as is illustrated in Figure 3, but because formate falls near the middle of the observed range of basicities, its inclusion has

(5) Muscio, O. J.; Meng, J. L., unpublished results in preparation.

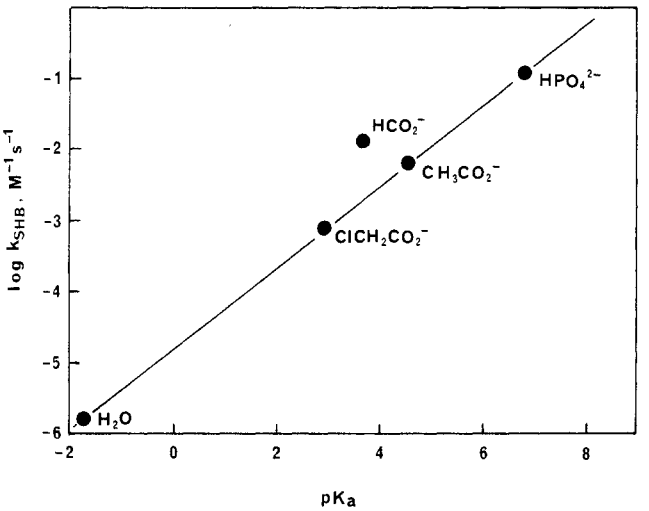
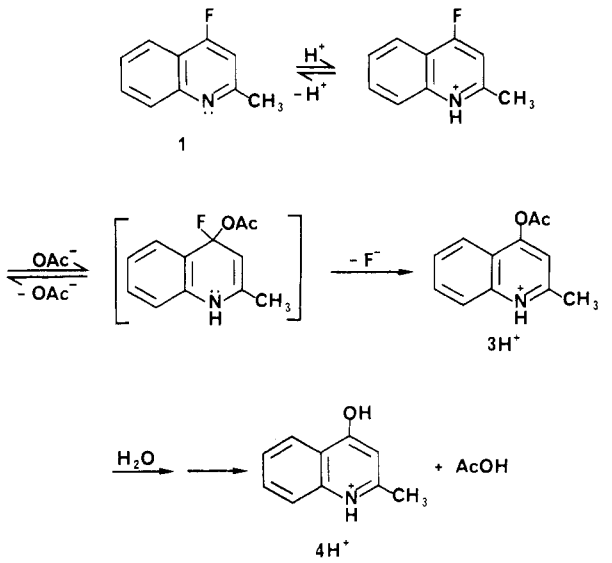


Figure 3. Brønsted plot for the buffer-base-catalyzed hydrolysis of 1 at 50 °C. Catalytic rate constants for buffer bases were obtained as the slopes of plots such as Figure 2. The point for formate was not included in the linear regression. The point for water was obtained from the average of the intercepts at zero buffer concentration of plots such as Figure 2, divided by the molarity of water (ca. 55 M).

Scheme I



little effect upon the slope, only shifting the intercept upward. Although this value for the Brønsted coefficient is less than that observed in the buffer-catalyzed hydrolyses of **2**,[1] it is still within the range (0.5–0.7) reported for nucleophilic substitution of activated aryl halides by oxyanions in hydroxylic solvent.[6]

It should be noted that no curvature is evident in Figure 3, even though one may expect some curvature in Brønsted plots for multistep nucleophilic substitutions as the pK_a values of the attacking nucleophiles increase and exceed that of the leaving group.[7] Such curvature may be attributed to a change in the rate-determining step. It has been demonstrated for certain amines and alkoxide ions that the rate of departure of a leaving group will be dependent upon its pK_a.[8] When this is the case, attack by the nucleophile may be rate-determining if it is strongly basic relative to the leaving group, while for nucleophiles less basic, departure of the leaving group from an intermediate formed in rapid equilibrium with the reactants will be rate-limiting. This was observed to be the case in reactions of a series of acetate esters with oxygen anion nucleophiles.[9]

Table III. Pseudo-First-Order Constants ($\times 10^{-3}$) for Buffer-Catalyzed Hydrolysis of 4-Acetoxyquinaldine at 50 °C

pH 4.1 acetate buffer		pH 5.1 acetate buffer	
M	k, s^{-1}	M	k, s^{-1}
–	–	0.042	3.6
0.031	5.0	0.031	3.1
0.020	3.9	0.021	2.6
0.010	2.9	0.010	2.0
0.005	2.4	–	–

In the case at hand, the pK_a of the fluoride leaving group is 3.1,[10] which is exceeded by the pK_a values of formate, acetate, and especially monohydrogen phosphate, while chloroacetate and water both have pK_a values below that of fluoride. However, the relationship is not clear-cut when the nucleophiles and leaving group have dissimilar structures,[11] which is the case here. When the structures are not similar, the pK_a at which the change will occur cannot be accurately predicted, and it may be that the buffers examined in this study do not fall within the pK_a range where curvature will occur. Alternatively, it may be that the electronic structures of the transition states for addition of the nucleophile and for departure of the leaving group are not sufficiently different in this case to lead to curvature. Taken to the limit, this leads to the possibility of concerted substitution.[12]

The reason for the positive deviation of formate is unclear. The deviation represents a catalytic activity approximately 8 times that expected from the Brønsted correlation of the other buffer systems. It seems unlikely that formate would react by a mechanism different from that followed by acetate and, presumably, chloroacetate. It may be possible that nucleophilic attack by formate is less sterically hindered than that of acetate or chloroacetate, but the effect seems large. No such effect was observed for formate relative to the other carboxylate bases in the hydrolysis of **2**, and it is not evident that the steric requirements for nucleophilic attack on **1** are so much more rigorous.

The proposed mechanism for nucleophilic catalysis is illustrated for acetate in Scheme I. No buldup of 4-acetoxyquinaldine (**3**), the postulated intermediate in this mechanism, was detected during the hydrolyses. For this mechanism to be valid, then, **3** must undergo hydrolysis under these reaction conditions faster than **1** itself. We have synthesized **3** and tested this requirement.

Kinetics of Hydrolysis of 3. The pseudo-first-order rate constants for the hydrolysis of acetate **3** are shown in Table III. As can be seen by comparison with the data for hydrolysis of **1** in Table I, **3** hydrolyzes faster than **1** at comparable acetate concentrations. Extrapolation of the data in Table III allows extension of the comparison to the higher buffer concentrations examined in the hydrolysis of **1**. Overall, we find that acetate **3** hydrolyzes

(6) Bordwell, F. G.; Hughes, D. L. *J. Am. Chem. Soc.* **1986**, *108*, 5991–5997.
(7) de Rossi, R. H.; Veglia, A. *J. Org. Chem.* **1983**, *48*, 1879–1883.
(8) Bernasconi, C. F.; Muller, M. C.; Schmid, P. *J. Org. Chem.* **1979**, *44*, 3189.
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(10) Broene, H. H.; DeVries, T. *J. Am. Chem. Soc.* **1947**, *69*, 1644–1652.
(11) Gold, V.; Oakenfull, D. G.; Riley, T. *J. Chem. Soc. B* **1968**, 515–519.
(12) Ba-Saif, S.; Luthra, A. K.; Williams, A. *J. Am. Chem. Soc.* **1987**, *109*, 6362–6368.

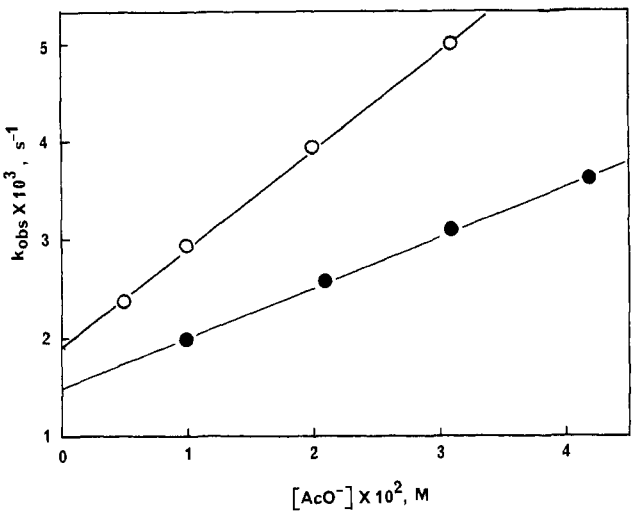


Figure 4. Pseudo-first-order rate constants vs concentration of acetate for the hydrolysis of **3** in acetate buffer solution at 50 °C: (○) pH 4.1; (●) pH 5.1.

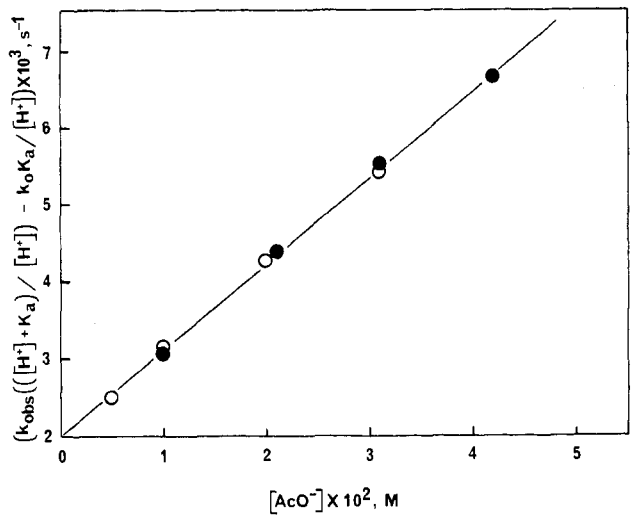


Figure 5. Fit of eq 3 to the pseudo-first-order rate constants for the hydrolysis of **3** in acetate buffers at 50 °C: (○) pH 4.1; (●) pH 5.1.

faster than the original fluoride substrate by factors of about 25 at pH 4.1 up to about 50 times faster at pH 5.1 at the lowest buffer concentration. The non-buffer-catalyzed water reaction of **3** is over 100 times faster than that of **1** at the higher pH. Thus, the necessary condition for catalysis of the hydrolysis of **1** by the acetate nucleophile is satisfied. The hydrolysis of **3** is sufficiently faster than that of **1** that the maximum concentration of **3** formed during the course of the reaction is negligible, and the rate constant determined by monitoring formation of **2** is essentially the same as that for disappearance of **1**.[13]

The hydrolysis of **3** is clearly catalyzed by the acetate buffer and, as was found for fluoride **1**, is acid-catalyzed, since reaction is faster at pH 4.1 than at 5.1 for a given acetate base concentration (Figure 4). We have not directly determined K_a for this compound because of its rapid hydrolysis and so cannot directly calculate the second-order rate constant for the buffer catalysis, which again presumably involves the protonated form of the substrate. However, K_a for **3** can be estimated from the relative slopes of the plots of observed rate constants vs acetate base concentration at the two different pH levels, assuming that the principal reactive form of **3** is its conjugate acid. A value of approximately 9.4×10^{-6} is obtained in this way.

The best fit of the observed rate constants is to the rate expression of eq 2, in which k_0 is the rate constant for non-buffer-catalyzed hydrolysis of the unprotonated substrate and k_{SH} is the rate constant for non-buffer-catalyzed hydrolysis of the substrate conjugate acid. Equation 2

$$k_{obsd} = k_0K_a/([H^+] + K_a) + k_{SH}[H^+]/([H^+] + K_a) + k_{SHB}[AcO^-][H^+]/([H^+] + K_a) \quad (2)$$

$$k_{obsd}(([H^+] + K_a)/[H^+]) - k_0K_a/[H^+] = k_{SH} + k_{SHB}[AcO^-] \quad (3)$$

was rearranged to eq 3 and the linear regression of $k_{obsd}(([H^+] + K_a)/[H^+]) - k_0K_a/[H^+]$ vs $[AcO^-]$ optimized by adjustment of K_a and k_0 until no further improvement in the correlation coefficient ($r = 0.9995$) could be obtained (Figure 5). This analysis also yielded a value of 9.4×10^{-6} for the acid dissociation constant of the conjugate acid of **3**, as well as $k_0 = 1.1 \times 10^{-3}$ s^{-1}, $k_{SH} = 2.0 \times 10^{-3}$ s^{-1}, and $k_{SHB} = 0.11$ M^{-1} s^{-1}. Because of the limited data available, these values must be considered tentative.

The relative magnitudes of the rate constants for non-buffer-catalyzed hydrolyses of **3** and its conjugate acid are of interest. It appears that the conjugate acid reacts only about twice as fast as the basic form. It might be expected that the conjugate acid would be much more reactive, as has been reported for *N*-acylimidazoles.[14] This is not always the case, as was shown in the hydrolysis of picrylimidazole,[15] for which the conjugate acid of the substrate underwent non-buffer-catalyzed hydrolysis only 8.5 times faster than the basic form, even though the positive charge in the imidazolium ion would be substantially delocalized onto the aryl-substituted nitrogen. In the present case the positive charge in the quinaldinium leaving group is remote from the acyl carbon of the acetoxy group, and delocalization of positive charge to the acetoxy-substituted ring carbon can be expected to be less important than the corresponding delocalization between nitrogens in the imidazolium ring.

Hydrolysis of **3** may involve nucleophilic addition at the aryl site or at the acyl carbon. The ^{18}O-labeling results reported below suggest that nucleophiles may add at either position, but hydrolysis results only from reaction at the acyl carbon.

^{18}O-Labeling Studies. The kinetic results are consistent with the proposed mechanism in which the buffer bases function as nucleophilic catalysts (Scheme I). However, an alternative in which they participate as general bases in a mechanism involving concerted proton transfer from nucleophilic water is also consistent.

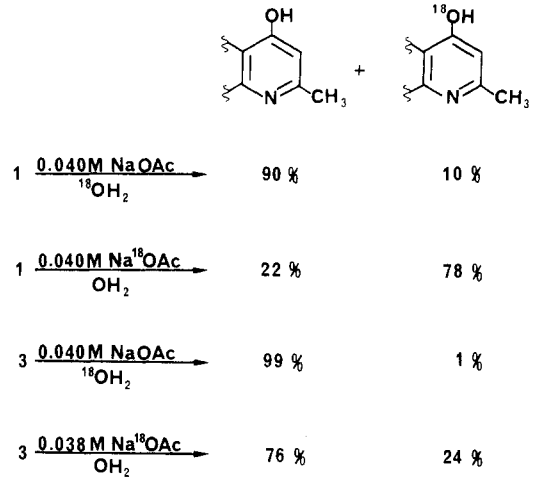
These two mechanisms can be distinguished through experiments in which **1** is hydrolyzed in the presence of either ^{18}O-labeled water or ^{18}O-labeled acetate. Since the oxygen found in the final product, 4-hydroxyquinaldine (**4**), must originate with either the water or the acetate, depending upon the mechanism, the degree of ^{18}O enrichment found in **4** should allow a clear determination of the mode of catalysis. The results of these experiments,

(13) Using the experimental rate constants for hydrolysis of **1** and **3** and the appropriate equations for consecutive, nonreversible reactions, we estimate that the maximum concentration of **3** during hydrolysis is no more than about 3% that of **1**, with a similar error in the observed pseudo-first-order rate constant for disappearance of **1** when the reaction is monitored by the formation of **2**.

(14) Fife, T. H.; Natrajan, R.; Werner, M. *J. Org. Chem.* **1987**, *52*, 740–746.

(15) de Rossi, R. H.; de Vargas, E. B. *J. Am. Chem. Soc.* **1981**, *103*, 1533–1540.

Scheme II



adjusted for the initial level of enrichment in the water or acetate, and for a small degree of exchange in the product under the reaction conditions, are summarized in Scheme II. We find that hydrolysis of 1 in ^{18}O-labeled water leads to only 10% enrichment in 4, while reaction in the presence of labeled acetate buffer results in 78% enrichment.

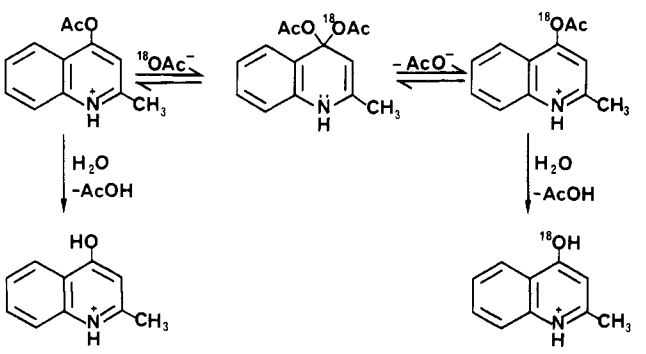
Although we expected these two experiments to yield results that would be the inverse of each other, there is an approximately 12% discrepancy between the two, which may be the result of a deficit in ^{18}O label in the products. A similar discrepancy was observed in the labeling experiments conducted in the hydrolysis of 2, and we think it likely that some exchange with natural oxygen may have occurred subsequent to hydrolysis, perhaps during GC–MS analysis.

These results may be compared to an analysis of the kinetics of the hydrolysis in acetate buffer at pH 4.1. Extrapolation to 0.040 M acetate gives $k_{obsd} = 2.44 \times 10^{-4}$ s^{-1}. Of this overall pseudo-first-order rate constant, approximately 0.50×10^{-4} s^{-1}, or 21% of the total reaction, should represent the non-buffer-catalyzed hydrolysis, as determined from the intercept at zero buffer concentration, while the remaining 79% can be attributed to acetate-catalyzed pathways. These figures are not strictly comparable with the results of the labeling experiments because the same ionic strength was not maintained in the latter, but it is clear that, with labeled acetate, two processes are important under these conditions: attack by water not catalyzed by acetate, and not leading to enrichment, and an acetate-catalyzed pathway involving nucleophilic attack by acetate and leading to enrichment. The same two pathways lead to the reverse results when the water is labeled and the acetate is not.

We have also examined the hydrolysis of intermediate acetate 3 with labeled water and acetate buffer. When 3 is hydrolyzed in ^{18}O-labeled water, the product is enriched only to the level of 1%, indicating that hydrolysis of 3 takes place by nucleophilic attack at the acyl carbon, not at the aryl site. As noted above, we have not determined whether the initial nucleophile in the acetate-catalyzed reaction is water, aided by acetate as a proton-transfer general base, or acetate, itself, as a nucleophilic catalyst.

Interestingly, when we hydrolyzed 3 in the presence of labeled acetate, 24% of the final product contained label (with the above corrections). This result can be understood as resulting from an exchange of acetate at the aryl site prior to hydrolysis and indicates that although hydrolysis of 3 takes place almost entirely at the acyl carbon, the acetate nucleophile also reversibly adds to the aryl carbon,

Scheme III



a reaction that is not observable except when the acetate is labeled (Scheme III).

Experimental Section

4-Fluoroquinaldine (1). 4-Aminoquinaldine (Aldrich, 98%) was purified by recrystallization from toluene. A solution of 4.6 g of sodium nitrite in 6 mL of water was added dropwise to a solution of 10.0 g (0.063 mol) of 4-aminoquinaldine in 60 mL of 48% fluoboric acid chilled in an acetone/dry ice bath to −10 °C. Upon completion of the addition, the mixture was allowed to stand for 5 min with continued cooling, and then the precipitate was collected by suction filtration on a prechilled Büchner funnel. The precipitate was washed twice with a cold 1:1 mixture of *n*-pentane and 2-propanol and then transferred to a beaker containing 150 mL of cold anhydrous diethyl ether, where it was allowed to warm to room temperature as the diazonium salt decomposed, liberating nitrogen. The mixture was transferred to a separatory funnel and made basic with 50% sodium hydroxide solution. The ether layer was separated and the aqueous layer extracted three times with a total of 300 mL of toluene. The combined organic fractions were dried, and the solvent was removed by rotary evaporation. The residue was taken up with pentane, leaving behind solid 4-hydroxyquinaldine. Evaporation of the pentane yielded 5.0 g (50% theoretical) of crude product as a brownish-red oil. Approximately 11 g of the crude product combined from several runs was distilled under vacuum to yield 4.1 g of pure 1 as a colorless oil, which freezes upon refrigeration, bp 58–64 °C (0.1 mmHg).

Anal. Calcd for $C_{10}H_8FN$: C, 74.52; H, 5.00; N, 8.69. Found: C, 74.12; H, 4.98; N, 8.76.

4-Acetoxyquinaldine (3). In 10 mL of dry methylene chloride were dissolved 0.50 g (3.1 mmol) of 4-hydroxyquinaldine and 0.42 g (4.2 mmol) of triethylamine. The resulting solution was cooled in an ice bath, and 0.33 g (4.2 mmol) of acetyl chloride was added with stirring. The reaction mixture was stirred in the ice bath for 2 h, washed with 10% $NaHCO_3$, and dried and the solvent removed by rotary evaporation. The residue was distilled under vacuum, yielding 0.40 g (61% theoretical) of clear, colorless product, bp 100–102 °C (0.2 mmHg).

Anal. Calcd for $C_{12}H_{11}NO_2$: C, 71.63; H, 5.51; N, 6.96. Found: C, 71.44; H, 5.52; N, 6.75.

pK_a of 1. The pK_a of 1 was determined spectrophotometrically at room temperature (23.5 °C) by using a Perkin-Elmer Lambda 3 spectrophotometer. To aliquots (1.0 mL) of a 0.010 M solution of 1 in ethanol were added incremental quantities of 5×10^{-4} M hydrochloric acid, and the resulting solutions were diluted with distilled water to a total volume of 50 mL. The pH of each solution was immediately determined with an Orion Research Model 601A pH meter using a glass electrode in combination with an SCE calibrated over the pH range 4.006–6.870. The experimental pH values covered the range 3.1–6.4. The absorbances for each solution at 270 and 310 nm were then determined. The first wavelength corresponds to an absorption maximum for 1, and the latter corresponds to that for its conjugate acid. The data for absorbances at each of these two wavelengths vs pH were fitted via an iterative routine to eq 4. Because 1 exists in essentially

$$A = A_{SH}([H^+]/([H^+] + K_a)) + A_S(K_a/([H^+] + K_a)) \quad (4)$$

a single form at the two pH extremes, the absorbances for unprotonated 1 at each of the two wavelengths and for its conjugate

acid at the same two wavelengths could be determined rather easily, and the value for K_a adjusted for the best fit. The results at the two wavelengths were in good agreement.

pK_a Values of Buffer Acids. pK_a for values for acetic, formic, chloroacetic, and phosphoric acids were determined under reaction conditions of 50 °C in 0.04 M solutions made at a constant 0.5 M ionic strength with sodium chloride. Aliquots of these solutions were titrated with 0.1 M KOH brought to a total ionic strength of 0.5 M with sodium chloride. The titrations were carried out by using an automatic titrator (Sargent-Welch Buret Master and Sargent-Welch Chemical Metering Dispenser) controlled by an Apple IIe computer equipped with a Cyborg Isaac 91a interface. The pH was monitored throughout each titration with an interfaced Orion SA 520 pH meter equipped with a glass electrode and calibrated at each end of the pH range covered. The pK_a was determined from the best fit to the experimental titration curve by software written for that purpose.

Kinetics. The methods used to follow the hydrolysis reactions of 1 and 3 are essentially the same as those described in the previous study,[1] except that spectrophotometric runs were monitored at 324 nm. The pH of each of the buffers was determined at 50 °C and an ionic strength of 0.5 M, which are the same conditions as the kinetic runs.

^{18}O-Label Studies. The reaction samples below were analyzed by GC–MS analysis as previously described.[1]

In order to examine the hydrolysis of 1 in ^{18}O-labeled water, we prepared acetate buffer by dissolving 2.7 mg of sodium acetate (0.033 mmol) and 5.2 μL of acetic acid (0.087 mmol) in 400 μL of labeled water (99% ^{18}O, Stohler Isotopes), giving a solution 0.08 M in acetate. A stock solution of substrate was prepared by adding 0.6 μL of 1 to 120 μL of labeled water (did not dissolve) and then adding 120 μL of the acetate buffer solution (1 dissolved). Aliquots (60 μL) of the resulting solution were placed in tubes, which were sealed with rubber septa and heated at 50 °C overnight. MS analysis of these aliquots indicated an enrichment of 12% when the natural abundance of heavy isotopes (0.8%) was subtracted. A sample of 4-hydroxyquinaldine was treated similarly and was found to incorporate about 2% ^{18}O. Subtraction of this value for exchange within the hydrolysis product gives 10% for the ^{18}O incorporation occurring during hydrolysis of 1. A similar value of 9% was obtained by using 90% ^{18}O-labeled water and dividing the observed enrichment by 0.9 to adjust for the lower level of enrichment in the water.

The hydrolysis of 2 was similarly examined in 90% ^{18}O-labeled water and, after the same corrections noted above, was found to incorporate only about 1–2% ^{18}O during reaction.

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^{1}H and ^{13}C Nuclear Magnetic Resonance Reinvestigation of the Dibenzo[*a*,*c*]cyclononatetraenyl Anion and Its 5,9-Diphenyl Derivative. Planarity vs Nonplanarity

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It is found that the dibenzo[*a*,*c*]cyclononatetraenyl anion is readily transformed into the stable 1*H*-cyclopenta[*l*]phenanthren-1-yl anion. Earlier reported NMR data of this compound were incorrectly assigned to a planar structure of the dibenzocyclononatetraenyl anion. The nonplanarity of the initially formed nine-membered ring anion was confirmed both experimentally and theoretically. The ring-closure process does not take place in the anion of the 5,9-diphenyl derivative, which retains a nonplanar conformation of the nine-membered ring.

Introduction

Cyclononatetraenyl anions form a class of compounds that have received considerable attention with respect to the relation between aromaticity and conformation.[1-5] While for instance neutral cyclononatetraene is found to be relatively unstable,[1c,d,6] various cyclononatetraenyl anions which constitute Hückel $4n + 2$ π systems tend to exhibit some degree of extra stability.[1-4] The cyclononatetraenyl (1^-) and the benzocyclononatetraenyl (2^-) anions can exist in an all-cis and a mono-trans form, both having some aromatic character[1,2] (Scheme I). For the monocyclic 1^-, the all-cis structure is found to be the more stable, while the mono-trans form is favored for 2^-. The barrier for isomerization from *mono-trans*-1^- to *all-cis*-1^- is appreciable: 29–34 kcal/mol. The cyclononabiphenylene anion (3^-) seems to prefer exclusively a nonplanar geometry,

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