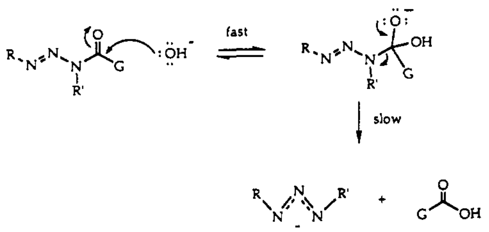
Scheme VI



1-aryltriazenes, for example, give a $k_{\mathrm{EtOH}}/k_{\mathrm{EtOD}}$ of 2.2.[3] There have been reports, however, of specific base catalysis in the hydrolysis of esters and amides.[17]

A deacylation mechanism consistent with specific base catalysis is shown in Scheme VI. It involves rapid reversible attack by hydroxide ion on the carbonyl carbon followed by rate determining heterolysis of the N(3)–acyl bond. This results in the formation of the triazenyl anion, which subsequently can either abstract a proton from solvent or, in the case of the chloroethyltriazenes, cyclize to 1-methyltriazoline. In each of the 3-acyl series, as the substituent on N(1) is varied, the value of $k_{\mathrm{OH^-}}$ follows the order: 2-chloroethyl >2-hydroxyethyl > methyl (Table IV). This observation is consistent with inductive electron withdrawal leading to stabilization of both the anionic tetrahedral intermediate, I, as well as the triazenyl anion, II.

The base-promoted dehydrohalogenation of CMM gives a $k_{\mathrm{H_2O}}/k_{\mathrm{D_2O}}$ of 0.42. This observation suggests an $(\mathrm{E1cB})_{\mathrm{R}}$ mechanism, rapid reversible proton removal followed by rate-limiting loss of chloride. Resonance stabilization of the anion by the adjacent triazene moiety may be responsible for the E1cB type mechanism.

The present work completes the general picture of the hydrolysis of 1,3-dialkyl-3-acyltriazenes in aqueous buffers. Three distinct mechanisms are observed, depending upon the pH of the medium. In acidic solutions, a specific acid-catalyzed pathway dominates. At near-neutral pH, decomposition is by an uncatalyzed route. In both of these mechanisms the same general mechanistic pattern is followed, heterolysis of the N(2)–N(3) bond to generate an alkyldiazonium ion derived solely from the N(1) alkyl group. Hydrolysis in alkaline solutions proceeds by a specific base-catalyzed pathway, which involves initial deacylation and results in the production of the parent 1,3-dialkyltriazene. Subsequent hydrolysis of this triazene can lead to the competitive formation of alkyldiazonium ions from both the N(1) and N(3) alkyl groups.

It has been shown that 1,3-dialkyl-3-acyltriazenes are potent biological alkylating agents[18] possessing significant antineoplastic properties.[19] The present work demonstrates that the specific mechanism by which these triazenes decompose dramatically influences the nature of the alkylating agent produced. This difference will have a profound influence on the interaction of 1,3-dialkyl-3-acyltriazenes with cellular constituents, particularly DNA.

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Supplementary Material Available: Copies of supporting ^{1}H NMR spectra (6 pages). This material is contained in many libraries on microfiche, immediately follows this article in the microfilm version of the journal, and can be ordered from the ACS; see any current masthead page for ordering information.

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Hydrolyses of 2- and 4-Fluoro N-Heterocycles. 4.[1] Proton Inventories of the Hydrolyses of 2-Fluoro-1-methylpyridinium Iodide, 4-Fluoroquinaldine, and 2-Chloro-1-methylpyrimidinium Triflate

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Rate constants for the hydrolyses of 2-fluoro-1-methylpyridinium iodide (3), 4-fluoroquinaldine (4), and 2-chloro-1-methylpyrimidinium triflate (5) in 2×10^{-3} M aqueous sulfuric acid, in D_2O/D_2SO_4, and in mixed H_2O/H_2SO_4–D_2O/D_2SO_4 media are reported. Significant solvent deuterium kinetic isotope effects are evident, with k_H/k_D = 2.07 for 3, 1.62 for 4, and 2.12 for 5. The results of the proton inventories for the hydrolyses of 3 and 5 are best fit by a form of the Gross–Butler equation for three nearly equivalent sites with fractionation factors of 0.78. The proton inventory of 4 does not yield a unique solution to the Gross–Butler equation, but the results are also consistent with three transition state sites with nearly equal fractionation factors of 0.72–0.78, as well as an additional transition-state site with $\phi > 1$ and a reactant site with $\phi \le 1$. These proton inventories are consistent with mechanisms in which nucleophilic addition of water in the rate-determining step is assisted by proton-transfer to a second water molecule, with development of an "immature hydronium ion" in the transition state. Mechanisms with cyclic proton transfer are also consistent, but are less satisfactory as hydrolysis routes.

In an earlier report[2] on the acid-catalyzed hydrolyses of 2-fluoropyridine (1) and 2-fluoropyrimidine (2), as well as several other related fluoropyridines and pyrimidines in hydrochloric acid solutions of up to 6 M concentration,

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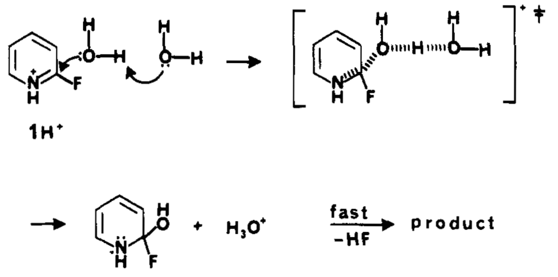
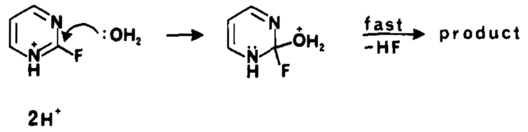
Scheme I



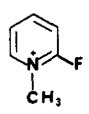
Scheme II

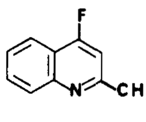


evidence was presented that the mechanisms for hydrolysis of these two classes of compounds differ in the role played by water. For the hydrolysis of the 2-fluoropyridines, attack by nucleophilic water upon the conjugate acids of the substrates appeared to be aided by at least one additional water molecule, functioning as a base in a proton-transfer role (Scheme I). In contrast, the evidence suggested that proton-transfer was not important in the hydrolysis of the 2-fluoropyrimidines, with a single water molecule functioning as the nucleophile without general base assistance (Scheme II). An examination of the hydrolyses of these and related compounds has been continued in an effort to more fully delineate the modes of catalysis.

A determination of solvent deuterium kinetic isotope effects through a proton inventory seemed the best approach for distinguishing the reactions paths suggested for 1 and 2. However, because these compounds are weakly basic, and their hydrolyses are acid-catalyzed, rather high acid concentrations were required for reaction, and even then 2, in particular, was not completely protonated. Since the deuterated aqueous acid had a higher effective acidity than the nondeuterated solution of equal concentration, this complicated efforts to carry out a proton inventory, although the solvent kinetic isotope effects were generally in the directions anticipated based upon the proposed mechanisms.[3]

These complications have been avoided in the hydrolyses of 2-fluoro-1-methylpyridinium iodide (3), which is not basic and not subject to acid catalysis, and of 4-fluoroquinaldine (4), which is sufficiently basic that it is essentially completely protonated even in relatively dilute mineral acid solutions. The hydrolyses of these compounds in aqueous carboxylic acid buffer solutions were found to be promoted by the buffer bases through nucleophilic catalysis.[1,4]


3


4

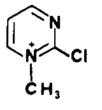

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Table I. First-Order Rate Constants ($k \times 10^4$, s^{-1}) for Hydrolysis of 3, 4, and 5 in Dilute Sulfuric Acid[a]

	T (°C)					
compd	45.0	50.0	55.0	60.0	65.0	70.0
3			1.93	2.92	4.52	6.67
4			1.04	1.69	2.81	3.66
5	12.9	19.1	29.0	44.7		

[a] In 1.88 M H_2SO_4, ionic strength held at 0.5 M with NaCl. The hydrolysis of 4 is acid catalyzed, but 4 is essentially completely protonated in this solution ($pK_a = 1.23 \times 10^{-5}$),[1] and its rate of hydrolysis is not dependent upon acid concentration in this region. Hydrolyses of 3 and 5 are not acid-catalyzed, and rates are also independent of acid concentration.

The results of proton inventories of the hydrolyses in the absence of carboxylate buffers of these compounds, as well as that of 2-chloro-1-methylpyrimidinium triflate (5), are now reported.

Results and Discussion

Kinetics of Hydrolysis in Dilute Sulfuric Acid. Hydrolyses of 3, 4, and 5 were carried out in 1.88×10^{-3} M aqueous sulfuric acid solutions held at ionic strength of 0.5 M with sodium chloride or in comparable deuterated media. Compound 4 has been shown to undergo acid-catalyzed hydrolysis through equilibrium protonation and to have an acid dissociation constant for its conjugate acid of 1.23×10^{-5}.[1] At the sulfuric acid concentrations used in the present study, the substrate is over 99% protonated, and the reaction rate was not sensitive to moderate changes in the acid concentration. Likewise, the hydrolysis of 3 has been shown not to be subject to acid-catalysis,[4] and its rate was insensitive to acid concentrations in this range, as was that of 5. Under these conditions, first-order kinetics were observed for 2 or 3 half-lives, although a slow drift in absorbance was noted at long reaction times, making necessary estimation of A_∞ by the method of Schwartz and Gelb,[5] as noted previously.[4]

The pseudo-first-order rate constants for hydrolysis of 3, 4, and 5 over a range of temperatures are shown in Table I. From these rate constants can be calculated the activation parameters $\Delta H^\ddagger = +18.0$ kcal/mol and $\Delta S^\ddagger = -20.8$ eu for 3, $\Delta H^\ddagger = +18.6$ kcal/mol and $\Delta S^\ddagger = -20.2$ eu for 4, and $\Delta H^\ddagger = 16.9$ kcal/mol and $\Delta S^\ddagger = -18.9$ eu for 5. These values for the entropies of activation are similar to those for the hydrolyses of 1 and related compounds in strongly acidic solution.[2] The latter were based on the intercepts of Bunnett–Olsen LFER plots[6] which yield second-order rate constants for the protonated substrates. This similarity in entropies of activation suggests that these compounds react by similar mechanisms. 2-Fluoropyrimidine (2), on the other hand, showed a significantly less negative entropy of activation, again based upon rate constants calculated through the Bunnett–Olsen LFER. This difference in entropy of activation was interpreted as being consistent with a mechanism not involving proton transfer in the rate-determining step.

Solvent Deuterium Kinetic Isotope Effects. Proton inventories for the hydrolyses of 3, 4, and 5 were carried out through determination of rate constants in mixtures of H_2O/H_2SO_4 and D_2O/D_2SO_4 of atom fraction deuterium (n) ranging from 0 to 1.[7] The results are shown in Tables

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[1] For the previous paper, see: Muscio, O. J., Jr.; Theobald, P. G.; Rutherford, D. R. *J. Org. Chem.* **1989**, *54*, 166–171.

[2] Clark, H. R.; Beth, L. D.; Burton, R. M.; Garrett, D. L.; Miller, A. L.; Muscio, O. J., Jr. *J. Org. Chem.* **1981**, *46*, 4363–4369.

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[5] Schwartz, L. M.; Gelb, R. I. *Anal. Chem.* **1978**, *50*, 1592–1594.

[6] Bunnett, J. F.; Olsen, F. P. *Can. J. Chem.* **1966**, *44*, 1917.

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Table II. First-Order Rate Constants for Hydrolysis of 1-Methyl-2-fluoropyridinium Iodide (3) at 65 °C in 2 × 10^{-3} M Sulfuric Acid of Atom Fraction of Deuterium (n)[a]

n[b]	no. of runs	$10^4 k_n$, s^{-1}, obsd	$10^4 k_n$, s^{-1}, calcd	
			eq 2[c]	eq 4[d]
0.000	5	4.46 ± 0.02[e]	4.46	4.46
0.249	3	3.76 ± 0.05	3.76	3.78
0.499	3	3.11 ± 0.03	3.14	3.16
0.749	7	2.56 ± 0.05	2.58	2.59
0.999	8	2.15 ± 0.06	2.12	2.08

[a] Ionic strength held at 0.5 M with NaCl. [b] Atom fraction of deuterium determined by NMR using standard addition method. [c] Three equivalent protons with $\phi = 0.778$; rms deviation of calculated rate constants from observed = 0.0264. [d] Two equivalent protons with $\phi = 0.683$; rms deviation of calculated rate constants from observed = 0.0414. [e] Error limits are standard deviations.

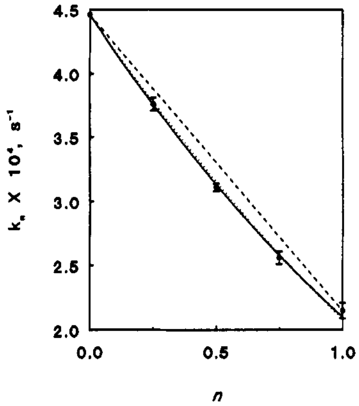

Figure 1. Proton inventory plot of the first-order rate constants, k_n, for the hydrolysis of 3 at 65 °C in 2 × 10^{-3} M aqueous sulfuric acid as a function of the atom fraction of deuterium (n) in the solvent. The data are taken from Table II. The solid line is calculated from eq 2, with $\phi^* = 0.778$. The dotted line was calculated from eq 4, with $\phi^* = 0.683$. The dashed straight line is drawn to emphasize the curvature.

II–IV. Significant solvent deuterium kinetic isotope effects are evident, with $k_H/k_D = 2.07$ for 3, 1.62 for 4, and 2.12 for 5. Solvent kinetic isotope effects of 2–3 are typically observed in reactions involving a proton-transfer in the rate-limiting step.[7,8]

Proton Inventory of the Hydrolysis of 3. The proton-inventory rate constants for hydrolysis of 3 are shown in Table II and plotted versus atom fraction of deuterium in Figure 1. The plot is clearly bowed downward, indicating contributions by more than one proton to the observed isotope effects. These results can be analyzed by the Gross–Butler equation,[7] which, since there are no reactant-state exchangeable protons other than those of the solvent, takes the form of eq 1.

$$k_n = k_0 \prod_{i}^{\mathrm{TS}} (1 - n + n\phi_i) \qquad (1)$$

To determine the minimum number of active protons, the data were fit to polynomials of increasing order as described by Schowen.[9] The quadratic term was significant at the 99% confidence level, and the cubic term was significant at the 99.5% confidence level. Higher order terms were not testable with only five data pairs to fit. Thus, at least three active sites are indicated. The simplest resulting form of the Gross–Butler equation is eq 2:

$$k_n = k_0(1 - n + n\phi^*)^3 \qquad (2)$$

The proton inventory data for 3 were fit to this equation by means of a nonlinear least-squares fitting routine yielding a fractionation factor of 0.778 (sum of squares of the residuals = 3.54 × 10^{-3}). The solid curve of Figure 1 was calculated with this value and eq 2. Models in which the three protons are not all equivalent, as might be anticipated in mechanisms such as that in Scheme I, in which the in-flight proton would be expected to exhibit a fractionation factor near 0.5,[7,10-12] were also examined. The appropriate form of the Gross–Butler equation for this mechanism is shown as eq 3.

$$k_n = k_0(1 - n + n\phi_a)(1 - n + n\phi_b)^2 \qquad (3)$$

The greater the difference between values of ϕ_a and ϕ_b the less well the experimental data was fit. The fit became rather poor for values of ϕ_a less than 0.65. For example, for $\phi_a = 0.60$, the best fit of eq 3 to the data gave $\phi_b = 0.88$ with a sum of squares = 8.84 × 10^{-3} and for $\phi_a = 0.50$, $\phi_b = 0.95$, sum of squares = 26.0 × 10^{-3}. Although marginally better fits can be obtained from models with increasing numbers of equivalent protons, such as five and seven protons (giving $\phi \approx 0.85$ and 0.89), the precision of the data is not sufficient to justify this extension to what would amount to a medium effect.

Although the polynomial test indicated three or more active sites, we also examined models with two active sites. The appropriate form of the Gross–Butler equation is eq 4.

$$k_n = k_0(1 - n + n\phi^*)^2 \qquad (4)$$

This equation was fit to the experimental data by nonlinear least-squares regression, but the fit was less satisfactory (sum of squares = 8.81 × 10^{-3}) than that obtained from the three equivalent protons model (Table II). Furthermore, the transition-state fractionation factor obtained from this model, 0.683, is almost identical to that of a full-fledged hydronium ion (0.69). The otherwise reasonable mechanistic model of a single water molecule making an unassisted nucleophilic attack on 3 would require that C–O bond formation be essentially 100% complete in the transition state of the rate-determining step.

There are at least two mechanisms nominally consistent with this result. In the first model, the rate-determining step is unassisted addition of water with a late transition state resembling the final adduct in a reaction similar to that illustrated for the acid-catalyzed hydrolysis of 2 in Scheme II. Other nucleophilic substitution reactions of 3 and its chloro analogue are known in which it is likely that the rate-determining step is addition of the nucleophile. The aminolysis of the 2-chloro-1-methylpyridinium salt by primary amines was reported to follow a Brønsted relationship with $\beta_{\mathrm{nuc}} = 0.66$.[13] More directly relevant is the observation that the carboxylate buffer catalyzed hydrolysis of 3, which takes place by nucleophilic catalysis, follows a Brønsted relationship with $\beta_{\mathrm{nuc}} = 0.66$ for nucleophilic attack by the carboxylate bases.[4] Significantly, the point for the noncatalyzed water reaction falls on the line of this Brønsted plot. Application of the value of β_{nuc} to the water reaction allows its use in estimation of fractionation factors. For nonassisted addition of water, the

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(8) Ehrhardt, R. L.; Gopalakrishnan, G.; Hogg, J. L. *J. Org. Chem.* **1983**, *48*, 1586–1590.

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(13) Brenelli, E. C. S.; Moran, P. J. S. *J. Chem. Soc., Perkin Trans. 2* **1989**, 1219–1222.

transition state will be intermediate between the reactant state, water ($\phi = 1$), and the product state, which will resemble a hydronium ion with $\phi = 0.69$. If β_{nuc} is a measure of the degree of bond formation in the transition state, the fractionation factor for the protons on the nucleophilic water in the transition state can be estimated from eq 5.[14] This yields $\phi^* = (0.69)^{0.66} = 0.783$. An even

$$\phi^* = (\phi^{\text{RS}})^{1-\beta}(\phi^{\text{PS}})^{\beta} \qquad (5)$$

higher value of 0.92 for ϕ^* has been reported for the transition-state protons of a single water molecule making an unassisted nucleophilic addition in the hydrolysis of 1-acetyl-3-methylimidazolium ion in acetonitrile.[15] The associated solvent kinetic isotope effect was 1.17 under these conditions, in which water was a dilute solute in the acetonitrile.

Values of $\phi^* = 0.78$ or more in conjunction with eq 4 do not reproduce either the observed solvent isotope effect of 2.07 or the proton inventory data reported here for the hydrolysis of **3**, which require $\phi^* = 0.68$ to fit the two proton model. However, the value $\phi^* = 0.783$ calculated above from the Brønsted slope for hydrolysis fits quite well with a three-proton model, as will be discussed below.

The second mechanism that might yield a two proton model with $\phi \approx 0.68$ is similar to the first, except that the rate-limiting step is postulated to be departure of the fluoride from the initial, hydronium ion-like intermediate. In this context, kinetic experiments in our laboratory for the aminolysis of **3** by substituted anilines may be significant. A Brønsted slope of 1.13 suggests that the positive charge on the anilinium nitrogen is fully developed in the transition state of the rate-determining step, which, consequently, may be fluoride departure.[16] However, it is important to note that the point for water does not fit the Brønsted correlation for the anilines, with the second-order rate constant for hydrolysis lying more than 1.2 log units above the line. Since the transition state for addition of water without proton transfer would be considerably more acidic than that for addition of aniline, it is doubtful that these results for aminolysis of **3** translate to its hydrolysis. It is likely that an intermediate resulting from unassisted addition by water, similar to that illustrated in Scheme II, would undergo proton transfer to another water in the surrounding solvent shell at close to diffusion-limited rate, forming a hydronium ion and a neutral intermediate that should rapidly eliminate fluoride. This model generates a true hydronium ion in which there would be *three* protons with $\phi = 0.69$ and does not reproduce the data.

The proton inventory data for the hydrolysis of **3** are most consistent, then, with a model in which three protons have roughly equal transition-state fractionation factors of $\phi_a \approx \phi_b \approx 0.78$. As noted above, this value is consistent with the Brønsted slope of 0.66, which then would correspond to the degree of proton transfer to the developing hydronium ion. This result is similar to that of a study of the water-catalyzed hydrolysis of the dimethylimmonium ion of benzophenone, in which the proton inventory was interpreted as indicating three equal transition-state fractionation factors of 0.768.[17] An "immature hydronium ion" was proposed for the transition state of the rate-determining step on the basis of this proton inventory.

Scheme III

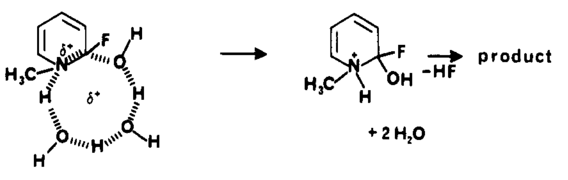

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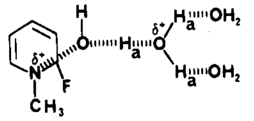
Table III. First-Order Rate Constants for Hydrolysis of 1-Methyl-2-chloropyrimidinium Triflate (5) at 55 °C in 2 × 10^{-3} M Sulfuric Acid of Atom Fraction of Deuterium (n)[a]

			$10^4\ k_n$, s^{-1}, calcd	
n[b]	no. of runs	$10^4\ k_n$, s^{-1} obsd	eq 3[c]	eq 4[d]
0.000	5	2.90 ± 0.03[e]	2.90	2.90
0.249	5	2.45 ± 0.02	2.44	2.45
0.499	9	2.01 ± 0.03	2.03	2.04
0.749	5	1.66 ± 0.005	1.67	1.67
0.999	5	1.37 ± 0.007	1.35	1.34

[a] Ionic strength held at 0.5 M with NaCl. [b] Atom fraction of deuterium determined by NMR using standard addition method. [c] $\phi_a = 0.775$, $\phi_b = 0.776$; rms deviation of calculated rate constants from observed = 0.0115. [d] Two equivalent protons with $\phi = 0.679$; rms deviation of calculated rate constants from observed = 0.0201. [e] Error limits are standard deviations.

As a result of proton inventory studies in mixed aqueous media, this initial interpretation of a proton transfer to water giving a hydronium ion has recently been revised[18] to one in which a cyclic proton transfer during nucleophilic attack results in addition of water across the C=N$^+$ bond. The corresponding transition state for **3** is shown in Scheme III, in which transition state **6** leads to cationic intermediate **7**. This does not seem an attractive mechanism for the hydrolysis of **3** because the nitrogen must now be deprotonated to allow departure of the fluoride leaving group, which, as will be seen, leads ultimately to the same intermediate formed more directly by a mechanism similar to that in Scheme I.

The proton inventory data for the hydrolysis of **3** clearly indicates fractionation at multiple transition-state sites. Transition state **8** is the most straightforward representation consistent with the data. It is similar to that shown in Scheme I, except that the proton being transferred has become essentially equivalent to the other two protons on the oxygen to which it has been transferred. This implies the possibility of consecutive transition states in which proton transfer is uncoupled from heavy atom motion.[17,19]



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Proton Inventory of the Hydrolysis of 5. Rate constants for the proton inventory of hydrolysis of **5** at 55 °C were obtained in somewhat greater precision (Table III) than those of **3** and **4** and are displayed graphically in Figure 2. Again, the proton inventory plot is bowed downward, as was that for **3**. When the data were fitted to polynomial equations of increasing order, the quadratic term was found to be significant at the 99% confidence level, but the cubic term was not significant at the 90% level, although the cubic expression did give a better fit (sum of squares of the residuals = 1.69×10^{-4} vs 4.43 ×

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(14) Schowen, R. L. *Prog. Phys. Org. Chem.* **1972**, 275.

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10^{-4} for the quadratic expression). The number of active sites and the corresponding fractionation factors can also be evaluated by Albery's "gamma method"[20] where the curvature parameter γ is defined by eq 6.

$$\gamma = 8 \ln [(k_{0.5}/k_0)/(k_1/k_0)^{1/2}]/[\ln (k_1/k_0)^2] \qquad (6)$$

The γ value calculated from the proton inventory data for **5** is 0.119 ± 0.241. The value for γ is 0.360 or less. (Negative values, which require fractionating reactant sites, are excluded since there are no reactant sites other than those of water, for which $\phi = 1.0$.) Since $1/\gamma = 2.77$ can be related to the minimum number of active sites required for the curvature of the proton inventory plot,[20] three or more sites are required. Although this could be consistent with a medium effect, a nonlinear least-squares fit of eq 3 to the data for **5** gives a relatively good fit, with $\phi_a = 0.775$ and $\phi_b = 0.776$ (sum of squares = 8.64×10^{-4}). A fit of the data to the two-proton eq 4, as expected from the value of γ, gives a poorer fit, $\phi = 0.679$ (sum of squares = 24.5×10^{-4}). It could be argued that the additional activation of the pyrimidinium ion by two aza nitrogens and the change in leaving group from fluoride to chloride might result in a larger β_{nuc} for **5** than that observed for **3**, which would make the two-proton unassisted attack model more plausible for **5** than it is for **3**. We do not have available a value of β_{nuc} for the hydrolysis of **5** that would allow us to distinguish clearly between these models. However, in view of the close similarity of the activation parameters and isotope effects for hydrolysis of **3** and **5**, it is likely that they react by similar mechanisms. Accordingly, the transition state most consistent with these results is the pyrimidinium analogue of **8**.

Proton Inventory of the Acid-Catalyzed Hydrolysis of 4. Rate constants for the hydrolysis of **4** in dilute sulfuric acid of various protium oxide–deuterium oxide mixtures are presented in Table IV, and the resulting proton inventory plot shown in Figure 3. Despite efforts to reduce the uncertainty through repeated runs, the rate constants are not known as precisely as are those for hydrolysis of **3** or **5**, which greatly limits the usefulness of the data, but it is clear that the curve does not bow downward, and may, indeed, bow upward. This is likely the result of an inverse isotope effect at one fractionation site. A good candidate for this site, not present in either **3** or **5**, is the proton on nitrogen in the conjugate acid of **4**, which is the species that actually reacts with water in this acid-catalyzed reaction.

A form of the Gross–Butler equation that may be appropriate is shown in eq 7, in which the three transition state sites of eq 2 (ϕ_b) are assumed, as well as an additional fractionation site in the reactant (ϕ_c) and transition (ϕ_a) states.

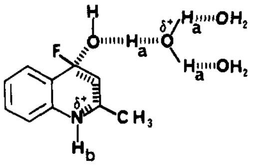
$$k_n = k_0(1 - n + n\phi_a)(1 - n + n\phi_b)^3/(1 - n + n\phi_c) \qquad (7)$$

Because of the degree of uncertainty in the rate constants, no unique best fit to the data is useful, but values of 1.40, 0.749, and 0.95 for ϕ_a, ϕ_b, and ϕ_c, respectively, generate a reasonably good fit (sum of squares = 1.86×10^{-3}), as shown by the solid line in Figure 2.

The values, themselves, are not unreasonable. The value of 0.762 attributable to an immature hydronium ion is similar to that determined for the hydrolysis of **3**. The other transition-state fractionation factor, $\phi_a = 1.40$, seems somewhat large. An exact model for the transition-state quinalidinium nitrogen is not available, but as a nucleophile adds to the adjacent carbon, the positive charge on the nitrogen decreases. Consequently, secondary amines may be reasonable rough models for a late transition state. As determined by ^{13}C NMR, a fractionation factor of 1.31 ± 0.09 has been reported[21] for diethylamine, and 1.43 ± 0.05 for pyrrolidine. A value of 1.0 for ϕ_c is about what would be expected for the proton on the quinaldinium conjugate acid reactant.

At the other end of the scale, values of 1.30, 0.784, and 1.00 for ϕ_a, ϕ_b, and ϕ_c, respectively, which include values of ϕ_a and ϕ_c closer to that which might be expected in this system, give a fair fit to the data (sum of squares = 3.88×10^{-3}), generating a curve that is near the dashed straight line of Figure 2. The value of 0.784 for ϕ_b is close to the value of 0.809 that can be calculated with eq 5 from the Brønsted slope $\beta_{\text{nuc}} = 0.57$ for the buffer-catalyzed hydrolysis of **4**, which includes the point for water reaction.[1] A fit essentially indistinguishable from that above is obtained from a model in which two transition-state protons have fractionation factors of 0.809, with the third having a fractionation factor of 0.735. Finally, a three-site hydronium model for unassisted addition of water also yields a reasonable fit with $\phi_a = 1.3$, $\phi_b = 0.69$ (two protons), and $\phi_c = 1.0$ (sum of squares = 2.12×10^{-3}).[22]

Because of the degree of uncertainty in the rate constants for hydrolysis of **4**, there is really no statistical justification for preferring any of the above proton inventory models. However, the results are at least consistent with transition-state structure **9**, which is similar to **8**, except for a catalytic proton on nitrogen. The three-site model for unassisted addition of water to give a hydronium ion-like transition state, although consistent with the kinetic data, is not consistent with the most likely models for the hydrolyses of **3** and **5**. In view of the similarity of structures of **3**, **4**, and **5**, and the similarity of the activation parameters for their hydrolyses, it is likely that they all react by the same mechanism.



9

Conclusions

Although the precision of the rate constants for hydrolysis of **3**, **4**, and **5** in mixed protium oxide–deuterium oxide vary, the resulting proton inventories are all consistent with transition states involving proton transfer from the nucleophilic water molecule. The best fit to the data, and the most likely mechanism, is one in which proton transfer results in formation of an immature hydronium ion in the rate limiting transition states, or equivalent "virtual transition states"[23] for consecutive steps. Although transition states involving cyclic proton transfer are also consistent with the proton inventory results, such proton transfer does not provide an attractive pathway for displacement of the halogen, especially in the hydrolysis of **4**, in which the site of nucleophilic attack is far removed from the quinaldinium nitrogen. Finally, a mechanism in

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[23] Schowen, R. L. In *Transition States of Biochemical Processes*; Gandour, R. D., Schowen, R. L., Eds.; Plenum Press: New York, 1978; pp 109–111.

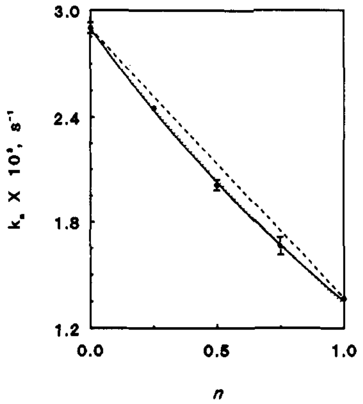

Figure 2. Proton inventory plot of the first-order rate constants, k_n, for the hydrolysis of **5** at 55 °C in 2×10^{-3} M aqueous sulfuric acid as a function of the atom fraction of deuterium (n) in the solvent. The data are taken from Table III. The solid line is calculated from eq 3, with $\phi_a = 0.775$ and $\phi_b = 0.776$. The dotted line was calculated from eq 4, with $\phi^* = 0.679$. The dashed straight line is drawn to emphasize the curvature.

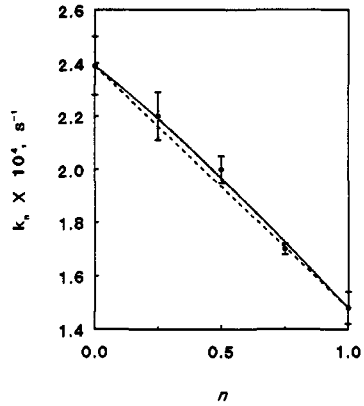

Figure 3. Proton inventory plot of the first-order rate constants, k_n, for the hydrolysis of **4** at 65 °C in 2×10^{-3} M aqueous sulfuric acid as a function of the atom fraction of deuterium (n) in the solvent. The data are taken from Table IV. The solid line is calculated from eq 4 and $\phi_a = 0.749$, $\phi_b = 1.40$, and $\phi_c = 0.95$. The dashed straight line is drawn to emphasize the curvature.

Table IV. First-Order Rate Constants for Hydrolysis of 4-Fluoroquinaldine (4) at 65 °C in 2×10^{-3} M Sulfuric Acid of Atom Fraction of Deuterium (n)[a]

			$10^4\ k_n$, s^{-1}, calcd	
n[b]	no. of runs	$10^4\ k_n$, s^{-1}, obsd	eq 7[c]	eq 7[d]
0.000	19	2.39 ± 0.11	2.39	2.39
0.249	7	2.20 ± 0.09	2.19	2.18
0.499	16	2.00 ± 0.05	1.97	1.95
0.749	17	1.70 ± 0.02	1.73	1.72
0.999[e]	13	1.48 ± 0.06	1.48	1.50

[a] Ionic strength held at 0.5 M with NaCl. [b] Atom fraction of deuterium determined by NMR using standard addition method. [c] $\phi_a = 1.40$, $\phi_b = 0.749$, and $\phi_c = 0.95$; rms deviation of calculated rate constants from observed = 0.0193. [d] $\phi_a = 1.30$, $\phi_b = 0.784$, and $\phi_c = 1.00$; rms deviation of calculated rate constants from observed = 0.0279. [e] Error limits are standard deviations.

which the rate-determining transition state involves a single water molecule with two fractionating protons ($\phi \approx 0.69$) is not consistent with the Brønsted slope $\beta = 0.66$ found for hydrolysis of **3**, nor with the results of the polynomial analysis of the proton inventory data for that substrate; it is also not consistent with the value calculated for γ from the data for **5**.

The latter conclusion is at variance with that drawn[2] for the acid-catalyzed hydrolysis of **2**, the nonmethylated fluoro analogue of **5**. This may be a consequence of the difference in leaving group. Water catalysis by proton transfer should be less important in the hydrolysis of **2** because nucleophilic addition is strongly facilitated by the ipso fluoride in that substrate, while the rate of nucleophilic attack on the less reactive chloride (**5**) would be increased by the proton transfer.

Experimental Section

NMR spectra were recorded on a Varian Gemini 200 instrument at 200 MHz (^{1}H) and 50 MHz (^{13}C) in TMS or DMSO-d_6 and reported in δ relative to internal TMS reference. Coupling constants are in Hz. UV spectra and kinetic data were obtained with a Perkin-Elmer Lambda 3 UV–vis spectrophotometer equipped with a P.E. Model 3600 data station. Protium oxide–deuterium oxide solutions were prepared by mixing in the appropriate molar proportions stock solutions of 1.88×10^{-3} M H_2SO_4 in H_2O and 2.0×10^{-3} M D_2SO_4 in D_2O, both made to ionic strengths of 0.5 M with NaCl. The deuterium atom fraction n was determined by ^{1}H NMR analysis by standard addition of incremental quantities of H_2O to solutions containing anhydrous sodium acetate as an internal standard and linear regression of the resulting relative integrations of the H(D)O and CH_3 peaks.

Preparation of 3, 4, and 5. The preparation of compounds **3** and **4** have been reported previously.[1,4] 2-Chloro-1-methylpyrimidinium triflate (**5**) was prepared by reaction of 2-chloropyrimidine (Aldrich) with methyl triflate. The latter was used as received from Aldrich, but the former was first recrystallized from methylene chloride. In a typical preparation, 0.36 g (3.1 mmol) of recrystallized 2-chloropyrimidine was placed in a 25-mL round-bottomed flask under an argon atmosphere in a glovebag. To the flask, equipped with a magnetic stirring bar, was added 10 mL of methylene chloride dried over 4A molecular sieves and 0.4 mL (0.58 g, 4.5 mmol) methyl triflate. The flask was equipped with a drying tube and removed from the glove bag. A white precipitate formed immediately, but the mixture was stirred in a hood overnight. The flask was returned to the glove bag and the precipitate collected by suction filtration, washed with CH_2Cl_2, and dried under vacuum in a desiccator: yield 0.75 g (68% th); ^{1}H NMR 3.67 (s, 3 H), 6.99, 1 H, J = 6.0), 8.85 (d of d, 1 H, J = 6.2, 2.8), 9.14 (d of d, J = 6.2, 2.8); ^{13}C NMR 104.12, 120.94 (q, J = 321.3), 147.57, 158.12, 162.02, 162.14. Anal. Calcd for $C_6H_6ClF_3N_2O_3S$: C, 25.86; H, 2.17; N, 10.05. Found: C, 26.09; H, 2.31; N, 9.99.

Kinetics. Kinetic runs were carried out by addition of a small aliquot of the substrate in an appropriate solvent (0.3 mL of 2×10^{-3} M **3** or 0.033 mL 1×10^{-2} M **5** in the mixed D_2O/H_2O media or 0.015 mL of 9×10^{-2} M **4** in anhydrous acetonitrile) was added to 3.0 mL of the mixed D_2O/H_2O media in a thermostated cell. Absorbances were monitored at 295 nm for **3**, 324 nm for **4**, and 304 nm for **5**, which represented absorbance maxima or shoulders of the respective hydrolysis product. Rate constants were calculated as described previously,[1,4] but were recalculated for **4** and **5** with a spreadsheet using the algorithm recommended by Ritchie,[24] which involves optimization of k and A_∞ by nonlinear regression. The resulting rate constants usually varied only slightly from those obtained earlier, but fit of the data to first-order kinetics was more readily evaluated through display of $A_{obs} - A_{calc}$ vs t.

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Registry No. **3**, 367-06-6; **4**, 703-62-8; **5**, 143859-73-8; D_2, 7782-39-0.

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