Kinetic Study of the Acid-Promoted Hydrolysis of Some Representative 2-Fluoro Nitrogen Heterocycles

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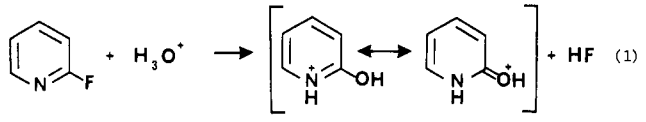
The acid-promoted hydrolysis of the 2-fluoro derivatives of pyridine, the four isomeric picolines, quinoline, pyrimidine, 4-methylpyrimidine, and 4,6-dimethylpyrimidine have been studied in hydrochloric acid over the concentration range of 0.05–8.0 F HCl. At each acid concentration, the reactions followed pseudo-first-order kinetics, and at low concentrations of acid, the rate of reaction increased linearly with h_0. However, at higher acid concentrations negative deviations from linearity were observed for all the substrates and rate maxima for all but the pyrimidines. These results were correlated with the decline in water activity by means of the Bunnett w and w^* relationships, as well as the Bunnett–Olsen LFER. The slopes of these correlations were suggestive of a proton-transfer role for water in the reactions of the less activated 2-fluoropyridines and of 2-fluoroquinoline, while the correlations indicate a nucleophilic role for water in the reactions of the more highly activated pyrimidines. Entropies of activation, calculated both from the pseudo-first-order rate constants, and from the values of $k_2°$ obtained from the intercepts of the LFER plot, were significantly more negative for the pyridine and quinoline systems for the pyrimidines. The above results are interpreted as consistent with nucleophilic attack by water in the rate-determining step for the reaction of the pyrimidines, while for the less activated substrates nucleophilic attack may be assisted by proton transfer to additional water molecules.

Hydrolysis of the carbon–fluorine bond in a variety of environments is promoted by hard acid cations, particularly the hydronium ion.[1] Several types of organic fluorides have been studied sufficiently for rate expressions to be determined and for reaction mechanisms to be proposed. Fluorine-substituted nitrogen heterocycles, a category of compounds that has evoked considerable pharmacological interest,[2] have not been intensively studied.

This paper presents kinetic data and observations from an extended study of the acid hydrolysis of certain of these 2-fluoro-substituted heterocycles (1–9, Chart I), including 2-fluoropyridines (1–5), 2-fluoroquinoline (6), and 2-fluoropyrimidines (7–9). Bradlow and Vanderwerf[3] reported that a number of 2-fluoropyridines undergo hydrolysis upon prolonged refluxing in 6 F HCl to yield the corresponding pyridones. No rate data were reported, although a reaction mechanism was proposed featuring a doubly protonated intermediate prior to the rate-determining step. Kinetic data for the present study support an intermediate bearing only a single proton.

Results and Discussion

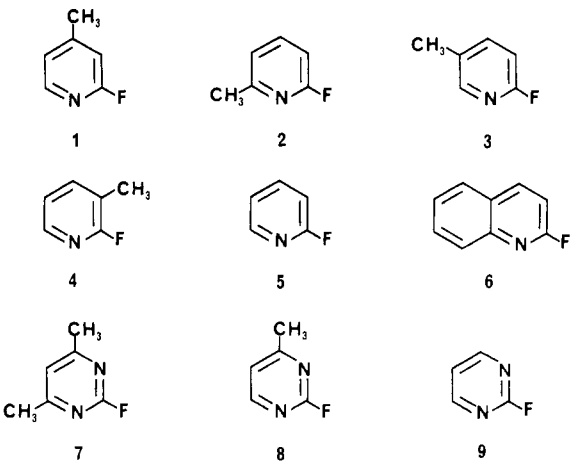
Illustrated by 2-fluoropyridine, the hydrolysis reactions studied take the general form of eq 1. Hydrolysis products



(1)

for the 2-fluoropyridines have been shown to be the corresponding pyridones.[3] 2-Hydroxyquinoline, the hydrolysis product of 2-fluoroquinoline, was isolated in this study and verified by spectral comparison with an authentic sample.

Chart I



Also, the formation of the pyrimidone from 2-fluoropyrimidine was monitored by UV absorption as a confirmatory test for product formation.

Hydrolysis reactions of all substrates were monitored by the fluoride electrode technique described in the Experimental Section. All substrates exhibited good first-order behavior for at least 2 half-lives. The slopes of the linear plots of log (unhydrolyzed substrate) vs. time were used to calculate the observed rate constants, k_ψ, which are pseudo-first-order rate constants.

Observed rate constants for all compounds studied are presented in Table I. Examination of these data reveals that in each case, the rate of reaction initially increases uniformly with acid concentation, but at high acid formalities the reaction rates exhibit distinctly negative deviation from the initial first-order dependence on acid activity.[4] For all but the most weakly basic substrates, i.e., the pyrimidines, the reaction rates reach their maximum values in media less than 3 F in HCl and decline thereafter with increasing acid concentration.

The response of the rate of hydrolysis of several representative substrates to increasing acidity of the medium

(1) See, for example: (a) C. A. Bunton and J. H. Fendler, *J. Org. Chem.*, 31, 2307 (1966); (b) H. R. Clark and M. M. Jones, *J. Catal.*, 24, 422 (1972); (c) C. C. Swain and R. E. T. Spalding, *J. Am. Chem. Soc.*, 82, 6104 (1960).

(2) (a) M. Stacey, J. C. Tatlow, and A. G. Sharpe, "Advances in Fluorine Chemistry", Vol. 3, Butterworth, London, 1963, pp 63–81; (b) C. Heidelberger, "Biological Approaches to Cancer Chemotherapy, a Symposium, Louvain, 1960", Vol. 47, Academic Press, London, 1961; *Chem. Abstr.*, 56, 1737a (1962); (c) A. Block, University Microfilms, Ann Arbor, MI, Order No. 62-4646; *Diss. Abstr.*, 23, 1165 (1962).

(3) H. L. Bradlow and C. A. Vanderwerf, *J. Org. Chem.*, 14, 509 (1949).

(4) D. G. Peters, J. M. Hayes, and G. M. Hieftje, "Chemical Separations and Measurements", W. B. Saunders Co., Philadelphia, PA, 1974, p 46.

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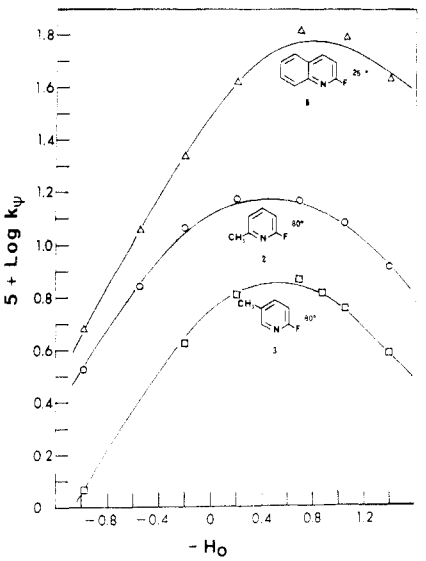


Figure 1. Plots of 5 + log (pseudo-first-order rate constants) vs. Hammett acidity functions for hydrolysis in hydrochloric acid: △, **6**, 2-F-Quin at 25 °C; ○, **2**, 2-F-6-MePy at 80 °C; □, **3**, 2-F-5-MePy at 80 °C. Smooth curves are calculated by an equation derived from the Bunnett w relationship.

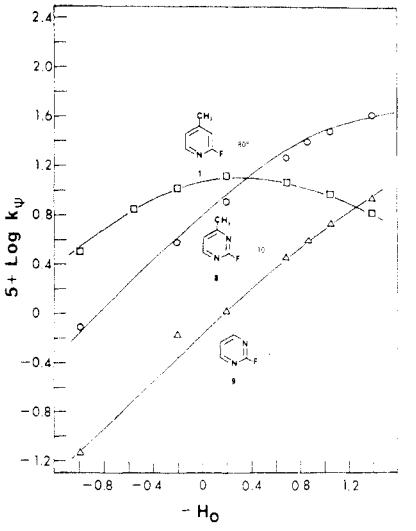


Figure 2. Plots of 5 log (pseudo-first-order rate constants) vs. Hammett acidity functions for hydrolysis in hydrochloric acid: □, **1**, 2-F-4-MePy at 80 °C; ○, **8**, 2-F-4-MePyrm at 10 °C; △, **9**, 2-F-Pyrm at 0 °C. Smooth curves are calculated by an equation derived from the Bunnett w relationship.

is illustrated graphically in Figures 1 and 2. Similar rate maxima in strongly acidic media have been observed in other acid-catalyzed hydrolysis reactions, including those of amides[5] and esters.[6] In such cases, the rate maxima have been attributed to two factors: (1) moderately basic substrates will approach complete protonation at the higher acidities, and any additional increase in acid concentration (or activity) cannot proportionately increase further the degree of protonation of the substrates; (2) the activity coefficients change, including that of the water itself. Water is often involved in the transition state, as a solvent of both substrate and transition state, of course, but also, in many cases, as the nucleophile, proton transfer agent, or both. The activity of water decreases with increasing acid activity in concentrated solutions of mineral acid; therefore, the rate of reaction tends to decrease if more water molecules, in whatever capacity, are involved in the transition state relative to the protonated substrate.[7]

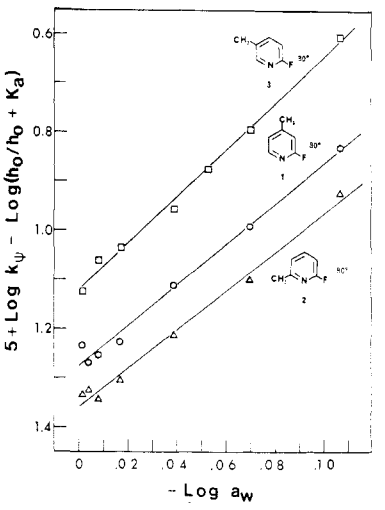


Figure 3. Bunnett w plot of 5 + log k_ψ + log $h_0/(h_0 + K_a)$ vs. -log (water activity in hydrochloric acid): □, **3**, 2-F-5-MePy at 80 °C; ○, **1**, 2-F-4-MePy at 80 °C; △, **2**, 2-F-6-MePy at 80 °C.

Zucker and Hammett first proposed that log k_ψ, where k_ψ is the observed pseudo-first-order rate constant of an acid-catalyzed reaction, should follow log [H^+] rather than $-H_0$, the Hammett acidity function, when a water molecule is included in the rate-determining step.[8,9] This Zucker–Hammett hypothesis, for which exceptions were found in the course of wide use, has been generally supplanted by other treatments. These treat the problem of water activity directly as in the w and w^* treatments of Bunnett,[7a] in the more refined analysis of Yates,[6d,e] and indirectly in the linear free energy relationship (LFER) of Bunnett and Olsen.[7b] The treatment of Yates requires knowledge of specific acidity functions for the substrate in question, as well as water activities and K_a values for the protonated substrate determined for each temperature used. Since these specific functions were not available to us, we have followed the less specific treatments of Bunnett.

Because most of the compounds under study are sufficiently basic to be substantially, but not entirely, protonated through the range of hydrochloric acid concentrations examined, it was necessary to compensate for variation in the degree of protonation of the substrates as the acid concentrations were varied. This was accomplished by using the appropriate functions, [log k_ψ – log $h_0/h_0 + K_a$)] vs. log a_w for the Bunnett w plot,[7a] [log k_ψ – log [H^+]/($h_0 + K_a$)] vs. log a_w for the Bunnett w^* plot,[7a] and [log k_ψ – log $h_0 + K_a$)] vs. H_0 + log [H^+] for the Bunnett–Olsen LFER plot.[7b] For the latter, we have plotted the indicated function rather than the preferred log k_ψ – log ([SH^+]/[S]) because we lack detailed information regarding the protonation ratio for our substrates at all acid concentrations examined.

By using these treatments, we have been able to utilize data not only from low acidities, where linear first-order relationships between acid concentration and rates are observed, but also at higher acid concentrations where this is no longer the case because of nearly complete protona-

(5) J. T. Edward and S. C. R. Meacock, *J. Chem. Soc.*, 2000 (1957).
(6) (a) D. Jacques, *J. Chem. Soc.*, 3874; (b) J. A. Leisten, *ibid.*, 1572 (1956); (c) C. A. Lane, *J. Am. Chem. Soc.*, **86**, 2521 (1964); (d) K. Yates and R. A. McClelland, *ibid.*, **89**, 2686 (1967); (e) K. Yates, *Acc. Chem. Res.*, **4**, 136 (1971).
(7) (a) J. F. Bunnett, *J. Am. Chem. Soc.*, **83**, 4956, 4968, 4973, 4978 (1961). (b) J. F. Bunnett and F. P. Olsen, *Can. J. Chem.*, **44**, 1917 (1966).
(8) L. Zucker and L. P. Hammett, *J. Am. Chem. Soc.*, **61**, 2791 (1939).
(9) F. A. Long and M. A. Paul, *Chem. Rev.*, **57**, 935 (1957).

Table I. Summary of Observed Rate Constants

	$10^5 k_\psi$, s^{-1}															
[HCl], F	2-F-4-MePy (1), 80 °C	2-F-6-MePy (2), 80 °C	2-F-5-MePy (3)		2-F-3-MePy (4), 80 °C	2-F-Py (5)			2-F-Quin (6)			2-F-4,6-$(Me)_2$-Pyrm (7), 10 °C	2-F-4-MePyrm (8), 10 °C	2-F-Pyrm (9)		
			65 °C	80 °C		50 °C	65 °C	80 °C	0 °C	15 °C	25 °C			0 °C	10 °C	25 °C
0.05	1.61	1.69	0.129		1.06	0.092	0.442	1.63								
0.10	3.19	3.34	0.270	1.16	2.08	0.199	0.795	3.14	0.33	1.89	4.85	1.44	0.80	0.072	0.451	2.21
0.25	7.11	6.97	0.593		5.18	0.457	2.07	7.64	0.90	3.66	11.4	3.44				
0.50	10.4	11.6	1.07	4.20	9.17	1.06	3.95	13.2	1.62	7.69	21.9	7.97	3.64	0.669	2.41	10.0
1.0	13.1	14.9	1.67	6.41	13.5	1.59	7.21	23.1	3.48	14.3	42.0	15.5	8.56	1.05	4.41	18.3
2.0	11.8	14.7	1.72	7.38	15.4	2.73	10.1	45.5	4.06	20.9	65.7	29.8	19.8	2.89	10.6	39.5
2.5			1.54	6.53	13.1	2.40	9.55	36.6					25.8	3.97	14.3	72.5
3.0	9.43	12.0	1.32	5.68	10.3	2.43	9.36	34.8	3.85	19.2	61.9	47.4	31.4	5.38	13.9	97.7
4.0	6.65	8.21	0.83	3.84	7.95	1.91	7.90	29.4	2.84	15.1	43.5	67.4	42.4	8.68	24.0	123.0
6.0					2.82		3.56	14.1							53.4	
8.0															85.8	

Table II. Rate Correlations

	substrate															
	3					5			6					9		
	1, 80 °C	2, 80 °C	65 °C	80 °C	4, 80 °C	50 °C	65 °C	80 °C	0 °C	15 °C	25 °C	7, 10 °C	8, 10 °C	0 °C	10 °C	25 °C
K_a	0.457	0.575	1.10	1.10	1.10		2.51			2.75		14.1	33.9		~100	
w	4.11	3.93	5.17	4.75	4.62	3.46	3.60	3.43	4.48	3.64	3.84	2.54	3.63	2.83	1.74	4.17
r^a	0.993	0.994	0.995	0.997	0.997	0.972	0.999	0.986	0.978	0.985	0.987	0.904	0.973	0.852	0.824	0.909
w^*	−3.20	−3.38	−3.09	−3.44	−1.82	−3.92	−2.66	−2.83	−2.81	−3.23	−3.53	−4.75	−3.42	4.56	3.94	−3.09
r^a	0.942	0.941	0.953	0.976	0.832	0.939	0.954	0.933	0.868	0.943	0.923	0.993	0.979	0.921	0.984	0.926
ϕ	0.550	0.524	0.682	0.641	0.724	0.457	0.565	0.536	0.595	0.545	0.509	0.366	0.505	0.366	0.321	0.590
r^a	0.981	0.978	0.977	0.984	0.987	0.955	0.990	0.974	0.956	0.976	0.964	0.943	0.993	0.836	0.871	0.941
$(5 + \log k_2^\circ)^b$	1.299	1.392	0.540	1.155	1.475	0.725	1.361	1.923	1.005	1.685	2.140	2.272	2.378	1.934	2.494	3.265

[a] Correlation coefficient. [b] Intercept.

Table III. Entropies of Activation Calculated from Observed Rate Constants[a]

	entropy			
[HCl], F	2-F-5-MePy (3)	2-F-Py (5)	2-F-Quin (6)	2-F-Pyrm (9)
0.05		−27.1		
0.10	−24.7	−28.4	−25.4	−11.0
0.25		−25.1	−27.2	
0.50	−26.4	−30.4	−24.4	−23.4
1.0	−26.1	−26.1	−26.7	−19.0
2.0	−21.0	−22.1	−18.5	−21.0
2.5	−22.1	−24.1		−16.0
3.0	−24.0	−25.7	−19.0	−13.0
4.0	−19.4	−24.4	−20.4	−19.4
6.0		−22.7		

[a] $\Delta S^\ddagger$ (cal/deg mol) at 25 °C.

tion of some of the substrates and because of activity coefficient effects.

Rate Correlations. Table II gives the slopes w, w^*, and ϕ for the three respective plots, the correlation coefficients of the linear regressions for each, and the intercepts (log $k_2°$, see below) for the Bunnett–Olsen LFER plots.

The correlations range from fair to excellent, with the more basic, less reactive substrates (pyridines **1**–**5** and 2-fluoroquinoline **6**) exhibiting rates that uniformly correlate best with the Bunnett w plot, while the rate data for the less basic, more reactive pyrimidines (**7**–**9**) correlated better with w^* or LFER plots. There was a pronounced downward curvature of the w plots at higher acidities for the pyrimidines **7**–**9**. Considerably less deviation from linearity was found in the w^* plots for these substrates.

In principle, each plot should have an intercept corresponding to log $k_2°$, the second-order rate constant at infinite dilution in water. As expected, the intercepts of the three plots were all similar but diverged from each other somewhat because of the differing degrees of curvature in the respective plots. The intercepts of the Bunnett–Olsen LFER plots were in every case intermediate between the w and w^* plots and were taken as most representative of the second-order rate constants.

The Bunnett and Bunnett–Olsen plots may themselves demonstrate best the fit of the experimental rate data to a model in which an increasing proportion of the substrate becomes protonated, while the activity of water decreases. However, a striking illustration of the fit is also provided by calculating simulated "observed" rate constants from the expression log k_ψ, calcd = log $k_2°$ + log $[h_0/(h_0 + K_a)]$ + w log a_w. The fitted curves of Figures 1 and 2 were calculated from this expression, which can be derived from the Bunnett model.

Relative Reactivities. Since the intercepts of the Bunnett–Olsen LFER plots correspond to -log $k_2°$, they provide a measure of the relative reactivities of the various substrates in their protonated forms. In general, the reactivities run parallel to the relative acidities; i.e., those factors that increase the acidity of the protonated substrate also activate it toward hydrolysis.

The single apparent exception to this trend is 2-fluoro-5-methylpyridine (**3**), which, while exhibiting the same K_a as the 3-methyl isomer (**4**), is appreciably less reactive than it or the 4- and 6-methylpyridines (**1** and **2**), even though the latter two have K_a's only about half of that of the former. With this exception, the reactivities of all substrates parallel the reactive acidities of the protonated forms. The relatively low reactivity of **3** is consistent with rate-determining nucleophilc attack on the protonated substrates, rather than rate-determining loss of fluoride, as will be discussed below.

Slopes of Rate Correlations. The values of the slopes w, w^*, and ϕ of the respective plots furnish additional clues to the mechanism of hydrolysis of these compounds. The slopes of the plots for the pyrimidines **7**–**9** fall mainly in the range expected for reactions involving water as a nucleophile in the rate-determining step, viz., $1.2 < w < 3.3$, $w^* < -2$, and $0.18 < \phi < 0.47$.[7] This is not true, however, for the more basic, less reactive 2-fluoroquinoline (**6**) and the 2-fluoropyridines (**1**–**5**). For these, w^* continues in almost all cases to fall in the range expected for nucleophilic attack by water. However, the values of w (3.43–5.17), for which the correlations are generally better than for w^*, and of ϕ as well (0.457–0.724) are more typical of reactions in which water has a proton-transfer role.

Activation Parameters. By itself, the trend just described is only suggestive of the possibility of a difference of mechanism, at least in the details of the transition state. However, similar differences between the more reactive substrates and the less reactive ones are found in their activation parameters $\Delta H^‡$ and $\Delta S^‡$.

These experimental parameters, calculated for **3**, **5**, **6**, and **9** from the variation of their pseudo-first-order rate constants with temperature at each acid concentration, include ΔH and ΔS for the protonation preequilibrium, as well as the true $\Delta H^‡$ and $\Delta S^‡$ for the rate-determining step. For the more basic substrates, however, these preequilibrium factors will tend to drop out of the experimental activation parameters as the substrates become nearly fully protonated at the higher acidities used. This effect is not apparent in the calculated $\Delta H^‡_{25}$ values (where the subscript refers to the temperature in degrees Celsius), and except for slightly lower $\Delta H^‡_{25}$ values for 2-fluoroquinoline (**6**), which may be due to the extra delocalization of electrons possible in the transition state of that substrate, there is little trend apparent among the calculated enthalpies of activation (**3**, 21.3 kcal/mol; **5**, 19.6 kcal/mol; **6**, 16.9 kcal/mol; **9**, 18.5 kcal/mol).

Although there is little variation in $\Delta H^‡_{25}$ with increasing acid concentration, we note a break in $\Delta S^‡_{25}$ at [HCl] ≥ 2 F, relative to lower acidities, for 2-fluoroquinoline (**6**), 2-fluoropyridine (**5**), and 2-fluoro-5-methylpyridine (**3**) (Table III). At [HCl] < 2 F, $\Delta S^‡_{25}$ averages -25.9, -27.4, and -25.6 eu, respectively, while the corresponding values at [HCl] ≥ 2 F are -19.3, -23.8, and -21.6 eu. While the differences in entropies of activation between the two acidity ranges are not great, there is almost no overlap of these values (except for a little among the values of 2-fluoropyridine), and the breaks are clear.

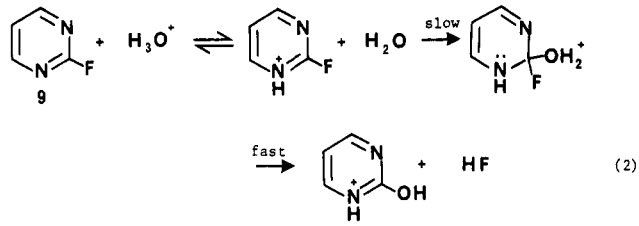
There is no such break apparent among the $\Delta S^‡_{25}$ values for 2-fluoropyrimidine (**9**), although the scatter is greater. This is to be expected, since this substrate is so weakly basic that a substantial fraction of it is unprotonated at even the greatest acidities examined. Since the protonation preequilibrium factors will be included in these experimental values of $\Delta S^‡_{25}$ for **9**, they are properly compared to the values occurring at lower acidities for the more basic substrates. For **9**, $\Delta S^‡_{25}$ averages -17.5 eu, substantially less negative than the -25.6 to -27.4 eu observed at lower acidities for the more basic substrates. Although the scatter of $\Delta S^‡_{25}$ values for **9** is rather substantial, even the most negative value, -23.4 eu, is more positive than any individual value calculated at the lower acidities for **3**, **5** and **6**.

Although this difference in $\Delta S^‡_{25}$ may be significant, it could be argued that it arises from the preequilibrium rather than the rate-determining step of the hydrolysis. Such is not the case, however, for activation parameters calculated from $k_2°$ values obtained from LFER intercepts. As with parameters calculated from the pseudo-first-order constants, no clear trend is apparent in the enthalpies of activation of these compounds, with the possible exception of a relatively low value for **6**, again ($\Delta H^‡_{25}$ for **6** of 16.7 kcal/mol and 21.3, 19.7, and 20.1 kcal/mol for **3**, **5** and **9**, respectively), but $\Delta S^‡_{25}$ for the hydrolysis of **9** is substantially more positive (0.0 eu) than for reaction of the less activated substrates (-20.5 to -21.8 eu).

The actual calculated values of these entropies of activation may in themselves not be entirely significant,[7b] but more negative entropies of activation clearly associate with the less highly activated, more basic substrates.

Mechanism. The above results are consistent with a rate-determing nucleophilic attack by water upon the

fluorine-bearing carbon of the protonated substrates, illustrated by reaction of **9** (eq 2).

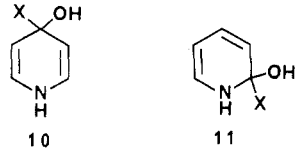


(2)

This mechanism is essentially that typical of nucleophilic aromatic substitutions such as those found in aryl halide systems activated by nitro groups[10] or in heteroaromatics upon reaction with strong nucleophiles such as thiophenoxide or methoxide.[11] In the present study, protonation of the ring nitrogen results in sufficient activation that nucleophilic attack by water is readily achieved. The rates are approximately first order in $[H^+]$ at low (<1 F) concentrations of hydrochloric acid, indicating a monoprotonated transition state for the rate-determining step, rather than the doubly protonated one suggested in an earlier study.[3]

Rate-determining nucleophilic attack upon the protonated substrate by water allows rationalization of additional experimental observations. It has been demonstrated that acid-catalyzed hydrolysis does not take place under usual conditions with 2-chloro- and 2-bromopyridine.[3] These compounds are much stronger bases than the fluoro analogue, and in view of the observed inverse relationship between basicity of the substrate and reactivity of the protonated form, they would be expected to be much less activated to nucleophilic attack.

In the same study,[3] the 4-halo analogues were reported to be much more reactive than the 2-halo compounds. This was attributed to the greater stability of *p*-quinoidal structures (**10**) relative to *o*-quinoidal types (**11**). This is



further evidence that formation of these intermediates by nucleophilic addition, and not departure of halogen, is rate-determining in these systems.

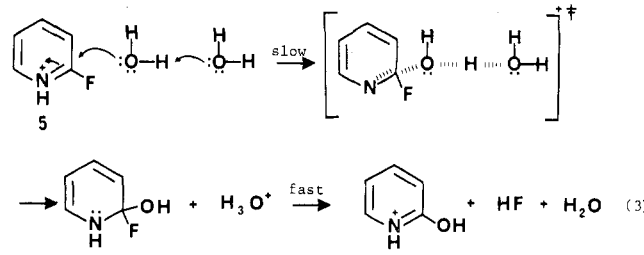
The same argument is useful in rationalizing the relative reactivity observed for **3**, 2-fluoro-5-methylpyridine. The more stable *p*-quinoidal resonance structure for delocalization of the lone pair of electrons on nitrogen places a lone pair on C(5) of the ring. Because of the resulting greater electron density on that carbon in the resonance hybrid, an electron-donating methyl on C(5) would destabilize the transition state more than one on C(3). Molecular orbital arguments for the isoelectronic pentadienyl carbanion agree in placing greater electron density on the carbon corresponding to C(5) of the ring.[12] The same relative reactivities of 5-methyl-vs. 3-methyl-2-halopyridines have been observed for reaction of 2-fluoropyridines[11a] and 2-bromopyridines[11b] with the strong nucleophiles methoxide and thiomethoxide. This effect further strengthens the conclusion that nucleophilic attack, and not fluoride departure, is rate determining since the latter would not be expected to be sensitive to a 5-methyl substituent.

On the other hand, although **6** is slightly less basic than **5**, and would therefore be expected to be somewhat more reactive when protonted, $k_2°$ calculated for the former by Arrhenius extrapolation to 80 °C is actually more than 150 times greater than for the latter at that temperature. This is much more than would be expected on the basis of the small difference in basicity and may be attributed to the greater delocalization of the lone pair developing on nitrogen in the transition state made possible by the quinoline ring system. As noted above, this effect may be responsible for the lower enthalpy of activation in the hydrolysis of **6**. Again, this is consistent with rate-determining nucleophilic attack but not with rate-determining elimination of fluoride.

We have interpreted our data in terms of rate-determining nucleophilic attack by water in the protonated substrate, with subsequent rapid elimination of HF in one or more steps. However, our results might also be consistent with a direct, one-step displacement of fluoride by water *provided* that C–O bond formation is considerably more advanced than C–F bond breaking in the transition state. Because this alternative mechanism, common in saturated systems (S_N2), has not, to our knowledge, been demonstrated in aromatic nucleophilic substitution, we prefer the proposed addition–elimination mechanism in the absence of compelling evidence for direct displacement.

We have no evidence that the reaction, other than in the initial protonation step, is reversible. It is possible that the hydrated intermediate might lose water in reverting to substrate, but this would be difficult if not impossible to detect, unless the reaction could be shown to be a completely reversible equilibrium in the presence of excess fluoride. This does not appear to be the case, since the reactions all exhibited good first-order behavior over a period of at least 2 half-lives, and limited experiments in which 5 was hydrolyzed in the presence of excess fluoride showed no significant rate effect. This places a constraint upon the possibility of generated fluoride acting as a nucleophile as the reaction progresses and indicates that such reversal is not important, at least at the fairly low fluoride concentration encounterd here. Supporting this conclusion is the observation that addition of Al(III) and Th(IV) salts had no effect upon the rate of hydrolysis. These cations complex F^- and would be expected to retard any reverse step.

Our observation that the less activated substrates exhibit more negative entropies of activation, as well as the Bunnett and Bunnett–Olsen rate correlation slopes, suggestive of a proton transfer role by water, indicates a probability that nucleophilic attack on these substrates is assisted by a second molecule of water. Such assistance is illustrated for the reaction of **5**, (eq 3; in this and subsequent discussions, the hydration sphere of substrate and transition state are not explicitly shown, although are certainly present). By participating in a proton-transfer role, the second water molecule increases the nucleophil-



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icity of the first, enabling it to attack less activated substrates. In effect, the more important proton-transfer becomes in the transition state, the more hydroxide-like the oxygen nucleophile becomes. Such assistance by the second molecule of water would therefore decrease the enthalpy of activation for nucleophilic attack on the less reactive substrates, so that in this case it is no more than that for the highly reactive substrates, but only at the cost of greater decrease in entropy during formation of the activated complex.

We have presented the mechanism for hydrolysis of the pyrimidines as distinct from that of the less activated 2-fluoroquinoline and the 2-fluoropyridines 1–6 by suggesting that nucleophilic attack takes place without proton transfer to a second water molecule in the reactions of the former compounds and with transfer in reaction of the latter. However, it may be that there is a continuous trend of an increasing degree of transfer in the transition state as the protonated substrate becomes less activated to nucleophilic attack and more assistance is required. In this case then, eq 3 would serve for all substrates examined, but with varying degrees of proton transfer in the transition state.

The mechanism we have proposed differs in two ways from an earlier one:[3] (1) the evidence demands a monoprotonated intermediate, not a doubly protonated one; (2) the evidence suggest that nucleophilic attack by water is assisted by proton transfer to a second water molecule when the substrate is not a highly activated pyrimidine. With regard to this point, it would be interesting to compare the deuterium kinetic isotope effect resulting from reaction in D_2O for **5** vs. **9**.

Although we favor the proposed mechanism as best rationalizing the available evidence, we caution that there are several points as yet unresolved. Although ^{19}F NMR studies indicate N-protonation in similar compounds,[13] it is possible that protic acids could assist in departure of the ring-substituted fluoride subsequent to the rate-determining step.

Experimental Section

Materials. 2-Fluoropyridine was obtained commercially (K and K Laboratories) and was used without additional purification. The isomeric 2-fluoromethylpyridines were prepared by the procedure of Roe et al.[14] and were fractionated at atmospheric pressure. The heart cut fractions were used for kinetic study. 2-fluoroquinoline was prepared by the halogen-exchange method of Hamer et al.[15] and fractionated under vacuum. All 2-fluoropyrimidines studied were prepared by the halogen-exchange method of Baram et al.[16] by starting with the corresponding 2-chloro compounds. Only 2-chloropyrimidine was commercially available (Pfaltz and Bauer, Inc.). The other precursors, 2-chloro-3-methylpyrimidine and 2-chloro-4,6-dimethylpyrimidine, were prepared by the diazotization method of Overberger and Kogon.[17]

Elemental analyses were obtained for the 2-fluoropyrimidines used. Elemental analyses found for each of the three compounds agreed with theoretical percentages with ±0.3% (actual) or ±2.0% (relative) in all cases. Purities for the other substrates were determined by gas chromatography using a flame-ionization detector. Peak areas indicative of 99+% purity were observed for each compound. Internal checks for purity, based on fluorine content, were made frequently by allowing the hydrolysis reactions to proceed for 10 or more half-lives and measuring total fluoride recoveries. These confirmed purity as 100 ± 2% of theoretical in all instances.

Acid hydrolysis media were prepard by dilution of standard 6.0 F HCl. Buffer and quenching components were reagent grade.

Rate Measurements. Stock solutions of the substrates were prepared by dissolving 4 ± 0.2 mmol of each compounds in 20 mL of absolute ethanol.

To start a kinetic run, a 2-mL aliquot of the stock solution was pipetted into 98 mL of previously thermostated acid. At timed intervals during the reactions, 5-mL aliquots of the hydrolyzate were withdrawn and discharged into 95-mL portions of sodium acetate solution containing 3 mol of sodium acetate for each mole of acid in the aliquot. This operation effectively quenched the hydrolysis reaction and achieved a solution pH of 5 ± 0.1. These solutions were subsequently analyzed for fluoride as a measure of the extent of hydrolysis attained at a particular reaction interval. Analysis was performed by comparing the response of an Orion selective ion electrode (Model 94-09) with a calibration curve developed from standard portions of potassium fluoride under identical solution conditions except for the substrate. A Beckman Research pH meter was used to measure cell potentials to 0.1 mV. The SCE was used as the reference electrode.

Measurement of pK_a. Dissociation constants for the 2-fluoromethylpyridines were obtained by the method of Brown and McDaniel,[18] which utilizes the relationship in eq 4, where A_{OH},

$$pK_a = -\log [H^+]_B + \log\frac{A_B - A_{OH}}{A_{H^+} - A_B} \quad (4)$$

A_B, and A_{H^+} are absorbancy readings for solutions of the free base and the half-protonated and completely protonated base, respectively. The hydrogen ion concentration term is that for half-protonation. Half-protonation of these bases was attained in approximately 1 F HCl. Protonation of the 4- and 6-methyl isomers (**1** and **2**) was essentially complete in 6 F HCl, and the 3- and 5-methyl isomers (**3** and **4**) were completely protonated in 8 F HCl (ascertained by constancy of absorbance maxima). Free-base absorbancy was obtained in 0.01 F NaOH. Bathochromic shifts of absorbance maxima were observed for each base as protonation increased, thereby necessitating absorbancy measurements for the various isomers over the following wavelength ranges: 3-Me, 260–267 nm; 5-Me, 264–271 nm; 4-Me, 253–259 nm; 6-Me, 259–267 nm. Measurements were made at 25 °C.

The dissociation constant for 2-fluoroquinoline (**6**) was determined by the graphical method of Stenstrom and Goldsmith[19] with minor modifications. Absorbancy measurements were made at 0 °C because of the tendency of **6** to hydrolyze. Also, absorbancy measurements were completed with a minimum lapse of time after addition of the substrate to previously thermostated acid solutions. A jacketed cell with circulating coolant was used to control the temperature while readings were taken. The cell compartment was purged with dry nitrogen to prevent fogging of the optical surfaces.

Dissociation constants for the three pyrimidine substrates (**7–9**) were determined spectrophotometrically by an adaptation of the procedure of Albert and Phillips.[20] Calculation of pK_a involves the expression shown in eq 5, where A_{MH^+} and A_M are the molar

$$pK_a = pH - \log\frac{A_{MH^+} - A}{A - A_M}$$

absorptivities of the protonated and free base, respectively, and A is the sum of the two at various pH values. Since the eight acid solutions used ranged from 0.01 to 12 F HCl, pH_a values were used throughout. Plots of pH_a vs. absorbance exhibited well-defined inflection points for all compounds except 2-fluoropyrimidine where the interpretation of the curve carries some uncertainty. The hydrolyzability of these compounds also necessitated measurements at 0 °C by using the same technique

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as described for 2-fluoroquinoline. Bathochromic shifts with protonation were pronounced for the following compounds: 2-F-Pyrm (245–256 nm), 2-F-4-MePyrm (248–260 nm), and 2-F-4,6-$(Me)_2$Pyrm (249–263 nm).

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Supplementary Material Available: Enthalpies of activation (Table IV), activation parameters (Table V), a Bunnett w plot for 6, 7, and 9 (Figure 4), and a Bunnett w^* plot for 7 and 9 (Figure 5) (4 pages). Ordering information is given on any current masthead page.

Alkoxyphosphonium Salts. 3. Kinetics and Thermodynamics in Alkylation by Alkoxyphosphonium Salts[1]

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Several methoxyphosphonium trifluoromethanesulfonates (triflates) are characterized by the rates of methyl transfer to the 2,4-dinitrophenoxide ion. In acetone at 25 °C, the measured second-order rate constants range from about 0.2 to about 40 M^{-1} s^{-1}, putting substances of this class among the most powerful methylating agents. The methylating power is confirmed by the measurement of the equilibrium extent of methylation of the counterion, the triflate ion. The Arbuzov rearrangement of trimethyl phosphite is slow with the catalyst methyl iodide but is fast enough with the catalyst methyltrimethoxyphosphonium triflate to allow calorimetric measurement for the conversion of trimethyl phosphite to dimethyl methylphosphonate; $\Delta H = -24 \pm 2$ kcal/mol. An earlier error in the measurement of the rate of this reaction is corrected, so that the mechanism of the methyl iodide catalyzed Arbuzov reaction of trimethyl phosphite is no longer in question; the first step is rate determining.

Alkoxyphosphonium salts have long been considered intermediates in the Michaelis–Arbuzov reaction, as well as in numerous other reactions. They are, however, seldom detected, indicating that they react very rapidly with nucleophiles. The preparation of a number of these salts as the trifluoromethanesulfonates (triflates) was recently described,[2] and the rapid reaction rate of methyltrimethoxyphosphonium triflate with iodide ion was measured by an inconvenient and specialized method. A few qualitative rates of reaction of some such salts have been measured;[3,4] methyldiethylmethoxyphosphonium ion reacts only rather slowly even with iodide ion.[5] In this paper a number of rates with a standard nucleophile are measured. Equilibrium constants with the weaker nucleophile, triflate ion, are also reported.

A curiously unanswered question about a reaction as general as the Michaelis–Arbuzov reaction is the driving force of the exothermicity of this reaction. Estimates based on bond energies are quite uncertain, giving results from −15 to −44 kcal/mol.[6-8] Using methyltrimethoxyphosphonium triflate as a catalyst, we have been able to make a calorimetric measurement of ΔH in one case.

Results

Rates. Rates of reaction of several methoxyphosphonium salts with potassium 2,4-dinitrophenoxide are reported in Table I. These rates were determined in acetone solution at 25 °C by the stopped-flow method using the fall in absorbance due to the dinitrophenoxide anion for the measurement. Parallel experiments by proton NMR did not give rate constants but confirmed, in each case where rate constants are given, the formation of 2,4-dinitroanisole.

Table I. Rate Constants for $CH_3OP^+CH_3RR'$ OTF^- with Potassium 2,4-Dinitrophenoxide in Acetone at 25 °C

R	R'	k per methoxy group, M^{-1} s^{-1}	δ [a]
OCH_3	OCH_3	44.3	53.1
OCH_3	Ph	10.8	78.5
Ph	Ph	7.0	74.5
OCH_3	Et	0.48	99.0
Et	Et	0.2 [b]	103.5

[a] ^{31}P chemical shift, from H_3PO_4.[2] These are in reasonable agreement with some earlier reports on related compounds: Murray, M.; Schmutzler, R.; Gründemann, E.; Teichmann, H. *J. Chem. Soc. B* **1971**, 1717. Schmidpeter, A.; Brecht, H. *Z. Naturforsch. B: Anorg. Chem., Org. Chem.* **1969**, *24B*, 179. [b] This salt was too unstable for good measurement. The rate constant is crudely estimated (see text).

We failed to get consistent simple kinetics with any of the phosphonium salts containing an aryloxy group. This presumably relates to the impossibility of getting pure samples and contamination of these samples with methyl triflate as described below in the discussion of equilibria. When diethylmethylmethoxyphosphonium triflate was used, a yellow color developed in its acetone solution at about the same rate that the yellow color of the dinitrophenoxide disappeared after mixing. The nature of this reaction was not established, and the rate constant reported is very rough, corresponding to a rather crude correction for the unknown process.

Table I also shows the ^{31}P NMR chemical shifts, and there appears to be a correlation between the reaction rates

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