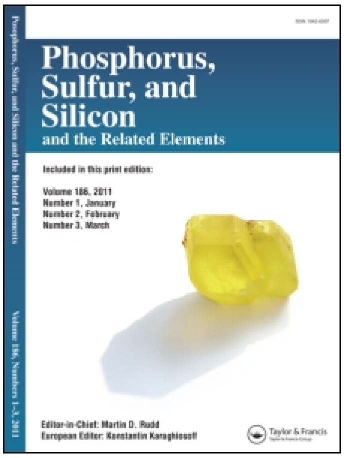

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KINETICS AND MECHANISM OF HYDROLYSIS OF METHYLPHOSPHONFLUORIDIC ACID

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KINETICS AND MECHANISM OF HYDROLYSIS OF METHYLPHOSPHONFLUORIDIC ACID

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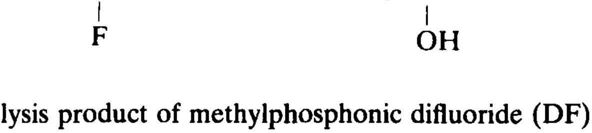
The acid catalyzed rate for hydrolysis of methylphosponfluoridic acid has been determined at several hydrogen ion concentrations and temperatures. The acid hydrolysis is second order (in acid and substrate). Assumed rate expressions, observed rate constants, and hydrogen ion concentrations were used to calculate the thermodynamic equilibrium constant ($K_a = 0.56$) and rate constants for acid catalysis. The activation energy E_a has been determined as 18.3 Kcal/mole. Finally, the acid catalyzed deuterolysis was determined to be about 1.47 times the rate of hydrolysis. The data suggest a two-step mechanism consisting of a rapid proton transfer, followed by slow hydration of the protonated complex.

I. INTRODUCTION

Pentavalent phosphorus compounds are biologically important and are involved in many endogenous metabolic processes; some are cholinesterase inhibitors in pesticide and chemical warfare agents. Because of their importance, their chemistry, especially hydrolysis reactions, has been studied and reviewed extensively.[1,2] Esters of pentavalent phosphorus have received particular attention, and the kinetics and mechanisms of their hydrolysis are fairly well characterized.[3] Hydrolysis can take place with cleavage of either the C—O or O—P bonds of the ester. Electron-withdrawing substituents to the phosphorus normally accelerate hydrolysis, and whereas base catalysis usually occurs, acid catalysis is also known.

The hydrolyses of pentavalent halo-phosphorus compounds have also been determined because some of their derivatives inhibit cholinesterase.[4–6] Like esters of phosphorus, they undergo general base catalysis, and electron-withdrawing groups on substituents accelerate the reaction. Acid catalysis of these compounds has received less attention. In the present study, we have determined the acid-catalyzed rate of hydrolysis of one such compound, methylphosphonfluoridic acid (MF)



$$CH_3\text{—}\underset{\displaystyle F}{\overset{\displaystyle O}{\overset{\|}{\underset{|}{P}}}}\text{—}OH + H_2O \xrightarrow{[H+]} CH_3\text{—}\underset{\displaystyle OH}{\overset{\displaystyle O}{\overset{\|}{\underset{|}{P}}}}\text{—}OH + HF. \tag{1}$$

MF is the hydrolysis product of methylphosphonic difluoride (DF), an intermediate in the synthesis of several cholinesterase inhibitors. The hydrolysis of DF proceeds rapidly; a half-life of 35 seconds at physiological temperature and pH has been reported.[7] The product MF hydrolyzes to methylphosphonic acid (MPA). Little information exists on the kinetics and mechanism of the MF hydrolysis, although a specific acid-base catalysis has been reported.[8]

Detailed knowledge of the hydrolysis of MF was needed in the course of toxicological studies with DF. This communication reports both the kinetics and a proposed mechanism for the acid-catalyzed hydrolysis of MF.

II. EXPERIMENTAL

Materials

Methylphosphonfluoridic acid was obtained by the disproportionation of DF with MPA. Equimolar quantities of DF and MPA were allowed to react together in a flask at room temperature, and monitored by ^{31}P NMR until the reaction was complete. The MF was purified by distillation and was shown to be >98% free of other phosphorus impurities by ^{31}P NMR. DF was supplied by the Chemical Research and Development Center at the Aberdeen Proving Ground. MPA was obtained by the reaction of dimethyl methylphosphonate (Aldrich Chemical Co., Milwaukee, WI) with concentrated HCl. Thus, excess HCl was added to dimethyl methylphosphonate in a beaker at 50°C. The beaker was placed in a hood, and allowed to react until no more HCl remained. Again, purity was checked by ^{31}P NMR and found to be greater than 95%.

The concentrations of the HCl solutions used for acid hydrolyses were determined by titration against standardized base. The phosphate buffers were made by dissolving NaH_2PO_4 in distilled water, adding solid NaOH pellets to the desired pH, and diluting to the final desired concentration.

All other reagents were obtained from commercial sources and were reagent grade or better.

Kinetics

About 20 ml of acid or buffer was placed in polyethylene screw cap vials and preheated in a water bath to ±0.2°C of the desired temperature. Normally, about 30 μl of MF was added (0.02 M) and the mixture was immediately capped and vigorously mixed. One-ml aliquots were removed at known times and added to 9 ml of 15% sodium acetate buffer (w/v) in plastic cups. After dilution in acetate buffer, the reaction was extremely slow, with less than 0.05% hydrolysis in a 2-hour period. Aliquots were analyzed for fluoride ion immediately after kinetic runs. Samples were allowed at least 15 minutes to come to thermal equilibrium after reaction quenching, and were always analyzed within 2 hours.

Fluoride ion concentrations were measured using an Orion model 94–09 fluoride electrode and an Orion 701A digital pH/mv meter. The electrode was calibrated daily using 10^{-1}, 10^{-2}, and 10^{-3} M reference solutions of NaF in sodium acetate. ^{31}P NMR spectra were acquired with a varian FT80A NMR spectrometer.

III. RESULTS

Observed rate constants were calculated by following the increase of fluoride ion concentration with time. Least squares analysis of $-\ln (F_\infty - F_t)$ vs t, where F_∞ and F_t are fluoride ion concentrations at time infinity and time t, respectively, yields F_0, fluoride at time 0, and k_{obs}, the observed rate constant. F_∞ was found by measuring fluoride ion concentrations at times greater than 10 reaction half-times.

The first order kinetic treatment (Figure 1) gave straight lines ($r^2 > 0.999$). Also, rates remained unchanged with differing initial concentrations of MF indicating that the reaction is first order. Observed rate constants for the hydrolysis of MF in graded concentrations of HCl at three temperatures are shown in Table I.

Figure 2 is a plot of $\log k_{obs}$ vs $\log [H+]$ for MF at 43.2°C. The slope of the line is 1.4. Analysis of various kinetic expressions showed that the catalyzed reaction rate could be predicted by Equation (2).

$$\frac{-dC}{dt} = [H+][CH_3P(O)OHF]k_H, \qquad (2)$$

where $C = [CH_3P(O)OHF] + [CH_3P(O)OF]^-$ at a given time. In Equation (2), it is taken into account that the rate of hydrolysis of the ionized form of MF, $[CH_3P(O)OF]^-$, is negligible compared to that of the acid conjugate, $[CH_3P(O)OHF]$. Substitution of the acid dissociation expression equivalent for

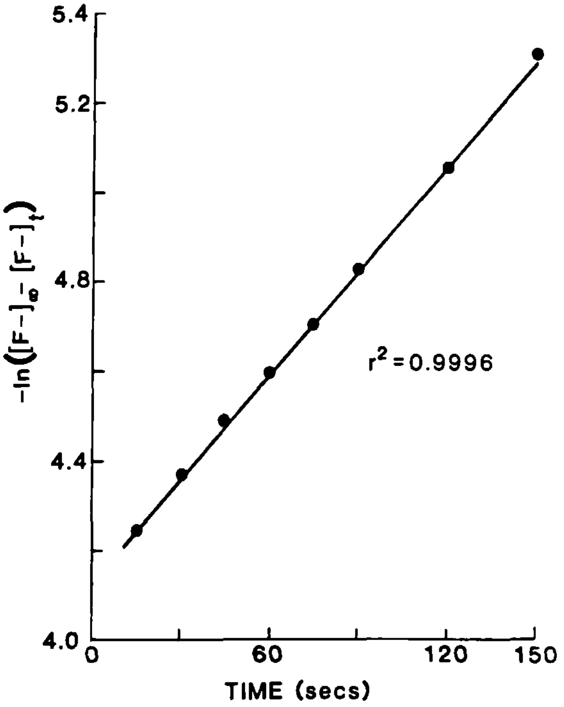


FIGURE 1 Hydrolysis of MF in 0.7 M HCl at 43.2°C, to 72% completion of reaction.

TABLE I

Experimental rate constants for the hydrolysis of MF in HCl

	0.4°C		24.3°C		43.2°C	
[HCl]	$10^5 \times k_{obs}$[a]	$10^4 \times k_H$[b]	$10^3 \times k_{obs}$	$10^3 \times k_H$	$10^3 \times k_{obs}$	$10^2 \times k_H$
0.30	—	—	—	—	2.29	2.08
					2.22	2.02
0.40	—	—	—	—	3.27	1.96
					3.22	1.93
0.50	3.95	1.67	0.766	3.25	4.63	1.96
	3.94	1.67	0.755	3.20	4.57	1.94
0.60	—	—	—	—	6.06	1.95
					6.01	1.94
0.70	7.74	1.99	1.25	3.21	7.81	2.01
	7.66	1.97	1.28	3.29	7.45	1.92
0.994	13.6	2.14	2.17	3.41	12.3	1.93
	13.5	2.12	2.11	3.32	13.5	2.12
	AV	1.93		3.28		1.98
		±0.21		±0.08		±0.06

[a] Units of $\sec^{-1}$; $k_H = \dfrac{k_{obs}([H+] + K_a)}{[H+]^2}$.

[b] Units of liter/moles × sec.

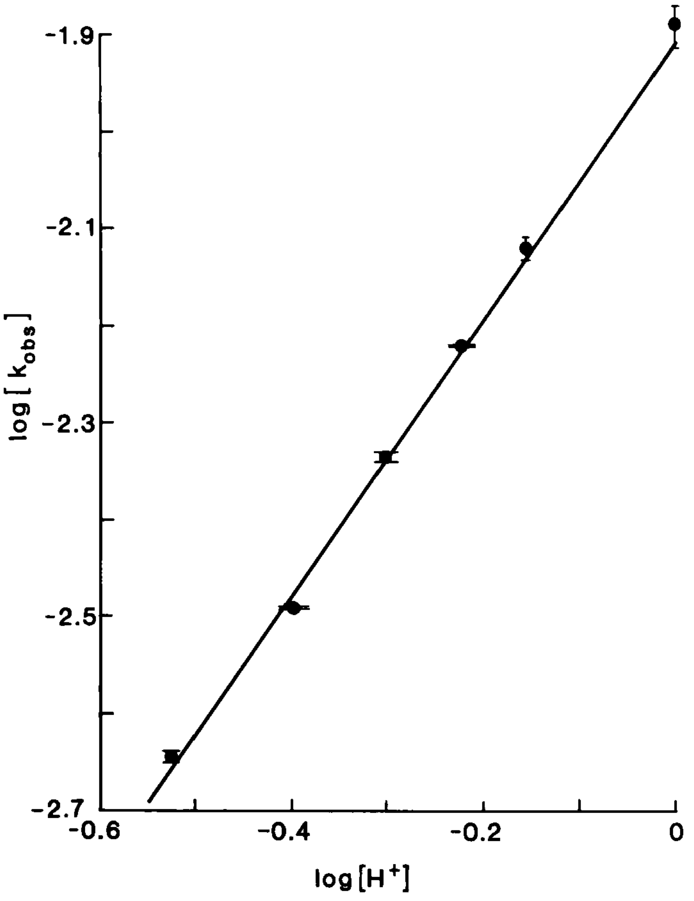


FIGURE 2 Plot of Log[H+] vs Log[k_{obs}] for MF at 43.2°C.

[$CH_3P(O)OHF$] in Equation (2) gives

$$\frac{-dC}{dt} = \frac{k_H[H+]^2C}{[H+] + Ka} = (k_{obs})C. \tag{3}$$

The acid hydrolysis constant of conjugated MF can be calculated from Equation (3).

$$k_H = \frac{k_{obs}([H+] + K_a)}{[H+]^2}. \tag{4}$$

The above data treatment has been used previously by others in the analyses of the hydrolysis of several fluorophosphoric acids.[9–11] Equation (3) can be rearranged to form an expression suitable for linear regression:

$$[H^+] = \frac{[H^+]^2}{k_{obs}} k_H - K_a. \tag{5}$$

By plotting $\frac{[H+]^2}{k_{obs}}$ vs[H+], the second order rate constant for acid catalysis, k_H, and thermodynamic equilibrium constant K_a were derived. Such a plot is shown in Figure 3 for acid catalysis at 43.2°C and yielded constants of $k_H = 1.98 \times 10^{-2}$

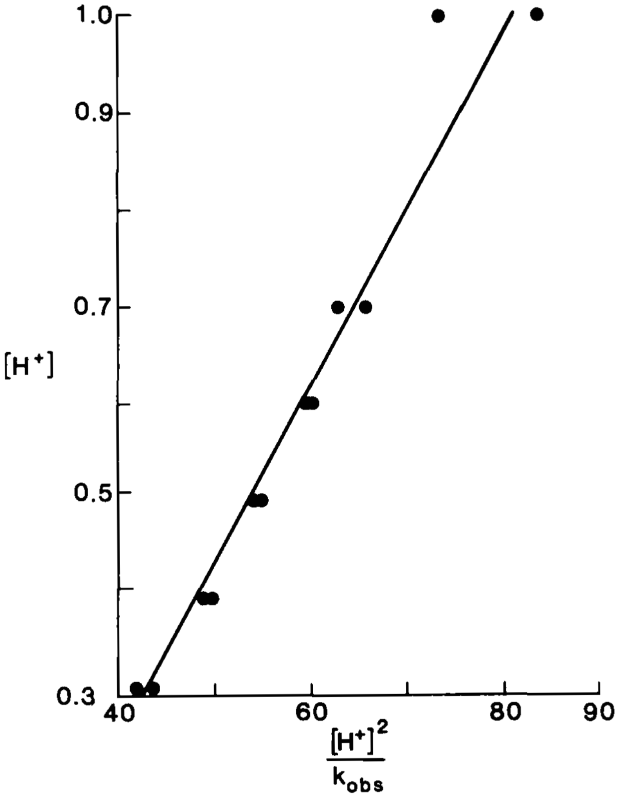


FIGURE 3 Linear regression analysis of MF. Plot of [H+] vs [H+]**2/k_{obs} at 43.2°C.

TABLE II

Experimental rate constants for the deuterolysis of MF in DCl at 43.2°C

[DCl]	$10^3 \times k_{obs}(D_2O)(sec^{-1})$	$10^2 \times k_D{}^{a,b}$
0.39	6.83	3.15
	6.62	3.05
0.49	8.66	2.89
	8.72	2.91
0.59	10.8	2.80
	10.7	2.77
Av		2.93 ± 0.15

[a] Calculated by Equation (4), and $K_a = 0.31$.
[b] Units of liter/mole × sec.

liter $mole^{-1}$ sec^{-1} and $k_a = 0.56$, respectively. At other temperatures, the limited number of points precluded the accurate determination of equilibrium constants, and the value of 0.56 was used in Equation (4) to calculate acid-catalyzed rate constants.

If a K_a of 0.56 is assumed at the lowest acid concentration of 0.3 N HCl, only about half of the MF will be dissociated to anionic MF^-. A slight correction (3%) was therefore made in defining acid concentration for hydrolysis of 0.02 N MF in 0.3 N HCl. For higher HCl concentrations, inconsequential errors are introduced by assuming the proton concentration is due solely to the HCl.

The rates of solvolysis of MF in three graded concentrations of DCl are shown in Table II. Because K_a in HCl is greater than in DCl, calculations of rate constants by Equation (4) using K_a values derived in HCl is improper.

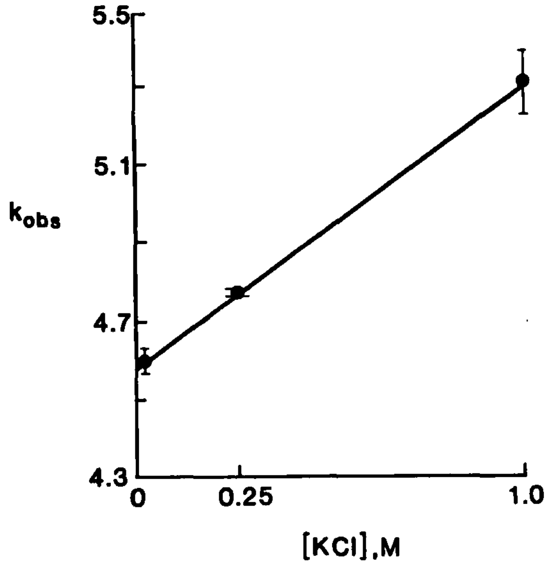


FIGURE 4 Effect of salt concentration on rates of hydrolysis.

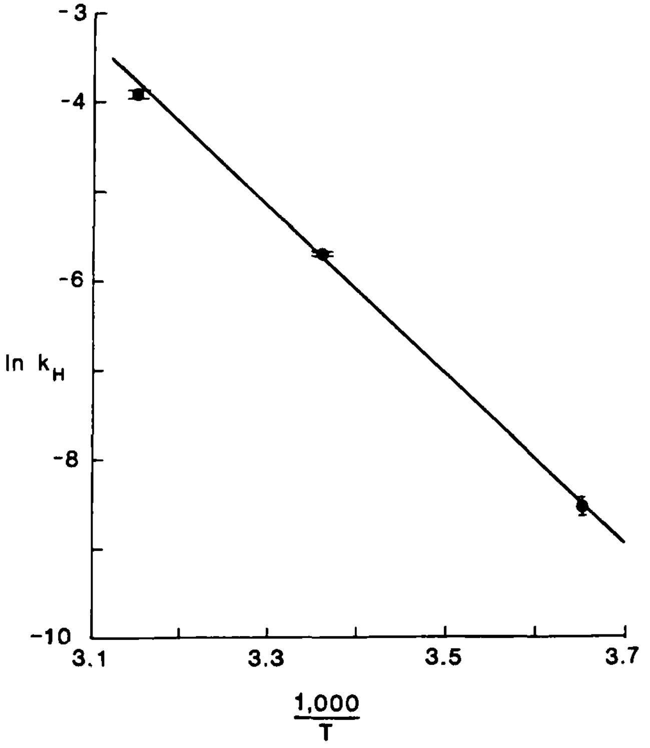


FIGURE 5 Arrhenius plot for the acid catalyzed hydrolysis of MF.

Unfortunately, the limited number of points available (3) was insufficient for calculation of K_a in DCl. Most acids in this range show ratios of K_a(HCl)/K_a(DCl) close to about 2.0.[12] For example, the equilibrium constants for H_2PO_3F in HCl and DCl are 0.8 and 0.45, respectively, for a ratio of 1.8.[9,11] Therefore, to calculate k_D by Equation (4), the K_a in HCl was divided by 1.8 to give 0.31. Using this value of K_a in DCl, the value of k_D calculated by Equation (4) is 2.93, and the ratio of k_D/k_H is 1.47.

The effect of ionic strength on acid hydrolysis is shown in Figure 4. Although KCl is added up to levels of 1 M, the rate varies by only 15%. Thus, the HCl catalysis of hydrolysis is largely a result of acid, and not salt effects.

The effect of temperature on the rate of acid hydrolysis of MF in acid is shown in Figure 5, where $\log k_H$ is plotted against inverse absolute temperature. The slope of the line gives the apparent Arrhenius activation energy, 18.3 kcal/mole.

Data for hydrolysis of MF at pH 7.4 in graded concentrations of phosphate buffer are shown in Table III. The rate does not vary linearly with phosphate concentration; however, a general acid-base catalysis was indicated. The half-time for the reaction at 0 buffer strength is greater than 60 days.

IV. DISCUSSION

With hydrogen ion concentrations between 0.3 and 1.0 M, the rate of hydrolysis of MF can be described as the reaction of only the uncharged conjugate acid. This

TABLE III

Hydrolysis of MF in phosphate buffer, pH 7.4 and 43.2°C

Buffer, *M*	$10^3 k_{obs}(\mathrm{Hrs}^{-1})$	$t_{1/2}$(Hrs)
0.25	0.49	1415
0.25	0.51	1359
0.5	1.02	680
0.5	1.07	648
1.0	4.45	156
1.0	4.61	150

conclusion is based on the close agreement between observed and calculated rate constants, where calculated rate constants assume a negligible contribution by the anionic form. At higher pHs, hydrolysis of MF is extremely slow (half-life 60 days). Lack of reactivity by the anionic form may be due to coulombic repulsion of nucleophiles by the negatively charged complex.

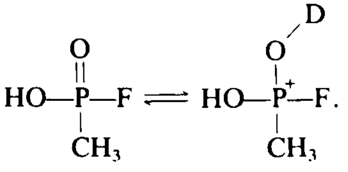
The mechanism of acid hydrolysis of MF can be inferred from: (1) comparison of the rates of reaction in H_2O and D_2O and (2) comparison of the rates of hydrolysis with compounds of similar structure.

Comparison of the rates of solvolysis of compounds in H_2O and D_2O has been used in deciding between acid-catalyzed reactions involving a rapid acid-proton transfer, followed by slow hydration of the protonated complex and proton transfer in the rate-determining step.[5]

$$CH_3P(O)OHF + H^+ \rightleftharpoons CH_3^+P(OH)OHF \qquad (6)$$

$$CH_3^+P(OH)OHF + H_2O \rightarrow CH_3P(O)(OH)_2 + HF + H^+.$$

Increased reaction rate in D_2O, as in the case of MF, can be attributed to a higher concentration of the deuterated species relative to the protonated species in H_2O:



$$HO{-}\overset{\overset{\displaystyle O}{\|}}{\underset{\underset{\displaystyle CH_3}{|}}{P}}{-}F \rightleftharpoons HO{-}\overset{\overset{\displaystyle O{-}D}{|}}{\underset{\underset{\displaystyle CH_3}{|}}{P^+}}{-}F. \qquad (7)$$

The latter species would be expected to be in higher concentration in D_2O because weak acids are less dissociated in heavy water, thus affording greater concentration of the reactive species for nucleophilic displacement. The considerably higher rates of solvolysis of MF in D_2O compared to in H_2O (ratio = 1.4) support this reaction mechanism.

The acid-catalyzed hydrolysis of a few compounds similar to MF have been determined, including FP(O)OHF and HOP(O)OHF.[9-11] Kinetic and thermodynamic hydrolysis parameters are compared in Table IV. The rate constants increase in the series $F < OH < CH_3$. However, the electronegativity decreases with the series $F > OH > CH_3$, as shown by the change in the pKa's of the products of the hydrolysis. Each pKa increases in a series, reflecting the decreasing stabilization of the negative charge on the acidic oxygen. The trend in the rate constants and in the electronegativity of the substituents agrees with the

TABLE IV

Kinetic and thermodynamic parameters for the acid catalyzed hydrolysis of RP(O)OHF

	Substituent (R)		
	F[b]	OH[c]	CH_3[d]
$10^4 k_H$(liter mole^{-1} sec^{-1})[a]	5.68 ± 0.13	10.7 ± 0.3	32.8 ± 0.8
$E_a \frac{(\text{Kcal})^g}{\text{Mole}}$	16.3 ± 1.0	16.7 ± 0.6	18.6 ± 0.1
$\Delta S^{R} \neq^{g}$	−20.7	−18.1	−10.5
pKa (hydrolysis products)	0.2	2.15[e]	2.38[f]

[a] At 25° ± 1.0°C.
[b] Values taken or calculated from Reference 9 unless noted.
[c] Values taken or calculated from Reference 10 unless noted.
[d] Values from this work unless noted.
[e] Values from Reference 13.
[f] Values from Reference 14.
[g] For the transition state.

proposed mechanism. Thus, less electronegative substituents, which stabilize the positive charge on the phosphorus, cause a shift in the equilibrium of Equation (6) to the protonated form and in turn to a faster overall rate.

Although all of the above observations appear to be consistent with the proposed mechanism, a previous study of the acid catalyzed deuterolysis of one of the compounds used for comparison, D_2PO_3F, suggested a different mechanism.[11] In that study, the ratio of k_{obs} (in D_2O)/k_{obs} (in H_2O) at 25°C was reported as 0.48. The authors concluded that this would be consistent with the same two step-mechanism; however, the relative *rates* of the two steps would necessarily be reversed. Thus, proton transfer occurs in the rate-determining step.

The apparent contradiction may be due to the incorrect calculation of the ratios of rates in D_2O relative to H_2O by Min *et al.*[11] Rate constants for deuterolysis were determined, but the authors did not specify the source of the rate constants for hydrolysis. These may have been taken from the previous work of Devonshire and Rosley,[9] or Clark and Jones,[10] or possibly determined by the authors. The rate constants derived in the previous two studies were in agreement within experimental error, when the data are extrapolated to 25°C (6.22 and 6.49 × 10^{-2} liter/mole × min, respectively.[9,10]

Direct comparisons of the rates of hydrolysis can lead to mechanistic confusion for experimentally derived rate constants at the same concentration of H^+ or D^+. At equal concentrations of H^+ or D^+, less of the conjugate acid will be dissociated in deuterated solvent. Thus, the rates of deuterolysis will appear high in comparison to those of hydrolysis. A better comparison is in the overall second order rate constants of hydrolysis and deuterolysis, k_H and k_D. The rate constant for deuterolysis given by Min *et al.* at 25° was 7.33 × 10^{-2} liter/mole × min.[11] By choice of either of the two previously determined constants, the k_D/k_H ratio is greater than unity, which is in agreement with our mechanism.

In both previous studies of hydrolysis, the above mechanism was suggested, although with less firm evidence.[9,10] Our data and those from the deuterolysis of D_2PO_3F, may not be reconcilable. A repetition of the work with D_2PO_3F, in conjunction with H_2PO_3F, would be useful in reconciling these data sets.

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