Solvolysis of Phosphoric Acid Esters. Hydrolysis of Methyl, Ethyl, Isopropyl, and *t*-Butyl Dihydrogen Phosphates

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The kinetics of hydrolysis of ethyl and isopropyl dihydrogen phosphates was studied in strongly acid media, up to 8 M $HClO_4$, at several temperatures. The rate of hydrolysis of ethyl dihydrogen phosphate is, at constant ionic strength, proportional to the perchloric acid concentration, the rates of both the neutral and the acid-catalyzed reactions being enhanced with increase in ionic strength of the medium. On the other hand, the rate of the acid-catalyzed hydrolysis of isopropyl dihydrogen phosphate is proportional to the Hammett acidity function, H_0, with a slope of 1.03. In strongly acid solutions, hydrolysis of isopropyl dihydrogen phosphate occurs with almost complete C–O bond fission. In moderately acid media, the rate of hydrolysis has a minimum at about pH 1.5, and a maximum at pH 4. The hydrolysis of the monoanion, which is predominant at pH 4, involves 100% P–O bond fission. The reactions of isopropyl dihydrogen phosphate are thus intermediate between those of primary alkyl dihydrogen phosphates (rate of acid-catalyzed hydrolysis linearly related to stoicheiometric acidity; rate maximum at pH 4) and those of tertiary alkyl dihydrogen phosphates (rate of acid-catalyzed hydrolysis proportional to H_0; no rate maximum at pH 4). Comparison of the rates of the hydrolysis in strongly acidic solutions in D_2O and in H_2O gives k_{D_2O}/k_{H_2O} = 1.20 ± 0.06, 1.32 ± 0.05, 1.46 ± 0.06, and 1.78 ± 0.10 for methyl, ethyl, isopropyl, and *t*-butyl dihydrogen phosphate, respectively.

The pioneering work on the kinetics of hydrolysis of alkyl dihydrogen phosphates is due to Bailly and Desjobert, who discovered the particular reactivity of the monoanions of these esters.[1]

In the series of alkyl dihydrogen phosphates, only the kinetics and mechanism of hydrolysis of the methyl,[2] and of the *t*-butyl[3] esters have been studied carefully. The kinetic behavior of these two esters differs considerably—methyl dihydrogen phosphate undergoes acid-catalyzed hydrolysis at a rate proportional to stoicheiometric acidity, and in moderately acid solutions exhibits a pronounced maximum at about pH 4, at which most of the substrate exists as the monoanion. On the other hand, *t*-butyl dihydrogen phosphate has an acid-catalyzed hydrolysis that is linearly related to the Hammett acidity function, H_0, and does not exhibit a maximum in rate in weakly acid solutions. It therefore seemed of interest to examine the borderline cases of ethyl and isopropyl dihydrogen phosphate, as model compounds for understanding the hydrolytic reactions of primary and secondary phosphate esters, many of which are important components in biological systems. Owing to the completely different mechanistic behavior of the methyl and *t*-butyl esters, simple interpolation to the secondary esters would not be reliable.

Results

A. Hydrolysis in Strongly Acid Solutions.—The hydrolysis of both ethyl and isopropyl dihydrogen phosphate in aqueous perchloric acid follows first-order kinetics. With both compounds, the rate increases rapidly with the perchloric acid concentration, and is subject to a positive salt effect—added sodium perchlorate considerably increases the rate of hydrolysis. For ethyl dihydrogen phosphate, the rate at constant ionic strength increases linearly with the perchloric acid concentration (see Table I and Figure 1). Considering the reaction in strongly acid solutions to be given by the simultaneous first-order hydrolysis of the neutral molecule (rate constant k_N), and by the second-order acid-catalyzed hydrolysis (rate constant k_A), we get for the observed first-order rate constant

$$k'_{obsd} = k_N + k_A[H^+] \qquad (1)$$

where $[H^+]$ is the stoicheiometric perchloric acid concentration. From the least-squares fit of the linear plot of k'_{obsd} against $[H^+]$, the specific rates for the hydrolysis of ethyl dihydrogen phosphate at 100° are as shown in Table II. Thus, the rates of both the neutral reaction, k_N, and of the acid-catalyzed reaction, k_A, are subject to an ionic strength effect.

TABLE I

FIRST-ORDER RATE CONSTANTS FOR HYDROLYSIS OF ETHYL DIHYDROGEN PHOSPHATE AT 100° AS A FUNCTION OF PERCHLORIC ACID CONCENTRATION[a]

$[HClO_4]$, M	A, 10^6k, sec^{-1}	B, 10^6k, sec^{-1}	C, 10^6k, sec^{-1}	D, 10^6k, sec^{-1}
0.5	2.05			
1.0	2.81	3.97	6.75	
2.0	4.87	6.29	9.91	18.31
3.0	6.60	7.34	13.57	
4.0	9.92		15.91	31.64
5.0	13.71			36.56
6.0	20.55			
8.0	53.92			

[a] A, without control of ionic strength; B, at ionic strength μ = 4; C, at ionic strength μ = 6; and D, at ionic strength μ = 8, using added $NaClO_4$. Average error is ±3%.

TABLE II

SPECIFIC RATE CONSTANTS k_N AND k_A FOR HYDROLYSIS OF ETHYL DIHYDROGEN PHOSPHATE AS A FUNCTION OF IONIC STRENGTH, μ

μ	10^6k_N, sec^{-1}	10^6k_A, l. mole^{-1} sec^{-1}
4	2.15 ± 0.55	1.89 ± 0.20
6	4.57 ± 0.71	2.75 ± 0.20
8	7.17 ± 1.0	5.88 ± 0.20

Applying the Zucker–Hammett criterion to the hydrolysis of ethyl dihydrogen phosphate, in strongly acidic solutions,[4] linear plots were obtained for log $(k_{obsd} - k_N)$ against log $[HClO_4]$, if the ionic strength

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[1] (a) M. C. Bailly, *Bull. Soc. Chim. France*, [5] **9**, 340, 405, 421 (1942); (b) A. Desjobert, *ibid.*, [5] **14**, 809 (1947); *Compt. Rend.*, **224**, 575 (1947).

[2] (a) C. A. Bunton, D. R. Llewellyn, K. G. Oldham, and C. A. Vernon, *J. Chem. Soc.*, 3574 (1958); (b) P. C. Haake and F. H. Westheimer, *J. Am. Chem. Soc.*, **83**, 1102 (1961).

[3] A. Lapidot, D. Samuel, and M. Weiss Broday, *J. Chem. Soc.*, 637 (1964).

[4] L. Zucker and L. P. Hammett, *J. Am. Chem. Soc.*, **61**, 2791 (1939).

was maintained constant. The slope was unity, and was unaffected by the ionic strength of the solutions. Thus at the ionic strengths 4, 6, and 8, the slopes were 1.01 ± 0.09, 1.12 ± 0.07, and 1.03 ± 0.04, respectively. The plot of log $(k_{obsd} - k_N) + H_0$ against log a_{H_2O} (where a_{H_2O} is the activity of water in the solution), recommended by Bunnett,[5] has a steadily decreasing curvature. In the range 3–6 M perchloric acid, the slope has the value $w = 4.0 \pm 0.3$. In the 3–8 M perchloric acid range, the alternative plot of log $(k_{obsd} - k_N)/[H^+]$ against log a_{H_2O} is linear, with a slope $w^* = -0.88 \pm 0.05$.

As shown in Table III the rate of hydrolysis of isopropyl dihydrogen phosphate does not increase linearly with the perchloric acid concentration, even if constant ionic strength is maintained. A linear relationship was, however, obtained by plotting log $(k_{obsd} - k_N)$ against the Hammett acidity function, H_0, where k_{obsd} is the observed first-order rate constant (without control of ionic strength, column A in Table II), and k_N is the specific first-order rate constant for uncatalyzed decomposition of the neutral species (see below). Values of H_0 were taken from Yates and Wai.[6] A least-squares fit of the plot gave a slope of 1.03 ± 0.04.

TABLE III

FIRST-ORDER RATE CONSTANTS FOR HYDROLYSIS OF ISOPROPYL DIHYDROGEN PHOSPHATE AT 100° AS A FUNCTION OF PERCHLORIC ACID CONCENTRATION[a]

$[HClO_4]$, M	A, 10^4k, sec^{-1}	B, 10^4k, sec^{-1}	C, 10^4k, sec^{-1}
1.00	0.53	2.66	9.26
2.00	1.61	4.80	17.30
3.00	3.74	7.30	29.20
4.00	10.50		45.2
5.00	31.50		75.0
6.00	97.40		

[a] A, without control of ionic strength; B, at ionic strength $\mu = 4$; and C, at ionic strength $\mu = 6$, using added $NaClO_4$.

The plots according to Bunnett[5] gave $w = 0.2 \pm 0.1$ and $w^* = -5$ which are linear in the range 2–6 M perchloric acid.

From the temperature dependence of the rate of acid-catalyzed hydrolysis of methyl, ethyl, and isopropyl dihydrogen phosphates, determined in 4 M perchloric acid (without added sodium perchlorate), values for the energy and entropy of activation were determined (see Table IV).

TABLE IV

TEMPERATURE EFFECTS ON RATES OF METHYL, ETHYL, AND ISOPROPYL DIHYDROGEN PHOSPHATE IN 4 M PERCHLORIC ACID

	10^6k_{obsd}, sec^{-1}		
Temp, °C	$CH_3OPO_3H_2$	$C_2H_5OPO_3H_2$	$C_3H_7OPO_3H_2$
72.2 ± 01			33.6 ± 0.3
84.7 ± 0.1	2.94 ± 0.10	1.65 ± 0.04	156 ± 1
100.0[a]	15.0 ± 0.20[b]	9.92 ± 0.24	1050
110.6[c]	32.6 ± 1.0	27.0 ± 0.8	
E_a, kcal mole^{-1}	25.2 ± 1.2	29.3 ± 1.0	31.0 ± 0.2
ΔS^*_{100}, eu	−16.3	−6.0	+8.2

[a] Refluxing water thermostat. [b] Bunton, *et al.*,[2a] obtained 15.0 × 10^{-6} sec^{-1}. [c] Refluxing toluene thermostat.

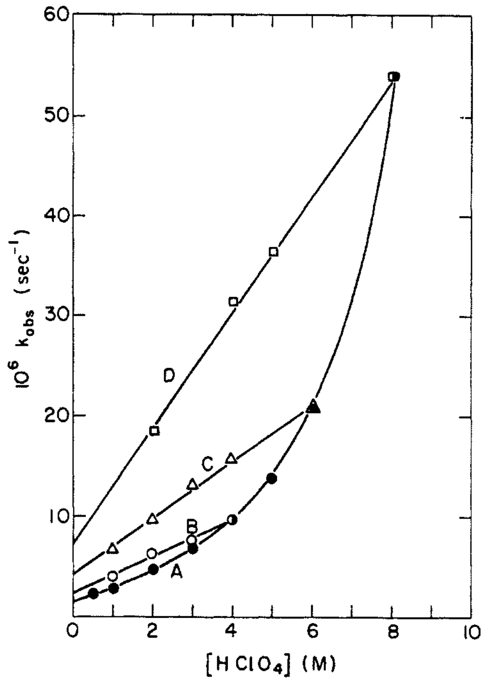

Figure 1.—Rates of hydrolysis of ethyl dihydrogen phosphate at 100° as a function of perchloric acid concentration, without control of ionic strength (A, ●) and with constant ionic strength $\mu = 4$ (B, ○), $\mu = 6$ (C, △), and $\mu = 8$ (D, □).

The solvent isotope effect on the acid-catalyzed hydrolysis was determined by measuring the rates (in 1.2 M perchloric acid and in 3.6 N sulfuric acid) in water and in deuterium oxide, respectively (see Table V). The deuterium oxide solutions contained 98.5 and 96.0% D in the perchloric and sulfuric acids, respectively. The solvent isotope effect on the hydrolysis of methyl dihydrogen phosphate had been determined before, but using water containing only 67.6% D, and k_{D_2O}/k_{H_2O} was 1.02.[2a] In the present work, using water with 98.5% D, the isotope effect was 1.20. For *t*-butyl dihydrogen phosphate in 2.06 M perchloric acid at 10°, an isotope effect, $k_{D_2O}/k_{H_2O} = 0.65$, was reported.[3] Probably at this acid concentration, the contribution of hydrolysis of the neutral molecule is still predominant. Therefore in the present work a higher acid concentration was used.

B. Hydrolysis of the Neutral Species.—As noted above, the rate of hydrolysis of the neutral molecule of *ethyl* dihydrogen phosphate at 100° is $k_N = 2.15 \times 10^{-6}$ sec^{-1} at ionic strength $\mu = 4$. For hydrolysis of the neutral molecule of *isopropyl* dihydrogen phosphate, at the same ionic strength, a much larger value of k_N is obtained by extrapolation from strongly acid solutions (Table II, column B). From the (nonlinear) plot of k_{obsd} as a function of perchloric acid concentration, extrapolation to 0 acid concentrations gives $k_N = 1.0 \times 10^{-4}$ sec^{-1}. The rate constants k_N at ionic strength $\mu = 0$ are 0.7×10^{-6} sec^{-1} and 0.3×10^{-6} sec^{-1} for ethyl and isopropyl dihydrogen phosphate, respectively. These rate constants k_N at $\mu = 0$ were obtained for ethyl dihydrogen phosphate from the intercept of the linear plot of log k_N (from the various intercepts in Figure 1) against μ,[2a] and for isopropyl dihydrogen phosphate from the intercept of the linear plot of results at pH 1.8–8 (see below, section D).

C. Determination of Acid Dissociation Constants.—Values of pK_1 and pK_2 for isopropyl dihydrogen

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[5] J. F. Bunnett, *J. Am. Chem. Soc.*, **83**, 4956, 4968, 4973, 4978 (1961).

[6] K. Yates and H. Wai, *ibid.*, **86**, 5408 (1964).

TABLE V

SOLVENT ISOTOPE EFFECT ON THE ACID-CATALYZED HYDROLYSIS OF ALKYL DIHYDROGEN PHOSPHATES[a]

R in ROPO$_3$H$_2$	Temp, °C	$10^6{}_{H_2O}$, sec^{-1}		$10^6k_{D_2O}$, sec^{-1}		k_{D_2O}/k_{H_2O}	
		[HClO$_4$]	[H$_2$SO$_4$]	[HClO$_4$]	[H$_2$SO$_4$]	[HClO$_4$]	[H$_2$SO$_4$]
Me	100		18.5		22.5		1.20 ± 0.06
Et	100	3.46	14.6	3.83	19.3	1.10 ± 0.03	1.32 ± 0.05
i-Pr	100	76.8	685.	121.6	1000	1.58 ± 0.05	1.46 ± 0.06
t-Bw	0		71.5		127.3		1.78 ± 0.10

[a] Rate Constants are k_{obsd}.

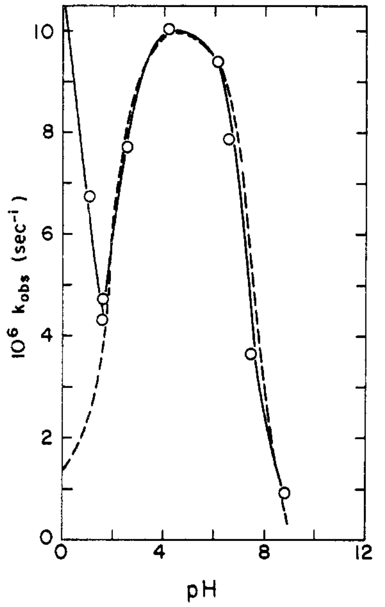

Figure 2.—Rates of hydrolysis of isopropyl dihydrogen phosphate at 100° as a function of pH: experimental results, full line; calculated line from the concentration of the monoanion, broken line.

phosphate at several temperatures from 14 to 50° were determined (see Table VI). Measurements of pH at higher temperatures are difficult. Therefore, extrapolation to 100° was made, using the equation of Harned and Embree[7] for the dependence of K_T on temperature T.

TABLE VI

THE DISSOCIATION CONSTANTS pK_1 AND pK_2 OF ISOPROPYL DIHYDROGEN PHOSPHATE AS A FUNCTION OF TEMPERATURE

Temp, °C	pK_1	pK_2
14.3	1.72 ± 0.05	7.03 ± 0.04
22.2	1.75 ± 0.02	7.02 ± 0.03
31.2	1.79 ± 0.04	7.03 ± 0.03
41.4	1.86 ± 0.02	7.07 ± 0.04
50.3	1.93 ± 0.04	7.07 ± 0.09

$$\mathrm{p}K_T = \mathrm{p}K_M + 5.0 \times 10^{-5}(T - T_M)^2 \qquad (2)$$

As was shown by these authors, the dissociation constants, K_T, of acids and bases in aqueous solutions have a maximum value, K_M, at a temperature, T_M. By rearranging eq 2 we get

$$\log K_T + 5.0 \times 10^{-5}T^2 = \log K_M + 5.0 \times 10^{-5}T_M{}^2 + (2 \times 5.0 \times 10^{-5}T_M)T \qquad (3)$$

From a least-squares fit of the linear plot of (log K_T + 5.0 × $10^{-5}T^2$) against T, the values of the slope and the intercept are obtained and from these the maximum values, K_M, of the dissociation constants, K_T, at the temperatures, T_M. Inserting the two parameters in eq 2, it is thus possible to derive the dissociation constants at 100°, pK_{100} as follows: first dissociation, T_M = 25 ± 3°; pK_M = 1.67 ± 0.01; pK_{100} = 1.92 ± 0.04; second dissociation, T_M = 19 ± 4°; pK_M = 7.02 ± 0.02; pK_{100} = 7.35 ± 0.05.

D. Hydrolysis of the Isopropyl Hydrogen Phosphate Monoanion.—Rate constants for hydrolysis of isopropyl phosphate in the pH range 1–9 are presented in Table VII and in Figure 2. Since the rate of hydrolysis in alkaline solutions is negligible, the reaction in this region can be described as occurring only by simultaneous unimolecular decomposition of the neutral molecule and of the monoanion

TABLE VII

FIRST-ORDER RATE CONSTANTS FOR HYDROLYSIS OF ISOPROPYL DIHYDROGEN PHOSPHATE AT 100° IN THE pH RANGE 1–9

pH[a]	Buffer soln	10^6k, sec^{-1}
1.07	0.10 *M* HClO$_4$	6.75
1.78	0.0245 *M* HCl + 0.050 *M* KCl	4.35
2.60	0.050 *M* KHP[b] + 0.040 *M* HCl	7.75
4.23	0.050 *M* KHP	10.0 ± 0.2
6.05	0.050 *M* KHP + 0.033 *M* NaOH	9.40
6.58	0.050 *M* KHP + 0.045 *M* NaOH	7.90
7.48	0.028 *M* HCl + 0.072 *M* B.S.[c]	3.64
8.83[d]	0.01 *M* borax	0.91

[a] Measurements for pH 1 to 7.5 were made at 25° and extrapolated to 100° by the method of S. Stene, *Rec. Trav. Chim.*, **49**, 1133 (1930). [b] KHP = potassium hydrogen phthalate. [c] B. S. = barbitone sodium. [d] "Handbook of Chemistry and Physics," 44th ed, Chemical Rubber Publishing Co., Cleveland, Ohio, 1962, p 1721.

$$k_{obsd} = k_N[\mathrm{AH_2}] + k_1[\mathrm{AH^-}] \qquad (4)$$

where [AH$_2$] and [AH$^-$] are the fractions of the substrate present as the neutral molecule and the monoanion, calculated from the acid dissociation constants, K_1 and K_2. Since [AH$_2$] + [AH$^-$] = 1, we get

$$k_{obsd} = (k_1 - k_N)[\mathrm{AH^-}] + k_N \qquad (5)$$

Therefore, a plot of k_{obsd} against [AH$^-$] should be linear, with a slope, $k_1 - k_N$, and an intercept, k_N. A least-squares fit of the data resulted in

$$k_1 = (9.6 \pm 0.5)10^{-6}\ \mathrm{sec^{-1}};\ k_N = (0.3 \pm 0.3)10^{-6}\ \mathrm{sec^{-1}}$$

A direct determination of k_1 is based on the observed rate constant at pH 4.23, at which 99.8% of the isopropyl phosphate appears as the monoanion. As seen in Table VII and in Figure 2, this maximal rate constant is k_1 = (10.0 ± 0.2)10^{-6} sec^{-1}. The hydrolysis of isopropyl phosphate is thus similar to that of the methyl and ethyl esters in having a rate maximum at about pH 4,[1,2] and differs from that of *t*-butyl phosphate, which has no maximum.[3]

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(7) H. S. Harned and N. D. Embree, *J. Am. Chem. Soc.*, **56**, 1050 (1934).

Energies and entropies of activation for hydrolysis of the monoanion were calculated from the rate constants at several temperatures (see Table VIII).

TABLE VIII
ENERGIES AND ENTROPIES OF ACTIVATION FOR HYDROLYSIS OF ISOPROPYL DIHYDROGEN PHOSPHATE MONOANION

Temp, °C	10^6k_1, sec^{-1}	E_a, kcal mole^{-1}	S^*_{100}, eu
72.2 ± 0.1	0.238 ± 0.004		
84.6 ± 0.1	1.55 ± 0.03		
100.0°	10.0 ± 0.2	32.1 ± 0.7	+2.4

The kinetics of hydrolysis of ethyl phosphate in moderately acid solutions was studied by Desjobert, who found that the variation of the rate constant of the hydrolysis with pH in the region pH 1–8 was paralleled by the variation in concentration of the monoanion species, and obtained $k_1 = 6.09 \times 10^{-6}$ sec^{-1} for the rate constant at 100°.[1b]

E. Points of Bond Fission during Hydrolysis.—Using ^{18}O-enriched water, the positions of bond fission during hydrolysis of ethyl and isopropyl dihydrogen phosphate were determined in 4 *M* perchloric acid, in which the reaction involves only the conjugate acid of the substrate, and also of isopropyl dihydrogen phosphate at pH 5.0, at which the molecule reacts only as the monoanion, all at 100°. The results are given in Table IX.

TABLE IX
POINTS OF BOND FISSION DURING THE HYDROLYSIS OF ETHYL AND ISOPROPYL PHOSPHATES

Substrate	Solution	Reacn time, min	Atoms % excess ^{18}O in Water	Atoms % excess ^{18}O in H_3PO_4	% P–O bond fission
Ethyl phosphate	4 *M* $HClO_4$	1260	16.5 ± 0.4	2.02 ± 0.02	48 ± 2
Isopropyl phosphate	4 *M* $HClO_4$	17	14.7 ± 0.2	0.05 ± 0.03	1.2 ± 0.7
	pH 5.0	1500	15.3 ± 0.2	4.3 ± 0.2	109 ± 7

In strongly acid solutions, hydrolysis of ethyl phosphate is seen to involve about 50% C–O bond fission, while that of isopropyl phosphate occurs with almost 100% C–O bond fission. At pH 5, the reaction occurs only with P–O bond fission.

The extent of isotopic oxygen exchange between the solvent and the ethyl dihydrogen phosphate, which occurred under the above conditions (1260 min in 4 *M* $HClO_4$ at 100°) is about 1%.

Discussion

A. Hydrolysis in Strongly Acidic Solutions.—The mechanistic investigation of the acid-catalyzed hydrolysis of the series of alkyl dihydrogen phosphates from methyl to *t*-butyl can use several diagnostic tools—the relative rates of reaction, activation parameters, the acidity function obeyed, solvent isotope effect, and the type of bond fission observed in hydrolysis in $H_2{}^{18}O$. Results summarized in Table X, show that by all criteria, a drastic change in mechanism occurs in going from ethyl to isopropyl dihydrogen phosphate. This must be assigned as a change from a bimolecular reaction, involving a water molecule in the rate-determining step, to a unimolecular dissociation.

The decrease in rate of acid-catalyzed hydrolysis from methyl to ethyl dihydrogen phosphate is similar to the decrease reported in going from ethyl to *n*-propyl dihydrogen phosphate.[8] The decrease may be due to steric hindrance to nucleophilic attack of the water molecule. On the other hand, the rate of hydrolysis of esters undergoing a unimolecular mechanism is enhanced by chain branching from isopropyl to *t*-butyl.

In the series methyl, ethyl, and isopropyl dihydrogen phosphate, the sensitivity of the rate of acid-catalyzed hydrolysis to the ionic strength of the solution increases markedly. This again supports a change in mechanism—the unimolecular heterolysis being more susceptible to increasing ionic strength.

The dramatic increase in rate of acid-catalyzed hydrolysis in going from ethyl to isopropyl dihydrogen phosphate is seen not to be due to a decrease in activation energy, which actually *increases* from the ethyl to the isopropyl ester, but rather to a marked change in entropy of activation, from −6.0 to +8.2 (see Table X). This change can be explained most simply by a relative decrease in the number of bound water molecules in forming the transition state.

Another marked change involved in going from ethyl to isopropyl dihydrogen phosphate concerns the acidity function. While with methyl and ethyl dihydrogen phosphate, the rate of hydrolysis is linearly related to stoicheiometric acidity, with isopropyl and *t*-butyl[3] dihydrogen phosphates, the rate is related to the Hammett acidity function. On the basis of the Zucker–Hammett hypothesis,[4] this indicates that for the first two substrate molecules, a water molecule participates in the rate-determining step, while for the last two molecules, no water molecule is involved. A similar conclusion is reached by using the functions $\log (k_{obsd} - k_N)/[H^+]$ or $\log (k_{obsd} - k_N) + H_0$ *vs.* $\log a_{H_2O}$, as suggested by Bunnett.[5]

The profound influence of structure on the mechanism of the acid-catalyzed hydrolysis affects not only the molecularity of the reaction, but also the point of bond fission. While for primary alkyl dihydrogen phosphates, a mixture of P–O and C–O bond fission is observed, the secondary and tertiary alkyl dihydrogen phosphates undergo only C–O bond fission.

A larger rate in deuterium oxide solution must be due to a preequilibrium proton transfer in which a larger fraction of the substrate is protonated when in deuterium oxide than when in water solution.[9] For methyl and ethyl dihydrogen phosphate, where these results on the basis of the Zucker–Hammett hypothesis suggest participation of a water molecule in the rate-determining step, partial compensation of the larger rate in deuterium oxide seems to be due to the weaker nucleophilic activity of deuterium oxide. For isopropyl dihydrogen phosphate, the acid-catalyzed hydrolysis of which is more of a unimolecular type, such compensation is much smaller. LD-Glucose-1 dihydrogen phosphate, which also is a secondary alkyl phosphate,[10] has a

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(8) E. Cherbuliez, H. Probst, and J. Rabinowitz, *Pharm. Acta Helv.*, **37**, 396 (1962).

(9) K. B. Wiberg, *Chem. Rev.*, **55**, 713 (1955).

(10) C. A. Bunton, D. R. Llewellyn, K. G. Oldham, and C. A. Vernon, *J. Chem. Soc.*, 3588 (1958).

TABLE X

MECHANISTIC COMPARISON OF ALKYL DIHYDROGEN PHOSPHATES UNDER ACID-CATALYZED HYDROLYSIS

R in $ROPO_3H_2$	10^6k_{obsd}, sec^{-1}	E_a, kcal $mole^{-1}$	S^*_{100}, eu	Acidity function obsd (with slope of 1)	% P–O bond fission	k_{D_2O}/k_{H_2O}	Suggested mechanism
Me	15.0[a]	25.2	−16.3	Log [H^+]	27	1.20	Bimolecular
Et	9.9[a]	29.3	−6.0	Log [H^+]	48	1.32	Bimolecular
i-Pr	1050[a]	31.0	+8.2	H_0	1	1.46	Unimolecular
α-D-Glucose-1				H_0[b]	0[b]	1.53[c]	Unimolecular
t-Bu				H_0[d]	0[d]	1.78[e]	Unimolecular

[a] Rate constant for 100° in 4 *M* perchloric acid. [b] Taken from ref 10. [c] In 3.00 *M* perchloric acid, at 25°, using 75% D_2O. Taken from ref 10. [d] Taken from ref 3. [e] Isotope effect for 0° in 3.6 *N* sulfuric acid. Present work.

similar isotope effect as isopropyl dihydrogen phosphate. The largest isotope effect, $k_{D_2O}/k_{H_2O} = 1.78 \pm 0.10$, is found for *t*-butyl dihydrogen phosphate, in the hydrolysis of which the effect of the nucleophilic activity of the solvent is thus much smaller.

B. Hydrolysis in Weakly Acidic Solutions.—While the acid-catalyzed hydrolysis of isopropyl dihydrogen phosphate is about a 100 times larger than that of the ethyl ester, the rate constants of reaction of the neutral species, k_N, and of the monoanion, k_1, are of the same order of magnitude. For hydrolysis at 100°, the values are listed in Table XI. The similarity of rates for the first three substrates suggests a similarity of mechanisms for reactions of the neutral molecule and the monoanion.

TABLE XI

THE RATE CONSTANTS FOR THE HYDROLYSIS OF THE NEUTRAL SPECIES AND THE MONOANION OF THE ALKYL PHOSPHATES

R in $ROPO_3H_2$	Temp, °C	10^6k_N, sec^{-1}	10^6k_1, sec^{-1}
Me	100	0.5[a]	8.23[a]
Et	100	0.7[b]	6.09[c]
i-Pr	100	0.3[b]	9.6[b]
t-Bu[d]	73.9	4830[d]	70[d]

[a] Reference 2a. [b] Present work. [c] Reference 1b. [d] Reference 3.

Experimental Section

Methyl dihydrogen phosphate (K & K Laboratories, Inc.) was used without further purification. *Anal.* Calcd for $CH_3Ba_2O_4P \cdot 4H_2O$: P, 13.6; equiv wt, 228. Found: P, 13.8; equiv wt (potentiometric titration with NaOH), 211.

Ethyl dihydrogen phosphate was prepared from sodium dihydrogen phosphate and ethyl iodide,[1b] and was separated from diethyl hydrogen phosphate by fractional crystallization of the barium salts.[11] *Anal.* Calcd for $C_2H_5BaO_4P \cdot H_2O$: P, 11.1; equiv wt, 279.4. Found: P, 11.0; equiv wt (potentiometric titration with NaOH), 281.4.

Isopropyl dihydrogen phosphate, obtained previously by other methods,[12] was prepared in the present work by the action of polyphosphoric acid on isopropyl alcohol, a procedure described before for other alcohols.[13] A mixture of polyphosphoric acid (0.7 mole) and isopropyl alcohol (0.7 mole) was refluxed for 6 hr on a water bath. The excess alcohol was then evaporated.

To the remaining oil a tenfold amount of water was added, the solution was brought to pH 9 with barium hydroxide, and the precipitate of barium orthophophosphate was centrifuged off. Carbon dioxide was then passed through the supernatant to remove most of the barium ions, and the solution was passed through the H^+ form of Dowex 50W × 12 cation exchanger, and was brought to pH 9 with cyclohexylamine. With addition of acetone, the dicyclohexylammonium salt of isopropyl dihydrogen phosphate was precipitated. After three crystallizations from water and acetone, white needles were obtaned, mp 212–214°, R_f 0.34 ± 0.01 (ascending paper chromatography on Whatman No. 1 paper in *n*-propyl alcohol–ammonia–water, 6:3:1).[14] *Anal.* Calcd for $C_{15}H_{35}N_2O_4P \cdot H_2O$: C, 50.6; H, 10.4; N, 7.8; P, 8.7. Found: C, 51.3; H, 10.6; N, 7.3; P, 8.8.

***t*-Butyl phosphate** dicyclohexylammonium salt: prepared by the method of Cramer, *et al.*,[15] was used, mp 191–192°.

Deuterium oxide (99.8 g/100 g of deuterium, Norsk Hydro-Elektrisk Kvaelstofaktieselskab) was used without further purification. Perchloric acid solutions were prepared by adding deuterium oxide up to 10.0 ml to a volumetric flask containing 1.00 ml of perchloric acid (70%, Fluka AG, puriss.). Similarly, sulfuric acid (British Drug Houses, ANALAR) was diluted with D_2O.

Rate measurements for methyl, ethyl, and isopropyl dihydrogen phosphates were made by thermostating solutions in sealed glass ampoules. The reaction was interrupted by cooling the tubes in ice–water, and determining the resulting orthophosphate by the colorimetric molybdate method.[16] The value for complete reaction was obtained by hydrolysis at 100° for 5–8 hr in about 5 *M* perchloric acid. Rate measurements for *t*-butyl dihydrogen phosphate were made in volumetric flasks (10 ml) kept in a water–ice mixture (0°). Aliquots (1 ml) were pipetted into a slight excess of aqueous sodium hydroxide to quench the reaction. The resulting orthophosphate was determined by the molybdate method at pH 4.[17] The value for complete reaction was obtained by hydrolysis at 100° for 5 hr.

Acid dissociation constants were determined by pH measurements on mixture of the salts of the alkyl dihydrogen phosphates (about 0.02 *M*) with hydrochloric acid, using a Radiometer TTT1 pH meter fitted with a scale expander. The titration cell was thermostated to within ±0.1°.

The first dissociation constant, pK_1, was determined by adding to the solution of the salt enough hydrochloric acid solution to have the phosphate as a mixture $RHPO_4^-$ (salt) and RH_2PO_4 (acid). pK_1 was obtained from the equation

$$pK_1 = pH - \log [(C_{salt} + C_{H^+})/(C_{acid} - C_{H^+})]$$

where C_{salt} and C_{acid} were derived from the initial concentration of the salt of the phosphate and the amount of hydrochloric acid added and C_{H^+} was calculated from the pH.

The second acid dissociation constant, pK_2, was obtained from the Henderson equation

$$pK_1 = pH + \log [q'/(q - q')]$$

where q and q' are the volumes of acid added at the equivalence point (one sodium atom) and the volume added at any other point before the equivalence point. Therefore q' and $(q - q')$ are proportional to the concentrations of the mono- and dianion, respectively.

Least-squares fits of linear plots, for acid dissociation constants and rate constants, were made with the CDC-1604A computer of this institute, using a FORTRAN program.

Oxygen isotope determinations were carried out by dissolving the phosphate esters in ^{18}O-enriched water. After more than one-half time, the orthophosphate was precipitated by adding barium

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chloride, and bringing the solution with sodium hydroxide to pH 9. The precipitate was washed, dissolved in hydrochloric acid, reprecipitated with sodium hydroxide, dissolved by shaking with the protonated form of Dowex 50W × 12 ion exchanger, brought to pH 4 with 3 *N* potassium hydroxide, and precipitated as KH_2PO_4 by addition of acetone and cooling overnight in a deep freeze. The potassium dihydrogen phosphate was washed with acetone, dried at 60° under reduced pressure, and analyzed for ^{18}O by the method of Boyer, *et al.*[18]

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Registry No.—Ethyl dihydrogen phosphate, 1623-14-9; isopropyl dihydrogen phosphate, 1623-24-1; methyl dihydrogen phosphate, 812-00-0; dicyclohexylammonium salt of isopropyl dihydrogenpho sphate, 7695-58-1; *t*-Butyl dihydrogen phosphate, 2382-75-4; *n*-propyl dihydrogen phosphate, 1623-06-9.

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The Thermal Decomposition of Metal O,O-Dialkylphosphorodithioates[1]

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The thermal decomposition of metal O,O-dialkylphosphorodithioates has been shown to be an autocatalytic reaction yielding olefins, mercaptans, hydrogen sulfide, and polymeric residue. The reaction is dependent on the structure of the alkyl groups and, for a series of divalent metals, on the size of the metal cation. Specifically, the rate of decomposition increases with increasing number of hydrogens on the β-carbon atoms in the alkyl groups and with decreasing metal cation size. These results, plus information on the sequence of product formation, product distribution, effect of added reagents, and deuteration of the alkyl groups, form the basis for a proposed reaction mechanism. The mechanism includes an isomerization followed by an intramolecular (*cis*) elimination as key steps to the formation of olefins.

The thermal decomposition of metal O,O-dialkylphosphorodithioates has been the subject of a number of investigations[2-7] but the detailed mechanism has not been clearly understood.

Hanneman and Porter[5] have recently examined the volatile olefins formed during the pyrolysis of zinc O,O-dialkylphosphorodithioates at 215 to 302°, and concluded that the decomposition proceeded through a carbonium ion mechanism. Luther and Sinha[6] have compared the formation of olefins, mercaptans, and hydrogen sulfide from 25 to 250° for zinc di-*n*-butyl and diisobutyl phosphorodithioates, and reached the conclusion that the thermal decomposition proceeded by a free-radical mechanism. Ashford, Bretherick, and Gould[7] examined the thermal decomposition of zinc di(4-methylpentyl-2)phosphorodithioate between 130 and 190°, and concluded that the mechanism of decomposition includes the partial isomerization of thiono- to thiolosulfur with subsequent decomposition of both isomers by one or more routes involving carbonium ions and free radicals. Several studies[2-4] have been concerned with the determination of the thermal decomposition temperature for gas evolution and for solid residue formation. From a chemical analysis of the gases and the residue, Feng[2] proposed a reaction involving release of an olefin, an isomerization to form a =P(SH)= group, and, finally, the formation of an interthioanhydride, which upon occurring for two or more alkyl groups in a given molecule leads to a polymeric structure.

Heretofore, none of the reported work involved a study with pure materials to determine both the effect of the cation and the structure of the alkyl group on the rate of thermal decomposition. This paper reports the results of such an investigation at 155°, and proposes a mechanism involving an isomerization and an intramolecular (*cis*) elimination of olefin from the thiolosulfur isomer as key steps in the decomposition scheme.

Experimental Section

Preparation of Metal O,O-Dialkylphosphorodithioates.—The O,O-dialkylphosphorodithioic acids and their ammonium salts were prepared essentially by the procedure of Wystrach, *et al.*[8] The ammonium salts were purified by recrystallization from isooctane or isooctane–ethyl alcohol mixtures.

The zinc (or other metal) salts were prepared by metathetic reactions using aqueous solutions of the ammonium salts and filtered aqueous solutions of $ZnCl_2$ (or the chloride, nitrate, or sulfate of the other metals) in stoichiometric amounts. Solid, insoluble metal salts were isolated by filtration and purified by recrystallization. Liquid products were extracted from the aqueous mixture with pentane, washed with water, and dried and the pentane was removed by evaporation under vacuum.

Table I lists the metal O,O-dialkylphosphorodithioates prepared. Zinc O,O-diisopropylphosphorodithioate was chosen initially as a representative compound for extensive investigation, since it is readily purified by recrystallization and hence well suited to our purpose. The deuterated zinc O,O-diisopropylphosphorodithioate was prepared from 2-propyl-1,1,1,3,3,-3-d_6 alcohol.

Apparatus and Procedure.—The apparatus used for the thermal decomposition of the metal O,O-dialkylphosphorodithioates is sketched in Figure 1. Liquids of proper boiling point (*o*-xylene, bp 144°; bromobenzene, bp 155°; decane, bp 174°) were refluxed in the jacket to obtain the desired, constant, reproducible reaction temperature. D is a water absorber containing a starch indicator in which the hydrogen sulfide was titrated continuously with standard potassium iodide–iodine solution. The manostat (F) maintains the system at about 1 atm by releasing water from the gas holder as gas is formed.

After purging the apparatus with nitrogen, a weighed sample of about 0.004 mole of the phosphorodithioate was placed in

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[1] Presented in part before the Division of Petroleum Chemistry, 149th National Meeting of the American Chemical Society, Detroit, Mich., April 1965.

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