Acid-Catalyzed Hydrolyses of Weakly Basic Phosphate Esters

C. A. BUNTON AND S. J. FARBER

Department of Chemistry, University of California at Santa Barbara, Santa Barbara, California 93106

Received January 27, 1969

The acid-catalyzed hydrolyses of *p*-nitrophenyl, 2,4-dinitrophenyl, bis-2,4-dinitrophenyl, and *p*-nitrophenyldiphenyl phosphate have been examined using hydrochloric, sulfuric, and perchloric acids in the range of 1–10 M. Plots of the first-order rate constant, k_ψ, against C_{H^+} generally show maxima which are not caused by extensive protonation of the substrate. Addition of THF increases the rate of hydrolysis of 2,4-dinitrophenyl phosphate at low acidities and decreases it at high acidities, but the log A factors and the activation energies are only slightly sensitive to changes in acid concentration or solvent composition, except for hydrolysis of *p*-nitrophenyldiphenyl phosphate. The values of $k_{\mathrm{H_2O}}/k_{\mathrm{D_2O}}$ are in the range of 0.7–1.1 and larger than generally found for A2 hydrolyses. These results suggest that proton transfers are partially rate limiting, and that initial-state effects are also important. The basicities of triphenyl and *p*-nitrophenyldiphenyl phosphates have been measured.

The rates of acid-catalyzed hydrolyses of weakly basic substrates generally increase steadily and smoothly with increasing hydrogen ion concentration, C_{H^+}.[1] Relations between rate constants and hydrogen ion concentration and acidity functions have been discussed extensively,[1] and attempts to relate reaction rates to water activity have had some success.[2] Recently it has been shown that the protonation of weak bases and the rates of acid-catalyzed hydrolysis of many weakly basic substrates can be fitted to a linear free-energy relation involving both hydrogen ion concentration and the Hammett's acidity function, *e.g.*, plots of log $k_\psi + H'_0$ against log $C_{\mathrm{H}^+} + H'_0$ are generally linear.[3] The slopes of these plots, ϕ can be related to the w values obtained by plotting log $k_\psi + H'_0$ against log $a_{\mathrm{H_2O}}$.

The rates of hydrolysis of basic substrates reach maxima in strong acid when the substrate is converted almost completely into its conjugate acid.[4] These maxima occur in moderately concentrated acid (typically $C_{\mathrm{H}^+} < 4\ M$) with basic substrates such as amides, and the variations of k_ψ with acidity can be explained moderately successfully in terms of the extent of protonation and parameters such as water activity.[4,5] With less basic substrates, such as carboxylic esters, these rate maxima occur in more concentrated acid.[6]

It is generally assumed that there is a rapid equilibrium protonation of the substrate, S, and that the conjugate acid is attacked by a water molecule, or decomposes spontaneously, in the rate-limiting step (eq 1–3). (In this formulation we omit water molecules which are involved in solvating or hydrogen bonding, and the nucleophile in the rate-limiting step may be an anion[7] rather than a water molecule.)

$$\overset{+}{\mathrm{H}} + \mathrm{S} \rightleftharpoons \mathrm{H}\overset{+}{\mathrm{S}} \text{ (fast, reversible)} \qquad (1)$$

$$\left.\begin{array}{l} \mathrm{H}\overset{+}{\mathrm{S}} + \mathrm{H_2O} \xrightarrow[\mathrm{A2}]{\text{slow}} \text{products} \\ \mathrm{H}\overset{+}{\mathrm{S}} \xrightarrow[\mathrm{A1}]{\text{slow}} \text{intermediate} \longrightarrow \text{products} \end{array}\right\} \text{(slow)} \qquad \begin{array}{r} (2) \\ (3) \end{array}$$

This general pattern of behavior does not fit the acid hydrolyses of some weakly basic substrates for which the rates increase to a maximum in moderately concentrated acid (1.5–8 M) and then decrease sharply. These rate maxima cannot be explained in terms of complete protonation of the substrate and have been observed in the acid hydrolyses of some (but not all) aryl phosphates,[8–12] phosphinates,[13] sulfites,[14] and some trifluoroacetates[15] and other carboxylic acid derivatives.[16,17] The actual behavior of monoaryl phosphates depends upon the presence of strongly electron-attracting substituents. For example, there is no acid-catalyzed hydrolysis with phenyl, or alkyl- or chloro-substituted phenyl phosphate, but nitro- or acetylphenyl phosphate is subject to acid catalysis with rate maxima in moderately concentrated acid.[9–12]

Some of these acid hydrolyses could be followed only in aqueous organic solvents,[9,13–15] because of the low solubility of some of the substrates in water, and we could suppose that changes in properties of the mixed solvent brought about by the acid could cause rate maxima, but this explanation cannot be applied to reactions in aqueous acids. In some of the systems the spontaneous hydrolysis makes an appreciable contribution to the over-all reactions, and the strong acid, as an electrolyte, could have a strong negative salt effect upon the spontaneous hydrolysis which could overcome a weak acid catalysis.[14–17] This explanation cannot be the complete answer because with some substrates the spontaneous hydrolysis is relatively slow, and in addition this combination of a negative salt effect upon a spontaneous hydrolysis and

---

(1) F. A. Long and M. A. Paul, *Chem. Rev.*, **57**, 935 (1957).

(2) J. F. Bunnett, *J. Amer. Chem. Soc.*, **83**, 4956 (1961), and accompanying papers.

(3) J. F. Bunnett and F. P. Olsen, *Can. J. Chem.*, **44**, 1899, 1917 (1966).

(4) J. T. Edward and S. C. R. Meacock, *J. Amer. Chem. Soc.*, **79**, 2000 (1957), and references cited.

(5) J. A. Leisten, *J. Chem. Soc.*, 765 (1959); R. B. Moodie, P. D. Wale, and T. J. Whaite, *ibid.*, 4273 (1963); K. Yates and J. B. Stevens, *Can. J. Chem.*, **43**, 529 (1965); C. A. Bunton, C. J. O'Connor, and T. A. Turney, *Chem. Ind.* (London), 1835 (1967).

(6) C. A. Lane, *J. Amer. Chem. Soc.*, **86**, 2521 (1964); K. Yates and R. A. McCelland, *ibid.*, **89**, 2686 (1967).

(7) C. A. Bunton, P. B. de la Mare, and J. G. Tillett, *J. Chem. Soc.*, 4754 (1958); C. A. Bunton, D. Kellerman, K. G. Oldham, and C. A. Vernon, *ibid.*, *B*, 292 (1966).

(8) A. Desjobert, *Bull. Soc. Chim. Fr.*, 683 (1968).

(9) P. W. C. Barnard, C. A. Bunton, D. Kellerman, M. M. Mhala, B. Silver, C. A. Vernon, and V. A. Welch, *J. Chem. Soc.*, *B*, 227 (1966); C. A. Bunton, E. J. Fendler, E. Humeres, and K-U. Yang, *J. Org. Chem.*, **32**, 2806 (1967).

(10) C. A. Bunton, E. J. Fendler, and J. H. Fendler, *J. Amer. Chem. Soc.*, **89**, 1221 (1967).

(11) C. A. Bunton, S. J. Farber, and E. J. Fendler, *J. Org. Chem.*, **33**, 29 (1968).

(12) C. A. Bunton and S. J. Farber, *ibid.*, **34**, 767 (1969).

(13) P. Haake and G. Hurst, *J. Amer. Chem. Soc.*, **88**, 2544 (1966); P. Haake, R. D. Cook, and G. Hurst, *ibid.*, **89**, 2650 (1967).

(14) J. G. Tillett, *J. Chem. Soc.*, 5138 (1960); C. A. Bunton and G. Schwerin, *J. Org. Chem.*, **31**, 842 (1966).

(15) C. A. Bunton and T. Hadwick, *J. Chem. Soc.*, 3248 (1958); 943 (1961).

(16) (a) M. L. Bender, Y. L. Chow, and F. Chloupek, *J. Amer. Chem. Soc.*, **80**, 5380 (1958); (b) C. A. Bunton, J. H. Fendler, S. Perry, and J. Rocek, *J. Chem. Soc.*, 6174 (1965).

(17) S. Marburg and W. P. Jencks, *J. Amer. Chem. Soc.*, **84**, 232 (1962).

a weak catalysis leads to rate *minima* in hydrolyses of cyclic anhydrides in aqueous acids.[16b]

There are certain characteristic features of these reactions which exhibit rate maxima in acid which are not associated with complete protonation of the substrate. (i) The reaction rate is sensitive to the water content of the solvent; *e.g.*, addition of aprotic solvents generally decreases the rate, and the w values[2] are large and positive. (ii) The entropies of activation are large and negative; *e.g.*, $\Delta S^* -30$ eu, and the enthalpies of activation tend to be low. (iii) The values of k_{H_2O}/k_{D_2O} are close to or slightly greater than unity, whereas typically for acid-catalyzed hydrolyses the values are as low as 0.4 and rarely go above 0.7.[18-20] (iv) The order of effectiveness of the acids as catalysts is $HCl > H_2SO_4 > HClO_4$. (v) At least for the hydrolysis of aryl phosphates the reactions are assisted by electron-attracting substituents, and $\rho \approx 0.5$,[10] whereas typically electronic effects are very small for acid-catalyzed hydrolyses, with $\rho \sim 0$.[21]

Characteristically these rate maxima are observed only with weakly basic substrates, *e.g.*, with trifluoroacetates,[15] but not with acetates or benzoates,[1-3] and with some aryl but not alkyl phosphates,[22] suggesting that the usual counterbalancing of electronic effects upon the basicity of a substrate and the rate of attack of water upon its conjugate acid are absent.[21]

Because the acid hydrolyses of nitrophenyl phosphates and phosphinates show these rate maxima, we could suppose that the hydrogen ion interacts with the nitro group, possibly by hydrogen bonding, but this explanation is untenable, because rate maxima are observed in the acid hydrolyses of di- and triphenyl phosphates.[9,11] Another possible explanation is that the rates of these particular hydrolyses are very sensitive to water activity, but it is then hard to explain why these hydrolyses should be so different from those of structurally similar, but less basic, substrates and why relations between reaction rate and water activity break down with some catalyzing acids.[2,9] Because these rate maxima are observed only with compounds of low basicity one might suppose that proton transfers are partially rate limiting. The values of w and ϕ parameters are characteristic of reactions for which proton transfers are slow.[2,3]

Much of the existing evidence is fragmentary, and therefore we have examined hydrolyses of mono-, di-, and triaryl phosphates using various acids in both water and aqueous organic solvents, and in water and deuterium oxide in an attempt to examine the generality of the effects and the way in which they depend upon the structure of the substrate. In addition we obtained approximate pK_a values of triphenyl and p-nitrophenyldiphenyl phosphate by the hydrogen-bonding method.[23]

Aryl phosphates were the most convenient substrates for this investigation because their hydrolyses can be followed in water and aqueous organic solvents, and the effects of structural variations can easily be studied systematically.

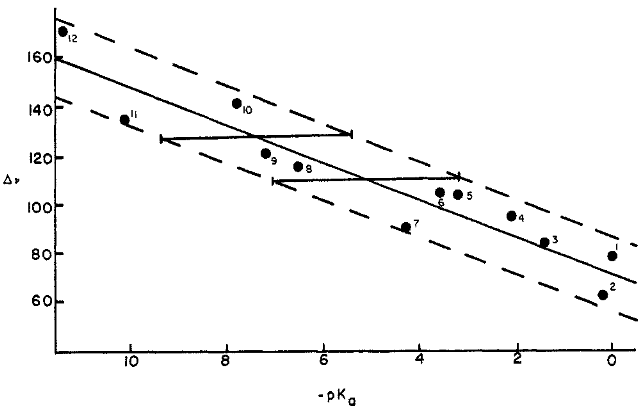


Figure 1.—Variation of hydrogen-bonding frequencies with basicity with CH_3OD in carbon tetrachloride: 1, N,N-dimethylformamide; 2, N,N-dimethylacetamide; 3, N,N-dimethylbenzamide; 4, tetrahydrofuran; 5, dioxane; 6, diethyl ether; 7, diisopropyl ether; 8, acetone; 9, methyl ethyl ketone; 10, methyl benzoate; 11, acetonitrile; 12, nitrobenzene.

Experimental Section

Materials.—The preparation and purification of the aryl phosphates and most of the other reagents and solvents have been described.[9-12] Tetrahydrofuran was refluxed over sodium and then redistilled, and the solvents for the infrared measurements were distilled before use. The boiling points of all the solvents agreed with literature values.

Kinetics.—The hydrolyses were followed spectrophotometrically using a Gilford spectrophotometer with a water-jacketed cell compartment. The reactions were followed in the cells, except for the slower runs and those at higher temperatures, where sealed tubes or stoppered flasks had to be used, and the hydrolysis of bis-2,4-dinitrophenyl phosphate where alkaline phosphatase was used to hydrolyze the 2,4-dinitrophenyl phosphate formed in the first step of the reaction.[12]

For the hydrolyses in D_2O samples of D_2SO_4 and DCl were initially diluted to give 8 and 7.9 M acid, and the concentrations were checked by titration. Part of these solutions was used for the hydrolyses in the more concentrated acid, and the rest was diluted with D_2O to give the 3 M solutions. Identical solutions were used for the hydrolyses of 2,4-dinitrophenyl and bis-2,4-dinitrophenyl phosphate.

Basicity Measurements.—The pK_a values of triphenyl and p-nitrophenyldiphenyl phosphate were determined by measuring the infrared stretching frequency of MeOD in dry carbon tetrachloride in the presence of various weak bases. Infrared frequency shifts, $\Delta\nu_{OD}$, of a weak acid in weak bases vary linearly with the pK of the base, and Arnett has concluded that pK values can be determined within approximately two units by this method.[23] Figure 1 shows a plot of $\Delta\nu_{OD}$ against pK_a for a number of bases. The pK_a values were taken from Arnett's review.[23] For triphenyl phosphate $\Delta\nu_{OD} = 128$ cm^{-1}, and for p-nitrophenyldiphenyl phosphate $\Delta\nu_{OD} = 110$ cm^{-1}. The horizontal bars are drawn at these values in Figure 1. The values of $\Delta\nu_{OD}$ were found to be independent of the concentrations of MeOD and the phosphates.

The concentrations used were [MeOD] = 0.25 M, and [$ArOPO(OPh)_2$] = 1.0 M, and the measurements were made using a Beckman IR-7 spectrophotometer at 31°. With a few bases the base and deuteriomethanol concentrations were increased up to threefold; the change in frequency was <2 cm^{-1}. With CH_3OH and CH_3OD in CCl_4, $\nu = 3355$ and 2490 cm^{-1}, respectively.

Oxygen Exchange of Triphenyl Phosphate.—Triphenyl phosphate was used as substrate for the oxygen-exchange experiments to avoid complications from the oxygen content of nitro groups in the other phosphates. Triphenyl phosphate was allowed to hydrolyze in 0.5 M $HClO_4$ in dioxane-$H_2{}^{18}O$ 75:25 (v/v) at 100° for one half-life (9 hr).[9] The reaction mixture was extracted with benzene; the organic layer was washed with water, then with 0.1 M NaOH (three times), and again with water and

---

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

(19) J. G. Pritchard and F. A. Long, *J. Amer. Chem. Soc.*, **78**, 6008 (1956); **80**, 4162 (1958).

(20) C. A. Bunton and V. J. Shiner, *ibid.*, **83**, 3207 (1961).

(21) C. K. Ingold, *J. Chem. Soc.*, 1032 (1930); R. W. Taft, *J. Amer. Chem. Soc.*, **75**, 4231 (1953), and references cited.

(22) C. A. Bunton, D. R. Llewellyn, K. G. Oldham, and C. A. Vernon, *J. Chem. Soc.*, 3574 (1958).

(23) E. M. Arnett, *Prog. Phys. Org. Chem.*, **1**, 223 (1964).

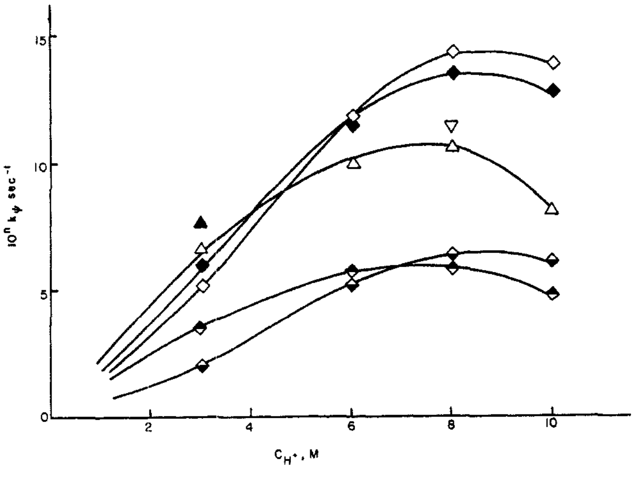


Figure 2.—Effect of addition of an aprotic solvent upon the acid hydrolysis of 2,4-dinitrophenyl phosphate: ◇, HCl in water at 25.0°; ◆, HCl in water + 2 mol % THF at 25.0°; ▽, HCl in water + 4 mol % THF at 25.0°; △, HCl in water + 6 mol % THF at 25.0°; ▲, HCl in water + 12 mol % THF at 25.0°; ⬙, HCl in water at 73.0°; ⬘, HCl in water + 2 mol % THF at 73.0°. At 25.0° $n = 5$; at 73.0° $n = 3$.

was dried over $MgSO_4$. The benzene was pumped off, giving 1 g of crude triphenyl phosphate which after two crystallizations from hexane had mp 49–50° (lit.[9] mp 49°). The triphenyl phosphate was heated *in vacuo* with guanidine hydrochloride and phenylenediamine hydrochloride and the evolved CO_2 was analyzed mass spectrometrically.[24] This degradation procedure does not sample the phenolic oxygen atoms.

Results

Basicity Measurements.—The pK_a values of -5.0 for triphenyl phosphate and -7.4 for *p*-nitrophenyl phosphate which we obtained from the frequency shifts of hydrogen bonds (Figure 1) are in the range expected from measurements on related compounds. For example Haake and Hurst have determined pK_a values for some phosphine oxides and phosphinic and phosphonic acids and esters, and for *p*-nitrophenyldiphenyl phosphinate the extrapolated $pK_a = -5.7$.[13] This value was based on direct measurements and on analogies with structural effects upon the basicities of benzyl ketones. Alkoxy and aryloxy groups have larger $-I$ effects than has phenyl,[25] *e.g.*, for phenoxy $\sigma^* = 0.85$ and for phenyl $\sigma^* = 0.215$, and the basicity of phosphoryl oxygen is sensitive to indirective effects;[13] therefore, *p*-nitrophenyldiphenyl phosphate would be expected to be less basic than *p*-nitrophenyldiphenyl phosphinate. An earlier value of $pK_a = -2.8$ for triphenyl phosphate[9] was determined using indicator methods and the scale of Lemaire and Lucas for perchloric–acetic acid mixtures.[26] There is a major problem in relating protonation equilibrium constants in acetic acid to those in water, because the correction almost certainly depends upon the nature of the base.[23] The basicity of the phosphonyl compounds examined by Haake and his coworkers were related to the H'_0 acidity scale,[13] which may not be the appropriate one for these bases, and comparison between hydrogen bonding measurements in CCl_4 and direct measurements in strong acids are fraught with uncertainty.[23] However, the results suggest that aryl phosphates, like phosphine oxides and their derivatives,[13] are protonated on phosphoryl oxygen. This is not to say that the proton resides on this atom in the transition state. We could not determine the basicities of the mono- and diaryl phosphate from frequency shifts of deuteriomethanol, and, because of the apparent error in the earlier value of pK_a for triphenyl phosphate in acetic acid, we did not use indicator methods for these compounds.

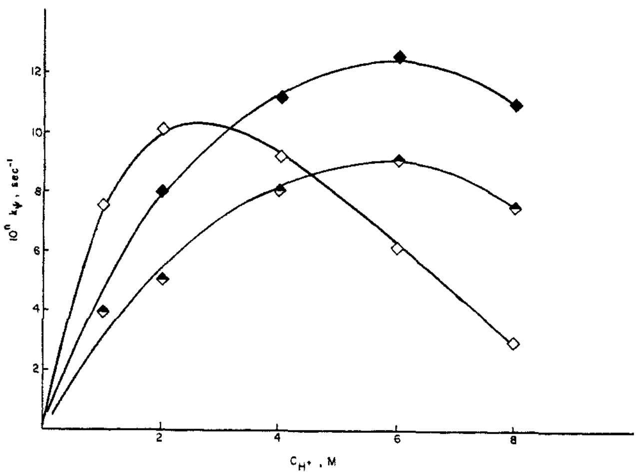


Figure 3.—Effect of addition of aprotic solvents upon the acid hydrolysis of *p*-nitrophenyldiphenyl phosphate: ◇, HCl in water + 2 mol % THF at 25.0°; ◆, HCl in water + 2 mol % THF at 100°; ⬘, HCl in water + 1.1 mol % dioxane at 100°. At 25.0° $n = 6$; at 100° $n = 4$.

Oxygen Exchange.—After 50% hydrolysis using water of 2.76 atom % excess abundance the phosphoryl oxygen atom of the isolated triphenyl phosphate had abundances of 0.014 and 0.011 atom % excess, showing that the oxygen exchange is negligibly slow. This result agrees with other evidence from experiments in neutral and basic solution that phosphoryl oxygen atoms generally exchange very slowly with water.[27]

Kinetics.—The values of the first-order rate constants k_ψ, are given in Tables I–IV and Figures 2 and 3, which illustrate the effects of changes in acidity and solvent composition. The mixed solvents used in the kinetic work were THF–water—2 mol % [1:10.9 (v/v)]; 4 mol % [1:5.33 (v/v)]; 6 mol % [1:3.48 (v/v)]; and 12 mol % [1:1.63 (v/v)]—and dioxane–water—1.1 mol % [1:19 (v/v)].

Relation between Reaction Rate and Acidity.—Generally plots of $\log k_\psi + H'_0$ against $\log a_{H_2O}$ were curved. For example, for the hydrolysis of bis-2,4-dinitrophenyl phosphate the plots are approximately parallel for the three acids with $w \sim 8$ at low acid concentrations and $w \sim 2.5$ at high acid concentrations.[12] Similar curved plots were obtained for the acid hydrolysis of *p*-nitrophenyldiphenyl phosphate.[11] However, good linear plots were obtained for the acid hydrolysis of *p*-nitrophenyl but not with 2,4- and 2,6-dinitrophenyl phosphates,[9,10] and Bunnett noted in his original discussion that these treatments were not always successful for phosphate esters.[2] We do not believe that this curvature indicates a mechanistic

---

(24) H. Dahn, H. Moll, and R. Menassé, *Helv. Chim. Acta*, **42**, 1225 (1959); C. A. Bunton and B. N. Hendy, *J. Chem. Soc.*, 627 (1963).

(25) R. W. Taft in "Steric Effects in Organic Chemistry," M. S. Newman Ed., John Wiley & Sons, Inc., New York, N. Y., 1959, Chapter 13.

(26) H. Lemaire and H. J. Lucas, *J. Amer. Chem. Soc.*, **73**, 5198 (1951).

(27) D. Samuel and B. L. Silver, *Advan. Phys. Org. Chem.*, **3**, 123 (1965); P. W. C. Barnard, C. A. Bunton, D. R. Llewellyn, C. A. Vernon, and V. A. Welch, *J. Chem. Soc.*, 2670 (1961).

TABLE I

ACID HYDROLYSIS OF 2,4-DINITROPHENYL PHOSPHATE[a]

C_{H^+}, *M*	HCl	H_2SO_4	$HClO_4$
3.00	5.23	5.64	4.73
3.00	209[b]	271[b]	202[b]
3.00		8.22[c]	
3.00		379[b,c]	
6.00	12.0	10.9	8.32
6.00	535[b]	532[b]	390[b]
8.00	14.5	9.24	
8.00	667[b]	415[b]	
8.00		13.9[c]	
10.0	14.1		
10.0	637[b]		

[a] Values of 10^5 k_ψ, sec^{-1}, at 25.0° unless specified. [b] At 73.0°. [c] D_2SO_4 in D_2O.

TABLE II

ACID HYDROLYSIS OF BIS-2,4-DINITROPHENYL PHOSPHATE[a]

C_{H^+}, *M*	HCl	H_2SO_4	$HClO_4$
2.00	1.41[b]		
2.00	16.7[c]		
3.00	2.26	2.85[b]	
3.00	1.90[d]	2.40[b,e]	
4.00	3.27[b]		2.00[b]
4.00	39.0[c]		26.0[c]
7.90	9.13[b]		
7.90	10.2[d]		
8.00		8.78[b]	
8.00		9.59[b,e]	
8.00		93.4[c]	
8.95			5.21
8.95			57.6[c]
10.0	14.7[b]		
10.0	131[c]		

[a] Values of 10^6 k_ψ, sec^{-1}, at 25.0° unless specified. [b] Reference 12. [c] At 50.0°. [d] DCl in D_2O. [e] D_2SO_4 in D_2O.

TABLE III

ACID HYDROLYSIS OF *p*-NITROPHENYL PHOSPHATE[a]

	C_{H^+}, *M*			
Solvent	1.00	2.00	4.00	6.00
H_2O	0.98	1.98	3.20	3.07
THF, 2 mol %	0.97	1.88	2.62	2.40
THF, 4 mol %	0.93		2.12	
THF, 6 mol %	0.92		1.87	
H_2O		116[b]	234[b]	230[b]
H_2O	729[c]	1050[c]	1150[c]	783[c]
Dioxane, 5 vol. %	710[c]	1023[c]	1110[c]	720[c]
Dioxane, 60 vol. %	611[c]	822[c]		

[a] Values of 10^6 k_ψ, sec.$^{-1}$, with HCl in water or aqueous organic solvents at 25.0° unless specified. [b] Aqueous HCl in water at 73.0°.[9] [c] $HClO_4$ at 100.0°.

TABLE IV

SOLVENT EFFECTS UPON THE ACID HYDROLYSIS OF *p*-NITROPHENYLDIPHENYL PHOSPHATE[a]

	C_{H^+}, *M*	
Solvent	2	6
THF, 2 mol %	10.1	6.14
THF, 6 mol %	8.97	3.85
THF, 12 mol %	6.70	2.60

[a] Values of 10^6 k_ψ, sec^{-1}, with HCl at 25.0° unless specified.

change, because plots of log $k_\psi + H'_0$ against log $C_{H^+} + H'_0$ are generally linear, and for bis-2,4-dinitrophenyl phosphate $\phi = 0.89$ for HCl, 1.00 for H_2SO_4, and 0.97 for $HClO_4$.[12] Similar, but slightly higher, ϕ values were obtained with other nitrophenyl phosphates.[9,10]

Arrhenius Parameters.—The values of the activation energies of the nitrophenyl phosphoric acids are relatively insensitive to the nature and concentration of the catalyzing agents (Table V). The actual values were determined at two temperatures only using the data given in Tables I–IV and Figures 2 and 3, and are therefore not particularly accurate, but only the trends in the values were needed for this discussion. All of the values were within the quoted limits. The range of acidities used in these experiments follow: for *p*-nitrophenyl phosphate, 2–6 *M* HCl, 1–7 *M* H_2SO_4, 1–6 *M* $HClO_4$ in water; for 2,4-dinitrophenyl phosphate, 3–10 *M* HCl, 3–8 *M* H_2SO_4, 3–6 *M* $HClO_4$ in water; for bis-2,4-dinitrophenyl phosphate, 4–10 *M* HCl, 8 *M* H_2SO_4, 4–9 *M* $HClO_4$ in water. The conditions for the hydrolyses of *p*-nitrophenyldiphenyl phosphate are specified in Table V. Because the log *A* values depend upon acidity we merely give the range in Table V, except for *p*-nitrophenyldiphenyl phosphate where the log *A* values vary considerably with acidity and are considerably smaller (*i.e.*, more negative values of ΔS^*) than for the other substrates. The log *A* values are in range expected for A2 hydrolyses and give negative entropies of activation, $\Delta S^* \sim -25$ eu, which are characteristic of acid hydrolyses in which water molecules are closely bound into the transition state.[2,28] The results given here strengthen and generalize those given earlier.[9-12]

TABLE V

ACTIVATION ENERGIES OF ACID HYDROLYSIS[a]

Phosphate	Acid	E^b	Log *A*
p-Nitrophenyl	HCl	18.6 ± 0.2	7.9–8.1
p-Nitrophenyl	H_2SO_4	18.8 ± 0.2[c]	7.9–8.1
p-Nitrophenyl	$HClO_4$	20.2 ± 1.2[c]	8.3–9.7
2,4-Dinitrophenyl	HCl	16.2 ± 0.3	7.3–8.2
2,4-Dinitrophenyl	H_2SO_4	16.5 ± 0.2	7.9–8.2
2,4-Dinitrophenyl	$HClO_4$	16.2 ± 0.2	7.4–7.9
Bis-2,4-dinitrophenyl	HCl	18.1 ± 1.0	8.4–9.5
Bis-2,4-dinitrophenyl	H_2SO_4	18.1	9.2
Bis-2,4-dinitrophenyl	$HClO_4$	19.0 ± 0.6	9.2–9.7
p-Nitrophenyldiphenyl	HCl	12.9[d,e]	4.5
p-Nitrophenyldiphenyl	HCl	14.2[d,f]	5.4
p-Nitrophenyldiphenyl	HCl	15.6[d,g]	6.2
p-Nitrophenyldiphenyl	HCl	17.3[d,h]	7.4
p-Nitrophenyldiphenyl	HCl	14.8[c,i,j]	5.4
p-Nitrophenyldiphenyl	HCl	16[g,c,i]	6.2
p-Nitrophenyldiphenyl	$HClO_4$	19[c,i,k]	7.4

[a] In water unless specified. [b] In kcal mol^{-1}. [c] Calculated using data from ref 9 and 11. [d] In water with 2 mol % THF. [e] 2 *M* HCl. [f] 4 *M* HCl. [g] 6 *M* HCl. [h] 8 *M* HCl. [i] Water–dioxane 95:5 (v/v). [j] 6 *M* HCl + 2 *M* LiCl. [k] 7.3 *M* $HClO_4$.

For the mono- and diaryl phosphates the rate variations with structure are associated more with changes in the activation energy than in the log *A* or ΔS^* values.

The situation is quite different for *p*-nitrophenyldiphenyl phosphate where the value of the activation energy is very sensitive to acidity (Table V).

Solvent Isotope Effects.—The solvent isotope effects (Table VI) are smaller than those generally found for A2 hydrolyses,[19,20] and for the hydrolyses of bis-2,4-dinitrophenyl phosphate in both hydrochloric and sul-

---

(28) L. L. Schaleger and F. A. Long, *Advan. Phys. Org. Chem.*, **1**, 1 (1963).

TABLE VI
DEUTERIUM SOLVENT
ISOTOPE EFFECTS[a]

Phosphate	Reagent	k_{H_2O}/k_{D_2O},
p-Nitrophenyl	2.4 M H_2SO_4	0.72[b]
2,4-Dinitrophenyl	3 M H_2SO_4	0.67
2,4-Dinitrophenyl	3 M H_2SO_4	0.72[c]
2,4-Dinitrophenyl	8 M H_2SO_4	0.67
Bis-2,4-dinitrophenyl	3 M H_2SO_4	1.18
Bis-2,4-dinitrophenyl	3 M HCl	1.19
Bis-2,4-dinitrophenyl	8 M H_2SO_4	0.91
Bis-2,4-dinitrophenyl	7.9 M HCl	0.90
p-Nitrophenyldiphenyl	1–4 M H_2SO_4	~1.0[d]

[a] At 25.0° unless specified. [b] At 73.0°.[9] [c] At 73.0°. [d] At 100°.[11]

furic acid k_{H_2O}/k_{D_2O} is greater than unity at low, but smaller at high, acid concentration.

Discussion

The basicities of at least the triaryl phosphates are so low (Figure 1) that we can exclude the possibility that these rate maxima are caused by complete substrate protonation. Another, but unlikely, possibility is that different mechanisms are operating on the two sides of the rate maxima, evidence against this hypothesis has been given.[9–13]

Strong acids can affect the rate of acid hydrolyses by providing hydrogen ions, by changing the activity coefficients of the substrate and the transition state, either by direct interaction or indirectly by changing the structure of the solvent and by affecting the nucleophilicity of the hydroxylic solvent and its ability to transfer protons; these effects may oppose each other and so lead to the observed rate maxima.

Addition of hydrogen ions should of itself always speed the acid hydrolysis of a weakly basic substrate. Differential effects of strong acids upon the activity coefficient of the substrate depend upon the anion (*e.g.*, perchlorates typically "salt-in" organic compounds, but chlorides generally have the opposite effect[29]), and these differences are in part responsible for the sequence of catalytic activities for A2 hydrolyses, which is $H_2SO_4 \sim HCl > HClO_4$[30] and which is followed for the acid hydrolyses of these aryl phosphates.

The solvent properties of water depend upon its hydrogen-bonded structure, and, irrespective of the model which is used to account for the properties of water, this structure should be affected by added ions.[31] Hydrogen, chloride, and other ions of low charge density tend to orient water around them, whereas an ion of low charge density, such as perchlorate, disrupts existing clusters. Low concentrations of aprotic solvents enhance the structure of water, as was determined for example by nmr spectral shifts,[32] whereas higher concentrations disrupt the existing structure, but we observe no sharp discontinuity in the kinetic solvent effects (Figures 2 and 3 and Tables I–V) which could be related to a change in mechanism or kinetic form caused by a change in solvent structure. However, the solvent effects are different for the acid hydrolyses of the aprotic ester *p*-nitrophenyldiphenyl phosphate compared with the aryl phosphoric acids.[9,11] The effects are larger for hydrolysis of the triaryl phosphate, especially at higher acidities (Figures 2 and 3 and Table IV; *cf.* ref 9 and 11), possibly because addition of the organic solvent stabilizes an aprotic triaryl phosphate but destabilizes the strongly hydrated transition states for all of the phosphates, whereas an aryl phosphoric acid, which can hydrogen bond to water, should not be stabilized by an aprotic solvent and added THF actually assists the hydrolysis of 2,4-dinitrophenyl phosphate at low acidity and retards it at high (Figure 2). In addition organic solvents generally retard A2 hydrolyses (except at very high concentrations) just as they decrease the protonating power of a strong acid.[33,34]

These differences in initial-state solvation of an aprotic compared with an acidic substrate could also be responsible for the different relations between activation energy and acid concentration for the different substrates. For hydrolysis of the aryl phosphoric acids the activation energies are only slightly sensitive to the nature and concentration of the mineral acid or the solvent, but they increase steadily with increasing acid concentration for the hydrolysis of *p*-nitrophenyldiphenyl phosphate and are sensitive to addition of the aprotic solvent (Table V). In addition for the hydrolysis of *p*-nitrophenyldiphenyl phosphate (Figures 2 and Table IV) the position of the rate maximum depends markedly upon the temperature, which is consistent with variations in the activation parameters with acidity. In alkyl halide solvolyses large solvent effects upon the activation energy have been shown to be caused by changes in the enthalpies of solution of the substrate,[35] and in the present system it is reasonable to assume that the effects of electrolytes and aprotic solvents upon the enthalpies of solution of the substrate and the transition state will be quite different for aprotic compared with protic substrates. For a number of aryl phosphates the rate maximum in hydrochloric acid disappears if the ionic strength is kept constant by addition of lithium chloride, which keeps the water activity constant, but could also keep other activity coefficients constant.[9–11] These particular salt effects therefore do not prove that the rate maxima are caused solely by decreasing water activity with increasing acidity.

In the foregoing discussion we have assumed that the differences in behavior of the triaryl phosphates compared with the aryl phosphoric acids can be explained in terms of initial-state effects, and it now remains to consider what reaction mechanisms are reasonable in terms of the relations between reaction rate and acidity.

---

(29) F. A. Long and W. F. McDevit, *Chem. Rev.*, **51,** 119 (1952).

(30) C. A. Bunton, J. A. Crabtree, and L. Robinson, *J. Amer. Chem. Soc.*, **90,** 1258 (1968), and references cited.

(31) H. S. Frank and M. G. Evans, *J. Chem. Phys.*, **13,** 507 (1965); G. Nemethy and H. Sheraga, *ibid.*, **36,** 3382 (1962); K. W. Miller and J. H. Hildebrand, *J. Amer. Chem. Soc.*, **90,** 3001 (1968); G. R. Choppin and K. Buijs, *J. Chem. Phys.*, **39,** 2042 (1963); R. K. McMullan and G. A. Jeffrey, *ibid.*, **31,** 1231 (1959).

(32) D. N. Glew, H. D. Mark, and N. S. Rath, *Chem. Commun.*, 265 (1968); A. Fratiello and D. C. Douglas, *J. Mol. Spectry.*, **11,** 465 (1963).

(33) C. A. Bunton and S. G. Perry, *J. Chem. Soc.*, 3070 (1960); J. Martinmaa and E. Tommila, *Suomen Kemi. B.*, **40,** 222 (1968).

(34) M. A. Paul and F. A. Long, *Chem. Rev.*, **57,** 1 (1957).

(35) F. Franks, E. M. Arnett, W. G. Bertrande, J. J. Burke, and P. M. Duggleby, *J. Amer. Chem. Soc.*, **85,** 1350 (1953); E. M. Arnett, W. G. Bertrande, J. J. Burke, and P. M. Duggleby, *ibid.*, **87,** 1541 (1965).

Reaction Mechanism.—It is generally assumed that the mechanism of A2 hydrolyses of weakly basic substrates can be interpreted in terms of the eq 4 and 5,

$$S + H \underset{k_{-1}}{\overset{k_1}{\rightleftarrows}} HS^+ \qquad (4)$$

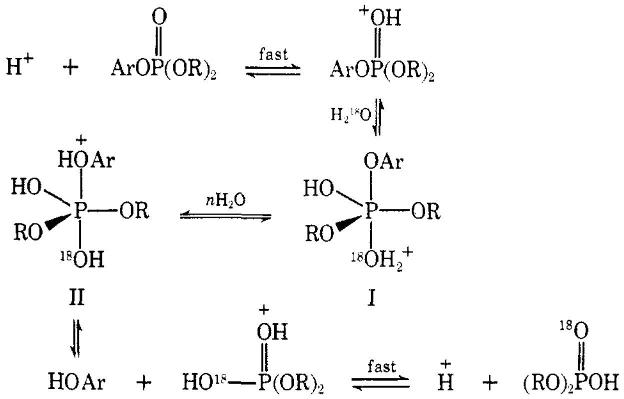
$$HS^+ + H_2O \xrightarrow{k_2} \text{products} \qquad (5)$$

where S and HS^+ are in equilibrium, and $k_2 \ll k_{-1}$, so that $k_\psi = C_{H^+} \times k_1k_2/k_{-1}$,[36] and most attempts to explain these rate maxima have been made on the assumption that reaction between the conjugate acid and water is rate limiting, and this assumption was used in attempts to explain the rate maxima observed in the acid hydrolyses of triaryl phosphates.[9,11] For example the variation of k_ψ with C_{H^+} for the acid hydrolysis of *p*-nitrophenyldiphenyl phosphate could be fitted reasonably well to a rate equation involving water activity to the first power and an empirical term for the variations of the activity coefficients of the initial and transition states with varying acid concentration.[11] The difficulty with this type of treatment is that the various parameters may not be independent of each other, and it is not clear why these rate maxima are found only for hydrolyses of a few weakly basic aryl phosphates, *e.g.*, for acid hydrolysis of nitrophenyl but not alkyl phosphates, and why electron-attracting substitutents assist hydrolysis.[8–12]

In his formulations of relations between rate constant and water activity, Bunnett also assumed that a fast equilibrium protonation of the substrate was followed by a rate-limiting decomposition of the conjugate acid. He concluded that high positive *w* values were characteristic of reactions which involve slow proton transfers, but it is hard to believe that a proton transfer is the only rate-limiting step for these acid hydrolyses of phosphate esters because electron-attracting substituents, which assist reaction, should hinder protonation but assist attack of water. We cannot explain the kinetic form of these hydrolyses in terms of a slow protonation of the substrate followed by rapid formation of products,[37] because this explanation would be inconsistent with the p*K* values for protonation of these phosphates, which would lead to a reaction rate which is much higher than that observed, but the proton transfer could be concerted with attack of water, and this possibility must be considered.

Martin has given an explanation for rate maxima in acid hydrolyses of weakly basic substrates in terms of reversible addition of water to a conjugate acid to give an intermediate which can revert to conjugate acid or give products by reactions involving the intervention of additional water molecules;[39] *e.g.*, as applied to aryl phosphates the reaction scheme could be written as shown in Scheme I.

SCHEME I



With increasing acidity and decreasing water activity the interconversion I $\rightleftarrows$ II could become slow, particularly if $n > 1$, and I could then revert preferentially to reactants. Possible objections to this scheme are that there could be oxygen exchange between water and the phosphoryl oxygen atom during acid hydrolysis, whereas no exchange is observed,[40] and in addition the deuterium solvent isotope effect might be expected to vary markedly with the acid concentration. However, if the lifetimes of I and II are too short for pseudorotation to occur, the oxygen atoms would not equilibriate and, provided that groups enter and depart only from the apical positions, the original labeled oxygen atom of the water would be lost from I.[43]

This explanation does not explain why electron-attracting substituents strongly assist acid hydrolysis of aryl phosphates and phosphinates, because electron attraction should hinder the initial protonation and the proton transfer to the aryloxy residue in the interconversion of I to II, nor does it explain the absence of acid catalysis in the hydrolysis of phenyl phosphate and the related alkyl- and chloro-substituted monoaryl phosphates.[9] A mechanism similar to that shown, but with fast proton transfers, is a very reasonable one for A2 hydrolyses of monoalkyl phosphates with phosphorus–oxygen bond fission.[44]

A possible way around the difficulty of explaining the effect of electron-withdrawing substituents is to suppose that loss of the aryloxy group can occur with partial rather than complete proton transfer to the aryl oxygen atom provided that electron-withdrawing substituents weaken the existing phosphorus–oxygen bond; *i.e.*, we could suppose that reaction followed the sequence shown in Scheme II. In other words the water molecules would be acting as general acid–base catalysts in giving an intramolecular partial proton transfer to the leaving group. Bell has suggested that proton transfer through a chain of water molecules may be important in some general acid catalyzed reactions.[45]

However, it is worthwhile considering other possible explanations of the kinetic and structural effects in which the water molecules could play a different role.

---

[36] C. K. Ingold, "Structure and Mechanism in Organic Chemistry," Cornell University Press, Ithaca, N. Y., 1953, Chapter XIV.

[37] This explanation has, however, been successfully applied to the hydrolysis of carboxylic ortho esters.[38]

[38] C. A. Bunton and R. B. deWolfe, *J. Org. Chem.*, **30**, 1371 (1965); A. J. Kresge and R. J. Preto, *J. Amer. Chem. Soc.*, **87**, 4593 (1965); E. H. Cordes, *Prog. Phys. Org. Chem.*, **4**, 1 (1967).

[39] R. B. Martin, *J. Amer. Chem. Soc.*, **84**, 4130 (1962).

[40] We note here that no exchange was found during the saponification of phenyl benzoate,[41] although it is found with some alkyl benzoates.[42] However, the possibility of oxygen exchange in the acid hydrolysis of phenolic esters has not been examined so far as we are aware.

[41] C. A. Bunton and D. N. Spatcher, *J. Chem. Soc.*, 1079 (1956).

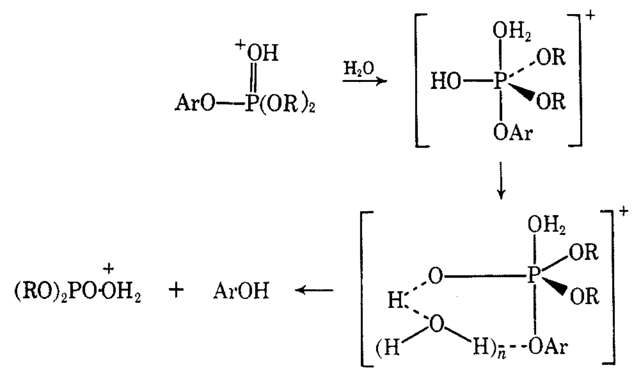
[42] M. L. Bender, *J. Amer. Chem. Soc.*, **73**, 1626 (1951); S. A. Shain and J. F. Kirsch, *ibid.*, **90**, 5848 (1968).

[43] F. H. Westheimer, *Accounts Chem. Res.*, **1**, 70 (1968).

[44] J. R. Cox and O. B. Ramsay, *Chem. Rev.*, **64**, 343 (1964).

[45] R. P. Bell, *Advan. Phys. Org. Chem.*, **4**, 1 (1966).

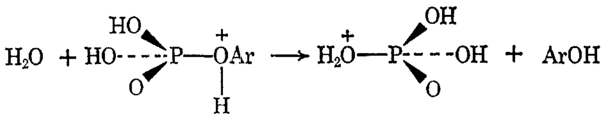
SCHEME II



Zimmerman has suggested that proton transfer, for example to amides, might be concerted with attack of water because the proton could be moving very rapidly back and forth between substrate and solvent, and therefore would remain on the substrate for only 10^{-3}–10^{-11} sec,[46] and Kice and Guaraldi have suggested that making and breaking of bonds to sulfur may be concerted with proton transfer in acid-catalyzed reactions of the weakly basic sulfinyl sulfones and thiosulfinates, *e.g.*, in their reactions with organic sulfides.[47] These explanations could be applied to hydrolyses of aryl phosphates, in particular because electron-attracting substituents should assist both attack of a nucleophile on phosphorus and breaking of the existing bond between phosphorus and the aryloxy group. In addition it is the less basic sulfur and phosphorus compounds which show unexpected kinetic behavior; *e.g.*, there is no reason to believe that proton transfer and nucleophilic attack are concerted in acid hydrolyses of either alkyl phosphates[44] or sulfinates.[47,48] The weakness of this explanation is that it is difficult to see why the nucleophilicity of water toward phosphorus should go down so sharply in moderately concentrated acid that there are rate maxima in these reactions, but not in others.

Therefore these ideas of Kice and Guaraldi and Zimmerman may not provide a complete explanation of the rate maxima in the acid-catalyzed hydrolyses of aryl phosphates. We can extend them by suggesting that attack of a water molecule is concerted with proton addition and that the attacking water molecule comes from the immediate hydration sphere of the proton.

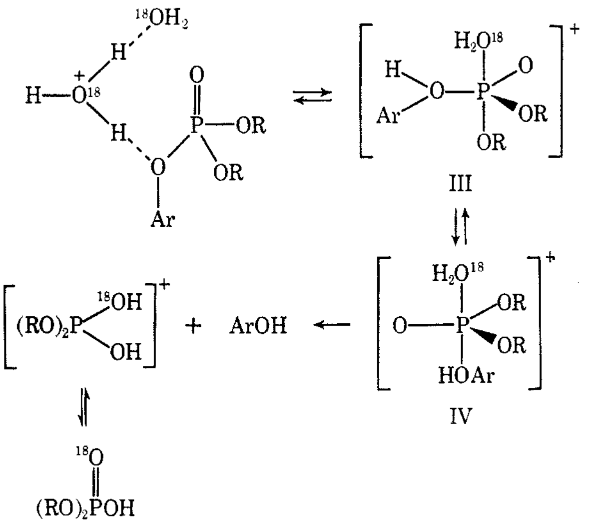
There is considerable evidence that nucleophilic displacements in phosphate derivatives occur with inversion of configuration,[43,49] and, if the acid-catalyzed hydrolysis of an aryl phosphate resembles an S_N2 process, with a trigonal bipyramidal transition state (eq 6), it would be difficult for the proton which is shown



$$H_2O + HO\cdots\overset{+}{P}(HO)(O)-\underset{H}{O}Ar \longrightarrow H_2\overset{+}{O}-P(OH)(O)\cdots OH + ArOH \quad (6)$$

as attacked to the aryloxy group to be closely solvated by the water molecule which is attacking the phosphorus atom. However, if the reaction were stepwise, attack by the proton upon oxygen could be concerted with addition of a water molecule to phosphorus, with the water being in the primary solvation shell of the hydronium ion, *e.g.*, Scheme III.

SCHEME III



In this mechanism the equatorial protonated aryloxy group in III moves preferentially into the apical position, as in IV, because of its high electronegativity, and then leaves from this position. This mechanism, like the earlier one, explains why there is no oxygen exchange between the phosphoryl and water oxygens, even though intermediates may revert to starting materials. We have assumed that, because of the low basicity of the aryl phosphate, there will be no acid catalysis unless the aryl group in a monoaryl phosphate contains electron-attracting substituents which make it possible for the water molecule to add to phosphorus while the proton is adding to oxygen. The chance of these two events being concerted will depend upon the number of water molecules which are hydrating the proton. It is generally assumed that in dilute acid four water molecules are closely bound to each proton, but this number must decrease as the acid concentration increases.[50] Therefore as long as $H_9O_4^+$ is the predominant acid the rate will increase with increasing acid concentration, but, when less hydrated species become predominant, the rate will begin to fall. (This argument does not depend upon $H_9O_4^+$ being the predominant species in dilute acid; all that is required is that the hydration number should decrease with increasing acidity.)

The hydration number of the proton should be less important in A2 hydrolyses of moderately basic substrates in which the substrate and conjugate acid are in equilibrium, and the reaction rate is simply that of the attack of water upon the standing concentration of conjugate acid, because the way in which the equilibrium is maintained is irrelevant to the kinetics. The rate-limiting step will then depend upon the availability of water molecules and only indirectly upon the hydration number of the proton.

---

[46] H. Zimmerman, *Angew. Chem. Intern. Ed. Engl.*, **3**, 157 (1964); **4**, 401 (1965).

[47] J. Kice and G. Guaraldi, *J. Amer. Chem. Soc.*, **89**, 4113 (1967).

[48] C. A. Bunton and B. N. Hendy, *J. Chem. Soc.*, 2562 (1962); 627 (1963).

[49] N. K. Hamer, *J. Chem., Soc., B*, 404 (1966).

[50] E. B. Robertson and H. B. Dunford, *J. Amer. Chem. Soc.*, **86**, 5081 (1964), and references cited.

There is evidence that proton transfer from a hydronium ion to carbon occurs directly and not through intervening water molecules.[51] However, some of this evidence comes from experiments in dimethyl sulfoxide rather than in water, and may not be relevant to proton transfers in water, and, because of the rapid mobility of the positive charge within the primary hydration sphere of the hydronium ion, the general mechanism could be written differently without invalidating the general hypothesis.

These two explanations for the kinetic and structural effects differ in that the first one assumes that intermediates are formed by addition of a proton and a water molecule to the substrate, but that many of these intermediates revert to reactants and that their chance of going on to product depends critically upon electron-attracting groups which make it easy for the existing P—O bond to break. On the other hand, the second assumes that electron-attracting groups so hinder protonation and assist water attack that these two processes become concerted and the hydrated proton is the reagent for both. Either explanation fits the observation that the values of k_{H_2O}/k_{D_2O} are much closer to unity than is general for A2 hydrolyses.

One problem with both explanations is that at first sight they suggest that the reactions should be subject to large primary deuterium isotope effects, because a proton is being transferred in rate-limiting steps. However, there are a number of reactions in which proton transfers between oxygen atoms are believed to be important in the rate-limiting step, but in which the deuterium isotope effects are small.[38,44,52] Rationalizations for this behavior have been given by a number of workers.[38,53] The transfer of a proton to a basic atom should always have a larger equilibrium constant in D_2O than in H_2O, and this effect should be opposed by loss of zero-point energy or by solvation of highly acidic centers in the transition state.[20] Therefore it is not surprising that the value of K_{H_2O}/k_{D_2O} may be slightly greater or less than 1, and it does not suggest that the variations in the solvent isotope effect in the acid hydrolysis of bis-2,4-dinitrophenyl phosphate (Table VI) are caused by changes in mechanism.

Reaction of Other Esters.—Concerted attack of water and a proton could also be involved in the hydrolyses of trifluoroacetic esters and cyclic aryl sulfites and could be responsible for the rate maxima observed in their acid hydrolyses.[14,15] However, negative salt effects upon the spontaneous hydrolysis and salting in of the initial state by the acid should also be important, especially because no rate maximum is observed in the acid hydrolysis of diphenyl sulfite and for this compound the spontaneous hydrolysis is very slow, whereas the spontaneous hydrolysis of diphenylene sulfite is relatively rapid.[14] Another example of a reaction of a carboxyl derivative in which electrolyte effects are very important is the hydrolysis of the conjugate acid of 1-acetylimidazole[17] where it was necessary to suppose that the electrolytes affect the rate specifically and by virtue of changes in the water activity. (It is interesting to note that this reaction, like those of the aryl phosphates, does not lead to oxygen exchange of the substrate.[54]) A difference between the A2 hydrolyses of the carboxyl derivatives and those of the aryl phosphates is that the former involve addition of water to a trigonal carbon to give a tetrahedral intermediate in which all the positions are identical, and therefore the oxygen atoms could equilibriate rapidly. Any of the explanations which we have considered fit the observation that there is no rate maximum in the A1 hydrolysis of diphenylmethyl trifluoroacetate, which requires only an equilibrium proton transfer followed by, or even concerted with, slow formation of a carbonium ion.[15]

Registry No.—*p*-Nitrophenyl phosphate, 330-13-2; 2,4-dinitrophenyl phosphate, 2566-26-9; bis-2,4-dinitrophenyl phosphate, 18962-97-5; *p*-nitrophenyldiphenyl phosphate, 10359-36-1.

Acknowledgments.—Support of this work by the National Science Foundation is gratefully acknowledged.

---

[51] M. M. Kreevoy and J. M. Williams, *J. Amer. Chem. Soc.*, **90**, 6809 (1968) and references cited.

[52] R. H. De Wolfe, K. Ivanetich, and N. F. Perry, *J. Org. Chem.*, **34**, 848 (1969).

[53] C. G. Swain, D. A. Kuhn, and R. L. Schowen, *J. Amer. Chem. Soc.*, **87**, 1553 (1965).

[54] C. A. Bunton, *J. Chem. Soc.*, 6045 (1963).