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The Hydrolysis of Bis(2,4-dinitrophenyl) Phosphate[1]

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The hydrolysis of bis(2,4-dinitrophenyl) phosphate to the monoester occurs with phosphorus–oxygen bond fission. From pH 4 to 7 the rate is independent of pH and the values of the activation entropy and enthalpy suggest that the rate-limiting step is attack of water; at higher pH attack of hydroxide ion becomes the predominant reaction. At pH 1–2 there is a minor contributing reaction of water with the undissociated aryl phosphate. Strong acids catalyze the hydrolysis and there are rate maxima at *ca.* 8 *M* with perchloric and sulfuric acid, but not with hydrochloric acid, and k_ψ increases linearly with C_{H^+} in mixtures of HCl + LiCl of constant ionic strength.

Except in highly acidic solutions the monoanion is the most important reactive species in hydrolysis of simple monoalkyl or aryl phosphates.[2] The initial reaction products are almost certainly the monomeric metaphosphate ion and the alcohol or phenol, and it is generally accepted that proton transfer to the leaving RO– group is essential for reaction.[3,4]

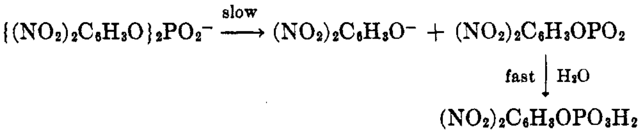
$$RO - PO_3^-H \longrightarrow ROH + PO_3^-$$

However, if the group R contains strongly electron-attracting groups as in acyl or some nitrophenyl phosphates, the dianion is also reactive, and may even be more reactive than the monoanion,[4–6] *e.g.*,

$$(NO_2)_2C_6H_3OPO_3^{2-} \longrightarrow (NO_2)_2C_6H_3O^- + PO_3^-$$

Monoanions of open-chain dialkyl and aryl phosphates are generally unreactive compared with those of monosubstituted phosphates.[2,7,8]

We were interested in finding out whether the substitution of strongly electron-attracting groups, *e.g.* nitro, into a diaryl phosphate, would make it possible to observe a unimolecular decomposition of the monoanion, *e.g.*



$$\{(NO_2)_2C_6H_3O\}_2PO_2^- \xrightarrow{\text{slow}} (NO_2)_2C_6H_3O^- + (NO_2)_2C_6H_3OPO_2 \xrightarrow[\text{fast}]{H_2O} (NO_2)_2C_6H_3OPO_3H_2$$

or whether nucleophilic attack upon phosphorus or carbon would be the rate-limiting step, as is generally observed with diaryl phosphates.[9] We were also interested in examining the relative reactivity of the mono- and bis(2,4-dinitrophenyl) phosphates toward hydroxide ion and mineral acid. The acid hydrolyses of some aryl phosphates and phosphinates show rate maxima in moderately concentrated acid,[6,9–12] and bis(2,4-dinitrophenyl) phosphate was also a convenient compound for the study of acid hydrolysis.

Nucleophilic attack by anions upon the phosphorus atom in anions of phosphate esters can occur in favorable cases, despite the electrostatic repulsions.[2] Intramolecular nucleophilic attack has been invoked in mechanisms for the alkaline degradation of ribonucleic acid,[13] and in hydrolysis of *p*-hydroxypropyl phosphates.[14] Hydroxide and alkoxide ions react with the

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[1] Support of this work by the National Science Foundation and the National Institute of Arthritis and Metabolic Diseases of the U. S. Public Health Service is gratefully acknowledged.

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

[3] There is some question as to the actual timing of the proton transfer,[4] and the involvement of water molecules in the transition state; *cf.* ref 2 and references cited therein.

[4] A. J. Kirby and A. G. Varvoglis, *J. Amer. Chem. Soc.*, **89**, 415 (1967).

[5] G. DiSabato and W. P. Jencks, *ibid.*, **83**, 1268, 4400 (1961).

[6] C. A. Bunton, E. J. Fendler, and J. H. Fendler, *ibid.*, **89**, 1221 (1967).

[7] *Cf.* ref 8 for discussions of the high reactivity of some cyclic phosphates.

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

[9] P. W. C. Barnard, C. A. Bunton, D. Kellermann, M. M. Mhala, B. Silver, C. A. Vernon, and V. A. Welch, *J. Chem. Soc., B*, 227 (1966).

[10] P. Haake and G. Hurst, *J. Amer. Chem. Soc.*, **88**, 2544 (1966).

[11] C. A. Bunton, E. J. Fendler, E. Humeres, and K. U. Yang, *J. Org. Chem.*, **32**, 2806 (1967).

[12] C. A. Bunton, S. J. Farber, and E. J. Fendler, *ibid.*, **33**, 29 (1968).

[13] J. R. Cox and J. P. Cleveland in the Symposium on Naturally Occuring Phosphate Esters, The Chemical Society, London, 1967.

[14] D. M. Brown and D. A. Usher, *J. Chem. Soc.*, 6558 (1965); D. G. Oakenfull, D. I. Richardson, and D. A. Usher, *J. Amer. Chem. Soc.*, **89**, 5491 (1967).

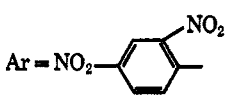
dianions of 2,4- and 2,6-dinitrophenyl phosphate,[4,6] and fluoride ions and amines attack the monoanion of bis(2,4-dinitrophenyl) phosphate.[15]

Experimental Section

Materials.—Bis(2,4-dinitrophenyl) phosphate was prepared from phosphorus oxychloride and 2,4-dinitrophenol.[16] Initially we followed the original method of stirring 2,4-dinitrophenol with phosphorus oxychloride in pyridine, but sometimes we then isolated 2,4-dinitrophenylpyridinium chloride, mp 183–184° (lit.[17] mp 184°). This pyridinium salt turned pink on treatment with alkali, probably because of formation of the open-chain derivative.[17] It seemed that we isolated this product when fortuitously the phenol had not dissolved completely in the pyridine, and for later preparations we used the following method. Recrystallized 2,4-dinitrophenol (2.76 g) and redistilled pyridine (2.5 ml) in redistilled CH_3CN (30 ml) were treated with $POCl_3$ (0.5 ml) at 0°, and the mixture was stirred for 10–15 min and then poured into ice-water (200 ml). The precipitate was separated by filtration and washed several times with ice water to remove pyridine. In a typical experiment 2.25 g of the crude pyridinium salt was isolated; after two recrystallizations from acetone–ether 1.42 g of pyridinium bis(2,4-dinitrophenyl) phosphate was isolated, mp 159–160° (lit.[16] mp 156–157°). Identical material was isolated using the original method,[16] and by carrying out the reaction with pyridine and CH_3CN which had not been distilled before use.

Kinetics.—The formation of 2,4-dinitrophenol was followed spectrophotometrically using a Gilford spectrophotometer.[6] Hydrolysis to inorganic phosphate is a two-stage reaction for which we required the rate constant, *k*, of the first stage. Therefore

$$(ArO)_2PO_2H \xrightarrow{k} ArOH + ArOPO_3H_2 \xrightarrow{k'} ArOH + H_3PO_4$$



for most of the kinetic runs we added portions of the reaction mixture to *E. coli* alkaline phosphatase (Worthington or Sigma) in Tris buffer, pH 8, so that any 2,4-dinitrophenyl phosphate was rapidly hydrolyzed. The enzymic hydrolysis took 30–90 min at 25°, and virtually no reaction of the bisdiaryl phosphate occurred in these conditions. At pH >13 the first step of the hydrolysis was so much faster than the second that we followed it in a jacketed cell in the spectrophotometer. At pH 6–8 the second step of the hydrolysis was so much faster than the first that we obtained the same experimental rate constants with or without addition of alkaline phosphatase.

The buffers were potassium hydrogen phthalate (pH 3–5), potassium dihydrogen phosphate (pH 6.5–7.8), sodium tetraborate (pH 7.50–10), and disodium hydrogen phosphate (pH 11–12). The pH was measured directly in the reaction solution. The first-order rate constants, k_ψ, are in sec^{-1}. A few experiments were carried out on the hydrolysis of the dianion of 2,4-dinitrophenyl phosphate following the method already described.[6]

Dissociation Constants.—The acidity of bis(2,4-dinitrophenyl) phosphate is too high for the dissociation constant to be measured by potentiometric titration, and therefore we measured the pH of a series of solutions of the free acid prepared by treating the salt with Dowex 50W-X8 resin. For a phosphate concentration, *C*, and a degree of ionization, α; $pH = \frac{1}{2}pK - \frac{1}{2}\log C - \log(1 - \alpha)$, and the value of $pK = 1$ was calculated by successive approximations.[11] There is an uncertainty of ±0.2 units in this value.

Bond Fission.—Hydrolysis was carried out in $H_2{}^{18}O$. The procedure for the isolation and isotopic analysis of inorganic phosphate followed that already described,[18] except that the first isolated barium salt was converted into the free acid with Dowex resin and thence into potassium dihydrogen phosphate which was heated *in vacuo* with a mixture of guanidine hydrochloride and phenylene diamine hydrochloride to give CO_2.[19]

In general the hydrolyses were carried to completion, but with 0.3 *M* NaOH the alkaline hydrolysis of the bis ester is so much faster than that of 2,4-dinitrophenyl phosphate that the hydrolysis could be stopped by decreasing the pH by addition of HCl solution after the first step was complete. The monoester was then hydrolyzed, with phosphorus–oxygen fission, by addition of *E. coli* alkaline phosphatase. This enzymic hydrolysis introduces one atom of the enriched water into the inorganic phosphate.[20]

Results

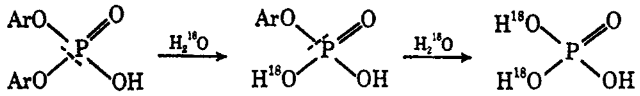
Bond Fission.—Hydrolysis under a variety of conditions gives largely phosphorus oxygen fission (Table I), because in the over-all hydrolysis two oxygen atoms in the inorganic phosphate are derived from the water.

Table I

Bond Fission

Conditions	Isotopic abundance[a] H₂O	Isotopic abundance[a] KH_2PO_4	Incorporation, %
3 *M* HCl, 45°	0.83	0.44	53
pH 6.0, 45°	0.80	0.40	50
pH 6.0, 45°	0.80	0.42	52
0.3 *M* NaOH, 25° [b]	0.82	0.33	40
0.3 *M* NaOH, 25° [b]	0.82	0.35	43

[a] Atom per cent excess above normal. [b] Reaction was stopped after six half-lives and the hydrolysis of 2,4-dinitrophenyl phosphate was then carried out enzymically.



Phosphatase-catalyzed hydrolysis has been shown to give phosphorus oxygen bond fission,[20] and the present results suggest that the phosphorus oxygen bond is broken in the nonenzymic hydrolysis of 2,4-dinitrophenyl phosphate.[21]

Kinetics.—The rate constants at pH 1-12 are given in Table II, and those in strong acid are given in

Table II

Hydrolysis of Bis(2,4-dinitrophenyl) Phosphate at pH 1–12[a]

pH	10^6k_ψ, sec^{-1}	pH	10^6k_ψ, sec^{-1}
1.00	1.05[b]	5.60	0.122[c,h]
2.00	0.378[b]	6.50	0.193[i]
3.30	0.179[c]	7.00	0.189[i]
4.00	0.178[c]	7.50	0.182[j]
5.00	0.177[c]	7.50	0.242[k]
5.00	0.200[d]	9.00	0.388[j]
5.00	0.586[c,e]	10.00	0.914[j]
5.00	2.09[c,f]	11.00	2.51[i]
5.00	17.8[c,g]	12.00	29.5[i]

[a] At 25.0° unless specified. [b] In $HClO_4$. [c] 0.01 *M* phthalate buffer. [d] 0.05 *M* phthalate buffer. [e] At 35.0°. [f] At 50.0°. [g] At 74.6°. [h] In D_2O using the pD scale of T. H. Fife and T. C. Bruice, *J. Phys. Chem.*, **65**, 1079 (1961). [i] 0.01 *M* phosphate buffer. [j] 0.015 *M* borate buffer. [k] 0.075 borate buffer.

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[15] A. J. Kirby and A. G. Varvoglis, *J. Chem. Soc., B*, 135 (1968).

[16] A. Azerad, D. Gautheron, and M. Vilkas, *Bull. Soc. Chim. Fr.*, 2078 (1963).

[17] H. L. Shamra, V. N. Shamra, and R. L. Vital, *Can. J. Chem.*, **44**, 1327 (1966), and references cited.

[18] C. A. Bunton, D. R. Llewellyn, C. A. Vernon, and V. A. Welch, *J. Chem. Soc.*, 1636 (1961).

[19] C. A. Bunton and B. N. Hendy, *ibid.*, 627 (1963).

[20] M. Cohn, *J. Biol. Chem.*, **180**, 771 (1949); C. A. Bunton, B. L. Silver, and C. A. Vernon, *Proc. Chem. Soc.*, 348 (1957).

[21] Preliminary experiments support this conclusion.

Table III, and at high pH in Table IV. The effects of added salts and solvents are given in Table V. The activation parameters are given in Table VI. There is a kinetic deuterium isotope effect on the spontaneous hydrolysis, and at 25.0° $k_{H_2O}/k_{D_2O} = 1.45$ (Table II). Increase in the buffer concentration increases k_ψ slightly because of a positive kinetic salt effect (Tables II and V).

TABLE III

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

C_{H^+}, M	HCl	H_2SO_4	$HClO_4$
0.10			0.105
1.00			0.479
2.00	1.41	1.74	0.944
2.00	1.60[b]		
3.00		2.85	
3.00		2.40[c]	
4.00	3.27	4.13	2.00
4.00	3.84[b]		
6.00	6.18	6.70	3.63
6.00	5.89		
6.00	16.6[d]		
6.00	70.7[e]		
7.90	9.13		
8.00		8.78	5.17
8.00		9.59[c]	
8.93			5.20
10.00	14.7	8.17	4.58

[a] Values of $10^6 k_\psi$, sec^{-1}, at 25.0° unless specified. [b] With LiCl, $I = 6.0$. [c] D_2SO_4 in D_2O. [d] At 35.0°. [e] At 50.0°.

TABLE IV

REACTION BETWEEN BIS(2,4-DINITROPHENYL) PHOSPHATE AND SODIUM HYDROXIDE[a]

C_{NaOH}, M	$10^6 k_\psi$, sec^{-1}	$10^4 k_2$, l. sec^{-1} mol^{-1}
0.10	30.1	30.1
0.10	9.79[b]	9.79
0.10	2.09[c]	2.09
0.15	48.0	32.0
0.20	66.3	33.2
0.30	111	37.1
0.30	112	37.3

[a] In water at 25.0° unless specified. [b] At 15.0°. [c] At 0.0°.

TABLE V

SALT AND SOLVENT EFFECTS UPON THE HYDROLYSIS OF THE MONOANION OF BIS(2,4-DINITROPHENYL) PHOSPHATE[a]

pH	Salt	$10^6 k_\psi$
		0.18[b]
5.00		17.8[c]
7.00		16.6[d]
5.00	1.5 M LiCl	20.1[e]
5.00	3.0 M LiCl	20.4[e]
5.00	6.0 M LiCl	0.265
6.50	1.5 M $LiClO_4$	0.118
6.50	3.0 M $LiClO_4$	0.095
7.85		0.032[e]
6.51		4.05[d,e]
7.85		4.66[d,e]
6.55		7.38[d,f]
7.50		7.86[d,f]

[a] At 25.0° with 0.01 M buffer unless specified. [b] Mean of values in aqueous 0.01 M buffer in the plateau region. [c] At 74.6°. [d] At 73.0°. [e] In H_2O-CH_3CN 1/1 v/v. [f] Dioxane-water 1/1 v/v.

TABLE VI

ACTIVATION PARAMETERS[a]

Conditions	ΔH^*	ΔS^*
Spontaneous[b]	18.8	−26
Spontaneous[c]	20.2	−25
0.1 M NaOH	16.6	−14
6.0 M HCl	18.5	−19

[a] Calculated for 1 M reagents at 25°. [b] At pH 5.0. [c] In H_2O-CH_3CN 1/1 v/v.

A few experiments were carried out on the hydrolysis of 2,4-dinitrophenyl phosphate to allow comparison between the hydrolysis of the bis and the mono compound. The results are given in Table VII.

TABLE VII

HYDROLYSES OF THE DIANION OF 2,4-DINITROPHENYL PHOSPHATE[a]

pH	Salt	$10^6 k_\psi$, sec^{-1}
		8.2[b]
		8.06[c]
6.5	1.5 M LiCl	19.6
6.5	3.0 M LiCl	24.2
6.5	1.5 M $LiClO_4$	21.1
6.5	3.0 M $LiClO_4$	20.2
7.0		27.6[d]

[a] At 25.0° with 0.01 M phosphate buffer. [b] Mean value for the dianion hydrolyses.[6] [c] In D_2O pD = 7.16; using the scale of T. H. Fife and T. C. Bruice, *J. Phys. Chem.* **65**, 1079 (1961); [d] H_2O-CH_3CN 1/1 v/v.

Discussion

Kinetic Form of the Hydrolysis.—The pH rate profile is simple. As shown in Figure 1 there is a region from pH 3 to 7 in which the rate is independent of pH and which merges at high pH into a region where the rate depends upon hydroxide ion concentration, and at low pH into a region in which there is acid catalysis. The line for pH > 12 is drawn with a slope of unity, but the slope of the line drawn between points at pH 0 and 1 has a slope of −0.7. There are several possible mechanisms whose importance can be estimated from the pH profile, and the dissociation constant of the diaryl phosphate.

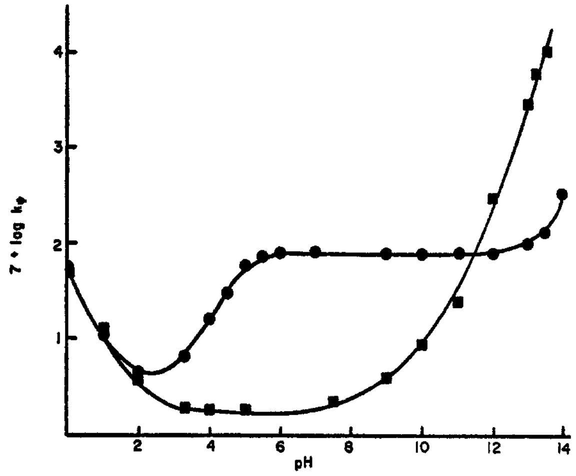
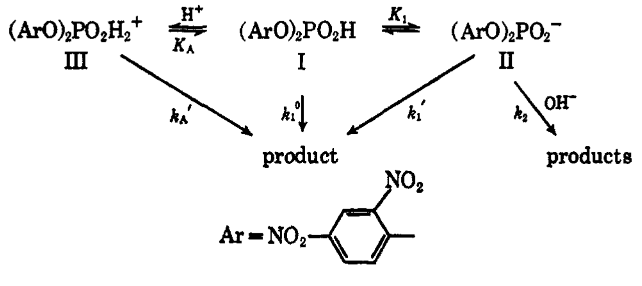


Figure 1.—Variation of k_ψ with pH at 25.0° for the hydrolysis of bis-2,4-dinitrophenyl phosphate (■) and 2,4-dinitrophenyl phosphate (●).

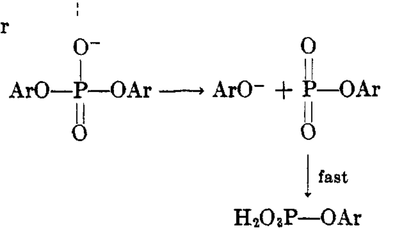


Hydrolysis at pH 3.5–7.—In the region pH 3.5–7 bis(2,4-dinitrophenyl) phosphate is present wholly as a monoanion (II), and the value of k_1', the first-order rate constant for the decomposition of II, is given by the constant value of $k_\psi = 1.8 \times 10^{-7}$ sec^{-1} at 25.0° in this pH region. The problem is to distinguish between the two possible mechanisms. We can eliminate the

bimolecular

$$ArO—PO_2^-—OAr + OH_2 \longrightarrow ArO^- + ArOPO_2H$$

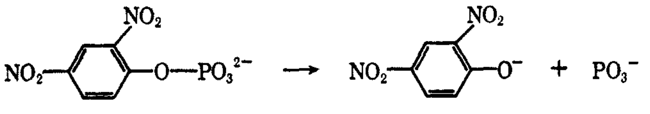
unimolecular



$$ArO—\overset{O^-}{\underset{O}{P}}—OAr \longrightarrow ArO^- + \overset{O}{\underset{O}{P}}—OAr \xrightarrow{\text{fast}} H_2O_3P—OAr$$

possibility of reaction between the undissociated acid (I) and hydroxide ion by calculating that the second-order rate constant for this reaction would have to be *ca.* 3×10^6 l. mol^{-1} sec^{-1}, and this value seems to be impossibly high, *e.g.*, the second-order rate constant for the reaction between hydroxide ion and a reactive triaryl phosphate, *e.g.*, *p*-nitrophenyldiphenyl phosphate, is 0.37 l. mol^{-1} sec^{-1} at 25°.[12] In addition such a reaction should be subject to a large solvent deuterium isotope effect, because of the isotope effects upon the autoprotolysis constant of water and the dissociation constant of the diaryl phosphate.[22]

The hydrolysis of monoanion II is approximately 30 times slower than the spontaneous hydrolysis of the dianion of 2,4-dinitrophenyl phosphate,[6] where the driving force of the reaction is provided by the dinegative charge on the phosphate residue, and this observation is consistent with hydrolysis by either mechanism.



We therefore examined several other mechanistic criteria, and drew analogies with the hydrolysis of the monoanions of simple alkyl and aryl phosphate monoanions and of dinitrophenyl phosphate dianions, because these reactions are believed to involve the unimolecular elimination of metaphosphate ion in the rate-limiting step.[2,4–6]

Addition of an inert solvent, such as acetonitrile, markedly decreases the rate of hydrolysis of II (Table V). There are only small solvent effects upon the hydrolysis of monoanions of monosubstituted phosphates,[5,23] whereas added organic solvents increase the rate of hydrolysis of the dianion of 2,4-dinitrophenyl phosphate, and the effect is especially large for dipolar aprotic solvents[24] (Table VII and ref 4 and 6).

Therefore analogies with the unimolecular hydrolyses of mono- and dianions of monosubstituted phosphates suggest that acetonitrile should not retard the hydrolysis of bis(2,4-dinitrophenyl) phosphate if it involved a unimolecular elimination to give a metaphosphate ester. However acetonitrile or dioxane might slow down bimolecular attack of water, possibly by decreasing its activity. In general bimolecular attack by water upon acyl compounds and related derivatives of inorganic acids is retarded by the addition of organic solvents.[5,25] These generalizations do not fit the qualitative solvent theory which was developed for nucleophilic substitution at saturated carbon.[26]

The deuterium solvent isotope effect is small, with $k_{H_2O}/k_{D_2O} = 1.45$ (Table II). This result is not particularly informative, because although similar values are frequently observed for bimolecular attack by water upon esters and related compounds[27] the solvent isotope effects for the unimolecular heterolysis of monoalkyl phosphate monoanions and the 2,4-dinitrophenyl phosphate dianion are also close to unity (Table VII and ref 2, 4, and 5). However the value of the solvent isotope effect suggests that hydrolysis of the monoanion of bis(2,4-dinitrophenyl) phosphate does not involve a transition state which is strongly hydrogen bonded to water and that water is not acting as a general base.[27,28]

Salt effects upon the rate of hydrolysis of the monoanion of bis(2,4-dinitrophenyl) phosphate are small (Table V). Added lithium chloride increases k_ψ, and lithium perchlorate decreases it. Kinetic salt effects upon hydrolysis of mono- and dianions of monosubstituted phosphate esters are also relatively small (Table VII and ref 4–6 and 29) and their variations do not provide useful mechanistic criteria. However, the bimolecular attack of water upon the acyl group of acetylphenyl phosphate is subject to a negative salt effect,[5] as are reactions of other acyl derivatives, and generally perchlorates are more effective than chlorides at retarding the attack of water upon esters and related compounds.[30] The kinetic salt effects are therefore consistent with a rate-limiting attack of water upon the monoanions or heterolysis to give a metaphosphate.

The effect of temperature upon rate provides the most useful evidence. For all spontaneous reactions of

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[22] K. B. Wiberg, *Chem. Rev.*, **55**, 713 (1955).

[23] P. A. T. Swoboda, Special Publication No. 8, The Chemical Society, London, 1957, p 41.

[24] However dipolar aprotic solvents do not have such large kinetic effects upon the hydrolysis of acyl phosphate dianions.[5]

[25] J. Hine, "Physical Organic Chemistry," McGraw Hill Book Co., Inc., New York, N. Y., 1962, p 159; C. A. Bunton, N. A. Fuller, S. G. Perry, and V. J. Shiner, *J. Chem. Soc.*, 2918 (1963); F. E. Jenkins and A. H. Hambly, *Aust. J. Chem.* **14**, 190, 205 (1961).

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

[27] T. C. Bruice and S. Benkovic, "Bio-Organic Mechanisms," W. A. Benjamin, Inc., New York, N. Y., Vol. 1, 1966, Chapter I.

[28] C. A. Bunton and V. J. Shiner, *J. Amer. Chem. Soc.*, **83**, 42, 3207 (1961).

[29] C. A. Bunton, D. R. Llewellyn, K. G. Oldham, and C. A. Vernon, *J. Chem. Soc.*, 3547 (1958).

[30] C. A. Bunton and T. Hadwick, *ibid.*, 3248 (1958); 943 (1961); J. G. Tillett, *ibid.*, 5138 (1960); C. A. Bunton, N. A. Fuller, S. G. Perry, and I. Pitman, *ibid.*, 4478 (1962); C. A. Bunton and G. Schwerin, *J. Org. Chem.*, **31**, 842 (1966).

monoalkyl and aryl phosphate monoanions and dianions the entropies of activation are close to zero, and the enthalpies of activation are approximately 30 kcal mol^{-1}, with hydrolysis of the dianions having slightly the more positive values of the entropy of activation.[2,4-6,9,11] The values of $\Delta S^* = -26$ eu and $\Delta H^* = 18.8$ kcal mol^{-1} for the spontaneous hydrolysis of monoanion II are not those which we would expect to observe for a unimolecular decomposition of II, but the negative entropy and the relatively low enthalpy of activation are to be expected for a bimolecular attack upon a phosphoryl phosphorus atom.[2,9,31] The activation enthalpy is increased by addition of acetonitrile which has little effect on the entropy (Table VI).

Quantitative interpretation of the activation parameters requires consideration of the entropies and enthalpies of both the initial and transition states,[32] but analogies with the activation parameters for other reactions of phosphate esters suggests that our qualitative conclusions are reasonable.

Comparison between the unimolecular mechanism of the hydrolysis of the 2,4-dinitrophenyl phosphate dianion, in which a metaphosphate ion is eliminated, and the slower hydrolysis of the bis(2,4-dinitrophenyl) phosphate monoanion in which attack of water is apparently faster than heterolysis suggests that the difference must be caused by the differing stabilities of the forming metaphosphate ion and the hypothetical metaphosphate ester. Hydration of the metaphosphate ion and its resonance stabilization should be much more effective than for an aryl metaphosphate, and two negative charges contribute to the driving force for heterolysis of the dianion, instead of one for the monoanion, so that bimolecular attack becomes the preferred mechanism for the hydrolysis of diaryl phosphate monoanions despite the negatively charged substrate and stability of the 2,4-dinitrophenoxide ion.

Hydrolysis at Low pH.—The pK of bis(2,4-dinitrophenyl) phosphate is *ca.* 1, and therefore the rate increase at pH <3 is caused by conversion of monoanion II into undissociated acid I, which could be hydrolyzed spontaneously and in an acid-catalyzed reaction

$$\begin{array}{l} \mathrm{ArOP(OAr)O_2H} \xrightarrow{\mathrm{H_2O}} \mathrm{ArOH} + \mathrm{ArOPO_3H_2} \\ \quad \mathrm{H^+}\big\downarrow \\ \mathrm{[ArOP(OAr)O_2H_2]^+} \xrightarrow{\mathrm{H_2O}} \mathrm{ArOH} + \mathrm{ArOPO_3H_2} + \mathrm{H^+} \end{array}$$

The over-all first-order constant, k_ψ, is given by

$$k_\psi = k_1'n' + k_1^0 n^0 + k_A f(C_{H^+})n^0$$

where n^0 and n' are the fractions present as undissociated diaryl phosphate and its monoanion, and the rate of the acid-catalyzed hydrolysis depends upon some function of the acid concentration. For dilute acid we assume that hydrolysis is first order with respect to hydrogen ion concentration, and from the rate constants at 25° in 1-3 M acid we calculate $k_A = 4.7 \times 10^{-6}$ l. mol^{-1} sec^{-1}; and k_1', the rate constant for hydrolysis of the monoanion, is 0.18×10^{-6} sec^{-1}.

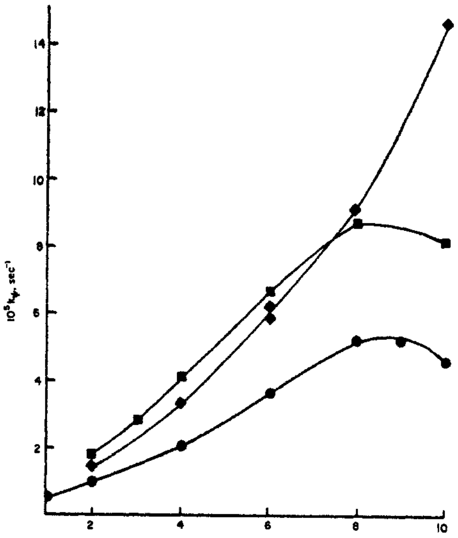
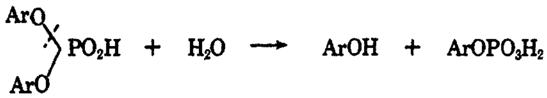


Figure 2.—Acid-catalyzed hydrolysis of bis-2,4-dinitrophenyl phosphate at 25.0°: ●, $HClO_4$; ■, H_2SO_4; ◆, HCl.

Using these rate constants and the proportion of monoanion calculated using pK = 1 we estimate $k_1^0 = 1.5 \times 10^{-6}$ sec^{-1} at pH 1 and 1.9×10^{-6} sec^{-1} at pH 2. Although k_1^0 cannot be determined accurately, because of the errors involved in estimating the proportion of the undissociated acid, these values show that hydrolysis of the undissociated diaryl phosphate contributes to the over-all reaction at pH 1-2. The reaction probably involves bimolecular attack by water upon I, but because of the difficulty of separating the contributions of the spontaneous hydrolysis from that of the acid-catalyzed hydrolysis we are not able to prove its mechanism.



$$(\mathrm{ArO})_2\mathrm{PO_2H} + \mathrm{H_2O} \longrightarrow \mathrm{ArOH} + \mathrm{ArOPO_3H_2}$$

I

The rates of hydrolysis of both mono- and bis-2,4-nitrophenyl phosphates are very similar at low pH (Figure 1).

Acid-Catalyzed Hydrolysis.—The rate of hydrolysis of the bisphosphate increases with increasing acid concentration and there are rate maxima in sulfuric and perchloric acids, but not with hydrochloric acid (Figure 2). These phenomena appear to be quite general for the hydrolyses of phenyl phosphates and phosphinates which contain strongly attracting substituents in the phenyl group,[6,9-12] except that this bisdiaryl phosphate shows no rate maximum in hydrochloric acid, unlike the other nitrophenyl phosphates and phosphinates.[6,9-12] In other systems it has been shown by direct determination of substrate basicity, or by the values of the deuterium solvent isotope effect, that these rate maxima are not caused by complete conversion of the substrate into its conjugate acid, as is found for the acid hydrolysis of weakly basic substrates such as carboxylic amides.[33] As is generally found for A2 hydrolyses perchloric acid is a less effective catalyst than sulfuric and hydrochloric acids.[34]

Several possible explanations for these phenomena

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(31) R. F. Hudson, "Structure and Mechanism in Organo-Phosphorus Chemistry," Academic Press, New York, N. Y., 1965, Chapter VIII.

(32) E. M. Arnett, P. M. Duggleby, and J. J. Burke, *J. Amer. Chem. Soc.*, **85**, 1359 (1963).

(33) Reference 26, Chapter XIV.

(34) C. A. Bunton, J. H. Crabtree, and L. Robinson, *J. Amer. Chem. Soc.*, **90**, 1258 (1968).

can be considered; for example, a reaction which was very sensitive to water activity could show such rate maxima in moderately concentrated acid. A high dependence of water activity is indicated by the *w* values, which are given by the slopes of plots of log $k_\psi + H_0$ against log a_{H_2O}.[35] However, the plots are curved, and the *w* values decrease from *ca.* 8 at low acid concentrations to *ca.* 3 at high. Large values are found for acid hydrolyses of other nitrophenyl phosphates and related compounds, although the plots are often curved.[6,9–12] However, for the acid hydrolysis of *p*-nitrophenyl phosphate it has been found that this relation between reaction rate and water activity fails for reactions in toluene-*p*-sulfonic acid and mixtures of lithium and hydrogen chloride.[9] In the present system k_ψ increases linearly with hydrogen ion concentration for solutions of lithium and hydrogen chloride of constant ionic strength (Table III), and the rate constant follows the relation

$$10^6 k_\psi = 0.8 + 9.3C_{H^+}$$

The water activity is essentially constant in these solutions.[36]

Bunnett's more recent treatment of plotting log $k_\psi + H_0$ against log $C_{H^+} + H_0$ [37] gives straight lines of slopes, of 0.97 for perchloric, 1.00 for sulfuric, and 0.89 for hydrochloric acid (calculated by using a least-squares treatment). These values are in the range found for acid hydrolyses of other aryl phosphates, and are similar to the values which Bunnett suggests are characteristic of hydrolysis involving slow proton transfers.[35,37] These nitrophenyl phosphates should be very weakly basic, and it is possible that proton addition could be concerted with attack of water, although the value of the deuterium solvent isotope effect $k_{H_2O}/k_{D_2O} = 1.19$ in 3 *M* sulfuric acid at 25° (Table III) shows that the exchangeable hydrogens are largely covalently bound in the transition state.[22,38,39]

The relative inefficiency of perchloric acid as a catalyst could arise in part from its ability to "salt-in" the phosphate ester, as has been found for some triaryl phosphates,[11,12] and for polar nonelectrolytes in general.[40a] However in other A2 hydrolyses of carboxylic esters and related compounds it seems that perchlorate ion destabilizes the transition state relative to the behavior of hydrogen sulfate or chloride ion, and this result may well be true in the present reaction.[31,34]

So far as we know the acid hydrolysis of bis(2,4-dinitrophenyl) phosphate is the only example of an acid-catalyzed hydrolysis of an aryl phosphate which does not have a rate maximum in hydrochloric acid, and the kinetic form for this reaction is just like those found for acid hydrolyses of weakly basic substrates at acidities in which there is very little protonation.[40b,41]

These acid hydrolyses of aryl phosphates and phosphinates have certain common features:[6,9–12] (i) the entropies of activation are negative by approximately −30 eu, (ii) the deuterium solvent isotope effect k_{H_2O}/k_{D_2O} is generally >1, (iii) the effectiveness of the acids is $HCl > H_2SO_4 > HClO_4$, (iv) the rate constant varies linearly with hydrogen ion concentration for mixtures of HCl and LiCl of constant ionic strength, for which the water activity is approximately constant, (v) there is a high dependence upon water activity as judged by Bunnett's *w* values; and (vi) the acid hydrolysis is assisted by electron-withdrawing groups, *e.g.*, NO_2 or CH_3CO, in sharp contrast to the general insensitivity of acid hydrolyses to electronic effects which is explained in terms of opposing effects upon substrate protonation and nucleophilic attack upon the conjugate acid.[42]

A major problem is the isolation of the factors which influence the kinetic form, because many of them are not independent parameters. For example the protonating power of an acid, as measured by Hammett's, or any other, acidity function, will depend upon water activity and the activity coefficients of the base and its conjugate acid,[43] and the logarithms of water activity and the activity coefficients are approximately linearly related with acid concentration, at least over limited ranges of concentration.[36] For these reasons we have to be cautious in analyzing the data by linear free-energy relationships involving acidity function, or by equations which involve both water activity and the activity coefficients of the substrates.

Hydrolysis at High pH.—Despite the negative charge upon the substrate the hydroxide ion readily attacks the phosphorus atom of bis(2,4-dinitrophenyl) phosphate monoanion. The second-order rate constant increases slightly with increasing concentration of hydroxide ion (Table IV), but $k_2 \sim 3 \times 10^{-3}$ l. mol^{-1} sec^{-1}. The bis monoanion is approximately 80 times more reactive toward hydroxide ion than is 2,4-dinitro phenyl phosphate dianion,[6] where $k_2 \sim 4 \times 10^{-5}$ l. mol^{-1} sec^{-1}, showing that the negative charge effectively inhibits anionic attack, but that powerful electron-attracting groups can minimize the importance of these electrostatic repulsions. The activation parameters for the attack of hydroxide ion upon bis(2,4-dinitrophenyl) phosphate monoanion are in the range expected for bimolecular nucleophilic substitution. Our results do not distinguish between attack upon the phosphorus atom concerted with departure of the leaving group and prior addition followed by elimination. However in some similar substitutions the former mechanism appears to be the more probable.[2,44–46]

Registry No.—Bis(2,4-dinitrophenyl) phosphate, 18962-97-5; bis(2,4-dinitrophenyl) phosphate monoanion, 18962-95-3; dianion of 2,4-dinitrophenyl phosphate, 18962-96-4.

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[45] R. F. Hudson and M. Green, *Angew. Chem. Intern. Ed. Engl.*, **2,** 11 (1963).

[46] The situation is different for cyclic esters.[8]