Reactions of Phosphonic Acid Esters with Nucleophiles. I. Hydrolysis

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and Martin Isaks

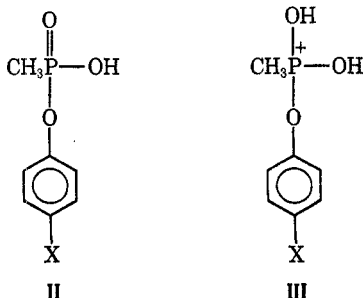*Metcalf Chemical Laboratories, Brown University, Providence, Rhode Island 02912*

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Phenyl methylphosphonic acid (PMP) and *p*-nitrophenyl methylphosphonic acid (*p*-NPMP) have been synthesized. The hydrolysis of PMP and its anion has been studied in acid, neutral, and basic solutions; the hydrolysis of the anion of *p*-NPMP was examined in neutral and basic media. We have observed nucleophilic attack by water on *p*-NPMP in neutral solution. In basic media, both PMP and *p*-NPMP react *via* nucelophilic attack by hydroxide ion at phosphorus. Near pH 9, calcium ions catalyze the hydrolysis of *p*-NPMP. PMP hydrolysis shows a rate maximum in moderately concentrated acid solutions.

In comparison with the large numbers of studies of the reactions between nucleophiles and neutral phosphorus esters, few data have been reported on the reactions of nucleophiles with phosphonic acid ester monoanions.[2–6] The monoanions of the monoesters of phosphoric acid exist over a very small pH range, so that broad surveys of their reactivity with nucleophiles have not been possible. This complication is avoided with the monoanions of phosphonic acid monoesters; virtually the entire pH range is available for study. Nucleophilic displacements on phosphonic acid ester monoanions are also of some practical importance since they may be used as model systems for the study of cholinesterase inhibition by certain organophosphorus compounds.[7,8] For these reasons, the investigation of the reactions of various classes of nucleophiles with phosphonic acid ester anions of the type I was initiated.

I
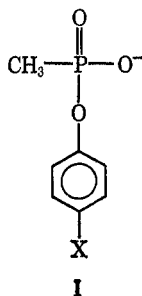
The first approach was an examination of the hydrolysis of phosphonic acid esters of type I in acid, neutral, and basic media. In highly acidic solution, I exists as the neutral species II, and possibly also the positively

II   III

charged species III. Phenyl methylphosphonic acid (PMP), IV, and *p*-nitrophenyl methylphosphonic acid (*p*-NPMP), V, were the substrates studied.

IV   V

We have also investigated the reactivity of a variety of other nucleophiles toward *p*-NPMP, the results of which are reported in other papers.[9,10]

Experimental Section

Substrates. 1. Phenyl Methylphosphonic Acid (PMP).—Two previous syntheses have been reported.[11,12] We used a new route based on partial hydrolysis of diphenyl methylphosphonate, which was prepared by condensation of methyl iodide and triphenyl phosphite followed by hydrolysis of the phosphonium iodide according to Berlin and Butler,[13] except that the reflux time was cut to 16 hr.[14] These procedures are based on the syntheses of Michaelis and Kaehne.[15] The ether wash of the phosphonium iodide was omitted and the material was decomposed directly with water. The diphenyl methylphosphonate was extracted into ether and this phase was washed with aqueous alkali. Removal of the ether yielded crude diphenyl methylphosphonate. Distillation gave a 68% yield of material, bp 173–180° (3 mm) [literature values: bp 145–148° (0.4 mm),[13] 190–195° (11 mm)[15]]. Diphenyl methylphosphonate (87.6 g, 0.35 mol) was added to a refluxing solution of 40 g (0.70 mol) of NaOH in 750 ml of water. Refluxing was continued for 25 min, at which time the oily layer of diphenyl methylphosphonate was no longer visible. The solution was rapidly cooled, neutralized to pH 7 with HCl, and extracted with ether to remove phenol. The aqueous phase was then strongly acidified and extracted with chloroform. Removal of the chloroform from the nonaqueous extract yielded crude phenyl

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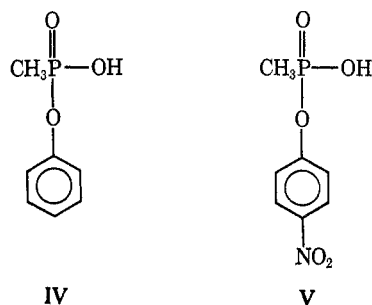
(2) J. R. Cox and O. B. Ramsay, *Chem. Rev.*, **64**, 317 (1964).

(3) (a) A. J. Kirby and W. P. Jencks, *J. Amer. Chem. Soc.*, **87**, 3209 (1965); (b) W. P. Jencks and M. Gilchrist, *ibid.*, **87**, 3199 (1965); (c) A. J. Kirby and A. G. Varvoglis, *J. Chem. Soc. B*, 135 (1968).

(4) T. C. Bruice and S. J. Benkovic, "Bioorganic Mechanisms," Vol. II, W. A. Benjamin, New York, N. Y., 1966, Chapters 5, 6.

(5) A. J. Kirby and S. G. Warren, "The Organic Chemistry of Phosphorus," Elsevier, New York, N. Y., 1967, Chapter 10.

(6) R. F. Hudson, "Structure and Mechanism in Organo-Phosphorus Chemistry," Academic Press, New York, N. Y., 1965, Chapters 4–8.

(7) R. D. O'Brien, "Toxic Phosphorus Esters," Academic Press, New York, N. Y., 1960.

(8) D. F. Heath, "Organophosphorus Poisons," Pergamon Press, New York, N. Y., 1961.

(9) E. J. Behrman, M. J. Biallas, H. J. Brass, J. O. Edwards, and M. Isaks, *J. Org. Chem.*, **35**, 3069 (1970).

(10) H. J. Brass, J. O. Edwards, and M. J. Biallas, *J. Amer. Chem. Soc.*, **92**, 4675 (1970).

(11) F. C. G. Hoskin, *Can. J. Chem.*, **35**, 581 (1957).

(12) K. A. Petrov, E. E. Nifant'ev, and R. F. Nikitina, *J. Gen. Chem. USSR*, **31**, 1592 (1961).

(13) K. D. Berlin and G. B. Butler, *J. Org. Chem.*, **26**, 2006 (1960).

(14) P. W. Morgan and B. C. Herr, *J. Amer. Chem. Soc.*, **74**, 4526 (1952).

(15) A. Michaelis and R. Kaehne, *Ber.*, **31**, 1048 (1898).

methylphosphonic acid as a viscous oil (47 g, 80%). The material was characterized as the silver salt.[11]

LiOH (140 ml, 2 M) was slowly added to 47 g of IV with cooling and stirring. The neutral solution was filtered and 1 l. of boiling acetone was gradually added while stirring. After standing overnight, 37 g of the lithium salt was filtered off. Additional material (9 g) was obtained by further additions of acetone for a final yield of 46 g (95%) of the lithium salt. The material was washed with acetone and ether and air-dried to yield a nonhygroscopic microcrystalline powder. A small portion was recrystallized from 95% ethanol. The uv spectrum of the salt in water gave 261 mμ (ϵ 483). Ir and nmr spectra were consistent with the assigned structure.

Anal. Calcd for $C_7H_8PO_3Li$: C, 47.2; H, 4.53; P, 17.4. Found: C, 47.6; H, 4.58; P, 17.6.

The pK_a of IV was determined by two techniques.[16] A 10-ml sample of a 0.10 M LiPMP solution was titrated with a 1.00 M HCl solution. The pH was measured (using a Beckman Model G pH meter) after each addition. A pK_a value of 1.28 was obtained which when corrected for ionic strength effects[17] was 1.39. The pK_a was also determined spectrophotometrically by measuring the fraction of total PMP present in the anionic form as a function of pH. Solutions were 1.00×10^{-3} M in phosphonate. pH values were adjusted with 0.10 M HCl-KCl solutions. After correction for ionic strength effects, the pK_a was found to be 1.47.

2. p-Nitrophenyl Methylphosphonic Acid (p-NPMP).[18]—The preparation of bis(p-nitrophenyl) methylphosphonate was carried out using a procedure analogous to that for diphenyl methylphosphonate.[11] Methylphosphonodichloride[19] (10 g, 0.075 mol) was placed together with p-nitrophenol (20 g, 0.145 mol) in a 100-ml flask, fitted with reflux condenser, drying tube, and thermometer. This mixture was heated slowly over a course of 3 hr to a temperature of 160°. Hydrogen chloride evolution began at 70°. The temperature was held at 160° for an additional hour. The black oily mixture was dissolved in toluene, treated with decolorizing charcoal, and then recrystallized twice from a mixture of toluene and ether to give 11.3 g (49%) of bis(p-nitrophenyl) methylphosphonate.

The hydrolysis of this phosphonate was carried out as follows: 5 g (0.0147 mol) of phosphonate was placed together with 0.0326 mol of NaOH (10% excess) in 100 ml of water and heated to boiling. After 5 min almost all of the phosphonate had dissolved. The solution was cooled, acidified to pH 3.5, and extracted with three 50-ml portions of ether. The ether layers gave a 110% yield of p-nitrophenol based on conversion of phosphonate to p-nitrophenyl methylphosphonic acid. The aqueous layer was then strongly acidified with concentrated HCl. (At this point some dark oily precipitate appeared; this was found to have no observable influence on the following steps.) The aqueous phase was continually extracted with ether for 2 hr. The ether solution was dried with anhydrous magnesium sulfate and the product was allowed to crystallize in the refrigerator. If no product appeared in 6–8 hr, n-hexane was added to the cloud point and the product then crystallized overnight. Recrystallization from refluxing ether gave 1.6 g of product in the form of white needles, mp 113–114°; this represents a yield of 48% p-NPMP based on phosphonate. The uv spectrum of p-NPMP in water gave 291 mμ (ϵ 9360). Ir and nmr spectra were consistent with the assigned structure. Neutralization equivalents of 219 and 220 were obtained; the calculated value is 217. Alkaline hydrolysis gave p-nitrophenol in 100.3% of the theoretical quantity.

Anal. Calcd for $C_7H_8NO_5P$: C, 38.72; H, 3.71; N, 6.45; P, 14.27. Found: C, 38.83; H, 3.80; N, 6.42; P, 14.44.

The spectra of the anions of phenol and p-nitrophenol yielded extinction coefficients of 2600 and 18,200 at 286 and 400 mμ, respectively; these values were used in the calculation of rate constants where appropriate.

Inorganic materials (reagent grade) were used without further purification. s-Collidine (2,4,6-trimethylpyridine) was distilled twice under nitrogen at reduced pressure, bp 35° (5 mm).

Analyses were performed by Galbraith Laboratories, Knoxville, Tenn.

Kinetics.—The rates of hydrolysis of the two aryl methylphosphonates were followed by observing the rate of formation of the phenolate ion at 286 mμ or of the p-nitrophenolate ion at 400 mμ. Molar absorptivities were measured on a Beckman Model DU spectrophotometer in 1-cm quartz cuvettes. A water blank was used. Where necessary, aliquots of reaction solutions were made basic before spectral analysis so that all of the phenol or p-nitrophenol (pK_a values 10.0 and 7.15, respectively) existed in the anionic forms. Reactions were carried out in volumetric flasks suspended in a constant temperature bath ($\pm0.1°$). Aliquots were withdrawn at appropriate time intervals. Some reactions were monitored in thermostated glass-stoppered cuvettes in the spectrophotometer. The pH values of solutions were maintained constant by use of appropriate buffers.

The decrease of PMP and p-NPMP concentrations in all hydrolysis experiments followed first-order kinetics at any specified pH. Runs were generally followed for at least one half-life. Several hydrolysis experiments in basic solution were carried out through ten half-lives and the predicted yields of phenolate or p-nitrophenolate ions were observed within an experimental error of $\pm3\%$. For basic hydrolysis of both substrates and neutral hydrolysis of p-NPMP, second-order rate constants were obtained by dividing the pseudo-first-order rate constant by the hydroxide ion or water concentrations as appropriate. Frequently, for slow reactions, the initial concentration of phosphonic acid ester was increased and the reaction carried out under pseudo-zero-order conditions. Division of the pseudo-zero-order rate constant by both initial substrate and hydroxide ion concentrations gave second-order rate constants in good agreement with those obtained by the pseudo-first-order technique.

In acid solutions it was necessary to prevent the loss of phenol from the acid solutions. Ground-glass stoppers were greased and the flasks were shaken before aliquots were removed to mix in any phenol that might have condensed on the cooler necks of the flasks.

Experiments in the Presence of Calcium Ion. Attempts to buffer reaction solutions with borate and phosphate in the presence of Ca^{2+} were unsuccessful due to the precipitation of the calcium salts. One series of experiments used 0.2 M NaOH to establish a pH of 9.0; however the rate began to drop after $\sim2\%$ of reaction due to a decrease in pH since the solution was unbuffered. In a second series, s-collidine was employed to maintain the pH of reaction solutions. Because of the limited solubility of s-collidine in water, kinetic experiments were performed in solutions containing 81% H_2O–19% EtOH by volume in which s-collidine is soluble up to at least 1.0 M. The pH of solutions of 0.05–0.60 M s-collidine in this solvent system is between 8.80 and 9.30.

(We assumed that the effect of the 19% ethanol on the accuracy of the pH measurements is negligible and comparative data in water indicate that this assumption is valid—see Table VI. The extinction coefficient of the p-nitrophenolate ion in 19% ethanol solution is within 3% of the value in water (1.82×10^4).)

(16) A. Albert and E. P. Serjeant, "Ionization Constants of Acids and Bases," Methuen and Co., London, 1962.

(17) See ref 16, p 59.

(18) In the course of our investigation a synthesis of p-NPMP by another method was reported: K. A. Petrov, R. A. Baksova, L. V. Korkhoyanu, L. P. Sinogeikina, and T. V. Skudina, *J. Gen. Chem. USSR,* **35,** 723 (1965).

(19) A sample of methylphosphonodichloride was kindly supplied by the U. S. Army Research Laboratories, Edgewood Arsenal, Md.

Results

Alkaline Hydrolysis.—Tables I and II give the results of a series of experiments in which hydroxide ion concentration, ionic strength, and temperature were varied. The stoichiometry of the reaction of both substrates is given in eq 1 and the rate law is given in eq 2. For p-
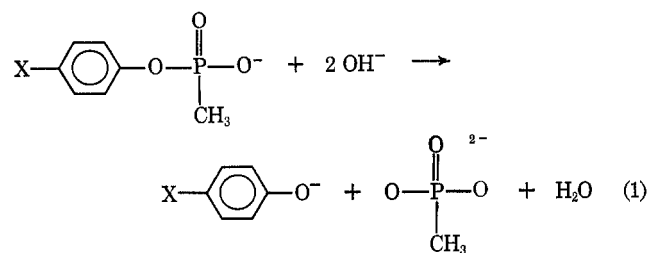
$$\text{rate} = k_2[\text{substrate}][\text{OH}^-] \qquad (2)$$

NPMP at constant ionic strength ($I = 3.36$) the quantity $k'/[\text{OH}^-]$, where k' is the pseudo-first-order rate

Table I

Alkaline Hydrolysis of Phenyl Methylphosphonic Acid

[NaOH], M	[Salt], M	I	[PMP] $\times 10^3$, M^a	Temp, °C	$k' \times 10^3$, min^{-1}	$k'/[OH^-] \times 10^3$, M^{-1} min^{-1}
2.120		2.12	2.00	78	7.97	3.76
1.060	1.060^b	2.12	2.00	78	3.64	3.43
0.424	1.696^b	2.12	2.00	78	1.37	3.23
0.212	1.908^b	2.12	2.00	78	0.668	3.15
0.106	2.014^b	2.12	2.00	78	0.334	3.15
0.212		0.21	2.12	78	0.288	1.36
0.212	0.85^c	1.06	2.12	78	0.523	3.44
0.212	1.91^c	2.12	2.12	78	0.730	3.76
0.212	1.91^b	2.12	2.12	78	0.668	3.15
2.12		2.12	2.00	78	7.83	3.69
2.12		2.12	2.00	68.5	3.73	1.76
2.12		2.12	2.00	58.8	1.60	0.755
2.12		2.12	2.00	39	0.228	0.108

^{a} Initial concentration of lithium phenyl methylphosphonate. ^{b} NaClO$_4$. ^{c} NaCl.

Table II

Alkaline Hydrolysis of p-Nitrophenyl Methylphosphonic Acid^a

[NaOH], M	[NaClO$_4$], M	I	Temp, °C	$k' \times 10^3$, min^{-1}	$k'/[OH^-] \times 10^3$, M^{-1} min^{-1}
3.38		3.38	30	21.5	6.36
1.69	1.67	3.36	30	7.27	4.30
1.69	1.67	3.36	30	7.39	4.37
0.845	2.50	3.35	30	3.21	3.80
0.339	3.00	3.34	30	1.13	3.33
0.169	3.22	3.39	30	0.572	3.38
0.169	1.69	1.86	30	0.424	2.51
0.169		0.17	30	0.237	1.40
0.169		0.17	39.4	0.630	3.73
0.169		0.17	50	1.44	8.52
0.169		0.17	60	3.24	19.2

^{a} The initial concentration of p-nitrophenyl methylphosphonic acid was 1.33×10^{-4} M.

constant, increases with increase in base concentration; however a plot of $k'/[OH^-]$ vs. $[OH^-]$ gives a line which extrapolates to 3.0×10^{-3} M^{-1} min^{-1} (Figure 1) and this intercept may be taken as the second-order rate constant for the reaction with hydroxide ion at 30°. A similar trend of smaller size can be seen in the data for PMP; the intercept has a value of 3.0×10^{-3} M^{-1} min^{-1} at 78° (Figure 1). The ionic strength effects given in Tables I and II are in the expected direction for the reaction between two particles of like charge sign;[20] their magnitude deserves no special comment. The variation of rate with temperature allowed calculation of activation parameters for both substrates; activation parameters were as follows: for PMP, $E_a = 19.8 \pm 0.3$ kcal/mol and $\Delta S^{\ddagger} = -23.5 \pm 0.8$ eu (78°); and for p-NPMP, $E_a = 17.3 \pm 0.4$ kcal/mol and $\Delta S^{\ddagger} = -25 \pm 1$ eu (30°).
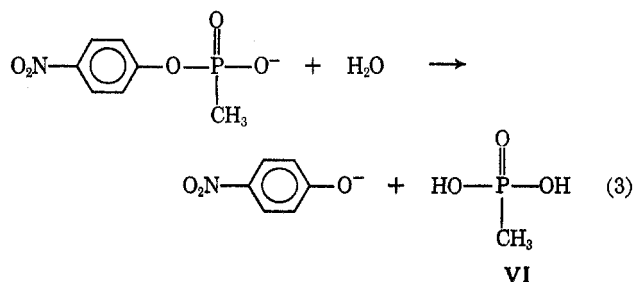
Hydrolysis in Buffered Solutions.—Below approximately pH 12 at 80° the rate of hydrolysis of PMP becomes too slow to follow conveniently. Table III shows data obtained at 60° for buffered solutions of p-NPMP from pH 7 to pH 12. The predicted first-order rate constant for hydroxide ion attack at pH 7 from the data of Table II is $\sim 2 \times 10^{-9}$ min^{-1}. The observed rate constant is about three powers of ten above this value, so another mechanism must be operating in this pH range. Since the rate does not seem to depend on pH (below pH 9) or on buffer concentration, we have attributed the observed rate to nucleo-

(20) K. J. Laidler, "Chemical Kinetics," McGraw-Hill, New York, N. Y., 1965, pp 220–221.

Table III

Hydrolysis of p-Nitrophenyl Methylphosphonate Ion in Buffer Solutions from pH 7 to pH 12^a

Buffer, M	[p-NPMP$^-$] $\times 10^4$, M	pH	k', min^{-1}
Phosphate, 0.04	1.33	11.90	2.60×10^{-4}
Carbonate, 0.08	1.33	10.25	2.05×10^{-5}
Phosphate, 0.08	1.33	7.05	2.80×10^{-6}
Carbonate, 0.08	2.00	10.25	$2.1 \times 10^{-5 \, b}$
Phosphate, 0.08	2.00	6.90	$2.9 \times 10^{-6 \, b}$
Phosphate, 0.02	2.00	6.90	$2.5 \times 10^{-6 \, b}$
Borate, 0.1	4.00	8.55	4.3×10^{-6}
Borate, 0.02^c	4.00	8.50	3.6×10^{-6}

^{a} Temp $= 60°$. ^{b} Final ionic strength made up to 0.16 with NaClO$_4$. ^{c} NaClO$_4$ = 0.08 M.

philic attack by water on p-NPMP. The stoichiometry for such an attack is given in eq 3 and the rate law in eq 4. (Compound VI will ionize to the methyl-

$$O_2N\text{—}\bigcirc\text{—}O\text{—}\overset{\displaystyle O}{\underset{\displaystyle CH_3}{\overset{\|}{P}}}\text{—}O^- + H_2O \longrightarrow$$

$$O_2N\text{—}\bigcirc\text{—}O^- + HO\text{—}\overset{\displaystyle O}{\underset{\displaystyle CH_3}{\overset{\|}{P}}}\text{—}OH \quad (3)$$

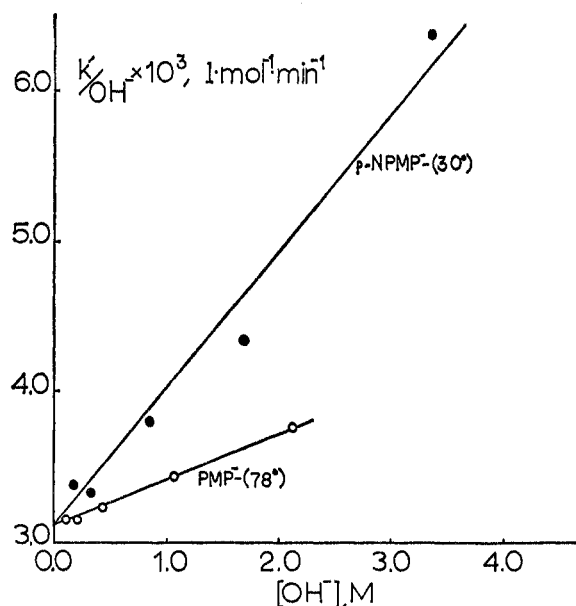**VI**

$$\text{rate} = k_2[p\text{-NPMP}][H_2O] \quad (4)$$

Figure 1.—Plot of pseudo-first-order rate constants divided by hydroxide ion concentration ($\times 10^3$ M^{-1} min^{-1}) vs. hydroxide ion concentration [M] for the reaction of hydroxide ion with PMP and p-NPMP; see Tables I and II.

phosphonate mono- or dianion in a rapid step after the rate-determining attack by water.)

Table IV gives the rate constants and activation parameters for water attack on p-NPMP.

TABLE IV
NUCLEOPHILIC ATTACK BY H_2O ON p-NITROPHENYL METHYLPHOSPHONATE[a]

pH[b]	Temp, °C	k', min^{-1}	k_2, M^{-1} min^{-1} [c,d]
7.60	29.7	1.18×10^{-7}	2.13×10^{-9}
7.50	60	4.34×10^{-6}	7.81×10^{-8}

[a] [p-NPMP$^-$] = $5.90 \times 10^{-4} M$.   [b] Buffer: 0.108 M KH$_2$PO$_4$–0.092 M NaOH.   [c] E_a = 23.8 kcal/mol.   [d] $\Delta S^{\ddagger}$ (60°) = -29.7 eu.

Acid Hydrolysis.—Data for the variation of the rate of hydrolysis of PMP as a function of acidity are presented in Table V; the activation parameters are also given. Figure 2 is a plot of k_{obs} against the calculated pH. A rate maximum is observed at approximately 3 M acid. No rate maximum is observed, however, if k_{obs}/a_{H_2O} (which is shown by the dotted line) is plotted instead of k_{obs} (Figure 2).

Catalysis by Added Calcium Ion.—Addition of Ca(NO$_3$)$_2$ to an aqueous solution of p-NPMP at pH 9.0 increased the rate of hydrolysis by approximately 12-fold (Table VI). The pseudo-first-order constant with 0.05 M Ca(NO$_3$)$_2$ present was 1.2×10^{-4} min^{-1} as compared to 8.0×10^{-6} min^{-1} in the absence of the added salt. In order to be certain that an ionic strength effect was not operating, the reaction was run in the absence of Ca(NO$_3$)$_2$ but with sufficient NaCl present to equal the ionic strength of the 0.05 M Ca-(NO$_3$)$_2$ experiments (*i.e.*, I = 0.15); the rate constant k' = 9.0×10^{-6} min^{-1} was found. Nitrate ion was found to be a weak nucleophile toward p-NPMP; the rate of hydrolysis of p-NPMP in the presence of 0.1 M NO$_3^-$ was equal to that of the rate at pH 9.0 without nitrate. We conclude that the rate enhancement when Ca(NO$_3$)$_2$ is present is due to the presence of Ca^{2+} ions.
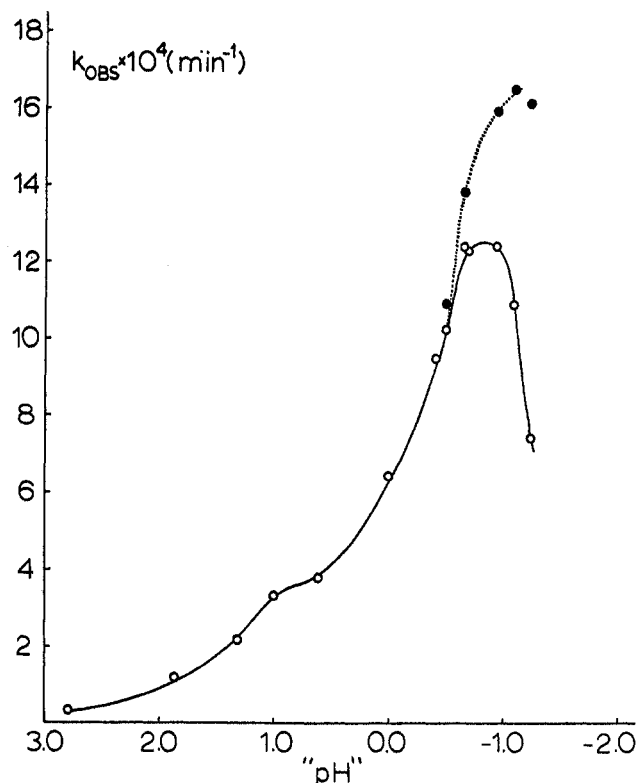

Figure 2.—(-O-) $k_{obs} \times 10^4$ (min^{-1}) vs. calculated pH for the hydrolysis of PMP in acid solution; (---●---) k_{obs} has been divided by a_{H_2O}. See Table V.

TABLE V
HYDROLYSIS OF PMP IN ACID SOLUTION

[PMP]$_t$ $\times$ 10^3, M[a]	[H$_2$SO$_4$], M	pH[b]	H_0[c]	Temp, °C	a_w[d]	$k_{obs} \times 10^4$, min^{-1}
2.0		2.80		80.5	1	0.33
2.0		1.90		80.5	1	1.22
2.0	0.024	1.32		80.0	1	2.15
2.0	0.050	1.00		80.4	1	3.32
2.0	0.119	0.62	+0.80	80.0	1	3.87
2.0	0.475	0.02	+0.10	80.0	0.98	6.45
3.0	1.189	−0.38	−0.30	80.0	0.95	9.54
2.0	1.610	−0.51	−0.60	80.0	0.94	10.25
2.0	2.375	−0.68	−0.95	80.4	0.90	12.4
5.0	2.500	−0.70	−1.12	80.0	0.89	12.3
9.0	4.325	−0.94	−1.90	80.0	0.78	12.4
10.0	6.125	−1.09	−2.80	80.0	0.66	10.9
10.0	9.300	−1.27	−4.50	80.0	0.46	7.43
2.0	2.375	−0.68		52.6	0.90	0.89[e]
2.0	2.375	−0.68		65.0	0.90	2.76[e]
2.0	0.024	1.32		52.6	1	0.087[e]
2.0	0.024	1.32		65.0	1	0.374[e]

[a] [PMP]$_t$ values are total concentrations of PMP added to the reaction mixtures as lithium phenyl methylphosphonate.   [b] Sulfuric acid was used except for the first two entries. The run at pH 2.8 was in 0.05 M chloroacetate buffer; the run at pH 1.9 was in 0.06 M KCl–HCl. The run at pH 1.32 was unaffected by the addition of sodium perchlorate to a final ionic strength of 2.   [c] M. A. Paul and F. A. Long, *Chem. Rev.*, **57**, 1 (1957).   [d] H. S. Harned and B. B. Owen, "Physical Chemistry of Electrolytic Solutions," 3rd ed, Reinhold, New York, N. Y., 1958, p 574; by linear extrapolation of the data at 0, 25, 40, and 60°.   [e] Arrhenius plots of the data at pH −0.68 and at 1.32 yield activation energies of 21.8 and 26.8 kcal/mol, respectively; calculated entropies of activation are −20.7 and −9.0 eu.

The rate of hydrolysis of p-NPMP in the presence of 0.05 M Ca(NO$_3$)$_2$ with the pH maintained at 9.0 by the addition of s-collidine in an 81% H$_2$O–19% EtOH sol-

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Table VI

Effect of Ca^{2+} on the Rate of Hydrolysis of p-NPMP^a

</div>

[NaCl], M	[Ca(NO$_3$)$_2$], M	pH	k', min^{-1}	Buffer	Solvent
	0.05	9.0^b	1.2 × 10^{-4}	None	H$_2$O
		9.0^b	8.0 × 10^{-6}	None	H$_2$O
	0.05	9.0	1.4 × 10^{-4}	s-Collidine	81% H$_2$O–19% EtOH
		9.0	9.0 × 10^{-6}	s-Collidine	81% H$_2$O–19% EtOH
0.15		9.0^b	9.0 × 10^{-6}	None	H$_2$O

^{a} [p-NPMP] = 1.20 × 10^{-3} M. ^{b} pH established by added NaOH.

vent system was unchanged from the experiments using NaOH to adjust pH in water. We feel therefore that a direct comparison of the data in the mixed solvent and those in pure water is legitimate. A series of kinetic experiments were performed at constant Ca-(NO$_3$)$_2$ concentration (0.05 M) and variable s-collidine concentration (from 0.0454 M to 0.610 M, Table VII). The reaction pH varied from 8.80 to 9.30; k' varied from ~7 × 10^{-5} min^{-1} at low s-collidine concentration and pH (~8.80) to ~2 × 10^{-4} min^{-1} at high s-collidine concentration and pH (~ 9.30).

Discussion

Alkaline Hydrolysis.—Experimental data show that the alkaline[2,4,5,21–24] hydrolysis of most neutral esters of phosphoric acid [(RO)$_3$PO] and phosphonic acids [(RO)$_2$(R')PO] and the neutral halides [(RO)$_2$POX, (RO)(R')POX, and (R)$_2$POX] proceed *via* direct nucleophilic substitution by hydroxide ion at the phosphorus atom. Hydroxide ion also reacts with mono-anions of the diesters of phosphoric acid and related

<div align="center">

Table VII

Dependence of Rate on Collidine Concentration and pH
at 0.05 M Ca(NO$_3$)$_2$^{a}

</div>

[Collidine], M	pH	k' × 10^4, min^{-1}
0.0454	8.90	0.67
0.0454	8.80	0.78
0.0755	8.82	1.04
0.0755	8.95	0.90
0.151	9.22	1.35
0.227	9.08	1.17
0.305	9.20	1.47
0.305	9.20	1.25
0.454	9.30	1.85
0.454	9.30	1.80
0.610	9.30	2.14
0.610	9.25	2.22

^{a} Temp = 60°, [p-NPMP] = 1.20 × 10^{-3} M, run in 81% H$_2$O–19% EtOH.

compounds[2,25,26] in a bimolecular fashion; with these compounds, however, the attack by hydroxide ion is predominately at the ester carbon, unless a good leaving group is bound to phosphorus.[2,4,26–28] The hydrolysis

of mono- and dianions of phosphate monoalkyl or aryl esters[2,25,29–39] are thought to proceed *via* a unimolecular elimination of the monomeric metaphosphate species PO$_3^-$ over a wide pH range (*i.e.*, pH 2–12). In most cases the monoanion ROPO$_3$H$^-$ is most reactive. At high pH, nitro-substituted monoaryl phosphates[35] apparently react with hydroxide ion *via* a bimolecular attack at both phosphorus and aromatic carbon; the unimolecular pathway (*i.e.*, spontaneous dianion heterolysis) may also proceed at high pH.[35]

The reactions of PMP and p-NPMP in aqueous alkaline solution can be interpreted as involving a bimolecular attack on the phosphorus atom by the hydroxide ion thereby displacing the phenolate and p-nitrophenolate anions (Tables I and II) [PMP, E_a = 19.8 ± 0.3 kcal/mol, $\Delta S^{\ddagger}$ = −23.5 ±0.8 eu (78°); p-NPMP, E_a = 17.3 ± 0.4 kcal/mol, $\Delta S^{\ddagger}$ = −25 ± 1 eu (30°)]. The activation parameters for these two phosphorus substrates are of the magnitude associated with bimolecular displacements on tetrahedral organophosphorus compounds.[40] Attack by hydroxide ion at aromatic carbon can be excluded on the grounds that the observed rate constants are too large. At 39° the value of k_2 for the hydroxide ion reaction with 1-chloro-4-nitrobenzene in 16.7% dioxane–83.3% H$_2$O is 1.34 × 10^{-6} M^{-1} min^{-1};[41] k_2 for hydroxide reaction with the dianion of p-nitrophenyl phosphate, p-NPP^{2-} at 39°, was found to be 4.9 × 10^{-7} M^{-1} min^{-1}.[3a] It was concluded that hydroxide ion most probably attacks the aromatic site of the p-NPP^{2-}, although the possibility of some hydroxide ion attack at phosphorus cannot be excluded. With p-NPMP, k_2 for the hydroxide ion reaction at 30° is 3.0 × 10^{-3} M^{-1} min^{-1} and for PMP, k_2 at 78° is 3.0 × 10^{-3} M^{-1} min^{-1}; these values are high compared to the expected displacements at carbon. We believe that the size of the rate constants for hydroxide ion attack on p-NPMP and PMP are most consistent with expectations for attack at phosphorus.

For both substrates k_2 increases linearly with in-

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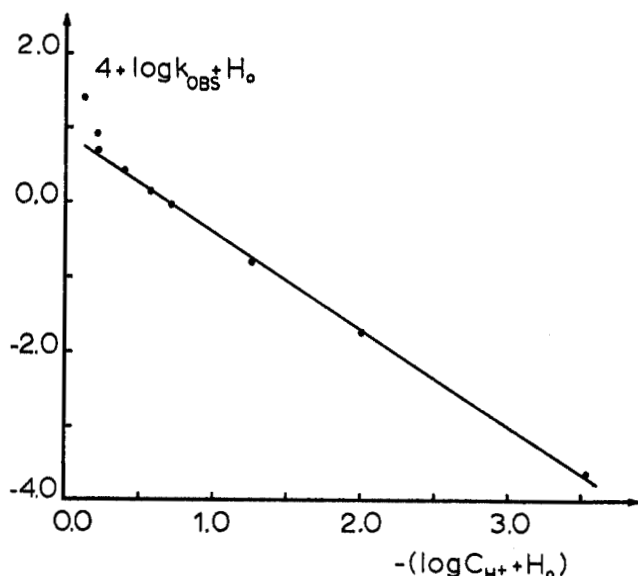
Figure 3.—Plot of $4 + \log k_{obs} + H_0$ vs. $-(\log C_{H^+} + H_0)$ for the hydrolysis of PMP in sulfuric acid solutions. See Table V.

creasing hydroxide ion concentration. The probable explanation for this observation is a salt effect, rather than a term which is second-order in base. The rate of hydrolysis of monoaryl phosphate ester dianions[35] is dependent on the size of the cations present, which suggests a close interaction of the cation with the arylphosphate dianion. A similar interaction between methylphosphonate monoaryl ester monoanions is a reasonable assumption.

Neutral Hydrolysis.—Hydrolysis of *p*-NPMP near neutral pH probably proceeds *via* a bimolecular displacement reaction involving water as a nucleophile. For *p*-nitrophenyl phosphate monoanion at pH 3.7 $k_1 = 4.15 \times 10^{-3}$ min^{-1} at 73.0°;[33] for *p*-NPMP, $k_2 = 1.30 \times 10^{-9}$ M^{-1} min^{-1} at 60.0°. It is worthy of note that the methyl group attached to phosphorus prevents a unimolecular breakdown of the monoanion to form the metaphosphate intermediate PO$_3$$^-$ as suggested in various phosphate hydrolyses. Therefore, a unimolecular mechanism for *p*-NPMP hydrolysis appears to be excluded. The value of $\Delta S^{\ddagger}$ for *p*-NPMP hydrolysis taken from the first-order rate constant (before correction for water concentration) is -21.9 eu; after correction, a value of -29.7 eu is obtained. These values are in the range expected for nucleophilic displacement by solvent water. The hydrolysis of the bis(2,4-dinitrophenyl) phosphate[26] monoanion in the pH region 3.5–7 gives a $\Delta S^{\ddagger}$ of -26 eu and the reaction is interpreted as a nucleophilic attack of water. Isotope data show that reaction is largely at phosphorus for this compound. With *p*-NPMP, attack at phosphorus is probable, but attack at aromatic carbon is not excluded by our data.

Acid Hydrolysis.—H$_2$O^{18} tracer studies of the hydrolysis of aryl phosphate and phosphonate esters in strongly acid media have shown that reaction occurs by P–O bond cleavage;[26,33,42,43] for aryl phosphonate esters, cleavage is assumed to occur also by P–O bond rupture. Further examination of the hydrolysis of aryl phosphate[26,33–36,44] and phosphinate esters[42] in strongly

acid media have shown the existence of rate maxima, such as that found here, if an electron-withdrawing substituent such as a nitro or acetyl function was present on the leaving group. (Triphenyl phosphate is a mild exception.) Although protonation of the substrate in the transition state is presumed to be important, the data do not indicate that any substantial portion of the substrate is converted to conjugate acid form at the rate maximum. For example, basicity measurements[45] have shown that *p*-nitrophenyl phosphate, triphenyl phosphate, and *p*-nitrophenyl diphenyl phosphate are not substantially protonated at the acid concentrations of maximum rates.

The article by Bunton and Farber[43] provides the most recent insight into the subject of rate maxima in the acid-catalyzed hydrolyses of weakly basic substrates. A possibly oversimplified explanation of these rate maxima is the incursion of an acid-catalyzed path for phosphate hydrolyses (causing a rate increase with acidity) and to a decrease in water activity which more than compensates for the rate increase. Other explanations given[43] are based on the presence of a strongly electron-attracting group on the leaving function (which case does not apply here). Our data for the hydrolysis of PMP is analogous to the phosphate and phosphinate cases. The rate maximum of PMP occurs in the range of acid concentration where similar aryl phosphorus esters have displayed rate maxima. The activation parameters for PMP hydrolysis are roughly the same as for the esters known to display maxima. The linear free energy approach of Bunnett and Olsen[46] has been applied to the hydrolysis of PMP. Figure 3 is a plot of $4 + \log k_{obs} + H_0$ vs. $-(\log C_{H^+} + H_0)$ from the data in Table V; the slope $\phi \cong 1.3$. The ϕ values for the hydrolysis of phosphates and PMP are quite similar.[26,34,35,44] The ϕ values are consistent with a strong dependence of the reaction rate on water activity, because of solvation of the transition state in which proton transfers may be important.

In Figure 3, a deviation is observed in low acid concentrations. Bunnett and Olsen[46] point out that nonlinearity in an LFER plot may occur when a substrate that is weakly basic "becomes protonated within the acid range of kinetic study." It is reasonable that the converse is also true and we interpret the deviation from linearity in Figure 3 as due to the partial conversion of phenyl methylphosphonic acid (PMP) to phenyl methylphosphonate and hydrogen ions.

We conclude that the mechanism for PMP hydrolysis in acid solution is probably similar to the hydrolysis of aryl phosphates when the aryl ring contains an electron-withdrawing group. Also it is probable that rate maxima for aryl organophosphorus esters is not confined solely to those cases where an electron-withdrawing substituent is bonded to the aryl ring. In addition to PMP, methyl methylphenylphosphinate and its *p*-methyl derivative show rate maxima at approximately 7 M HClO$_4$.[47]

Hydrolysis with Added Calcium Ion.—Catalysis of the hydrolysis reactions of the neutral and anionic species of organophosphorus esters by metal ions has been reported.[4,5] The enhanced rate of the hydrolysis

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of p-NPMP in the presence of added calcium ions is another example of such catalysis.

Since rapid attack by s-collidine at the phosphorus site is unlikely due to the presence of methyl groups in the 2 and 6 positions,[2-4,10] the larger part of the increase in k' with increasing s-collidine concentration (Table VII) is most probably caused by the corresponding increase in pH. The hydrolysis of Sarin[48] has been shown to be catalyzed by the addition of divalent metal ions where the catalyzing species is the hydroxy complex $[M(H_2O)_{x-1}(OH)]^+$ formed by the ionization of the aquated metal ion $[M(H_2O)_x]^{2+}$. A calcium-hydroxo complex of the type VII can be invoked to explain the catalysis of the hydrolysis of p-NPMP by added calcium ions. At 60°, the pK_a for the ionization of $[Ca(H_2O)_x]^{2+}$ (eq 5) is 12.3.[49]

$$Ca(H_2O)_x^{+2} \rightleftarrows [Ca(H_2O)_{x-1}(OH)]^+ + H^+ \qquad (5)$$
$$VII$$
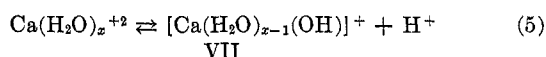
It has been reported[48] that the second-order rate constant $(k_2)_{OH-}$ for the uncatalyzed attack of hydroxide ion on Sarin and $(k_2)_{Mg}$, the second-order rate constant for attack by $[Mg(H_2O)_{x-1}(OH)]^+$, are roughly equal. With p-NPMP, $(k_2)_{OH-} = 1.9 \times 10^{-2} M^{-1}$ min^{-1} at

60° and $(k_2)_{Ca} = 4.2 M^{-1}$ min^{-1} at a calcium ion concentration of 0.05 M. Thus, with the monoanionic substrate the reactivity of $[Ca(H_2O)_{x-1}(OH)]^+$ is approximately 200 times greater than that of OH$^-$. According to the data presented[49] the reactivity of the calcium ion should be somewhat lower than that of the magnesium ion (based on pK_a values) so that, in fact, the ratio of $(k_2)_{Mg}/(k_2)_{OH-}$ could conceivably be greater than 200. The difference in behavior between Sarin and p-NPMP is reasonable on the basis of two effects. First, the positively charged metal ion should be more strongly attracted to the anion of p-NPMP than to the neutral Sarin. Second, hydroxide ion should have more difficulty attacking the anion of p-NPMP than Sarin. Both effects are based on electrostatic factors and both should increase the relative effectiveness of cation catalysis toward p-NPMP.

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Reactions of Phosphonic Acid Esters with Nucleophiles. II. Survey of Nucleophiles Reacting with p-Nitrophenyl Methylphosphonate Anion

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Rate constants have been determined for the reactions of a variety of nucleophiles with the anion of p-nitrophenyl methylphosphonic acid (p-NPMP). The reaction in each case is second order, first order each in nucleophile and in substrate. The orders of reactivity are compared. The bulkiness of the nucleophile near the donor site is important. Certain anionic nucleophiles display a large α effect; peroxide, hydroxamate, and hypochlorite ions are the most reactive of those investigated. Fluoride ion reacts with p-NPMP, but chloride and bromide ions do not. Thiophenolate ion is about 50 times as reactive as the phenolate ion. The relative reactivity of hydroperoxide ion as compared with hydroxide ion is similar to that observed for neutral phosphorus substrates. The data are explained by a mechanism in which the nucleophile attacks the substrate at the phosphorus atom.

This paper continues a survey of the reactivities of various nucleophiles with phosphonic acid ester monoanions. The anion of p-nitrophenyl methylphosphonic acid (p-NPMP) was chosen as the substrate for this study because of its reactivity. As noted in the previous paper in this series,[2] phosphonic acid esters exist as monoanions over a wide pH range so that an investigation of nucleophiles of varying basicity was possible.

Experimental Section

Synthesis of p-nitrophenyl methylphosphonic acid and techniques of following the release of the p-nitrophenolate anion have been previously described.[2] Either the pseudo-first-order or pseudo-zero-order kinetic method was used. Measurements of pH were made on a Leeds and Northrup Model 7401 or a Beck-

man Model G meter. The buffers used and their concentrations are described in Tables I-II. When the reaction pH was less than 9, 2 ml of the reaction mixture was diluted with 1 ml of a 1 M K_2CO_3 solution (cell capacity 3.3 ml) in order to insure that the phenol was completely in its anionic form (pK_a p-nitrophenol = 7.15).[3] The pH of the resulting solution was approximately 11 and the absorbance was corrected for dilution. Alternatively the pH of the solution was measured and the fraction of p-nitrophenol present as the anion was calculated. For each nucleophile studied, a blank was run to correct for the hydrolysis of p-NPMP due to hydroxide and water attack; this blank consisted of a solution containing exactly the same components as the reaction solution except for the nucleophile.

Nucleophiles. A. Peroxides.—Methyl hydroperoxide was prepared according to the directions of Rieche and Hitz.[4] However, since it was not necessary to use water-free peroxide, the following simplification was used. The ether extraction was omitted. The material obtained from the first distillation was distilled once more and cut into five approximately equal fractions. The fractions were analyzed for hydrogen peroxide and

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