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]

$$Ca(H_2O)_x{}^{+2} \rightleftarrows \underset{\text{VII}}{[Ca(H_2O)_{x-1}(OH)]^+} + H^+ \qquad (5)$$

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.

Registry No.—PMP, 13091-13-9; PMP anion, 24903-87-5; *p*-NPMP, 1832-64-0; *p*-NPMP anion, 24886-86-0.

Acknowledgment.—We gratefully acknowledge the support of the Department of the U. S. Army.

---

[48] J. Epstein and W. A. Mosher, *J. Phys. Chem.*, **72**, 622 (1968), and references therein.

[49] J. Bjerrum, G. Schwarzenbach, and L. G. Sillen, *Chem. Soc., Spec. Publ.* **No. 6** (II), 1 (1957).

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

E. J. BEHRMAN,[1a] MICHAEL J. BIALLAS, HERBERT J. BRASS,[1b] JOHN O. EDWARDS,[1c]
AND MARTIN ISAKS

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

Received December 17, 1969

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 Beckman 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

---

[1] (a) Department of Biochemistry, The Ohio State University, Columbus, Ohio 43210. (b) In partial fulfillment of the requirements for the Ph.D. Thesis of H. J. B. (to be submitted to the Graduate School of Brown University). (c) To whom inquiries should be addressed.

[2] E. J. Behrman, M. J. Biallas, H. J. Brass, J. O. Edwards, and M. Isaks, *J. Org. Chem.*, **35**, 3063 (1970).

[3] J. Bjerrum, G. Schwarzenbach, and L. G. Sillen, *Chem. Soc., Spec. Publ.*, **No. 6** (I), 1 (1957).

[4] A. Rieche and F. Hitz, *Ber.*, **62**, 2458 (1929).

TABLE I

RATE CONSTANTS FOR THE REACTION OF NUCLEOPHILES WITH *p*-NITROPHENYL METHYLPHOSPHONATE ANION

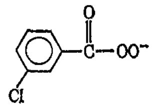
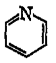
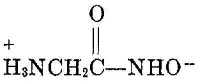
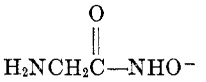
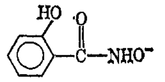
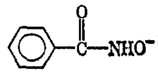
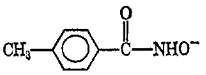
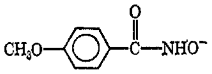
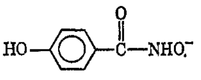
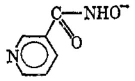
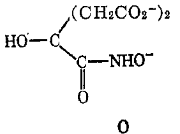
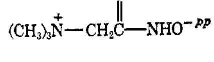
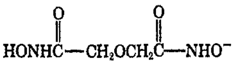
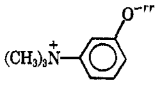
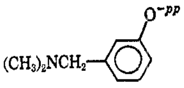
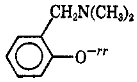
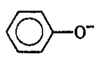
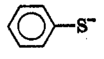
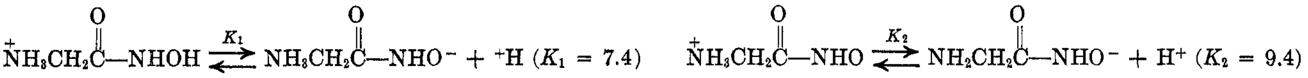
Nucleophile	Registry no.	Temp, °C	pK_a[a,b]	pH	Ionic strength	Nucleophile[c] concn range, *M*	[*p*-NPMP] × 10^4, *M*	k_2, M^{-1} min^{-1}
OH^-		30	15.74[d]	...[e]	3.36	0.169–3.36	1.33	3.00×10^{-3}
		30	15.74	...[f]	0.17	0.169	1.33	1.40×10^{-3}[g]
		60	15.74	...[f]	0.17	0.169	1.33	1.92×10^{-2}[g]
H_2O		30	−1.74[d]	7.55[h]	0.16	55.5	5.90	2.13×10^{-9}[i]
OCl^-	7790-92-3	30	7.7[d]	10.2[j]	0.21	0.0181	12.5	2.74×10^{-3}
F^-	16984-48-8	60	3.45[d]	7.00–7.05[k]	0.15	0.12	2.00	7.20×10^{-4}
HOO^-	7722-84-1	30	11.6[l]	...[m]	0.443–0.553	0.055–0.165	1.33	1.55×10^{-1}
CH_3OO^-	3031-73-0	30	11.5[l]	...[n]	0.447–0.564	0.177–0.234	1.33	3.20×10^{-3}
$(CH_3)_3COO^-$	75-91-2	30	12.8[l]	...[o]	0.474–0.965	0.140–0.290	1.33	1.0×10^{-3}
	937-14-4	30	7.6[p]	10.8[q]	1.42	0.05	2.00	6.6×10^{-3}[r]
H_2NNH_2	302-01-2	60	7.77[s,t]	9.67[u]–10.31	0.05–0.1	0.074–0.185	9.40	1.92×10^{-3}[t]
NH_2OH	7803-49-8	60	6.0[d]	7.1[v]	0.034	0.1	2.00	3.3×10^{-3}
	110-86-1	30	5.23[w]	8.70[x]	0.05–0.1	0.414–0.745	13.5–24.7	6.71×10^{-6}[aaa]
		60	5.23[w]	8.60[x]–8.80	0.05–0.1	0.0495–0.0988	14.1	1.62×10^{-4}
$CH_3CH_2CH_2NH_2$	107-10-8	60	10.60[w]	11.58–11.71[u]	0.05–0.10	0.121–0.726	1.18	3.66×10^{-3}
$H_2NCH_2CO_2H$	56-40-6	30	9.60[d,y]	9.3[z]	0.22	0.22	1.30	4.0×10^{-5}
 $\overset{+}{H_3N}CH_2\overset{\overset{O}{\parallel}}{C}—NHO^-$	5349-80-4	30	7.4[aa]	8.50[bb]	0.10	0.1	2.7	2.0×10^{-4}
				9.28[cc]	0.21	0.124	3.5	1.7×10^{-3}
				9.35[dd]	0.11	0.1	2.7	1.0×10^{-3}
 $H_2NCH_2\overset{\overset{O}{\parallel}}{C}—NHO^-$		30	9.4[aa]	10.00[ee]	0.3	0.1	1.3	2.5×10^{-3}
				10.60[ff]	0.4	0.1	1.3	2.3×10^{-3}
				10.60[gg]	0.12	0.1	2.7	2.2×10^{-3}
	89-73-6	30	7.4[hh]	8.5[ii]	0.3	0.05	2.7	2.3×10^{-3}
			7.4	9.3[jj]	0.3	0.05	2.7	3.3×10^{-3}
			7.4	9.8[kk]	0.3	0.05	2.7	3.3×10^{-3}
 [ll]	495-18-1	30	8.75[mm]	9.85[j]	0.34	0.093	1.33–5.32	2.0×10^{-3}
	2318-82-3	30	8.93[cc]	9.62[cc]	0.25	0.061	3.50	2.01×10^{-3}
	10507-69-4	30	9.03[mm]	9.70[cc]	0.27	0.067	3.50	1.84×10^{-3}
	24886-97-3	30	9.03[mm]	9.40–9.68[cc]	0.27	0.064–0.068	3.50	1.19×10^{-3}
	5657-61-4	30	8.30[mm]	9.88[nn]	0.25	0.045	3.50	3.07×10^{-4}
	24886-99-5	30	8.94[p,oo]	9.86[cc]	0.25	0.041	3.50	5.70×10^{-4}
 $(CH_3)_3\overset{+}{N}—CH_2\overset{\overset{O}{\parallel}}{C}—NHO^-$ [pp]	24887-00-1	30	7.14[qq]	7.56[cc]	0.25	0.0945	3.50	1.50×10^{-4}

TABLE I (*Continued*)

Nucleophile	Registry no.	Temp, °C	pK_a[a,b]	pH	Ionic strength	Nucleophile[c] concn range, *M*	[*p*-NPMP] × 10^4, *M*	k_2, M^{-1} min^{-1}
 $HONH\overset{O}{\overset{\|}{C}}-CH_2OCH_2\overset{O}{\overset{\|}{C}}-NHO^-$ [pp]	24887-01-2	30	9.24[qq]	9.45[cc]	0.22	0.0693	3.50	1.12×10^{-3}
	2498-27-3	30	8.12[ss]	9.30[tt]	0.096	0.035	16.7	1.03×10^{-4}
	24887-03-4	30	8.88[ss]	8.93[tt]	~0.1	0.072	17.5	$\leq 4.4 \times 10^{-5}$
	24887-04-5	30	8.62[ss]	9.15[tt]	~0.1	0.128	17.5	$\leq 2.5 \times 10^{-5}$
	3229-70-7	30	9.98[d]	10.0[j]	0.3	0.0366–0.183	13.3	1.2×10^{-5}
		60	9.98[d]	11.6[vv]	0.08	0.075		6.6×10^{-4}
		30	11.02[ww]	10.91[xx]	~0.35[yy]	0.362–0.413	13.3	1.3×10^{-5} [zz]
	13133-62-5	30	8.02[ww]	11.42–12.17[xx]	~0.35[yy]	0.0259–0.0323	13.3	7.0×10^{-4} [zz]

[a] For conjugate acid of nucleophile. [b] Values are at 20–30°. [c] Total nucleophile added; uncorrected for fraction existing in acid form; correction was applied for rate constant calculation. [d] "Handbook of Chemistry and Physics," R. C. Weast and S. M. Selby, Ed., 47th ed, The Chemical Rubber Company, 1966. [e] Hydroxide ion concentration varied. [f] 0.169 *M* NaOH. [g] E_a = 17.3 kcal/mol; $\Delta S^{\ddagger} = -25$ eu. [h] 0.108 *M* KH_2PO_4–0.092 *M* NaOH buffer. [i] See ref 2. [j] 0.2 *M* carbonate buffer. [k] 0.2 *M* phosphate buffer. [l] A. J. Everett and G. J. Minkoff, *Trans. Faraday Soc.*, **49,** 410 (1953). [m] 0.388 *M* NaOH. [n] 0.330 *M* NaOH. [o] 0.330–0.675 *M* NaOH. [p] Measured potentiometrically by us. [q] 0.50 *M* carbonate buffer. [r] Corrected for peracid decomposition—see Experimental Section. [s] From R. L. Hinman, *J. Org. Chem.*, **23,** 1587 (1958). [t] Statistically corrected. [u] 0.16 *M* boric acid–NaOH buffer. [v] 0.02 *M* phosphate buffer. [w] Data in ref 3. [x] 0.16 *M* boric acid–sodium borate buffer. [y] For equilibrium $H_2NCH_2CO_2H \rightleftharpoons H_2NCH_2CO_2^- + H^+$. [z] pH established using mixtures of 10 ml of 1.0 *M* glyine and 5 ml of 1.0 *M* NaOH solutions. [aa] Measured by us potentiometrically:



$$\overset{+}{N}H_3CH_2\overset{O}{\overset{\|}{C}}-NHOH \underset{}{\overset{K_1}{\rightleftharpoons}} NH_3CH_2\overset{O}{\overset{\|}{C}}-NHO^- + {}^+H\ (K_1 = 7.4) \qquad \overset{+}{N}H_3CH_2\overset{O}{\overset{\|}{C}}-NHO \overset{K_2}{\rightleftharpoons} NH_2CH_2\overset{O}{\overset{\|}{C}}-NHO^- + H^+\ (K_2 = 9.4)$$

[bb] In water. [cc] 0.134 *M* carbonate. [dd] 0.0048 *M* NaOH. [ee] 0.013 *M* NaOH–0.174 *M* Na_2CO_3. [ff] 0.13 *M* Na_2CO_3. [gg] 0.012 *M* NaOH. [hh] Data in ref 21. [ii] 0.185 *M* pH 10 carbonate buffer–0.069 *M* NaOH. [jj] 0.185 *M* pH 9 carbonate buffer–0.069 *M* NaOH. [kk] 0.191 *M* pH 9 carbonate buffer–0.035 *M* NaOH. [ll] See Table II. [mm] R. Swidler, R. F. Plapinger, and G. M. Steinberg, *J. Amer. Chem. Soc.*, **81,** 3271 (1959). [nn] Added as sodium salt. [oo] A. F. Endres and J. Epstein, *J. Org. Chem.*, **24,** 1497 (1959). [pp] Added as hydrochloride salt. [qq] Determined by us spectrophotometrically. [rr] Added as the hydriodide salt. [ss] J. Epstein, *et al.*, *J. Amer. Chem. Soc.*, **86,** 3075 (1964). [tt] 0.13 *M* borate buffer. [uu] Data in ref 10. [vv] 0.005 *M* phosphate buffer. [ww] In 50:50 MeOH:H_2O volume. [xx] Apparent pH; 0.33 *M* K_2CO_3 was used as base. [yy] Ionic strength approximate since pK_a values of carbonic acid in 50:50 MeOH:H_2O are not known. [zz] Run in 50:50 MeOH: H_2O by volume. [aaa] E_a = 21.3 kcal/mol, $\Delta S^{\ddagger} = -22$ eu.

for methyl hydroperoxide. Hydrogen peroxide was determined specifically by reaction with titanium sulfate.[5] Total peroxide was measured by the standard iodometric procedure using a reaction time for iodide oxidation of about 90 min. The first fraction proved to be 3.85 *M* in MeOOH and 0.001 *M* in H_2O_2 and was used without further purification.

Measurement of the rate of reaction of the anion of *m*-chloroperoxybenzoic acid is complicated by the occurrence of the following side reactions.[6]

$$RCO_3^- + OH^- \longrightarrow RCO_2^- + HOO^- \qquad (a)$$

$$RCO_3^- + RCO_3H \longrightarrow 2RCO_2^- + O_2 + H^+ \qquad (b)$$

$$RCO_3^- + RCO_3H \longrightarrow RCO\text{-}OO\text{-}COR + HOO^- \qquad (c)$$

$$RCO_3^- + HOOH \longrightarrow RCO_2^- + O_2 + H_2O \qquad (d)$$

The reaction was run in carbonate buffer at pH 10.8 at which the half-time for the disappearance of *m*-chloroperoxybenzoic acid alone is 457 min. The rate of appearance of *p*-nitrophenol under these conditions measured using the pseudo-zero-order technique for the first 60 min was 7 × 10^{-8} mol/l.-min. The maximum concentration of H_2O_2 measured simultaneously by ceric ion titrimetry was 7.2 × 10^{-4} *M*. At various time intervals aliquots were withdrawn from the reaction and titrated according to the method of Greenspan and MacKellar[7] for both hydrogen peroxide and peracid. Corrections were made for HOO^- attack on *p*-NPMP and the corrected value is reported in Table I.

B. Hydroxamic acids. Unsubstituted, *p*-methyl-, *p*-methoxy-, and *p*-hydroxybenzhydroxamic acids were prepared according to the method of Hauser and Renfrow.[8] Glycinehydroxamic acid was synthesized by the procedure of Safir and Williams.[9] The betaine, 3-pyridyl, citric, and glycinehydroxamic acids were kindly supplied by the Department of the Army, Edgewood Arsenal, Md. Determination of the pK_a values[10] of betaine, citric, and glycinehydroxamic acids were made by titrating approximately 0.01 *M* solutions of the acid (exact concentrations were determined by weight of acid used) with a 0.1246 *M* NaOH solution. Each acid sample was dissolved in 50 ml of deionized

---

[5] G. M. Eisenberg, *Ind. Eng. Chem., Anal. Ed.*, **15,** 327 (1943).

[6] (a) J. D'Ans and J. Mattner, *Angew. Chem.*, **63,** 368 (1951); (b) J. F. Goodman, P. Robson, and E. R. Wilson, *Trans. Faraday Soc.*, **58,** 1846 (1962); (c) J. F. Goodman and P. Robson, *J. Chem. Soc.*, 2871 (1963); (d) E. Koubek, G. Levey, and J. O. Edwards, *Inorg. Chem.*, **3,** 1331 (1964), plus other references therein.

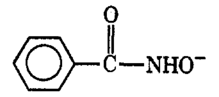
[7] E. P. Greenspan and D. G. MacKellar, *Anal. Chem.*, **20,** 1061 (1948).

[8] C. R. Hauser and W. B. Renfrow, Jr., "Organic Syntheses," Coll. Vol. II, A. H. Blatt, Ed., Wiley, New York, N. Y., 1943, p 67.

[9] S. R. Safir and J. H. Williams, *J. Org. Chem.*, **17,** 1298 (1952).

[10] A. Albert and E. P. Serjeant, "Ionization Constants of Acids and Bases," Methuen and Co., London, 1962.

TABLE II

STUDY OF  REACTION WITH p-NPMP[a–c]

$[N]$,[d] M	$[p\text{-NPMP}] \times 10^4$, M	pH	Buffer	Buffer concn, M	I	$k_2 \times 10^3$, M^{-1} min^{-1}
0.0324	10.6	8.43	Phosphate	0.1	0.25	1.71
0.0933	5.32	9.89	Carbonate	0.2	0.34	1.95, 1.77
0.0924	1.33	9.83	Carbonate	0.2	0.34	2.21, 2.32
0.100	5.32	12.23	Phosphate	0.164	0.44	1.99
0.019	5.32	8.12	Citrate	0.018	0.23	1.51
0.090	5.32	9.70	Carbonate	0.2	0.33	1.84
0.0816	5.32	9.40	Carbonate	0.2	1.81[e]	2.46
0.050	5.32	10.40	Carbonate	0.2	0.35	1.80

[a] Temp = 30°. [b] $pK_a(C_6H_5CONHOH) = 8.75$. [c] Corrected where appropriate for benzhydroxamic acid (acid form) in solution [d] N = anionic form of benzhydroxamic acid. [e] Added $NaClO_4$.

water containing ~0.1 N KCl. pK_a values were determined from the half-neutralization point.

C. Phenols.—m-Hydroxyphenyltrimethylammonium iodide, m-hydroxybenzyldimethylamine hydrochloride, and o-hydroxy benzyldimethylamine hydriodide were supplied by the Department of the Army, Edgewood Arsenal. At 60° the reaction of phenoxide ions with undissociated phenols to form colored materials interferes with the assay of the p-nitrophenolate anion. Interference was minimized by a run at pH 11.6 in 0.005 M phosphate buffer in which two flasks were used, one containing 0.125 M and the other 0.05 M phenoxide ion. The change in molar absorptivity with time in these flasks was corrected for the relatively small change observed at this pH in the absence of p-NPMP. The difference in the corrected molar absorptivity changes between the two was then taken as the rate due to 0.075 M phenoxide ion.

D.—All other reagents were commercial products of the highest purity obtainable and further purified by conventional methods where necessary.

Hypochlorite solutions were standardized by reaction with a known excess of hydrogen peroxide[11] followed by acidification and back-titration with a standard ceric solution.

50:50 MeOH:Water (by Volume).—Apparent pK_a values of phenol and thiophenol were determined by titrating 0.1 M solutions of the acid form of these compounds with a standardized 0.1 M KOH solution. Aliquots of base were added to each acid solution and the "pH" measured. Based upon the concentrations of ions present after each addition of base, a pK_a value was calculated. The average of the pK_a values determined within a titration was taken as the value for the particular titration.

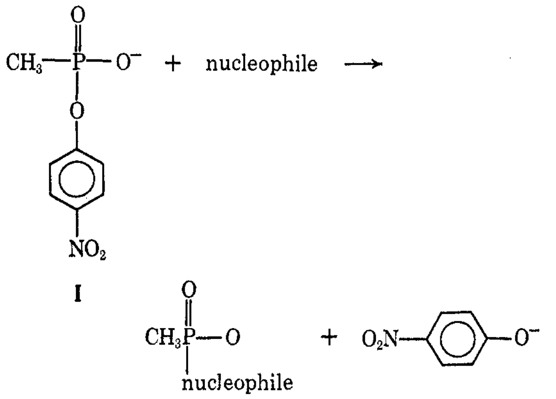
Kinetic experiments were carried out in this solvent system in the same manner as in the aqueous medium. Care was taken to avoid evaporation of methanol. The pK_a of p-nitrophenol was not determined since the pH values of reaction solutions in 50:50 MeOH:water were always high enough to preclude the possibility of any p-nitrophenol existing in the undissociated form.

Results

The second-order rate constants for the reaction of a series of nucleophiles with the p-NPMP monoanion in aqueous solution are given in Table I. The rate is first-order each in both substrate and nucleophile (eq 1)

$$\text{rate} = k_2[p\text{-NPMP}][\text{nucleophile}] \qquad (1)$$

suggesting a SN2(P) bimolecular mechanism.[12,13] The stoichiometry of the probable rate-determining step is the reaction of 1 mol of nucleophile with 1 mol of p-NPMP (eq 2); an anionic nucleophile is used for illustrative purposes. Subsequent to the rate-determining step, compounds of type II may be hydrolyzed by the solvent; a study of this latter reaction was not made. There was no evidence for specific or general acid and base catalysis other than in the hydrolysis case discussed in the previous paper.[2] Since both hydroxide ion and water have been found to react as nucleophiles with p-NPMP, the rate constants in Table I have been corrected for attack by these species.



I

II

(2)

The activation parameters (Table I) for both negatively charged and neutral nucleophiles are consistent with a bimolecular mechanism. Several reagents examined showed no detectable reactivity toward the phosphorus site of p-NPMP. The rate of release of p-nitrophenolate ion is identical with that of the combined hydroxide–water rate. These reagents were Cl^-, Br^-, CN^-, NCO^-, NCS^-, HONHCO-OC-NHO$^-$, $B(OH)_4^-$, HPO_4^{2-}, PO_4^{3-}, HCO_3^-, and CO_3^{2-}. The latter five were used as constituents in the buffers for the study of reactive nucleophiles. Table II gives data for the reaction of the benzhydroxamate anion with p-NPMP under conditions of varying nucleophile and substrate concentrations, buffer nature, buffer concentration, and ionic strength. The second-order rate constant k_2 is independent of benzhydroxamate and p-NPMP concentrations as well as buffer. At the ionic strength used ($I \geqslant 0.25$), k_2 was found to increase only slightly with increasing ionic strength. Thus, although the kinetic experiments whose data are given in Table I were not performed at constant ionic strength, we think that the values of the rate constants are not substantially altered by this variation. Table II shows

---

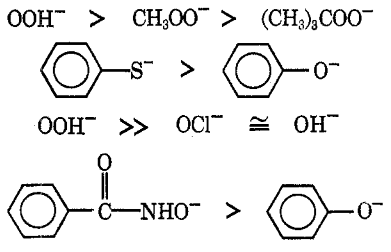
(11) I. M. Kolthoff and E. B. Sandell, "Textbook of Quantitative Inorganic Analysis," 3rd ed, Macmillan, New York, N. Y., 1952, p 560.

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

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

that k_2 is independent of pH above the pK_a of benzhydroxamic acid. At reaction pH values below the pK_a of benzyhydroxamic acid (8.75 at 25°), k_2 is somewhat lower than at higher pH values after correction for benzhydroxamate existing as the conjugate acid, but this may result from use of a slightly incorrect value of the pK_a which is itself reasonably sensitive to ionic strength.[14]

The basic forms of the nucleophiles presented in Table I were the reactive species detected under the experimental conditions. A Brönsted plot[15] is given in Figure 1 for nucleophiles reacting with p-NPMP at 30°. The scatter is obvious. However, four series of interesting comparisons of orders of reactivity may be made.



Nucleophiles containing an unshared pair of electrons on an atom adjacent to the attacking atom (α nucleophiles) appear to be most reactive.[16] For example, although hydroxide ion is $\sim 10^8$ more basic than the hypochlorite ion, they are approximately equally reactive. The hydroperoxide ion is $\sim 10^4$ less basic than hydroxide, yet it is $\sim 10^2$ more reactive. Second-order rate constants for attack by hydroperoxide and hydroxide anions on neutral tetrahedral phosphorus esters have been reported.[17-21] A log-log plot (Figure 2) for the reactions of HO_2^- with these esters $vs.$ the reactions of OH^- with these esters is linear with a slope of unity. When plotted on this graph the point for p-NPMP falls on the correlation line; this indicates a similar mechanism for our anionic substrate and the many neutral phosphorus substrates.

The fluoride ion is reactive toward the anion of p-NPMP, whereas chloride and bromide are not. At pH 7.00–7.05, fluoride reactivity is not complicated by the presence of HF and HF_2^-.[22]

Zwitterionic nucleophiles, containing a positively charged site as well as a negatively charged site, do not seem to be unusually reactive toward p-NPMP (Table I, Figure 1). In fact, the monoanionic glycinehydroxamate ($H_2NCH_2CO\text{-}NHO^-$) is is more reactive than the zwitterionic species ($H_3N^+\text{-}CH_2\text{-}CO\text{-}NHO^-$) (as shown in Table I), and the favorable electrostatic situation in forming a transition state is presumably compensated for by a reduction of electron density at the reaction site. Quaternary ammonium substituents on aromatic nucleophiles, however, tend to increase the nucleophilicity of phenolates. Thus, m-trimethylammonium phenolate anion displays a low but detectable reactivity toward p-NPMP while o- and m-benzyldimethylamine phenolate anions do not (Table I).

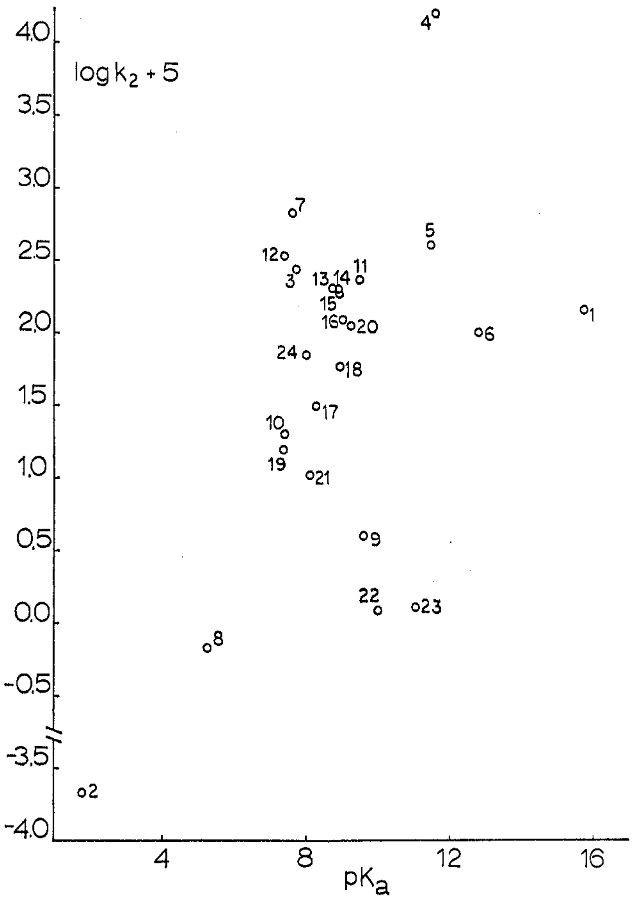


Figure 1.—A plot of log k_2 + 5 $vs.$ pK_a of the conjugate acid of nucleophiles reacting with p-NPMP: (1) hydroxide, (2) water, (3) hypochlorite ion, (4) hydroperoxide ion, (5) methyl hydroperoxide ion, (6) t-butyl hydroperoxide ion, (7) m-chloroperoxybenzoate ion, (8) pyridine, (9) glycine, (10) glycinehydroxamic acid, (11) glycinehydroxamate ion, (12) o-hydroxybenzhydroxamate ion, (13) benzhydroxamine ion, (14) p-methylbenzhydroxamate ion, (15) p-methoxybenzhydroxamate ion, (16) p-hydroxybenzhydroxamate ion, (17) nicotinhydroxamate ion, (18) citric monohydroxamate trianion, (19) trimethylammonium glycinehydroxamate zwitterion, (20) $HONHCOCH_2OCH_2CO\text{-}NHO^-$, (21) m-trimethylammonium phenolate zwitterion, (22) phenolate ion, (23) phenolate ion (50:50 MeOH:H_2O), (24) thiophenolate ion (50:50 MeOH:H_2O).

Considerable difficulty was experienced in the investigation of thioanion nucleophiles. The mercaptide ions were slowly oxidized to the corresponding disulfides. It is not known whether this oxidation was by the nitro group on the aromatic ring of the substrate or by trace amounts of oxidizing impurities such as oxygen. In any event, the disulfide, being insoluble, produced a cloudy solution; from such a solution with thiophenolate ion, diphenyl disulfide was isolated and identified. In general, the resulting cloudy aqueous solutions made spectrophotometric determinations of the p-nitrophenolate ion impossible. A 50:50 MeOH-H_2O solvent system was used in which many disulfides are soluble. However in this system the calculated second-order rate constants, k_2, were not constant but increased with decreasing initial concentration of the anionic

---

(14) R. Swidler and G. M. Steinberg, *J. Amer. Chem. Soc.*, **78**, 3594 (1956).

(15) J. N. Brönsted and K. J. Pedersen, *Z. Physik. Chem.*, **108**, 185 (1924).

(16) J. O. Edwards and R. G. Pearson, *J. Amer. Chem. Soc.*, **84**, 16 (1962).

(17) L. Ginjaar, Ph.D. Thesis, Leiden University, 1960.

(18) L. Larsson, *Acta Chem. Scand.*, **12**, 723 (1958).

(19) B. Gehauf, J. Epstein, G. B. Wilson, B. Witten, S. Sass, V. F. Bauer, and W. H. C. Rueggeberg, *Anal. Chem.*, **29**, 278 (1957).

(20) J. Epstein, M. M. Demek, and D. H. Rosenblatt, *J. Org. Chem.*, **21**, 796 (1956).

(21) A. L. Green, G. L. Sainsbury, B. Saville, and M. Stansfield, *J. Chem. Soc.*, 1583 (1958).

(22) F. A. Cotton and G. Wilkinson, "Advanced Inorganic Chemistry," Wiley-Interscience, New York, N. Y., 1962, p 291.

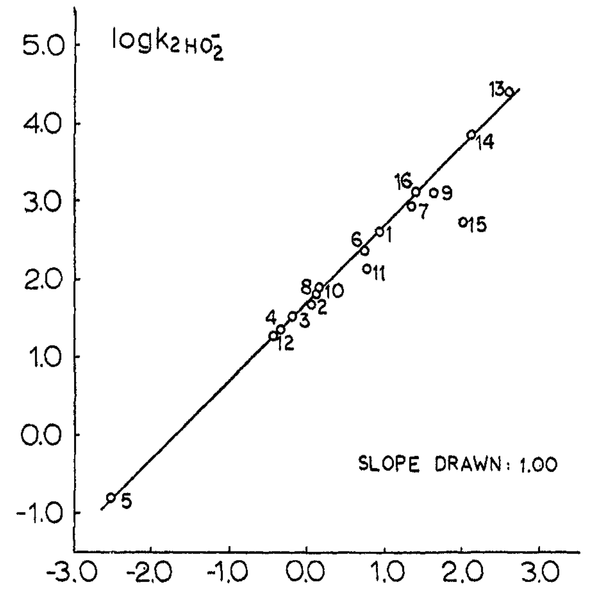


Figure 2.—Log–log plot of the second-order rate constants for the reactions of HO_2^- and OH^- with organophosphorus esters.

R_1	R_2	No.
	$R_1R_2\overset{O}{\overset{\|}{P}}OC_6H_4(p\text{-}NO_2)$ – 25°	
$-OC_2H_5$	$-C_2H_5$	1
-O-*i*-Pr	-*i*-Bu	2
$-OC_2H_5$	$-OC_2H_5$	3
-O-*n*-Pr	-*n*-Pr	4
$-O^-$	$-CH_3$	5 (30°)
	$R_1R_2\overset{O}{\overset{\|}{P}}OC_6H_4(o\text{-}NO_2)$ – 25°	
$-OCH_3$	$-OCH_3$	6
$-OC_2H_5$	$-C_2H_5$	7
$-OC_2H_5$	$-OC_2H_5$	8
	$R_1R_2\overset{O}{\overset{\|}{P}}OC_6H_4(m\text{-}NO_2)$ – 25°	
$-OCH_3$	$-CH_3$	9
$-OCH_3$	$-OCH_3$	10
$-OC_2H_5$	$-C_2H_5$	11
$-OC_2H_5$	$-OC_2H_5$	12
	$R_1R_2\overset{O}{\overset{\|}{P}}\text{-}F$ – 25°	
$-OCH_3$	$-OCH_3$	13
$-OC_2H_5$	$-OC_2H_5$	14
-O-*n*-Pr	-O-*n*-Pr	15
-O-*i*-Pr	$-CH_3$	16

form of the sulfur nucleophile.[23a] The pK_a values for phenol and thiophenol in H_2O are 9.98[3,10] and 6.52,[23b] respectively. In 50:50 MeOH–H_2O solutions, they are 11.02 and 8.02 as measured here. The rate constant for the thiophenoxide ion, which showed only a slight increase in k_2 upon decrease in initial thiophenoxide concentration, is the only sulfur nucleophile reported in Table I. Rate constants for phenoxide ion in both H_2O and 50:50 MeOH–H_2O were determined for comparative purposes. Thiophenoxide ion reactivity is seen to be ~50 times as great as phenoxide ion reactivity even though the former is $\sim 10^3$ less basic than the latter.

Discussion

Prior to this investigation reactions of neutral nucleophiles with tetrahedral organophosphorus ester anions have been demonstrated;[24-30] however, little data on the reactivity of anionic nucleophiles toward anionic substrates are available. This study reveals that both neutral and anionic compounds react as nucleophiles in a bimolecular fashion with monoaryl ester monoanions, in this case *p*-NPMP. Analogies can be drawn to the reactivities of other organophosphorus esters. The reactions of amines are discussed separately, although several amines are listed in Table I for comparative purposes.

Generally the reactivities of various classes of nucleophiles in tetrahedral organophosphorus substitution reactions cannot be correlated with basicity;[12,17,26,31] this has been shown for neutral phosphorus esters on which most kinetic studies have been performed. However, reactivity can be correlated with nucleophile basicity where nucleophiles containing a common reacting group are examined.[17,24,25,27,31] For example, the rate of reaction of isopropyl methylphosphorofluoridate[17,32] (Sarin) with representative nucleophiles of various classes does not correlate simply with nucleophile basicity; however linear Brönsted relationships are found with specific classes such as hydroxamates,[21] catechols,[33] and amines.[34] A similar result is obtained with *p*-NPMP. Figure 1 shows that reactivity is poorly correlated with nucleophile basicity. However the rates for reaction of pyridines[35] yield a linear Brönsted relation. A correlation of hydroxamate ion reactivity with basicity cannot be made since the pK_a values of the hydroxamic acids studied (Table I) are not sufficiently different for comparative purposes.

The orders of reactivity obtained with *p*-NPMP are similar to those obtained with other organophosphorus esters. The α effect has been shown to be operative in tetrahedral organophosphorus displacements;[17,18,21,32-34,36,37] this is also observed with *p*-NPMP. Peroxides, hypochlorite, and hydroxamates are the most reactive nucleophiles studied. It appears that anionic nucleophiles exhibit a definite α effect while neutral nucleophiles display at best a small one; hydrazine and hydroxylamine are not extremely reactive with *p*-NPMP.

---

(23) (a) This is explicable on the basis of reduction of the nitro group by mercaptide ion (RS^-) producing the corresponding disulfide. RS^- was always present in excess of *p*-NPMP; thus at higher RS^- concentrations, more of the $-NO_2$ group was reduced than at lower RS^- concentrations leading to a lower calculated rate constant. The rate of release of *p*-nitrophenolate anion is the method used to monitor the reaction, so the apparent variation in k_2 with RS^- is believed to be an artifact of the system. (b) B. Miller, *J. Amer. Chem. Soc.*, **84**, 403 (1962).

(24) A. J. Kirby and W. P. Jencks, *ibid.*, **87**, 3209 (1965).

(25) W. P. Jencks and M. Gilchrist, *ibid.*, **87**, 3199 (1965).

(26) T. C. Bruice and S. J. Benkovic, "Bioorganic Mechanisms," Vol. 2, W. A. Benjamin, New York, N. Y., 1966, Chapter 6, and references therein.

(27) G. Di Sabato and W. P. Jencks, *J. Amer. Chem. Soc.*, **83**, 4393 (1961).

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

(29) G. O. Dudek and F. H. Westheimer, *J. Amer. Chem. Soc.*, **81**, 2641 (1959).

(30) R. Blakely, Thesis, Harvard University, 1963.

(31) Reference 13, Chapter 6, and references therein.

(32) L. Larsson, *Svensk Kem. Tidskr.*, **70**, 405 (1958).

(33) J. Epstein, D. H. Rosenblatt, and M. M. Demek, *J. Amer. Chem. Soc.*, **78**, 341 (1956).

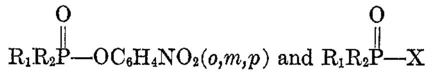
(34) P. Cannon, private communication.

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

(36) J. Epstein, V. E. Bauer, M. Saxe, and M. M. Demek, *ibid.*, **78**, 4068 (1956).

(37) N. G. Lordi and J. Epstein, *ibid.*, **80**, 509 (1958).

The relative reactivities of hydroperoxide and hydroxide anions are of special interest. The second-order rate constant, $(k_2)_{HO_2^-}$, for the attack of HO_2^- on *p*-NPMP is approximately 50 times as great as $(k_2)_{OH^-}$, the second-order rate constant for attack by hydroxide ion. Previous studies[17-21,32] show that the ratio $(k_2)_{HO_2^-}/(k_2)_{OH^-}$ is near 50 for attack by these two nucleophiles on various neutral organophosphorus esters of the type



$$R_1R_2\overset{O}{\overset{\|}{P}}—OC_6H_4NO_2(o,m,p) \text{ and } R_1R_2\overset{O}{\overset{\|}{P}}—X$$

where R_1 is an alkoxy group, R_2 is an alkyl or alkoxy group, and X is a halogen; this is reflected in the linear free energy relation in Figure 2. Bimolecular displacements at tetrahedral phosphorus appear to be partially governed by the stereochemistry of the attacking reagent.[13,31,38] The constant ratio for attack by HO_2^- and HO^- at tetrahedral phosphorus indicates that the manner in which these anions react must be independent of variation in R_1 and R_2, as well as charge on the substrate.

The reactivities of HOO^-, CH_3OO^-, and $(CH_3)_3COO^-$ toward *p*-NPMP are in the ratios 155:3:1; toward *p*-nitrophenylacetate this ratio has been found to be 18:5:1.[39,40] These ratios are suggestive of an increased dependence of reactivity on bulkiness of the nucleophile in displacements at tetrahedral phosphorus relative to carbonyl carbon. Dependence of reactivity on amine steric effects has been shown to be greater for tetrahedral phosphorus than carbonyl carbon.[35]

Fluoride ion has the reputation of being an effective nucleophile toward tetrahedral phosphorus. This has been shown with diisopropyl phosphorochloridate[41] (DClP) and acetylphosphate monoanion.[27] The nature of the nucleophilic species with these two substrates is in doubt, however. The reactions of DClP were carried out in absolute ethanol where the extent of ion pairing of the nucleophiles is not known. The reaction of fluoride and acetylphosphate was run in acidic solution where HF and HF_2^- are present.[22] Fluoride ion does not react with phosphate dianions, but does react with phosphoramidate monoanion.[25] Fluoride ion reactivity toward the monoanions of mono- and bis(2,4-dinitrophenyl) phosphates has been reported.[28] Table I shows that the reactivity of fluoride ion toward *p*-NPMP is roughly equal to that of phenolate ion. Chloride and bromide ion reactivity was not detected.

Mercaptide ions have been reported to be equally effective[23b] or less effective nucleophiles[41] toward tetrahedral phosphorus than are similar oxygen nucleophiles. This is in contrast to the reactivity at aliphatic carbon where the more polarizable mercaptide ions are more reactive.[42] The reactivities of thiophenoxide and phenoxide ions are approximately equal toward O,O-diphenyl phosphorochlorothioate[23b] in "90%" *t*-butyl alcohol–dioxane; however the necessary correction for ion pairing was not made. In ethanol, PhS^- is less reactive than PhO^- with diisopropyl phosphorochloridate.[41] With *p*-NPMP in 50:50 $MeOH:H_2O$, PhS^- is about 50 times as reactive as PhO^-, reversing the previously reported order of reactivity. Clearly, a further study to clarify the relative reactivities of sulfur and oxygen nucleophiles toward tetrahedral phosphorus is warranted.

Registry No.—*p*-NPMP anion, 24886-86-0.

Acknowledgment.—We gratefully acknowledge the support of the Department of the Army. We are also indebted to M. Boyle, R. DiPrete, and K. Klein for their assistance.

---

[38] I. Dostrovsky and M. Halmann, *J. Chem. Soc.*, 516 (1953).

[39] W. P. Jencks and M. Gilchrist, *J. Amer. Chem. Soc.*, **90**, 2622 (1968).

[40] (a) M. C. Sauer, unpublished results; (b) J. E. McIsaac, Jr., H. Mulhausen, and E. J. Behrman, Abstracts, 156th National Meeting of the American Chemical Society, Atlantic City, N. J., Sept 1968, Organic Section, paper 70.

[41] I. Dostrovsky and M. Halmann, *J. Chem. Soc.*, 508 (1953).

[42] C. G. Swain and C. B. Scott, *J. Amer. Chem. Soc.*, **75**, 141 (1953); J. O. Edwards, *ibid.*, **76**, 1540 (1954).