1,3,4-Triphenyl-2-naphthol.—Dry gaseous hydrogen chloride was bubbled through a solution of 100 mg (0.25 mmol) of the reduction product in 5 ml of acetic acid at reflux for 1.5 hr. The reaction mixture was cooled and poured into water. The aqueous solution was extracted with two 10-ml portions of ether; the ethereal solution was dried over sodium sulfate, filtered, and concentrated to give a crystalline material which, after being washed with cold, anhydrous ether, was collected. There was obtained 80 mg (84%) of 1,3,4-triphenyl-2-naphthol, mp 231°. Recrystallization from benzene–ligroin gave crystals of mp 232–233°; ir 3400 (s), 1190 (s), 1280 (s), and 950 cm^{-1} (s); nmr τ 2.4–3.0 (aromatic), 4.9 (s, 1 H); mass spectrum M$^+$ m/e 372 (calcd for $C_{28}H_{20}O$, 372).

Anal. Calcd for $C_{28}H_{20}O$: C, 90.29; H, 5.41. Found: C, 90.11; H, 5.55.

β-Nitrostyrene was prepared according to the "Organic Syntheses" procedure[9] on a 0.2-mol scale; after recrystallization from ethanol the product (23.7 g, 79%) had mp 58–59° (lit.[9] mp 59°).

3-Phenylphthalide from the reduction of *o*-benzoylbenzoic acid with zinc dust in aqueous acetic acid had mp 114–115° (lit.[10] mp 114–115°).

1,3-Diphenyl[*c*]benzofuran.—Phenylmagnesium bromide and 3-phenylphthalide in a solution of THF and ether led to the benzofuran product; after recrystallization from benzene–ethanol, it had mp 129–131° (lit.[10] mp 128–131°).

1,2,4-Triphenyl-3-nitro-1,4-oxido-1,2,3,4-tetrahydronaphthalene was prepared by heating 0.7 g (2.6 mmol) of 1,3-diphenyl[*c*]-benzofuran, 0.4 g (2.6 mmol) of nitrostyrene, and 20 ml of ethanol at reflux for 3 hr. The reaction mixture was cooled and filtered; the pale yellow material collected (1.1 g, 100%) had mp 155–158° (lit.[12] mp 163°).

1,2,4-Triphenyl-3-nitronaphthalene.—A suspension of 0.85 g (2.0 mmol) of the oxidotetrahydronaphthalene addition product in 5 ml of 30–32% hydrobromic acid in acetic acid (Eastman Organic Chemicals) was allowed to stand for 4 hr. It was then heated to reflux for several minutes, cooled in an ice bath, and filtered. The tan, crystalline material was washed with acetic acid; the white, crystalline material obtained (0.40 g, 51%) had mp 206–210° (lit.[12] mp 216–218°).

1,2,4-Triphenyl-3-aminonaphthalene.—1,2,4-Triphenyl-3-nitronaphthalene (0.45 g, 1.1 mmol), 2 g (31 g-atoms) of zinc, and 20 ml of glacial acetic acid were heated at reflux for 3.5 hr. The reaction mixture was poured into water and extracted with ether. The ethereal solution was dried, filtered, and concentrated to give white, crystalline product (0.3 g, 75%) having mp 254–256° (lit.[12] mp 256–257°).

1,3,4-Triphenyl-2-naphthol was obtained by adding 0.3 g (0.9 mmol) of the corresponding amine to 3 ml of glacial acetic acid and 0.5 g (4.5 mmol) of isoamyl nitrite. The reaction mixture was allowed to stand for 15 min; it was then slowly poured into a boiling 10% aqueous solution of sulfuric acid. As soon as the addition was complete, the solution was cooled in an ice bath and the precipitate was collected, washed with cold ether, and dried. This material, mp 231–233°, was identical in spectral characteristics with that formed through the degradation of the 2:1 adduct.

Anal. Calcd for $C_{28}H_{20}O$: C, 90.29; H, 5.41. Found: C, 89.98; H, 5.62.

Registry No.—1, 39495-51-7; 2, 39495-52-8; 3, 38028-34-1; diphenylketene, 525-06-4; 1,1-diphenylethylene, 530-48-3; 3,4-dihydro-1-hydroxy-1,4,4-triphenyl-2(1*H*)-naphthalenone, 38028-35-2; 3,4-dihydro-1-hydroxy-1,4,4-triphenyl-2(1*H*)-naphthalenone acetate, 38028-36-3; 3,4-dihydro-1,4,4-triphenyl-2-naphthalenazobenzene, 38028-37-4; 1,3,4-triphenyl-2-naphthol, 38028-38-5; 1,3-diphenyl[*c*]benzofuran, 5471-63-6; β-nitrostyrene, 102-96-5; 1,2,4-triphenyl-3-nitro-1,4-oxido-1,2,3,4-tetrahydronaphthalene, 39495-59-5; 1,2,4-triphenyl-3-nitronaphthalene, 39495-60-8; 1,2,4-triphenyl-3-aminonaphthalene, 39495-61-9.

The Oxidative Hydrolysis of *p*-Hydroxyphenyl Phosphates[1]

RICHARD J. BROOKS, CLIFFORD A. BUNTON,* AND JAMES M. HELLYER

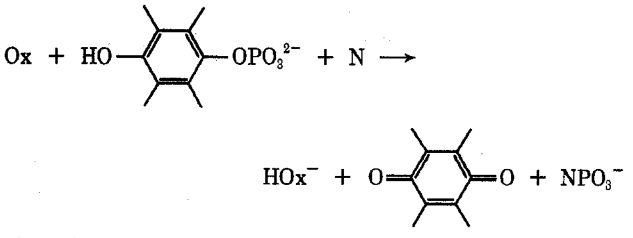
Department of Chemistry, University of California, Santa Barbara, California 93106

Received December 22, 1972

Periodic acid and its anions react with *p*-hydroxyphenyl phosphate (I) and the mono- (II) and dimethyl (III) esters, following second-order kinetics with no evidence for buildup of a periodate intermediate in high concentration. Both periodic acid and its monoanion are reactive species, and the reaction rates are greatest at low pH except for I, where the fastest reaction, at pH 7–8, involves a trianionic transition state, probably with elimination of a metaphosphate ion. Phosphorus–oxygen fission is important in the reaction of I at pH 1 and 6.5.

The oxidation of quinol phosphates can generate a phosphorylating agent, and the reaction has been examined and used synthetically.[2,3] The oxidants have generally been halogens or metal ions.

These reactions have been discussed as models for oxidative phosphorylation in biological systems, and the isolation of *p*-quinones from biological systems supported this hypothesis.[4] In addition, the involvement of quinones in biological phosphorylation has been demonstrated,[5] and quinone-induced phosphorylations have been observed in chemical systems.[6] Oxidatively induced chemical phosphorylations have recently been reviewed.[7] There are, however, certain weaknesses to this hypothesis, notably the difficulty of explaining the initial formation of the quinol phosphate and the observation that the oxidation in some



(where OX and N are respectively the oxidant and nucleophile)

---

(1) Support of this work by the Arthritis and Metabolic Diseases Institute of the USPHS is gratefully acknowledged.

(2) V. M. Clark, D. W. Hutchinson, G. W. Kirby, and A. R. Todd, *J. Chem. Soc.*, 715 (1961).

(3) T. Wieland and F. Patterman, *Ber.*, **92**, 2917 (1959); C. D. Chambers and J. Q. Chambers, *J. Amer. Chem. Soc.*, **88**, 2922 (1966); C. D. Snyder and H. Rapoport, *ibid.*, **89**, 1269 (1967).

(4) For general discussion, see T. C. Bruice and S. Benkovic, "Biorganic Mechanisms," Vol. II, W. A. Benjamin, New York, N. Y., 1968, p 91.

(5) P. G. Phillips, B. Revsin, E. G. Drell, and A. F. Brodie, *Arch. Biochem. Biophys.*, **139**, 59 (1970).

(6) V. M. Clark, D. W. Hutchinson, A. R. Lyons, and R. J. Roschnik, *J. Chem. Soc. C*, 233 (1969).

(7) G. M. Blackburn and J. S. Cohen, *Top. Phosphorus Chem.*, **6**, 187 (1969).

cases is not a phosphorylation, but gives carbon–oxygen fission,[8,9] and alternative reactions have been considered as chemical models for oxidative phosphorylation.

Periodic acid and its anions will quantitatively oxidize quinols and their esters to quinones,[10] and the kinetics of these oxidations have been thoroughly examined.[11] Kaiser and his coworkers have also considered the oxidative cleavage of *p*-hydroxyphenyl sulfate as a model for biological sulfate transfer, although in cleavage of the sulfates, as with the phosphates, there is considerable aryl–oxygen fission.[12]

Aqueous periodic acid will oxidatively hydrolyze carboxylic esters of *p*-quinol, and this reaction has been studied kinetically;[13] we have extended this investigation to the oxidative hydrolysis of *p*-hydroxyphenyl phosphates. A preliminary account of part of this work has been given.[14] The reaction occurs in water under mild conditions, whereas other oxidants have to be used in nonaqueous solvents, and the halogens can substitute into the aromatic group unless the reactive positions are blocked.[2–4]

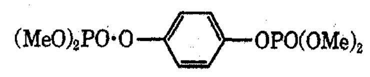
The formation of an intermediate, probably metaphosphate ion, PO_3^-, in the rate-limiting step of hydrolysis of mono- and dianions of many monosubstituted phosphate esters is generally assumed,[4,15] and a key aim of this research was to find evidence for formation of this intermediate in the oxidative cleavage of a quinol phosphate under mild aqueous conditions. With this aim in mind we used *p*-hydroxyphenyl phosphate (I), which can generate an intermediate which could eliminate metaphosphate ion, and compared its reactivity with those of the corresponding mono- and dimethyl esters (II and III) where metaphosphate ion elimination cannot occur.

Experimental Section

Materials.—*p*-Hydroxyphenyl phosphate (I) was prepared as its barium or cyclohexylamine salt by the method of Wieland and Patterman.[3] The barium salt was converted into the acid using Dowex 50W-X8 in its acid form, and neutralization with cyclohexylamine at pH 7.0 gave the bicyclohexylammonium salt, mp 202° dec (lit. mp 205°).[3]

The dimethyl ester III[16,17] was prepared by refluxing *p*-quinone (56 mmol) with dimethyl phosphite (56 mmol) in 300 ml of dry benzene under dry N_2,[16] or in anhydrous methanol with a catalytic amount of NaOMe.[17] The crude product was precipitated from benzene by addition of petroleum ether (bp 30–60°) and was purified by recrystallization from hot water, mp 73–75° (lit. mp 71–72°,[16] 75°[17]). The nmr spectrum (60 MHz, $CDCl_3$) had a doublet at δ 3.70 and 3.88 and a multiplet at δ 6.9 with areas 1.4:1.

When this reaction was carried out with excess dimethyl phosphite and no added solvent, we obtained a white solid, mp 109–114°. Comparison of the mass spectrum of this solid with that of the dimethyl ester suggested that reaction with excess dimethyl phosphite gave the tetramethyl ester IV.



IV

The monomethyl ester II was prepared as its lithium salt by demethylating III (0.0144 mol) in refluxing dried acetone (350 ml) with dried LiCl (0.014 mol) and glacial acetic acid (0.01 ml) for 12 hr. (The acetic acid was added to suppress formation of the phenoxide ion.) The lithium salt of II separated as fine white crystals, and it was washed several times with dry acetone. The melting point was 282° dec. The nmr spectrum (60 MHz, D_2O) had a doublet δ 3.46 and 3.64 (J = 11 Hz) and a multiplet at δ 6.63–7.11 with relative areas 2.9:4.0. The ir spectrum (Nujol mull) had free and hydrogen-bonded hydroxyl absorptions at 3450–3510 and 3100–3200 cm^{-1}.

Anal. Calcd. for $C_7H_8LiO_5P$: C, 40.0; H, 3.8; P, 14.7. Found: C, 39.9; H, 3.9; P, 14.5.

The periodate solutions were made up using periodic acid or sodium periodate in deoxygenated, distilled, deionized water, and were stored in the dark under N_2. Their concentrations were determined using KI in hydrogen carbonate buffer followed by titration with thiosulfate.

p*K* Measurements.—The p*K* values of I and II were determined using solutions of the free acid obtained by treating the salts with Dowex 50W-X8 resin (acid form). The conventional titration method[18] using KOH was used to determine pK_2 = 6.14 at 25° for I.

The values of pK_1 = 1.4 at 25° for both I and II were determined by pH measurements at various concentrations of the aryl phosphoric acids.[19] The concentration of I was determined by hydrolyzing it using alkaline phosphatase followed by the colorimetric determination of inorganic phosphate.[20] The diester II was hydrolyzed using snake venom alkaline phosphodiesterase followed by alkaline phosphatase.

Kinetics.—The reactions were followed spectrophotometrically with excess periodate under first-order conditions, using a Gilford spectrophotometer with a water-jacketed cell compartment. The increasing absorbance due to formation of *p*-quinone was followed at 247 nm, and the ester concentrations were 6–10 × 10^{-5} *M*. The first-order rate constants, k_ψ, sec^{-1}, were unaffected by these changes in ester concentration. Generally the reactions were followed using 1-mm stoppered cells, but for the slower reactions of the dimethyl ester III samples were withdrawn from stoppered volumetric flasks. The rate constants were calculated using the simple integrated rate equation or by Guggenheim's method.[21] Because of instability of *p*-quinone in alkali we could not work at high pH.

The pH was controlled with dilute acid at low pH. Periodate acts as its own buffer at pH 2.5–4.0 and 8.0, and the other buffers were acetate, pH 4–6; phosphate, pH 6–7.5; borate, pH >8. Added salt or buffer slightly affects k_ψ, and the values quoted were obtained at a given periodate concentration by extrapolation to zero added buffer, except for runs at low pH in acid. For experiments at low pH, the rate constants were very similar for reactions catalyzed by H_2SO_4 or $HClO_4$.

Bond Fission.—The oxidative hydrolysis of *p*-hydroxyphenyl phosphate was carried out at pH 1.0 and 6.5 at 25° in $H_2{}^{18}O$. The substrate concentration was *ca.* 0.1 *M*, 0.4 *M* periodic acid was used for the reaction at pH 1, and 0.12 *M* periodate at pH 6.5. Inorganic phosphate was isolated and analyzed mass spectrometrically by methods described elsewhere.[22] There is considerable P–O fission (Table I).

Results

Kinetics.—Under all our conditions oxidation was much faster than hydrolysis. The values of k_ψ ex-

---

[8] W. Durckheimer and L. A. Cohen, *Biochemistry*, **3**, 1948 (1964).

[9] A. Lapidot and D. Samuel, *Biochim. Biophys. Acta*, **65**, 164 (1962); *J. Amer. Chem. Soc.*, **86**, 1886 (1964).

[10] E. Alder, I. Falkehag, and B. Smith, *Acta Chem. Scand.*, **16**, 529 (1962).

[11] E. T. Kaiser and S. W. Weidman, *J. Amer. Chem. Soc.*, **86**, 4354 (1964); *Tetrahedron Lett.*, 497 (1965).

[12] E. T. Kaiser, D. F. Mayers, S. W. Wiedman, and O. R. Zaborsky, *J. Amer. Chem. Soc.*, **86**, 4555 (1967).

[13] C. A. Bunton and J. M. Hellyer, *J. Amer. Chem. Soc.*, **89**, 6252 (1967).

[14] C. A. Bunton and J. M. Hellyer, *Tetrahedron Lett.*, 187 (1969).

[15] J. R. Cox and O. B. Ramsay, *Chem. Rev.*, **64**, 317 (1964); ref 4, Chapter 5; C. A. Bunton, *Accounts Chem. Res.*, **3**, 257 (1970).

[16] F. Ramirez and S. Dershowitz, *J. Org. Chem.*, **22**, 1282 (1957); F. Ramirez, H. J. Kugler, and C. P. Smith, *Tetrahedron Lett.*, 261 (1965).

[17] P. I. Sanin, E. S. Voronkv, E. S. Shepelva, and B. I. Ionin, *Dokl. Akad. Nauk SSSR*, **132**, 145 (1960); *Chem. Abstr.*, **57**, 11120 (1962).

[18] A. Albert and E. P. Serjeant, "Ionization Constants of Acids and Bases," Wiley, New York, N. Y., 1962, p 30.

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

[20] C. H. Fiske and Y. Subba Row, *J. Biol. Chem.*, **66**, 375 (1925).

[21] A. A. Frost and R. G. Pearson, "Kinetics and Mechanism," 2nd ed, Wiley, New York, N. Y., 1961, Chapter 3.

[22] C. A. Bunton and J. M. Hellyer, *J. Org. Chem.*, **34**, 2798 (1969).

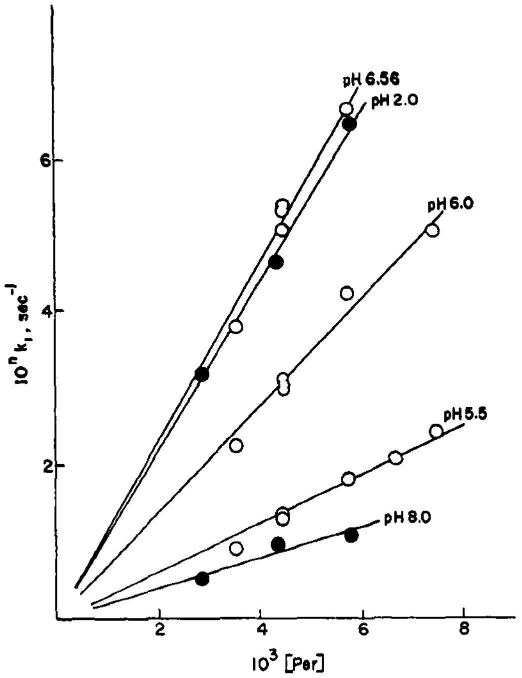


Figure 1.—Variation of first-order rate constants with periodate concentration for *p*-hydroxyphenyl phosphate (I), open circles, $n = 3$, and for *p*-hydroxyphenyl methylphosphate (II), solid circles, $n = 4$.

TABLE I

BOND FISSION IN THE REACTION OF *p*-HYDROXYPHENYL PHOSPHATE[a]

pH	N_{H_2O}	$N_{KH_2PO_4}$	P–O fission %
1.0	1.37	0.22	64
1.0	1.37	0.21	61
6.5	0.75	0.17	91
6.5	0.75	0.17	91

[a] At 25.0°; the isotopic abundances, *N*, are in atom % excess over normal.

trapolated to zero added buffer gave k_1, the first-order rate constant with respect to phosphate ester. Plots of k_1 against the periodate concentration (Per) were linear with close to zero intercepts (some examples are shown in Figure 1), and their slopes gave the second-order rate constants, k_2, for oxidation of the phosphate esters by periodate (Figures 2 and 3 and Table II).

TABLE II

REACTION OF *p*-HYDROXYPHENYL DIMETHYLPHOSPHATE[a]

Acid	[LiClO$_4$], *M*	10^2k, l. mol^{-1} sec^{-1} Obsd	10^2k, l. mol^{-1} sec^{-1} Calcd[c]
3 *M* $HClO_4$		1.96	
3 *M* $HClO_4$	0.50	3.24	
3 *M* $HClO_4$	1.00	5.00	
2 *M* $HClO_4$		0.95	
2 *M* $HClO_4$	0.50	1.37	
2 *M* $HClO_4$	1.00	1.92	
2 *M* H_2SO_4		0.95	
1 *M* $HClO_4$		0.46	
1 *M* $HClO_4$	0.50	0.55	
1 *M* $HClO_4$	1.00	0.65	0.36
0.50[b]		0.32	0.32
1.00[b]		0.28	0.26
1.50[b]		0.17	0.18
2.00[b]		0.12	0.12

[a] At 25.0°. [b] pH. [c] Calcd for k_2^0, $= 3.4 \times 10^{-3}$ l. mol^{-1} sec^{-1}.

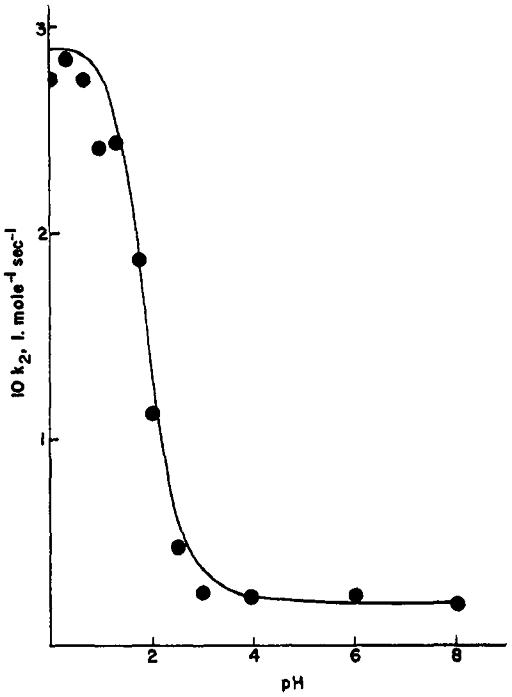


Figure 2.—Variation of the second-order rate constants, k_2, with pH for the reaction of *p*-hydroxyphenyl methylphosphate (II) at 25.0°. The line is calculated.

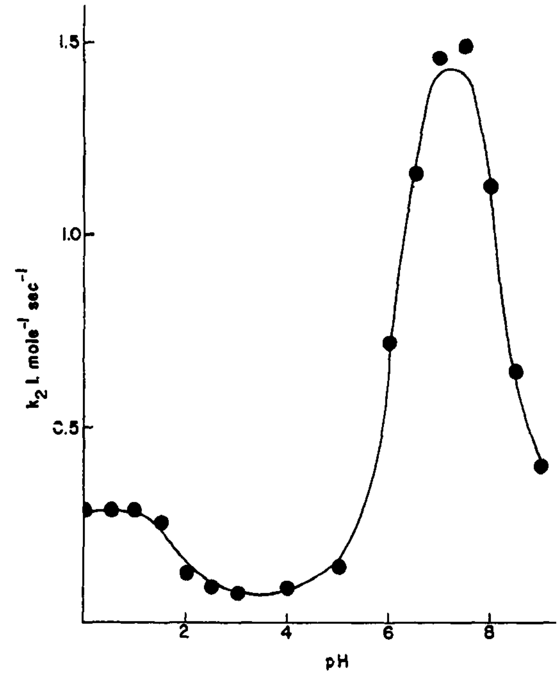


Figure 3.—Variation of second-order rate constants, k_2, with pH for the reaction of *p*-hydroxyphenyl phosphate (I) at 25.0°. The line is calculated.

The observations of second-order kinetics under all conditions show that there is no buildup of a periodate–substrate complex, in accord with the existing evidence on periodate oxidations of quinols and related compounds.[11,13]

Relation between Rate and pH. Reaction of *p*-Hydroxyphenyl Dimethylphosphate (III).—The rates of oxidative hydrolysis of the dimethyl ester show a very simple pH dependence. The periodate dianion, $H_3IO_6^{2-}$

(Per^{2-}), appears unreactive toward quinols and their derivatives, and for reaction of III we can write

$$v = k_2[\text{Per}][\text{P}] = \{k_2^0[\text{Per}^0] + k_2^-[\text{Per}^-]\}[\text{P}] \qquad (1)$$

where P is the phosphate ester, the superscripts denote charge, and [Per] is the stoichiometric concentration of periodate.

The relative amounts of undissociated acid and periodate monoanion can be calculated using the apparent first dissociation constant, K_1, at the various ionic strengths of the solutions interpolated from existing results.[23] (The values of 10^2K_1 were 5.5, 3.5, and 2.0 at ionic strengths of 1.0, 0.1, and 0.01, respectively.) Our kinetic treatment does not distinguish between the hydrated ($H_4IO_6^-$) and dehydrated (IO_4^-) forms of the periodate monoanion. However, IO_4^- is the predominant species,[23] and should be a better oxidant than $H_4IO_6^-$.

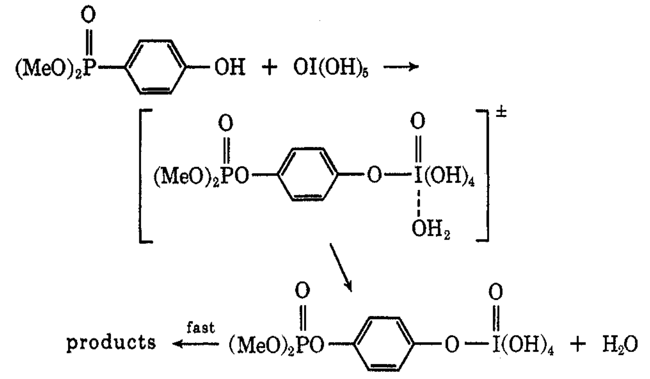
The second-order rate constants, k_2, for reaction of III vary linearly with the relative amount of undissociated periodic acid in the pH range 0.5–2, with $k_2^0 = 0.34 \times 10^{-2}$ l. mol^{-1} sec^{-1}, and k_2^- is negligibly small. These rate constants are compared with those for the other reactions in Table III. The observed and calculated rate constants are in satisfactory agreement for pH 0.5–2 (Table II). Undissociated periodic acid in dilute aqueous solution exists as H_5IO_6, and we assume that it is the reactive oxidant except possibly in solutions of high ionic strength. The positive electrolyte effects and the increase in k_ψ at acid concentrations >1 *M* (Table II) could be caused by partial dehydration of H_5IO_6 giving H_3IO_5, which should be a more effective electrophile and oxidant (HIO_4 is a strong electrolyte and would not exist to any appreciable extent under the reaction conditions).[23] Another possibility is that formation of the transition state is assisted by loss of water, *e.g.*,

TABLE III

SECOND-ORDER RATE CONSTANTS[a]

Substrate	Second-order rate constants[a] k_2^0	k_2^-	k_2^{2-}	k_2^{3-}
I	0.26	0.91	0.08	1.65
II	0.26	0.64	0.02	
III	0.0034	~0		

[a] At 25.0°.



and that moderately concentrated acid or added electrolyte "dehydrates" the transition state.

One problem with this explanation based on dehydration is that for the oxidation of *p*-hydroxyphenyl phosphate and its monomethyl ester II the values of k_ψ are independent of acid concentration once the reagents are converted fully into their undissociated acids, *i.e.*, at acid concentrations > 0.1 *M* (Figures 2 and 3). Therefore there are differences in the relations between rate constant and acid concentration (or ionic strength) for reactions of the dimethyl ester III and I and II. These differences may not be related to differences in mechanism, but could be caused by different electrolyte effects upon the activity coefficients of the hydrophobic dimethyl ester III and the more hydrophilic compounds I and II. Electrolyte effects are often observed in hydrolyses of hydrophobic phosphate esters.[24]

Reaction of *p*-Hydroxyphenyl Methylphosphate (II).—In the oxidative hydrolysis of the monomethyl ester II, periodic acid (Per^0) or its monoanion (Per^-, *i.e.*, $IO_4^- + H_4IO_6^{2-}$) could attack the undissociated phosphoric acid or its monoanion, and the overall rate equation is

$$v = k_2^0[\text{P}^0][\text{Per}^0] + k_2^-[\text{P}^0][\text{Per}^-] + k_2^{2-}[\text{P}^-][\text{Per}^-] \qquad (2)$$

where P^- is the monoanion of II.

In formulating eq 2 we assume that periodate dianion is unreactive toward the phosphate monoanion, because the observed second-order rate constants, k_2, fall to a constant value (Figure 2) and do not increase when the concentration of $H_3IO_6^{2-}$ increases. The second and third terms of eq 2 could be written as involving other ionic species; *e.g.*, kinetically we cannot differentiate between the terms $[\text{P}^0][\text{Per}^-]$ and $[\text{P}^-][\text{Per}^0]$.

In calculating the rate constants in eq 2 we take $k_2^{2-} = 0.02$ l. mol^{-1} sec^{-1} (the limiting value of k_2 in the region pH 6–8). The rate constants k_2^0 and k_2^- were then calculated by using the concentrations of the various ionic species calculated from the dissociation constants of the phosphate ester and periodic acid, and the values of k_2 at the pH's used in the kinetic runs. From these data we calculate $k_2^0 = 0.26$ l. mol^{-1} sec^{-1}, and $k_2^- = 0.64$ l. mol^{-1} sec^{-1}.

There is good agreement between the observed and calculated values of k_2 (Figure 2).

Reaction of *p*-Hydroxyphenyl Phosphate (I).—In analyzing the variation of k_2 with pH for reaction of I we have to take into account the undissociated phosphoric acid as well as its mono- and dianions, and the various periodate species, and again we cannot differentiate kinetically between reactions of various ionic species which generate transition states of like charge. We arbitrarily write the rate equation as

$$v = (k_2^0[\text{P}^0] + k_2^-[\text{P}^-])[\text{Per}^0] + (k_2^{2-}[\text{P}^-] + k_2^{3-}[\text{P}^{2-}])[\text{Per}^-] \qquad (3)$$

The rate constants in eq 3 were calculated by considering various pH regions separately; *e.g.*, at low pH we can ignore reactions of the phosphate dianion, and at high pH we can ignore reactions of the undissociated phosphoric acid, because the concentrations of these species are so low that reactions involving

---

[23] C. E. Crouthamel, H. V. Meek, D. S. Martin, and C. V. Banks, *J. Amer. Chem. Soc.*, **71**, 3031 (1949); C. E. Crouthamel, A. M. Hayes, and D. S. Martin, *ibid.*, **73**, 82 (1951); G. J. Buist and J. D. Lewis, *Chem. Commun.*, 66 (1965).

[24] P. W. C. Barnard, C. A. Bunton, D. Kellerman, M. M. Mhata, B. Silver, C. A. Vernon, and V. A. Welch, *J. Chem. Soc. B*, 227 (1966); C. A. Bunton, S. J. Farber, and E. J. Fendler, *J. Org. Chem.*, **33**, 29 (1968).

them would have to have rate constants as large as those for diffusion-controlled reactions to contribute to the overall reaction.

We calculate the following rate constants (l. mol^{-1} sec^{-1})—k_2^0 = 0.27, k_2^- = 0.91, k_2^{2-} = 0.02, and k_2^{3-} = 1.65—using the second-order rate constants for the overall reaction and the acid dissociation constants of the reactants, taking the apparent second dissociation constant of periodic acid[23] as 4.7 × 10^{-9}. The calculated values of k_2 (Table III) fit the experimental points reasonably well (Figure 3). (The values of k_2^- and k_2^{2-} differ from those given in ref 14, because in calculating the earlier values we did not take into account ionic strength effects on the acid dissociation of periodic acid.) There is no decrease of reaction rate with increasing acid; *e.g.*, in 2 *M* $HClO_4$, the second-order rate constant is 2.87 l. mol^{-1} sec^{-1}, and in 1 *M* acid it is 2.88 (*cf.* Figure 3).

Discussion

Under all conditions there was no buildup of a periodate ester, and the rate-limiting step is formation of a periodate ester which decomposes rapidly to products, or the periodate ester (E) is in equilibrium with reactants and decomposes slowly to products, *i.e.*, $k_b \gg k_p$, in Scheme I.

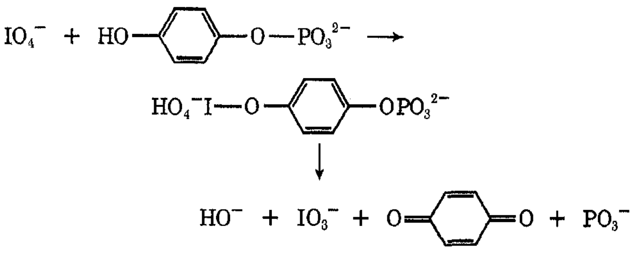
SCHEME I

$$P + Per \underset{k_b}{\overset{k_f}{\rightleftharpoons}} E \xrightarrow{k_p} \text{products}$$

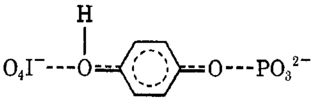
We cannot distinguish between these two possibilities using only kinetic measurements, but at least for the oxidative hydrolysis of *p*-hydroxyphenyl phosphate (I) we can draw mechanistic conclusions.

Mechanism of Oxidation of *p*-Hydroxyphenyl Phosphate.—The obvious feature of Figure 3 is the rate maximum at pH 7–7.5. In this pH region the probable reactants are the phosphate dianion, which should be a better nucleophile than the monoanion. In Scheme II, we assume that the reactive form of the periodate monoanion is IO_4^- (*cf.* ref 23). This mechanism explains the phosphorus–oxygen fission observed at pH 6.5 (Table I).

SCHEME II



In Scheme II we show formation and breakdown of the periodate ester as discrete steps, but they could be concerted. Elimination of metaphosphate ion from phosphate ester dianions occurs readily if P–O bond breaking is favored,[25] as it could be in forming periodate ester, *e.g.*, IV, or in species generated by loss of IO_3^- from it.



IV

This monoanion–dianion reaction appears to involve metaphosphate elimination in a slow step following the general mechanism proposed by Todd and his coworkers,[2] and it occurs under physiological conditions.

The reaction involving a dianionic transition state makes little overall contribution to the overall reaction, and there is considerable uncertainty in the actual value of k_2^{2-} for reaction of *p*-hydroxyphenyl phosphate (Table III).

The rate constant, k_2^0, is calculated for the reaction between two undissociated acids, although other reaction schemes could give the same kinetic form, and, in the same way, the reaction involving a monoanionic transition state (rate constant k_2^-) could be written differently. These reactions may not involve elimination of metaphosphate ion, although there is considerable P–O fission at pH 1. Either formation of a periodate–substrate complex is the rate-limiting step or the complex decomposes slowly, probably by attack of water.

To date analogies between the oxidative hydrolysis of quinol phosphates and their possible biological role have not been clear-cut, largely because extensive carbon–oxygen fission was observed in the chemical systems.[4,7–9] The reaction between a periodate monoanion and the dianion of *p*-hydroxyphenyl phosphate occurs at low temperature and under mild conditions in water and with extensive phosphorus–oxygen bond fission, and could therefore provide a simple chemical model for oxidation-induced phosphorylation.

Reactions of the Methyl Esters.—Three reactions are involved in the oxidative cleavage of the monomethyl ester II. Although k_2^- is relatively large (Table III), the contribution of the corresponding reaction is not large because at no pH are both reactants the predominant species. The rate constant k_2^0 is not particularly large, probably because formation of a periodate ester from H_5IO_6 involves elimination of water, but it is difficult to study the mechanisms of any of these three reactions in isolation.

The second-order rate constant for the reaction of periodic acid with the dimethyl ester III is slower than the corresponding reactions of the other esters (Table III). Two factors could be involved in this low reactivity of the dimethyl ester.

(1) The PO_3Me_2 group could be more electron attracting than either PO_3HMe or PO_3H_2 because of hydrogen bonding of water to the acidic hydrogens. The Hammett σ_p values are more negative for OH than OMe.[26]

(2) Nucleophilic attack upon the aryl or phosphoryl groups of the intermediates could be sterically hindered by the methyl groups.

Although the fit between the observed and calculated k_2 values is satisfactory over most of the pH

---

(25) G. DiSabato and W. P. Jencks, *J. Amer. Chem. Soc.*, **83**, 1268, 4400 (1961); A. J. Kirby and A. G. Varvoglis, *ibid.*, **88**, 1823 (1966); C. A. Bunton, E. J. Fendler, and J. H. Fendler, *ibid.*, **89**, 1221 (1967).

(26) J. Hine, "Physical Organic Chemistry," McGraw-Hill, New York, N. Y., 1962, p 87.

range (Figures 1 and 2, Table III), there are some deviations at relatively high concentrations of acid, the observed values being lower than those calculated for the monomethyl phosphate II, as was observed in the periodate oxidation of quinols,[11] but not of their carboxylic esters.[13] However, for the dimethyl ester the observed values are greater than those calculated (Table II), but because of the complex equilibria it is difficult to predict the sign or magnitude of what are probably kinetic or equilibrium electrolyte effects.

Relation with Periodate Oxidations of Quinols and Their Derivatives.—The reactions of *p*-quinol or its monomethyl ether with periodic acid are much faster than those of the undissociated phosphate esters, or the corresponding carboxylic esters.[11,13] For reaction of periodic acid with *p*-quinol the second-order rate constant is 71.7 l. mol^{-1} sec^{-1} at 25°,[11] whereas for *p*-hydroxyphenyl acetate[13] it is 19.6×10^{-4} l. mol^{-1} sec^{-1}, and for the phosphates I and II it is 0.26 l. mol^{-1} sec^{-1}. These low reactivities of the esters can be explained in part in terms of electron withdrawal by the acetyl and phosphoryl groups. (The σ_p values follow: [26]CH_3CO, +0.50, and PO_3H^-, +0.26.) In addition, decomposition of intermediates requires an extensive molecular reorganization, much more than in the decomposition of the corresponding intermediates in the oxidation of *p*-quinol. This explanation implies that formation of the periodate intermediate in the ester oxidations is reversible, with an unfavorable equilibrium constant, because it would be difficult to explain the rate constants solely in terms of the electronic effects of the phosphoryl groups upon formation of a periodate ester.

Registry No.—I, 940-75-0; II lithium salt, 39478-13-2; III, 1665-78-7; IV, 39478-14-3; dimethyl phosphite, 868-85-9.

Sulfonium Salts. VI. The Halogenation of Thiophane. Reaction Products

G. EDWIN WILSON, JR.,* AND RICHARD ALBERT[1]

Department of Chemistry, Polytechnic Institute of Brooklyn, Brooklyn, New York 11201

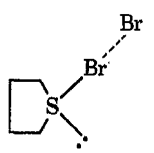
Received February 21, 1973

Bromination of thiophane in methylene chloride solution provides *trans*-2,3-dibromothiophane, isolated after methanolysis as *trans*-3-bromo-2-methoxythiophane (**3**). Chlorination of thiophane in methylene chloride solution provides 2-chlorothiophane (**10**) and 2,3-dichlorothiophane (**11**) identified after methanolysis as 2-methoxythiophane (**9**) and *trans*-3-chloro-2-methoxythiophane (**10**). The nmr spectrum of **3** suggests a highly favored conformation in solution with the substituents disposed diaxially on the thiophane ring.

The bromination of diethyl sulfide to produce unidentified fuming oils was described by Rathke in 1869.[2] The reaction was investigated by others, who obtained α-halo sulfides[3] and α,β-unsaturated sulfides[4] using a variety of halogenating agents. In some cases halogenation led to rupture of the carbon–sulfur bond with subsequent reactions ensuing from the sulfenyl halide generated.[3,5] In most cases such fragmentation appeared to be favored over α-substitution because decomposition of the halosulfonium salt intermediate could lead to a stable carbonium ion. We considered that a comparison of the results for halogenations of thiophanes with those of oxathiolanes[5a] would help in evaluating the importance of conformational effects on α-substitution in a five-membered ring and the importance of carbonium ion stabilization as an aid to carbon–sulfur bond fragmentation. Here we report results for the halogenation of the parent compound, thiophane, which indicate that α-substitution can be highly favorable in five-membered, sulfur-containing rings.

Results and Discussion

Bromination.—Bromination of thiophane in cold carbon tetrachloride solution provided an orange, crystalline adduct of sulfide with bromine. Recrystallization at low temperature from methylene chloride provided crystals whose molecular structure was found to be as shown.[6]



When the bromine complex of thiophane was allowed to react with cyclohexene, *trans*-1,2-dibromocyclohexane was produced. With water, the sulfoxide was formed. In methylene chloride solution at temperatures as low as 10°, hydrogen bromide was evolved and the orange color of the solution faded to a faint yellow. Thiophane could be readily identified by vpc as a reaction product, but the remaining materials were too unstable to handle. Removal of methylene chloride

---

[1] (a) Taken in part from the dissertation of Richard Albert, submitted in partial fulfillment of the requirements for the degree of Doctor of Philosophy at the Polytechnic Institute of Brooklyn. (b) NASA Trainee, 1966–1969.

[2] B. Rathke, *Justus Liebigs Ann. Chem.*, **152**, 181 (1869).

[3] For lead references, see G. E. Wilson, Jr., and M. G. Huang, *J. Org. Chem.*, **35**, 3002 (1970).

[4] H. Bohme and H. Gran, *Justus Liebigs Ann. Chem.*, **577**, 6B (1952).

[5] (a) G. E. Wilson, Jr., *J. Amer. Chem. Soc.*, **87**, 3785 (1965); (b) D. S. Tarbell and D. P. Harnish, *ibid.*, **74**, 1862 (1952); (c) D. C. Gregg, K. Hazelton, and T. F. McKeon, Jr., *J. Org. Chem.*, **18**, 36 (1953); (d) K. C. Schreiber and V. P. Fernandez, *ibid.*, **26**, 2478 (1961); (e) M. L. Wolfrom, H. G. Garg, and D. Horton, *ibid.*, **29**, 3280 (1964), and references cited therein; (f) H. Kwart and P. S. Strilko, *Chem. Commun.*, **767** (1967), and references cited therein; (g) J. M. Stewart and C. H. Burnside, *J. Amer. Chem. Soc.*, **75**, 243 (1953); (h) N. J. Leonard and G. E. Wilson, Jr., *ibid.*, **86**, 5307 (1964).

[6] G. Allegra, G. E. Wilson, Jr., E. Benedetti, C. Pedone, and R. Albert, *J. Amer. Chem. Soc.*, **92**, 4002 (1970).