Tetrahedron Letters No.3, pp. 187-190, 1969. Pergamon Press. Printed in Great Britain.

THE OXIDATION OF p-HYDROXYPHENYL PHOSPHATE BY PERIODIC ACID

C. A. Bunton and J. Hellyer
Department of Chemistry, University of California at Santa Barbara
Santa Barbara, California 93106

(Received in USA 26 October 1968; received in UK for publication 10 December 1968)

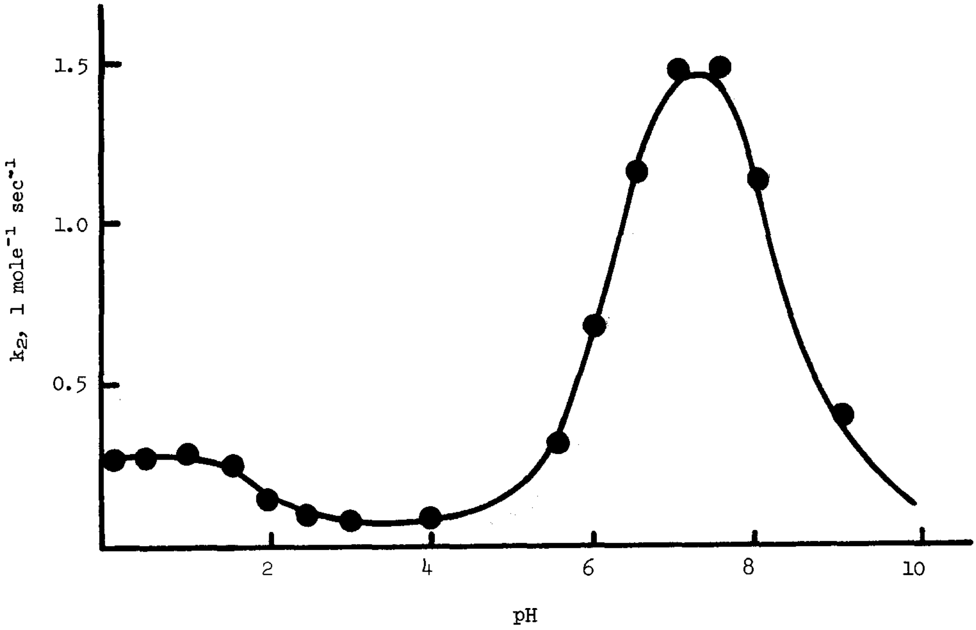
The oxidation of quinol phosphates has been studied extensively as a model for biological phosphorylations, and the reaction has considerable synthetic utility (1,2,3). Halogens and metal ions have been used as oxidants, and the reaction has also been carried out electrochemically. However the reaction often involves aryl-oxygen cleavage rather than phosphorylation (4,5). The corresponding oxidative cleavage of quinol monosulfate has been suggested as a possible model for biological sulfate transfer, although here too there is considerable aryl-oxygen bond fission (6). Periodic acid is an effective reagent for the oxidation of quinols, and quinol monoethers and monoesters to quinones (7,8) and we now report the kinetic form of the periodate oxidation of p-hydroxyphenyl phosphate (I). The reaction proceeds smoothly and cleanly under mild "physiological" conditions, i.e. in water at 25.0° and pH 0-9.

The reaction is first order with respect to each reactant over the concentration ranges: [periodate] 7×10^{-5} - 9×10^{-3} M, and [I] 9×10^{-5} - 3.6×10^{-4} M, in water at 25.0°. There is no evidence for the build-up of an intermediate periodate ester as is found in many glycol oxidations (9). Both perchloric and sulfuric acid were used to control the acidity at pH < 3, and the rates were independent of the nature of the acid. For pH 4-9 the second order rate constants, k_2, were measured over a range of buffer and electrolyte concentrations, and were extrapolated to zero ionic strength. The variation of k_2 with pH in water at 25.0° is shown in Fig. 1 (solid points). The complexity of the pH profile, as opposed to the simple ones observed in other periodate oxidations of quinols and their derivatives (7,8) arises from the possibility of reactions involving the aryl phosphoric acid and its mono- and dianion, and the rates (mole l^{-1} sec^{-1}) can be fitted to equation (1):

$$\text{rate} = (0.27\,[H_2P] + 0.40\,[H\bar{P}])\,[H_5IO_6] + (0.065\,[H\bar{P}] + 1.65\,[P^{2-}])\,([I\bar{O}_4] + [H_4I\bar{O}_6]) \quad (1)$$

(where P^{2-} = HO  OPO_3^{2-})

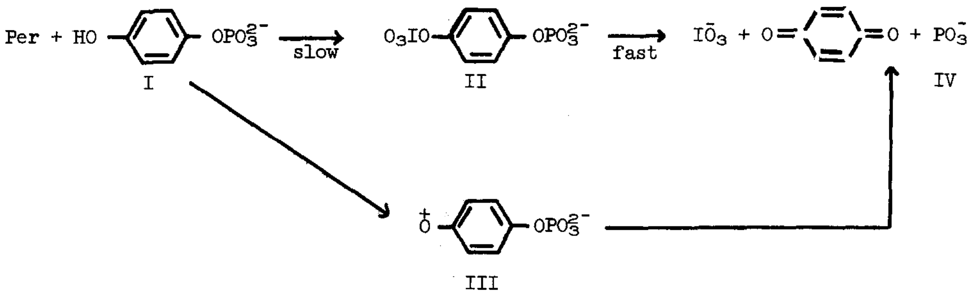
Fig. 1



The solid line in Fig. 1 is calculated using equation (1) and the relative ionic concentrations calculated using the acid dissociation constants: for periodic acid (apparent K values) (10), $K_1 = 2 \times 10^{-2}$; $K_2 = 4.7 \times 10^{-9}$: and for (I) $K_1 = 4 \times 10^{-2}$; $K_2 = 7.3 \times 10^{-7}$ (determined by pH titration). The experimental values of k_2 fit equation (1) reasonably well, and the decrease of k_2 at high pH shows that reactions involving the phenoxide ion or the periodate dianion are unimportant. Over the whole pH range the rate of reaction with periodate is very much faster than hydrolysis of (I), and we can exclude hydrolysis followed by oxidation of quinol as a possible mechanism, as was found for the oxidations of other quinol esters (6,8).

The various contributing reactions whose rate constants are given in equation (1) are chemically reasonable, in that periodic acid should be a better electrophile than its monoanion, as was found for the oxidation of quinols and their derivatives (7,8), and the reactivity of phosphoric acid and its anions should follow the sequence $P^{2-} > H\bar{P} > H_2P$. However we cannot from variations of k_2 with pH distinguish between reaction of say the periodate and phosphate monoanions and the dianion of one reagent with the undissociated acid of the other.

Possible mechanisms are shown below for the reaction of quinol phosphate dianion with a monomeric periodate species (Per):



(The states of ionization of (II) and (III) and the state of hydration of (II) are assumed.)

With the information available we cannot as yet distinguish between a slow formation and a rapid decomposition of (II), or electrophilic attack upon the phenolic hydroxyl group concerted with P-O bond fission, or formation of the cationic oxygen species (III) followed by or concerted with loss of metaphosphate ion which should react rapidly with water. We were unable to detect any intermediate spectrophotometrically using a stopped-flow apparatus.

Preliminary experiments using $H_2{}^{18}O$ at pH 1.0 and 6.5 followed by isotopic analysis of the inorganic phosphate showed that the reactions involve largely P-O fission.

The periodate oxidation of other quinol phosphates is currently being studied, and quinol dimethyl phosphate is much less reactive than quinol phosphate. In water at 25.0° the values of k_2, l. mole^{-1} sec^{-1} are: pH 1; 2.78×10^{-3}: pH 1.5; 1.73×10^{-3}; pH 2; $\sim 1 \times 10^{-4}$. Elimination of metaphosphate ion cannot occur in this reaction, and the large difference in reactivity suggests that elimination of metaphosphate ion may be kinetically important in the oxidation of quinol phosphate. The pH profile for the oxidation of p-quinol dimethyl phosphate is very similar to those found for the periodate oxidations of quinol and its monoethers and monoesters (7,8). In these reactions the pH profile could be interpreted in terms of bimolecular reactions between the substrate and periodic acid or its monoanion, with the periodic acid being much more reactive than the monoanion.

Acknowledgement. We thank the Institute of Arthritis and Metabolic Diseases of the USPHS for support of this work.

REFERENCES

(1) T. C. Bruice and S. Benkovic, "Bio-Organic Mechanisms," Vol. II, Benjamin, New York, 1968, p. 91 and references cited.

(2) C. A. Chambers and J. Q. Chambers, *J. Am. Chem. Soc.*, **88**, 2922 (1966).

(3) C. D. Snyder and H. Rapoport, *J. Am. Chem. Soc.*, **89**, 1269 (1967).

(4) A. Lapidot and D. Samuel, *Biochim. Biophys. Acta*, **65**, 164 (1962).

(5) W. Durckheimer and L. A. Cohen, *Biochemistry*, **3**, 1948 (1964).

(6) E. T. Kaiser, D. F. Mayers, S. W. Weidman and O. R. Zaborsky, *J. Am Chem. Soc.*, **86**, 4555 (1967).

(7) E. T. Kaiser and S. W. Weidman, *J. Am. Chem. Soc.*, **86**, 4354 (1964).

(8) C. A. Bunton and J. Hellyer, *J. Am. Chem. Soc.*, **89**, 6252 (1967).

(9) C. A. Bunton in "Oxidation in Organic Chemistry," Part A, Ed. K. B. Wiberg, Academic Press, New York, 1965, Chap. VI.

(10) C. E. Crouthamel, H. V. Meek, D. S. Martin, and C. V. Banks, *J. Am. Chem. Soc.*, **71**, 3031 (1949); C. E. Crouthamel, A. M. Hayes and D. S. Martin, *J. Am. Chem. Soc.*, **73**, 82 (1951).