Chromatography of 0.57 g. on Florisil gave 0.13 g. of crude III. Crystallization from acetone-hexane gave 90 mg. of III, m.p. 220–226°, identical in its infrared spectrum with an authentic sample. Lit.^{3c} m.p. 226–232°.

B. A mixture of 1 g. of I and 25 ml. of acetic anhydride was heated on the steam-bath for 2 hours, then worked up in the usual way to give 0.52 g. of an oil. This was triturated with ether to give 0.34 g. of a solid, m.p. 200° dec.; chromatography of 0.3 g. on Florisil gave 60 mg. of crude III. Crystallization from acetone-hexane gave 30 mg. of III, m.p. 220–225° (structure confirmed by infrared spectrum and mixture m.p.).

11β,17α,21-Trihydroxy-1,4-pregnadiene-3,20-dione 21-acetate (IV) *from 11β,17α,21-trihydroxy-1,4-pregnadiene-3,20-dione bis-semicarbazone* (II). A mixture of 0.5 g. of II, 3.75 ml. of acetic anhydride, and 10 ml. of pyridine was heated on the steam-bath 2 hours, then worked up as in the previous experiment to give 0.49 g. of an oil. Chromatography of 0.40 g. on Florisil gave 50 mg. of crude IV. Crystallization from acetone-hexane gave 20 mg. of IV, m.p. 220–229°, identical in its infrared spectrum with an authentic sample. Lit.^{3c} m.p. 237–239°.

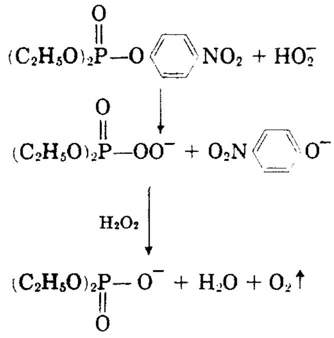
CHEMICAL RESEARCH AND DEVELOPMENT DIVISION
SCHERING CORPORATION
BLOOMFIELD, NEW JERSEY

Reaction of Paraoxon with Hydrogen Peroxide in Dilute Aqueous Solution

JOSEPH EPSTEIN, MARY M. DEMEK, AND DAVID H. ROSENBLATT

Received January 16, 1956

The perhydroxyl ion reacts with suitable substrates, such as benzonitrile[1] and isopropyl methylphosphonofluoridate[2] to produce unisolable[3] perhydroxylated intermediates; the latter are capable of further reaction with hydrogen peroxide, whereby oxygen and hydrolysis products of the substrates are formed. The net effect is to accelerate markedly the basic hydrolysis of the substrates at a given *p*H. In the present report it is shown that the hydrolysis of paraoxon (O,O-diethyl O-*p*-nitrophenyl phosphate) is similarly accelerated by hydrogen peroxide, *i.e.*, *via* the perhydroxyl ion, most likely according to the following equation (by analogy with reactions of alkaline hydrogen peroxide with isopropyl methylphosphonofluoridate):



The reaction, which can be followed through appearance of the strongly colored *p*-nitrophenoxide ion, is of first order with respect to both substrate and perhydroxyl ion, as in the previously cited instances. Although perhydroxyl is a less basic ion than hydroxyl,[4] its reaction rate with paraoxon is about 10^2 times as rapid as that of hydroxyl ion. Interatomic distances[5] between the hydrogen and the charged oxygen of the perhydroxyl ion (1.91 Å) and between the phosphorus and oxygen[6] of either the P=O bond or P—O—NO$_2$ groups (1.55–1.76 Å) are sufficiently close to permit the operation of a push-pull mechanism, such as has been used to explain the extraordinary reactivities of catecholate ions with isopropyl methylphosphonofluoridate.[7] It is visualized that an attack by the negatively charged perhydroxyl ion upon the phosphorus atom simultaneous wth a pull on the phosphoryl oxygen (or the *p*-nitrophenoxide oxygen) by the perhydroxyl hydrogen facilitates the cleavage of the phosphorus to oxygen (phenoxide) bond.

---

(1) Wiberg, *J. Am. Chem. Soc.*, **75**, 3961 (1953); **77**, 2519 (1955).

(2) Wilson, Gehauf, and Rueggeberg, *Abstracts of the Pittsburgh Conference on Analytical Chemistry and Applied Spectroscopy*, Feb. 27, 1956, p. 23; J. Epstein and V. E. Bauer, *Abstracts of the Pittsburgh Conference on Analytical Chemistry and Applied Spectroscopy*, Feb. 27, 1956, p. 24.

(3) The existence of the perhydroxylated intermediate has been postulated through its ability, in the case of the isopropyl methylphosphonofluoridate derivative, to oxidize certain amines, such as *o*-tolidine, rapidly to yellow dyes.[2]

(4) Edwards, *J. Am. Chem. Soc.*, **76**, 1540 (1954), has pointed out the importance of two factors in the rates of displacement reactions, namely, the relative basicity of the attacking anion toward protons and a parameter, E_n (the "nucleophilic constant"), related to the electrode potential of the anion. For displacements on phosphorus in aqueous solution, E_n may be assumed to be rather unimportant, as compared to the influence of the basicity of the anion. Thus, we have observed that the thiosulfate ion which, according to Edwards, has a very high nucleophilic constant, has scarcely any effect on the rate of decomposition of isopropyl methylphosphonofluoridate in aqueous solution. Hence, in comparing the activity of two anions, only "basic" strength should be important, and greater reactivity might be expected of the anion possessing higher basicity.

(5) The distance between the hydrogen and charged oxygen was calculated on the basis of data taken from Milas, in Kirk and Othmer, *Encyclopedia of Chemical Technology*, Interscience Encyclopedia, Inc., New York, 1951, Vol. 7, p. 729. The H—O—O bond angle was taken as 101.5°, the O—O bond distance as 1.48 Å and the O—H bond distance as 1.01 Å.

(6) Van Wazer, in Kirk and Othmer, *Encyclopedia of Chemical Technology*, Interscience Encyclopedia, Inc., New York, 1953, Vol. 10, p. 466.

(7) Epstein, Rosenblatt, and Demek, *J. Am. Chem. Soc.*, **78**, 341 (1956).

EXPERIMENTAL

Apparatus. A Klett-Summerson photoelectric colorimeter with a No. 42 filter was used for estimation of *p*-nitrophenoxide. Temperature was maintained to within 0.5° of the designated temperature by means of a water-bath. A Beckman Model G *p*H meter was used for all *p*H measurements. Corrections to the *p*H for sodium ion concentration were made by means of a nomograph supplied by Beckman Instruments Inc.

Materials. Paraoxon supplied by the Chemical Division of the Chemical Corps, Chemical and Radiological Laboratories, was *ca.* 95% pure by chemical analysis[8] and contained *ca.* 2% *p*-nitrophenol according to measurements of color immediately developed in aqueous solution of *p*H 10. A 0.3% stock solution of paraoxon in acetone was diluted with water to make up mixtures for kinetic studies; such mixtures never contained more than 0.2% acetone. Buffers consisted of sodium phosphate mixtures (0.025 *M* final concentration) for *p*H 9 to 11 and 0.01 to 0.1 *N* sodium hydroxide for the higher *p*H range. Solutions of C. P. *p*-nitrophenol in the appropriate buffers were used to construct calibration curves for *p*-nitrophenoxide concentration.

Kinetic procedures. Reactant solutions were brought to the desired temperature and mixed rapidly in 100-ml. volumetric flasks, which then were placed in the water-bath. Aliquots were withdrawn from time to time and the color was measured against that of reagent blank.

The actual time of reading was used for the kinetic data, rather than the time of sampling; the interval between sampling and reading was only about 15 seconds. It was thus unnecessary to quench the reaction before reading and even where the reaction half-life was very short, no error of consequence was thereby introduced.

Results. p-Nitrophenoxide concentrations (C_t) at various time intervals were determined by comparison with the calibration curve. Pseudo-first order rate constants (k_1) were calculated[9] from the linear plots obtained (*i.e.*, 2.303 times the slope) when $\log (C_\infty - C_t)$ was plotted against time (where C_∞ is the concentration of *p*-nitrophenol when reaction is complete). That the reaction is first order at a given *p*H, with respect to hydrogen peroxide as well as the paraoxon concentration, is shown by the constancy of k_2' values in Table I where $k_2' = k_1/[H_2O_2]$. True second order rate constants (Tables II and III) were obtained from the equations $k_b = k_1/[OH^-]$ for base-catalyzed hydrolysis[10] or $k_2 = (k_1 - k_b[OH^-])/[HO_2^-]$ for the perhydroxyl reaction[11] where $[HO_2^-]$ was calculated from the *p*H and the acid dissociation constant[12] of hydrogen peroxide (1.98×10^{-12} at 25° and 3.46×10^{-12} at 37°).

TABLE I

REACTION OF PARAOXON WITH HYDROGEN PEROXIDE AT *p*H 11.3, T = 25°C.

Paraoxon (Mol. liter^{-1})	$[H_2O_2] \times 10^3$ (Mol. liter^{-1})	k_1 (Min.$^{-1}$)	$k_2' \times 10^{-1}$ (Liter mol.$^{-1}$ min.$^{-1}$)
10^{-5}	3.5	4.6×10^{-2}	1.31
	7.0	9.8×10^{-2}	1.40
	14.0	1.69×10^{-1}	1.21
	21.0	3.3×10^{-1}	1.57
2×10^{-5}	3.5	4.7×10^{-2}	1.34
	7.0	1.03×10^{-1}	1.47
	14.0	2.04×10^{-1}	1.46
	17.4	3.08×10^{-1}	1.77

TABLE II

AQUEOUS HYDROLYSIS OF PARAOXON[a] (T = 25°C.)

*p*H	$[OH^-]$ (Mol. liter^{-1})	k_1 (Min.$^{-1}$)	k_b (Liter mol.$^{-1}$ min.$^{-1}$)
10.06	1.14×10^{-4}	6.24×10^{-5}	0.547
11.23	1.68×10^{-3}	8.75×10^{-4}	.521
11.84	6.86×10^{-3}	4.33×10^{-3}	.631
12.23	1.68×10^{-3}	1.06×10^{-2}	.631

[a] Initial concentration of paraoxon = 3×10^{-5} M. At 37° k_b was 0.94.

TABLE III

HYDROLYSIS OF 10^{-5} *M* PARAOXON WITH 3.5×10^{-5} *M* HYDROGEN PEROXIDE (T = 37°C.)

*p*H	$[OH^-]$ (Mol. liter^{-1})	$[HO_2^-] \times 10^4$ (Mol. liter^{-1})	k_1 (Min.$^{-1}$)	$k_2 \times 10^{-1}$ (L. mol.$^{-1}$ min.$^{-1}$)
9.53	8.09×10^{-5}	0.406	4.7×10^{-3}	11.3
10.07	2.81×10^{-4}	1.37	1.22×10^{-2}	8.7
10.77	1.41×10^{-3}			8.6*
11.3	4.77×10^{-3}	14.3	1.19×10^{-1}	8.0

* Average k_2 value for determinations using concentrations of hydrogen peroxide of 14.7, 34.4, and 44.0×10^{-3} *M*.

CHEMICAL WARFARE LABORATORIES
ARMY CHEMICAL CENTER, MARYLAND

---

(8) Performed by Mr. Samuel Sass, of the Chemical and Radiological Laboratories.

(9) Frost and Pearson, *Kinetics and Mechanism*, John Wiley and Sons, Inc., New York, 1953, p. 8–53.

(10) Values of K_{H_2O} are 2.39×10^{-14} at 37° (by interpolation) and 1.008×10^{-14} at 25°, according to Glasstone, *Textbook of Physical Chemistry*, 2nd ed., D. van Nostrand Co., New York, 1947, p. 992.

(11) Substitution of the perhydroxyl ion concentration in data shown in Table I gives a k_2 value of 5.06×10^1 liter mol.$^{-1}$ min.$^{-1}$ at 25°C.

(12) Calculated from the value of 1.55×10^{-12} at 20.1°C, taken from Kargin, *Z. anorg. u. allgem. Chem.*, **183**, 77 (1929), and from the heat of ionization, 8603 calories, according to Joyner, *Z. anorg. Chem.*, **77**, 103 (1912).

Substitution of Halogens by Deuterium in Organic Compounds Without Undesired Exchange of Hydrogen by Deuterium

BØRGE BAK

Received March 2, 1956

The inconvenience associated with the use of the conventional *Grignard* technique for introducing deuterium into organic compounds is well known. A method having wider applicability and, if possible, experimentally simpler would therefore seem to be of rather great interest. It is believed that the method described below has these advantages to a certain extent. Table I summarizes results obtained in successful attempts to prepare deuterated species of a variety of organic compounds.

EXPERIMENTAL

Except for the methyl iodide and methylene iodide the compound to be deuterated was mixed with Zn-dust and