

A Kinetic Study of the Reaction of *iso*Propoxy-methyl-phosphoryl Fluoride (Sarin) with Hydrogen Peroxide

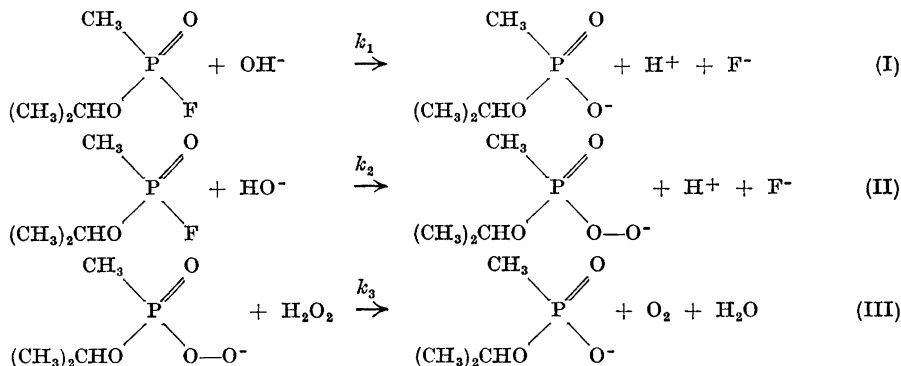
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The reaction of *isopropoxy-methyl-phosphoryl fluoride* (Sarin) and hydrogen peroxide has been investigated and the bimolecular rate constant and energy and entropy of activation of the formation of *isopropoxy-methyl-perhydroxy-phosphine oxide* have been calculated. It has been suggested that the reaction involves a nucleophilic attack of the perhydroxyl ion on the phosphorus atom, and that the transition state is stabilized by the formation of a hydrogen bond between the perhydroxyl ion and the oxygen atom of the phosphoryl group. It has been shown that the decomposition of the peroxy acid proceeds by two competitive reactions, the rate constants of which have been calculated.

The reaction of organic phosphorus compounds with hydrogen peroxide plays an important role in the Schönemann reaction. The principle of this reaction is the oxidation of amines, such as benzidine, to coloured products by hydrogen peroxide in the presence of various phosphorus compounds¹. The reaction has been made the basis of a sensitive method for the quantitative determination of nerve gases^{2,3}.

In this connection it was of interest to study the reaction between Sarin and alkaline solutions of hydrogen peroxide in the absence of an oxidizable amine. Gehauf *et al.*² have discussed the mechanism of this reaction and have postulated the following scheme for the formation and decomposition of *isopropoxy-methyl-perhydroxy-phosphine oxide*. In the same scheme the alkaline hydrolysis of Sarin (I) is also given.



The same mechanism has also been proposed by Epstein *et al.*⁴ in the study of the reaction between diethyl *p*-nitrophenyl phosphate (Paraoxon) and hydrogen peroxide. The present report is an attempt to make a detailed investigation of the reaction of Sarin with hydrogen peroxide at various pH-values and temperatures.

EXPERIMENTAL

Materials. Sarin was synthesized in this institute and freshly distilled before use⁵. A stock solution of Sarin in dioxane, E. Merck c.p. purified from peroxides and redistilled over sodium, was prepared. The concentration of Sarin in this solution was 8.0 mM.

Hydrogen peroxide (about 30 %), E. Merck anal. reagent. The exact concentration was determined by titration with 0.1 N solution of potassium permanganate.

Paper chromatographic technique. The final products of the reaction were analyzed by means of paper chromatographic technique. A solution containing 0.5 % Sarin and 0.5 % hydrogen peroxide in 0.1 M ammonium hydroxide was prepared. At this pH the reaction is almost instantaneously completed. By means of a micropipette 5 μ l of this solution were placed on a filter paper, Whatman No. 1, and the spot was dried in hot air. Ascending technique was used, and the chromatogram was run at 25°C. An acid solvent with the following composition was used: *n*-butanol:ethanol:acetic acid:water (8:2:1:3)⁶. After the drying, phosphorus was developed by spraying the paper with an acid solution of ammonium molybdate and treating the dried paper with hydrogen sulfide⁷.

Kinetic measurements. The kinetics of the reaction were studied in a manner similar to that described for the hydrolysis of Sarin and its analogues by means of an automatic recording titrator⁵. Two types of experiments were performed.

Procedure I. In the first series of experiments the reaction rate constant, k_2 (Reaction II), was determined by excess of hydrogen peroxide at 25°C at the pH-values 7.70, 8.00 and 8.50, and at 35°C at the pH-values 7.70 and 8.00. A solution containing 38.00 ml of 0.10 M potassium chloride and 1.00 ml of appropriately diluted hydrogen peroxide was adjusted by the titrator to a preselected pH-value, after which 1.00 ml of the stock solution of Sarin was added. The initial concentration of Sarin was 0.20 mM in every run and the initial concentration of hydrogen peroxide varied between 2.50 and 10.00 mM. The reaction was allowed to terminate, and the concentrations of Sarin at different times were calculated from the recorded amount of alkali consumed in the reaction. Such a calculation presupposes that the *isopropoxy-methyl-hydroxy-phosphine oxide* as well as the *isopropoxy-methyl-perhydroxy-phosphine oxide* formed in the reaction is totally ionized in the prevailing pH range.

Procedure II. In a second series of experiments which were performed at 25°C and pH 8.50, the initial concentration of Sarin was the same as mentioned above but that of the hydrogen peroxide was 0.50 mM. The initial and final concentrations of hydrogen peroxide were determined colorimetrically with titanium sulphate⁸. In other respects the same experimental technique was used as described under I. The spontaneous decomposition of hydrogen peroxide was checked during 2 h in a separate run and was found to be insignificant.

In two runs 1.00 ml of sample was withdrawn from the reaction vessel at intervals and added to 2.00 ml of a 1.25 % solution of *o*-tolidine in acetone and 2.00 ml of water. The optical density of the mixture was determined after 2 min in a 5 cm absorption cell at 4 250 Å with a Beckmann spectrophotometer, Type B. From these measurements it was possible to determine at which time during the reaction the concentration of the "peroxyphosphorus acid" attained its maximum value. A determination of the actual concentration of the peroxy acid, however, would be very difficult, because the rate of the colour reaction is unknown.

Determination of dissociation constants. The mixed dissociation constant, K'_a , of *isopropoxy-methyl-hydroxy-phosphine oxide* was determined by potentiometric titration of a 5 mM hydrolysate of *isopropoxy-methyl-phosphoryl chloride* in 0.10 M potassium chloride solution with 0.1 M sodium hydroxide. The details of the procedure and the calculations are described in an earlier paper⁹. Two runs at 25°C gave $pK'_a = 2.10 \pm 0.05$.

Owing to the instability of the "peroxyphosphorus acid" formed it has not been possible to determine its dissociation constant. However, presuming that the relationship

between the dissociation constants of the "phosphorus acid" and the peroxy acid is the same as that between those of a carboxylic acid and the corresponding peroxy acid¹⁰, pK_a of the "peroxyphosphorus acid" may be estimated at 5–6.

RESULTS AND DISCUSSION

Formation of *isopropoxy-methyl-perhydroxy-phosphine oxide*

The formation of a "peroxyphosphorus acid" as an intermediate in the reaction of Sarin with hydrogen peroxide has been supported by the fact that the reaction mixture oxidizes thiosulphate ion to sulphate ion². According to Feigl this anomalous oxidation of thiosulphate has been attributed to peroxy acids¹¹. Also the oxidation of certain amines by hydrogen peroxide in the presence of organic phosphorus compounds indicates the formation of this intermediate. Furthermore the fluorine atom is split off more rapidly than the oxygen molecule is formed².

In the reaction two equivalents of acid were formed. On the basis of the estimated value of the dissociation constant of the "peroxyphosphorus acid", this acid was considered as totally ionized in the pH range in question. The subsequent decomposition of the peroxy acid according to Reaction III will then not cause any further consumption of alkali. The concentration of Sarin at different times was therefore calculated from the amount of alkali consumed. When hydrogen peroxide is in excess, the reaction can be treated as a pseudo first-order reaction. When the logarithm of the concentration of Sarin (c_{PF}) was plotted against the time a straight line was obtained as appears in Fig. 1. It is also shown in the figure that at low concentrations of hydrogen peroxide the curve deviates from the straight line at the end of the reaction, indicating that the decrease of the hydrogen peroxide concentration can only be neglected in the first part of the reaction.

From the curves obtained the observed rate constants, k_{obs} , were calculated. It is obvious from Table 1 that, at the lower pH-values, where sponta-

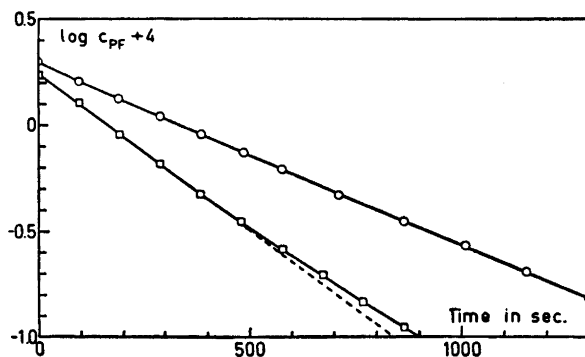


Fig. 1. First order plots for the reaction of Sarin with hydrogen peroxide when initial concentrations of hydrogen peroxide are 10.0 mM (O) and 2.5 mM (□) at pH 7.70 and 8.50, respectively, at 25°C.

Table 1. The rate constants for the reaction of Sarin with hydrogen peroxide at various temperatures and pH-values. The initial concentration of Sarin was 0.20 mM.

$t^{\circ}\text{C}$	pH	$\text{c}_{\text{H}_2\text{O}_2}$, mM	$k_{\text{obs}} \times 10^3 \text{ sec}^{-1}$	$k_1 \times 10^3 \text{ sec}^{-1}$	$k_2 \times 10^{-3} \text{ l mole}^{-1} \text{ sec}^{-1}$
25.0	7.70	5.00	1.04	0.017	1.40
	7.70	5.00	1.04	0.017	1.40
	7.70	10.00	2.00	0.017	1.36
	7.70	10.00	1.93	0.017	1.31
	8.00	5.00	1.96	0.034	1.32
	8.00	5.00	1.96	0.034	1.32
	8.00	10.00	3.70	0.034	1.26
	8.00	10.00	3.98	0.034	1.35
	8.50	2.50	3.39	0.106	1.42
	8.50	2.50	2.98	0.106	1.24
35.0	7.70	5.00	2.60	0.058	2.18
	7.70	5.00	2.40	0.058	2.01
	7.70	5.00	2.37	0.058	1.98
	8.00	2.50	2.42	0.116	1.97
	8.00	2.50	2.40	0.116	1.96
	8.00	2.50	2.59	0.116	2.12

neous hydrolysis is negligible, k_{obs} , at constant pH, is proportional to the concentration of hydrogen peroxide, which indicates a bimolecular reaction mechanism. The variation of rate with pH shows that the perhydroxyl ion is the active component in the reaction.

The true second-order rate constant, k_2 , was calculated from the expression:

$$k_2 = \frac{k_{\text{obs}} - k_1}{c_{\text{HO}_2^-}} \quad (1)$$

where the observed rate constant is corrected for the rate constant of the spontaneous hydrolysis, k_1 , found from earlier experiments⁵. According to the law of mass action the perhydroxyl ion concentration is:

$$c_{\text{HO}_2^-} = \frac{K'_{\text{H}_2\text{O}_2} \cdot c^{\circ}_{\text{H}_2\text{O}_2}}{a_{\text{H}^+} + K'_{\text{H}_2\text{O}_2}} \quad (2)$$

where $c^{\circ}_{\text{H}_2\text{O}_2}$ is the total concentration of hydrogen peroxide and $K'_{\text{H}_2\text{O}_2}$, the mixed dissociation constant. The values of $K'_{\text{H}_2\text{O}_2}$ at 25°C and 35°C in 0.10 M potassium chloride solution were estimated at 2.92×10^{-12} and 4.66×10^{-12} , respectively, from the thermodynamic constants given by Evans and Uri¹². When $a_{\text{H}^+} \gg K'_{\text{H}_2\text{O}_2}$, which is valid in the present pH range, eqn. (2) is reduced to:

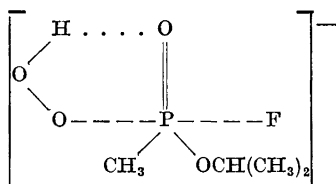
$$c_{\text{HO}_2^-} = \frac{K'_{\text{H}_2\text{O}_2} \cdot c^{\circ}_{\text{H}_2\text{O}_2}}{a_{\text{H}^+}} \quad (3)$$

The values of k_2 at 25°C and 35°C are given in Table 1 and their mean values were found to be $k_2^{25} = (1.34 \pm 0.06) \times 10^3 \text{ l mole}^{-1} \text{ sec}^{-1}$ and $k_2^{35} = (2.04 \pm 0.09) \times 10^3 \text{ l mole}^{-1} \text{ sec}^{-1}$. From these rate constants the energy of activation

was calculated as 7.7 ± 1.6 kcal mole⁻¹ and the entropy of activation as -20 ± 5 E.U.

The facts that straight line plots are obtained from the experiments and that k_2 is independent of pH, support the hypothesis that *isopropoxy-methyl-perhydroxy-phosphine oxide* is totally ionized in the present pH range.

The mechanism of the reaction of Sarin with perhydroxyl ions may be considered to be analogous to that of the alkaline hydrolysis of Sarin, *i.e.* it involves a nucleophilic attack of the perhydroxyl ion on the phosphorus atom. The rate of this reaction has been shown to be about 50 times greater than that of the alkaline hydrolysis. This difference may be due to perhydroxyl ion being more nucleophilic than hydroxyl ion in spite of the greater basicity of the latter. Another reason for the greater rate of reaction is that perhydroxyl ion will contribute to the stabilization of the transition state by the formation of a hydrogen bond such as,



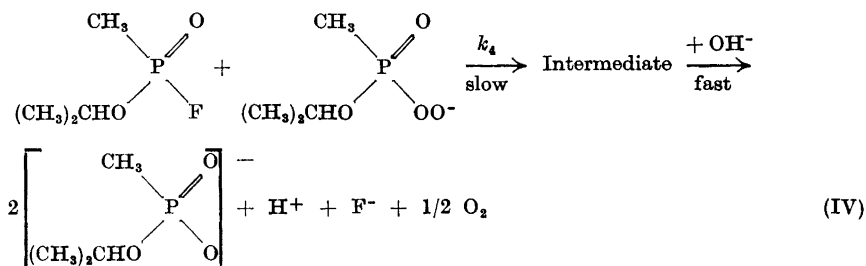
The formation of a hydrogen bond in the association of phenol with Sarin has been demonstrated in an infra-red spectroscopic study¹³. It has also been shown in this study that the absorption band of the P=O group shifts to lower frequency corresponding to a bond weakening, and that of the P—F group shifts to higher frequency corresponding to a bond strengthening. These results indicate that a hydrogen bond to the oxygen atom in the P=O group is formed. Thus it seems very probable that such a hydrogen bond also will be formed between the perhydroxyl ion and the oxygen atom in the P=O group in the transition state as suggested above.

Decomposition of *isopropoxy-methyl-perhydroxy-phosphine oxide*

The decomposition of the "peroxyphosphorus acid" shown in Reaction III has been supported by the consumption of two moles of hydrogen peroxide and the evolution of one mole of oxygen per mole of Sarin² when excess of hydrogen peroxide was used. By means of paper chromatography only a single final product containing phosphorus was found, and this was identified from its R_F value as *isopropoxy-methyl-hydroxy-phosphine oxide*, *i.e.* the same product as was formed in the spontaneous hydrolysis⁵.

For the detailed kinetic study of the decomposition only a slight excess of hydrogen peroxide was used. In this case the spontaneous hydrolysis of Sarin was obvious, and it was necessary to take it into consideration in the calculations. To get a conception of the magnitude of the rate constant k_3 , two separate calculations of the constant k_2 were made. In one case it was assumed that $k_3 \gg k_2$ and in the other that $k_3 \ll k_2$. The differential equations obtained

were evaluated by means of graphical integration analogously to the method described by Wideqvist¹⁴. The constant k_2 for the two cases was calculated after various times of reaction. For a value of k_3 between these extreme values, k_2 might increase with time when the calculations are based on the first assumption, and decrease when the calculations are based on the second one. It was, however, found that in both alternatives k_2 was increasing which indicates that Sarin reacts in an additional way to the one which was postulated before. A supplementary reaction such as the following is probable:



For the Reactions I—IV the following differential equations can be set up:

$$\frac{dc_{\text{PF}}}{dt} = -k_1 c_{\text{PF}} - k_2 c_{\text{PF}} c_{\text{HO}_2^-} - k_4 c_{\text{PF}} c_{\text{POO}^-} \quad (4)$$

$$\frac{dc_{\text{H}_2\text{O}_2}}{dt} = -k_2 c_{\text{PF}} c_{\text{HO}_2^-} - k_3 c_{\text{POO}^-} c_{\text{H}_2\text{O}_2} \quad (5)$$

$$\frac{dc_{\text{POO}^-}}{dt} = k_2 c_{\text{PF}} c_{\text{HO}_2^-} - k_3 c_{\text{POO}^-} c_{\text{H}_2\text{O}_2} - k_4 c_{\text{PF}} c_{\text{POO}^-} \quad (6)$$

The differential equations were treated by means of a recording electronic computer (Precision Analog Computing Equipment, Electronic Associates, Inc.). The known values of c_{PF}^0 , $c_{\text{H}_2\text{O}_2}^0$, $c_{\text{POO}^-}^0$, k_1 and k_2 were put into the equations and k_3 and k_4 were varied until the recorded curve of the function c_{PF} against t coincided with the experimental one. The best agreement was obtained when $k_3 = 3.0 \text{ l mole}^{-1} \text{ sec}^{-1}$ and $k_4 = 3.5 \text{ l mole}^{-1} \text{ sec}^{-1}$ as appears from Fig. 2. For comparison the curves obtained from some other values of the constants k_3 and k_4 are given in the same figure.

In Fig. 3 the functions c_{PF} , c_{POO^-} and $c_{\text{H}_2\text{O}_2}$ against t are given with the values of k_3 and k_4 found above. From the c_{POO^-} curve it is shown that the maximum concentration of "peroxyphosphorus acid" is reached after 900 sec. From the colorimetric determination the maximum concentration was found to be between 800 and 900 sec which agrees fairly well with the calculated value. From the $c_{\text{H}_2\text{O}_2}$ curve the amount of hydrogen peroxide consumed in the reaction after 7 000 sec was estimated as 1.30 moles per mole of Sarin. The corresponding value from the determinations of the concentrations of hydrogen peroxide at the start and at the end of the reaction (after 4 h) was found to be 1.42. It is possible that the discrepancy between the found

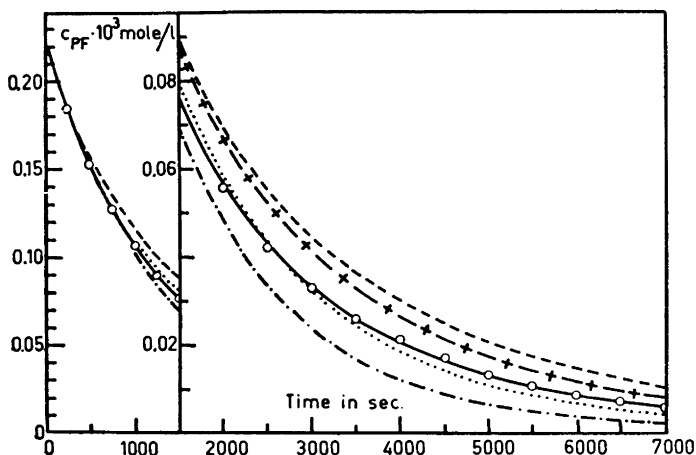


Fig. 2. The computed curves for the function c_{PF} against t at pH 8.50 and 25°C at various values of k_3 and k_4 .

$$k_1 = 0.106 \times 10^{-3} \text{ sec}^{-1}; k_2 = 1.34 \times 10^3 \text{ l mole}^{-1} \text{ sec}^{-1}$$

$k_3 \text{ l mole}^{-1} \text{ sec}^{-1}$	$k_4 \text{ l mole}^{-1} \text{ sec}^{-1}$	Designation
3.0	3.5	— — — — —
5.0	1.0	- - - - -
0.50	1.0
0.50	3.0	- . - . - .
1.0	0.10	- + - +

The experimental values are designed O.

and calculated consumption of hydrogen peroxide depends upon the spontaneous decomposition of hydrogen peroxide which has been neglected in the calculations.

In the determination of the rate constant, k_2 , the influence of Reaction IV is practically negligible, because in those experiments the concentration of hydrogen peroxide was so high that Reaction III predominated over Reaction IV.

From the experimental data obtained no conclusions concerning the mechanisms of Reaction III can be drawn. Reaction IV probably proceeds over a peroxyphosphorus formed by a nucleophilic attack of the peroxy acid on the phosphorus atom of the Sarin molecule. The hydrolysis of the intermediate is certainly very fast. There is a possibility that the intermediate is hydrolysed to one molecule "peroxyphosphorus acid" and one molecule "phosphorus acid" in contrast to what is stated in Reaction IV. However, the good agreement obtained between the experimental and calculated curves argues against the latter hypothesis and favours the process given in Reaction IV.

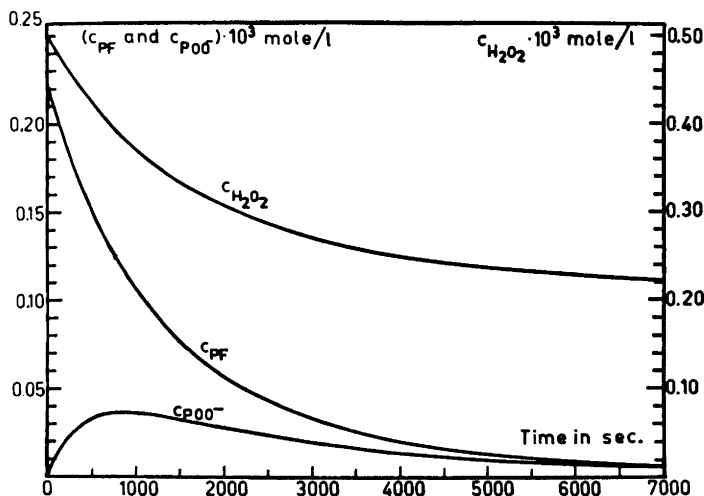


Fig. 3. The computed curves for the functions c_{PF} , c_{POO^-} and $c_{H_2O_2}$ against t at pH 8.50 and 25°C. $k_1 = 0.106 \times 10^{-3} \text{ sec}^{-1}$, $k_2 = 1.34 \times 10^3 \text{ l mole}^{-1} \text{ sec}^{-1}$, $k_3 = 3.0 \text{ l mole}^{-1} \text{ sec}^{-1}$ and $k_4 = 3.5 \text{ l mole}^{-1} \text{ sec}^{-1}$.

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