948. *Reactions of Esters of Phosphorothioic Acid. Part I. A Comparison of the Hydrolyses of Triethyl Phosphorotrithiolate and Triethyl Phosphate.*

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Measurements have been made of the rates of hydrolysis of triethyl phosphorotrithiolate and phosphate under acidic, neutral, and alkaline conditions. It has been shown, by isolation of ethanethiol, that such hydrolysis of the former compound involves fission of the P–S bond. Towards alkaline hydrolysis the thiolester is 1500 times more reactive than the oxygen ester, mainly owing to a difference in the Arrhenius frequency factors. In acid and in neutral solution the rates of hydrolysis for both esters are similar, and much smaller than in alkali. The theoretical implications of these results are discussed.

WHILST the rates of hydrolysis and positions of bond-fission have been determined for some triesters of orthophosphoric acid, such as trimethyl [1, 2, 3] and triphenyl phosphate,[2, 3] little work has been done on esters derived from thiols and orthophosphoric acid, *e.g.*, triethyl phosphorotrithiolate, $(EtS)_3PO$. The aim of this study has been to compare the hydrolysis of triethyl phosphorotrithiolate with that of triethyl phosphate, and to determine the position of bond-fission for the thiolester.

In the hydrolysis of trimethyl phosphate both possible positions of bond-fission have been observed;[2, 3] thus in alkaline hydrolysis the P–O bond is broken, whilst in neutral and acid hydrolysis C–O fission occurs. Carbon–oxygen bond-fission also occurs in trialkyl phosphates when these esters act as alkylating agents, *e.g.*, for phenols,[4] alcohols,[5] and

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[1] Blumenthal and Herbert, *Trans. Faraday Soc.*, 1945, **41**, 611.
[2] Barnard, Bunton, Llewellyn, Oldham, Silver, and Vernon, *Chem. and Ind.*, 1955, 760.
[3] Vernon, *Chem. Soc. Symposium*, Cambridge, 1957.
[4] Dutton and Noller, *J. Amer. Chem. Soc.*, 1933, **55**, 424.
[5] Toy, *ibid.*, 1944, **66**, 499.

amines.[6] The two possible positions of bond-fission would, in the hydrolysis of triethyl phosphorotrithiolate, yield different products: P–S fission would give ethanethiol and diethyl phosphorodithiolate; and C–S fission would give ethanol and diethyl phosphorodithiolothionate, $(EtS)_2PS{\cdot}OH$. The latter compound would be expected to hydrolyse further, giving hydrogen sulphide and diethyl phosphorodithiolate.[7]

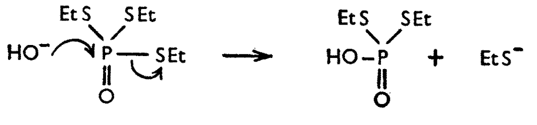
Triethyl phosphorotrithiolate had been prepared previously,[8, 9, 10] but no details of its acid- or alkali-catalysed hydrolysis were given. However, Hudson and Keay[11] have found that with di*iso*propyl methylphosphonodithiolate P–S fission occurs in both types of hydrolysis. In the present work an attempt to estimate ethanethiol, at points throughout the hydrolysis, by the iodometric method[12] used by Hudson and Keay, was unsuccessful; poor end-points, possibly owing to reaction between iodine and unchanged thiolester, were observed. The products of the reaction, from the nature of which the position of bond fission could be inferred, were therefore investigated by direct isolation.

Because of the insolubility of triethyl phosphorotrithiolate in water, alkali-catalysed hydrolysis of this ester and of triethyl phosphate was studied in 50% aqueous dioxan. Second-order rate-coefficients were constant in any one run; collected values are shown in Table 1.

Reaction of the thiolester is clearly of the second order, and therefore presumably bimolecular, since the rate-coefficient varies only slightly with concentration of hydroxide ion, and also because the solvolytic reaction is very slow at this temperature. The small decrease observed in k_2 as the concentration of hydroxide ion is increased would be expected[13] for a reaction between the hydroxide ion and a neutral molecule. It is not possible to decide from the kinetic results whether the hydrolysis involves a one-stage synchronous displacement, or a rapid reversible formation of a quinquecovalent intermediate. However, isotope studies[14] on the bimolecular solvolysis of diethyl phosphorochloridate show no evidence for the reversible formation of an intermediate. Since the hydrolysis proceeds by fission of the P–S bond it is suggested that the most likely formulation for the alkaline hydrolysis of the thiolester is:

TABLE 1. *Second-order rate-coefficients for the alkali-catalysed hydrolysis of* $(EtS)_3PO$ *and* $(EtO)_3PO$ *in 50% aqueous dioxan.*

Temp.	[KOH] (N)	[Ester] (M)	$10k_2$ (l. mole^{-1} min.$^{-1}$)	Temp.	[KOH] (N)	[Ester] (M)	$10k_2$ (l. mole^{-1} min.$^{-1}$)
		$(EtS)_3PO$				$(EtO)_3PO$	
0°	0·0615	0·0227	0·834	40·9°	0·0546	0·0326	0·0177
0	0·0612	0·0246	0·858	82·0	0·0703	0·0388	0·277
25	0·0644	0·0193	7·52				
25	0·1172	0·0233	7·18				
25	0·0748	0·0221	7·51				



This mechanism is analogous to that proposed for the alkaline hydrolysis of trimethyl phosphate in water.[2]

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[6] Thomas, Billman, and Davis, *J. Amer. Chem. Soc.*, 1946, **68**, 895.

[7] Pischchimuka, *J. Chim. Ukraine*, 1925, **1**, 87.

[8] *Idem, J. Russ. Phys. Chem. Soc.*, 1912, **44**, 1406.

[9] Lippert and Reid, *J. Amer. Chem. Soc.*, 1938, **60**, 2370.

[10] Chapman and Saunders, *J.*, 1948, 1010.

[11] Hudson and Keay, *J.*, 1956, 3269.

[12] Böhme and Schran, *Chem. Ber.*, 1949, **82**, 456.

[13] C. K. Ingold, " Structure and Mechanism in Organic Chemistry," Bell and Sons Ltd., London, 1953, p. 347.

[14] Dostrovsky and Halmann, *J.*, 1956, 1004.

For comparison the rate of alkaline hydrolysis of triethyl phosphate was measured in the same solvent. Although it was not shown rigorously that this hydrolysis is of the second order, it is considered to be so (*a*) because constant second-order coefficients are found in any one run, (*b*) because the neutral solvolytic rate is slow, and (*c*) from analogy with the alkaline hydrolysis of trimethyl phosphate.[2] The oxygen-ester was found to be less reactive than the thiolester; thus the calculated rate at 25° was 1500 times slower. The Arrhenius parameters, which are given in Table 2, show that this difference is due mainly to the lower Arrhenius frequency factor of the oxygen-ester. The activation energies are comparable, though even here the values indicate that the thiolester is the more reactive. It is usually considered that the frequency factor is, in transition-state theory, a measure of the entropy of activation. Therefore the lower entropy of activation of the oxygen-ester suggests that in this compound a more rigid transition state is formed.

TABLE 2. *The Arrhenius parameters for the alkaline hydrolysis of* $(EtS)_3PO$ *and* $(EtO)_3PO$ *in* 50% *aqueous dioxan.*

	E (kcal. mole^{-1})	log *PZ* (l. mole^{-1} min.$^{-1}$)
$(EtS)_3PO$	14·1	10·2
$(EtO)_3PO$	14·9	7·6

Hudson and Keay[11] observed that in the alkaline hydrolyses of di*iso*propyl methylphosphonodithiolate and methylphosphonate the thiolester had, first, a lower activation energy (11·4 compared with 14·9 kcal. mole^{-1}) and, secondly, a higher Arrhenius frequency factor (log *PZ* 7·3 compared with 5·4). These workers attributed the increase in the frequency factor to the greater covalent radius of sulphur than of oxygen. Thus the *iso*propyl group was removed further from the reaction site in the thiolester, and caused less strain in the formation of the transition state. Similar considerations also apply to triethyl phosphorotrithiolate. Schaefgen,[15] and Rylander and Tarbell[16] pointed out an additional factor influencing the entropy of activation in the alkaline hydrolysis of ethyl thiolacetate and of ethyl acetate, suggesting that the oxygen-ester is hydrated, by hydrogen bonding, to a greater extent than is the thiolester, and that the consequent steric hindrance would cause the oxygen-ester to have a lower entropy of activation. It seems possible that this argument is also relevant to the phosphoric esters, for it has been noticed that, whilst triethyl phosphate is completely miscible with water, triethyl phosphorotrithiolate is only slightly soluble; rough experiments suggest a figure less than 0·2% at 25°. This difference in solubility is attributed to hydration, through hydrogen bonding, of the oxygen-ester.

Acid-catalysed hydrolysis of these two esters was studied in 60% aqueous dioxan, because the Hammett acidity function, H_0, has been measured in this solvent.[17] The medium was made up from 60% aqueous dioxan and 60% perchloric acid, further dioxan being added so as to keep the water : dioxan ratio constant. The first-order rate-coefficients for the neutral solvolysis, and for the acid-catalysed hydrolysis, of the two esters are shown in Table 3. The hydrolysis of the thiolester, which proceeds by fission of the P–S bond, shows acid-catalysis clearly, and over a limited range the rate is proportional to stoicheiometric acidity, and not to the H_0 function. There is, on the contrary, a tendency at higher acidities for the increase in rate to be less that that required by a linear relation. On the basis of the Hammett–Zucker hypothesis[18] this means that the rate-determining step involves a water molecule. Consequently, the mechanism of this hydrolysis is considered to be nucleophilic attack by water on the phosphorus atom of the protonated ester, $(EtS)_3$, $P{=}\overset{+}{O}H$. The rate of the reaction was not altered on the addition of sodium perchlorate, although a small decrease[13] might have been forecast for this type

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[15] Schaefgen, *J. Amer. Chem. Soc.*, 1948, **70**, 1308.
[16] Rylander and Tarbell, *ibid.*, 1950, **72**, 3021.
[17] Bunton, Ley, Rhind-Tutt, and Vernon, *J.*, 1957, 2327.
[18] L. P. Hammett, " Physical Organic Chemistry," McGraw Hill Book Co., New York, 1940, p. 276.

of reaction. The cause of the non-linearity of the rate with stoicheiometric acidity at the higher acid concentrations is not known. It is of interest that this phenomenon has been observed in the acid-catalysed hydrolysis of other phosphoric esters.[3] It seems unlikely that it is due to approach towards complete protonation of the ester, and it has been suggested [3] that it is due to a decrease in the activity of water, in mixed-solvent systems at high acid concentrations.

TABLE 3. *First-order rate-coefficients for the neutral solvolysis and the acid-catalysed hydrolysis of* $(EtS)_3PO$ *and* $(EtO)_3PO$ *in* 60% *aqueous dioxan at* 82°.

$[HClO_4]$ (N)	$[NaClO_4]$ (N)	10^5k_1 (min.$^{-1}$)	$[HClO_4]$ (N)	$[NaClO_4]$ (N)	10^5k_1 (min.$^{-1}$)
	$(EtS)_3PO$			$(EtO)_3PO$	
0	0	0·25	0	0	0·53
0	0·515	1·16	0	0·27	0·60
0·049	0	2·0	0·27	0	2·52
0·27	0	7·13	Solvolysis in water at 82°		9·50
0·27	0·26	7·15			
0·385	0	8·16			
0·938	0	15·1			
1·436	0	21·9			

An acid-catalysed hydrolysis was found also for triethyl phosphate in 60% aqueous dioxan; and, in contrast to the case of alkaline hydrolysis, the rate was not significantly different from that of the thiolester. However, no valid comparison can be made here, because the position of bond-fission is not known: analogy with trimethyl phosphate [2] suggests C–O fission. Presumably the reactive conjugate acid of the thiolester has a proton attached to the phosphoryl-oxygen atom, nucleophilic attack on phosphorus being thereby made easier. This mechanism leads to P–S fission. In the oxygen-ester, on the other hand, C–O fission being assumed, the reactive conjugate acid must contain a proton attached to an ether-oxygen atom. The near-identity of the rates of the two processes is clearly fortuitous.

It is of interest that, whereas triethyl phosphate shows acid-catalysed hydrolysis in 60% aqueous dioxan, in water the hydrolysis of trimethyl phosphate is independent of acid concentration.[2] Presumably this is because the neutral solvolysis rate is strongly solvent-dependent, and in water the rate is sufficiently great to mask acid-catalysis. Thus, at 82°, for triethyl phosphate, neutral solvolysis in water is four times faster than acid-catalysed (0·27N-$HClO_4$) solvolysis in 60% aqueous dioxan, and 20 times faster than neutral solvolysis in this solvent. Consistently, the neutral rates of both esters, in 60% aqueous dioxan, are accelerated by addition of sodium perchlorate; the increase for the oxygen-ester is, however, smaller than might be expected.

The bond energies, quoted by Hudson and Keay [11] (P–S, 45—50 kcal. mole^{-1}; P–O, 95—100 kcal. mole^{-1}), suggest that the P–S would be more readily broken than the P–O bond. Although this is in accordance with the results now presented for the alkaline hydrolysis, yet if bond energies were of major importance in determining the relative rates of hydrolysis a greater difference in the activation energies might be expected for these two esters.

EXPERIMENTAL

Triethyl Phosphorotrithiolate.—Phosphoryl chloride (13 ml.; freshly distilled) was added dropwise with stirring to an ice-cold solution of ethanethiol (37·6 g.) and triethylamine (61·2 g.) in dry ether (200 ml.). On completion of the addition, the mixture was boiled under reflux for 2 hr. Triethylamine hydrochloride was filtered off and washed with ether. The combined ethereal filtrates were evaporated under reduced pressure, and the residual oil was distilled, yielding the ester (81%), b. p. 85—89°/0·2 mm., n_D^{25} 1·5764. This material contained an impurity which was hydrolysed, in alkali, much faster than the pure thiolester and was shown not to be diethyl phosphorodithiolochloridate.

The crude ester (27 g.) was dissolved in a mixture of dioxan (140 ml.) and water (60 ml.) containing potassium hydroxide (0·1 g.). After storage overnight, dioxan and water were removed under reduced pressure, and the residue was dissolved in ether (50 ml.), washed with water, and dried ($CaSO_4$). After removal of ether, distillation afforded the pure ester, b. p. 89°/0·2 mm., n_D^{25} 1·5676 (Found: C, 31·3; H, 6·5; S, 41·9; P, 13·7. Calc. for $C_6H_{15}OS_3P$: C, 31·3; H, 6·5; S, 41·7; P, 13·5%).

Triethyl phosphate was prepared from sodium ethoxide and phosphoryl chloride;[19] the fraction with the following properties was collected: b. p. 97—98°/15 mm., n_D^{25} 1·4036.

Kinetic Experiments.—Purified dioxan[20] was used; the term " x% aqueous dioxan " refers to a solvent prepared by mixing x volumes of purified dioxan with $(100 - x)$ volumes of distilled water.

Alkaline Hydrolysis.—Hydrolysis of the thiolester in 50% aqueous dioxan, in the presence of potassium hydroxide, was followed by acid–base titration. Since ethanethiol is relatively acidic, the stoicheiometric equation for the hydrolysis is:

$$(EtS)_3PO + 2OH^- \longrightarrow (EtS)_2PO{\cdot}O^- + EtS^- + H_2O$$

and the appropriate integrated rate equation is:

$$k_2 = \frac{2{\cdot}303}{t(b - 2a)} \cdot \log_{10} \frac{a(b - 2x)}{b(a - x)}$$

where a is the initial molarity of the thiolester, b is the initial molarity of the hydroxide ion, and x is the amount of the thiolester, expressed as a molarity, hydrolysed after time, t.

For hydrolysis of triethyl phosphate, the rate equation is:

$$k_2 = \frac{2{\cdot}303}{t(b - a)} \log_{10} \frac{a(b - x)}{b(a - x)}$$

corresponding to the stoicheiometric equation:

$$(EtO)_3PO + OH^- \longrightarrow (EtO)_2PO{\cdot}O^- + EtOH$$

About 1·5 g. of the ester were accurately weighed in a 250 ml. graduated flask which was then brought to thermal equilibrium in a thermostat. To it was added a solution of potassium hydroxide (*ca.* 0·05N) in 50% aqueous dioxan, which had been brought to the same temperature. Aliquot parts (10 ml.) were withdrawn at intervals and diluted with water, and excess of alkali was titrated against 0·02N-hydrochloric acid (phenolphthalein). It was shown that ethanethiol did not interfere with this titration. Calculated and experimental infinity values agreed well.

The following results for the hydrolysis of 0·01934M-triethyl phosphorotrithiolate in 50% aqueous dioxan containing potassium hydroxide (0·0644N) at 25° are typical:

Time (min.)	0	3·4	10·3	14·2	18·9	24·2	29·5	38·5	58·4	∞
Titre (0·02N-HCl)	32·22	30·80	28·70	27·88	27·18	26·49	25·80	25·07	24·24	22·55
$10k_2$ (l. mole^{-1} min.$^{-1}$)		7·59	7·77	7·61	7·43	7·37	7·67	7·66	7·07	

The initial reading was taken 2 min. after mixing.

Acid-catalysed Hydrolysis.—Since it was noticed that in acid and neutral solutions the rates of hydrolysis were increased by oxygen, all the kinetic runs under these conditions were done under oxygen-free nitrogen. Standard solutions of the esters were prepared in 60% aqueous dioxan–perchloric acid mixtures, which had previously been freed from oxygen by boiling under reflux in a stream of oxygen-free nitrogen. Equal volumes of the ester solution were dispensed from an automatic pipette into " Monax " tubes, the air was displaced by

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[19] Evans, Davies, and Jones, *J.*, 1930, 1310.

[20] A. I. Vogel, " A Textbook of Practical Organic Chemistry," Longmans, Green and Co., London, 1948, p. 175.

oxygen-free nitrogen, and the tubes were sealed. After appropriate intervals in the thermostat, tubes were removed, washed with distilled water, and smashed under distilled water. The perchloric acid was neutralised by the addition, from an automatic pipette, of potassium hydroxide solution of such a strength as to be almost exactly equivalent to the initial concentration of perchloric acid. Excess of acid, produced by hydrolysis, was then estimated by titration with *ca.* 0·02N-potassium hydroxide to phenolphthalein. Infinity values were calculated from the weight of the ester taken. The following data for the hydrolysis, at 82°, of triethyl phosphorotrithiolate (1·0622 g./100 ml.) in 60% aqueous dioxan containing perchloric acid (0·938N) are typical. The sealed tubes contained 5·26 ml. of the acid solution; after they had been broken under distilled water, 0·875N-potassium hydroxide (5·52 ml.) was added, and the residual acid was titrated against 0·0182N-potassium hydroxide.

Time (hr.)	0	18·42	25·17	42·42	49·92	66·42	73·92	∞
Titre (ml.)	8·45	10·40	11·18	12·30	13·40	14·70	15·35	21·80
10^4k_1 (min.$^{-1}$)		1·43	1·51	1·34	1·55	1·59	1·65	

Products of Hydrolysis of Triethyl Phosphorotrithiolate.—The ester (0·11 g.) was dissolved in oxygen-free 60% aqueous dioxan (5 ml.), containing perchloric acid (1·2N), sealed in a "Monax" tube under oxygen-free nitrogen, and heated at 82° for 4 days. After being cooled to 0° the tube was opened, and the contents transferred to a small two-necked flask fitted with a reflux condenser, the top of which was connected to a trap containing 5% mercuric cyanide solution (3 ml.). A slow stream of nitrogen was passed through the acid solution, which was then heated to the b. p. The mercuric salt of ethanethiol was precipitated in the trap in nearly quantitative yield; the solid was completely soluble in hot ethanol from which it readily crystallised (m. p. and mixed m. p. 78°). No mercuric sulphide was formed, even on prolonged boiling. A similar result was obtained on alkaline hydrolysis of the ester (0·11 g.), at 25° for 24 hr., in 50% aqueous dioxan (5 ml.) containing potassium hydroxide (0·1N). Since the solvolysis of the thiolester in 60% aqueous dioxan is slow, a tube from a kinetic run, which had been kept at 82° for five weeks, was treated with acid, as above. The yield of the mercuric salt of ethanethiol was low (10%), but corresponded fairly well with the extent of hydrolysis. No mercuric sulphide was produced.

cyclo*Hexylamine Diethyl Phosphorodithiolate.*—Triethyl phosphorotrithiolate (2 g.) was added to 60% aqueous dioxan (40 ml.) containing sodium hydroxide (1 g.). The emulsion was shaken for 12 hr. at room temperature, after which the solution was clear. The water and dioxan were removed by distillation under reduced pressure, the solid residue was dissolved in water (20 ml.), and unchanged ester removed by washing the aqueous solution with ether (10 ml.). Sodium ions were removed on a column of ion-exchange resin, IR-120, in its hydrogen form. The acid eluate was neutralised with *cyclo*hexylamine, and reduced to small volume. The cyclo*hexylamine salt* crystallised readily as fine needles (1·6 g.), m. p. 182—183°, unchanged on recrystallisation from water (Found: C, 41·8; H, 8·5; N, 4·9; P, 10·9; S, 22·2. $C_{10}H_{24}O_2NS_2P$ requires C, 42·1; H, 8·4; N, 4·9; P, 10·9; S, 22·4%).

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