Solvolysis of Methyl *OS*-Ethylene Phosphorothioate

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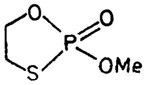
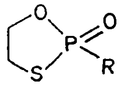
Rate and product studies of the aqueous hydrolysis of methyl *OS*-ethylene phosphorothioate are reported. The rate dependence is similar to that previously reported for methyl ethylene phosphate but no exocyclic P–O cleavage is observed throughout the pH range 0—14. Solvolysis in neutral or alkaline solution results in almost exclusive P–S cleavage but endocyclic P–O cleavage increases with increasing acidity and predominates below pH 1·5. These results are shown to be consistent with the intervention of pentacovalent intermediates but the interpretation of the alkaline region is different from that proposed for methyl ethylene phosphate. It is suggested that pentacovalent intermediates are not involved in nucleophilic displacements on *OS*-diester anions of phosphorothioic acid.

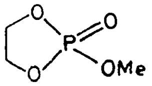
In an earlier communication [1] we reported that methyl *OS*-ethylene phosphorothioate (I) underwent base solvolysis with almost exclusive P–S cleavage and that this contrasted with the behaviour of *OS*-ethylene phosphorothioate anion (IIa) and, probably, the phosphonate analogue (IIb) also although this latter had only been postulated as intermediate.[2] Since methyl ethylene phosphate (III) has been the subject of a detailed rate and product study [3] and that recently anomalous stereochemical results have been reported for the nucleophilic displacement of thiols from mixed *OS*-esters of phosphorus acids [4,5] we undertook a comparable study on (I).



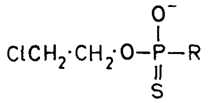
(I)



(II) a;R = O⁻
b;R = Ph



(III)



$ClCH_2{\cdot}CH_2{\cdot}O{-}\overset{O^-}{\underset{S}{P}}{-}R$ (IV) a;R = OMe b;R = Ph

The ester (I) was prepared by oxidation of methyl *OS*-ethylene phosphorothioite [6] with N_2O_4 but owing to difficulty in preparing *OS*-ethylene phenylphosphonothioite * this procedure could not be used to obtain (IIb). We found however that the solvolysis of the anion of *O*-2-chloroethyl methyl phosphorothioic acid (IVa) underwent solvolysis in water at a rate independent of pH in the range pH 8·0—10·5 and gave the same products as did (I) under these conditions. It was therefore anticipated that 2-chloroethyl phenylphosphonothioate anion (IVb) would behave similarly and we used this procedure for generating (IIb) *in situ*. Since the initial cyclisation is slower than the breakdown this procedure unfortunately cannot be used for rate measurements on (IIb) nor for product studies over a wide range of pH.

RESULTS

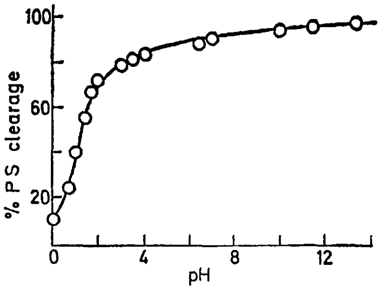
The solvolysis of (I) in aqueous solution at 25·0° (μ = 0·100) was followed titrimetrically using a pH-stat. In the range pH 2·5—7·0 the reaction was first order in substrate with a base consumption of 1·00 ± 0·05 mol/mol (I) but above pH 7 subsequent reaction of the primary solvolysis product rendered rate measurements impossible. First-order rate constants are given in the Table.

Solvolysis rates at 25·0° (= 0·100) ± 4%

pH (±0·02)	$10^4k/s^{-1}$	pH	$10^4k/s^{-1}$
2·50	18	5·50	2·3
3·00	5·5	6·50	6·0
3·50	2·2	7·00	20
4·00	0·95	6·00[a]	5·1
5·00	0·57	6·00[b]	7·7

[a] 0·050M-NaOAc. [b] 0·100M-NaOAc.

No significant amount of methanol was detected (g.l.c.) in the solvolysis mixture at any pH. 2-Mercaptoethyl methyl phosphate was determined by reaction with iodine under conditions where *S*-2-hydroxyethyl methyl phosphorothioate and (IIa) did not react with the reagent. *S*-2-Hydroxyethyl phosphorothioate dianion is oxidised by iodine [7] but the absence of methanol in the solvolysis mixture indicates that this cannot be formed in significant amounts. Above pH 7 2-mercaptoethyl methyl phosphate eliminated ethylene sulphide (which could not be estimated owing to ready polymerisation under the conditions of the reaction) and methyl phosphate dianion which was estimated from paper chromatograms.[8] The results are shown in the Figure. Although in the reaction mixtures conducted in alkaline solution small amounts *ca.* 5% of other phosphorus-containing products were observed they did not include



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* Professor S. Trippett has since informed us of a successful preparation of this very labile ester.

[1] D. C. Gay and N. K. Hamer, *Chem. Comm.*, 1970, 1564.

[2] D. C. Gay and N. K. Hamer, *J. Chem. Soc. (B)*, 1970, 1123.

[3] R. Kluger, F. Covitz, E. Dennis, and F. H. Westheimer, *J. Amer. Chem. Soc.*, 1969, **91**, 6066.

[4] L. P. Rieff, L. J. Szafraniec, and H. S. Aaron, *Chem. Comm.*, 1971, 366.

[5] N. J. De'ath, K. Ellis, D. J. H. Smith, and S. Trippett, *Chem. Comm.*, 1971, 714.

[6] L. S. Kovalev, N. A. Razumova, A. A. Petrov, *Zhur. obshchei Khim.*, 1969, **39**, 869.

[7] A. F. Cook, M. J. Holmann, and A. L. Nussbaum, *J. Amer. Chem. Soc.*, 1969, **91**, 6479.

[8] D. A. Usher, *J. Chromatog.*, 1963, **12**, 262.

(IIa) or *S*-2-hydroxyethyl methyl phosphorothioate anion and may have arisen from traces of polymer in (I) or by bimolecular reaction of the thiolate anion competing with the relatively slow intramolecular elimination reaction. These by-products were not observed in the solvolysis of (IVa) which gave 100% methyl phosphate dianion and ethylene sulphide (40% monomer isolated). Solvolysis of (IVb) under the same conditions gave *S*-2-hydroxyethyl phenylphosphonothioate [2] exclusively.

DISCUSSION

In the pH range 2·5—7·0 the observed first-order rate constants give a good fit to an equation of type (1)

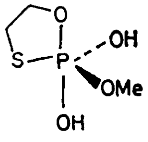
$$k_{obs} = k_{H^+}[H^+] + k_0 + k_{OH}[OH]^- \qquad (1)$$

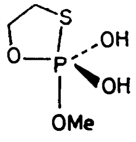
with $k_{H^+} = 0{\cdot}53$ l mol^{-1} s^{-1}, k_0 $3{\cdot}2 \times 10^{-5}$ s^{-1} and $k_{OH} = 2 \times 10^4$ l mol^{-1} s^{-1}. Not only does this rate dependence parallel that found for the aqueous solvolysis of (III) [3] but the actual values of k_{H^+} and k_0 are remarkably similar. The hydroxide rate constant is much larger for (I) than for (III) but this not untypical for alkaline solvolysis rates of *OOS*-triesters of phosphorothioic acid compared with similar trialkyl phosphates.[9] Owing to the very large rate constant for the alkaline hydrolysis and difficulties caused by buffering it was not possible to examine the effect of a series of bases on the rate of solvolysis nevertheless the rate enhancement produced by acetate ion (k_{cat} $5{\cdot}4 \times 10^{-3}$ l mol^{-1} s^{-1}) parallels its effect on the solvolysis of (III) and is doubtless general base catalysis.[10] On present evidence therefore it seems clear that, in the pH range studied, the rate-determining step in the solvolysis of both (I) and (III) is the same and represents the rate of attack of the nucleophile on phosphorus. [A detailed kinetic analysis has been given in the case of the solvolysis of (III) [3] but in view of uncertainty in the values of many of the rate and equilibrium constants we shall not attempt to apply it to the present rather more complex system.]

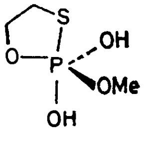
The product distribution profile is much simpler than that found for (III) and differs also in that it does not appear possible to assign consistent values to the relative amounts of P–O and P–S cleavage for individual terms in the rate expression. This latter is quite reasonable if the solvolysis involves intermediates whose breakdown determines the product distribution but whose formation is rate determining. Of significance also is the complete absence of exocyclic ring-cleavage resulting in loss of methanol over the entire pH range.

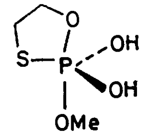
It is convenient to consider the product profile in terms of general scheme adopted for (III) making the usual assumption as to the positions of entering and leaving groups [11] and the preferred conformations of the various pentacovalent intermediates [12] (the actual details of the pseudorotation mechanism [13] are unimportant at this level). Further we shall assume that initial attack gives an intermediate with cyclic oxygen apical. This last seems to be necessary to account for the base-solvolysis products of *OS*-ethylene phosphate (IIa), the phosphonothioate (IIb) [2] and, probably, for recent stereochemical observations on mixed *OS*-esters of phosphorus acids.[4,5] Four conformations ($JH_2 \cdots MH_2$) need to be considered along with their mono-anions and dianions. From our initial assumptions we should expect attack of the nucleophile on (I) to lead initially to a J-type conformation.

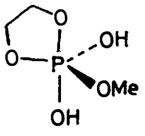
On the above basis the large increase in endocyclic P–O cleavage in strongly acidic solution {which, as with (III) obeys a relation of the form $f = a/(1 + b[H^+])$ where f is the fraction of P–S cleavage with $a = 0{\cdot}64$, $b = 6{\cdot}1$}, coupled with absence of appreciable exocyclic P–O cleavage implies that, in this region, acid-catalysed opening of JH_2 overtakes the rate of pseudorotation to KH_2 or LH_2. Similarly the monotonic increase in P–S cleavage which predominates at pH 1·4 becoming almost exclusive above pH 7·0 implies that the neutral JH_2 and JH^- undergo at least one pseudorotation at a rate which is comparable with or faster than breakdown. Owing to uncertainty as to the values of various pK_a values of JH_2 *etc.* [estimated as *ca.* 9 and *ca.* 13 for (V)] there exists doubt as to relative amounts of the various species over the pH range and it is possible that the dianionic species are not important below pH 14·0. Pseudorotation of JH_2 is expected from other work to be facile and, since JH^- may transform to KH^- or LH^- by a single pseudorotation about O^- as pivot, it seems reasonable for this to occur more readily than P–O cleavage of JH^-. However the solvolysis products (III) in pH range 7—13 were interpreted on the assumption that opening of the monoanion of (V) proceeded faster than pseudorotation and there seems at present no simple convincing explanation for the difference in behaviour between this case and the one under study here—particularly in view of our premise that, other factors

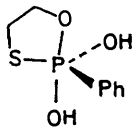

JH_2


KH_2


LH_2


MH_2


(V)


(VI) a; R = Et
b; R = H

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[10] S. A. Khan and A. J. Kirby, *J. Chem. Soc.* (*B*), 1970, 1172.

[11] F. H. Westheimer, *Accounts Chem. Res.*, 1968, **1**, 70.

[12] D. S. Frank and D. A. Usher, *J. Amer. Chem. Soc.*, 1967, **89**, 6360.

[13] P. Gillespie, P. Hofmann, H. Klusacek, D. Marquarding, S. Pfohl, F. Ramirez, E. A. Tsolis, and I. Ugi, *Angew. Chem. Internat. Edn.*, 1971, **10**, 687.

being approximately equal, the pentacovalent intermediates prefer to keep the cyclic oxygen apical.

Although we cannot assess the importance of dianionic species (J^{2-} *etc.*) in determining the solvolysis products it is quite possible that they contribute significantly in the strongly alkaline region. Using the argument advanced by Westheimer and his co-workers in their study of (III) in this region pseudorotation of J^{2-} to K^{2-} followed by P–S cleavage is reasonable. It is certain however that, whether the solvolysis proceeds *via* mono- or di-anion intermediates, these are different from those involved in the solvolysis of *S*-2-hydroxyethyl methyl phosphorothioate or the opening of (IIa) with methoxide[2] under the same conditions which result in P–O cleavage. Although the dianion M^{2-} is unlikely to undergo pseudorotation prior to breakdown (since this would involve placing O^- apical) our present results indicate that this need not be so for the monoanion MH^-. Hence we suggest that pentacovalent intermediates are not involved in the base solvolysis of *S*-2-hydroxethyl methyl phosphorothioate anion or (IIa) but that these follow a concerted $S_N2(P)$ pathway. This conclusion is in complete accord with all available data on nucleophilic displacements on phosphate diester anions.[14,15]

The solvolysis of the cyclic phosphonothioate (IIb) does, in all probability, involve a pentacovalent intermediate and this should resemble that formed in the solvolysis of ethyl *S*-2-hydroxyethyl phenylphosphorothioate [2] under similar conditions. Since the latter was found to undergo pseudorotation at a rate comparable with expulsion of ethoxide it is at first sight somewhat anomalous that no P–S cleavage was observed at pH 8·0 from (IIb). There is no real conflict here since in the case of (VIa) the endocyclic P–O cleavage is reversible under the conditions of solvolysis whereas this is not so for (VIb). Provided therefore that the endocyclic P–O cleavage is much faster than either pseudorotation or exocyclic P–O cleavage this result is quite consistent with our others.

It is clear from the above that there is a close parallel between the solvolytic mechanism of (I) and (III) both in the rate-determining step and in that the product distribution can be rationalised in terms of pentacovalent intermediates. What is less clear is the apparent conflicting interpretation of their behaviour in the pH range above 7·0 but since this region requires a detailed knowledge of pK_a values and rates of pseudorotation which are, at present, unavailable, it does not seem profitable to discuss this at length here. Finally we point out that there is still no adequate explanation for the contrasting behaviour of (IIa) and (IIb) relative to acyclic analogues.

EXPERIMENTAL

Solvents and reagents were purified according to published procedures. Inorganic reagents were AnalaR grade.

^1H N.m.r. spectra were measured on a Varian HA 100 spectrometer.

Paper chromatograms were run on Whatman No. 7 paper in isopropyl alcohol–ammonia (*d* 0·880)–water (7 : 1 : 2) and phosphorus-containing spots estimated by the method of Usher.

Methyl OS-*Ethylene Phosphorothioate*.—To a solution of methyl *OS*-ethylene phosphorothioite (1·3 g) in dichloromethane (10 ml) at −70° was added, dropwise with stirring, a solution of nitrogen dioxide (1·4 g) in dichloromethane (10 ml) until the red colour which first appeared changed suddenly to a blue-green. The oxides of nitrogen and solvent were removed *in vacuo* at room temperature and the residue was distilled to give the product (1·0 g), b.p. 72—73°/0·01 mmHg (Found: C, 23·2; H, 4·6; P, 20·2. $C_3H_7O_3PS$ requires C, 23·4; H, 4·6; P, 20·1%); τ (C_6D_6) 7·3 (2H, m), 6·6 (3H, d, *J* 13 Hz), and 6·2 (2H, m).

Sodium 2-Chloroethyl Methyl Phosphorothioate.—To a vigorously stirred solution of sodium hydroxide (9·0 g) in aqueous dioxan was added dropwise during 30 min 2-chloroethyl methyl phosphorochloridothioate (from methyl phosphorodichloridothioate, 2-chloroethanol, and 2,4,6-collidine in ether solution; the crude material had b.p. 49—51°/0·15 mmHg and was used without further purification) (2·2 g) dissolved in dioxan (5 ml). After stirring 2 h at room temperature the mixture was neutralised (dil. HCl) and evaporated to dryness *in vacuo* at room temperature. The residue was extracted with ethanol (2 × 25 ml) and the extracts concentrated to give a pale yellow gum which was taken up in chloroform. After filtration an equal volume of ether was added and when set aside at −30° the product (1·3 g), m.p. 104—105·5°, crystallised (Found: C, 15·4; H, 4·2; P, 13·8; Cl, 15·4. $C_3H_7ClNaO_3PS,H_2O$ requires C, 15·7; H, 3·9; P, 13·4; Cl, 15·4%), τ (D_2O) 6·5 (3H, d, *J* 13 Hz), 6·3 (2H, t, *J* 5 Hz), and 5·9 (2H, m).

Lead O-*2-Chloroethyl Phenylphosphonothioate*.—Hydrolysis of *O*-2-chloroethyl phenylphosphonothioate [16] (2·6 g) by the above procedure gave the sodium salt as a gum (2·5 g) which although pure on the basis of paper chromatograms and ^1H n.m.r. could not be crystallised. To a solution of this (2·5 g) in water (20 ml) was added lead nitrate (2·2 g) in water (25 ml) whereupon the crude product precipitated. After extraction into warm acetone followed by evaporation there was obtained the crystalline product (3·9 g) (Found: C, 27·1; H, 2·8. $C_8H_9ClO_2PPb_{\frac{1}{2}}S,H_2O$ requires C, 26·9; H, 3·1%). The solution of the Na salt in D_2O had τ 2·0—2·7 (5H, m), 6·0 (2H, m), and 6·4 (2H, t, *J* 6 Hz).

Lithium S-*2-Hydroxyethyl Methyl Phosphorothioate*.—A solution of sodium *S*-2-hydroxyethyl methyl phosphorothioate was prepared from disodium methyl phosphorothioate (1·7 g) by the procedure reported for the corresponding ethyl ester [2] and passed through a column (20 × 2 cm) of Amberlite IR 120; (Li^+ form). The eluate and washings were evaporated to dryness, and the residue was taken up in ethanol; after concentration dry acetone was added to it. The crystalline product (1·2 g) had m.p. 182—184° (Found: C, 20·5; H, 4·1; P, 17·4. $C_3H_8LiO_4PS$ requires C, 20·3; H, 4·0; P, 17·5%), τ (D_2O) 7·18 (2H, d of t, *J* 14 Hz, *J* 6·5 Hz), 6·44 (3H, d, *J* 12 Hz), and 6·28 (2H, t, *J* 6·5 Hz).

Rate Measurements.—To a thermostatted solution of potassium chloride (0·100M) under N_2 the ester (I) (*ca.* 0·5 mmol) was added from a 50 µl Hamilton syringe; the pH was maintained at a predetermined value (±0·02) by the

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[14] A. J. Kirby and M. Younas, *J. Chem. Soc.* (*B*), 1970, 1165.

[15] S. J. Benkovic and E. J. Sampson, *J. Amer. Chem. Soc.*, 1971, **93**, 4009.

[16] U.S.P. 3,342,583 (*Chem. Abs.*, 1968, **69**, 53,371).

addition of sodium hydrogen carbonate (0·200M) by means of an automatic titrator (Radiometer TTT11). Reactions were followed to 80% completion and good first-order plots were obtained.

Product Studies.—Solvolyses were carried out in O_2-free water with a concentration of substrate *ca.* 5×10^{-3}M. Reactions in the pH range 2—7 were conducted on a pH stat. and at the ends of the pH scale in hydrochloric acid or sodium hydroxide of appropriate strength the mixture being quenched after an appropriate time to prevent decomposition of the product.

(a) *Methanol Determination.*—A portion (5 ml) of the solvolysis mixture containing butanol (0·01%) was distilled at 10 mmHg (to remove sodium salts) and the distillate was collected in a trap cooled to −70°. (Using standard mixtures it was shown that this did not affect the composition significantly.) The distillate was then examined on an F11 gas liquid chromatogram with flame ionisation detector on a column (8 ft × 0·25 in) of 10% sorbitol–silicone oil on Chromosorb W (60—80 mesh) at 80°.

No trace of methanol was found in any of the solvolysis mixtures although the method would have readily detected <5 mol % of methanol.

(b) 2-*Mercaptoethyl Methyl Phosphate Determination* (Reactions Conducted at pH <7·0 under N_2).—The reaction mixture from the solvolysis was cooled to 0°, brought to pH *ca.* 5, and then sodium acetate (0·5 g) and potassium iodide (1·0 g) was added. The mixture was titrated rapidly at 0° against standard aqueous iodine (0·02M) with starch as indicator. It was demonstrated that this procedure was stoicheiometric (±3%) for 2-mercaptoethanol and that sodium *S*-2-hydroxyethyl methyl phosphorothioate did not react. Results agreed with those obtained by reaction with an excess of iodine at 0° for 15 s followed by titration of the excess of reagent with standard thiosulphate.

(c) *Methyl Phosphate Determination* (*Reaction Conducted at pH* >7·0).—The reaction mixture was brought to pH *ca.* 10 and was then set aside for 2—3 h to complete the decomposition of 2-mercaptoethyl methyl phosphate; after this time the polymeric ethylene sulphide was filtered off. The ^{1}H n.m.r. spectrum in D_2O of the solid obtained by evaporation of the filtrate showed only the lines expected of methyl phosphate dianion. Paper chromatography showed that in addition to disodium methyl phosphate R_F 0·12 traces of two other phosphorus-containing products were present R_F 0·44, 0·61, whereas authentic samples of sodium *OS*-ethylene phosphorothioate and sodium *S*-2-hydroxyethyl methyl phosphorothioate had R_F 0·70 and 0·52 respectively. Estimation of the ratio of the phosphorus in the slower spot to the two faster ones combined showed that it comprised 95% of the total.

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