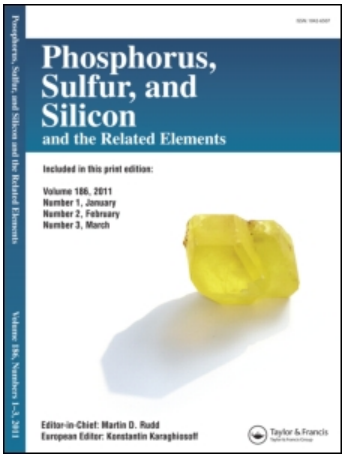

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OXIDATIVELY-INDUCED FORMATION OF DIALKYL HYDROGENPHOSPHONATES FROM PHOSPHOROTHIONATES

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Communication

OXIDATIVELY-INDUCED FORMATION OF DIALKYL HYDROGENPHOSPHONATES FROM PHOSPHOROTHIONATES

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Peracid oxidation of triester and related phosphorothionates and diester phosphorothioic acids with excess magnesium monoperoxyphthalate in water gives, among other products, dialkyl hydrogenphosphonates in yields of up to 70%. Hydrogenphosphonate formation is facilitated by the presence of a good leaving group in the starting material.

Key words: peracid oxidation; pesticide; phosphite; hydrogenphosphonate; phosphorothionate.

Each of more than 60 important commercial phosphorothionate insecticides is bioactivated by cytochrome P-450-mediated oxidation to a potent phosphorylating agent for acetylcholinesterase.[1,2] These biological oxidations also lead to cleavage of phosphorus-sulfur bonds resulting in a great variety of metabolites and environmental degradation products.[1] In model studies, *m*-chloroperoxybenzoic acid (MCPBA) has been widely used as a biomimetic oxidant to effect reaction in organic solvents.[3,4] Under these conditions phosphorothionates are desulfurated forming the corresponding phosphates or their ester cleavage products[4] and phosphorothiolates give either phosphinyloxysulfonates or products derived from reaction with the solvent or with *m*-chlorobenzoic acid.[5]

To approximate more closely physiological conditions, we studied the oxidation of phosphorothionates in aqueous media using the water-soluble magnesium monoperoxyphthalate (MMPP) as oxidant. Under these conditions a different product distribution is obtained and noteworthy is that hydrogenphosphonates are generated as significant to major products. The formation of dialkyl hydrogenphosphonates under the oxidative reaction conditions was unanticipated since they represent reduction at the phosphorus center relative to the starting material. For example, diethyl phenyl phosphorothionate **2** ($\delta\ ^{31}P$ +59.82) reacted quantitatively with three equivalents of peracid (1.5 equivalents of MMPP) in water to give three major phosphorus-containing products (Table I). Two of these, diethyl phenyl phosphate ($\delta\ ^{31}P$ −8.60) and diethyl phosphate ($\delta\ ^{31}P$ −2.43), were not unexpected representing the oxidative desulfuration and ester-cleavage products, respectively.

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TABLE I

Products from Reaction of Triester and Related Phosphorothionates and a Diester Phosphorothioic Acid with Three Molar Equivalents of Peracid in Water

No.	Compound[a]	Product yield (mol %)[b] $(RO)_2P(O)R'$	$(RO)_2P(O)OH$	$(RO)_2P(O)H$
Triester and Related Phosphorothionates $(RO)_2P(S)R'$				
1	$(EtO)_2P(S)OEt$	81	10	9
2	$(EtO)_2P(S)OC_6H_5$[c]	52	20	26
3	$(EtO)_2P(S)OC_6H_4$-4-NO_2	38	28	29
4	$(MeO)_2P(S)OC_6H_4$-4-NO_2	33	24	34
5	$(MeO)_2P(S)Cl$	0	32	52
6	$(EtO)_2P(S)NC(O)C_6H_4C(O)$	0	27	70
Diester Phosphorothioic Acid $(RO)_2P(O)SH$				
7	$(EtO)_2P(O)SH$	—	70	30

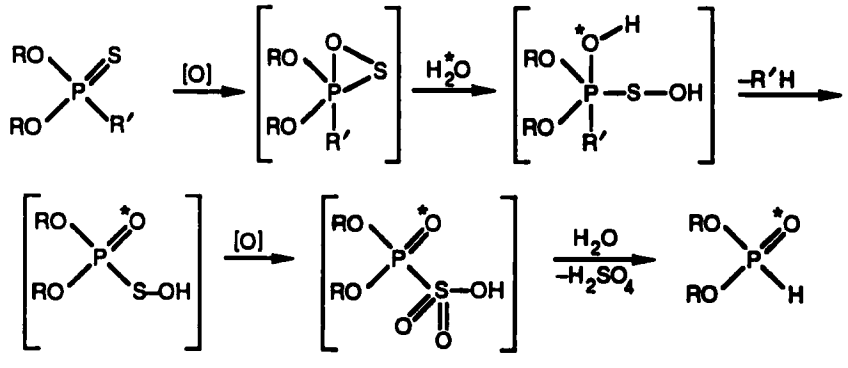
[a] The agrochemicals are: **2**-SV-1, used as an oxidase inhibitor to synergize the potency of insecticides; or dietholate, employed to extend the persistence of herbicides in soils; **3** and **4**, parathion and methyl parathion insecticides, respectively; **6**-ditalimfos fungicide.

[b] Unreacted starting material accounted for most of the remaining compound.

[c] Product yields of $(RO)_2P(O)R'$, $(RO)_2P(O)OH$ and $(RO)_2P(O)H$ are 36, 13, and 29%, respectively, with 2 molar equivalents MMPP and 32, 10 and 13%, respectively, with 1 molar equivalent MMPP.

The third component[6] (δ ^{31}P +8.12) proved of greater interest and was assigned as a hydrogenphosphonate on the basis of the characteristic magnitude of the ^{31}P-^{1}H coupling value (J = 716 Hz in H_2O; 691 Hz in $CDCl_3$). To confirm these structural assignments, authentic standards were added to the reaction mixture. In each case there was enhancement of the relevant ^{31}P-resonances in both the ^{1}H-coupled and ^{1}H-decoupled spectra. The identity of diethyl hydrogenphosphonate was further confirmed in subsequent experiments, where this product was obtained in high yield (e.g., from **6**), by direct ^{1}H-NMR and GC-MS examination of a chloroform extract of the reaction mixture. These spectral data also proved to be identical to those from the authentic sample.

One plausible mechanism for the formation of the hydrogenphosphonates is presented in the Scheme (R′ = the leaving group, *e.g. O*-aryl, *O*-alkyl, Cl or imidate; * indicates the position of ^{18}O). The initial oxidation product is presumably a phosphoroxathiirane, a generally accepted intermediate in the oxidative desulfuration of the thionophosphoryl group.[1,4] In non-hydroxylic solvents this collapses



expelling elemental sulfur and generating the corresponding phosphate as the major product.[4] In aqueous media, however, the yield of this product is variable (Table I) suggesting that the intermediate undergoes other reactions. One possibility is attack by water at the phosphorus center to give the five-coordinate phosphorus intermediate, with subsequent cleavage of the leaving group to form the phosphoro(thioperoxoic) acid (PSOH isomer). Although this species was not detected in the present study it has been recently reported from oxidation of phosphorothioic acids.[7] In support of this suggestion, when the oxidation was carried out in $H_2{}^{18}O$, quantitative incorporation of ^{18}O was observed into the hydrogenphosphonate. This clearly indicates that the phosphoryl oxygen atom is derived from the solvent rather than the oxidant. Moreover, in comparing product yields from different starting materials the formation of hydrogenphosphonates is favored from compounds with an inherently good leaving group attached to phosphorus (Table I). Under these circumstances displacement of the leaving group by solvent attack at the phosphorus center becomes favorable relative to opening of the implied phosphoroxathiirane intermediate which would otherwise lead to desulfuration. Assuming that the phosphorus-sulphur bond is still intact at this point, formation of the hydrogenphosphonates necessarily requires nucleophilic attack at the sulfur with displacement of electrons towards phosphorus, *viz* a reduction reaction relative to the phosphorus atom. This can be rationalised by hydrolysis of the thioperoxoic acid or of its further oxidation product(s). In principle, this hydrolysis could occur at any degree of oxidation of the sulfur, but the route involving the higher oxidation number as shown (Scheme) is considered more likely since the center is more electrophilic in this state.

The occurrence and significance of the described reactions in biologically-mediated phosphorothionate oxidations remains to be established.

EXPERIMENTAL

^{31}P-NMR spectra were recorded, with and without ^1H-decoupling, on a Bruker WM 300 instrument (121.5 MHz) for solutions in $CDCl_3$ or $H_2O:D_2O$ (9:1). Positive ^{31}P shifts are downfield from external trimethyl phosphate. ^1H-NMR spectra were recorded on the same instrument (300 MHz) for $CDCl_3$ solutions and chemical shifts are quoted relative to Me_4Si (internal). GC-MS was run on a Hewlett Packard 5985B system. GC involved a Supelco SPB5 column (30 m × 0.25 mm i.d. × 20 μm film thickness) with He as carrier gas at a pressure of 15 p.s.i. and flow rate of 30 cm/sec. The GC was temperature programmed from 80° with an initial hold of 3 min, to 260° at 10°/min, with a final hold of 4 min. Mass spectra were obtained in the chemical ionization mode with CH_4 as reagent gas. Peak identifications and GC-MS assignments were confirmed by direct comparisons with authentic samples. MMPP (80%, used without further purification) and diethyl phosphite (diethyl hydrogenphosphonate) were from Aldrich.

General procedures. The phosphorothionate (0.1 mmol) as a solution or dispersion in H_2O or $H_2{}^{18}O$ (400 μL) was oxidised with MMPP (generally 1.5 molar equivalents, *i.e.* 3 molar equivalents of peracid) for 24 hr at 25°C. The pH of the solution dropped from ~5 to ~3.5 during the course of the reaction. The sample was analysed by ^{31}P-NMR after addition of acetone (200 μL), when necessary, to achieve a homogeneous solution. Authentic standards were then added (approximately 0.5 equivalents relative to the starting phosphorothionate) and the spectra recorded again. In similar experiments, the oxidation mixture was extracted with $CDCl_3$, the organic extract dried and the ^1H-NMR spectrum recorded, giving diethyl hydrogenphosphonate δ^1H 1.37 (t, CH_3, J = 7.1 Hz); 4.16 (dq, CH_2, J = 7.1, 7.1 Hz); 6.81 (d, PH, J = 691 Hz). The $CDCl_3$ was subsequently evaporated, the residue dissolved in ether and an ethereal solution of diazomethane added. After methylation was complete (to avoid interference from acidic components) the products were analysed by GC-MS, establishing the presence of diethyl hydrogenphosphonate Rt = 3.95 min; CIMS *m/z* 179 (M + 41, 6%), 167 (M + 29, 11%), 139 (M + 1, 100%), 111 (27%).

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