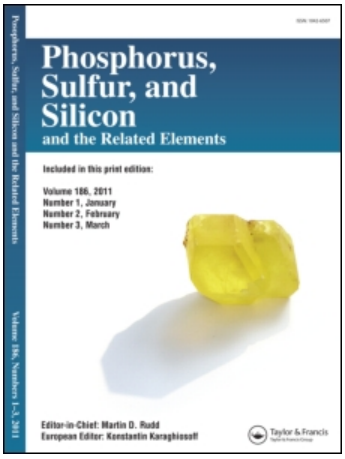

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STEREOCHEMISTRY OF OXIDATIVELY-INDUCED TRANSFORMATION OF DIESTER PHOSPHOROTHIOIC ACIDS AND TRIESTER PHOSPHOROTHIONATES TO DIESTER HYDROGENPHOSPHONATES

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STEREOCHEMISTRY OF OXIDATIVELY-INDUCED TRANSFORMATION OF DIESTER PHOSPHOROTHIOIC ACIDS AND TRIESTER PHOSPHOROTHIONATES TO DIESTER HYDROGENPHOSPHONATES

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The individual diastereoisomers of two diester phosphorothioic acids are converted to diester hydrogenphosphonates with retention of configuration at phosphorus on treatment with magnesium monoperoxyphthalate (three equivalents of peracid) in water. Analogous oxidation of the diastereoisomers of two triester phosphorothionates gives hydrogenphosphonates with inversion of configuration. These stereochemical relationships for the phosphorothioic acids are generally consistent with a mechanism involving oxidation directly at sulfur then nucleophilic attack at that center leading to hydrogenphosphonate formation such that the configuration is retained. For the phosphorothionates, a plausible mechanism involves initial oxidative activation of the thiophosphoryl functionality, attack at the phosphorus center by the solvent such that a substituent is displaced with inversion of configuration, and then further oxidation at sulfur and subsequent reaction as with the phosphorothioic acids.

Key words: Hydrogenphosphonate; peracid oxidation; phosphorothioic acid; phosphorothionate; stereochemistry.

Triester and related phosphorothionates, including several important pesticides, and their diester phosphorothioic acid cleavage products undergo oxidative conversion to dialkyl hydrogenphosphonates on treatment with magnesium monoperoxyphthalate (MMPP) in water.[1] Hydrogenphosphonates are also minor products from *m*-chloroperoxybenzoic acid (MCPBA) oxidation of phosphorothioic acids in hydroxylic solvents.[1,2] This is an interesting reaction for two reasons: the phosphorus atom in the hydrogenphosphonate is reduced relative to its oxidation state in the starting material; the newly-introduced phosphoryl oxygen atom originates from the solvent and not the oxidant.[1] To rationalize this result, $(RO)_2P(O)SO_3H$ was proposed as a key intermediate since nucleophilic attack at sulfur would displace electrons towards phosphorus leading to cleavage of the P—S bond, thereby making the phosphorus center electron rich and capable of abstracting a proton from the reaction medium.[1]

One approach to further define this reaction is to employ stereochemical probes, reactants which have previously proven useful in defining the mechanisms of oxidation and cleavage of thiophosphorus compounds. For example, peracid oxidation of phosphorothionates and phosphorothiolates is complex and is related to the starting material, the oxidant and the solvent.[3,4] Whereas the phosphorothionate

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to oxon (P=S → P=O) transformation occurs with retention of configuration,[3] the oxidation of phosphorothiolates can result in products involving retention, inversion, or racemization.[4] In this contribution, we consider the stereochemical aspects of the conversion of phosphorothioic acids and phosphorothionates to hydrogenphosphonates and discuss the mechanistic implications of this transformation.

RESULTS AND DISCUSSION

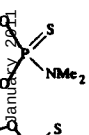
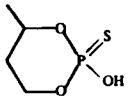
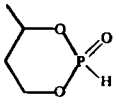
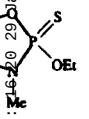
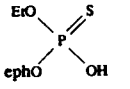
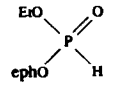
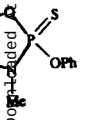
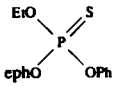
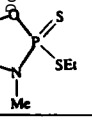
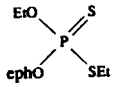
The diester phosphorothioic acids and triester phosphorothionates studied represent the range of compounds previously noted[1] to yield diester hydrogenphosphonates on peracid oxidation in water. Specifically, we prepared the individual diastereomers of known configuration of a cyclic (**1**) and an acyclic (**2**) diester phosphorothioic acid, an acyclic triester phosphorothionate (**3**), and an acyclic triester phosphorodithioate (**4**) (Table I). Compounds **1** and **5** (which served as a precursor for **2**) are known, with their preparation and stereochemical assignments described by Mikołajczyk and Łuczak[5] and Cooper *et al.*,[6] respectively. The diastereomers of **2** were derived from acid-catalyzed hydrolysis of cyclic phosphoramidothionate **5**, a reaction which proceeds with inversion of configuration at phosphorus.[6] The individual diastereomers of **3** and **4** were produced by acid-catalyzed ethanolysis of the individual diastereomers of **6** and **7**, respectively, a reaction which also proceeds with inversion,[7] and **6** and **7**, in turn, were correlated with their oxons, compounds of established stereochemistry.[6,8] Confirmation for the stereochemical assignments of the diastereoisomers of **1** was also provided by their conversion with peracid to the known **8**-oxons.[9]

Dialkyl hydrogenphosphonates **1′** and **2′** were produced in yields of 14–58% as the major organo-extractable products on peracid oxidation of the individual diastereomers of **1–4** (Table I). Di- and triester phosphates accounted for most of the remaining products. Each of the diester hydrogenphosphonates showed the large coupling constant (718–746 Hz) characteristic of the P—H linkage and was stereochemically-pure except for (S_p)-**2′** which formed from (R_p)-**4** in 84% diastereomeric excess. The stereochemistry of each starting cyclic phosphoramidothionate was correlated with the respective di- or triester phosphorothionate and finally with each product hydrogenphosphonate (Table I). Thus, the isomers of **1′** are known compounds of established configuration.[5] For **2′**, each isomer was converted back to the corresponding phosphorothioic acid **2** by treatment with elemental sulfur. In both cases the diastereomerically-pure phosphorothioic acids were formed quantitatively, and since addition of sulfur to the hydrogenphosphonate takes place with retention of configuration[5,10] the **2′** precursor to **2** resonating at 7.1 ppm (^{31}P) was assigned as (S_p) and the one at 6.9 ppm as (R_p). These results establish that conversion of diester phosphorothioic acids **1** and **2** to the corresponding diester hydrogenphosphonates does not involve any change of configuration at phosphorus whereas for the triester phosphorothionates the process proceeds with inversion (Table I).

The reactions of diester phosphorothioic acids (**1** and **2**) are rationalized as sequential oxidation at sulfur to intermediate **C** and then **D**, followed by the attack

TABLE I

mical Relationships of Cyclic Phosphoramidothionates, Di- and Triester Phosphorothionates Formed on Acid Hydroly
olysis, and Diester Hydrogenphosphonates Produced on Oxidation with Magnesium Monoperoxyphthalate in Water[a]

hosphoramidothionates			Di- and triester phosphorothionates from acid hydrolysis/ethanolysis				Diester hydrogenphosphonates from peracid oxidation				
cture	config.	^{31}P NMR	no	structure[b]	config.	^{31}P NMR	no	structure[b]	config.	^{31}P NMR	y
	<u>trans</u>[c]	71.1	<u>1</u>		<u>cis</u>	50.5	<u>1</u>′		<u>cis</u>	4.9/718[d]	
	<u>cis</u>	70.6			<u>trans</u>	53.5			<u>trans</u>	0.9/740	
	S_p	80.8	<u>2</u>		R_p	52.1	<u>2</u>′		S_p	7.1/743	
	R_p	79.4			S_p	53.1			R_p	6.9/734	
	S_p	75.1	<u>3</u>		R_p	65.5	<u>2</u>′		R_p	6.9/731	
	R_p	75.7			S_p	65.2			S_p	7.1/744	
	S_p	99.9	<u>4</u>		R_p	99.7	<u>2</u>′		S_p	7.1/746	
	R_p	99.6			S_p	99.5			R_p	6.9/733	

emical assignments and ^{31}P NMR data for chemically-correlated compounds are given on the same line.

gnates (-)-ephedrine as a substituent.

<u>trans</u> refer to the relationship between the C_4 methyl group and the exocyclic oxygen or nitrogen atom.

oling constants in Hz.

of H_2O at the oxidized sulfur leading to cleavage and formation of the trivalent phosphorous acid **E** which isomerizes into the more stable hydrogenphosphonate **1′** or **2′** (Figure 1). For triester phosphorothionates **3** and **4** the mechanism appears to be more complex. Initial oxidation presumably involves activation of the thiophosphoryl group such that **3** and **4** form intermediate **A** which, in turn, hydrolyzes through trigonal bipyramidal intermediate **B** to give **C**, which further reacts as above (Figure 1). To account for the observed stereochemical correlations, the hydrolysis at phosphorus must occur with inversion of configuration, as expected for displacement of a leaving group on reaction with the solvent.[11]

In conclusion, the results of the stereochemical studies reported here are consistent with the previously-proposed mechanism[1] for the oxidatively-induced formation of hydrogenphosphonates from diester phosphorothioic acids and triester phosphorothionates, and they demonstrate that the conversions are stereospecific for both classes of starting materials.

EXPERIMENTAL

Spectroscopy. NMR spectra were recorded with a Bruker WM-300 Spectrometer at 300 MHz (^{1}H) or 121.5 MHz (^{31}P) for solutions in $CDCl_3$ or H_2O:D_2O (9:1). Chemical shifts are referenced to internal tetramethylsilane for ^{1}H and external trimethyl phosphate in $CDCl_3$ for ^{31}P (Relative to this standard 85% H_3PO_4 resonates at $-\delta$ 2·5). They are reported on the δ scale with positive shifts downfield from the reference and coupling constants in Hz. Product distributions were determined by integration of the resonances in the ^{31}P NMR spectra obtained on direct analyses of the reaction mixtures with an appropriate inverted gate delayed acquisition pulse sequence to minimize nuclear Overhauser effects. Yield and diastereomeric excess in each case were based on this NMR method. Cyclic phosphoramidothionates **5–8** gave appropriate $[MH]^+$ and $[MH + 29]^+$ ions and fragmentation patterns on chemical ionization-mass spectrometry. Spectroscopic data for known compounds were consistent with those in the literature.

Individual diastereomers of cyclic phosphoramidothionates **5–8.** Phosphoramidothionates **5–7** were prepared by coupling the corresponding phosphorochloridothionates with (1*R*, 2*S*)-(—)-ephedrine (each

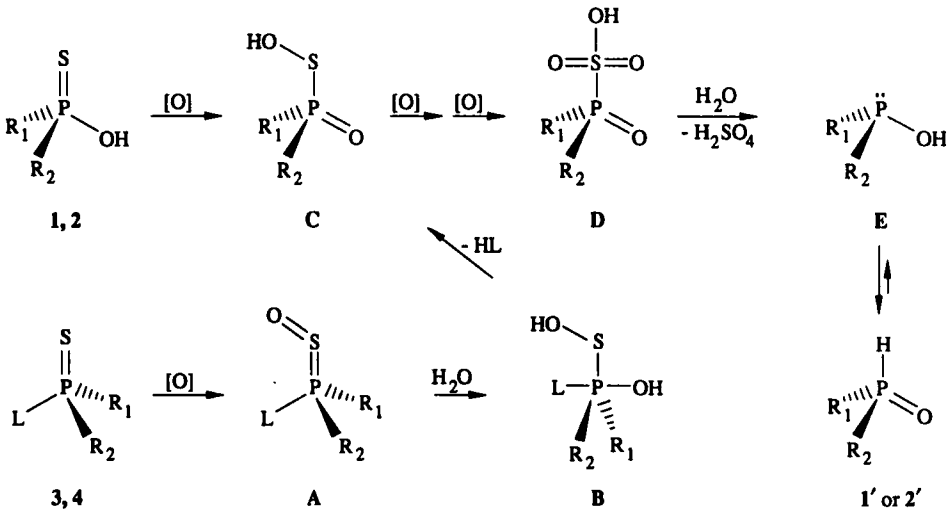


FIGURE 1 Schemes for oxidation of diester phosphorothioic acids and triester phosphorothionates to diester hydrogenphosphonates with monoperoxyphthalate in water showing the stereochemical relationships involved. L = leaving group.

TABLE II

^{1}H-NMR Parameters of Stereomers in Table I

		2-XR[a]	3-Me	4-H	4-Me	5-H	5-Ph	6-H
6	R_p	7.24	2.88	3.68	0.69	5.73	7.33	
	S_p	7.25	2.81	3.72	0.79	5.51	7.35	
7	R_p	1.36, 2.95	2.73	3.65	0.84	5.56	7.34	
	S_p	1.40, 3.01	2.75	3.70	0.78	5.71	7.35	
8	*cis*	2.85		4.79	1.34	1.67, 1.84		4.21, 4.59
	trans	2.55		4.55	1.42	1.77, 2.06		4.28, 4.34
		POEt	POCH	Ph	CH_3CH	CH_3—N	P—H	
2	R_p	1.19, 4.02	6.00	7.31, 7.42	1.25, 3.36	2.81		
	S_p	1.40, 4.21	6.25	7.27, 7.45	1.19, 3.55	2.75		
2'	R_p	1.20, 4.20	6.05	7.36, 7.58	1.31, 3.62	2.91	6.98/717Hz[b]	
	S_p	1.09, 3.92	6.17	7.34, 7.49	1.28, 3.58	2.90	7.10/741Hz[b]	

[a] OPh in **6**, SEt in **7** and NMe_2 in **8**.
[b] P—H coupling constants.

10 mmol) in dichloromethane (50 mL) containing triethylamine (20 mmol) at 5°C for 18 h. For **8**, the phosphorochloridothionate was coupled with dimethylamine by bubbling the amine into the solution. The reaction mixtures were filtered, dried (Na_2SO_4), the solvent evaporated, and the products were separated by preparative chromatography using silica gel GF chromatoplates of 2 mm gel thickness with product detection by UV light or 0.5% $PdCl_2$ in 1N HCl as the spray reagent. Three to four sequential developments on the same chromatoplate gave adequate resolution with conditions as follows (compound, solvent system, configuration of phosphorus atom, and *Rf*): **5**, hexane-ethyl acetate 1:1, S_p 0.40, R_p 0.45; **6**, hexane-ether 4:1, S_p 0.25, R_p 0.20; **7**, cyclohexane-chloroform 3:1, S_p 0.30, R_p 0.35; **8**, benzene-cyclohexane 1:1, *trans* 0.25, *cis* 0.30. Assignments of the ^{31}P chemical shifts for **5–8** are given in Table I and of the ^{1}H spectra for **6–8** are reported in Table II.

*Diester phosphorothioic acids (**1** and **2**) and triester phosphorothionates (**3** and **4**) from acid hydrolysis and ethanolysis of individual diastereomers of* **5–8**. Acid hydrolysis converted **8** to **1** (2M aqueous H_2SO_4, 80°C, 6 h) and **5** to **2** (aqueous HCl, pH 3, 90°C, 10 h), each in quantitative yield. Similarly, acid ethanolysis (4N HCl in ethanol, 25°C, 1 h) converted **6** to **3** and **7** to **4**, also quantitatively. Workup for **1** involved extraction into chloroform, drying the chloroform (Na_2SO_4), and evaporation of the solvent. Compound **2** was recrystallized from H_2O [(R_p)-**2** mp 111–113°C; (S_p)-**2** mp 199–201°C] and **3** and **4** were used directly after evaporation of the hydrolysis solvents at reduced pressure. Relevant NMR data are given in Tables I and II.

Peracid oxidation. MMPP (80%, used without further purification) and MCPBA (commercial 85%, used after enrichment to 99%) were from Aldrich. A standard procedure was used for all MMPP oxidations of phosphorothionates (**1–4**). Thus the thiophosphorus compound (0.1 mmol) in H_2O (450 μL) was treated with 1.5 molar equivalents of MMPP for 20 min and then D_2O (50 μL) was added and the sample was analyzed by ^{31}P NMR. The aqueous solution was subsequently extracted with $CDCl_3$ (0.5 mL), the organic phase separated, dried (Na_2SO_4) and filtered and its ^{1}H NMR spectrum recorded directly. Oxidation of **6**, **7** and **8** was carried out in $CDCl_3$ by addition of equimolar MCPBA. The ^{1}H and ^{31}P NMR spectra of the reaction mixtures (which contained primarily the oxons of **6**, **7** and **8**) were recorded without further purification.

Sulfuration of diester hydrogenphosphonates. Hydrogenphosphate **2'**, formed from MMPP oxidation of **2** in water, was extracted into chloroform and the solution dried over Na_2SO_4. Each isomer of **2'** was treated with elemental sulphur as a suspension in benzene-ether 1:1 at 25° for 18 h. After filtration and evaporation of the solvent the resulting oils were dissolved in $CDCl_3$. The ^{1}H and ^{31}P NMR established that diastereomerically pure **2** was formed, quantitatively, in both cases.

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11. The study of triester phosphorothionates was extended to peracid oxidation of individual diastereomers of cyclic phosphoramidothionate **5** under the standard reaction conditions. (R_p)-**5** yields (S_p)-**2'** (80% diastereomeric excess) and (S_p)-**5** gives (R_p)-**2'** (stereochemically pure) in 45–47% yields. These stereochemical correlations show that, mechanistically, the process must differ somewhat from that for the triesters **3** and **4** since direct displacement of the leaving amino group by H_2O as noted above would give a product with the alternative stereochemistry to that which is observed. This implies that the endocyclic amino leaving group is not in an apical position in the initially-formed trigonal bipyramid, perhaps because of steric constraints associated with the five-membered ring and/or the poor apicophilicity of the nitrogen atom. Therefore, the nitrogen leaving group may be displaced from an equatorial position or the initial trigonal bipyramid may undergo pseudorotation in which the leaving group then takes an apical position. In either case cleavage of the P—N bond yields similar intermediates to those described above leading to the final hydrogenphosphonate.