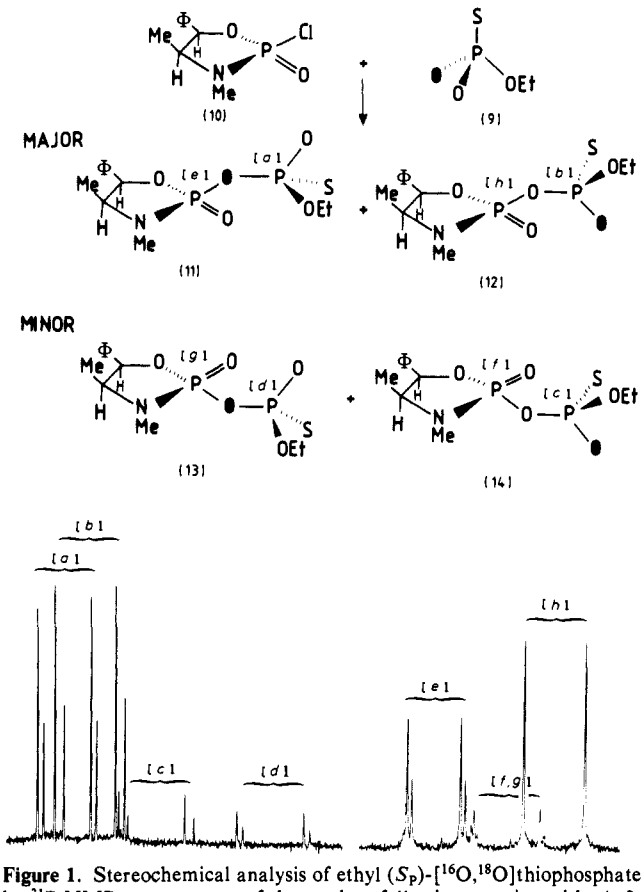

Figure 1. Stereochemical analysis of ethyl (S_P)-[^{16}O,^{18}O]thiophosphate by ^{31}P NMR spectroscopy of the product following reaction with *cis*-2-chloro-3,4(*S*)-dimethyl-5(*S*)-phenyl-1,3,2-oxazaphospholidin-2-one. The spectrum was recorded on a Bruker AM-300 at 121.5 MHz and processed with Gaussian multiplication (Gaussian broadening 0.1 Hz, line broadening −0.3 Hz). The assignments are as shown with the downfield resonances (thiophosphoryl center) at ca. +46 ppm and the upfield resonance (1,3,2-oxazaphospholidine center) at ca. +7 ppm.[12]

these syntheses exploit the stereocontrolled displacement reactions of 2-substituted 1,3,2-oxazaphospholidine-2-thiones, which have established precedent in the work of Inch et al.[10]

The major objective has been the development of a general method for the configurational analysis of isotopically chiral thiophosphate monoesters. During the course of our work on the stereochemistry of phosphoryl transfer from P^1,P^1-disubstituted pyrophosphates,[4] we synthesized the unlabeled diastereomeric pyrophosphates corresponding to **11** and **12**. These were readily distinquished by high-field ^{31}P NMR spectroscopy and form the basis of the configurational analysis reported here. S_P-*O*-Ethyl [^{16}O,^{18}O]thiophosphate (**9**) (^{18}O enrichment ca. 33%) was synthesized by the route shown in Scheme I. The absolute configuration follows from the synthesis. Reaction of **9** with the *cis*-2-chloro-1,3,2-oxazaphospholidin-2-one (**10**) derived from (−)-ephedrine gave rise to the pyrophosphate derivatives **11**–**14**. The high-field ^{31}P NMR spectrum together with the assignments are shown in Figure 1. Resonances corresponding to centers **e** and **h** can be unambiguously assigned since the 1,3,2-oxazaphospholidine phosphorus center is attached to ^{18}O in diastereosomer **11** but not in diastereoisomer **12**, hence only one set of resonances will be split by the stereospecific incorporation of ca. 33% ^{18}O. On the basis of the bond-order dependence of the ^{18}O shift[11] on the thiophosphoryl signal, resonances **a** can be assigned to the diastereoisomer **11** in which the ^{18}O is located in the bridging position and resonances **b** can be assigned to the diastereoisomer **12**. The additional minor resonances seen in Figure 1 are due to structures **13** and **14**, which are epimeric at the ring phosphoryl center with respect to **11** and **12**.[13] R_P-*O*-Ethyl [^{16}O,^{18}O]thiophosphate would give rise to a ^{18}O shift on h rather than **e** and the magnitude of the ^{18}O shifts on **a** and **b** would be reversed. The downfield ^{31}P resonances arise from diastereoisomer **11** (in which the new chiral center at the thiophosphoryl position has the R_P configuration) while the upfield ^{31}P NMR resonances arise from diastereoisomer **12** (in which the new chiral center has the S_P configuration). We have established that this assignment holds for **6a** (R = *p*-nitrophenyl) and **6b** (R = ethyl), and it may hold for a wide range of R groups. The above assignments form the basis of our method for studying the stereochemical course of simple thiophosphoryl-transfer reactions.[14] The above analysis strategy is potentially general and may allow extension to the study of a range of hydrolysis reactions leading to phosphorus acids of the type $R^1R^2PO_2^-$ ($R^1 \neq R^2$).[15]

Acknowledgment. This work was supported by a grant from the SERC.

(9) Abbott, S. J.; Jones, S. R.; Weinman, S. A.; Knowles, J. R. *J. Am. Chem. Soc.* **1978**, *100*, 2558. The extension of the published route to isotopically chiral phosphate monoesters to the synthesis of *thio*phosphate monoesters is *non*trivial; the thiophosphorochloridate is significantly less reactive, the acid ring opening step can lead to competing loss of sulfur, and finally the removal of the ephedrine framework is difficult. Full details will be published elsewhere.

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(12) The ^{31}P NMR data from the spectrum shown in Figure 1 are as follows: diastereoisomer **11** δ ($CDCl_3$) +7.14 (d, J_{PP} = 25.9 Hz, 1,3,2-oxazaphospholidin-2-one, ^{18}O shift 2.28 Hz), +46.39 (d, J_{PP} = 25.9 Hz, R_P thiophosphoryl center, ^{18}O shift 2.84 Hz); diastereoisomer **12** δ ($CDCl_3$) +6.65 (d, J_{PP} = 29.7 Hz, 1,3,2-oxazaphospholidin-2-one), +46.29 (d, J_{PP} = 29.7 Hz, S_P thiophosphoryl center, ^{18}O shift 4.46 Hz).

(13) The trans diastereoisomers **13** and **14** apparently do not arise from trace amounts of the trans chloro compound analogous to **10** but are due to an epimerization reaction.

(14) Cullis, P. M.; Iagrossi, A., following paper in this issue.

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Thiophosphoryl-Transfer Reactions: Stereochemical Course of Solvolysis of *p*-Nitrophenyl Thiophosphate in Protic Solvent and the Possible Role of Thiometaphosphate

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There is much current interest in monomeric metaphosphate as a possible intermediate in nucleophilic displacement reactions of monosubstituted phosphate esters[1] and, in particular, in relation to enzyme-catalyzed phosphoryl-transfer reactions.[2] Stereochemical,[3,4] kinetic,[5,6] and thermodynamic[7] evidence suggests that metaphosphate is so reactive that it does not have a significant lifetime in *protic* solvents (although many other three-coordinate P(V) compounds have appreciable stabilities[8,9]). In contrast,

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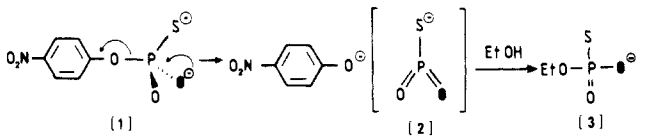
0002-7863/86/1508-7870$01.50/0

Scheme I



stereochemical studies on analogous phosphoryl-transfer reactions in *aprotic* solvents have found them to proceed with extensive racemization[10-12] which leaves open the possibility of an intermediate with an appreciable lifetime. Further to our studies on monomeric metaphosphate[10,11] we have been interested in the properties and lifetime of the closely related *thio*metaphosphate, this being the closest relative of metaphosphate itself. We report here one of *the first stereochemical investigations of a simple thiophosphoryl-transfer reaction.*

Thiophosphate monoesters undergo nucleophilic displacement reactions more rapidly than their oxy counterparts, in marked contrast to the corresponding di- and triesters.[13] This enhanced reactivity has been explained in terms of a facile dissociative breakdown to give monomeric thiometaphosphate, Scheme I. Utilizing isotopically chiral *p*-nitrophenyl [^{16}O,^{18}O]thiophosphate (**1**) we have sought stereochemical evidence pertinent to this point. *p*-Nitrophenyl (*R*)-[^{16}O,^{18}O]thiophosphate (**1**) (ca. 75% ^{18}O enrichment at the labeled site) was synthesized by the route described in the preceding paper. The absolute configuration followed from the synthesis and the enantiomeric purity (≥90% R_P) was independently established by our general method of analysis, Figure 1C.[14] The dianion (100 mM)[15] in ethanol was solvolyzed at 50 °C for 3 h. The product ethyl [^{16}O,^{18}O]thiophosphate (**3**) was isolated by ion-exchange chromatography and subjected to the stereochemical analysis described in the accompanying paper. Since an ^{18}O shift is clearly evident on both sets of upfield resonances,[16] Figure 1A, one can conclude that *the product was largely racemic*, as indicated by the ^{31}P NMR resonance assignments shown. The enantiomeric excess in the product ethyl [^{16}O,^{18}O]thiophosphate (**3**) can be quantified from the relative intensities of the resonances in Figure 1A and corresponds to thiophosphoryl transfer occurring with ca. 80% racemization and a 20% excess of the S_P configuration which would arise from thiophosphoryl transfer occurring with inversion of configuration. Independent experiments established that (i) ethyl (*S*)-[^{16}O,^{18}O]thiophosphate does not racemize under the solvolysis conditions, Figure 1B, and (ii) the starting material, *p*-nitrophenyl (*R*)-[^{16}O,^{18}O]thiophosphate, reisolated from a solvolysis reaction carried out to 50% completion (50 °C, 1.5 h), had not racemized (within experimental error), Figure 1C.[14] It is therefore clear that the *racemization arises during the thiophosphoryl-transfer reaction.*

The simplest interpretation of this result is that the reaction proceeds via a dissociative reaction involving the monomeric thiometaphosphate intermediate **2**. Furthermore, in contrast to analogous phosphoryl-transfer reactions in protic solvent in which the putative metaphosphate intermediate is so reactive that the reaction follows a concerted preassociative mechanism,[3,5-7] the thiometaphosphate intermediate must be sufficiently long-lived to allow partial loss of stereochemical integrity.

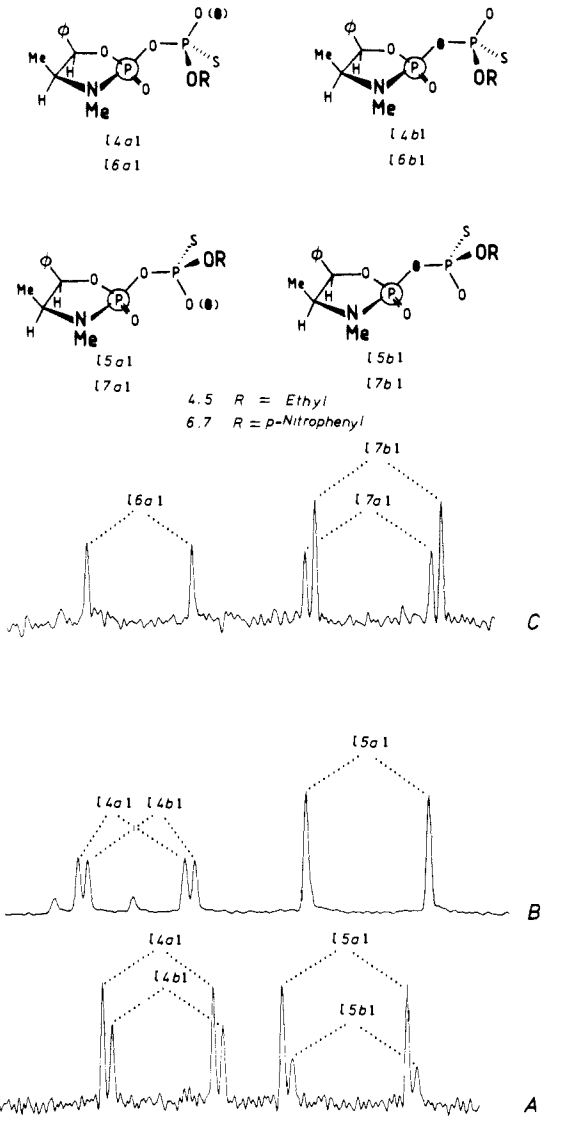


Figure 1. ^{31}P NMR spectra showing the 1,3,2-oxazaphospholidin-2-one resonances (resonances e and h in the preceeding paper) at ca. +7 ppm of the products from the stereochemical analysis of (A) ethyl [^{16}O,^{18}O]thiophosphate obtained from the solvolysis of *p*-nitrophenyl (R_P)-[^{16}O,^{18}O]thiophosphate dianion in ethanol at 50 °C, (B) ethyl (S_P)-[^{16}O,^{18}O]thiophosphate (ca. 50% enriched at the ^{18}O site) after being subjected to conditions identical with the solvolysis reaction, and (C) *p*-nitrophenyl (R_P)-[^{16}O,^{18}O]thiophosphate reisolated from the solvolysis reaction. The spectra were recorded on a Bruker AM-300 at 121.5 MHz and processed with Gaussian multiplication (GB 0.1 Hz; LB −0.5 Hz).

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(13) Breslow, R.; Katz, I. *J. Am. Chem. Soc.* **1968**, *90*, 7376.
(14) The spectrum in Figure 1C is actually of starting material reisolated from a thiophosphoryl-transfer reaction; however, the spectrum for the starting material analyzed directly from the synthesis was identical. Although we believe there to be essentially no **6b** present, the lower limit on this is determined by the signal-to-noise ratio. A conservative estimate of the enantiomeric excess is therefore 90 ± 10%. The departure of the ratio of **7a** to **7b** from 1:3 arises from dilution of the isotope during the synthesis; no attempt to quantify this has been made since the configurational analysis does not depend on absolute intensities.
(15) *p*-Nitrophenyl (*R*)-[^{16}O,^{18}O]thiophosphate was dissolved as its triethylammonium salt and the solution buffered by addition of sodium bicarbonate. ^{31}P NMR chemical shift arguments support the proposal that the dianion is present in solution and the leaving group exists as the phenolate anion as judged by the UV/visible spectrum. Preliminary results with the corresponding tetrabutylammonium salt indicate a similar degree of racemization thus tending to exclude nucleophilic participation of the counterion as a possible source of the observed racemization.
(16) The racemization can also be demonstrated on the downfield resonances corresponding to the thiophosphoryl phosphorus center (see preceeding article) since these are all split into three due to the presence of ^{18}O in the bridging and nonbridging positions of *both* diastereoisomers.

Note Added in Proof. Professor Berkovic has recently reported preliminary observations of partial racemization during the hydrolysis of *p*-nitrophenyl thiophosphate monoanion (Domanico, P.; Mizrahi, V.; Berkovic, S. J. In *Mechanisms of Enzymatic Reactions: Stereochemistry*; Frey, P. A., Ed.; Elsevier: Amsterdam, 1986; pp 127–137).

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