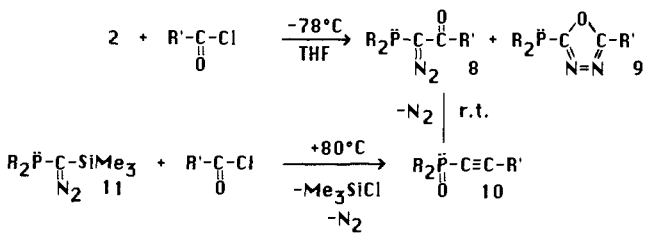
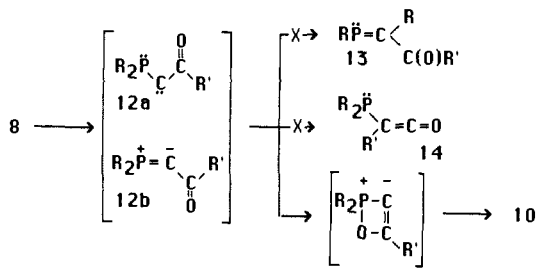
Scheme II



8a, 9a, 10a : R = $(i\text{-Pr})_2N$, R' = t-Bu

8b, 9b, 10b : R = $(i\text{-Pr})_2N$, R' = p-Tolyl

Scheme III



row element is involved, the carbenoid character is competitive, as recently shown for -S-N,[8] -C-SF_3,[9] and even -Si-Si-[10] derivatives.

Acknowledgment. We thank the CNRS (GRECO Basses Coordinences) for support of this research.

Supplementary Material Available: Microanalytical, mass spectral, IR, and NMR (^1H, ^{13}C, ^{31}P, ^{15}N) data (3 pages). Ordering information is given on any current masthead page.

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Thiophosphoryl-Transfer Reactions: A General Synthesis and Configurational Analysis of O-Substituted [^{16}O,^{18}O]Thiophosphates

Paul M. Cullis,* Anna Iagrossi, and Andrew J. Rous

Department of Chemistry, The University Leicester LE1 7RH, England

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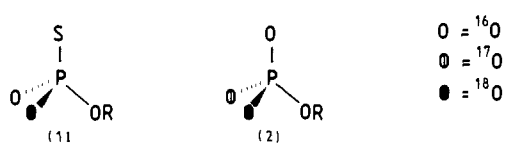
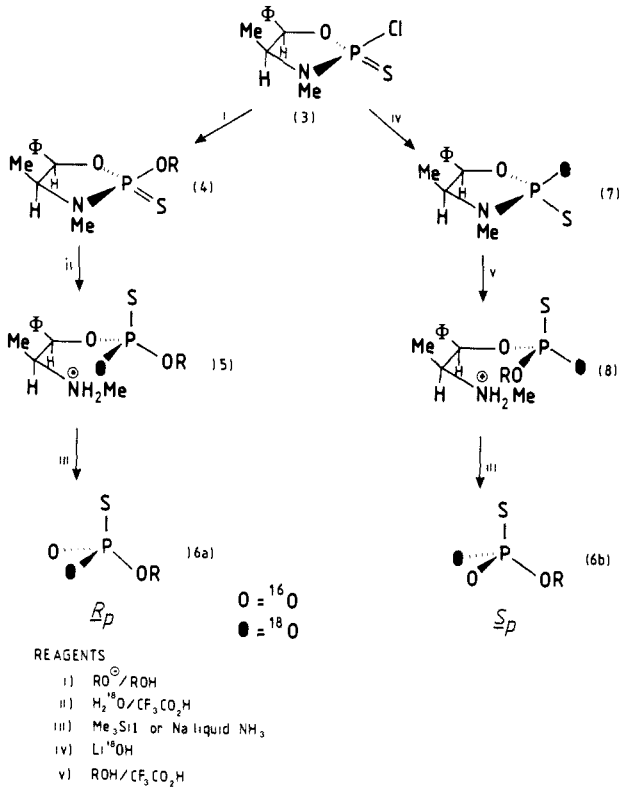
[^{16}O,^{18}O]Thiophosphate (**1**) and [^{16}O,^{17}O,^{18}O]phosphate (**2**) esters have been utilized extensively to determine the stereochemical course of many enzyme-catalyzed thiophosphoryl-[1] and



phosphoryl-transfer[2] reactions. Although the stereochemical courses of some simple chemical phosphoryl-transfer reactions have recently been determined,[3,4] hitherto *simple thiophosphoryl*-transfer reactions have not been studied. With existing methods these would in fact be difficult to determine. Such studies would be of interest since (i) the stereochemical course of enzyme-catalyzed thiophosphoryl-transfer reactions has frequently been assumed to be the same as for the natural phosphoryl-transfer reaction and it would be pertinent to determine whether these reactions are indeed stereochemically equivalent[5] and (ii) thiophosphate monoesters have been reported to react more rapidly via a dissociative reaction than the corresponding phosphate esters.[6] We report here the first simple chemical configurational analysis of structures such as **1** (R = alkyl or aryl)[7] together with general synthetic routes to simple [^{16}O,^{18}O]thiophosphate monoesters (**1**).[8]

Our two general routes to isotopically chiral [^{16}O,^{18}O(or ^{17}O)]thiophosphate monoesters of either the R_P or S_P absolute configuration are shown in Scheme I. By analogy with the previously published route(s) to [^{16}O,^{17}O,^{18}O]phosphate esters,[9]

Scheme I



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(5) The demonstration for a number of enzymes that phosphoryl and thiophosphoryl transfer proceed with the same stereochemical course (see ref 1 and 2) would suggest that within the constraints of the enzyme active site these two reactions are equivalent.
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(7) Two configurational analyses have been reported for AMPS ^{18}O and other nucleoside [^{18}O]thiophosphates: the first relies on the stereospecific enzyme-catalyzed phosphorylation of the *pro-R/S* oxygen as the key step (Sheu, K.-F. R.; Frey, P. A. *J. Biol. Chem.* **1977**, *252*, 4445); the second method has assigned the absolute configurations of the *O,S*-dimethyl nucleoside triesters by relating these to the *O*-methyl nucleoside diesters which have been assigned on the basis of the known stereoselectivity of snake venom phosphodiesterase (Cummins, J. H.; Potter, B. V. L. *J. Chem. Soc., Chem. Commun.* **1985**, 851). Neither method was suitable for our proposed study.
(8) Previous syntheses of isotopically chiral thiophosphate monoesters based on the *meso*-hydrobenzoin route (Cullis, P. M.; Lowe, G. *J. Chem. Soc., Perkin Trans. 1* **1981**, 2317. Jarvest, R. L.; Lowe, G. *J. Chem. Soc., Chem. Commun.* **1979**, 364) have been reported but not extensively applied. Similarly [γ-^{16}O,^{18}O,S]ATP and [^{18}O]AMPS have been synthesized by routes that would not easily be extendible to simple thiophosphate esters.

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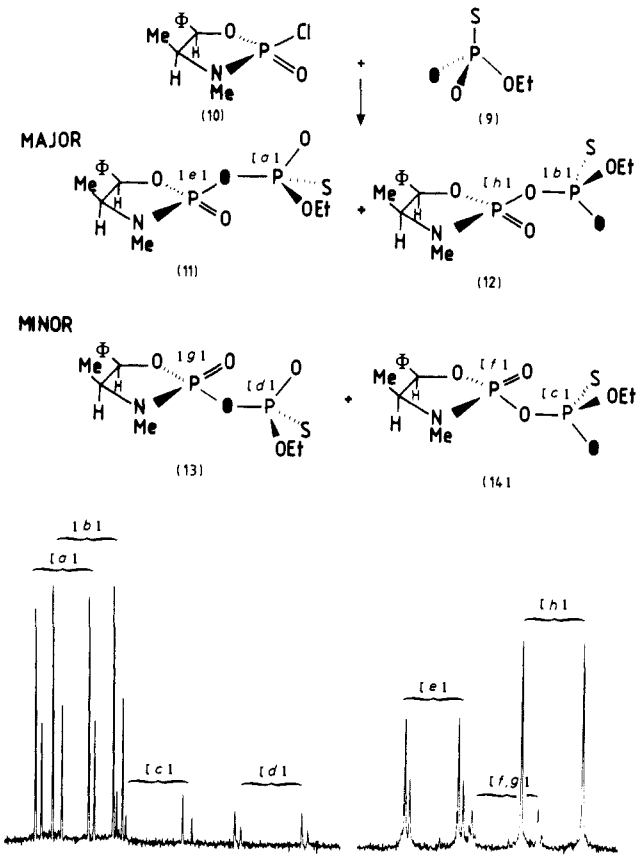

Figure 1. Stereochemical analysis of ethyl (S_P)-[^{16}O,^{18}O]thiophosphate by ^{31}P NMR spectroscopy of the product following reaction with *cis*-2-chloro-3,4(*S*)-dimethyl-5(*S*)-phenyl-1,3,2-oxazaphospholidin-2-one. The spectrum was recorded on a Bruker AM-300 at 121.5 MHz and processed with Gaussian 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.

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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.

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

Paul M. Cullis* and Anna Iagrossi

Department of Chemistry, The University Leicester LE1 7RH, England

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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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