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A GENERAL CONFIGURATIONAL ANALYSIS OF O-SUBSTITUTED [^{16}O,^{18}O]THIOPHOSPHATES

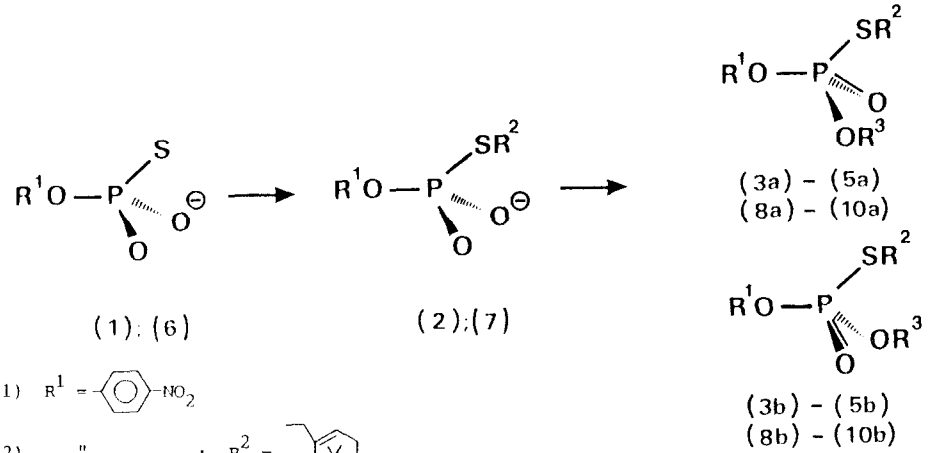
Paul M. Cullis,* Rajinder Misra and David J. Wilkins

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

Abstract: O-Substituted [^{16}O,^{18}O]thiophosphates can be configurationally analysed by ^{31}P n.m.r. spectroscopy after S-alkylation with myrtenyl bromide followed by O-derivatisation either with dimethyl sulphate, diphenyl diazomethane or benzoyl chloride.

Thiophosphoryl transfer reactions using [^{16}O,^{18}O]thiophosphate esters have been used extensively as stereochemical probes for enzyme catalysed phosphoryl transfer reactions.[1,2] In order to investigate the stereochemical course of simple chemical thiophoshoryl transfer and to probe the existence or otherwise of monomeric thiometaphosphate[3] we recently reported a general synthesis of O-substituted [^{16}O,^{18}O]thiophosphates.[4] The corresponding configurational analysis relied upon the conversion of the conventional prochiral centre into diastereomeric pyrophosphates by reacting the O-substituted [^{16}O,^{18}O]thiophosphate with the cis 2-chloro-1,3,2-oxaza-phospholidin-2-one derived from (-) ephedrine.[4] The location of the ^{18}O within the two diastereoisomers by the magnitude of the ^{18}O-isotope shift induced on the ^{31}P n.m.r. resonances[5] assigns the absolute configuration of the initial O-substituted [^{16}O,^{18}O] thiophosphate. Two problems were apparent with this analysis, firstly there was some loss of stereochemical control in the derivatisation reaction leading to four diastereoisomers instead of two,[6] secondly, because the chiral auxillary was a phosphorus centre this introduced a phosphorus-phosphorus coupling in the ^{31}P n.m.r. spectrum thus reducing the sensitivity by a factor of two. We report here an alternative general configurational analysis that addresses these problems.

Using 4-nitrophenyl thiophosphate **(1)** and ethyl thiophosphate **(6)** as representative examples we have developed the following sequence, Scheme. Reaction with myrtenyl bromide[7] occurs selectively on sulphur to give the diesters **(2)** and **(7)** respectively. The thiophosphoryl centre could be converted into the diastereomeric triesters **(3)** and **(8)** by reaction with dimethyl sulphate. ^{31}P n.m.r. spectroscopy of the products **(3)** and **(8)** showed that the diastereosomers of **(3)** differed in chemical shift by 0.078 ppm (9.4 Hz at 121MHz) however, for **(8)** the difference in chemical shifts was significantly smaller, 0.031 ppm (3.7Hz at 121MHz) and did not appear to vary significantly with solvent, Table. Ideally, the diastereomeric separation should exceed the ^{18}O double bond shift (0.05ppm, ca. 6Hz at 121MHz) for the n.m.r. interpretation to be straightforward. The small separation of the diastereoisomers of **(8)** presumably is due to the modest difference between methyl and ethyl in conferring chirality; to increase the discrimination diphenyldiazomethane was used to alkylate the prochiral oxygen of **(6)** to give the triester **(9)**. Although the diastereoisomers **(9a)** and **(9b)** showed a larger



(1); (6) (2); (7) (3a) - (5a) (8a) - (10a) (3b) - (5b) (8b) - (10b)

(1) R^1 = -C6H4-NO2

(2) " ; R^2 =

(3) " ; " ; R^3 = $-CH_3$

(4) " ; " ; R^3 = $-CHPh_2$

(5) " ; " ; R^3 = -COPh

(6) R^1 = $-CH_2CH_3$

(7) " ; R^2 =

(8) " ; " ; R^3 = $-CH_3$

(9) " ; " ; R^3 = $-CHPh_2$

(10) " ; " ; R^3 = -COPh

difference in chemical shift than for **(8)**, 0.052 ppm (C_6D_6), this difference was still close to the $P=^{18}O$ n.m.r. shift for phosphate esters. A satisfactory difference in chemical shifts was obtained when benzoyl chloride was used to derivatise the prochiral oxygens in **(2)** and **(7)** to give the corresponding acyl thiophosphates **(5)** and **(10)**. In particular, for ethyl thiophosphate **(6)**, diastereoisomers **(10a)** and **(10b)** are separated by 0.068ppm (8.2 Hz at 121MHz) which ensures that the various isotopomers of **(10a)** and **(10b)** do not overlap when ethyl [^{16}O,^{18}O]thiophosphate is taken through the sequence.

TABLE:

Compound	Diastereomeric separation in Hz at 121MHz
(3)	9.4 ($CDCl_3$)
(5)	12.0 ($CDCl_3$)
(8)	3.7 ($CDCl_3$)
	3.9 (CD_3OD)
	3.5 (C_6D_6)
(9)	4.4 ($CDCl_3$)
	6.3 (C_6D_6)
(10)	8.2 ($CDCl_3$)

The ^{31}P n.m.r. shown in Figure 1A illustrates the configurational analysis of R_p-4-nitrophenyl [^{16}O,^{18}O]thiophosphate (1) prepared by our general route.[4] Since the absolute configuration follows from the synthesis the absolute configurations of (5a) and (5b) can be assigned on the basis of the observation of a double bond ^{18}O shift on the down field diastereoisomer and a single bond ^{18}O shift on the upfield diastereoisomer. The downfield isomer has the R_p configuration.

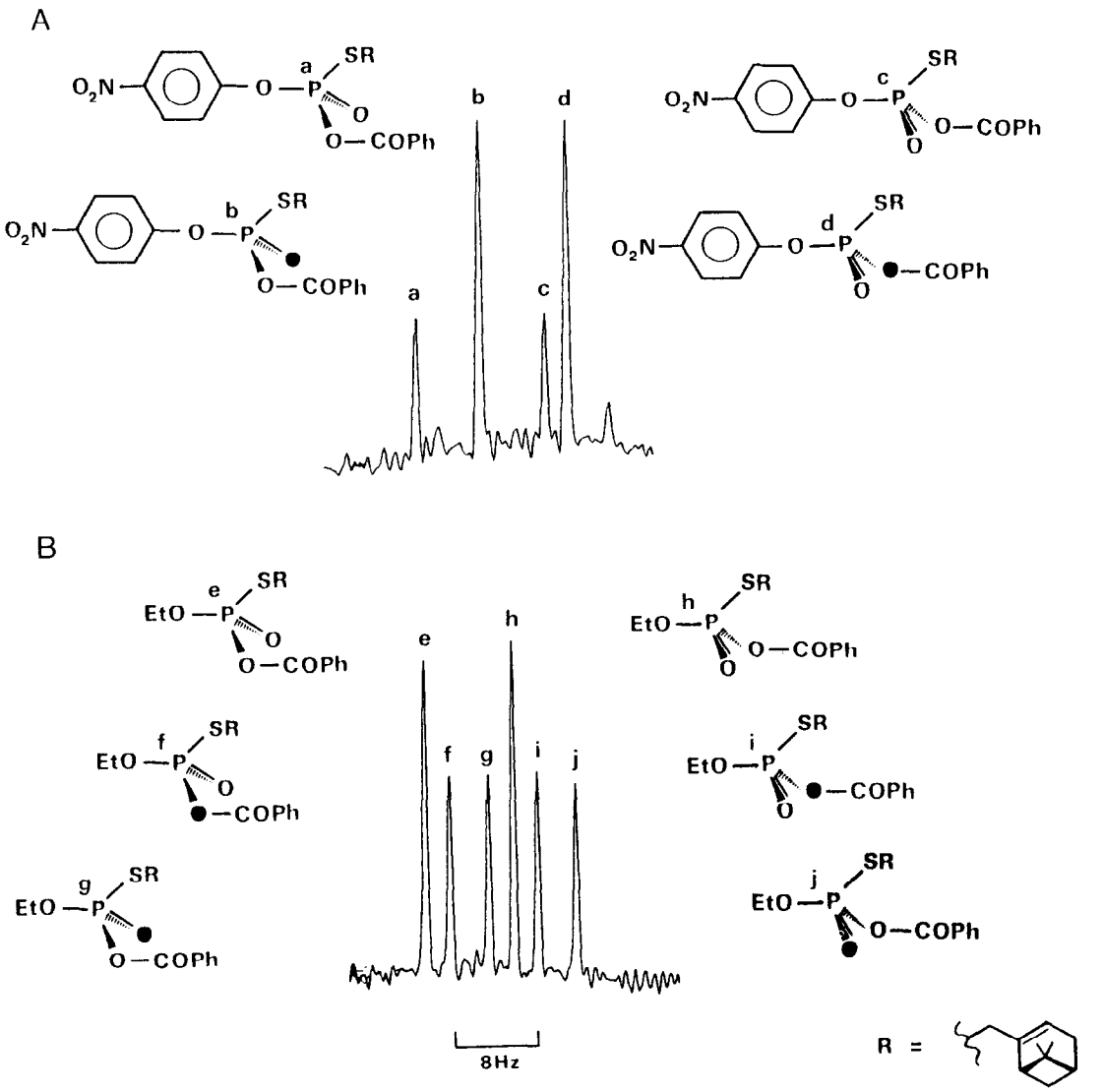


Figure: High field ^{31}P n.m.r. spectra (Bruker AM-300, 121.5MHz) of (A) compound (5) derived from R_p-4-nitrophenyl [^{16}O,^{18}O]thiophosphate (1) and (B) compound (10) derived from racemic ethyl [^{16}O,^{18}O]thiophosphate (6).

Figure 1B shows the stereochemical analysis of racemic ethyl [^{16}O,^{18}O]thiophosphate **(6)** with assignment as shown. The assignment of the absolute configuration of **(10)** was achieved by carrying out the same analysis on authentic R_p-O-ethyl [^{16}O,^{18}O]thiophosphate; the downfield resonance is assigned to the R_p diastereoisomer. It is important to note that each of the steps in the sequence shown in the Scheme proceed essentially quantitatively, as judged by ^{31}P n.m.r. spectroscopy, such that the configurational analyses can be performed as a "one-pot" reaction without need of purification steps.

The above configurational analysis is potentially general and is currently being used to probe the participation of monomeric thiometaphosphate in the solvolysis reactions of thiophosphate monoesters.

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