Free Monomeric Thiometaphosphate in Protic Solvents: Complete Racemisation at Phosphorus in the Ethanolysis of 4-Nitrophenyl Thiophosphate

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The ethanolysis of the monoanion of R_P-4-nitrophenyl [^{18}O]thiophosphate (**1**) proceeds with a large degree of racemisation (*ca.* 80%) and the dianion with complete racemisation, the corresponding solvolysis of the monoanion in aqueous ethanol giving ethyl thiophosphate (**3**) with *ca.* 70% racemisation; these data provide the first direct support of a freely-solvated monomeric thiometaphosphate intermediate (**2**) in the case of the solvolysis of the dianion in ethanol and a relatively long-lived intermediate for the monoanion in ethanol and in aqueous ethanol.

Monomeric metaphosphate has proved to be an enigmatic reactive intermediate. Much early work on the hydrolysis of phosphate monoesters was interpreted in terms of a free monomeric metaphosphate intermediate[1] and yet recent stereochemical,[2] thermodynamic,[3] and kinetic studies[4] agree that such reactions do not proceed *via* a free intermediate. More recently still, stereochemical[5] and positional isotope exchange[6] studies have provided persuasive evidence in favour of a comparatively free intermediate in phosphoryl transfer reactions conducted in aprotic and less nucleophilic protic solvents. We report here on stereochemical studies pertinent to the lifetime of the related monomeric thiometaphosphate intermediate.

O-Substituted thiophosphates display many of the characteristics of a dissociative pathway in the nucleophilic displacement reactions that they undergo.[7] There is little sensitivity to the nature of the nucleophile; in the hydrolysis reaction they show a typical bell shaped pH–rate profile; they hydrolyse faster than the corresponding phosphate esters both as the monoanion and the dianion, in contrast to the reduced reactivity of thiophosphate di- and tri-esters in associative nucleophilic displacement reactions. To probe the lifetime of the putative monomeric thiometaphosphate we studied the stereochemical course of thiophosphoryl transfer reactions of R_p-4-nitrophenyl [^{16}O,^{18}O]thiophosphate (**1**).[8]

The bis(tetra-n-butylammonium) salt of (**1**) was solvolysed in ethanol at 45 °C for *ca.* 45 min to give ethyl [^{16}O,^{18}O]thiophosphate (**3**) as the major product together with reisolated starting material. Both thiophosphate monoesters (**1**) and (**3**) were subjected to configurational analysis[9] and the high field ^{31}P n.m.r. spectra are shown in Figure 1. The ethyl [^{16}O,^{18}O]-thiophosphate (**3**) obtained from the solvolysis reaction was completely racemised. The reisolated (**1**) was *ca.* 95% R_p, which is identical to the material as synthesised indicating that the starting material did not racemise during the reaction. Furthermore, we have shown that the product is configurationally stable under the conditions of the solvolysis reaction. The thiophosphoryl transfer reaction has been conducted at

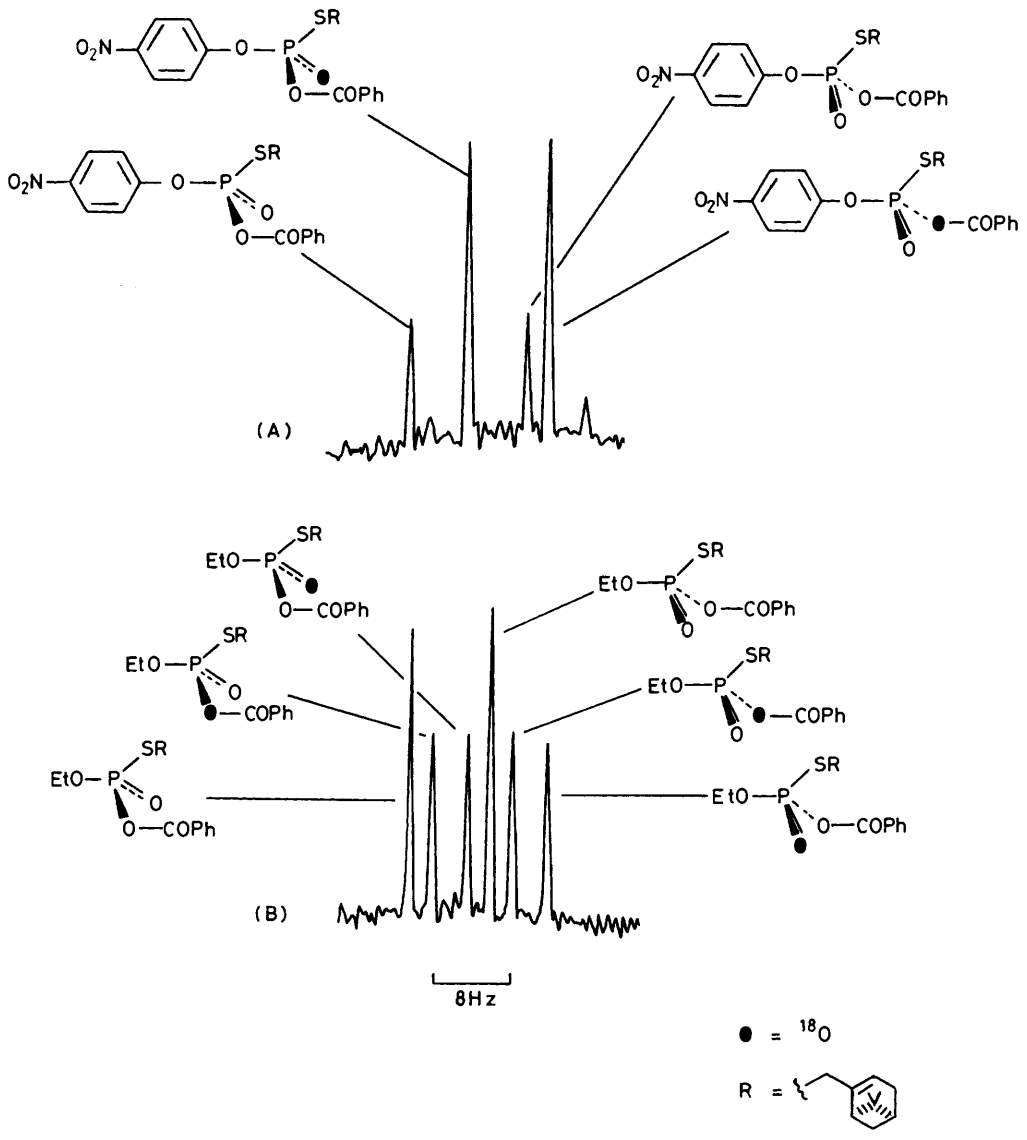
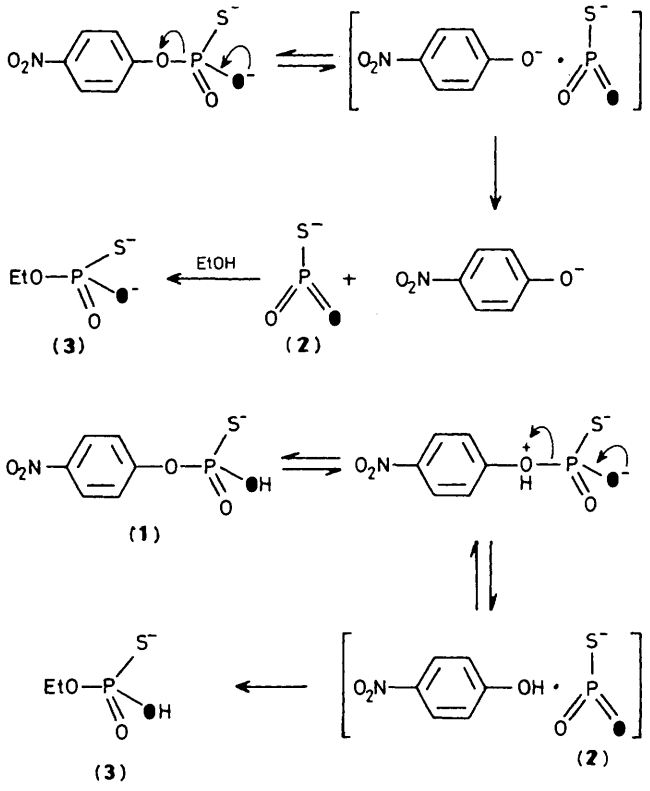


Figure 1. (A) The ^{31}P n.m.r. spectrum (Bruker AM-300, 121.5 MHz) of (**1**) reisolated from the ethanolysis of the dianion; derivatised by *S*-alkylation with myrtenyl bromide (10-bromopin-2-ene) and *O*-benzoylation with benzoyl chloride. (B) The ^{31}P n.m.r. spectrum (Bruker AM-300, 121.5 MHz) of (**3**) from the ethanolysis of the dianion of (**1**); derivatised as in (A).

two widely different concentrations of starting material (75 and 7.5 mM), and, within experimental error, these proceeded at similar rates with the same stereochemistry. These observations are powerful arguments against the involvement of any bimolecular processes and would support the proposal for the intermediacy of a free monomeric thiometaphosphate. Previously[8] it was unclear whether we were dealing with the mono- or di-anion since the triethylammonium salt was used. There was also the remote possibility that the tertiary amine was involved as a nucleophilic catalyst in the reaction, offering a trivial explanation for the observed racemisation. The use of the bis(tetra-n-butylammonium) salt clearly addresses both of these problems. The observation of complete racemisation of configuration provides the first direct evidence for a freely solvated thiometaphosphate intermediate (Scheme 1).

The mono triethylammonium salt of (**1**) was solvolysed in neat ethanol for 4 h at room temperature and the product subjected to configurational analysis. Both the starting material (**1**) and the product (**3**) were shown to be configurationally stable under these conditions. The observed 80% racemisation with 20% excess inversion of configuration in the product must therefore arise during the thiophosphoryl transfer steps and supports a long-lived thiometaphosphate intermediate (**2**).

In the first stereochemical study of a simple phosphoryl transfer reaction[2] it was shown that the methanolysis of the phenyl phosphate monoanion or 2,4-dinitrophenyl phosphate dianion in aqueous methanol occurs with complete inversion of configuration. For direct comparison we have now determined the stereochemical course of the thiophosphoryl transfer from 4-nitrophenyl thiophosphate to ethanol conducted in aqueous alcohol. The sodium salt of (**1**) (0.2 mmol) in ethanol–water (1 : 1.5 mol ratio) at a nominal pH of 6.8 was heated at 60 °C for 90 min to give (**3**), inorganic thiophosphate and remaining starting material in approximately equal amounts. Although under these conditions the dianion of (**1**)



Scheme 1

predominates (the apparent pK_a was determined to be *ca.* 4.8 under these conditions) we believe that the reaction proceeds through the monoanion since raising the pH by one unit reduces the rate considerably. Stereochemical analysis of the isolated (**3**) showed that significant racemisation (*ca.* 70%) had accompanied the thiophosphoryl transfer, with *ca.* 30% excess S_P (**3**) arising from inversion of configuration. Control experiments indicated that the racemisation arises during the thiophosphoryl transfer. This result is in marked contrast to the corresponding phosphoryl transfer reactions which proceed stereospecifically, establishing a clear mechanistic difference between phosphoryl and thiophosphoryl transfer reactions in aqueous solutions. This finding may be pertinent to the widespread use of thiophosphoryl transfer to probe the mechanism of enzyme catalysed phosphoryl transfer.[10]

In conclusion, we have shown significant racemisation of configuration during thiophosphoryl transfer reactions independent of the counterion (sodium, tetrabutylammonium, triethylammonium), ionised states (mono- or di-anion), solvent (neat ethanol, aqueous ethanol) and concentration of the thiophosphate monoester, and in particular, the complete racemisation observed in the solvolysis of the dianion of (**1**) provides the first direct evidence for a freely solvated monomeric thiometaphosphate intermediate in hydroxylic solvent.

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