Differences in Mechanisms of Nucleophilic Substitution at Phosphorus in *S*-Alkyl Alkylphosphonothioates and *S*-Alkyl phosphorothioates

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Summary Whereas most phosphono-derivatives are hydrolysed more rapidly by hydroxide than the corresponding phosphoro-derivatives, the reverse situation holds for *S*-alkyl phosphonothioates and *S*-alkyl phosphorothioates; this reversal of the more usual pattern may be related to a stereochemical difference in that nucleophilic substitution in *S*-alkyl alkylphosphonothioates proceeds with *inversion* of configuration, whereas *retention* of configuration is observed for similar reactions with *S*-alkyl phosphorothioates.

ALKYL phosphonic halides and dialkyl (aryl) alkylphosphonates are hydrolysed in alkali more rapidly than the corresponding phosphoro-derivatives.[1] The usually accepted explanation as to why phosphoro-compounds are hydrolysed less readily and are less susceptible to nucleophilic attack at phosphorus than their phosphono-analogues is that electron release from substituents with lone pairs of electrons increases the electron density at phosphorus making bond formation with the nucleophile more difficult.

TABLE. Rates of hydrolysis of phosphonothioates and phosphorothioates

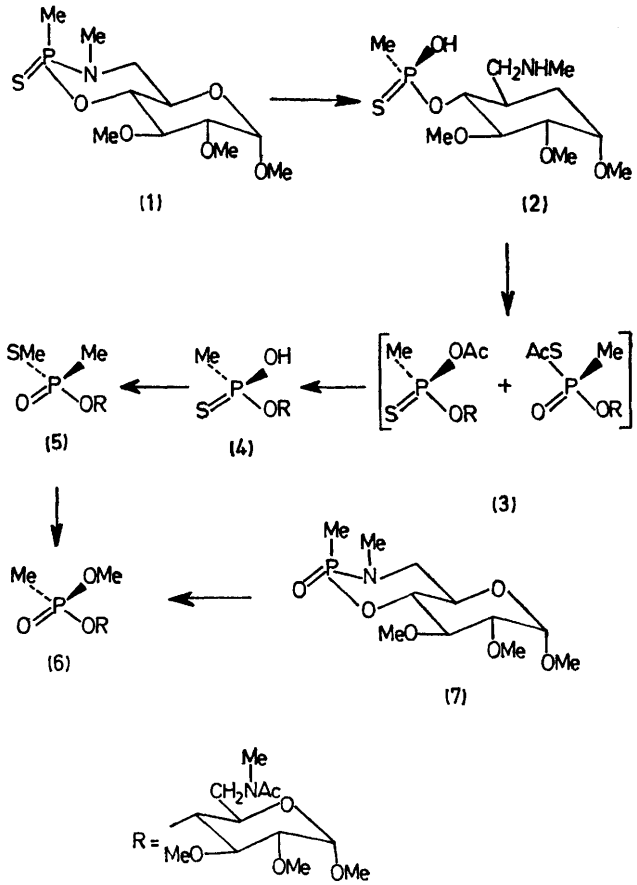
Compound[a]	Second-order hydrolysis rate,[b] k_{OH}/l mol^{-1} s^{-1}
(A)	$3{\cdot}8 \times 10^{-3}$
(B)	$6{\cdot}6 \times 10^{-3}$
(C)	0·16
(D)	0·42

(A), R = Pr (B), R = Pr
(C), R = $CH_2CH_2NMe_3I^-$ (D), R = $CH_2CH_2NMe_3I^-$

[a] For comparison k_{OH} values for ethyl methylphosphonofluoridate and diethyl phosphorofluoridate were 52 and 2·9 l mol^{-1} s^{-1} respectively. [b] Rates were measured conductiometrically in water containing propan-2-ol (5% v/v), total ionic strength 0·1M with sodium nitrate. For preparation see ref. 12

In these terms *S*-alkyl alkylphosphonothioates would be expected to react more rapidly with nucleophiles than the corresponding *S*-alkyl phosphorothioates whereas the reverse is true (see Table). Although there is no obvious explanation for this in terms of electron distribution, the finding, reported below, that alkoxides displace *S*-alkyl groups from *S*-alkyl phosphorothioates with *retention* of configuration, whereas similar displacements from *S*-alkyl alkylphosphonothioates occur with *inversion* of configuration makes it possible that there is a stereochemical explanation for the apparent anomaly (provided that displacements from phosphoro-halides, like displacements from phosphono-halides[2] occur with inversion of configuration).

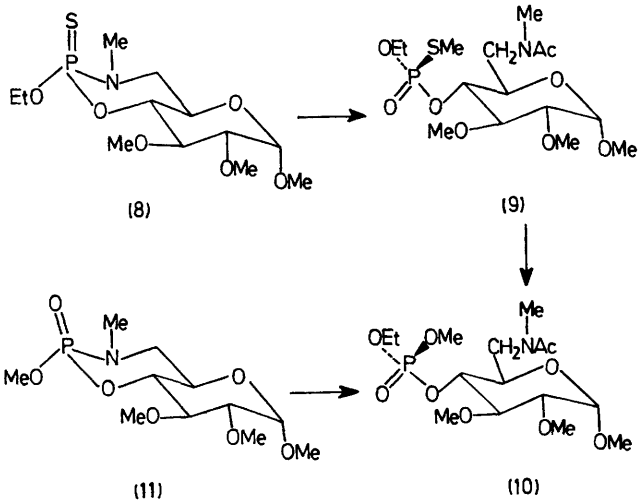
Although many optically active phosphono-derivatives of established configurations have been used for stereochemical studies,[3] it has not been possible until recently to carry out similar studies with phosphoroderivatives; only a few optically active acyclic phosphoro-derivatives have been prepared[4] and configurational assignments have not been reported. Now however, optically active acyclic phosphoro- and phosphono-derivatives with well defined configurations at phosphorus may be prepared conveniently by ring opening of 1,3,2-dioxa-[5,6] and oxathiaphosphorinans[6] and tetrahydrooxazaphosphorines[7] formed from suitably substituted carbohydrate derivatives. The use of such derivatives to compare the stereochemical outcome of nucleophilic displacements of *S*-alkyl groups in *S*-alkyl alkylphosphonothioates and *S*-alkyl phosphorothioates is outlined below.



SCHEME 1

The reaction sequence in Scheme 1 confirmed the well established result[8,9] that *S*-alkyl alkylphosphonothioates undergo base-promoted P–S bond cleavage with inversion of configuration at phosphorus. The tetrahydro-1,3,2-oxazaphosphorine carbohydrate derivative (**1**),[7] on treatment with dilute aqueous HCl at room temperature underwent

P–N bond cleavage with inversion of configuration at phosphorus to afford (**2**). With acetic anhydride in pyridine at room temperature, (**2**) afforded the mixture of mixed anhydrides, (**3**). The mixed anhydrides[10] were treated with dilute aqueous cold NaOH for 30 min to



SCHEME 2

afford the thioacid (**4**), which was not isolated but was converted into (**5**) by direct addition of methyl iodide to the alkaline reaction mixture. The *S*-methyl derivative (**5**), purified by chromatography over silica, was obtained in 76% yield from (**1**). The reactions in the sequence (**2**) to (**5**) do not break any P–X bonds and do not affect the configuration at phosphorus. Compound (**5**) was converted into (**6**) in 50% yield and with inversion of configuration by treatment with cold 1M NaOMe in MeOH for 1 h. The configuration of (**6**) was established when it was also prepared by sequential treatment of (**7**)[7] with ethanolic HCl (P–N bond cleavage with inversion of configuration) and Ac_2O in pyridine. The n.m.r. spectra of samples of (**6**) prepared either from (**5**) or (**7**) established their common identity. The diastereoisomer, epimeric at phosphorus, had a different spectrum.

The reaction sequence in Scheme 2 in which (**10**) (in yields of 50 and 72% respectively) was formed either from (**9**) or (**11**) in similar fashion to that described above, established that (**9**), with NaOMe, gave (**10**) with retention of configuration at phosphorus. [The formation of (**9**) (in 85% yield) from (**8**)[7] in similar fashion to the formation of (**5**) from (**1**), established the configuration of (**9**).]

The observation that the *S*-methyl phosphorothioate (**9**) was converted into the corresponding methyl phosphate (**10**) with retention of configuration is consistent with the assumption that in *S*-methyl phosphorothioates oxygen is more apicophilic than sulphur;[11] thus the initial five-co-ordinate trigonal bipyramid intermediate is formed by attack of methoxide at phosphorus opposite an oxygen ligand with displacement of -S-Me occurring from a basal position or from an apical position following pseudorotation. In contrast, the configurational inversion[8,9] observed in *S*-alkyl phosphonothioate reactions is consistent with attack by methoxide at phosphorus opposite sulphur rather than oxygen; recent kinetic studies support this view.[9] These results provide further evidence for the variability of the relative apicophilicities of oxygen and sulphur, depending on the nature of the other ligands attached to phosphorus.[11] Further, these results may imply that whereas a five-co-ordinate intermediate is formed in the phosphorothioate series it may not be necessary to invoke such an intermediate in the phosphonothioate series and it may be more accurate to consider displacements in the phosphonothioate series as proceeding by a $S_N2(P)$ mechanism.

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