Epimerisations and Non-stereospecific Reactions of 1,3,2-Oxazaphospholidin-2-ones and -2-thiones

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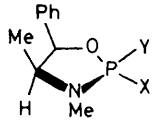
cis-2-Chloro-3,4-dimethyl-5-phenyl-1,3,2-oxazaphospholidin-2-one (**1a**) reacts with *O*-ethyl thiophosphate with *ca.* 10% inversion and 90% retention of configuration and with fluoride ion with complete loss of stereochemistry, and (**1a**) and the corresponding -2-thione (**2a**) are epimerised to the more stable *trans*-isomers by pyridine and other nucleophilic catalysts; these reactions formally require an unexpected in-line exocyclic displacement at a phosphorus centre held in a five-membered ring.

The stereochemistry of displacement reactions of 2-substituted 1,3,2-oxazaphospholidin-2-ones (X = O) and -2-thiones (X = S) derived from (−)-ephedrine have been extensively studied by Inch and co-workers.[1,2] It is generally accepted that such systems are configurationally stable and that exocyclic displacement reactions at phosphorus held in a five-membered ring proceed with retention of configuration because of the strong preference for the ring to be placed axial–equatorially in the pentaco-ordinate intermediate.[3] We report here that *cis*-2-chloro-3,4-dimethyl-5-phenyl-1,3,2-oxazaphospholidin-2-one (**1a**) reacts non-stereospecifically with *O*-ethyl thiophosphate (90% retention and 10% inversion). This reaction has recently been used in the synthesis of [^{16}O,^{17}O,^{18}O]thiopyrophosphates[4] and the configurational analysis of isotopically chiral *O*-alkylthiophosphate.[5] Furthermore, compound (**1a**) and the corresponding -2-thione (**2a**) are epimerised by nucleophilic catalysts, and in particular pyridine, in a reaction that formally requires an exocyclic displacement that proceeds with *inversion* of configuration. This has important implications for the synthesis of isotopically chiral phosphate[6] and thiophosphate[5] monoesters and for the use of the phosphorochloridates (**1**) and (**2**) as chiral derivatising agents in the determination of the enantiomeric excess of chiral alcohols and amines,[7] and [^{16}O,^{18}O]thiophosphate monoesters.

Compound (**1a**) can be prepared as the major diastereoisomer (*cis* : *trans ca.* 10 : 1) by the reaction of (−)-ephedrine with phosphoryl chloride in the presence of triethylamine and can be isolated in pure form either by silica gel chromatography or by recrystallisation.[1] Reaction of the pure (**1a**) with *O*-ethyl thiophosphate bis(tributylammonium) salt in dioxane gave a mixture of two major diastereoisomers (**3a** and **b**) that arise because of the generation of a new chiral centre at the thiophosphoryl phosphorus, together with two minor diastereoisomers arising from partial loss of stereochemical control at the oxazaphospholidine phosphoryl centre. Careful analysis of the purity of (**1a**) has established that this does *not* arise from a contaminating amount of (**1b**) and the epimerisation occurs during the coupling reaction. In view of the absolute stereochemical control usually observed in the exocyclic displacement reactions of such systems we have looked for the origins of this loss of stereochemical control. The phosphorochloridate (**1a**) was observed to be completely configurationally stable in solution in the presence of tributylamine. Furthermore, the coupling reaction was monitored by ^{31}P n.m.r. spectroscopy and at 50% reaction there was no evidence for the epimerisation of (**1a**). There are two alternative explanations for this result: either the initial nucleophilic displacement reaction occurs non-stereospecifically, or the products (**3a** and **b**) epimerise during the course of the reaction. Samples taken from a coupling reaction after 24 and 48 h showed closely similar relative amounts of the minor diastereoisomers (**3c** and **d**), suggesting that the loss of stereochemical integrity occurs in the displacement reaction.

When the above reaction was carried out in pyridine the products (**3a** and **b**) and (**3c** and **d**) were produced in comparable amounts. Under these conditions we have established that the loss of stereochemical control arises from competing epimerisation of the starting material (**1a**). In contrast with a previous report,[2] we observe that in pyridine the pure *cis*-material (the kinetic product) epimerises to the *trans*-compound (the thermodynamic product). The equilibration of (**1a**) can be monitored directly by ^{31}P n.m.r. spectroscopy ($t_{\frac{1}{2}}$ *ca.* 12 h at room temperature) [Figure 1; δ(^{31}P), pyridine, 24.0 p.p.m. *trans*; 19.54 p.p.m. *cis*]. The



(**1a**) X = O; Y = Cl
(**1b**) X = Cl; Y = O
(**2a**) X = S; Y = Cl
(**2b**) X = Cl; Y = S
(**3a** and **b**) X = O; Y = OP(O)(S)OEt
(**3c** and **d**) X = OP(O)(S)OEt; Y = O
(**4a**) X = O; Y = F
(**4b**) X = F; Y = O

(**9**) X or Y = O or 

(**10**) X or Y = S or OMe

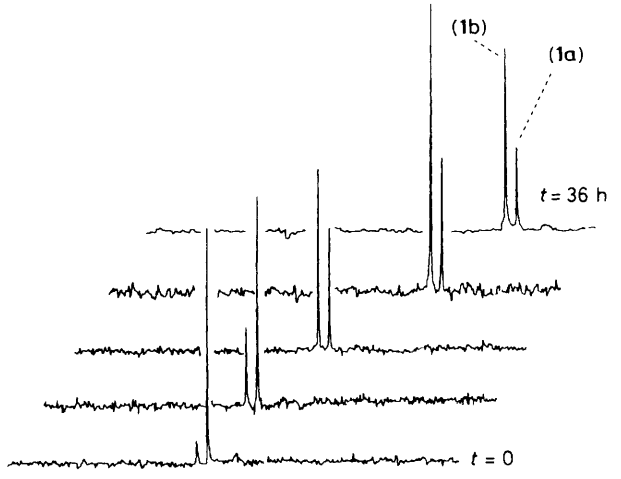
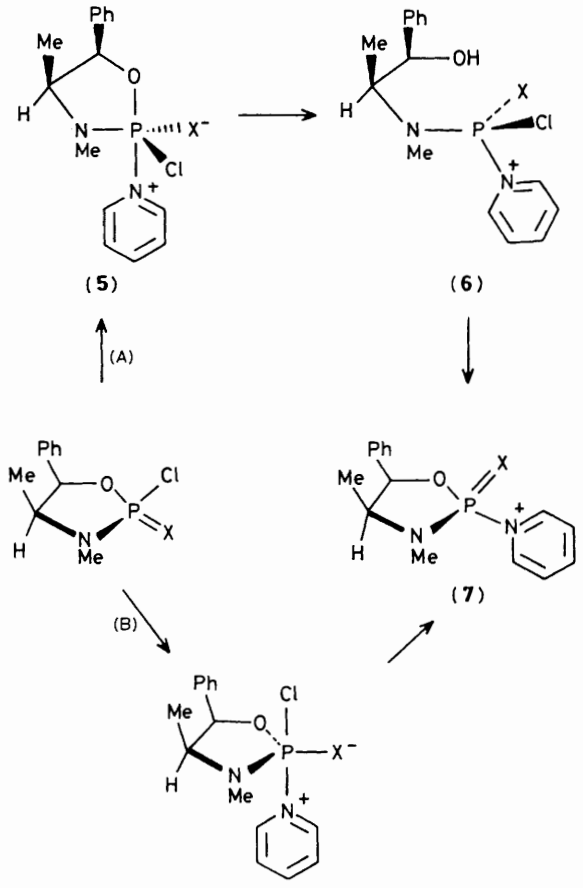


Figure 1. The ^{31}P n.m.r. spectra of the epimerisation reaction of the *cis*-compound (**1a**) in anhydrous pyridine.

thermodynamic mixture favours the *trans*-material by *ca.* 2:1 and is obtained starting from either the pure *cis*-(**1a**) or pure *trans*-(**1b**). When (−)-ephedrine and phosphoryl chloride reacted in pyridine the *trans*-product (**1b**) was obtained as the major isomer directly. The isolated material is identical with the minor isomer reported by Inch [m.p. 110—111 °C; δ(^{1}H) $CDCl_3$: 0.80 (3H, d, *J* 7 Hz), 2.65 (3H, d, *J* 13 Hz), 3.70 (1H, ddq, *J* 7 and 7 Hz†), 5.54 (1H, dd, *J* 7 and 7 Hz), and 7.3 (5H, ArH)]. Similarly the *cis*-1,3,2-oxazaphospholidine-2-thione (**2a**) is obtained as the major isomer on reaction of (−)-ephedrine with thiophosphoryl chloride in benzene in the presence of triethylamine. Treatment of the isolated pure *cis*-compound (**2a**) with anhydrous pyridine led to the thermodynamic mixture of epimers at phosphorus with the *trans*-compound favoured by *ca.* 3:1. This reaction was considerably slower ($t_{\frac{1}{2}}$ *ca.* 16 h at 50 °C) than the corresponding reaction of (**1a**), as would be expected from the known difference in reactivity of trisubstituted thiophosphates as compared to phosphates in associative nucleophilic substitution reactions.[8] With exocyclic substituents other than halogen no such epimerisations were observed. However, in seeking other examples of exocyclic displacement reactions not involving amine nucleophiles that proceed non-stereospecifically we have observed that when either (**1a**) or (**1b**) is treated with one equivalent of tetrabutylammonium fluoride in tetrahydrofuran (THF) identical mixtures of the epimeric cyclic fluorides (**4a**) and (**4b**) were produced. The reaction is instantaneous and it was not possible to determine whether the epimers arise in the first displacement step or as a result of epimerising the initial product.

The mechanism of these epimerisation reactions is of considerable interest. Presumably in the case of pyridine the amine must be acting as a nucleophile since no other nucleophile is present. We cannot rigorously exclude the possibility that a trace of base hydrochloride is formed and that this is responsible for the epimerisation. However, the chloro compound (**1a**) does *not* epimerise in anhydrous acetone in the presence of LiCl. Furthermore, when lutidine was used in place of pyridine the rate of the epimerisation was considerably reduced. The lowest energy pathway for a direct exocyclic displacement at phosphorus held within a five-membered ring will be the adjacent mechanism involving a pseudorotation step; however this leads to retention of configuration at phosphorus.[2,3] The mechanism for the epimerisation must therefore be multistep and two principal pathways for this type of reaction can be considered (Scheme 1). Firstly, a mechanism involving initial ring opening, pathway (A), could account for our observations, as has been suggested for the epimerisation of the cyclic phosphorochloridate[9] and thiophosphorochloridate[10] derived from *meso*-hydrobenzoin. Alternatively, a direct in-line displacement, *via* the pentaco-ordinate intermediate (**8**), would invert the configuration at phosphorus, pathway (B), and would eventually give the epimeric chloro compound after displacement of the pyridinium ligand by chloride *via* the normal adjacent displacement (with retention).

Since no intermediates that were detectable by ^{31}P n.m.r. spectroscopy accumulated during the reaction it is difficult to distinguish between these two pathways. A pathway involving diequatorial placement of the five-membered ring would be unusual because of the presumed increased strain in the phosphorane. However, the energetic cost of moving a five-membered ring from axial–equatorial to the diequatorial position in a phosphorane plus the energy associated with moving the lone pairs on the ring heteroatoms from their preferred orientation in the equatorial plane has been estimated to be only *ca.* 20 kcal mol^{-1} (cal = 4.184 J) and this in part can be offset by the relative apicophilicities of the other substituents, *i.e.* the chlorine.[11] The possibility of direct in-line displacement, pathway (B), should not therefore be discounted.



Scheme 1

With other nucleophilic catalysts such as *N*-methylimidazole and *N*,*N*-dimethylaminopyridine epimerisation was also observed with both (**1a**) and (**2a**); however, the appearance of other resonances in the ^{31}P n.m.r. spectra make firm mechanistic conclusions difficult. The ^{31}P chemical shifts of these additional resonances suggest species in which the 1,3,2,-oxazaphospholidine ring is still intact. The most reasonable structures would be (**9**) in which the nitrogen nucleophile is still attached; support for this was obtained by demonstrating that addition of methanol led to formation of the cyclic triester (**10**) as a mixture of epimers in the case of (**2a**) with *N*-methylimidazole.[12]

The observation of exocyclic displacement reactions at phosphoryl and thiophosphoryl centres held in a five-membered ring proceeding with inversion of configuration, albeit at comparatively slow rates (with the exception of fluoride ion), is unexpected. Importantly, when using such systems to generate isotopic chirality at phosphorus,[4—6] particularly when the reaction involves a very weak nucleophile, the stereochemical integrity of the intermediates should not be assumed. Furthermore, in advocating the use of such systems

† This coupling constant appears to be incorrectly assigned in the original publication.[1]

as chiral auxillaries to determine the enantiomeric excess of chiral alcohols and amines[7] one should be aware of the potential loss of stereochemical control, and the use of pyridine and other nucleophilic catalysts should be avoided.

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