

The Stereochemical Course of Exocyclic Displacement Reactions of a Five-ring Phosphinate Ester

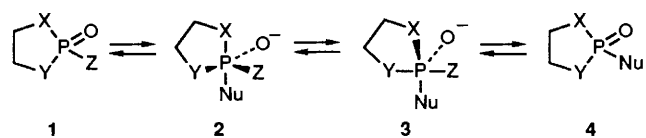
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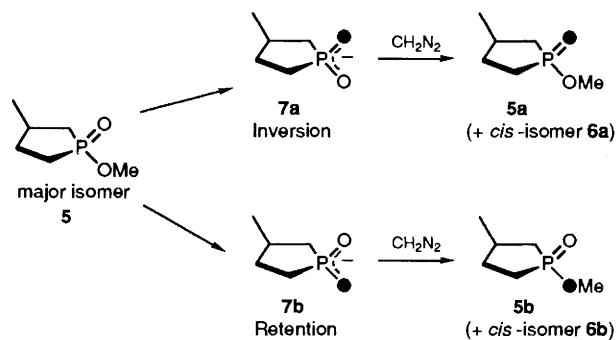
The stereochemical course of the exocyclic displacement reaction of a five-ring phosphinate (1-methoxy-3-methylphospholan-1-oxide) has been shown to proceed with inversion of configuration, which rules out a pathway involving a single pseudorotation step and suggests a direct in-line displacement with the ring diequatorial in the pentacoordinate intermediate or transition state.

It is well established that in displacement reactions with pentavalent phosphorus constrained in a five-membered ring the nucleophile approaches in-line with one of the ring substituents such that the first formed trigonal bipyramidal intermediate has the ring spanning axial-equatorial positions

thereby relieving ring strain in the transition state,¹ Scheme 1. It is frequently assumed that this is the case even for the parent phospholan where both ring substituents on phosphorus are carbon.² Hitherto no direct experimental evidence for or against this assumption appears to have been published.³ We



Scheme 1



Scheme 2

report here the stereochemical course of the hydrolysis reaction of 1-methoxy-3-methylphospholan-1-oxide which demonstrates that this is *not* the case. The alternative mechanism in which the ring is diequatorial in the intermediate and/or transition state seems to be of lower energy.

Studies on displacement reactions at phosphorus constrained within a five-membered ring have provided much of our current understanding of mechanistic organophosphorus chemistry.¹ A cornerstone of this field is that exocyclic displacement reactions on such systems proceed with retention of configuration because of the strong preference for the ring to span axial-equatorially in the trigonal bipyramidal intermediate⁴ e.g. **2** in Scheme 1. The loss of the exocyclic leaving group from an axial position must therefore be preceded by a pseudorotation step and hence overall retention of configuration. Systems in which this phenomenon has been demonstrated have invariably contained two heteroatoms directly bonded to phosphorus. In addition to the intrinsic preference of the five-membered ring to span axial-equatorial positions, the relative apicophilicity of the heteroatoms facilitates the initial placement of one of the groups axially (as in **2**) and also allows pseudorotation to an isomeric pentacoordinate intermediate of similar energy (as in **3**), Scheme 1.

Recent work by Gorenstein^{2a} and by Kluger^{2b} has shown that when one of the heteroatoms is changed to carbon as in ethyl (or methyl) propylphosphonate (**1**; X = O, Y = CH₂, Z = OEt) on hydrolysis the exocyclic displacement reaction no longer takes place because the pseudorotation step is unfavourable since it requires the carbon substituent on phosphorus to move to the axial position (**3**; X = O, Y = CH₂, Z = OEt). The products observed all arise from endocyclic ring cleavage because of the unfavourable pseudorotation step. In this study we have been interested in the exocyclic displacement reaction of a cyclic phosphinate for which endocyclic ring cleavage is not possible.

1-Methoxy-3-methylphospholan-1-oxide can be readily prepared by an adaptation of literature procedures⁵ as a mixture of racemic diastereoisomers **5** and **6**. Careful chromatography on basic alumina afforded a partial separation of the diastereoisomers, leading to fractions enriched in one of the isomers as judged from the high field ³¹P NMR spectrum [δ_p (CDCl₃) 79.81 (s) (major) and 79.74 (s) (minor) (15:1)]. Assignment of the relative configurations of these two diastereoisomers has not been made previously but we have tentatively assigned the *trans* configuration, structure **5**, to the major isomer in this mixture. Interestingly, consideration of Scheme 2 shows clearly how we have been able to determine

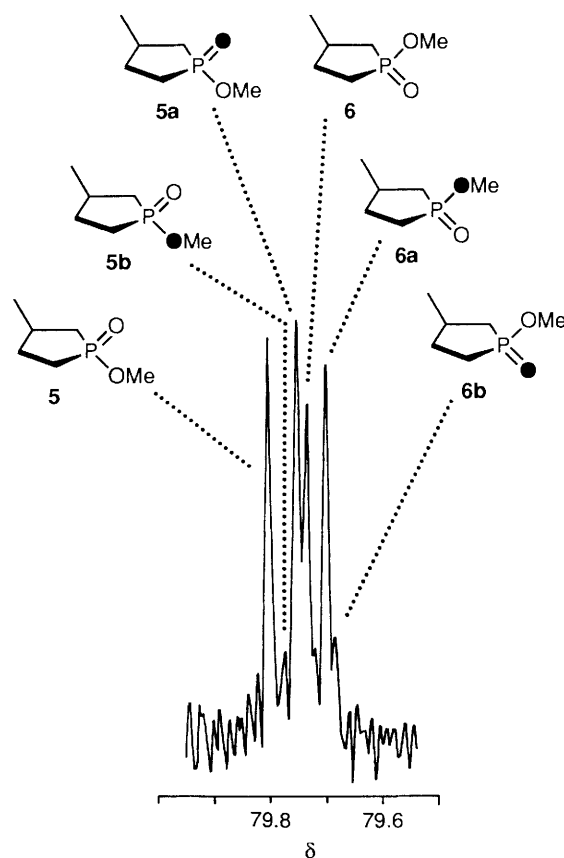
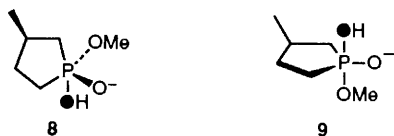


Fig. 1 ³¹P NMR spectrum (Bruker AM 300; 121.5 MHz) of the products from the hydrolysis of a mixture containing predominantly the *trans*-1-methoxy-3-methylphospholan-1-oxide **5** (**5**:**6** 15:1) in ¹⁸O-hydroxide (ca. 60 atom%) following methylation with diazomethane. The magnitudes of the upfield ¹⁸O-induced shift of the ³¹P NMR resonance are known to be bond-order dependent; in this system a P=¹⁸O induces an upfield shift of 0.051 ppm whilst a P-¹⁸O induces a shift of 0.032 ppm.

the stereochemical course of the hydrolysis in base using ¹⁸O-labelled hydroxide without needing to be confident of the relative configurations. The key to this is the fact that both the starting material and the final product are the 1-methoxy-3-methylphospholan-1-oxide. Focusing on the same diastereoisomer in both the starting material and the ultimate product mixture it can be seen that the stereochemical course of the hydrolysis step can be deduced directly from the location of the isotope in this diastereoisomer. If the reaction proceeds with inversion of configuration **5** will have ¹⁸O in the P=O **5a** and for **6** the ¹⁸O will appear in the P-OMe **6a** but if it proceeds with retention of configuration in **5** the ¹⁸O will end up in the P-OMe **5b** and for **6** it will appear in the P=O **6b**. The result would be the same if the major diastereoisomer **5** was in fact of the *cis* configuration.

1-Methoxy-3-methylphospholan-1-oxide (0.25 mmol, **5**:**6** 15:1) was dissolved in dioxane-¹⁸O-water (1:1, 0.5 ml; ca. 60 atom% ¹⁸O) and sodium hydroxide (0.25 mmol) was added. The hydrolysis at room temperature was monitored by ³¹P NMR spectroscopy and was shown to be complete after 22 h. The free acid of **7** was obtained by acidifying with trifluoroacetic acid and extraction with chloroform. The chloroform solution was washed with water, dried (MgSO₄) and the resulting material was directly methylated with diazomethane in diethyl ether to give a mixture of the *trans*-**5** and *cis*-**6** diastereoisomers. The high field ³¹P NMR spectrum of the resulting mixture is shown in Fig. 1, together with the assignment of the isotopomers. The ratio of the isotopomers is, within experimental error, the same as the ratio of the diastereoisomers **5** and **6** in the starting material indicating



that the reaction proceeded stereospecifically. [Similar experiments were conducted with differing proportions of the diastereoisomers (3 : 1 and 4 : 1) and in each case the diastereoisomeric ratio in the starting material was within experimental error the same as the isotopomer ratio.] As shown in Fig. 1 the diastereoisomer **5** in the product, which corresponds to the major diastereoisomer in the starting material, contained ^{18}O predominantly in the $\text{P}=\text{O}$ indicating that the reaction proceeds stereospecifically with *inversion of configuration*. Clearly, this result excludes a mechanism in which the five-ring initially spans the axial–equatorial positions in the pentacoordinate intermediate, as in **8**. The simplest explanation of the stereochemical observations would involve an in-line displacement reaction with the five-ring spanning diequatorially as in **9**. Whether **9** is an intermediate in a truly addition–elimination mechanism or a transition state in a concerted process is not addressed in these experiments. Comparing **8** with **9** it is clear that the difference in energy on exchanging an axial methoxy and an equatorial methylene group must be greater than the difference in energy between an axial–equatorial *vs* diequatorial all carbon ring. Although the energy required to place a five-membered ring containing heteroatoms diequatorially is estimated to be rather high (*ca.* 88 kJ mol^{-1}), only a proportion of this is associated with angle strain.^{2c,6} A considerable proportion of this unfavourable energy is associated with the rotation of the lone pairs on the equatorial heteroatoms from their preferred orientation in the

equatorial plane to the less favourable axial plane. The ring strain for a simple phospholan is estimated to be between 33 to 42 kJ mol^{-1} while the difference in apicophilicities between an alkyl and an alkoxy substituent is estimated to be *ca.* 42 kJ mol^{-1} . The closeness of these two energy differences means that there is likely to be a rather fine balance between in-line displacement and the adjacent attack followed by a pseudo-rotation but interestingly the lowest energy pathway in simple systems involves the ring being placed diequatorial contrary to that normally assumed.

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