# Chemical Studies of the Stereochemistry of 2-Substituted-1,3,2-dioxaphosphorinan-2-ones

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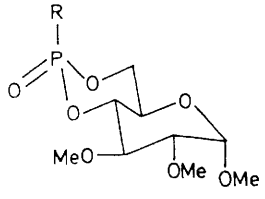
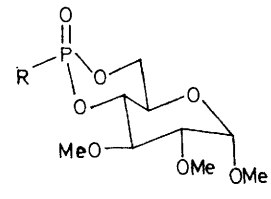
*Summary* The configurations at phosphorus in glucopyranoside 4,6-(*R*)- and (*S*)-methylphosphonate derivatives are established chemically by their conversion, by sequential addition of PhMgBr and EtMgBr, into (*S*)- and (*R*)-ethylmethylphenylphosphine oxides respectively; for the formation of 1,3,2-dioxaphosphorinans by phosphorus dihalide–diol reactions the kinetic preference for the thermodynamically less stable isomers depends on steric interactions in twist ring transition intermediates and the subsequent equilibration depends on the relative stabilities of the chair conformers.

RECENT studies[1–4] have shown that 1,3,2-dioxaphosphorinan-2-ones with electronegative 2-substituents such as alkoxy, aryloxy, or halide (and the stable isomers of similar dioxaphosphorinans that are substituted in the 4-, 5-, or 6-positions) adopt chair conformations in which the 2-substituent is orientated axially. The situation is less clear for dioxaphosphorinans substituted with 2-alkyl, phenyl, or arylalkyl substituents and for these compounds stereochemical preference cannot be predicted. Hitherto, conformational and configurational studies of dioxaphosphorinanes have depended on physical methods such as n.m.r. and i.r. spectroscopy,[1,2] *X*-ray crystallography,[3] and dipole moment measurements.[4] Here, a more chemical approach for establishing the configurations at phosphorus in the chiral 2-methyl-1,3,2-dioxaphosphorinan-2-ones (**1**) and (**2**) is described and from a comparison of the rates of formation of (**1**) and (**2**) and the corresponding 2-ethoxy-derivatives (**3**) and (**4**), it is suggested that the 1,3,2-dioxaphosphorinan rings in (**1**) and (**2**) have chair conformations.

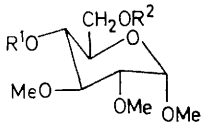
The phosphonates (**1**), m.p. 96—98°, $[\alpha]_D$ + 72° ($CHCl_3$) and (**2**) m.p. 205°, $[\alpha]_D$ + 114° ($CHCl_3$), were prepared by treatment of $MePOCl_2$ and compound (**5**) in ether with triethylamine and were separated by chromatography over silica in benzene–acetone–methanol (7:1:1) [(**1**), $R_F$ 0·27; (**2**), $R_F$ 0·35] before being crystallised from $Pr^i_2O$. An indication of the configuration at phosphorus in (**1**) was obtained by treating (**1**) briefly with PhMgBr in warm benzene to afford the 4(*S*)-methylphenylphosphinate (**6**), as a syrup, $[\alpha]$ + 38° ($CHCl_3$), $R_F$ 0·15 in acetone–light petroleum which on prolonged treatment with a ten-fold excess of EtMgBr in boiling benzene afforded *S*-(—)-ethylmethylphenylphosphine oxide[5] (**7**) $[\alpha]_D$ — 23°(MeOH). Similarly *R*-(+)-ethylmethylphenylphosphine oxide, $[\alpha]_D$



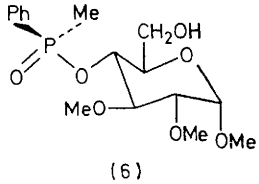
(1) R = Me
(3) R = OEt



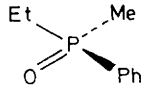
(2) R = Me
(4) R = OEt



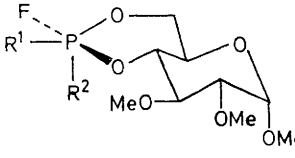
(5) $R^1 = R^2 = H$
(8) $R^1 = H$, $R^2 = P(:O)FMe$
(9) $R^1 = CH_2Ph$, $R^2 = OH$
(10) $R^1 = CH_2Ph$, $R^2 = P(:O)FMe$



(6)



(7)



(11) $R^1$ = Me, $R^2$ = =O
(12) $R^1$ = =O, $R^2$ = Me
(13) $R^1$ = =O, $R^2$ = OEt

+ 21° (MeOH) was obtained from compound (**2**). Since Grignard reactions of phosphorus esters have been shown to proceed with inversion of configuration[5] it was probable that the configurations at phosphorus in (**1**) and (**2**) are *R* and *S* respectively, as illustrated. Sequential nucleophilic displacement reactions, such as those used for investigating the absolute configuration at phosphorus in (**1**) and (**2**), afford potentially important practical procedures for the stereospecific synthesis of optically active phosphorus compounds and extensions of the above approach with (**1**), (**2**), and other carbohydrate phosphate derivatives are being investigated.

TABLE. *Spectroscopic data for* 1,3,2-*dioxaphosphorinan*-2-*ones*

| Compound | $\nu_{P=O}$ cm$^{-1}$ [a] | $\delta$ ($^{31}$P)[b] |
|---|---|---|
| (**1**) | 1254 (KBr)<br>1270 ($CDCl_3$) | −25·5 |
| (**2**) | 1235 (KBr)<br>1238 ($CDCl_3$) | −31·5 |
| (**3**) | 1294 ($CHCl_3$)<br>1300 ($CCl_4$) | +7·5 |
| (**4**) | 1265 ($CHCl_3$)<br>1268 ($CCl_4$) | +4 |

[a] I.r. spectra were measured using a Perkin-Elmer 357 Grating Spectrophotometer; [b] N.m.r. spectra were measured at 40·5 MHz in $CDCl_3$ with a JEOL-JNM-4H-100 spectrometer and the $^{31}$P chemical shifts are in p.p.m. from 85% $H_3PO_4$.

T.l.c. observations during the preparation of (**1**) and (**2**) gave the impression that (**1**) preponderated initially in the reaction mixture and then rearranged, in part, into (**2**). This situation was investigated in the following way. The n.m.r. spectrum in $CDCl_3$ of the mixture of the diastereoisomeric phosphonofluoridates (**8**) [prepared by treatment of (**9**) with $MePOF_2$ and $Et_3N$ in ether to give (**10**), and subsequent catalytic hydrogenolysis of (**10**) over Pd–EtOAc] showed a pair of quartets centred at $\delta$ 1·73 and 1·67. Following addition of triethylamine to the solution, the formation of (**1**) and (**2**) was monitored by n.m.r. spectroscopy. At first the P–*Me* doublet at $\delta$ 0·63 ($J_{P-Me}$ 16·9 Hz) which was characteristic of (**1**) preponderated but at equilibrium (**2**) (P–*Me*, $\delta$ 1·60 p.p.m.; $J_{P-Me}$ 18·2 Hz) was clearly the thermodynamically more stable product. The isomeric fluoridates disappeared from the reaction mixture at essentially the same rate thus showing that the rate of racemisation was greater than the rate of dioxaphosphorinan formation. These results are most easily rationalised on the assumption that the transition intermediate leading to the formation of (**1**) is in the twist ring conformation (**11**) in which the P–Me group occupies a sterically unhindered pseudoequatorial orientation. The transition intermediate (**12**), which leads to (**2**), has the P–Me in the unfavoured pseudoaxial orientation. If it is further postulated that once a 1,3,2-dioxaphosphorin-2-one ring is formed the conformation preference is for a chair rather than a twist ring or boat conformation, it is a logical consequence that equilibration of (**1**), in which the 2,4-diaxial interactions are a destabilising influence, into (**2**) should occur. For the formation of (**1**) and (**2**) by direct treatment of (**5**) with $MePOCl_2$, similar stereochemical considerations almost certainly apply and the initial preferential formation of (**1**) is consistent with the twist ring hypothesis irrespective of whether phosphorylation of the hydroxy-group at C-4 or C-6 in the sugar residue occurs first.

The twist ring transition intermediate hypothesis also accounts for the observation that when (**5**) and $EtOPOCl_2$ in ether were treated with $Et_3N$, compound (**4**) preponderated initially but rearranged in the reaction mixture into the more stable isomer (**3**), m.p. 115°, from $Pr^i_2O$, $[\alpha]_D$ + 114° ($CHCl_3$). The more rapid formation of (**4**) is consistent with the axial preference of electronegative substituents in 1,3,2-dioxaphosphorinans, only if a non-chair conformation such as (**13**) is invoked and the subsequent conversion of (**4**) into (**3**) is consistent with the well established conformational preference of 2-alkoxy-1,3,2-dioxaphosphorinan-2-ones.[1-4]

Supporting spectroscopic evidence for the configurations and conformations assigned to (**1**)—(**4**) is provided by i.r. and n.m.r. data (Table). It has been shown by Majoral and Navech[2] that in 1,3,2-dioxaphosphorinan-2-ones the phosphoryl stretching bonds are at higher frequency and the $^{31}$P chemical shifts are at higher field where the P=O is equatorially rather than axially orientated.

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