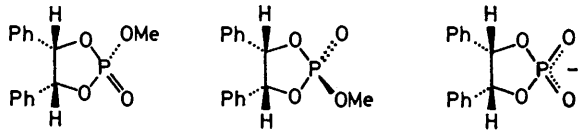
The Stereochemistry of 2-Substituted-2-oxo-4,5-diphenyl-1,3,2-dioxaphospholans and the Related Chiral [^{16}O,^{17}O,^{18}O]Phosphate Monoesters

By PAUL M. CULLIS, RICHARD L. JARVEST, GORDON LOWE,* and BARRY V. L. POTTER
(*The Dyson Perrins Laboratory, Oxford University, South Parks Road, Oxford* OX1 3QY)

Summary 2-Methoxy-2-oxo-4,5-diphenyl-1,3,2-dioxaphospholan prepared by the method of Ukita is shown to be the *trans*-diastereoisomer; it follows that our [^{16}O,^{17}O,^{18}O]phosphate monoesters have the (*S*)-configuration.

UKITA has shown that *meso*-hydrobenzoin and phosphorus trichloride oxide react in pyridine to give a single diastereoisomer of 2-chloro-2-oxo-4,5-diphenyl-1,3,2-dioxaphospholan, which readily reacts with an alcohol to give a single diastereoisomer of the cyclic phosphate triester.[1] 2-Methoxy-2-oxo-4,5-diphenyl-1,3,2-dioxaphospholan (Ukita's triester) prepared in this way has previously been assigned the *cis*-configuration (**1**),[2] since it differed in melting point and ^1H n.m.r. parameters from the *trans*-diastereoisomer (**2**) (Table 1), whose structure had been



(1) (2) (3)

established by *X*-ray crystallography.[3] For a number of diastereoisomers of cyclic five-membered phosphate esters and amides, it has been shown that the configuration can be assigned with some confidence on the basis of the deshielding effect of the P=O group, the H-4 and H-5 protons of a *cis*-diastereoisomer resonating 0·1—0·4 p.p.m. to lower field than the related *trans*-diastereoisomer.[4] The data in Table 1 appeared to fulfil this expectation.

The synthetic route to Ukita's triester has been developed into a general method of synthesis of chiral [^{16}O,^{17}O,^{18}O] phosphate esters.[2] A method of analysis of chiral [^{16}O,^{17}O,^{18}O]phosphate esters based on ^{31}P n.m.r. spectroscopy has also been developed which led to the unexpected conclusion that the cyclisation of phosphate monoesters to cyclic six-membered phosphate diesters occurs with retention of configuration at phosphorus.[5] Although the factors which control the stereochemical course of substitution at phosphorus in phosphate esters are not well understood,[6] this conclusion, together with the finding that the stereochemical course of the enzymic hydrolysis of isotopically labelled adenosine 3′,5′-phosphate occurs with retention of configuration,[7] whereas adenosine 3′,5′-(S_P)phosphorothioate is hydrolysed by the same enzyme with inversion of configuration,[8] led us to reconsider the stereochemistry of Ukita's triester.

TABLE 1. Comparison of the properties of Ukita's triester[1] with those of authentic *trans*-2-methoxy-2-oxo-4,5-diphenyl-1,3,2-dioxaphospholan (**2**).[3] The ^1H n.m.r. data of Ukita's triester are from our own work.[2]

Newton–Campbell triester (**2**)	Ukita's triester
M.p. 74—75 °C	M.p. 101—102 °C
δ_H ($CDCl_3$)	δ_H ($CDCl_3$)
3·76(d, J_{PH} 11·4 Hz, Me),	3·96(d, J_{PH} 11·5 Hz, Me),
5·45(d, J_{PH} 9·0 Hz, 2 CH)	5·76(d, J_{PH} 7·9 Hz, 2 CH)

Treatment of the pyridinium salt of the cyclic phosphate diester (**3**)[9] with diazomethane gave a mixture of the diastereoisomers (**1**) and (**2**) in the approximate ratio of 1 : 2. The ^1H and ^{31}P n.m.r. data of the two diastereoisomers derived in this way are shown in Table 2. The assignments were made by adding to this mixture authentic *trans*-diastereoisomer (**2**), prepared by the method of Newton and Campbell,[3] which enhanced the intensity of one set of resonances. Addition of Ukita's triester to the mixture enhanced the intensity of the same set of resonances in both the ^1H and ^{31}P n.m.r. spectra. Moreover, a mixture of Ukita's triester and the authentic *trans*-diastereoisomer (**2**) in approximately equal amounts showed resonances only of the *trans*-diastereoisomer in both the ^1H and ^{31}P n.m.r. spectra. Ukita's triester is therefore *trans*-2-methoxy-2-oxo-4,5-diphenyl-1,3,2-dioxaphospholan (**2**) and it is evident that the ^1H n.m.r. data of Newton and Campbell (Table 1) are inaccurate. Having unequivocally assigned the *cis*- and *trans*-diastereoisomers to the n.m.r. data, it is worth noting that the *correct* ^1H n.m.r. data shown in Table 2 are in

accord with the expectation[4] that the ring protons (H-4 and H-5) in the *cis*-diastereoisomer resonate at lower field (0·14 p.p.m.) than those in the *trans*-diastereoisomer.

TABLE 2. ^1H and ^{31}P n.m.r. data for the *cis*- and *trans*-diastereoisomers of 2-methoxy-2-oxo-4,5-diphenyl-1,3,2-dioxaphospholan prepared from the cyclic phosphate diester (**3**) by treatment with diazomethane.

trans	*cis*
δ_H ($CDCl_3$)	
3·96(d, J_{PH} 11·6 Hz, Me)	4·05(d, J_{PH} 11·6 Hz, Me)
5·76(d, J_{PH} 7·9 Hz, 2 CH)	5·90(d, J_{PH} 7·9 Hz, 2 CH)
δ_P ($CHCl_3$)[a]	
+13.36 p.p.m.	+14.23 p.p.m.

[a] Positive chemical shifts are downfield from trimethyl phosphate.

There remains, however, the discrepancy between the melting points (Table 1). Newton and Campbell purified the triester by sublimation,[3] whereas Ukita recrystallised the triester from methanol–light petroleum.[1] We had previously found difficulty in recrystallising Ukita's triester to constant melting point, although it was pure by ^1H and ^{31}P n.m.r. spectroscopy. We have now found that *rapid low temperature* (−78 °C) recrystallisation from methanol–hexane gives crystals, m.p. 74—75 °C, but if Ukita's triester is kept in methanol at room temperature for several hours, ring opening occurs to give dimethyl 1-(2-hydroxy-1,2-diphenylethyl)phosphate as the sole product, m.p. 101—103 °C. It seems likely that the product reported by Ukita *after recrystallisation from methanol–light petroleum* was this acyclic triester, in spite of the analytical data which were in good agreement with that required for the cyclic triester.

When 2′,3′-diacetyladenosine is phosphorylated by 2-chloro-2-oxo-4,5-diphenyl-1,3,2-dioxaphospholan (prepared *in situ* from *meso*-hydrobenzoin and phosphorus trichloride oxide) in pyridine, only one diastereoisomer is obtained. If the cyclic phosphorochloridate is prepared in tetrahydrofuran (THF) with only 2 equiv. of pyridine, both diastereoisomers are formed which react with 2′,3′-diacetyladenosine in the presence of a further equivalent of base to give both diastereoisomers of the cyclic phosphate triester. This is analogous to the observations made during the preparation of the diastereoisomers of 2-methoxy-4,5-diphenyl-1,3,2-dioxaphospholan-2-thione.[10] The ^{31}P n.m.r. chemical shifts [δ_P + 11·4 p.p.m. (*trans*) and δ_P + 12·1 p.p.m. (*cis*) in THF; the assignments were made by comparison with the relative ^{31}P chemical shifts in Table 2]† indicate, as expected, that the single diastereoisomer formed in pyridine (δ_P + 11·4 p.p.m. in THF) has the *trans* stereochemistry, *i.e.* it has the same stereochemistry as Ukita's triester.

The recognition that Ukita's triester is *trans*-2-methoxy-2-oxo-4,5-diphenyl-1,3,2-dioxaphospholan (**2**) means that our general method of synthesis[2] gives chiral [^{16}O,^{17}O,^{18}O] phosphate esters with the (*S*)-configuration. It also means that the cyclisation of D-glucose 6-[^{16}O,^{17}O,^{18}O]phosphate and adenosine 5′-[^{16}O,^{17}O,^{18}O]phosphate occurs with *inversion of configuration* at phosphorus, contrary to our earlier conclusion.[5] Finally, it follows that isotopically labelled adenosine 3′,5′-phosphate is hydrolysed by beef heart cyclic AMP phosphodiesterase with *inversion of configuration* at phosphorus.[7] This is in agreement with the observed stereochemical course of hydrolysis of adenosine 3′,5′-(S_P)phosphorothioate,[8] and of 2′-deoxyadenosine 3′,5′-phosphate,[11] catalysed by the same enzyme.

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† Positive chemical shifts are downfield from trimethyl phosphate.

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