1*H*-Tetrazole Catalysed Reactions of Trialkyl Phosphites: Observation of a Five-membered Cyclic Hydrophosphorane Intermediate during the Transesterification

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1*H*-Tetrazole-catalysed transesterification of a trialkyl phosphite with an alcohol and a ^{31}P NMR experiment in the case of 4,4,5,5-tetramethyl-2-(3-phenylpropoxy)-1,3,2-dioxaphospholane showed the existence of the corresponding cyclic five-coordinate hydrophosphorane as an intermediate.

The transesterification of trialkyl phosphites has been reported to be promoted by acids such as phosphoric acid,[1] diethyl hydrophosphonate[2] and aluminium chloride.[2] We have now found that 1*H*-tetrazole (pK_a 4.89) also smoothly catalyses the transesterification. Since the phosphite approach is extensively employed for the synthesis of phosphoric esters such as nucleotides and phospholipids it appeared of interest to explore the catalytic action of the tetrazole. Here, we describe the tetrazole-catalysed reactions of some phosphorus triesters in both the presence and absence of alcohols and some of its mechanistic features.

In a typical experiment, tributyl phosphite **1** in dichloromethane was treated with equimolar amounts of 3-phenylpropyl alcohol and tetrazole at ambient temperature for 22 h † to afford a mixture of transesterification products, which were analysed after oxidation with *m*-chloroperbenzoic acid (*m*CPBA); the latter was necessary because of the instability of the primarily formed phosphites (Table 1). HPLC analysis of the products

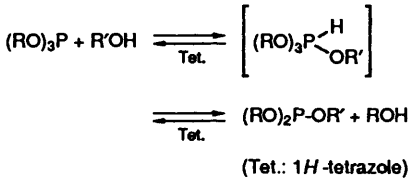
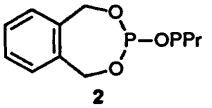
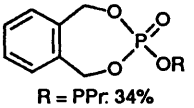
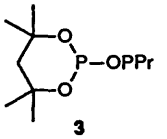
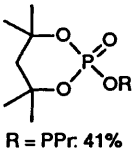
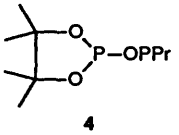
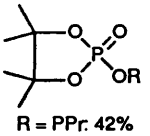
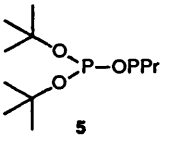
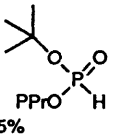


Fig. 1

showed that tributyl phosphate, dibutyl 3-phenylpropyl phosphate, and butyl di-3-phenylpropyl phosphate were formed in 21, 36 and 16% yields respectively accompanied by 6% of dibutyl hydrophosphonate.‡ Tris-3-phenylpropyl phosphate was not observed. Similar treatment of the seven- **2**, six- **3** and five-membered cyclic phosphites **4** with benzyl alcohol gave mainly a mixture of two ring-conserved 3-phenylpropyl and benzyl phosphates respectively after oxidation with *m*CPBA. The results were consistent with the observation in ^{31}P NMR experiments that the transesterification of the six-membered cyclic phosphite **3** with 3-phenylpropyl alcohol in $CDCl_3$ showed only one peak at 128.12 ppm even after 3 days. In the absence of the alcohol in the same experiment, a peak corresponding to the tetrazolide was not detected.[3] On the other hand, exposure of an acyclic analogue of **3** and **4**, di-*tert*-butyl 3-phenylpropyl phosphite to tetrazole both in the presence and in the absence of 3-phenylpropyl alcohol afforded exclusively *tert*-butyl 3-phenylpropyl hydrophosphonate.

To the best of our knowledge, no direct observation of an

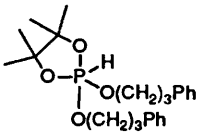
Table 1 Tetrazole-catalysed reactions of various phosphites[a]

Phosphite[b]	Alcohol[c]	Products and Yields[d,e]
$(BuO)_3P$ **1**	PPrOH	$(BuO)_3P(O)$: 21% $(BuO)_3P(O)$-OPPr: 36% $BuOP(O)(OPPr)_2$: 16%
 **2**	BzlOH	 R = PPr: 34% R = Bzl: 28%
 **3**	BzlOH	 R = PPr: 41% R = Bzl: 30%
 **4**	BzlOH	 R = PPr: 42% R = Bzl: 15%
 **5**	PPrOH	 : 85% [quant.(room temp., 4h without PPrOH]

[a] Equimolar amounts of the reaction components were stirred in CH_2Cl_2 at ambient temperature for 22 h and then oxidized with *m*CPBA. [b] All phosphites except for tributyl phosphite were prepared by the reactions of the corresponding phosphoramidites with 3-phenylpropyl alcohol and characterized by ^1H- and ^{31}P NMR spectroscopy. [c] PPrOH = 3-phenylpropyl alcohol and BzlOH = benzyl alcohol. [d] All new compounds were characterized by ^1H- and ^{31}P NMR spectroscopy as well as elemental analysis. [e] A mixture of transesterified phosphates were isolated by preparative TLC on silica gel and analysed by HPLC using authentic specimens. Yield of *tert*-butyl 3-phenylpropyl hydrophosphonate indicates isolated yield.

† When the reaction in $CDCl_3$ was monitored by means of ^{31}P NMR, an almost equimolar amount of a new product, presumably dibutyl 3-phenylpropyl phosphite was observed accompanied by the starting tributyl phosphite within 5 min after the reaction was initiated.

‡ These phosphates, prepared independently from the appropriate phosphorochloridates and alcohols as authentic specimens, were characterized by spectroscopic and elemental analyses; the tributyl phosphate was purchased.



6

Fig. 2

intermediate in the transesterification has been reported although a protonated phosphonium salt was postulated.[2] When the reaction of the five-membered cyclic phosphite **4** with 3-phenylpropanol in the presence of tetrazole in $CDCl_3$ was monitored by ^{31}P NMR spectroscopy, the spectrum which exhibited a doublet of quintets due to the coupling with the proton on the phosphorus (J 666.5 Hz) and two alcoholic methylene (J 18.7 Hz) at −24.95 ppm (80% H_3PO_4 as external standard) suggested the existence of the hydrophosphorane **6** as a minor component.[4] Its concentration during the reaction was kept constant for >2 days under anhydrous conditions, suggesting that **6** exists in an equilibrium reaction. Such a five-coordinate intermediate could not be detected in other cases by the same analysis. These differences probably arise because a phosphorane containing a five-membered ring is more stable than an acyclic one.[5] As a special case, transesterification of *o*-phenylene 8-quinolyl phosphite* with phenol was reported to proceed *via* a hydrophosphorane which was observed by ^{31}P NMR.[4a] Novel bicyclic phosphoramidites were shown to react with alcohols to yield the hydrophosphoranes which were transesterified with other alcohols without any catalyst.[4b,c] Therefore, it seems likely that phosphorane is an intermediate of the acid-catalysed transesterification, which would be formed spontaneously from a phosphite and an alcohol in the presence of an acid or *via* phosphonium salt.[6] The experimental result for *tert*-butyl phosphite **5** suggests strongly the formation of a phosphonium salt. The present mechanistic feature will be applicable to acid-catalysed hydrolysis of a phosphite.[7]

The present study suggests that workers in this area should take note of the following possibilities. In the phosphoramidite method for the phosphorylation of an alcohol, an excess of tetrazole is generally used for the rapid formation of phosphite. The excess of tetrazole could cause transesterification to give a mixture of phosphites, especially where an excess of an alcohol is employed and the reaction time is prolonged. The possibility should be also noted of the alkyl di-*tert*-butyl phosphite derived from di-*tert*-butyl phosphoramidite and the alcohol[8] being decomposed to the corresponding alkyl *tert*-butyl hydrophosphonate by the action of the remaining tetrazole.

Acknowledgements

This work was partially supported by a Grant-in-Aid for Scientific Research on Priority Areas from the Ministry of Education, Science and Culture, Japanese Government and Tokuyama Science Foundation.

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* It is possible for the amino group in the quinoline ring to play an important role in phosphorane formation. For other related examples, see J.-S. Tang, M. A. H. Laramay, V. Young, S. Ringrose, R. A. Jacobson and J. G. Verkade, *J. Am. Chem. Soc.*, 1992, **114**, 3129, and literature references cited therein.

Paper 2/02686D
Received 22*nd May* 1992
Accepted 10*th June* 1992