Stereochemistry of Hydrolysis at an Acyclic Phosphoryl Centre leading to an Achiral Phosphorus Acid

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Alkaline hydrolysis of S_P-methyl methylphenylphosphinate in 60% $H_2{}^{18}O$ has been shown to involve predominant (>90%) inversion of configuration at phosphorus; esterification of the resulting acid with the diazocompounds (**2**) gave, *inter alia*, diastereoisomeric menthyl esters; the isotopic labelling of these was deduced from the ^{18}O isotopic chemical shifts in their ^{31}P n.m.r. spectra.

The stereochemistry of nucleophilic substitutions at phosphoryl centres has been studied extensively.[1] However, it has not hitherto been possible to investigate the stereochemistry of hydrolyses since these lead to achiral acids. We now describe a general method that allows the stereochemistry of such hydrolyses to be established.

Alkaline hydrolysis of S_P-methyl methylphenylphosphinate[2]† (**1**) in 60% $H_2{}^{18}O$, followed by acidification at 0 °C with conc. HCl to pH *ca.* 1 and extraction with CH_2Cl_2, gave labelled methylphenylphosphinic acid. Mass spectrometry and ^{31}P n.m.r. spectroscopy (isotopic shift[3] of 5.6 Hz in methanol) showed that, as with methyl diphenylphosphinate,[4] hydrolysis involved complete attack at phosphorus and that no subsequent exchange of oxygen had occurred. When unlabelled phosphinic acid was dissolved in alkaline 60% $H_2{}^{18}O$ and isolated by the above procedure, no ^{18}O was incorporated.

A mixture of the diazocompounds (**2**) was prepared by oxidation with silver oxide‡ in xylene at −25 °C of the hydrazone prepared from (−)-menthone. At some point, epimerisation of the isopropyl group occurred. Esterification of methylphenylphosphinic acid with (**2**) gave menthyl, isomenthyl, neomenthyl, and neoisomenthyl methylphenylphosphinates in each case as two diastereoisomers. The menthyl esters are known[5] and their absolute configurations have been established; we have made those of isomenthol and neomenthol. Figure 1(a) shows the ^{31}P n.m.r. spectrum of the mixture of esters obtained from unlabelled phosphinic acid and Figure 1(b) shows the corresponding spectrum of the mixture from the above ^{18}O-labelled acid.

Clearly, in these esters, the isotopic upfield shift caused by a P,^{18}O single bond is *ca.* 4.6 Hz whereas that due to a P,^{18}O double bond is *ca.* 7.3 Hz. In Figure 1(b) resonance 6, which is due to R_P-menthyl ester, shows the presence of a major additional peak, at higher field, due to ^{18}O labelling. The isotopic shift is 4.7 Hz which corresponds to the presence of a P,^{18}O single bond; this isomer is therefore labelled as in (**3**). Similarly resonance 2, which is due to S_P-menthyl ester, shows the presence of a major labelled isomer with an isotopic shift of 7.1 Hz. This shift corresponds to the presence of a P,^{18}O double bond and the major labelled S_P-isomer is therefore (**4**). These major labelled products correspond to inversion of configuration at phosphorus in the hydrolysis of (**1**). However, there are minor ^{18}O-labelled menthyl isomers corresponding to *ca.* 8% of retention of configuration in this reaction and minor isomers due to retention are also clearly visible in for example the up-field neomenthyl resonances. This result is somewhat surprising; the expected energy differences in the trigonal bipyramidal intermediates leading to inversion and retention can not be substantially reflected in the relevant transition states.

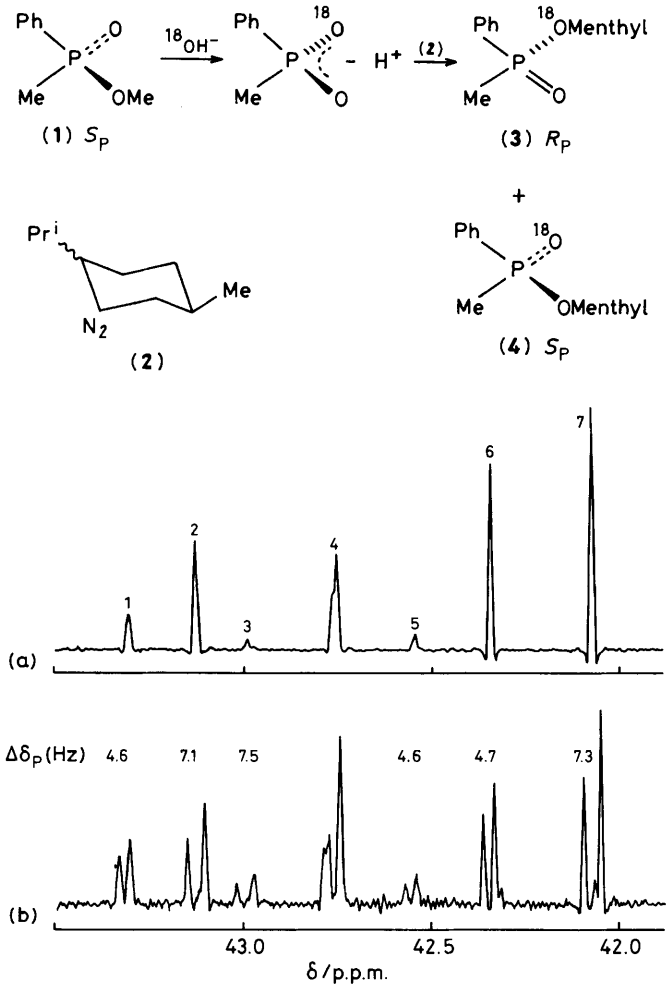

Figure 1. ^1H-Decoupled 162 MHz ^{31}P n.m.r. spectra, in diethyl ether/CD_3OD (2 : 1) of the methylphenylphosphinates obtained from the diazocompounds (**2**) and (a) unlabelled methylphenylphosphinic acid; and (b) the acid obtained from alkaline hydrolysis of S_P-methyl methylphenylphosphinate in 60% $H_2{}^{18}O$. 2 and 6 menthyl; 1 and 4, isomenthyl; 3 and 5, neoisomenthyl; 4 and 7, neomenthyl. In diethyl ether, the overlapping isomenthyl and neomenthyl signals (peak 4) are resolved and show isotopic shifts of 7.4 and 4.6 Hz respectively.

Extension of this method to a study of hydrolysis at other phosphoryl centres requires a knowledge of the absolute configuration of the corresponding menthyl esters either by *X*-ray analysis or by a reliable stereochemical correlation.

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† $[\alpha]_D^{18}$ − 55.0 (*c* 7.3, benzene). No R_P isomer could be detected by the method of Harger (ref. 6) and the ester is at least 98.5% S_P.

‡ We have been unable to prepare silver oxide that will carry out this oxidation (ref. 7) but some commercial samples are successful, albeit in low (<20%) yield.

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