New Methods for Probing the Chirality of ^{18}O-Labelled Phosphinic Acids

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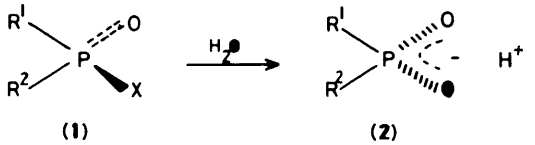
The chirality of singly ^{18}O-labelled methyl(phenyl)phosphinic acid can be probed by conversion into the diastereoisomeric myrtenyl esters by the action of myrtenyl bromide on the potassium salt of the acid in Me_2SO in the presence of 18-crown-6. The Mitsunobu reaction applied to the esterification of singly labelled methyl(phenyl)phosphinic acid with myrtenol gives some doubly labelled ester. The minor retention of configuration at phosphorus that occurs in the alkaline hydrolysis of (S_P)-methyl methyl(phenyl)phosphinate is due to racemisation of the ester by methoxide ion formed in the hydrolysis. Alkaline hydrolysis of the corresponding (S_P)-menthyl ester occurs with >98% inversion of configuration at phosphorus.

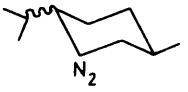
The stereochemistry of hydrolysis of the phosphoryl compounds (**1**) can be studied using ^{18}O-labelling if the chirality of the resulting phosphinic acid (**2**) can be established. One method that we have used[1] is to esterify (**2**) with the optically active diazo compound (**3**); the resulting menthyl esters, of known absolute configuration in the case of R^1 = Me, R^2 = Ph, show upfield isotopic shifts due to the presence of either a P–^{18}O single bond (0.028 p.p.m.) or a P=^{18}O double bond (0.047 p.p.m.) from which the chirality of (**2**) can be deduced. In general, conversion of the acid (**2**) into diastereoisomeric esters with any optically active alcohol, without breaking P–O bonds, would give the same information provided that the absolute configurations of the diastereoisomers could be established. This paper describes our investigations of suitable esterification procedures.

One method of esterifying carboxylic acids with the preservation of C–O bonds in the acid is the Mitsunobu reaction[2] using triphenylphosphine and diethyl azodicarboxylate (DEAD). This reaction involves inversion of configuration at the carbon of the reacting alcohol and is thought to proceed *via* the betaine (**4**) and the alkoxyphosphonium carboxylate (**6**). In the absence of carboxylic acid, dialkoxyphosphoranes (**5**) are formed.[3]

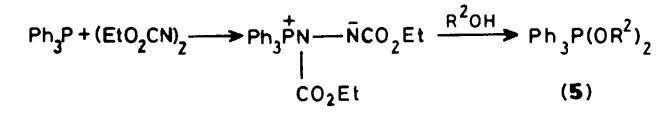


(**1**) (**2**)

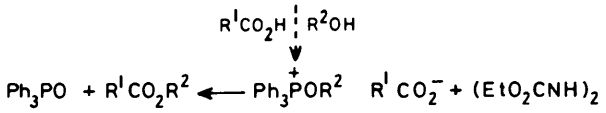
● = ^{18}O



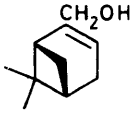
(**3**)



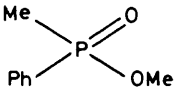
(**4**) (**5**)



(**6**)



(**7**)



(**8**)

Treatment of methyl(phenyl)phosphinic acid with (−)-(1*R*)-myrtenol (**7**) in the presence of triphenylphosphine and DEAD gave diastereoisomeric myrtenyl phosphinates showing a difference in their ^{31}P chemical shifts of 0.07 p.p.m. In spectra taken at 121 MHz this difference allows easy observation of the expected isotopic shifts in ^{18}O-labelled material.

One of the potential sources of error in the study of the alkaline hydrolysis of (**1**) is the possibility of oxygen exchange with water during the generation of the acid (**2**). This was avoided by converting the initial phosphinate into either the tetrabutylammonium salt and carrying out the Mitsunobu reaction on this in the presence of triethylammonium trifluoromethanesulphonate as a proton source, or into the tributylammonium salt. Application of these techniques to the salt obtained on hydrolysis of racemic methyl methyl(phenyl)phosphinate (**8**) in 55% $H_2{}^{18}O$ containing 2 mol equiv. of $K^{18}OH$, gave a mixture of labelled myrtenyl phosphinates whose ^{31}P n.m.r. spectrum is shown in Figure 1. Each diastereoisomer shows the expected isotopic peaks due to a P–^{18}O single bond (3.5 Hz upfield) and P=^{18}O double bond (5.7 Hz upfield). However, there are also small peaks (arrowed) due to *ca.* 3% of doubly-labelled diastereoisomers. This double labelling did not arise in the alkaline hydrolysis of (**8**); methylation of the potassium salt by the method of Lowe[4] gave a methyl ester which contained no double labelling, and no double labelling was detected in the esters produced using the diazocompounds (**3**). Double labelling was introduced in the Mitsunobu reaction perhaps *via* the pyrophosphate (**10**) formed by attack of phosphinate anion on the cation (**9**). Since the

(**9**) (**10**)

process involves a change in the original stereochemistry at phosphorus we concluded that the Mitsunobu reaction was not a reliable method for probing the chirality of ^{18}O-labelled phosphonic acids and this view was strengthened by experiments with menthol.

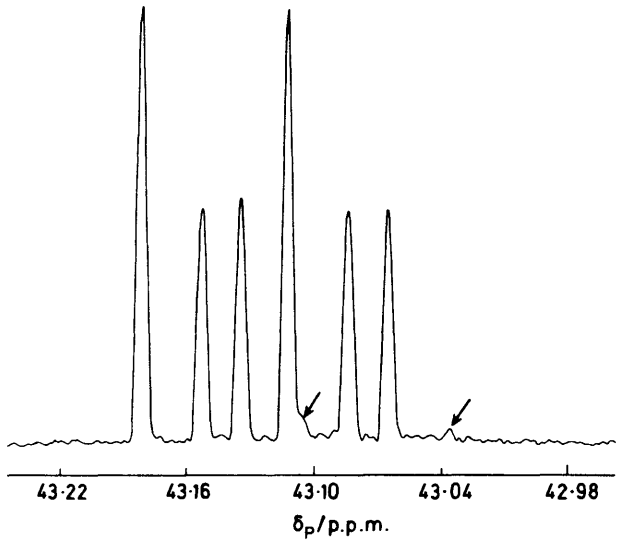


Figure 1. ^{1}H-Decoupled 162 MHz ^{31}P n.m.r. spectrum of the myrtenyl phosphinates obtained from the alkaline hydrolysis of racemic methyl methyl(phenyl)phosphinate in 55% $H_2{}^{18}O$ and coupling of the triethylammonium phosphinate with (−)-myrtenol in the presence of DEAD

Menthol reacted with methyl(phenyl)phosphinic acid in Mitsunobu reactions only under vigorous conditions. With an excess of menthol at 80 °C for 5 min without solvent, phosphinic acid singly labelled with 60% ^{18}O gave diastereoisomeric *menthyl* phosphinates[5] having only double-bonded ^{18}O. Neomenthol did not react under these conditions. The menthyl esters must have been formed by attack of menthol on the phosphoryl centre of the cation (**9**) with P–O bond fission.

The work-up of Mitsunobu reactions is greatly assisted by the use of (*p*-dimethylaminophenyl)diphenylphosphine whose oxide is readily extracted into aqueous acid.[6]

The formation of myrtenyl methyl(phenyl)phosphinates from singly labelled ^{18}O acid without either P–O bond cleavage or double labelling in the product was finally accomplished by reaction of the potassium phosphinate with myrtenyl bromide in Me_2SO at room temperature in the presence of 18-crown-6. The mixture of diastereoisomers was isolated by t.l.c. on silica in the presence of triethylamine. Figure 2(a) shows the ^{31}P n.m.r. spectrum of the myrtenyl phosphinates obtained by applying these procedures to the salt obtained from the hydrolysis of racemic methyl methyl(phenyl)phosphinate in 60% $H_2{}^{18}O$ containing 3.3 mol equiv. of KOH and Figure 2(b) shows the corresponding ^{31}P n.m.r. spectrum starting from the (R_P)-methyl ester (**11**).

Use of the diazo compounds (**3**) showed that alkaline hydrolysis of the ester (**11**) occurs with predominant inversion of configuration at phosphorus. It therefore follows that the myrtenyl diastereoisomer in Figure 2(b) showing a predominant P–^{18}O single bond isotopic shift, *i.e.* the low field isomer, is S_P and that the high field isomer, showing a predominant P=^{18}O double bond isotopic shift, is R_P. Figure 2(b) shows that, in agreement with previous results,[1] hydrolysis of the phosphinate (**11**) under these conditions is not entirely stereospecific; the presence of 14% of a high field isomer showing a P–^{18}O single bond isotopic shift and correspondingly of 15% of low field isomer showing a P=^{18}O double bond isotopic shift, show that the hydrolysis involved about 14% of retention of configuration at phosphorus. This retention was larger than in previous experiments (*ca.* 8%).[1]

It was subsequently found that the exact amount of retention of configuration at phosphorus in the alkaline hydrolysis of compound (**11**) decreased as the dilution of the hydrolysis

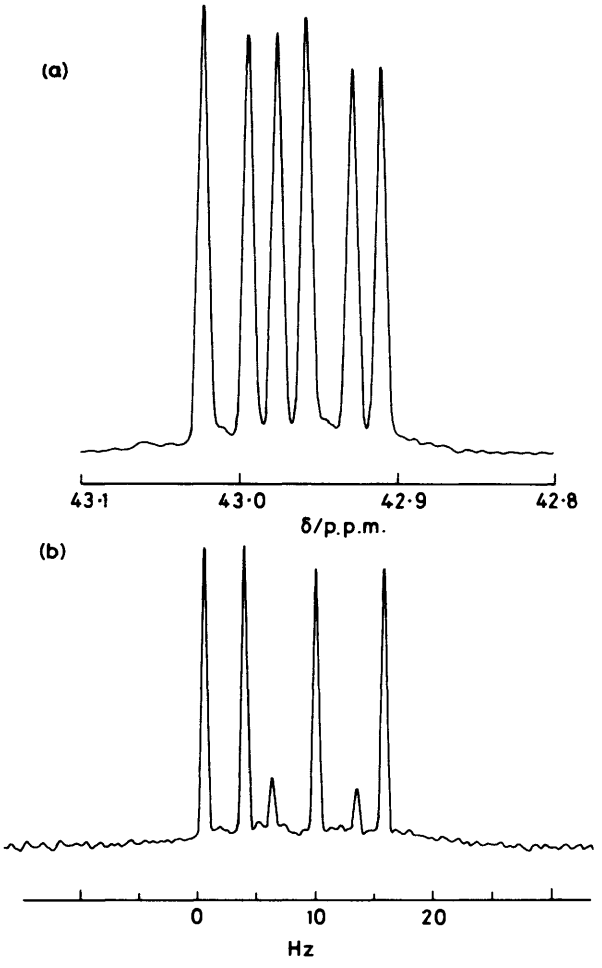
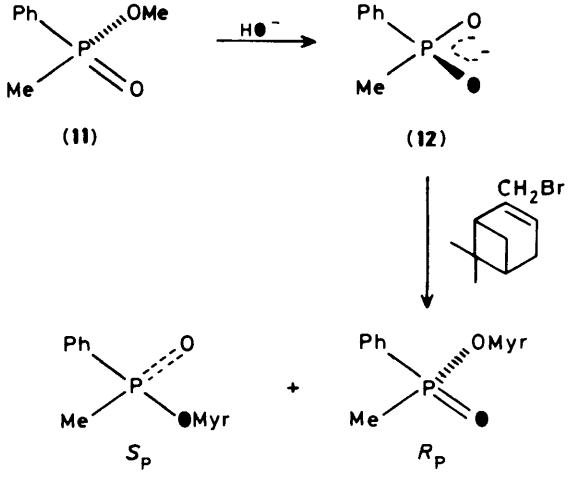


Figure 2. ^{1}H-Decoupled ^{31}P n.m.r. spectra of the myrtenyl phosphinates obtained from the hydrolysis of methyl methyl(phenyl)-phosphinate in 55% $H_2{}^{18}O$ and coupling of the salt with myrtenyl bromide in Me_2SO in the presence of 18-crown-6; (a) 162 MHz spectrum starting from the racemic ester and (b) 121 MHz spectrum starting from the R_P-ester



increased, suggesting that retention came about through racemisation of starting material by methoxide ions produced in the hydrolysis.[7] This racemisation was shown to be occuring by hydrolysis of the R_P-ester (**11**), at the same concentration as above but in the presence of 1 mol equiv. of KOH, to 85% completion and recovery of starting material. Proton n.m.r.

in the presence of (R_P)-phenyl-t-butylphosphinothioic acid[8] showed that this consisted of 84% R_P and 16% S_P isomers.

Nucleophilic attack on the phosphorus of phosphinate esters is very much affected by the size both of the substituents attached directly to phosphorus and of the alkoxy group.[9] The relatively slow alkaline hydrolysis of (R_P)-menthyl methyl(phenyl)phosphinate was therefore investigated by the above techniques (80% $H_2{}^{18}O$–myrtenyl bromide) in the expectation that racemisation of starting material by attack of menthoxide anion would be very slow. This proved to be the case; there were no detectable myrtenyl diastereoisomers corresponding to retention of configuration at phosphorus and the hydrolysis occurred with >98% inversion at phosphorus.

Experimental

^{31}P N.m.r. spectra were recorded in CH_2Cl_2 at 121 or 160 MHz; positive chemical shifts are to low field of the standard, 85% H_3PO_4.

Esterification of Methyl(phenyl)phosphinic Acid with Myrtenol Using the Mitsunobu Reaction.—Diethyl azodicarboxylate (0.52 g) was added slowly to a stirred solution of triphenylphosphine (0.79 g) and (−)-myrtenol (0.30 g) in THF (20 ml) at room temperature. After 15 min, methyl(phenyl)phosphinic acid (0.31 g) in THF (5 ml) was added and the solution set aside for 1 h. Dilute aqueous sodium hydrogen carbonate (50 ml) was then added and the mixture extracted with ether. The extracts were dried and evaporated. T.l.c. of the residue on silica eluting with 1% Et_3N–20% ether–hexane gave a 1:1 mixture of the diastereoisomeric myrtenyl methyl(phenyl)phosphinates, δ_P 43.18 and 43.11 p.p.m.; δ_H 7.9—7.3 (5 H, m), 5.45 (1 H, br s), 4.2 (2 H, m), 2.6—1.9 (5 H, m), 1.6 (3 H, d, *J* 14 Hz), 1.2 (3 H, s), 1.1 (1 H, m), and 0.73 and 0.70 (each 3 H, equal singlets).

Hydrolysis of Methyl Methyl(phenyl)phosphinate and Esterification of the Acid Using the Mitsunobu Reaction on the Tributylammonium Salt.—(±)-Methyl methyl(phenyl)phosphinate (0.1 g) was added to a stirred solution of KOH (70 mg) in $H_2{}^{18}O$ (99%; 73 μl) plus $H_2{}^{16}O$ (27 μl) at 90 °C. After 1 h, the mixture was diluted with water (15 ml) and stirred gently with the $(Bu_3NH)^+$ form of Dowex-50 (10 ml) for 1 h before being filtered. The solution was extracted with light petroleum (2 × 50 ml) and then freeze dried.

(*a*) *Esterification with menthol.* The above salt (86 mg), triphenylphosphine (115 mg), and (−)-menthol (150 mg) were stirred together at 80 °C and diethyl azodicarboxylate (77 mg) was slowly added. After 2 h at 80 °C, the mixture was dissolved in dichloromethane; δ_P(162 MHz) 41.2269 (relative intensity 1), 41.1805 (0.32), 40.5720 (0.76), and 40.5258 (0.23). Flash chromatography on silica gave (R_P)-menthyl methyl(phenyl)phosphinate (8 mg), and S_P-isomer (28 mg), and an intermediate mixed fraction (20 mg), identified by comparison of their ^1H n.m.r. spectra with those of authentic samples.[5] The triphenylphosphine oxide isolated contained 24% ^{18}O as shown by mass spectrometry (V.G. MicroMass 16B).

(*b*) *Esterification with myrtenol.* To a stirred solution of the above salt (86 mg), (−)-myrtenol (0.1 g), and triphenylphosphine (0.16 g) in THF (3 ml) at room temperature, was slowly added diethyl azodicarboxylate (0.11 g). After 30 min, ether (20 ml) was added and the solution washed with water, dried, and evaporated. T.l.c. on silica, presoaked and eluted with 1% Et_3N–20% EtOH–light petroleum gave the myrtenyl methyl(phenyl)phosphinates (37 mg) which showed the ^{31}P n.m.r. spectrum recorded in Figure 1.

General Procedure for the Hydrolysis of Methyl Methyl(phenyl)phosphinate and Esterification of the Acid Using Myrtenyl Bromide.—The ester was stirred at 90 °C for 30 min with aqueous KOH, the solution diluted with water (*ca.* 5 ml), titrated to pH 7 with 1M-H_2SO_4, and freeze dried. The residue was dissolved in Me_2SO (*ca.* 3 ml) containing 18-Crown-6 (1 equiv. relative to K^+) and myrtenyl bromide (3 equiv. relative to the ester) and set aside at room temperature for 2 h. Water (50 ml) was then added and the mixture extracted with light petroleum. The extract was washed with dilute aqueous sodium chloride, dried, and evaporated. Highfield ^{31}P n.m.r. analysis was possible at this stage. Purification was achieved by t.l.c. on silica, presoaked and eluted with 1% Et_3N–20% EtOH–light petroleum.

(*a*) The racemic methyl ester (0.1 g) in $H_2{}^{18}O$ (99%; 0.14 ml) and $H_2{}^{16}O$ (0.024 ml) containing KOH (0.112 g) gave the myrtenyl ester (85 mg) which showed the ^{31}P n.m.r. spectrum shown in Figure 2(a).

(*b*) The R_P-methyl ester (50 mg) in $H_2{}^{18}O$ (99%; 78 μl) and $H_2{}^{16}O$ (35 μl) containing KOH (60 mg) gave the myrtenyl ester (40 mg) which showed the ^{31}P n.m.r. spectrum shown in Figure 2(b).

(*c*) The R_P-methyl ester (0.1 g) in $H_2{}^{18}O$ (99%; 1 ml) and $H_2{}^{16}O$ (1 ml) containing KOH (0.1 g) gave the myrtenyl ester whose ^{31}P n.m.r. spectrum showed that 4% retention of configuration at phosphorus had occurred during the hydrolysis.

Partial Hydrolysis of R_P*-Methyl Methyl(phenyl)phosphinate.*—(R_P)-Methyl ester (>99% R_P) was added to rapidly stirred aqueous KOH at room temperature and the reaction was monitored by ^{31}P n.m.r. of the mixture (δ_P 52.4 ⟶ 32.5). When the required partial hydrolysis was achieved the solution was diluted with water and extracted with dichloromethane. The extract was dried and evaporated, the residue dissolved in $CDCl_3$, and the ^1H n.m.r. spectrum (300 MHz) recorded after the addition of 1 equiv. of (R_P)-phenyl-t-butylthiophosphinic acid. Integration of the two methoxy signals ($\Delta\delta$ 0.05 p.p.m.) gave the enantiomeric composition of the unhydrolysed methyl ester.[8] Methyl ester (mg), water (ml), KOH (equiv.), % hydrolysis, %R_P in the recovered ester: 50, 0.6, 0.8, 60, 97.1; 200, 4, 1, 88, 97.2; 100, 0.2, 1, 85, 84.2.

Hydrolysis of R_P*-Menthyl Methyl(phenyl)phosphinate.*—The (R_P)-menthyl ester (0.25 g) was heated at 130 °C for 24 h in a sealed vial with a vigorously stirred mixture of $H_2{}^{18}O$ (99; 0.8 ml), $H_2{}^{16}O$ (0.2 ml), KOH (95 mg), and dioxane (1 ml). Water (40 ml) was then added and the solution extracted with ether (2 × 30 ml). The aqueous layer was titrated to pH 7 with 1M-H_2SO_4 and freeze dried. The residue was esterified with myrtenyl bromide as above. The ^{31}P n.m.r. spectrum of the resulting myrtenyl esters showed no detectable S_P (P=^{18}O) or R_P (P–^{18}O) isomers.

Acknowledgements

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References

1 S. Trippett and C. L. White, *J. Chem. Soc., Chem. Commun.*, 1984, 251.
2 O. Mitsunobu, *Synthesis*, 1981, 1.
3 M. von Itzstein and I. D. Jenkins, *Aust. J. Chem.*, 1983, **36**, 557.
4 R. L. Jarvest, G. Lowe, and B. V. L. Potter, *J. Chem. Soc., Perkin Trans. 1*, 1981, 3186.
5 O. Korpium, R. A. Lewis, J. Chickos, and K. Mislow, *J. Am. Chem. Soc.*, 1968, **90**, 4842.
6 S. Trippett and D. M. Walker, *J. Chem. Soc.*, 1961, 2130.
7 M. Green and R. F. Hudson, *Proc. Chem. Soc.*, 1962, 307.
8 M. J. P. Harger, *J. Chem. Soc., Perkin Trans. 2*, 1980, 1505.
9 P. Haake, C. E. Diebert, and R. S. Marmour, *Tetrahedron Lett.*, 1968, 5247; R. D. Cook, C. E. Diebert, W. Schwarz, P. C. Turley, and P. Haake, *J. Am. Chem. Soc.*, 1973, **95**, 8088.

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