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Accurate *In Situ* $^{31}P\{^1H\}$ Assay of Enantiopurity in α-Hydroxyphosphonate Esters using a Diazaphospholidine Derivatizing Agent☆

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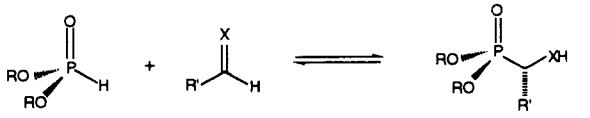
Abstract: *A rapid, convenient and efficient in situ assay of enantiomeric excess in α-hydroxyphosphonate esters is reported exploiting $^{31}P\{^1H\}$ NMR analysis of the diastereoisomers formed upon condensation with a phosphorochloridite reagent containing a chiral diazaphospholidine ring. Use of this chiral framework affords chemical shift dispersions >5 ppm between diastereoisomers. Accurate integrations are thus possible once account is taken of differential n.O.e. effects and spin lattice T_1 relaxation times of the phosphorus nuclei.*

One of the main objectives of our organophosphorus research programme[1] is the development of efficient catalytic enantioselective hydrophosphonylation processes, based on the Pudovik reaction (Scheme 1).[2] Such processes would have a major impact in the asymmetric synthesis of α-hydroxy and α-aminophosphonic acids and their esters, compounds which are known to possess broad-based physiological activities.[3]

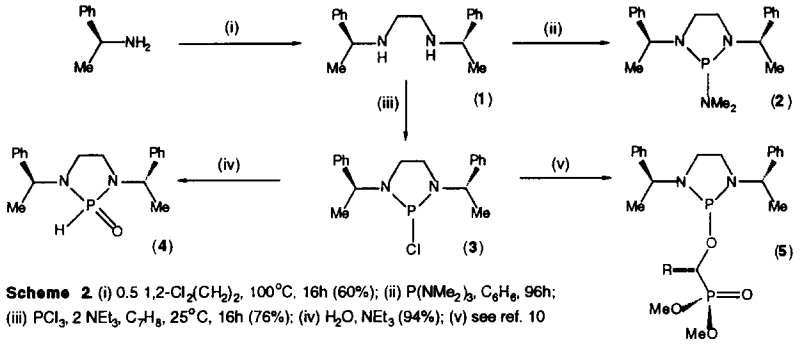


Scheme 1
X = O; NR (R = alkyl, aryl)

The accurate determination of both (a) enantioselectivities (e.e.) and (b) absolute configurations of the product α-functionalised phosphonate esters are crucial to this work. We envisaged that it would be possible to address both of these features through $^{31}P\{^1H\}$ analysis of the diastereoisomers formed upon reaction of the phosphonate esters with a suitable chiral derivatizing agent (CDA). Indeed, the use of chiral derivatizing (and solvating) agents provides a valuable alternative to optical rotation, lanthanide shift reagents and chromatographic methods in the analysis of chiral alcohols and amines.[4]

Several considerations influence the choice of CDA for a specific application: (i) the CDA should be synthesised readily and handled easily, (ii) reaction with the substrate should be facile, afford only two possible diastereoisomeric products and proceed without kinetic resolution or racemisation, (iii) NMR spectra should provide adequate chemical shift dispersion and (iv) due consideration should be given to data collection and processing. Various CDA's[5] have been designed to assay a wide range of chiral alcohols, amines and thiols and a great deal of information is now known about the selection of conditions and reagents. Indeed, the applications of ^{31}P NMR methods for the determination of enantiopurity has appeared recently.[5g]

A number of existing CDA's could potentially be used also in the analysis of α-hydroxyphosphonate esters but we have selected to use one particular phosphorochloridite reagent containing the same chiral diazaphospholidine ring system as that reported by Feringa and co-workers[6] in the determination of enantioselectivity in chiral alcohols, amines and thiols. We find that this reagent satisfies all of the criteria outlined above.



Scheme 2 (i) 0.5 1,2-$Cl_2(CH_2)_2$, 100°C, 16h (60%); (ii) $P(NMe_2)_3$, C_6H_6, 96h; (iii) PCl_3, 2 NEt_3, C_7H_8, 25°C, 16h (76%); (iv) H_2O, NEt_3 (94%); (v) see ref. 10

We address here the first of the above problems, the development of a rapid, clean, efficient *in situ* assay for the determination of enantiomeric excess in α-hydroxyphosphonate esters. Our emphasis is on achieving a high level of accuracy in the assay which in turn depends upon the accurate integration of $^{31}P\{^1H\}$ NMR resonances. Accurate integrations neccessitate careful consideration of a number of important experimental features including, (i) achieving a chemical shift dispersion sufficient to afford good base-line separation, (ii) measuring spin lattice relaxation times T_1 for the phosphorus nuclei in the diastereoisomers in order to select an appropriate pulse delay which in turn will influence the (iii) appropriate ^1H decoupling settings.

Feringa reported the synthesis of chiral, air-stable phosphorotriamidite **2** by the condensation of *N,N'*-bis[1-(*S*)-phenylethyl]-1,2-ethylenediamine (**1**) with $P(NMe_2)_3$ (Scheme 2). Although **2** is straightforward to handle, we find its reaction with α-hydroxyphosphonate esters to be prohibitively slow (several hours at room temperature) for an *in situ* assay. However, replacement of the dimethylamino group in **2** with the better leaving group chloride results in significantly more facile esterification of the phosphonate ester (seconds at room temperature). Thus, *N,N'*-bis[1-(*S*)-phenylethyl]-1,2-ethylenediamine (**1**)[7] reacts smoothly with PCl_3 in toluene solvent to afford phosphorochloridite **3** as pale yellow, pentane soluble crystals in 76% isolated yield (δ_P 167.82 ppm, $CDCl_3$). Although phosphorochloridite **3** is sensitive to moisture in solution,[8] it is handled readily at room temperature in $CDCl_3$ under an inert atmosphere and may be stored thus as a solid for many months without decomposition. Recent detailed studies by Alexakis and co-workers have demonstrated clearly the uses of chlorophosphoridate CDA's containing C_2-symmetric diamino auxiliaries in terms of the rapidity of reaction with a range of protic substrates and the stability of the auxiliaries towards displacment or racemisation.[5d]

R	δ_P[a] (6)	$\delta_{P(III)}$[b] (5x and 5y)	$\delta_{P(V)}$[b] (5x and 5y)
a C_6H_5	25.04	127.75(16.8) 122.21(14.2)	23.55(14.2) 23.54(16.8)
b 1-$C_{10}H_7$	24.58	127.87(17.1) 122.27(14.5)	23.77(14.4) 23.68(17.2)
c 2-$C_{10}H_7$	24.15	128.13(16.5) 123.37(15.1)	23.47(15.7) 23.47(15.7)
d 2-BrC_6H_4	23.98	126.95(14.3) 121.55(13.1)	22.93(12.6) 22.81(13.2)
e 3-BrC_6H_4	23.46	128.78(16.3) 124.02(14.6)	22.74(16.3) 22.71(14.4)
f 4-BrC_6H_4	23.46	128.68(16.0) 124.40(15.1)	22.83(15.7) 22.83(15.7)
g 4-MeC_6H_4	24.47	127.64(17.1) 122.16(14.6)	23.78(14.4) 23.77(17.4)
h 4-MeOC_6H_4	24.48	127.91(17.7) 122.53(15.0)	23.85(16.8) 23.85(16.8)
i 4-$O_2NC_6H_4$	22.86	126.34(10.0) 124.62(13.0)	21.75(10.9) 21.74(12.8)
j 2-$O_2NC_6H_4$	22.54	129.73(14.6) 126.62(14.8)	21.84(14.8) 21.80(14.8)
k 2-$Ph_2PC_6H_4$	24.59	128.61(17.4)[c] 122.74(17.1)[c]	23.44(17.0) 23.42(17.5)

Table 1 [a] In $CDCl_3$; 300 K; ppm; 101.268 MHz. [b] In $CDCl_3$; 298 K; 101.268 MHz; 52.6 μmol. solutions with respect to phosphonate; in parentheses ($^3J_{PP}$ in Hz).[9] [c] $^5J_{PP}$ = 3.0 Hz observed only to the P(III) nucleus.

A variety of α-hydroxyphosphonate esters of the form $(MeO)_2P(O)CHR(OH)$ **6** have been synthesised in racemic form, by the reaction of $(MeO)_2P(O)H$ with RCHO in THF solvent at -78°C in the presence of

$LiN(SiMe_3)_2$, and mixed phosphorus(III)—phosphorus(V) adducts of the form **5** (diastereoisomers **x** and **y**) prepared by reaction of **6** with **3** *in the NMR tube*. Reaction proceeds *quantitatively, rapidly and without kinetic resolution*[9] *in $CDCl_3$ solvent.* $^{31}P\{^1H\}$ NMR data are reproduced in Table 1.[10]

The presence of two phosphorus atoms within the same molecule of **5** allows us to select the nucleus which affords the greater chemical shift dispersion: in all cases that we have examined it is the phosphorus(III) nucleus which results in the better chemical shift dispersion ($\Delta\delta_P$) as illustrated in Table 2 [*ca.* 1.7—5.8 ppm for the P(III) nuclei and *ca.* 0.01—0.1 ppm for the P(V) nuclei]. Similar oxidation state trends have been reported by other workers.[4,5] Most important for our studies however, the dispersions obtained in this system are significantly larger than those reported for a variety of other alcohols, amines and thiols, which are commonly found in the range 0.1—2.0 ppm,[6] and affords excellent baseline separations (Figure).

Since accurate integration of the phosphorus resonances is required in order to assay enantioselectivity, it is necessary to take account of possible differences in n.O.e. and spin lattice (T_1) relaxation effects. This, in turn, involves selecting suitable pulse delay times and ^1H decoupling patterns. Effectively, the pulse delay is governed by the *difference* in P(III) spin-lattice relaxation times T_1 for both diastereoisomers (ΔT_1).[11] Inversion recovery experiments on each of the esters **5** reveal that the ΔT_1 values are all *ca.* 0.1 s such that a delay time of 5 x T_1 or 0.5 s would be adequate. However, we have chosen to employ a 3 s pulse delay in order to cover the eventuality of possible deviations under a different set of temperature and concentration conditions. In each case examined, inverse gated ^1H decoupling was employed to reduce the risks of differential n.O.e. effects and in this regard also, the 3 s pulse delay minimises n.O.e. build-up. As a result of these experimental protocols we are able to determine the e.e. of the racemic products accurately to within 1% and in many cases to within 0.5%.

R	$\Delta\delta_{P(III)}$[a]	T_1[P(III)][b]	$\Delta\delta_{P(V)}$[a]	%(5 x)-%(5 y)[c]	E.e.[d]
a C_6H_5	5.54	2.5; 2.4	0.01	50.1 : 49.9	0.2
b 1-$C_{10}H_7$	5.60	2.2; 2.2	0.09	50.3 : 49.7	0.6
c 2-$C_{10}H_7$	4.76	2.1; 2.0	0.00	50.1 : 49.8	0.3
d 2-BrC_6H_4	5.40	2.3; 2.2	0.12	50.0 : 50.0	0.0
e 3-BrC_6H_4	4.76	2.4; 2.3	0.03	49.7 : 50.3	0.6
f 4-BrC_6H_4	4.28	2.3; 2.2	0.00	49.7 : 50.3	0.6
g 4-MeC_6H_4	5.48	2.3; 2.2	0.01	49.5 : 50.5	1.0
h 4-$MeOC_6H_4$	5.38	2.2; 2.1	0.00	50.2 : 49.8	0.4
i 2-$O_2NC_6H_4$	1.72	2.3; 2.3	0.01	49.9 : 50.1	0.2
j 4-$O_2NC_6H_4$	3.11	2.2; 2.2	0.04	49.8 : 50.2	0.4
k 2-$Ph_2PC_6H_4$	5.87	1.8; 1.7	0.02	50.4 : 49.6	0.8

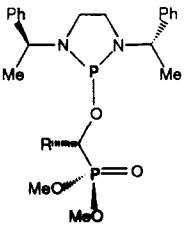


Table 2 [a] In $CDCl_3$; 300 K; ppm; 101.268 MHz. [b] Determined by inversion recovery in $CDCl_3$; 300 K; secs.; 101.268 MHz; high frequency diastereoisomer given first. The values of T_1 given are an average of the values calculated for each line of the P(III) doublet. [c] High frequency resonance first. Determined by automated phasing and electronic integration of resonances that have essentially identical peak shapes for each diastereoisomer (Figure).[9] [d] E.e. of **5** determined as |%**5** x - %**5** y|.

The above levels of precision are obtained also in the assay of scalemic α-hydroxyphosphonate esters. Thus, exploiting the influencial work of Wynberg,[12] we find that the Pudovik reaction between $(MeO)_2P(O)H$ (0.2 M) and PhCHO (0.2 M) in three different solvent systems, tetrahydrofuran (THF); CH_2Cl_2 and toluene:CH_2Cl_2 (1:1 v/v) solvents in the presence of quinine as catalyst (5 mol%) affords $(MeO)_2P(O)CHPh(OH)$ in *ca.* 95% yield after 4 days at room temperature with e.e.'s of 2.9(2)%, 5.4(3)% and 4.5 (2)% respectively[13] as assayed (at least five separate determinations) using **3**.[14]

We are currently addressing the next two problems, (i) the use of CDA **3** as a means to determine absolute configurations of α-hydroxyphosphonate esters through $^{31}P\{^1H\}$ NMR analysis[15] and (ii) examining the general potential of chiral amino alcohols and other amphoteric species capable of multiple site interactions to catalyse the Pudovik reaction enantioselectively.[16]

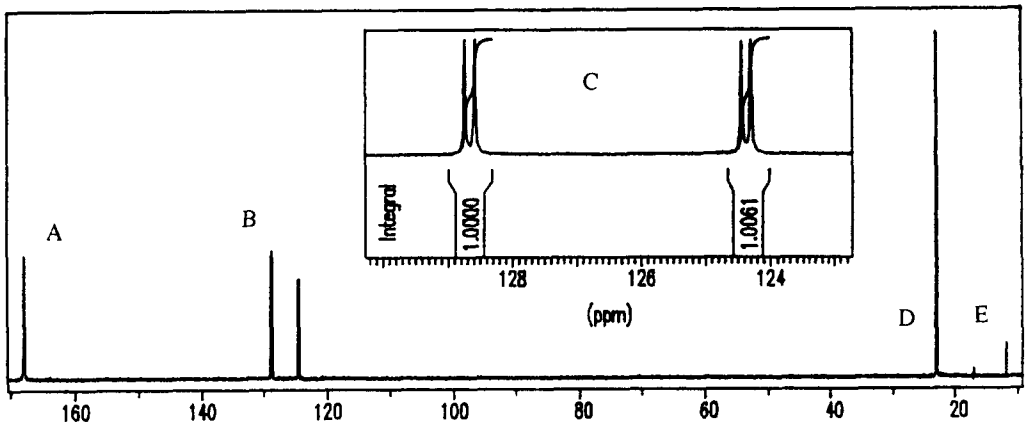


Figure $^{31}P\{^{1}H\}$ NMR of **5f**: in ppm. A = unreacted **3**; B = P(III) resonances of $\mathbf{5f_x}$ and $\mathbf{5f_y}$; C = expansion of B (data collected as described in reference 9); D = P(V) resonances of $\mathbf{5f_x}$ and $\mathbf{5f_y}$; E = **4** caused by trace hydrolysis of **3**.

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8. Phosphorochloridite (**3**) reacts smoothly with one equivalent of water to afford the H-phosphonate ester (**4**) which has been subsequently examined as a phosphonylating agent towards unsaturated organic substrates. Devitt, P. G.; Kee, T. P. *Tetrahedron*, submitted for publication.

9. In our normal assay procedure (ref. 10), CDA **3** is used in excess and the data of Table 2 reflect this; however, even when **3** is the limiting reagent, there is no evidence of kinetic resolution from the integrated intensities.

10. *In Situ Enantioselectivity Assay using Chiral Derivatising Agent 3*.- A sample of the α-hydroxyphosphonate ester **6** under investigation (52.6 μmol.) was weighed out into a 5 mm NMR tube (quantities varied from *ca.* 11-21 mg depending upon R) in a dry-nitrogen filled glove box. To this solid was added 0.6 cm^3 of a dry $CDCl_3$ deoxygenated solution comprising CDA **3** at (0.125 M) and triethylamine at (0.25 M) at room temperature which affords a molar ratio of **6** : **3** : NEt_3 of *ca.* 1 : 1.4 : 2.9. The tube was sealed under nitrogen with cling-film and shaken briskly by hand to ensure complete dissolution. The reaction mixture remained clear throughout, neither the adducts nor the triethylammonium chloride precipitated from solution at this level of concentration. After 15 mins., the $^{31}P\{^{1}H\}$ NMR spectrum (101.268 MHz) was collected (256 scans) at 300 K on a Bruker ARX 250 MHz spectrometer over a spectral width of 3048.8 Hz centred on the phosphorus(III) resonances, (3.8 μsec pulse width; 8192 data points; 1.344 sec. aquisition time and 0.74 Hz digital resolution) with a 3 sec. pulse delay between scans to allow for complete relaxation and inverse-gated proton decoupling to reduce nuclear Overhauser effects. Slight line-broadening (2 Hz) was applied to aid sensitivity. The FID's were Fourier

transformed and phased automatically, the same phase corrections being applied for each sample. Automated electronic integration gives the relative proportions of diastereoisomers as listed in Table 2 from which enantioselectivities can be computed readily. Following this, the spectrum was re-aquired over 26316 Hz (0.62 sec. aquisition; 1.6 Hz digital resolution; 0.3 sec. pulse delay and broad-band ^{1}H decoupling) to ensure complete conversion of **6** to **5**, the presence of excess CDA **3**, and to obtain the chemical shifts of the phosphorus(V) nuclei (Table 1).

11. For a more pertinent discussion of this point see; Short, A. B; Durham, L. J.; Mosher, H. S. *J. Org. Chem.*, **1983**, *48*, 3125.

12. Wynberg, H.: Smaardijk, A. A. *Tetrahedron Letts.*, **1983**, *24*, 5899.

13. Esd's are determined from the equation, $\{\Sigma_n(x_i - x)^2/n(n-1)\}^{1/2}$ where x is the mean value of n (at least 5) determinations. See; Schultz, A. J.; Brown, R. K.; Williams, J. M: Schrock, R. R. *J. Am. Chem. Soc.*, **1981**, *103*, 170.

14. It has been reported that the use of a strong base such as NEt_3 in conjunction with phosphorochloridite CDA's can lead to side reactions in the derivatisation of some alcohols.[5d] Tests with CDA **3** and both NEt_3 and the milder base, N-methylimidazole reveal there to be essentially no difference in the measured e.e.'s from these quinine-catalysed reactions.

15. For example; Hammerschmidt, F.; Li, Y-F. *Tetrahedron* **1994**, *50*, 10253. Analyses of $^{2}J_{PH}$, $^{3}J_{PH}$ and δ_H chemical shifts from $^{1}H\{^{31}P\}$ experiments on esters **5** reveals trends which suggest that the cross referencing of one derivative will also suffice to assign the remainder by inference. These trends will be described in the full account of this work.

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