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Accurate Assay of Enantiopurity of 1-Hydroxy- and 2-Hydroxyalkylphosphonate Esters

Ewa Żymańczyk-Duda, Mariusz Skwarczyński, Barbara Lejczak* and Paweł Kafarski

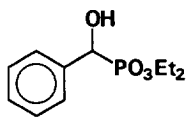
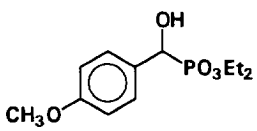
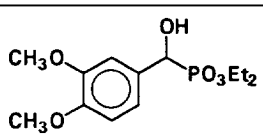
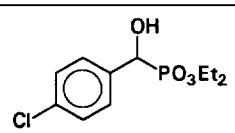
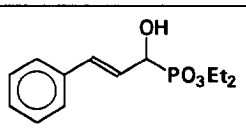
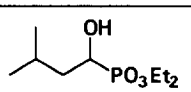
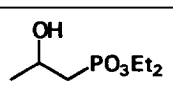
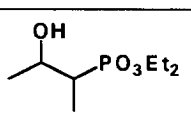
Institute of Organic Chemistry, Biochemistry and Biotechnology, Technical University of Wroc³aw, Wybrze¿e Wyspiañskiego 27, 50-370 Wroc³aw, Poland

Abstract: Enantiomerically pure (R_P)-tert-butylphenylphosphinothioic acid and quinine were successfully used for the direct determination of the enantiomeric purity of diethyl 1-hydroxyalkylphosphonates. Only quinine was effective as a chiral solvating agent for the determination of the enantiomeric excess of diethyl 2-hydroxyalkylphosphonates.

Phosphonic acid analogues of hydroxy acids display promising biological properties.[1] Additionally they are attractive starting materials for the synthesis of aminoalkylphosphonic acids, compounds which also display diverse and useful biological properties with possible applications ranging from medicine to agriculture.[2] For proper evaluation of the biological activity of both classes of compounds the availability of enantiomerically pure compounds of defined configuration is indispensable. The growing interest towards the asymmetric synthesis of hydroxyphosphonates [3] has induced a concomitant effort to develop new and efficient methods to evaluate their enantiomeric excess. Previously reported methods for the determination of the enantiomeric purity of dialkyl 1-hydroxyalkylphosphonates include: the use of ^1H and ^{31}P n.m.r. spectroscopy of their diastereomeric derivatives, namely Mosher esters,[3e,4] camphanic esters,[3k] mandelate esters,[5] phosphono depsipeptides,[6] and diazaphospholidine derivatives,[7] and the use of ^1H n.m.r. spectroscopy of 1-(1-naphthyl)ethylamine salts of their monobenzyl esters.[8] For the determination of the enantiomeric excess of diethyl 2-hydroxyalkylphosphonates obtained by reduction of the corresponding ketophosphonates with baker's yeast chiral g.c. was used.[9]

In this paper we report the application of quinine and (R_P)-*tert*-butylphenylphosphinothioic acid as chiral solvating agents for direct, rapid, clean and simple ^{31}P n.m.r. enantiomeric excess determination of hydroxyalkylphosphonates. Quinine[10] and *tert*-butylphenylphosphinothioic acid[11] were recently successfully used for the determination of the enantiomeric excess of β-hydroxyesters and various alcohols respectively, by means of ^1H n.m.r. spectroscopy. Our emphasis is on achieving a high level of accuracy in the assay which in turn depends on the accurate integration of ^{31}P n.m.r. resonances, especially by achieving a chemical shift dispersion sufficient to afford good base-line separation. Results given in the Table, alongside those obtained using Mosher's approach,[4] clearly indicate that both reagents gave good results in the case of diethyl 1-hydroxy-alkylphosphonates. If considering diethyl 2-hydroxyalkylphosphonates only the quinine method yields satisfactory results. It is also worth noting that the shift difference of the ^{31}P n.m.r. signal ($\Delta\delta$) for both enantiomers increased with increasing amine to hydroxyphosphonate molar ratio with the optimum at the 4:1 value. For example for a racemic mixture of diethyl 1-hydroxybutyphosphonate observed shift difference was: 0.05 for 1:1 molar ratio, 0.17 for 1:2 ratio and 0.26 for 4:1 quinine to hydroxyphosphonate molar ratio.

Table. Determination of the enantiomeric excess (ee) by the use of quinine and (R_P)-*tert*-butylphenyl-phosphinothioic acid as chiral solvating agents.

Compound	$[\alpha]_{273}$ [°]	ee from literature	quinine		phosphinothioic acid	
			ee	$\Delta\delta^f$	ee	$\Delta\delta^f$
	+2.5	9 %[a]	4 %	0.18	5%	0.22
	-6	18 %[a]	2%	0.17	1%	0.20
	-14.5	43%[a]	39 %	0.17	36%	0.21
	-27	81 %[a]	78%	0.17	77%	0.21
	-11.5	34%[b]	28%	0.17	23%	0.20
	-30	88 %[b]	85%	0.17	83%	0.19
	-20	46 %[b]	52%	0.08	56%	0.19
	+3	7 %[b]	11%	0.21	14%	0.17
	-8	86%[b]	84%	0.16	84%	0.26
			11.5%[e]	0.15	10.5%[e]	0.23
			27%[e]	0.15	24%[e]	0.30
	+7.5	97%[c]	95%	0.16	ineffective	
	+5	100% [d]	98%	0.21	ineffective	

[a] by comparison with specific rotation values given by Yokomatsu et al.[1d]

[b] by ^{31}P n.m.r. spectroscopy of Mosher's derivatives [4]

[c, d] by means of g.c. on chiral phase,[9] mixture of diastereoisomers in 1:2 ratio (two stereogenic centers present)

[e] determined directly from the reaction mixture

[f] shift nonequivalence in ppm observed on a Bruker DRX (121.49 MHz) spectrometer in $CDCl_3$ in relation to 85% H_3PO_4 (external standard)

Replacement of quinine by brucine, cinchonine, ephedrine and 1-phenylethylamine did not result in resolution of ^{31}P n.m.r. signals derived from enantiomers of either 1-hydroxy- or 2-hydroxyalkylphosphonates. Only a small excess (1.1-1.2 fold) of (R_P)-*tert*-butylphenylphosphinothioic acid is sufficient for good separation of n.m.r. signals.

Samples of diethyl 1-hydroxyalkylphosphonates of varying enantiomeric excess were available from previous studies on the hydrolysis of diethyl 1-butyryloxyalkylphosphonates by wild-type bacterium *Pseudomonas fluorescens*,[12] whereas diethyl 2-hydroxyalkylphosphonates were obtained by reduction of corresponding diethyl 2-oxoalkylphosphonates by baker's yeast. The experiments in which crude reaction mixtures obtained by simple extraction of the media after the biocatalytic processes were used (they contained substrates which were also visible in n.m.r. spectra) indicated that both chiral solvating agents might be successfully used for the direct determination of the reaction course.

The observed differences of enantiomeric excesses given by the quinine and phosphinotioate approach and Mosher's method are most likely due to the formation of hydroxyphosphonic acid monoesters observed in some cases during work up of the reaction mixtures after acylation of hydroxyphosphonates with α-methoxy-α -(trifluoromethyl)phenylacetic acid . They are probably formed during purification of the reaction mixtures by means of extraction.

Thus, in ^{1}H and ^{31}P n.m.r. spectra of Mosher ester derivatives additional sets of peaks of low intensity were observed in the regions used for the determination of enantiomeric purity, namely the region of hydroxyphosphonate phosphorus absorption in phosphorus spectra and characteristic CHP region in proton spectra.

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