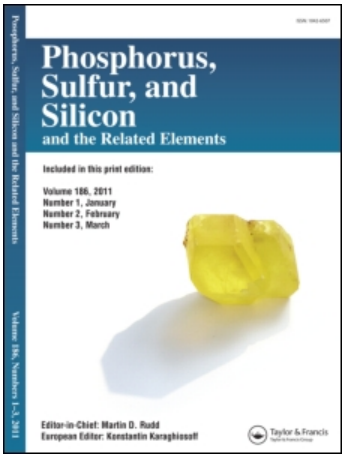

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^{31}P NMR ENANTIOMERIC EXCESS DETERMINATION OF 1-HYDROXYALKYLPHOSPHONIC ACIDS VIA THEIR DIASTEREOISOMERIC PHOSPHONODIDEPSIPEPTIDES

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N-protected L-aminoacids are convenient derivatizing reagents for enantiomeric excess determination of chiral 1-hydroxyalkylphosphonic acids by the ^{31}P NMR spectroscopy. 1-Hydroxyalkylphosphonic acid esters coupled with N-protected L-aminoacids by means of the DCC method give the diastereoisomers which are quantitatively distinguishable in the ^{31}P NMR spectra. The values of ^{31}P NMR nonequivalence (0.06–0.60 ppm) differ with the change of the L-aminoacids and the protecting groups. The easily available Boc-L-Val and Boc-L-Phe in optically pure form seem to be promising chiral derivatizing agents. The measured enantiomeric excess of preweighed, enantiomerically enriched samples are in excellent agreement with the expected values.

Key words: Chiral derivatizing agent (CDA); enantiomeric excess; 1-hydroxyalkylphosphonic acids; phosphonodidepsipeptides; ^{31}P NMR.

Chiral organophosphorus analogues of natural products are becoming increasingly important as biologically active compounds. Optically pure 1-hydroxyphosphonates are convenient intermediates in the preparation of various analogues.[1–4] Therefore, methods for the enantiomeric purity determination of the chiral starting hydroxyphosphonates are desirable. Recently, we proposed the enantiomeric excess determination of free 1-aminoalkylphosphonic acids from the ^{31}P NMR spectra of their Pd(II) complexes.[5] However, 1-hydroxyalkylphosphonic acids do not form the diastereoisomeric pairs with palladium ions, distinguishable in NMR, so this method could not be used. Enantiomeric purity of chiral hydroxyphosphonates has been previously proved with ^{19}F and ^{31}P NMR via Mosher's derivatives of their esters.[6] Mosher's reagents have frequently been criticised for inadequate enantiomeric purity of commercial samples and asymmetric induction during derivatization.[7,8] In addition, ^{19}F NMR is not routinely available to most chemists. In this paper we report the application of easily available N-protected L-aminoacids in optically pure form as chiral derivatizing agents.

RESULTS AND DISCUSSION

The enantiomeric purity of 1-hydroxyalkylphosphonic acids (**I**) and their dibenzyl esters (**II**) has been proved by ^{31}P NMR spectroscopy of their diastereoisomeric phosphonodidepsipeptides (**IV** and **V**). The pairs of 1-hydroxyalkylphosphanic acid ester and N-protected aminoacid which were coupled by means of the DCC method

and the ^{31}P NMR data of the resulting phosphonodidepsipeptides, (−)L or (+)L, are collected in Table 1. The conversions are depicted in the Scheme. ^{31}P NMR spectra had shown the persisence of two distinguishable diastereoisomers when the racemate or enantiomerically enriched samples of chiral 1-hydroxyalkylphosphonic acid esters were used. Measuring the integrals of the diastereoisomer signals allows one to determine the enantiomeric excess of the products. The integral ratios $\alpha = [-]/[+] = 1$ were obtained for all racemic sample with a maximum deviation of

TABLE I

^{31}P NMR chemical shifts of the phosphonate groups in the diastereoisomeric phosphonodidepsipeptides

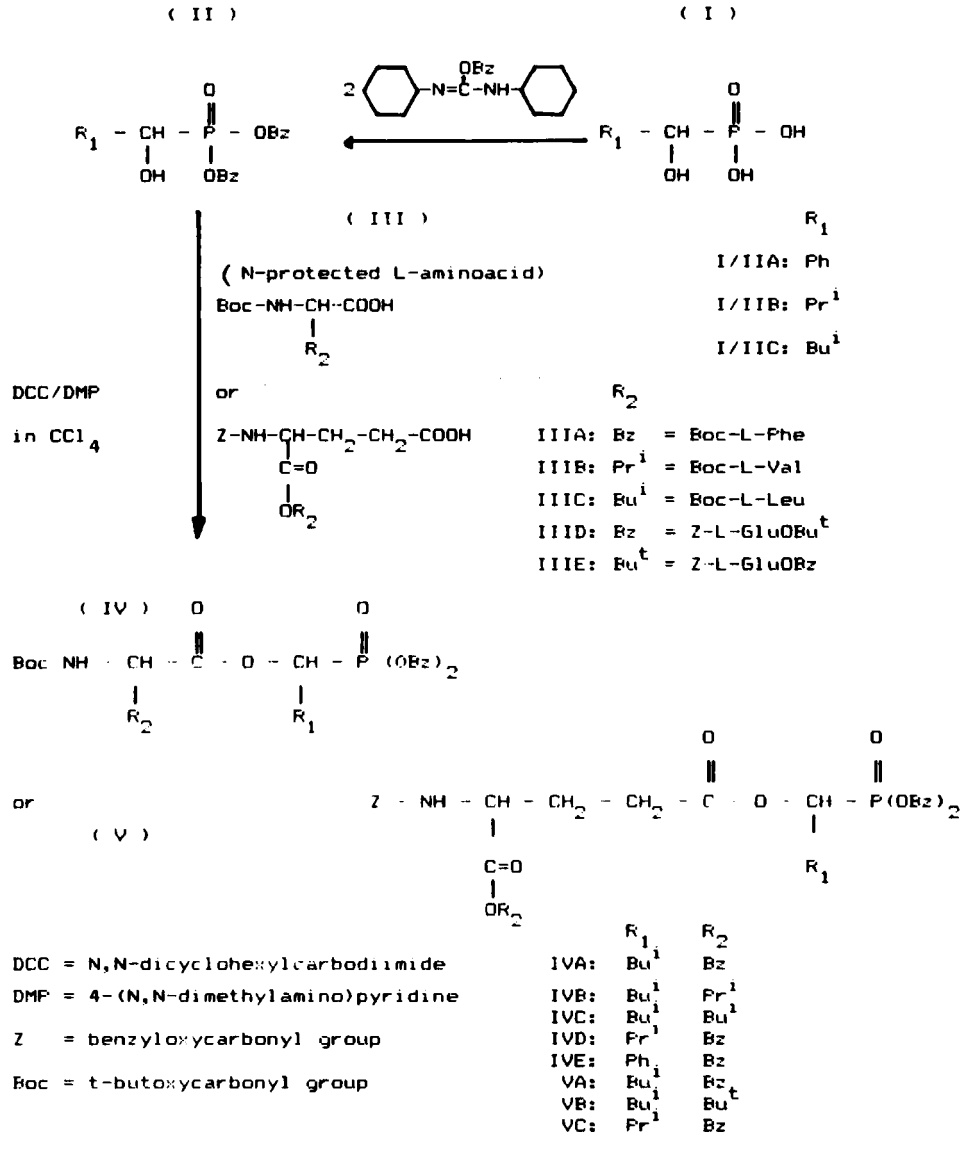
PDP[a]	HPE	N-L-AA	δ(^{31}P) [ppm] L(+)	δ(^{31}P) [ppm] L(−)	integrals ratio $\alpha = [-]/[+]$	$\Delta\delta$ [ppm]
IVA	(+) IIC	Boc-L-Phe	21.86			
	(−)			22.28		
	rac[d]		21.86	22.28	0.98	0.42
	rac: (−)		21.86	22.28	3.14	0.42
IVB	(−) IIC	Boc-L-Val		22.51	1.02	0.33
	rac		22.19	22.52		
IVC	(−) IIC	Boc-L-Leu		22.38	1.03	0.16
	rac		22.18	22.34		
VA	(−) IIC	Z-L-GluO-Bz	22.68		[b]	0.06
	rac		22.68	22.75		
VB	(−) IIC	Z-L-GluO-Bu^t		22.72	[b]	0.00
	rac		22.72			
1[c]	(+)	Boc-L-Val	19.57		[b]	0.60
	rac		19.57	20.17		
2[c]	(+)	Boc-L-Ala	19.57		[b]	0.20
	rac		19.57	19.77		
3[c]	(+)	Boc-L-Leu	19.67		[b]	0.20
	rac		19.67	19.87		
IVD	(+) IIB	Boc-L-Phe	20.41		[b]	0.17
	rac		20.43	20.26		
VC	(+) IIB	Z-L-GluO-Bu^t	21.90		[b]	0.06
	rac		21.90	21.84		
IVE	(+) IIA	Boc-L-Phe	18.30			
	rac		18.30	18.50	0.97	0.20
	rac: (+)		18.32	18.52	0.315	0.20

[a] Phosphonodidepsipeptides (PDP) obtained from N-protected L-aminoacids (N-L-AA) and (−) or (+) or mixture of 1-hydroxyalkylphosphonic acid dibenzylesters (HPE) as indicated in the table.

[b] Signals not well separated to be integrated correctly.

[c] Data reported previously from Jeol FX60 spectrometer at 24.3 MHz for 1-hydroxy-isopropylphosphonic acid bis(diphenylmethyl)esters.

[d] Racemate.



SCHEME 1.

3%. The $\alpha = 1$ value for the racemic samples is evidence for the absence of diastereoselectivity during the whole process. A 10% excess of N-protected aminoacids in the coupling reaction was used to transform quantitatively 1-hydroxyalkylphosphonic acid esters into didepsipeptides and to avoid asymmetric induction during derivatization. Also, the NMR samples were taken from a crude product as one of the diastereoisomers could be preferred during the precipitation or crystallization and the original enantiomeric excess could be changed.

The values of ^{31}P NMR nonequivalances $\Delta\delta = 0.16–0.60$ ppm between the respective diasteroisomers (−)L and (+)L are comparable to those obtained with

^{19}F and ^{31}P NMR and Mosher's reagent. The largest $\Delta\delta$ values (0.17–0.42 ppm) were noted for the didepsipeptides with the phenyl or isopropyl groups attached to the asymmetric α-carbons.

The ^{31}P NMR nonequivalence depends on the distance between the asymmetric centers. In case of γ-glutamylphosphonodepsipeptides (**V**), when two additional carbon atoms separate the asymmetric centers, $\Delta\delta$ is relatively low (0–0.06 ppm). The only product in which we were unable to observe nonequivalence was **VB**. However, changing the protecting groups improved the nonequivalence value (e.g. **VA** and **VB**). To calculate the enantiomeric excess correctly the integrals of well separated signals are desired. The separation can be improved by using spectrometers operating at higher resonance frequencies. The previously reported[9] $\Delta\delta$ data for bis(diphenylmethyl)esters **1**, **2** and **3** from a spectrometer operating at 24.3 MHz, also relatively large (0.2–0.6 ppm), showed that the signals are not separated adequately to be quantitatively integrated. It seems to us, that the Boc-L-Phe and Boc-L-Val could be used as a promising chiral derivatizing agent in the groups of chiral hydroxyphosphonates.

To check if ^{31}P NMR spectroscopy is capable of quantifying the diastereoisomers, the spectra of preweighted samples of phosphonodidepsipeptides **IVA** (+)L:rac-L; (−)L:rac-L and **IVE** (+)L:rac-L were recorded. The enantiomeric excess from the integral ratios (α) had not differed by more than 1% from the expected value.

This method was applied to the enantiomeric excess determination of enriched **IIC** and **IIA**. The mixtures with a molar ratio of 1:1 (ee% = 50%) were preweighed

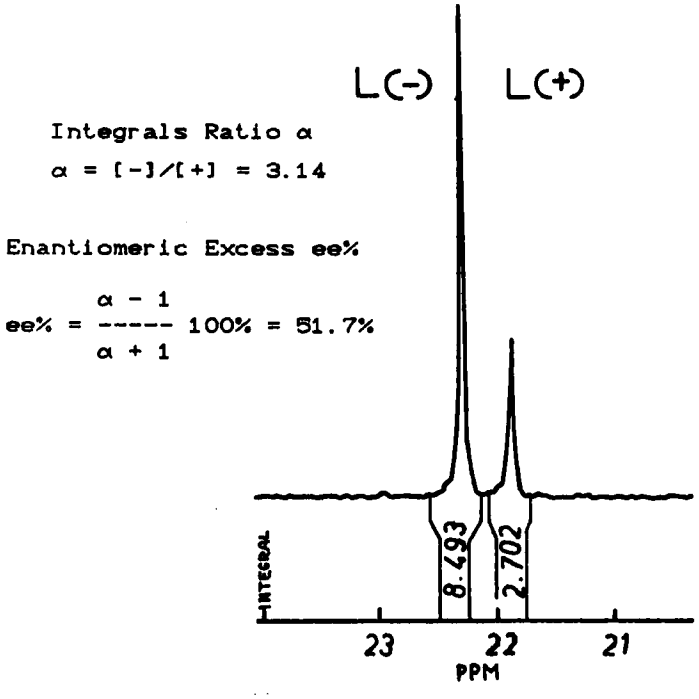


FIGURE 1 $^{31}P(^{1}H)$ NMR spectrum of compound **IVA**. 1-Hydroxyisobutylphosphonic acid dibenzyl ester was used as a preweighed mixture (1:1) from pure (−) and racemate.

from racemic and pure enantiomer of (−)**IIC** and (+)**IIA**, respectively. Samples were coupled with a 10% molar excess of Boc-L-Phe and the spectra of crude product were recorded (Figure 1). The values of ee% = 51.7% were obtained for both samples, in good agreement with the expected 50%.

EXPERIMENTAL

1-Hydroxyalkylphosphonic acids (**I A–C**) and their dibenzyl esters (**II A–C**) were obtained by general methods described previously.[10] The general procedure for coupling of phosphonodidepsipeptides (**IV A–E** and **V A–C**) by means of DCC is as follows: (*a*) To a solution of N-protected L-aminoacid **III A–E** (1.1 mmol) and dibenzyl 1-hydroxyalkylphosphonate **II A–C** (1 mmol) in 10 ml CCl_4 was added DCC (1.1 mmol) and DMP (1.1 mmol). (*b*) The reaction mixture was stirred at room temperature for 6 h and N,N-dicyclohexylurea was filtered off. The filtrate was evaporated to dryness and ethyl acetate 20 ml was added to the residue. (*c*) The solution was washed successively with 1 M $KHSO_4$ (2 × 15 ml), water (15 ml), 5% $NaHCO_3$ (2 × 15 ml), dried with $MgSO_4$ and evaporated to dryness.

The ^{31}P NMR spectra of the products in $CDCl_3$ were recorded on a FT-NMR spectrometer Bruker MSL-300 at 121.5 MHz. An 85% H_3PO_4 solution was used as an external reference. Typical conditions: spectral width 20000 Hz, number of scans 50–100 and digital resolution 1.2 Hz per data point.

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