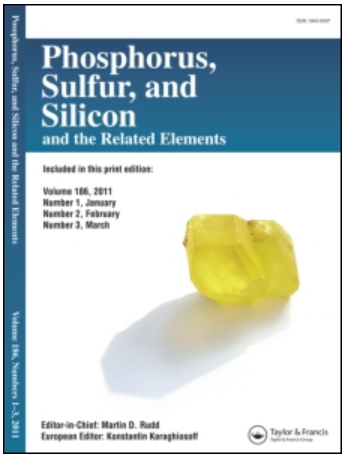

Phosphorus, Sulfur, and Silicon and the Related Elements
Publication details, including instructions for authors and subscription information:
http://www.informaworld.com/smpp/title~content=t713618290

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To cite this Article Głowacki, Zdzisław and Hoffmann, Maria(1991) '^{31}P NMR NON-EQUIVALENCE OF THE DIASTEREOISOMERIC PHOSPHONODIDEPSIPEPTIDES. PART II', Phosphorus, Sulfur, and Silicon and the Related Elements, 63: 1, 171 — 175
To link to this Article: DOI: 10.1080/10426509108029440
URL: http://dx.doi.org/10.1080/10426509108029440

Phosphorus, Sulfur, and Silicon, 1991, Vol. 63, pp. 171–175
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^{31}P NMR NON-EQUIVALENCE OF THE DIASTEREOISOMERIC PHOSPHONODIDEPSIPEPTIDES. PART II[1]

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(Received April 16, 1991; in final form May 13, 1991)

^{31}P chemical shifts are reported for 24 different models of diastereoisomeric phosphonodidepsipeptides coupled from the N-protected L-aminoacids and dibenzyl esters of chiral 1-hydroxyalkylphosphonic acids. The ^{31}P NMR nonequivalence variations with the changing of didepsipeptide structure, solvent and temperature were investigated. Amide *cis-trans* isomerism were observed in the case of Z-L-proline derived didepsipeptides.

Key words: Enantiomeric excess; 1-hydroxyalkylphosphonic acids; ^{31}P magnetic nonequivalence; phosphonodidepsipeptides.

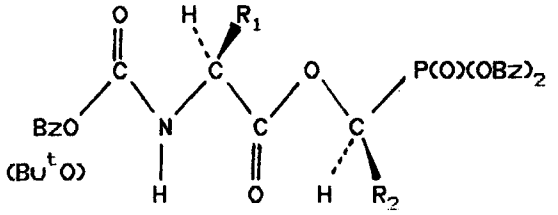
INTRODUCTION

In the first part[1] we presented convenient methods for enantiomeric composition determination of chiral 1-hydroxyalkylphosphonic acids from the ^{31}P NMR spectra of their diastereoisomeric phosphonodidepsipeptides, derivatives of the N-protected natural aminoacids. In order to study correlations between the structure of the phosphonodidepsipeptides and the diastereotopic chemical shift nonequivalences, more than 20 additional phosphonodidepsipeptides were synthesized and their ^{31}P NMR spectra were recorded in different conditions.

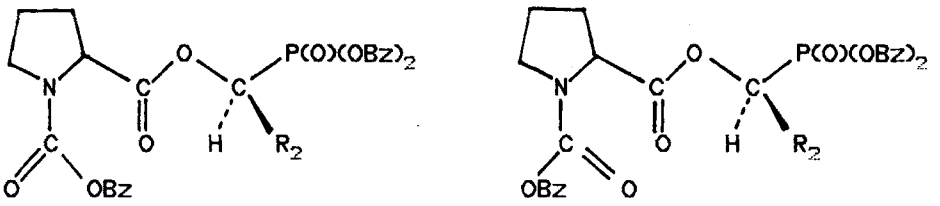
NMR spectra of aminoacids, peptides, their derivatives[2–5] and phosphonic analogs[1,6,7] are frequently used to measure enantiomeric composition, to follow racemization during coupling reaction or to follow resolution processes, also to control diastereoisomeric purity of the resulting product.

RESULTS AND DISCUSSION

The pairs of 1-hydroxyalkylphosphonic 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 (**1–24**, depicted in Scheme I), L(+) or L(−), are collected in Table I. ^{31}P NMR spectra showed the persistence of two distinguishable diastereoisomers when the racemate samples of chiral 1-hydroxyalkylphosphonic acid esters were used. NMR spectra of Z-L-proline derivatives **24** are more complex than those of other aminoacid didepsipeptides, the latter showed signals of only the transoid form (Z conformer).[9,10] Amide *cis-trans* isomerism has been the subject of a number of studies, especially that of proline residue, in dipeptides, polypeptide and in protein structures.[10–12] Both, cisoid and transoid forms, are observed in the



Transoid form of didepsipeptides 1 - 23.



Cisoid and transoid forms of proline didepsipeptides 24.

SCHEME I

^{31}P NMR spectra of **24**. The coalescence of the two peaks was recorded near 330 K in $CDCl_3$ solution. The difference between $\delta^{31}P$ of *cis* and *trans* forms depends on didepsipeptide configuration, and is larger for L(−) isomer (0.144 ppm and 0.053 ppm of L(−) and L(+), respectively). Higher sample temperature destruct the defined conformational preference and reduce the differences between cis and trans conformer as well as magnetic nonequivalence of diastereoisomers. The same effects are observed when the H-bonded structure of didepsipeptide is destroyed by polar solvents such as pyridine or DMSO (1 and 2).

The variations of $\Delta\ \delta^{31}P$ with the substituent at the hydroxyphosphonates asymmetric centre and the N-protected L-aminoacids, are collected in Table II. The best chiral derivatizing agent is Boc-N-protected phenylalanine ($\Delta\ \delta^{31}P$ = 0.50 − 0.20 ppm). Assuming, the similar conformer population of the didepsipeptide reported in the table, the observed $\delta^{31}P$ anisochrony is related only to R_2. Highest $\Delta\ \delta^{31}P$ values were recorded for isopropyl and isobutyl at the chiral centre, surprisingly the anisotropic phenyl revealed smallest magnetic differentiation. The protecting groups (Z- or Boc-) do not change the magnitude of nonequivalence.

Only for two of the here reported hydroxyphosphonates the absolute configurations have been determined; S(−) configuration of dimethyl α-hydroxybenzylphosphonate[13] and R(−) of dibenzyl 1-hydroxyisopentylphosphonate.[14] ^{31}P NMR signals of L-aminoacids and R-hydroxybenzyl- and R-hydroxyisopentyl-phosphonates didepsipeptides are always shifted to lower field (**2, 5, 12, 21** and **24**).

TABLE I

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

PDP[1]	N-L-AA	R_1	R_2	$\delta(^{31}P)$ L(+)	$\delta(^{31}P)$ L(−)	$\Delta\delta$ [ppm]	Notes
1	Boc-L-Phe.	Bz	(+)i-Pr	20.408			a*, $CDCl_3$
			rac	20.434	20.866	0.432	a*, $CDCl_3$
				21.022	21.514	0.492	$CDCl_3$
				21.096	21.582	0.486	b, $CDCl_3$
				21.461	22.049	0.588	benzene
				21.401	21.785	0.384	pyridine
2			S(+)i-Bu	21.867			$CDCl_3$
			R(−)		22.279		$CDCl_3$
			rac	21.865	22.280	0.415	$CDCl_3$
				22.514	22.929	0.415	benzene
				22.421	22.719	0.298	pyridine
				22.103	22.411	0.308	DMSO
3			rac n-Pr	22.108		0.415	$CDCl_3$
				21.693			
4			rac Me	22.492		0.389	$CDCl_3$
				22.103			
				22.818		0.372	b, benzene
				22.446			
5			R(+)Ph	18.505			a*, $CDCl_3$
			rac	18.517	18.318		a*, $CDCl_3$
6	Z-L-Phe	Bz	rac i-Pr	21.563		0.434	$CDCl_3$
				21.129			
7			rac i-Bu	22.355		0.414	$CDCl_3$
				21.941			
8			rac n-Pr	21.974		0.415	$CDCl_3$
				21.559			
9			rac Me	22.379		0.390	b, $CDCl_3$
				21.989			
10			rac Ph	18.723		0.196	$CDCl_3$
				18.527			
11	Boc-L-Val	i-Pr	(+)i-Pr	21.249			$CDCl_3$
				21.246	21.665	0.419	$CDCl_3$
12			R(−)i-Bu		22.513		$CDCl_3$
				22.188	22.528	0.340	$CDCl_3$
13			rac n-Pr	22.167		0.316	$CDCl_3$
				21.851			
14			rac Me	22.522		0.207	$CDCl_3$
				22.315			
				22.802		0.202	b, benzene
				22.600			
15			R(+) Ph	18.751			$CDCl_3$
			rac	18.728		0	$CDCl_3$
16	Z-L-Val	i-Pr	rac i-Pr	22.310		0.356	$CDCl_3$
				21.954			
17			rac i-Bu	21.634		0.416	$CDCl_3$
				21.218			
18	Boc-L-Ile	sec-Bu	rac i-Pr	21.651		0.421	b, $CDCl_3$
				21.230			
19			rac i-Bu	22.555		0.308	b, $CDCl_3$
				22.247			
20			rac Ph	18.738		0	b, $CDCl_3$
				18.670		0	$CDCl_3$
21	Boc-L-Leu	i-Bu	R(−)i-Bu		22.347		$CDCl_3$
			rac	22.177	22.338	0.161	$CDCl_3$

TABLE I (*continued*)

PDP[1]	N-L-AA	R_1	R_2	$\delta(^{31}P)$ L(+)	$\delta(^{31}P)$ L(−)	$\Delta\delta$ [ppm]	Notes
22			rac Me	22.463 22.360		0.103	$CDCl_3$
				22.808 22.663		0.145	b, benzene
23	Z-L-Leu	i-Bu	rac i-Bu	22.284 22.094		0.190	$CDCl_3$
24	Z-L-Pro		R(−) i-Bu		22.727 22.583		303°K, $CDCl_3$
					22.612 22.499		320°K, $CDCl_3$
					22.495		330°K, $CDCl_3$
			rac	22.459 22.406	22.738 22.594	0.233	303°K, $CDCl_3$
			rac	22.293	22.468	0.175	330°K, $CDCl_3$

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

[a]*ERRATUM: these data were not correctly rewritten in Table I of the Part I (ref. 1), 1a* recorded on Jeol FX90Q at 36.27 MHz.

[b]Bruker AC-200 at 80.02 MHz, all other spectra from Bruker MSL-300 at 121.5 MHz.

Boc = t-butoxycarbonyl group, Z = benzyloxycarbonyl group.

TABLE II

The variations of $\Delta\ \delta^{31}P$ (ppm) between L(+) and L(−) with the substituent at the hydroxyphosphonates asymmetric centre and the N-protected L-aminoacids

	N-protected aminoacid		
	Boc-Phe	Z-Phe	Boc-Val
R_2	{	$\Delta\delta^{31}P$	}
i-Pr	0.492	0.434	0.419
i-Bu	0.415	0.414	0.340
n-Pr	0.415	0.415	0.316
Me	0.389	0.390	0.207
Ph	0.199	0.196	0

EXPERIMENTAL

The general procedure for coupling of phosphonodidepsipeptides **1–24** by means of DCC have been reported previously.[1,8] The ^{31}P NMR spectra of the products in $CDCl_3$ (benzene, pyridine or DMSO) were recorded on a FT-NMR spectrometer Bruker MSL-300 at 121.5 MHz and Bruker AC-200 at 81.02 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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