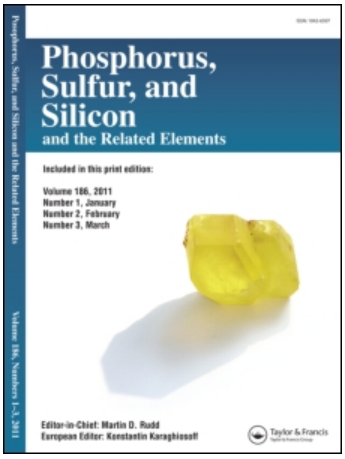

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THE ASSIGNMENT OF ACYCLIC STEREOISOMERS. II. CONFORMATIONAL ANALYSIS OF 3-PHOSPHONYL-2-BENZOYLAMINOPROPIONIC ACID METHYL-ESTERS†

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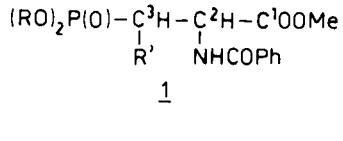
The conformational analysis of 3-phosphonyl-2-benzoylaminopropionic acid methyl esters, which occur as diastereomeric pairs of enantiomers owing to two present chiral centres, has been managed successfully by means of ^{31}P, ^{13}C, ^{1}H and ^{15}N chemical shifts as well as the characteristically different coupling constants between the ^{1}H, ^{13}C and ^{31}P nuclei. In this light, the diastereomers involved could be assigned readily.

Key words: NMR; phosphorus analogous aspartic acid derivatives; conformational analysis; acylic diastereomer assignment.

INTRODUCTION

Within the work on phosphorus substituted amino carbonic acids the synthesis of P-analogous aspartic acid derivatives was of special interest. During the course of this investigation a series of 3-phosphonyl 2-benzoylaminopropionic acid methyl-esters, **1–2**, of various substituents R and R′ has been prepared.[2]



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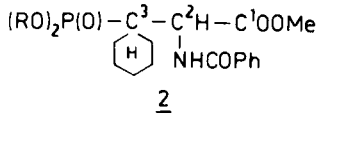

2

No.	R	R′
1a	-Et	-C_6H_4OMe (p)
1b	-Et	-C_6H_5
1c	-Et	-$C_6H_3(OMe)_2$ (m, p)
1d	-isoPr.	-C_6H_4OMe (p)
1e	-isoPr.	-C_6H_5
1f	-nBu	-C_6H_4OMe (p)
1g	-Me	-C_6H_4OMe (p)
1h	-Me	-C_6H_5
1i	-Et	-isoPr.
2a	-Et	
2b	-isoPr.	

When recording the ^{1}H NMR spectra of these compounds, then, in the cases of **1**, the spectra of isomeric mixtures owing to two present chiral centres have been

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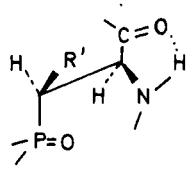
obtained. In order to assign these stereoisomers, the conformational analysis of the present flexible species ought to be included. Both topics are the object of the present paper.

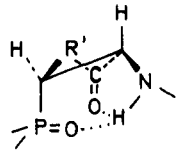
RESULTS AND DISCUSSION

The NMR parameters of the compounds **1–2** studied are given in Tables I and II. In Table III, the free and associated N-H vibrations, obtained from the IR-spectra, together with the $^3J(^{15}N, ^1H)$ coupling constants, both properly indicating the stereochemistry wanted, are shown for compound **1a**.

As to be seen from these NMR results two stereoisomers have been obtained only for compounds **1a** and **1d**. These are the erythro/threo stereoisomers owing to the adjacent chiral centres, which are still pairs of enantiomers; the latter ones, however, cannot be differentiated due to the achiral medium present. In terms of stereochemistry, these diastereomers should be named more exactly as RR/SS (threo) and RS/SR (erythro) stereoisomers. The calotte models represent them as strongly sterically strained; restricted rotation about C^2,C^3 seems possible therefrom. Additionally, due to the NH proton present, several intramolecular hydrogen bond possibilities to the ester carbonyls and the P=O, respectively, do exist. In the light of these observations just mentioned, the following rotamers about the C^2,C^3 bond for the two different stereoisomers can be achieved (only one enantiomer studied):



A
erythro S/R



B
threo S/S

(i) Both the ^{31}P and the ^{15}N chemical shifts of the erythro/threo stereoisomers are characteristically different, (e.g. **1a**: $\Delta\delta^{31}P = 4.1$ ppm; $\Delta\delta^{15}N = 2.0$ ppm).

(ii) Concerning the vicinal coupling constants: only if **A** in the case of the erythro and **B** in the case of the threo stereoisomer are the preferred rotamers, the coupling constants collected do agree. The values, with reference to the gauche/anti arrangement of the nuclei involved, are in line with results obtained previously.[3–6] All other suggested *J*-combinations disagree; thus, beside the erythro/threo stereoisomerism also the conformational arrangement about the C^2,C^3 bond is available.

(iii) The intramolecular hydrogen bonds involved are indicated by means of associated NH valence vibrations obtained from the corresponding IR spectra.

If the C^3-chiral centre disappears—comp. **2**—then only the R/S enantiomeric pair, not to be distinguished in the present achiral medium, is obtained. The

TABLE I

NMR parameter, obtained from the proton spectra, of compounds **1** and **2**

Comp.	stereo-chemistry	Chemical shifts δ (ppm) H^3	H^2	R′	C^1OOMe	NH	R
1a (C_6D_6)	erythro	3.7	5.8	3.30	3.25	7.70	3.5–4.3 1.1 and 0.9
	threo	4.0	5.5	3.22	3.37	9.05	3.4–4.1 1.1 and 0.7
1b (C_6D_6)	erythro	4.0	5.8	—	3.24	7.8	3.9 1.0 and 0.8
1c ($CDCl_3$)	erythro	3.8	5.4	3.83 3.84	3.65	n.o.	4.1 1.1 and 1.3
1d (C_6D_6)	erythro	3.9	5.7	3.26	3.24	7.8	4.49 and 4.36 0.8, 1.0, 1.2
	threo	3.9	5.5	3.24	3.39	9.0	4.65 and 4.36 0.6, 1.0, 1.1
1e (C_6D_6)	erythro	3.9	5.8	—	3.16	7.8	4.75 and 4.45 0.7, 1.0, 1.1, 1.2
1f (C_6D_6)	erythro	3.8	5.8	3.29	3.25	7.8	3.7–4.1 0.7
1q (C_6D_6)	erythro	3.9	5.8	3.25	3.22	n.o.	3.45 and 3.2 —
1h ($CDCl_3$)	erythro	3.9 —	5.8	—	3.65	7.0	3.4 and 3.2 —
2a (C_6D_6)		— —	5.7	—	3.34	9.04	4.6 1.1, 1.2
2b (C_6D_6)			5.8	—	3.33	9.1	3.7–4.1 1.1 and 1.0

TABLE II

NMR parameter obtained from the spectra of compounds **1–2**

Comp.	Stereo-chemistry	Chemical shifts δ (ppm)					
		C^3	C^2	R′	OMe	C^1	C(O)N
1a	erythro	45.0	54.0	54.7	51.8	170.5	166.8
(C_6D_6)	threo	46.0	55.8	54.7	52.0	172.0	170.0
1b	erythro	45.5	53.9	—	51.9	175.5	166.9
(C_6D_6)							
1c	erythro	45.1	53.0	55.9	52.5	170.6	167.1
($CDCl_3$)				55.9			
1d	erythro	45.3	54.2	54.8	51.8	170.4	167.0
(C_6D_6)	threo	44.6	56.0	54.8	52.0	170.8	166.5
1e	erythro	46.2	54.1	—	51.7	170.3	166.9
(C_6D_6)							
1f	erythro	44.5	54.2	48.8	51.9	170.9	166.9
(C_6D_6)							
1g	erythro	44.4	53.8	54.7	51.9	170.5	166.8
(C_6D_6)							
1h	erythro	45.2	52.8	—	52.4	170.2	167.0
($CDCl_3$)							
2a		41.0	51.8	—	51.6	171.0	167.0
(C_6D_6)							
2b		41.5	51.3	—	51.9	170.5	166.8
(C_6D_6)							

n.o. = not obtained

TABLE III

IR data of the scelecton vibrations and the $^3J(^{15}N, ^1H^3)$ coupling constants of the stereoisomers of compound **1a**

Stereoisomer	Degree of association	$\tilde{\nu}_{NH}$	$\tilde{\nu}_{CO(Me)}$	$\tilde{\nu}_{P=O}$	$\tilde{\nu}_{(N)CO}$	$^3J(^{15}N, ^1H^3)$ (Hz)
erythro	free	3440	1760	1256	1676	3
	assoc.	3328	1740	—	—	
threo	free	—	1760	1252	1676	3
	assoc.	3340	1740	1238		

preferred conformer, however, is identical with *B* due to the $^3J(^{31}P, ^1H) = 37.3$ Hz and the $^3J(^{31}P, ^{13}C) < 2$ Hz as well.

With these assigned conformers in hand, the ^1H NMR spectroscopic behaviour of the two stereoisomers, becomes quite clear.

(i) In **A** the carboxyester methyl group is situated near to the C^3-phenyl substituent and, owing to steric reasons, is in the shielding area of the anisotropy cone. Because of no such possibility in **B**, the ester methyl in conformer **A** is high field shifted by 0.12 ppm.

(ii) Inversely, the phosphonyl alkyl groups are in **B** under the same influence, but of the NHCO-phenyl substituent, and are high field shifted accordingly.

(iii) The low field shift of the NH proton in **B** (**1a**: $\delta_{NH} = 9.05$ ppm) compared to **A** (**1a**:$\delta_{NH} = 7.70$ ppm) is due to the different intramolecular association to the ester carbonyl and the P=O function, respectively.

The presence of enantiomers (RR/SS and RS/SR) for the different stereoisomers has been studied by means of optically active Eu(HFC)$_3$† LIS reagent. With increasing amounts, the sharp methyl signals are splitted. Racemic mixtures of the enantiomers are present because the ratio of the enantiomers is 1:1 and no optical rotation obtained.

EXPERIMENTAL

The NMR spectra have been recorded using a Bruker WP 200 NMR spectrometer (^1H at 200.13 MHz, ^{13}C at 50.327 MHz, ^{31}P at 81.026 MHz and ^{15}N at 20.282 MHz) and the chemical shifts referenced to TMS (^1H and ^{13}C), 85%ic phosphoric acid (^{31}P), or CH_3—NO_2(^{15}N). Low field shifts according to the standards mentioned, have positive sign. The IR spectra have been recorded using a VEB Carl-Zeiss Jena M 80 IR spectrometer. For the NMR-measurements the samples were dissolved in deuterated benzene, for the IR-measurements in benzene.

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† Eu(HFC)$_3$ = tris-(3-(Heptafluoropropylhydroxy-methylene)-D-camphorato) Eu (III).