A 1H, 13C, 31P and 15N NMR study of (pyrrolidine-2,2-diyl)bisphosphonic acid, tetraalkyl(pyrrolidine-2,2-diyl)bisphosphonates and acyclic tetraethyl bisphosphonates

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Gilles Olive[†], Marcel H.P. van Genderen[‡*]

[†] Laboratory of Polymer Chemistry and Coatings Technology

[‡] Laboratory of Macromolecular and Organic Chemistry

Eindhoven University of Technology, P.O. Box 513, 5600 MB Eindhoven, The Netherlands.

Tel: +31-40-2473139. Fax: +31-40-2451036.

[*] To whom correspondence should be addressed.

ABSTRACT:

A multinuclear NMR study (^{1}H, ^{13}C, ^{31}P, ^{15}N) was performed on a series of new cyclic pyrrolidine bisphosphonates and acyclic bisphosphonates. Values are reported and discussed for the chemical shifts and coupling constants of the various nuclei.

KEYWORDS: NMR; ^{1}H NMR; ^{13}C NMR; ^{31}P NMR; ^{15}N NMR; tetraalkyl bisphosphonates; bisphosphonic acid

INTRODUCTION

Gem-bisphosphonates or *gem*-bisphosphonic acids can complex well with calcium and magnesium.[1] As a result their use in various areas, for instance in the medical field[2], as plant growth regulators[3] and in the nuclear industry[2], has been known for some time. We report here a multinuclear NMR study, in particular nitrogen-15, of new tetraalkyl bisphosphonates in a cyclic series and acyclic forms. It is interesting that these compounds can be labeled with ^{15}N for a direct study in biological material, which has been a considerable problem for several decades.[4]

EXPERIMENTAL

The synthesis of compounds **1** to **6** (Figure 1) has been described[5,6] and the synthesis and full characterization of **7** and **8** will be published in a forthcoming paper.

^{1}H, ^{13}C and ^{31}P NMR spectra were measured at 25 ºC on Bruker AC-100, AC-200 and AMX-400 spectrometers. ^{1}H spectra were recorded at 100, 200 and 400 MHz. ^{13}C spectra were recorded at 25.18, 50.32 and 100.65 MHz. ^{31}P spectra were recorded at 40.54 MHz. ^{15}N NMR spectra were measured at 25 ºC on a Varian Unity Inova 500 spectrometer at 50.65 MHz. In all cases, a field-frequency lock on the solvent ^{2}H signal was used. Chemical shifts are reported in ppm downfield from the standards, which were: TMS ($\delta = 0$) or residual HDO in aqueous NaOD ($\delta = 4.81$) for ^{1}H spectra, TMS ($\delta = 0$) for ^{13}C spectra, external 85% H_3PO_4 ($\delta = 0$) for ^{31}P spectra, and external CD_3NO_2 ($\delta = 0$) for ^{15}N spectra. Samples were prepared in C_6D_6, $CDCl_3$ or aqueous NaOD (50 mg Na/ml D_2O), in concentrations of 50-100 mg/ml for ^{1}H, ^{13}C and ^{31}P spectra in 5-mm tubes, and in a 80:20 (v/v) ratio of compound and solvent for natural abundance ^{15}N measurements in 10-mm tubes. Acquisition parameters for ^{1}H spectra were: pulse width 2-6 μs (45° pulse), 16 transients, 4 s acquisition time, 2 s relaxation delay, spectral width 10 ppm (1-4 kHz), 8-32 K data points, 0.24 Hz resolution. ^{1}H spectra were obtained with line broadening (lb = 0.1). Acquisition parameters for ^{13}C spectra were: pulse width 3 μs (45° pulse), 100 transients, 0.7-1.4 s acquisition time, 5 s relaxation delay, spectral width 6-24 kHz, 16-32 K data points, 0.74-1.45 Hz resolution. ^{13}C spectra

were obtained with line broadening (lb = 1) and ^{1}H broadband decoupling. Acquisition parameters for ^{31}P spectra were: pulse width 5 μs (90° pulse), 80 transients, 5 s acquisition time, 3 s relaxation delay, spectral width 16 kHz, 16 K data points, 2 Hz resolution. ^{31}P spectra were obtained with ^{1}H broadband decoupling. Acquisition parameters for ^{15}N spectra were: pulse width 10 μs (90° pulse: 20.5 μs), 400 transients, 1.9 s acquisition time, 10 s relaxation delay, spectral width 8 kHz, 30000 data points, 0.5 Hz resolution. ^{15}N spectra were obtained with line broadening (lb = 1) and inverse-gated ^{1}H broadband decoupling.

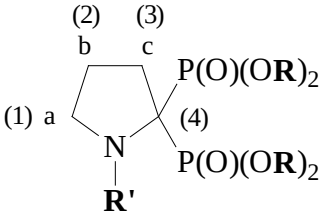
RESULTS AND DISCUSSION

For all bisphosphonates, except **1**, the ^{15}N spectrum (Table 1) shows a triplet, indicating that the two phosphorus nuclei are equivalent. This means that the ring pseudorotation is very fast for **2** to **5**, as previously reported for the nitroxide[7] (confirmed by the fact that we obtained triplets in ^{13}C NMR). The two-bond coupling constants between phosphorus and nitrogen are in the range 2-9 Hz, which agrees with the few instances of $^{2}J_{NP}$ reported in the literature.[8,9] It is evident that the linear compounds **6**, **7** and **8** have smaller coupling constants (6.3, 6.1 and 5.2 Hz respectively) than the cyclic structures.

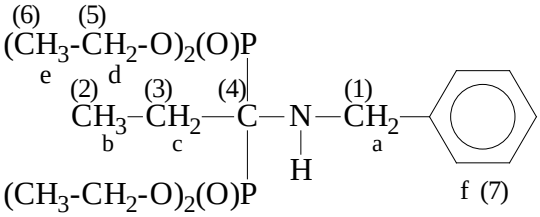
Except for **1** (due to a different solvent) and for the picrate of **2**, the ^{15}N chemical shifts of the cyclic forms **2-4** are all similar (max. change 0.5 ppm) and no correlation with the structure was found. Cyclic **5** has a different chemical shift because it is a tertiary amine (the donating methyl group induces an upfield shift). All ^{15}N chemical shifts (Table 1) for amines **2-8** are very different from the starting materials (respectively -264.3 ppm for the pyrrolidine-2-one, -271.9 ppm for *N*-methyl pyrrolidone, -262.1 ppm for the precursor of **6**, -242.0 ppm for the precursor of **7**, and -244.5 ppm for the precursor of **8**).

It is also not possible to make a correlation between the structure and the chemical shift in the ^{31}P spectra (Table 1). In all cases we see only one line in the ^{31}P spectra. Hence the two phosphorus nuclei are equivalent and the ring pseudorotation is very fast for **1-5**. For ^{1}H (Table 2) and ^{13}C NMR (Table 3) there are some cases (for example for **3**) where the methyl groups are not equivalent,

presumably free rotation around the P-C bond is prevented.[10] The analysis of the ^{13}C spectra (Table 3) for the α and β-carbons of the phosphonate ester groups, that is an AA'X system, has been described in reference 5.



	R'	R
1	H	H
2	H	(5) (6) CH_2-CH_3 d e
3	H	(5) (6) $CH(CH_3)_2$ d e
4	H	(5) (6) (7) (8) CH_2-CH_2-CH_2-CH_3 d e f g
5	(7) CH_3 f	(5) (6) CH_2-CH_3 d e



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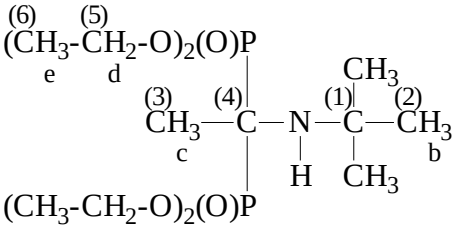

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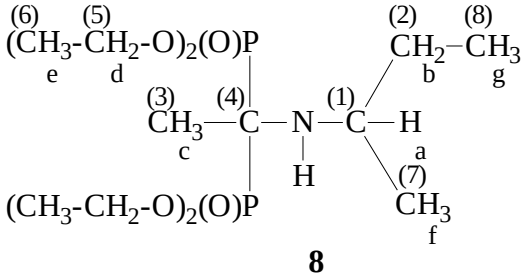

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Figure 1. Structures and numbering of the compounds studied.
Letters refer to protons and numbers to carbons

Table 1. ^{31}P and ^{15}N NMR spectral data for bisphosphonates **1**-**8**: $\delta(^{31}P)$ and $\delta(^{15}N)$ (ppm)
(Parentheses indicate coupling constants in Hz)

	^{31}P			^{15}N	
	δ	Solvent	Ref	δ	Solvent
1	15.9	Na/D_2O[d]	5	-312.8	Na/D_2O[d]
2	22.5	$CDCl_3$	5	-340.7 (8.7)[a]	C_6D_6
Picrate of 2	16.2	$CDCl_3$	5	-12.2[b] -15.4[c] -322.1 (2.2)	$CDCl_3$
3	21.2	$CDCl_3$	5	-340.3 (9.3)	C_6D_6
4	22.7	$CDCl_3$	6	-340.5 (8.5)	C_6D_6
5	21.8	$CDCl_3$	6	-344.8 (8.3)	C_6D_6
6	21.5	$CDCl_3$	6	-340.4 (6.3)	C_6D_6
7	22.5	$CDCl_3$		-324.3 (6.1)	C_6D_6
8	23.3	$CDCl_3$		-330.8 (5.2)	C_6D_6

[a] -341.6 (8.6) in $CDCl_3$, [b] nitro ortho, [c] nitro para, [d] 50 mg Na/ml D_2O

Table 2. ^{1}H NMR spectral data for bisphosphonates **1**-**8**: δ(^{1}H) (ppm)
(Parentheses indicate the pattern of coupling and
the coupling constants in Hz)

	a	b	c	d	e	f	g	Solvent Frequency	Ref
1	3.21 (t, 7.0)	1.85 (quint., 7.0)	2.17 (sept., 7.1[e]; 14.5[f])					Na/D_2O[c] 200	5
2	2.88 (t, 6.5)	1.69 (quint., 6.8)	2.42 (tt, 7.2[e] ; 17.7[f])	4.17 (m)	1.11 (t, 7.1[e]) 1.10 (t, 7.1[e])			C_6D_6 400	5
Picrate of 2	3.64 (t, 6.9)	2.15-2.67 (m)		4.24 (m)	1.36 (t, 7.1[e]) 1.33 (t, 7.1[e])	8.86[a] (s)	7.99[b] (s)	$CDCl_3$ 100	5
3	2.95 (t, 6.5)	1.75 (quint., 6.8)	2.37 (tt, 7.3[e] ; 17.7[f])	5.00 (m) 4.87 (m)	1.31 (d, 6.2[e]) 1.28 (d, 6.3[e]) 1.27 (d, 6.4[e]) 1.22 (d, 6.1[e])			C_6D_6 400	5
4	2.97 (t, 6.5)	1.76 (quint., 6.9)	2.49 (tt, 7.3[e] ; 17.8[f])	4.27 (m) 4.22 (m)	1.56 (m)	1.33 (sext., 7.5[e]) 1.32 (sext., 7.3[e])	0.83 (t, 7.4[e]) 0.82 (t, 7.4[e])	C_6D_6 400	6
5	2.84 (t, 6.6)	1.84 (quint., 6.6)	2.43 (m)	4.21 (m)	1.34 (t, 7.1[e])	2.79 (t, 1.7)		$CDCl_3$ 200	6
6	4.11 (m)	1.12 (t, 7.5[e])	2.13 (tq, 7.5[e] ; 15.0[f])	4.21 (m)	1.32 (t, 7.1[e]) 1.31 (t, 7.1[e])	7.24 (m)		$CDCl_3$ 400	6
7		1.24 (s)	1.74 (t, 18.4[f])	4.1 - 4.3 (m)	1.33 (q, 7.0)			$CDCl_3$ 400	
8	2.9 (m)	1.3[d] (m) 1.1[d] (m)	1.41 (t, 17.4[f])	4.02 (m)	1.15 (t, 7.2[e])	0.87 (d, 6.4[e])	0.68 (t, 7.4[e])	$CDCl_3$ 400	

[a] aromatics, [b] $-NH_2^+$, [c] 50 mg Na/ml D_2O, [d] the two protons are not equivalent, [e] H-H coupling, [f] P-H coupling

Table 3. ^{13}C NMR spectral data for bisphosphonates **1**-**8**: $\delta(^{13}C)$ (ppm)
(Parentheses indicate coupling constants with ^{31}P in Hz)

	(1)	(2)	(3)	(4)	(5)	(6)	(7)	(8)	Solvent Frequency	Ref
1	48.6	25.4	31.3	65.8 (t, 118.0)					Na/D_2O[i] 50	5
2	47.7 (t, 4.0)	26.5 (t, 3.1)	31.2 (t, 3.0)	62.8 (t, 151.8)	63.4 (t, 5.3)[f] 62.7 (t, 5.8)[f]	16.6 (t, 5.5)[g] 16.5 (t, 7.2)[g]			C_6D_6 100	5
Picrate of 2	49.3 (t[e])	24.2 (t[e])	31.2 (t[e])	63.3 (t, 145.4)	65.0 (d[e])	16.4 (t[e])	160.6[a] 141.0[c] 128.7[d] 126.2[b]		$CDCl_3$ 100	
3	47.7 (t, 4.6)	26.4 (t, 3.3)	31.0 (t, 3.4)	63.1 (t, 151.1)	71.7 (t, 6.2)[f] 70.8 (t, 6.7)[f]	24.7 24.4 24.0 (t, 6.2)[g] 23.8 (t, 6.7)[g]			C_6D_6 100	5
4	48.1 (t, 4.3)	26.8 (t, 3.2)	31.5 (t, 3.0)	63.2 (t, 152.0)	67.8 (t, 3.2)[f] 67.1 (t, 3.5)[f]	33.5 (t, 2.7)[g] 33.4 (t, 2.7)[g]	19.4	14.1	C_6D_6 100	6
5	55.3 (t, 4.7)	23.6 (t[e])	32.2 (4.6)	64.2 (153.0)	62.2 (m)	16.1 (t[e])	37.3 (t[e])		$CDCl_3$ 50	6
6	47.9 (t, 6.5)	8.5 (t, 6.5)	23.5 (t[e])	62.8 (t, 140.1)	63.1 (t, 3.2)[f] 62.8 (t, 3.1)[f]	16.5 (t[e])	140.5[a] 128.3[b] 128.2[c] 127.0[d]		$CDCl_3$ 100	6
7	52.6 (t, 5.7)	32.4	15.8 (t, 5.5)	58.9 (t, 145.0)	64.0 (t, 3.7)[f] 62.5 (t, 4.1)[f]	16.3 (m)			$CDCl_3$ 100	
8	48.4 (t, 6.1)	32.1	15.6 (t, 4.2)	57.5 (t, 143.0)	63.2 (t, 3.8)[f] 62.3 (t, 3.8)f	16.2 (t, 3.0)[g]	10.1	22.3	$CDCl_3$ 100	

[a] quaternary aromatic, [b] meta aromatics, [c] ortho aromatics, [d] para aromatic, [e] coupling can not be resolved because they are to small, [f] $^2J_{CP}(+^4J_{CP'})$[h], [g] $^3J_{CP}$[h], [h] see ref 5, [i] 50 mg Na/ml D_2O

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