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tetraalkyl(pyrrolidine-2,2-diyl)bisphosphonates and
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► **To cite this version:**

Gilles Olive, Marcel H.P. van Genderen. A ^1H , ^{13}C , ^{31}P and ^{15}N NMR study of (pyrrolidine-2,2-diyl)bisphosphonic acid, tetraalkyl(pyrrolidine-2,2-diyl)bisphosphonates and acyclic tetraethyl bisphosphonates. *Magnetic Resonance in Chemistry*, 2000, 38 (5), pp.379-381. hal-00660649

HAL Id: hal-00660649

<https://hal.science/hal-00660649>

Submitted on 17 Jan 2012

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

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ABSTRACT:

A multinuclear NMR study (^1H , ^{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; ^1H 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 field², as plant growth regulators³ and in the nuclear industry², 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 ¹⁵N 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.

¹H, ¹³C and ³¹P NMR spectra were measured at 25 °C on Bruker AC-100, AC-200 and AMX-400 spectrometers. ¹H spectra were recorded at 100, 200 and 400 MHz. ¹³C spectra were recorded at 25.18, 50.32 and 100.65 MHz. ³¹P spectra were recorded at 40.54 MHz. ¹⁵N NMR spectra were measured at 25 °C on a Varian Unity Inova 500 spectrometer at 50.65 MHz. In all cases, a field-frequency lock on the solvent ²H 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 ¹H spectra, TMS ($\delta = 0$) for ¹³C spectra, external 85% H₃PO₄ ($\delta = 0$) for ³¹P spectra, and external CD₃NO₂ ($\delta = 0$) for ¹⁵N spectra. Samples were prepared in C₆D₆, CDCl₃ or aqueous NaOD (50 mg Na/ml D₂O), in concentrations of 50-100 mg/ml for ¹H, ¹³C and ³¹P spectra in 5-mm tubes, and in a 80:20 (v/v) ratio of compound and solvent for natural abundance ¹⁵N measurements in 10-mm tubes. Acquisition parameters for ¹H spectra were: pulse width 2-6 μ s (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. ¹H spectra were obtained with line broadening (lb = 0.1). Acquisition parameters for ¹³C spectra were: pulse width 3 μ s (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. ¹³C spectra

were obtained with line broadening ($lb = 1$) and ^1H broadband decoupling. Acquisition parameters for ^{31}P spectra were: pulse width $5\ \mu\text{s}$ (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 ^1H broadband decoupling. Acquisition parameters for ^{15}N spectra were: pulse width $10\ \mu\text{s}$ (90° pulse: $20.5\ \mu\text{s}$), 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 ^1H broadband decoupling.

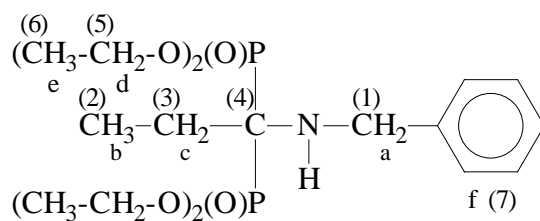
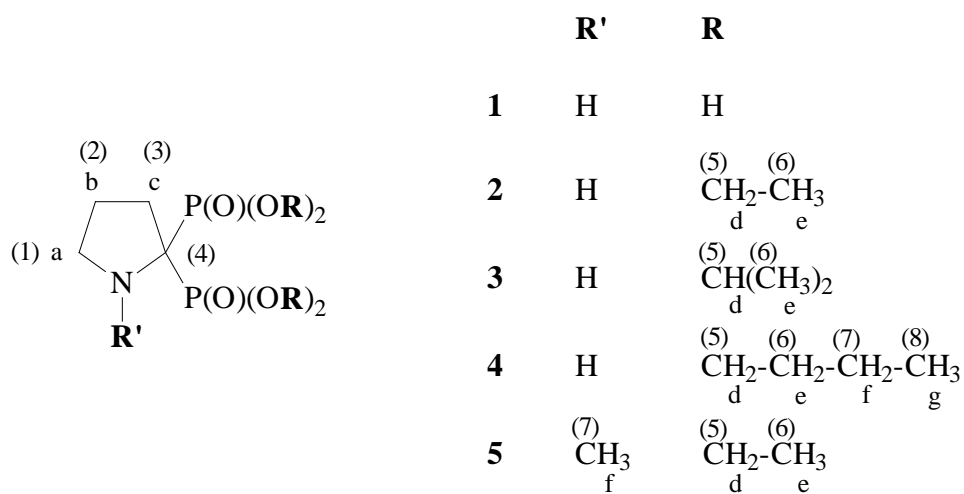
RESULTS AND DISCUSSION

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 nitroxide⁷ (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 $^2J_{\text{NP}}$ 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.

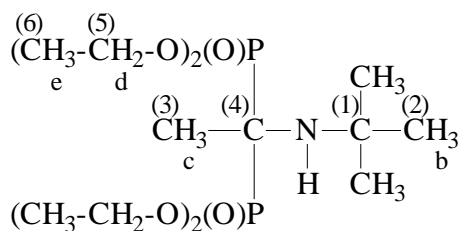
Except for **1** (due to a different solvent) and for the picrate of **2**, the ^{15}N chemical shifts of the cyclic forms **2-4** are all similar (max. change 0.5 ppm) and no correlation with the structure was found. Cyclic **5** has a different chemical shift because it is a tertiary amine (the donating 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 ^1H (Table 2) and ^{13}C NMR (Table 3) there are some cases (for example for **3**) where the methyl groups are not equivalent,

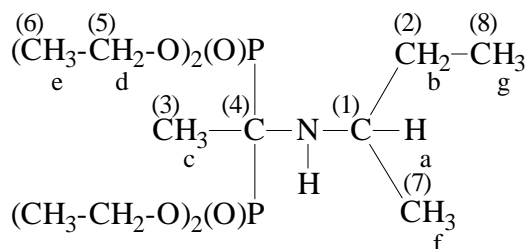
presumably free rotation around the P-C bond is prevented.¹⁰ The analysis of the ¹³C spectra (Table 3) for the α and β -carbons of the phosphonate ester groups, that is an AA'X system, has been described in reference 5.



6



7



8

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**: $\delta(^{31}\text{P})$ and $\delta(^{15}\text{N})$ (ppm)

(Parentheses indicate coupling constants in Hz)

	^{31}P			^{15}N	
	δ	Solvent	Ref	δ	Solvent
1	15.9	Na/D ₂ O ^d	5	-312.8	Na/D ₂ O ^d
2	22.5	CDCl ₃	5	-340.7 (8.7) ^a	C ₆ D 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 ₆ D ₆
4	22.7	CDCl ₃	6	-340.5 (8.5)	C ₆ D ₆
5	21.8	CDCl ₃	6	-344.8 (8.3)	C ₆ D ₆
6	21.5	CDCl ₃	6	-340.4 (6.3)	C ₆ D ₆
7	22.5	CDCl ₃		-324.3 (6.1)	C ₆ D ₆
8	23.3	CDCl ₃		-330.8 (5.2)	C ₆ D ₆

^a -341.6 (8.6) in CDCl₃, ^b nitro ortho, ^c nitro para, ^d 50 mg Na/ml D₂O

Table 2. ^1H NMR spectral data for bisphosphonates **1-8**: $\delta(^1\text{H})$ (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 ₂ O ^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 ₆ D 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 ₆ D 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 ₆ D 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 -NH₂⁺, ^c 50 mg Na/ml D₂O, ^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**: $\delta(^{13}\text{C})$ (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 ₂ O 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 ₆ D 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 ₆ D 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 ₆ D 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 too small, ^f $^2J_{\text{CP}}(+^4J_{\text{CP}})$, ^g $^3J_{\text{CP}}$, ^h see ref 5, ⁱ 50 mg Na/ml D₂O

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