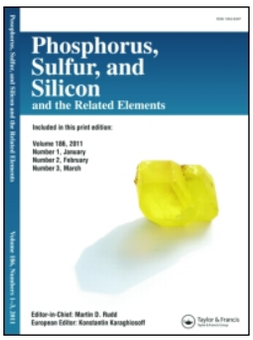

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NMR and symmetry in bisphosphonates $R^1R^2N\text{-}CH[P(O)(OMe)_2]_2$

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ABSTRACT

(Amino-methylene)bisphosphonates $R^1R^2N\text{-}CH[P(O)(OMe)_2]_2$ bearing achiral and chiral substituents (R^1 = Ph, R^2 = H, Me; and R^1 = PhCH(Me), R^2 = Me, Bn) were synthesized and characterized in $CDCl_3$ by ^1H, $^1H\{^{31}P\}$, $^{13}C\{^1H\}$, $^{31}P\{^1H\}$, and ^{31}P NMR spectra. $[P(O)(OMe)_2]_2$ fragments from achiral compounds give rise to complex ^1H NMR spectra characteristic for the $[A_3M_3X]_2$ ^1H NMR spectra while chiral compounds yield $A_3G_3M_3T_3XY$ type spectra. Aspects of molecular symmetry governing the multiplet patterns are discussed and precise spectral parameters are calculated by line-shape iterations.

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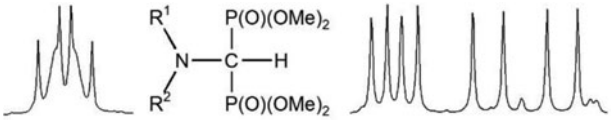
GRAPHICAL ABSTRACT



Introduction

H. Gross and B. Costisella reported the first synthetic routes to tetraethyl (dimethylamino-methylene)bisphosphonate $Me_2N\text{-}CH[P(O)(OEt)_2]_2$ **1**.[1–3] Quaternization of **1** at nitrogen led to $Me_3N^+\text{-}CH[P(O)(OEt)_2]_2$ X^- (X^- = $CH_3OSO_3^-$, J^-, ClO_4^-) **2**, which was converted into a betaine $Me_3N^+\text{-}C^-[P(O)(OEt)_2]_2$ **3** and a carbanion sodium salt, $Me_2N\text{-}C^-[P(O)(OEt)_2]_2$ Na^+ **4**.[4,5] Although these tetraethyl esters **1–4** possess a mirror plane in the molecular structure, their methylene protons are pairwise chemically nonequivalent (diastereotopic), giving rise to separate resonance lines. Hence, the very complex ^1H NMR spectra of **1–4** representing $[(ABM_3)(CDN_3)X]_2$ spin systems for the corresponding $[P(O)(OCH_2CH_3)_2]_2$ fragments were not fully explained in the early studies using low field NMR spectrometers. Only partial results were accessible and reported.

A tetramethyl ester $Me_2N\text{-}CH[P(O)(OMe)_2]_2$ **5**, which is analogous to **1**, is conveniently accessible according to the following scheme:[2]

$$Me_2NCH(OMe)_2 \xrightarrow[-2\ MeOH]{+\ 2\ HP(O)(OMe)_2} Me_2NCH[P(O)(OMe)_2]_2$$

5

While $Me_2N\text{-}CH[P(O)(OEt)_2]_2$ **1** is stable at ambient temperature the liquid $Me_2N\text{-}CH[P(O)(OMe)_2]_2$ **5** rearranges at room temperature in a slow auto-quaternization to asymmetric, a solid, crystalline, betainic form.

$$\mathbf{5} \longrightarrow Me_3N^+CH[P(O)(OMe)_2][P(O)(OMe)O^-]$$

6

In subsequent years (amino-methylene)bisphosphonic acids and esters have attracted practical interests in synthetic chemistry. With the advent of Green Chemistry[6] attention was drawn towards microwave (MW)-assisted syntheses of (amino-methylene)bisphosphonates by three-component condensations pioneered by the Budapest team of G. Keglevich and described in Ref. 7 A collection of corresponding references for this interesting field is listed in E. Bálint´s recent paper.[7]

For NMR spectroscopic reasons we wanted to disturb the molecular symmetry of (amino-methylene)bisphosphonates $R^1R^2N\text{-}CH[P(O)(OMe)_2]_2$ by introducing asymmetry at nitrogen by using $R^1 \neq R^2$ or at a carbon in substituent R^1. Applying MW techniques described in[7] the following compounds were obtained:

$$R^1R^2NH + (MeO)_3CH + H(P)(OMe)_2 \xrightarrow[-\ 3\ MeOH\ \ no\ solvent]{MW,\ N_2\ 110°C,\ 1h} R^1R^2N\text{-}CH[P(O)(OMe)_2]_2$$

3.5-4.5 eq. 7 - 10

Compound	7[8]	8	9	10
R^1	Ph	Ph	(R)-α-Me-Bn	(R)-α-Me-Bn
R^2	H	Me	Me	Bn

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In memoriam of Professor Harry R. Hudson.

Nitrogen in compounds Ph-N(H)-CH[P(O)(OMe)$_2$]$_2$ **7** and Ph-N(Me)-CH[P(O)(OMe)$_2$]$_2$ **8** undergo rapid inversion on the NMR time scale at room temperature and, hence are effectively nonchiral under NMR aspects, a dynamically averaged spectrum of the invertomers is observed. But the α-carbon from the α-methylbenzyl substituent Ph-CH(CH$_3$) in Ph-CH(Me)-N(Me)-CH[P(O)(OMe)$_2$]$_2$ **9** and Ph-CH(Me)-N(CH$_2$Ph)-CH[P(O)(OMe)$_2$]$_2$ **10** is chiral and, hence compounds **9** and **10** give rise to interesting hitherto unknown NMR spectra of asymmetric bisphosphonates, which will be described and analyzed in the following sections.

Results and discussions

Symmetric methyl esters R^{1}R^{2}N-CH[P(O)(OMe)$_2$]$_2$ (R^1 = R^2 = achiral) give rise to trivial spectra for corresponding R^{1}R^{2}N-CHP$_2$ parts but rather complex patterns for [P(O)(OMe)$_2$]$_2$ fragments.

Example 1: Me$_2$N-CH[P(O)(OCH$_3$)$_2$]$_2$ 5

The ^{1}H NMR spectrum of (CH$_3$)$_2$N-CH[P(O)(OCH$_3$)$_2$]$_2$ **5** is characterized by simple triplets for (C*H*$_3$)$_2$NHP$_2$ (due to $^4J_{PH}$ coupling) and NC*H*P$_2$ ($^2J_{PH}$), while a complex [A$_3$M$_3$X]$_2$ pattern is obtained for the [P(O)(OC*H*$_3$)$_2$]$_2$ unit. The geminal methoxy groups from P(O)(OCH$_3$)$_2$ in the neighborhood of a prochiral carbon center are chemically nonequivalent (diastereotopic). However, they are pairwise chemically equivalent to the methyl protons denoted by A′ and M′ in the other P(O)(OCH$_3$)$_2$ group as depicted in Figure 1.

This [A$_3$M$_3$X]$_2$ spin system is characterized by four parameters, which are linear combinations of the PH-coupling constants $^3J_{PH}$ and $^5J_{PH}$, in addition to the geminal PP-coupling constant $^2J_{PP}$:

1. $N_{AX} = J_{AX} + J_{AX'} = {}^3J_{PH+} {}^5J_{PH}$
2. $L_{AX} = J_{AX} - J_{AX'} = {}^3J_{PH-} {}^5J_{PH}$
3. $N_{MX} = J_{MX} + J_{MX'} = {}^3J_{PH+} {}^5J_{PH}$
4. $L_{MX} = J_{MX} - J_{MX'} = {}^3J_{PH-} {}^5J_{PH}$
5. $J_{XX'} = {}^2J_{PP}$

All other long range couplings of type $^nJ_{HH}$ are zero. This complex spectrum was not fully understood during those pioneering years of bisphosphonate chemistry. Using the guidelines developed for the [A$_a$M$_m$X]$_2$ type spectrum of [Me(^{t}Bu)P(S)]$_2$ and related structures[8] attempts were made to analyze the ^{1}H NMR spectrum of this [P(O)(OCH$_3$)$_2$]$_2$ fragment shown in Figure 2 by grid net search simulations. The resulting spectral parameters are listed in Table 1 below.

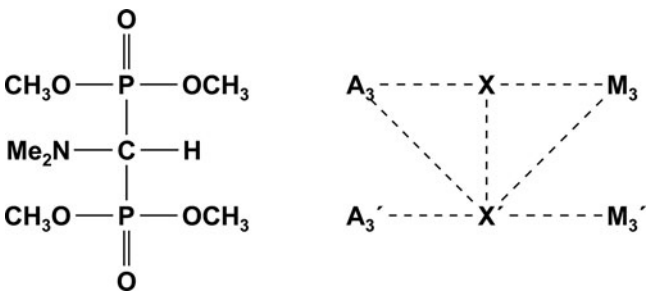

Figure 1. [A$_3$M$_3$X]$_2$ spin system for the [P(O)(OCH$_3$)$_2$]$_2$ fragment of compound **5**.

Table 1. NMR data for the methoxy region of a 100 MHz ^{1}H NMR spectrum from Me$_2$N-CH[P(O)(OCH$_3$)$_2$]$_2$ **5** (in CDCl$_3$). Solution 1: Results from grid net search for parameters L_{AX}, L_{MX} and J_{XX} with step widths of 0.25 Hz. $\nu_H{}^*$ = relative resonance frequency [Hz] if the center of methoxy region $(\nu_A + \nu_M)/2$ is defined to 0 Hz. Spectral half width is set to 0.25 Hz. An alternative is found with solution 2.

Parameter	Solution	$\nu_H{}^*$ [Hz]	N [Hz]	L [Hz]	$^3J_{PH}$ [Hz]	$^5J_{PH}$ [Hz]	$^2J_{PP}$ [Hz]
POC*H*$_3$ (I) A$_3$	1	+0.50	11.00	5.25	8.13	2.88	16.25
POC*H*$_3$ (II) M$_3$	1	−0.50	11.10	6.25	8.68	2.43	16.25
POC*H*$_3$ (I) A$_3$	2	+0.50	11.00	9.2	10.1	0.9	60
POC*H*$_3$ (II) M$_3$	2	−0.50	11.10	10.1	10.6	0.5	60

So a first guess of the characteristic geminal coupling constant $^2J_{PP}$ yielded a numerical value near 16 Hz for the symmetric compound **5**. The spectral habitus of [A$_a$M$_m$X]$_2$ spectra is invariant to the sign of $^2J_{PP}$, hence only the absolute values for $^2J_{PP}$ are obtained. $^2J_{PP}$ is not accessible by ^{13}C satellites in the ^{31}P{^{1}H} NMR spectrum of symmetric **5**, only a simple singlet was observed since $^2J_{PH}$ and $^4J_{PH}$ are too small, as discussed in subsequent sections. This low value of $^2J_{PP}$ seemed agreeable and supported by further observations:

1) The asymmetric betaine Me$_3$N$^+$-CH[*P*(O)(OMe)$_2$][*P*(O)(OMe)O$^-$] **6** gives rise to an XY type ^{31}P{^{1}H} NMR spectrum but exhibits two singlets only where $^2J_{PP}$ is not resolved, and hence close to or equal zero Hz. Data for **6** are listed in Table 2.
2) For two chiral (1-hydroxy-methylene)bisphosphonic acids R*-C(OH)[P(O)(OH)$_2$]$_2$ numerical values of 21.1 Hz and 27.5 Hz were found for $^2J_{PP}$. This interesting observation was reported by C. E. McKenna *et al.* in a publication dealing with aspects of medicinal chemistry.[9]

Examples 2: Achiral Bisphosphonates: Ph-N(H)-CH[P(O)(OMe)$_2$]$_2$ **7** and Ph-N(Me)-CH[P(O)(OMe)$_2$]$_2$ **8**

Tetramethyl (phenylamino-methylene)bisphosphonate **7** is identified in ^{1}H NMR by a triplet for NC*H*P$_2$ centered at 4.2413 ppm and a corresponding coupling constant $^2J_{PH}$ of −23.9 Hz. The [P(O)(OC*H*$_3$)$_2$]$_2$ fragment shows two overlapping deceptively simple triplets (dst) for the A$_3$ and M$_3$ parts of an [A$_3$M$_3$X]$_2$ system. Nonequivalent methyl groups POC*H*$_3$ (I) and POC*H*$_3$ (II) are located at 3.7965 and 3.8149 ppm with N_{AX} = 10.8 Hz and N_{MX} = 10.8 Hz. (See Figure 3).

Manual grid net search for simulations with **DAISY**[10] under **TOPSPIN**[10] led to the missing parameter $^2J_{PP}$ = 60 ± 5 Hz, which is surprisingly high. Further coupling constants are found in ranges: $^3J_{PH}$ = 10.3 to 10.8 Hz and $^5J_{PH}$ = 0.5 to 0 Hz. Hence

Table 2. NMR Parameters δ_P, $^2J_{PP}$, N, and $^2J_{PH}$ of Me$_3$N$^+$-CH[P(O)(OMe)$_2$][P(O)(OMe)O$^-$] **6** (in CDCl$_3$), obtained from: a) proton decoupled ^{31}P{^{1}H} and b) from proton-coupled 36.4 MHz ^{31}P NMR spectra. The geminal coupling $^2J_{PP}$ - close to zero - is not resolved (n. r.).

		a)		b)	
Parameter	P	δ_P [ppm]	$^2J_{PP}$ [Hz]	$^3J_{PH}$ [Hz]	$^2J_{PH}$ [Hz]
P(O)(OCH$_3$)$_2$	X	15.36	n. r.	11.2	−22.3
P(O)(OMe)O$^-$	Y	− 1.20	n. r.	11.3	−15.5

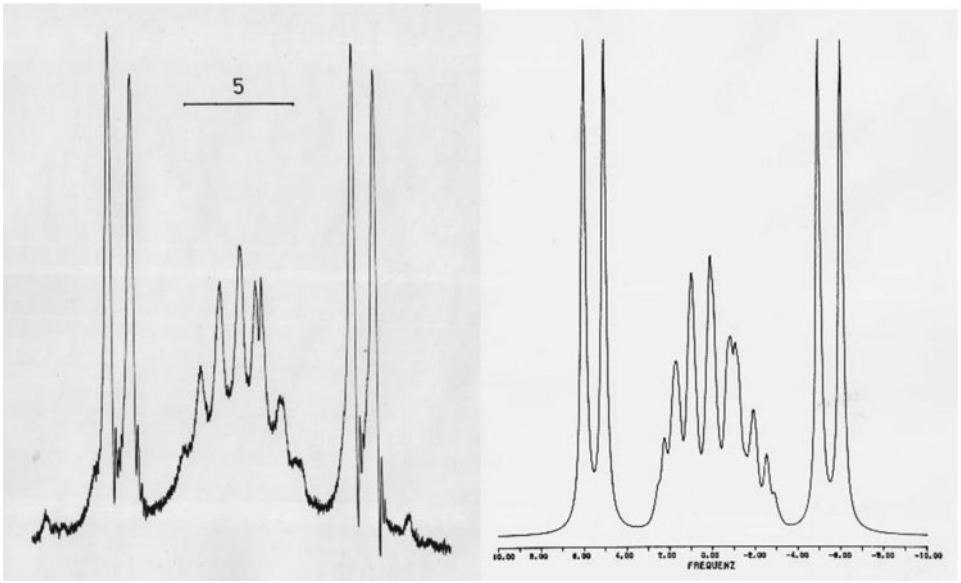

Figure 2. Methoxy region of the 100 MHz ^{1}H NMR spectrum of Me_2N-CH[P(O)$(OCH_3)_2]_2$ **5** in $CHCl_3$. Left: experimental. Right: simulated solution 1 with parameters shown in Table 1.

the combined parameters L_{AX} and L_{MX} are obtained with $^{3}J_{PH}$ - $^{5}J_{PH}$ = 9.8 to 10.8 Hz (special case with $N_{AX} = N_{MX}$ and $L_{AX} = L_{MX}$). Expectation ranges given above are valid for an experimental spectral half width HW = 2 Hz.

In the 500 MHz ^{1}H NMR spectrum the phenyl group C_6H_5-N in **7** appears with broadened lines exhibiting at first sight three patterns: doublet (6.7016, H_{ortho}), triplet (7.2037, H_{meta}), and triplet (6.7994, H_{para}). Corresponding coupling constants $^{n}J_{HH}$ (n = 3–5) for this $[AC]_2B$ spectrum are accessible by iteration only.

Results reported above are obtained from solutions of **7** in $CDCl_3$, aged about one week and measured at 500 MHz ^{1}H NMR at Düsseldorf. The NH proton is revealed as a very broad line around 3.5 ppm close to the methoxy region. But if **7** is

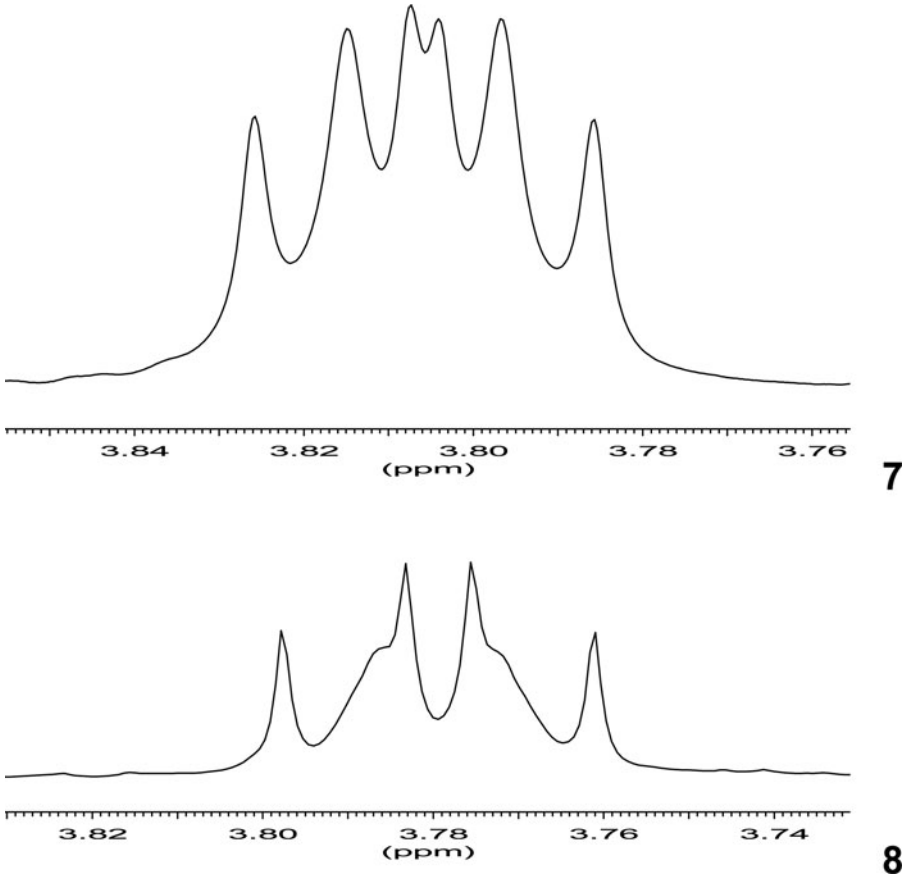

Figure 3. Methoxy regions in 500 MHz ^{1}H NMR spectra of **7** (upper) and **8** (lower).

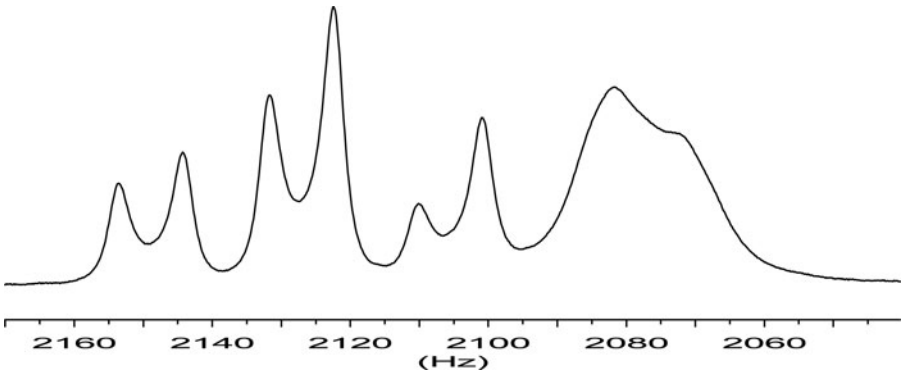

Figure 4. 500 MHz ^{1}H NMR spectrum of a fresh solution of **7** in $CDCl_3$. $ABMX_2$ approximation for the $HNCHP_2$ part of **7**. Iterated parameters: $\delta_H(CH) = 4.244$ ppm. $\delta_H(NH) = 4.146$ ppm. $^3J_{HH} = 8.9$ Hz. $^2J_{PH} = -22$ Hz. $^3J_{PH} = 2$ Hz. Spectral half widths: HW(*CH*) = 3.4 Hz. HW(N*H*) = 11.0 Hz.

freshly prepared, dissolved in dry $CDCl_3$, and rapidly measured, than a spectrum is obtained, where the NH proton is coupled with the CH proton in the ***HN*C*HP*$_2$** fragment approximating the B-part of an $ABMX_2$ system. Lines are selectively broadened by the quadrupolar nitrogen ^{14}N (M-part) as shown in Figure 4:

$^{13}C\{^1H\}$ NMR spectra also reflect the molecular symmetry of **7**: $NCHP_2$ is characterized by a triplet at 50.10 ppm with $^1J_{PC} = 147.8$ Hz. Two nonequivalent methoxy groups $POCH_3$ (I) and $POCH_3$ (II) are responsible for two deceptively simple triplets at 53.85 and 54.29 ppm with N_C (I) = 5.8 and N_C (II) = 5.6 Hz resp. In this context two linear combinations N_C and L_C are defined:

1. $N_C = {}^2J_{PH} + {}^4J_{PH}$
2. $L_C = {}^2J_{PH} - {}^4J_{PH}$

If $^4J_{PH}$ is negligibly small, than N_C represents effectively the geminal coupling $^2J_{PC}$. A corresponding spectrum for the methoxy region of **7** is shown in the top trace of Figure 5.

The phenyl group C_6H_5-N in **7** appears in text book quality with three characteristic singlet signals: (113.80 ppm, C_{ortho}), (129.34 ppm, C_{meta}), (119.43 ppm, C_{para}). In addition a triplet is observed (145.91 ppm, C_{ipso}) with $^3J_{PC} = 4.0$ Hz.

Finally the $^{31}P\{^1H\}$ NMR spectrum of **7** exhibits a singlet at $\delta_P = 21.11$ ppm. Since $I^2J_{PP}I >> IL_CI$ the relevant coupling parameter $^2J_{PP}$ is not accessible neither by $^{13}C\{^1H\}$ nor by $^{31}P\{^1H\}$ NMR techniques for AXX′ or AXY type systems of the ***CO*P*C*P*** fragment.

The evaluation of NMR spectra from tetramethyl (N-methylphenylamino-methylene)bisphosphonate **8** follows routes described above. An additional signal in ^{1}H NMR is observed for the N-C*H*$_3$ group: a broadened triplet at $\delta_H = 3.1610$ ppm with $^4J_{PH} = 0.9$ Hz. By $^{13}C\{^1H\}$ NMR the N-methyl group N-CH_3 is detected at $\delta_C = 35.95$ ppm as a singlet, where $^3J_{PC}$ is not resolved. The $^{31}P\{^1H\}$ NMR spectrum of **8** exhibits a singlet at $\delta_P = 21.34$ ppm.

Data for compounds **7** and **8** are listed in Tables 3 and 4.

Examples 3: Chiral bisphosphonates: Ph-CH(CH_3)-N(CH_3)-CH[P(O)(OCH_3)$_2$]$_2$ **9** and Ph-CH(CH_3)-N(CH_2Ph)-CH[P(O)(OCH_3)$_2$]$_2$ **10**.

Introducing the chiral substituent R^{1*} = Ph-CH(CH_3) into the skeleton of tetramethyl (amino-methylene)bisphosphonates $R^{1*}R^2$-NCH[P(O)(OCH_3)$_2$]$_2$ removes the symmetry and chemical equivalence for the pairs of phosphorus atoms and $POCH_3$ groups, which were found in achiral bisphosphonates **7** and **8**.

Table 3. 500 MHz ^{1}H NMR data for achiral bisphosphonates **7** and **8** (in $CDCl_3$).

		Compound		
Fragment	Parameter	**7**	**8**	
$NCHP_2$	δ_H	4.2413	4.6470	[ppm]
	$^2J_{PH}$	−23.9	−25.9	[Hz]
$POCH_3$ (I)	$\delta_H(A_3)$	3.7965	3.7721	[ppm]
	N_{AX}	10.8	11.1	[Hz]
	L_{AX}	9.8 – 10.8	10.1–11.1	[Hz]
	$^3J_{PH}$	10.3 – 10.8	10.6–11.1	[Hz]
	$^5J_{PH}$	0 – 0.5	0–0.5	[Hz]
$POCH_3$ (II)	$\delta_H(M_3)$	3.8149	3.7867	[ppm]
	N_{MX}	10.8	11.1	[Hz]
	L_{MX}	9.8 – 10.8	10.1–11.1	[Hz]
	$^3J_{PH}$	10.3 – 10.8	10.6–11.1	[Hz]
	$^5J_{PH}$	0 – 0.5	0–0.5	[Hz]
	$^2J_{PP}$	60 ± 5	60 ± 5	[Hz]
N-CH_3	δ_H	—	3.1610	[ppm]
	$^4J_{PH}$	—	0.9	[Hz]
C_6H_5-N	δ_H(ortho)	6.7016	6.8634	[ppm]
	δ_H(meta)	7.2037	7.2579	[ppm]
	δ_H(para)	6.7994	6.8174	[ppm]

Hence the $NCHP_2$ group gives rise to XY type (as opposed to X_2) spectra in $^{31}P\{^1H\}$ NMR, as shown in Figure 6 below. XY-type spectral analysis yielded the following numerical data for **9**: $\delta_P(P_X) = 24.04$ ppm, $\delta_P(P_Y) = 22.96$ ppm, $^2J_{PP} = 61.2$ Hz. **10**: $\delta_P(P_X) = 24.66$ ppm, $\delta_P(P_Y) = 23.87$ ppm (br), $^2J_{PP} = 64.9$ Hz. By XY analysis only absolute values for $^2J_{PP}$ are accessible. It seems noteworthy that P_Y of **10** reveals a broader spectral half width than P_X. This might indicate

Table 4. 125 MHz ^{13}C NMR data for achiral bisphosphonates **7** and **8** (in $CDCl_3$).

		Compound		
Fragment	Parameter	**7**	**8**	
N-CH_3	δ_C	—	35.95	[ppm]
$NCHP_2$	δ_C	50.10	56.62	[ppm]
	$^1J_{PC}$	147.8 Hz.	146.2	[Hz]
$POCH_3$ (I)	δ_C	53.85	53.49	[ppm]
	N_C	5.8	6.4	[Hz]
$POCH_3$ (II)	δ_C	54.29	53.70	[ppm]
	N_C	5.6	5.8	[Hz]
C_6H_5-N	δ_C(ortho)	113.80	113.98	[ppm]
	δ_C(meta)	129.47	129.34	[ppm]
	δ_C(para)	119.43	118.89	[ppm]
	δ_C(ipso)	145.91	149.66	[ppm]
	$^3J_{PC}$(ipso)	4.0	3.3	[ppm]

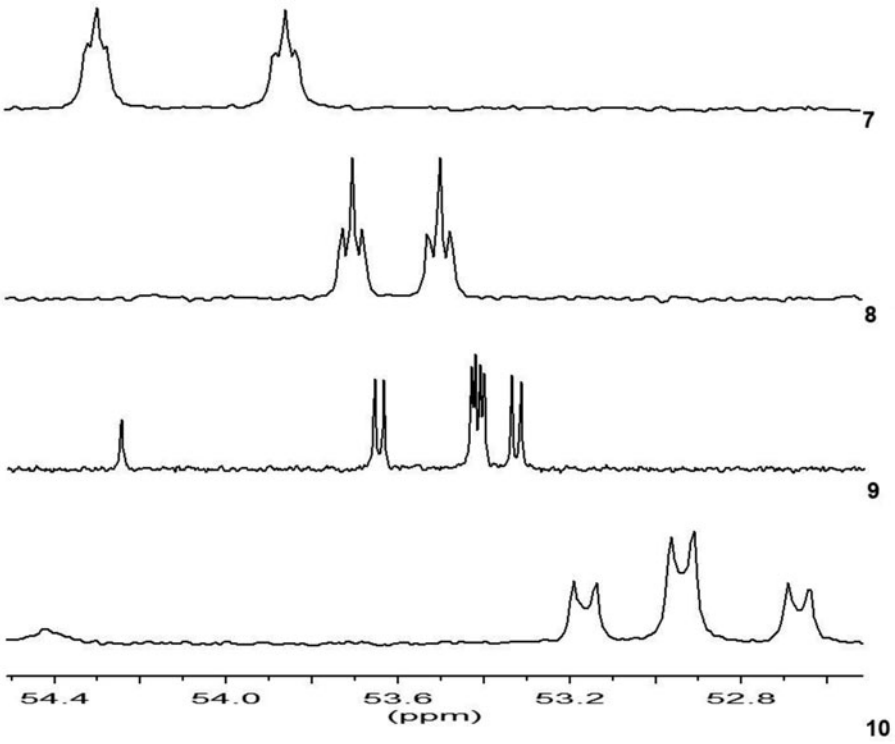

Figure 5. Methoxy region of the 125 MHz $^{13}C\{^1H\}$ NMR spectra. of compounds **7**–**10**.

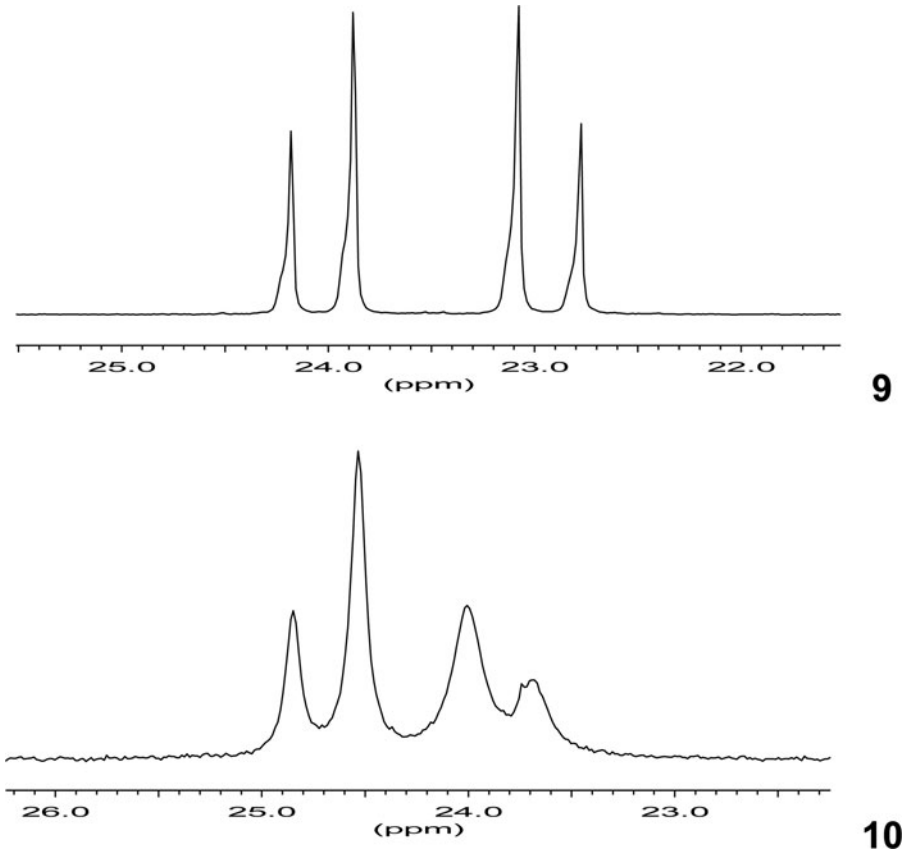

Figure 6. 202 MHz $^{31}P\{^1H\}$ NMR spectra of compounds **9** and **10** (in $CDCl_3$). Upper: **9**. Lower: **10**, a stronger coupled XY system with line broadening for P_Y in high field resonances.

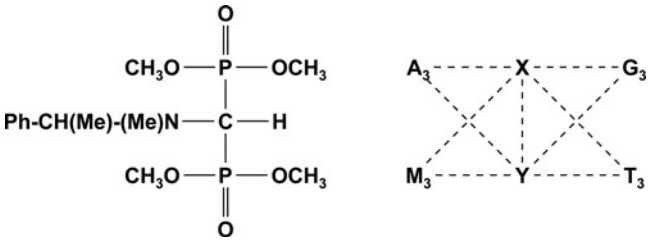

Figure 7. $A_3G_3M_3T_3XY$ spin system for $[P(O)(OCH_3)_2]_2$ fragment of compound **9**.

a dynamic situation, possibly slow intramolecular rotations in **10**.

In addition the proton NC*H*P_2 of **9** appears in ^{1}H NMR as a doublet of doublets (instead of a triplet) with parameter: δ_H = 3.6888 ppm, $^2J_{PH} = -26.5$ Hz; $^2J_{PH} = -24.3$ Hz. In ^{1}H NMR of **10** the NC*H*P_2 proton is obscured by methoxy resonances, but $^1H\{^{31}P\}$ reveals δ_H = 3.6928 ppm. Hence $^2J_{PH}$ data are not accessible for **10**.

The $[P(O)(OCH_3)_2]_2$ fragments are easily understood: $A_3G_3M_3T_3XY$ spin systems are expected in ^{1}H NMR spectra following Figure 7:

Indeed four doublets for the individual methoxy groups POC*H*$_3$ (I) to (IV) are observed by ^{1}H NMR. Vicinal couplings $^3J_{PH}$ are obtained, while the long range $^5J_{PH}$ is not resolved. By decoupling the phosphorus spins XY four singlets are seen in $^1H\{^{31}P\}$ NMR (see Figure 8). Numerical data from spin analysis are listed in Table 5.

The evaluation of $^{13}C\{^1H\}$ NMR spectra of **9** and **10** follows outlines given above. Numerical results are summarized in Table 6. Here it seems sufficient to point interests towards unusual observations: Signals for ^{13}C spins marked bold C_6H_5-***C***H(***C***H_3)-N(***C***H_2-***C*****$_6$**H_5)-CH[P(O)(O***C***H_3)$_2$]$_2$ are broadened. And the $^{31}P\{^1H\}$ signal of $\boldsymbol{P}_Y$ in **10** is broadened as well (see Figure 6). Those effects indicate slow intramolecular rotations in the sterically crowded structure of **10**.

Table 5. 500 MHz ^{1}H NMR parameters for chiral bisphosphonates **9** and **10**. [(a)] HW = 4.0 Hz; [(b)] HW = 1.5 Hz; [(c)] HW = 2.0 Hz; br: broad lines; n.r.: not resolved. Spin assignments were confirmed by HSQC and H,H COSY spectra.

Fragment	Parameter	**9**	**10**	
Ph-CH(*C*H_3)-N	δ_H	1.3757	1.2429	[ppm]
	$^3J_{HH}$	6.6	n.r. br	[Hz]
C-N(*C*H_3)-C	δ_H	2.7389	—	[ppm]
NC*H*P_2	δ_H	3.6868	3.6928	[ppm]
	$^2J_{PH}$	26.54	n.r.	[Hz]
	$^2J_{PH}$	24.32	n.r.	
POC*H*$_3$ (I)	δ_H	3.7089	3.6510	[ppm]
	$^3J_{PH}$	10.8	10.4	[Hz]
POC*H*$_3$ (II)	δ_H	3.7616	3.6717	[ppm]
	$^3J_{PH}$	10.8	10.2	[Hz]
POC*H*$_3$ (III)	δ_H	3.8220	3.7066	[ppm]
	$^3J_{PH}$	10.8	10.7	[Hz]
POC*H*$_3$ (IV)	δ_H	3.8335	3.7269	[ppm]
	$^3J_{PH}$	10.8	10.6	[Hz]
				[Hz]
Ph-C*H*(Me)-N	δ_H	4.1148	4.3528	[ppm]
	$^3J_{HH}$	6.6	n.r. br	[Hz]
	$^4J_{PH}$	3.2		
N-C*H*$_2$-Ph	$\delta_H(H_A)$	—	4.4063	[ppm]
	$\delta_H(H_B)$	—	4.1663	[ppm]
	$^2J_{HH}$	—	−15.0	[Hz]
Ph-CH$_2$-N	δ_H(ortho)	—	7.5136 [a] br	[ppm]
	δ_H(meta)	—	7.3195[b]	[ppm]
	δ_H(para)	—	7.2226[c]	[ppm]
Ph-CH(CH$_3$)-N	δ_H(ortho)	7.3503	7.3731[a] br	[ppm]
	δ_H(meta)	7.3089	7.3011[b]	[ppm]
	δ_H(para)	7.2447	7.2189[c]	[ppm]

Table 6. 125 MHz ^{13}C NMR data for chiral bisphosphonates **9** and **10**. br: broad lines. Spin assignments were confirmed by HSQC and H,H-COSY spectra.

		Compound		
Fragment	Parameter	**9**	**10**	
Ph-CH(*C*H_3)-N	δ_C	22.14	20.04 br	[ppm]
N-*C*H_3	δ_C	37.66 br	—	[ppm]
	$^3J_{PC}$	3.0 d	—	[Hz]
POCH_3 (I)	δ_C	52.81	53.16	[ppm]
	$^2J_{PC}$	7.0	6.3	[Hz]
POCH_3 (II)	δ_C	53.04	52.93	[ppm]
	$^2J_{PC}$	6.9	6.4	[Hz]
POCH_3 (III)	δ_C	53.06	52.93	[ppm]
	$^2J_{PC}$	6.8	6.4	[Hz]
POCH_3 (IV)	δ_C	53.64	52.66	[ppm]
	$^2J_{PC}$	6.9	6.1	[Hz]
C_6H_5-*C*H_2-N	δ_C	—	54.80 br	
NC*H*P_2	δ_C	56.33 dd	55.55 t	[ppm]
	$^1J_{PC}$	148.8	143.3	[Hz]
	$^1J_{PC}$	136.4	143.3	[Hz]
C_6H_5-*C*H(CH$_3$)-N	δ_C	64.08	61.71 br	[ppm]
	$^3J_{PC}$	3.3	n.r.	
	$^3J_{PC}$	9.1	n.r.	
C$_6$H$_5$-CH(CH$_3$)-N	δ_C(ortho)	127.8664	128.11	[ppm]
	δ_C(meta)	128.5241	128.28	[ppm]
	δ_C(para)	127.4960	127.31	[ppm]
	δ_C(ipso)	144.5736	143.95	[ppm]
C$_6$H$_5$-CH$_2$-N	δ_C(ortho)	—	128.23 br	[ppm]
	δ_C(meta)	—	128.37 br	[ppm]
	δ_C(para)	—	126.62 br	[ppm]
	δ_C(ipso)	—	141.82 br	[ppm]

Conclusions

Novel (amino-methylene)bisphosphonates are accessible via microwave-assisted synthesis. R^1R^2N-CH[P(O)(OMe)$_2$]$_2$ with achiral substituents R^1 and R^2 give rise to complex $[A_3M_3X]_2$ spectra for the $[P(O)(OMe)_2]_2$ fragments. Laborious grid net search led to tentative data around 60 Hz for geminal coupling constants $^2J_{PP}$. Those results are confirmed by accurate data for $^2J_{PP}$ obtained from chiral $R^{1*}R^2$N-CH[P(O)(OMe)$_2$]$_2$ where R^{1*} = Ph-CH(Me). Corresponding $A_3G_3M_3T_3XY$ spectra are presented. All functional groups in achiral and chiral bisphosphonates **7**-**10** were characterized by NMR data.

Experimental

NMR spectra were measured using spectrometers at Düsseldorf (90, 500, 600 MHz proton frequency, BRUKER, Karlsruhe, Germany), and Norwich (100 MHz for ^{1}H, VARIAN). Solvent: $CDCl_3$. References: internal TMS for ^{1}H and ^{13}C, external 85% H_3PO_4 for ^{31}P NMR. Spectra were evaluated with **TOPSPIN**[10] while simulations and iterations were performed with **DAISY**.[10] Compounds $(CH_3)_2$N-CH[P(O)(OCH$_3$)$_2$]$_2$ **5** and $(CH_3)_3N^+$-CH[P(O)(OCH$_3$)$_2$][P(O)(OCH$_3$)O$^-$] **6** were provided by Henkel KGaA, Düsseldorf, Germany. Compounds **7**-**10** were synthesized by the Budapest team:

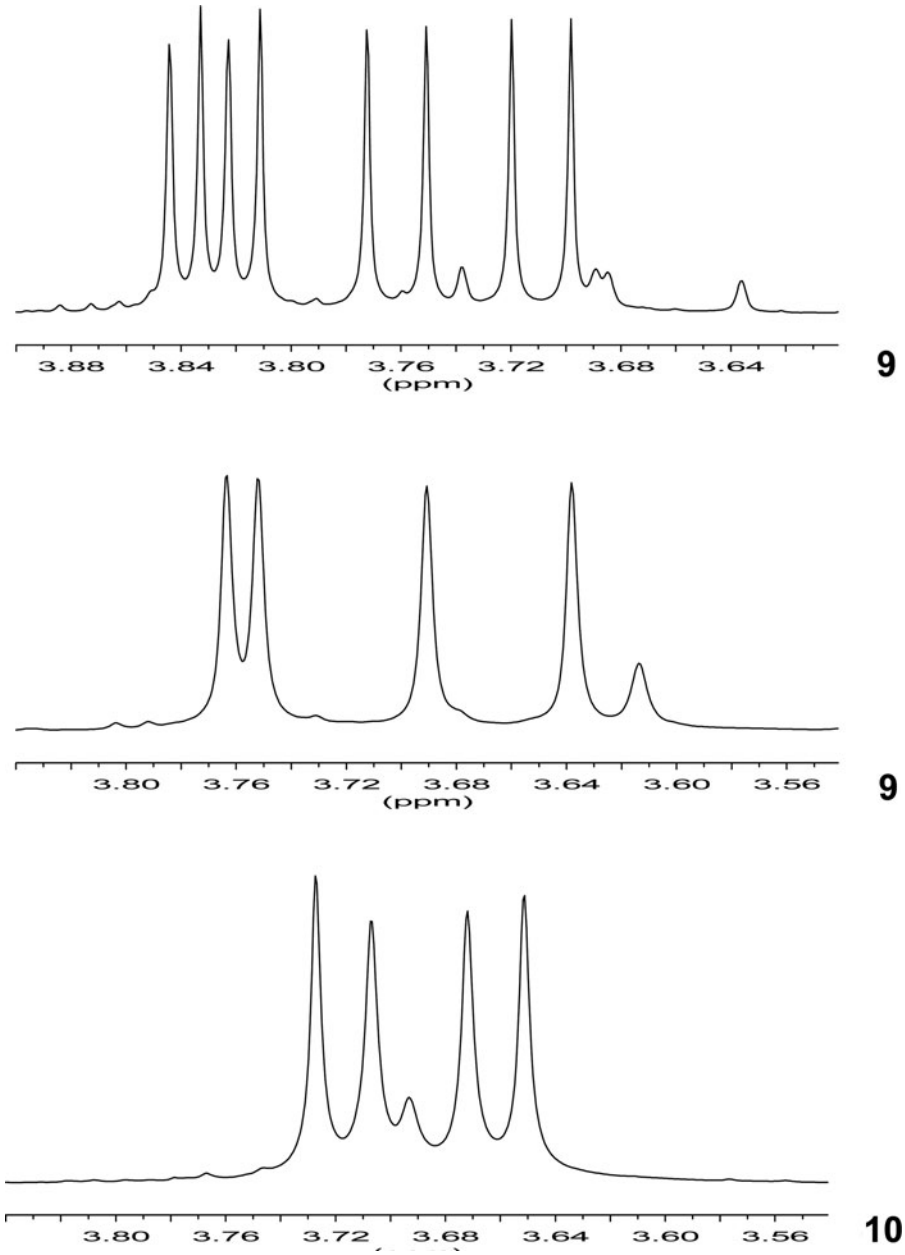

Figure 8. Methoxy regions of **9** and **10**. Upper: 500 MHz ^{1}H NMR of **9**. ^{1}H{^{31}P} of **9** middle) and **10** (lower). Additional signals: **9**: C*H*P$_2$ (3.6868 ppm), **10**: C*H*P$_2$ (3.6928 ppm).

General procedure[7] for tetramethyl (amino-methylene) bisphosphonates (7–10)

A mixture of 1.0 mmol amine (aniline: 0.09 mL, *N*-methylaniline: 0.11 mL, (*R*)-*N*-methyl-α-methylbenzylamine: 0.15 mL, (*R*)-*N*-benzyl-α-methylbenzylamine: 0.21 mL), 1.0 mmol (0.11 mL) trimethyl orthoformate and dimethyl phosphite [3.5 mmol (0.32 mL) or 4.5 mmol (0.41 mL)] was heated at 110 °C for 1 h in a closed vial under N_2 atmosphere in a CEM Discover Microwave reactor equipped with a pressure controller applying 10-15 W. The crude products **7–10** were purified by column chromatography on silica with dichloromethane/methanol (97:3) or ethyl acetate as eluents. Following this general procedure compounds **7–10** were prepared:

Tetramethyl (phenylamino-methylene)bisphosphonate 7

Yield: 63% (0.10 g) of compound **7** as pale yellow crystals; Mp: 168–169. This compound was reported in our recently published paper.[7] $C_{11}H_{19}NO_6P_2$. $[M]^+ = 323.1$. GC-MS: $[M]^+ = 323$. LC-MS: $[M + H]^+ = 324.1$. HRMS: $[M + H]^+ = 324.0760$. For NMR data see text above.

Tetramethyl (N-methylphenylamino-methylene) bisphosphonate 8

Yield: 24% (0.08 g) of compound **8** as colorless oil. $C_{12}H_{21}NO_6P_2$. $[M]^+ = 337.1$. GC-MS: $[M]^+ = 337$. For NMR data see above.

Tetramethyl (N-methyl-α-methylbenzylamino-methylene) bisphosphonate 9

Yield: 38% (0.14 g) of compound **9** as colorless oil. $C_{14}H_{25}NO_6P_2$. $[M]^+ = 365.1$. LC-MS: $[M + H]^+ = 366.1$. For NMR data see text above.

Tetramethyl (N-methyl-α-methylbenzylamino-methylene) bisphosphonate 10

Yield: 36% (0.16 g) of compound **10** as colorless oil. $C_{20}H_{29}NO_6P_2$. $[M]^+ = 441.2$. LC-MS: $[M + H]^+ = 442.2$. For NMR data see text above.

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