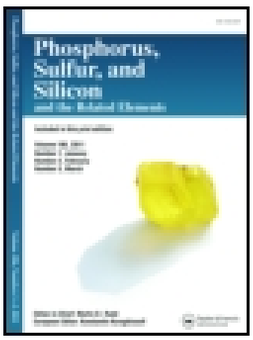

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NMR and Symmetry in Bisphosphonates $R^1R^2N\text{-}CH[P(O)(OMe)_2]_2$

In memoriam of Professor Harry R. Hudson

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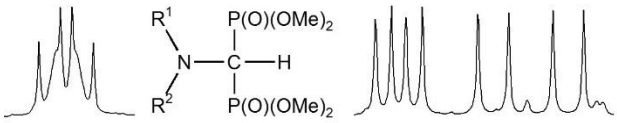
Abstract



(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 $[A_3M_3X]_2$ ^{1}H 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.

Keywords

(Amino-methylene)bisphosphonates, methyl esters, multinuclear NMR, spin systems, line-shape iterations, grid net search.

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Introduction

H. Gross and B. Costisella reported the first synthetic routes to tetraethyl (dimethylamino-methylene)bisphosphonate Me_2N-CH[P(O)$(OEt)_2]_2$ **1**.[1-3] Quaternization of **1** at nitrogen led to Me_3N^+-CH[P(O)$(OEt)_2]_2$ X^- (X^- = $CH_3OSO_3^-$, J^-, ClO_4^-) **2**, which was converted into a betaine Me_3N^+-C^-[P(O)$(OEt)_2]_2$ **3** and a carbanion sodium salt Me_2N-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 non-equivalent (diastereotopic), giving rise to separate resonance lines. Hence, the very complex ^{1}H 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.

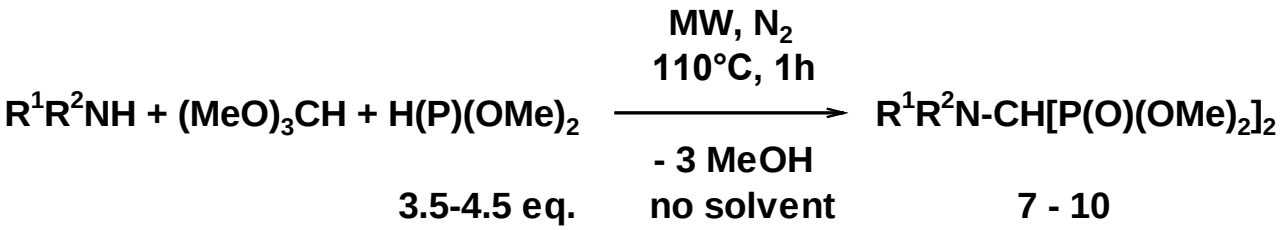
A tetramethyl ester Me_2N-CH[P(O)$(OMe)_2]_2$ **5**, which is analogous to **1**, is conveniently accessible according to the following scheme:[2]

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

5

While Me_2N-CH[P(O)$(OEt)_2]_2$ **1** is stable at ambient temperature the liquid Me_2N-CH[P(O)$(OMe)_2]_2$ **5** rearranges at room temperature in a slow auto-quaternization to asymmetric ~~Me_3N^+-CH[P(O)$(OMe)_2$][P(O)(OMe)O^-]~~ **6**, a solid, crystalline, betainic form.

In subsequent years (amino-methylene)bisphosphonic acids and esters have attracted ~~much~~ 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.[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:



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

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 non-chiral 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_2Ph)-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^1R^2N-CH[P(O)$(OMe)_2]_2$ ($R^1 = R^2$ = achiral) give rise to trivial spectra for corresponding R^1R^2N-CHP_2 parts but rather complex patterns for [P(O)$(OMe)_2]_2$ fragments.

Example 1: Me_2N-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 $(CH_3)_2NHP_2$ (due to $^4J_{PH}$ coupling) and NC*H*P_2 ($^2J_{PH}$), while a complex $[A_3M_3X]_2$ pattern is obtained for the [P(O)$(OCH_3)_2]_2$ unit. The geminal methoxy groups from P(O)$(OCH_3)_2$ in the neighborhood of a prochiral carbon center are chemically non-equivalent (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 This $[A_3M_3X]_2$ 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 $[A_aM_mX]_2$ type spectrum of $[Me(^tBu)P(S)]_2$ and related structures[8] attempts were made to analyze the ^1H 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.

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 $[A_aM_mX]_2$ 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 $^{31}P\{^1H\}$ 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_3N^+-CH[*P*(O)$(OMe)_2$][*P*(O)(OMe)O^-] **6** gives rise to an XY type $^{31}P\{^1H\}$ 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 the ~~linear~~ combined parameters L_{AX} and L_{MX} are obtained with $^3J_{PH}$ - $^5J_{PH}$ = 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$_6$H$_5$-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 $^nJ_{HH}$ (n = 3-5) for this [AC]$_2$B 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 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****HP₂*** 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 ~~confirm as well~~ also reflect the molecular symmetry of **7**: N*C*HP_2 is characterized by a triplet at 50.10 ppm with $^1J_{PC}$ = 147.8 Hz. Two non-equivalent methoxy groups PO*C*H_3 (I) and PO*C*H_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:

6 $N_C = {}^2J_{PH} + {}^4J_{PH}$

7 $L_C = {}^2J_{PH} - {}^4J_{PH}$

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 δ_P = 21.11 ppm. Since $|^2J_{PP}| >> |L_C|$ 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 ***C****O****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 δ_H = 3.1610 ppm with $^{4}J_{PH}$ = 0.9 Hz. By ^{13}C{^{1}H} NMR the N-methyl group N-*C*H$_3$ is detected at δ_C = 35.95 ppm as a singlet, where $^{3}J_{PC}$ is not resolved. The ^{31}P{^{1}H} NMR spectrum of **8** exhibits a singlet at δ_P = 21.34 ppm.

Data for compounds **7** and **8** are listed in **Table 3** and **Table 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$_2$Ph)-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**. Hence the ~~significant~~ NCH*P*$_2$ group gives rise to XY type (as opposed to X$_2$) spectra in ^{31}P{^{1}H} 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, $^{2}J_{PP}$ = 61.2 Hz. **10**: $\delta_P(P_X)$ = 24.66 ppm, $\delta_P(P_Y)$ = 23.87 ppm (br), $^{2}J_{PP}$ = 64.9 Hz. By XY analysis only absolute values for $^{2}J_{PP}$ are accessible. It seems noteworthy that P$_Y$ of **10** reveals a broader spectral half width than P$_X$. This might indicate 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, $^{2}J_{PH}$ = -26.5 Hz; $^{2}J_{PH}$ = -24.3 Hz.

In ^{1}H NMR of **10** the NC*H*P_2 proton is obscured by methoxy resonances, but ^{1}H{^{31}P} reveals δ_H = 3.6928 ppm. Hence $^{2}J_{PH}$ 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 POCH_3 (I) to (IV) are observed by ^{1}H NMR. Vicinal couplings $^{3}J_{PH}$ are obtained, while the long range $^{5}J_{PH}$ is not resolved. By decoupling the phosphorus spins XY four singlets are seen in ^{1}H{^{31}P} NMR. (See **Figure 8** below. Numerical data from spin analysis are listed in **Table 5**.

The evaluation of ^{13}C{^{1}H} 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{^{1}H} signal of ***P***$_Y$ in **10** is broadened as well (see **Figure 6**). Those effects indicate slow intramolecular rotations in the sterically crowded structure of **10**.

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 $^{2}J_{PP}$. Those results are confirmed by accurate data for $^{2}J_{PP}$ 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 $(CH_3)_2N\text{-}CH[P(O)(OCH_3)_2]_2$ **5** and $(CH_3)_3N^{+}\text{-}CH[P(O)(OCH_3)_2][P(O)(OCH_3)O^{-}]$ **6** were provided by Henkel KGaA, Düsseldorf, Germany. Compounds **7**-**10** were synthesized by the Budapest team:

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.

Acknowledgements

Thanks are due to Ms. Beate Rau for dedicated NMR measurements using the 500 MHz and 600 MHz spectrometers at Düsseldorf. Compounds **5** and **6** were provided by Dr. W. Plöger, formerly Henkel KGaA, Düsseldorf, Germany. Special thanks are due to Prof. R. K. Harris, formerly UEA Norwich, GB, for supporting our early attempts to understand the $[A_3M_3X]_2$ spectra. Particular thanks are due to the Hungarian Scientific Research Fund.: Grant number: Erika Bálint, (PD111895).

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Table 1: NMR data for the methoxy region of a 100 MHz ^{1}H NMR spectrum from Me_2N-$CH[P(O)(OCH_3)_2]_2$ **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. ν_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	ν_H* [Hz]	*N* [Hz]	*L* [Hz]	$^{3}J_{PH}$ [Hz]	$^{5}J_{PH}$ [Hz]	$^{2}J_{PP}$ [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

Table 2: NMR Parameters δ_P, $^2J_{PP}$, *N*, and $^2J_{PH}$ of Me_3N^+-$CH[P(O)(OMe)_2][P(O)(OMe)O^-]$ **6** (in $CDCl_3$), obtained from: a) proton decoupled $^{31}P\{^1H\}$ 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.).

Parameter	P	δ_P [ppm]	$^2J_{PP}$ [Hz]	$^3J_{PH}$ [Hz]	$^2J_{PH}$ [Hz]
		a)		b)	
$P(O)(OCH_3)_2$	X	15.36	n. r.	11.2	-22.3
$P(O)(OMe)O^-$	Y	-1.20	n. r.	11.3	-15.5

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

Fragment	Parameter	Compound		
		7	**8**	
NC*H*P_2	δ_H	4.2413	4.6470	[ppm]
	$^{2}J_{PH}$	-23.9.	-25.9	[Hz]
POC*H*$_3$ (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]
	$^{3}J_{PH}$	10.3 – 10.8	10.6 - 11.1	[Hz]
	$^{5}J_{PH}$	0 – 0.5	0 - 0.5	[Hz]
POC*H*$_3$ (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]
	$^{3}J_{PH}$	10.3 – 10.8	10.6 - 11.1	[Hz]
	$^{5}J_{PH}$	0 – 0.5	0 - 0.5	[Hz]
	$^{2}J_{PP}$	60 ± 5	60 ± 5	[Hz]
N-C*H*$_3$	δ_H	-	3.1610	[ppm]
	$^{4}J_{PH}$	-	0.9	[Hz]
C_6*H*$_5$-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]

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

Fragment	Parameter	Compound		
		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]

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]
	$^{3}J_{HH}$	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]
	$^{2}J_{PH}$	26.54	n.r.	[Hz]
	$^{2}J_{PH}$	24.32	n.r.	
POC*H*$_3$ (I)	δ_H	3.7089	3.6510	[ppm]
	$^{3}J_{PH}$	10.8	10.4	[Hz]
POC*H*$_3$ (II)	δ_H	3.7616	3.6717	[ppm]
	$^{3}J_{PH}$	10.8	10.2	[Hz]
POC*H*$_3$ (III)	δ_H	3.8220	3.7066	[ppm]
	$^{3}J_{PH}$	10.8	10.7	[Hz]
POC*H*$_3$ (IV)	δ_H	3.8335	3.7269	[ppm]
	$^{3}J_{PH}$	10.8	10.6	[Hz]
				[Hz]
Ph-C*H*(Me)-N	δ_H	4.1148	4.3528	[ppm]
	$^{3}J_{HH}$	6.6	n.r. br	[Hz]
	$^{4}J_{PH}$	3.2		
N-C*H*$_2$-Ph	$\delta_H(H_A)$	-	4.4063	[ppm]
	$\delta_H(H_B)$	-	4.1663	[ppm]
	$^{2}J_{HH}$	-	-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.

Fragment	Parameter	Compound		
		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]
PO*C*H_3 (I)	δ_C	52.81	53.16	[ppm]
	$^2J_{PC}$	7.0	6.3	[Hz]
PO*C*H_3 (II)	δ_C	53.04	52.93	[ppm]
	$^2J_{PC}$	6.9	6.4	[Hz]
PO*C*H_3 (III)	δ_C	53.06	52.93	[ppm]
	$^2J_{PC}$	6.8	6.4	[Hz]
PO*C*H_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	
N*C*HP_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$_6H_5$-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$_6H_5$-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]

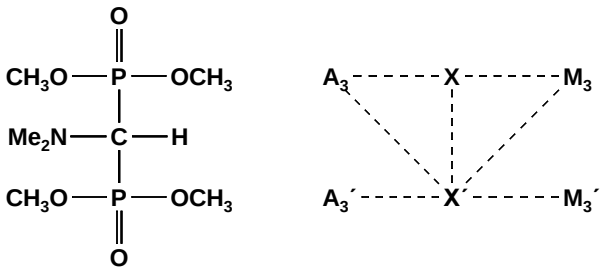

Figure 1: $[A_3M_3X]_2$ spin system for the $[P(O)(OCH_3)_2]_2$ fragment of compound **5**.

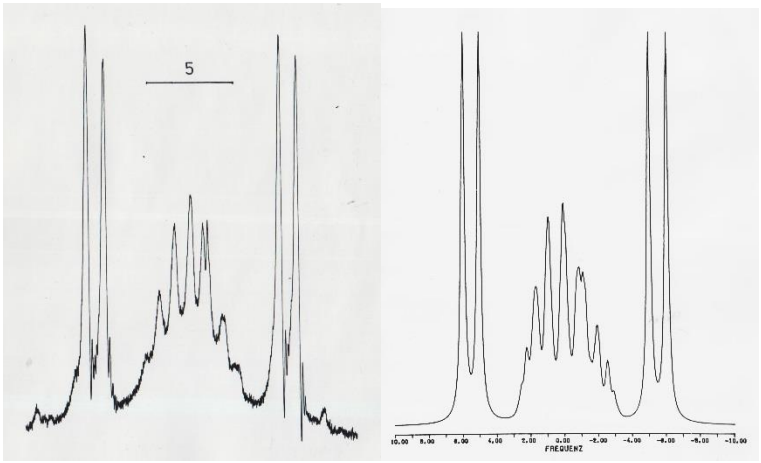

Figure 2: Methoxy region of the 100 MHz ^{1}H NMR spectrum of $Me_2N\text{-}CH[P(O)(OCH_3)_2]_2$ **5** in $CHCl_3$. Left: experimental. Right: simulated solution 1 with parameters shown in

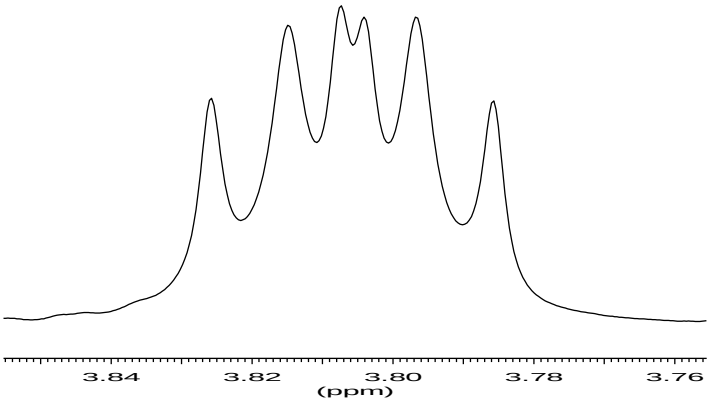

Figure 3: Methoxy regions in 500 MHz ^{1}H NMR spectra of **7** (upper) and **8** (lower).

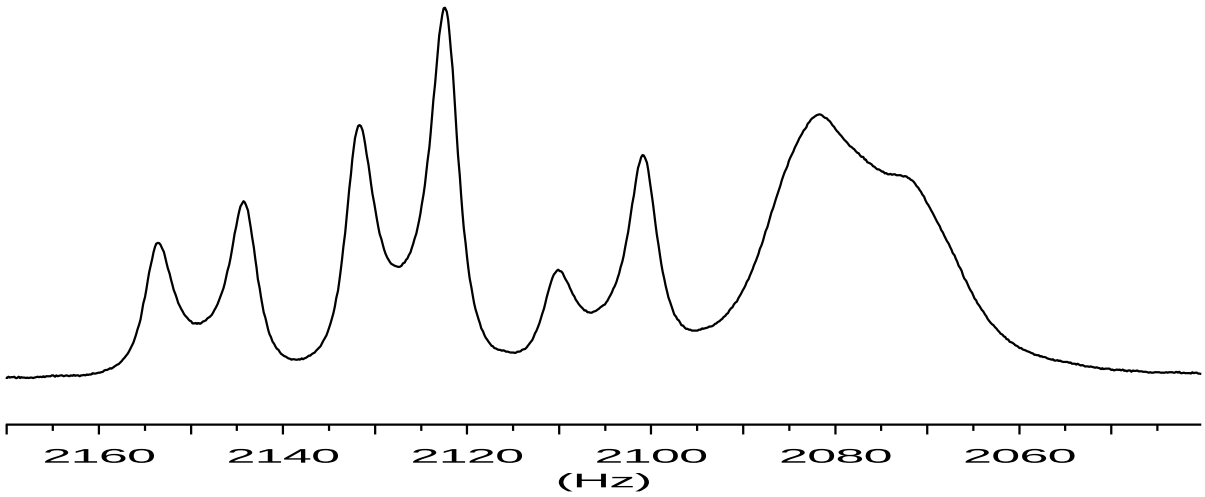

Figure 4: 500 MHz ^{1}H NMR spectrum of a fresh solution of **7** in $CDCl_3$. $ABMX_2$ approximation for the $HNCHP_2$ part of **7**. Iterated parameters: δ_H(C*H*) = 4.244 ppm. δ_H(N*H*) = 4.146 ppm. $^{3}J_{HH}$ = 8.9 Hz. $^{2}J_{PH}$ = -22 Hz. $^{3}J_{PH}$ = 2 Hz. Spectral half widths: HW(C*H*) =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

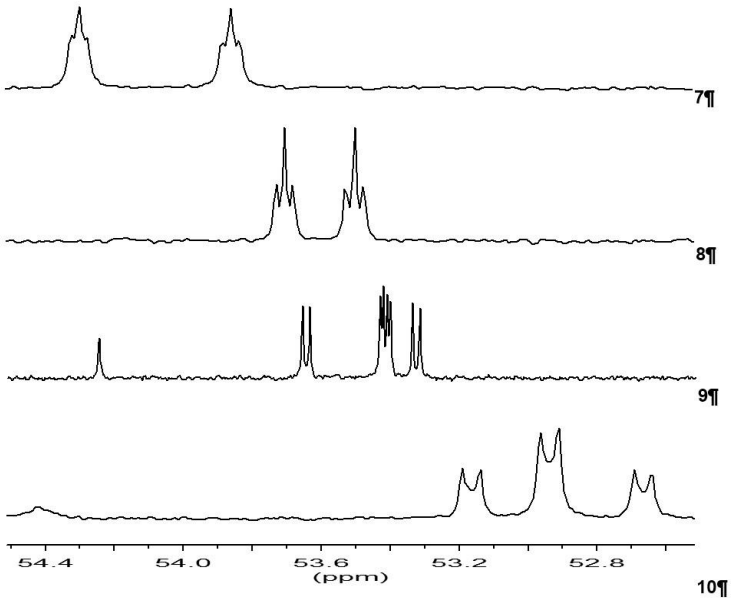

Figure 5: Methoxy region of the 125 MHz $^{13}C\{^{1}H\}$ NMR spectra. of compounds **7**-**10**.

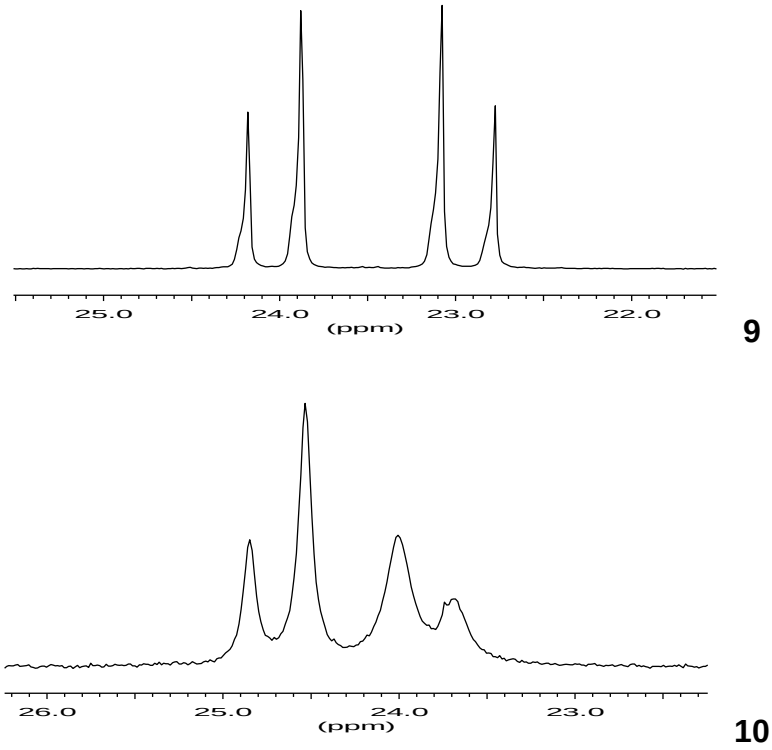

Figure 6: 202 MHz $^{31}P\{^{1}H\}$ NMR spectra of compounds **9** and **10** (in $CDCl_3$). Upper: **9**. Lower: **10**, a stronger coupled XY system with line broadening for P_Y in high field resonances.

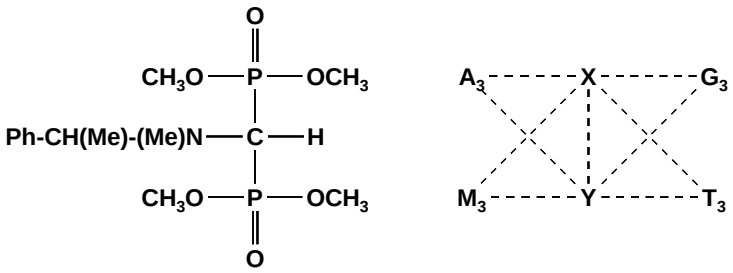

Figure 7: $A_3G_3M_3T_3XY$ spin system for $[P(O)(OCH_3)_2]_2$ fragment of compound **9**.

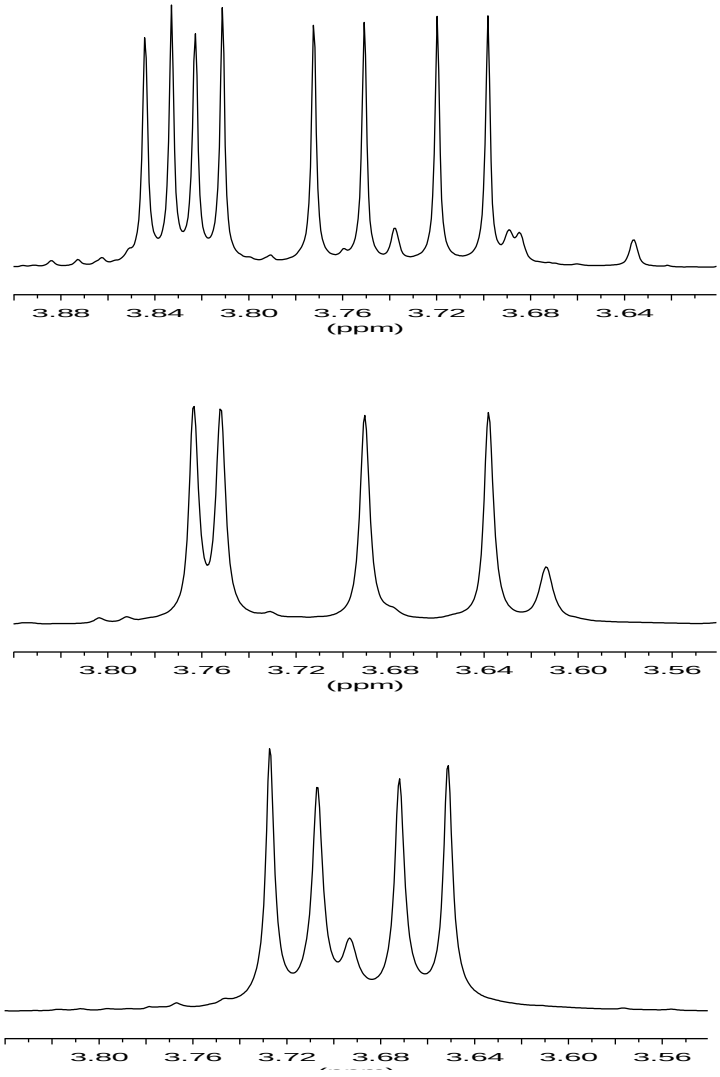

Figure 8: Methoxy regions of **9** and **10**. Upper: 500 MHz ^{1}H NMR of **9**. ^{1}H{^{31}P} of **9** middle) and **10** (lower). Additional signals: **9**: C*H*P$_2$ (3.6868 ppm), **10**: C*H*P$_2$ (3.6928 ppm).