N-Dimethylphosphinoyl-substituted Aminomethanephosphonic Acids

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Dedicated to Professor Vadim A. Davankov on the occasion of his 70th birthday

Three new *N*-phosphinoyl-substituted aminomethanephosphonic acids have been synthesized and characterized: dimethylphosphinoylmethyl-imino-bis(methanephosphonic acid) (**1**), [3-(dimethylphosphinoyl)-propyl]-imino-bis(methanephosphonic acid) (**2**), and *N*-benzyl-*N*-dimethylphosphinoylmethyl-aminomethanephosphonic acid (**3**). The latter was isolated as a hydrochloride **3** · **HCl**. The acids have been prepared *via* Moedritzer-Irani reaction from the corresponding dimethylphosphinoyl-substituted primary and secondary aliphatic amines. Their structures have been confirmed by elemental analysis, IR, ^{1}H, ^{31}P{^{1}H}, ^{13}C{^{1}H} NMR spectroscopy, electrospray ionization mass spectrometry, and single-crystal X-ray diffraction.

Key words: Phosphinoyl-substituted Aminomethanephosphonic Acids, Moedritzer-Irani Reaction, Aminophosphonic Acids, X-Ray Diffraction, Electrospray Ionization Mass Spectrometry

Introduction

Tertiary phosphine oxides containing amino groups (ATPOs) take an important place among organophosphorus compounds and have found interesting synthetic applications [1 – 13]. Due to the phosphinoyl group some of those ATPOs possess lower basicity [14, 15] compared to the parent non-phosphorus-containing amines. It has been shown that these compounds exhibit sufficient nucleophilicity to react readily with different reagents forming *e. g.* ureas, thioureas and nitrosourea derivatives, Schiff bases, thiazolo- and pyrazolopyrimidine derivatives, epoxide-amine diols, oligomers and polymers. Some of these ATPOs were also used for the preparation of organometallic complexes [16, 17], and their derivatives and organometallic complexes were shown to have biological and antitumor activity [8, 11, 17].

It is known that primary and secondary amines may be used for the preparation of α-aminoalkanephosphonic acids *via* several synthetic methods [18]. Recently it has been shown that aminomethyl-dimethylphosphine oxide, the simplest tertiary phosphine oxide modified with a primary amino group, is a valuable precursor for the preparation of dimethyl and diethyl esters of substituted aminomethanephosphonic acids by addition of dimethyl or diethyl phosphites to the corresponding Schiff bases [5a, 5b], or more conveniently *via* one-pot Kabachnik-Fields reactions. Both routes lead to esters which can be cleaved to the parent *N*-phosphinoyl-substituted aminomethanephosphonic acids [5b].

The present work is a continuation of our previous investigations on the application of tertiary phosphine oxides modified with primary and secondary amino groups as precursors for the preparation of new organophosphorus compounds. It is aimed at the direct synthesis of unknown phosphinoyl-substituted aminomethane-phosphonic acids, starting from differently substituted ATPOs. These acids are expected to show biological activities, typical for α-aminoalkanephosphonic acids, and to react as potent phosphorus-containing complexones, with an additional coordina-

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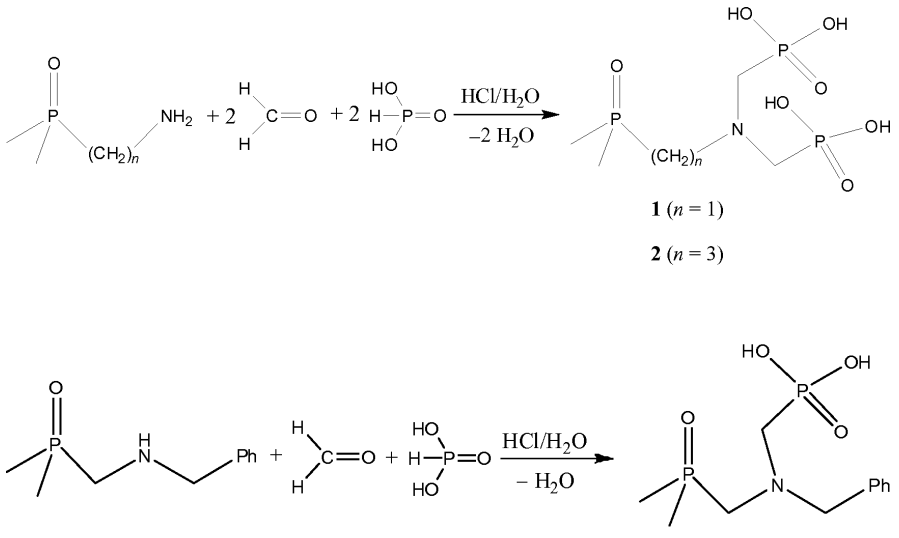


Scheme 1.

tion centre, *viz.* the P=O group at the tertiary phosphine oxide substituent.

Results and Discussion

The *N*-dimethylphosphinoyl-substituted iminomethanephosphonic acids **1**, **2** and **3** · **HCl**, the hydrogen chloride of **3**, were prepared from the starting ATPOs (aminomethyl-dimethylphosphine oxide, 3-aminopropyl-dimethylphosphine oxide and *N*-benzylaminomethyl-dimethylphosphine oxide) according to Scheme 1.

This type of phosphorus-containing amines has not been used up to now in Moedritzer-Irani reactions, and the reported *N*-dimethylphosphinoyl-substituted aminomethanephosphonic acids have not been known until the present investigation. They have been prepared in refluxing hydrochloric acid/water media, using the standard procedure [19]. After evaporation of the water from the reaction mixtures, transparent, colorless or slightly yellowish viscous liquids were obtained. From those syrupy liquids the acids were isolated and purified *via* recrystallization from ethanol, ethanol/water or ethanol/isopropanol mixtures.

In previous reports only primary and secondary aliphatic amines were employed in the Moedritzer-Irani reaction [18–20]. Aminomethyldimethylphosphine oxide is a weaker base (pK_b value of 7.76 [14]) compared to usual primary and secondary aliphatic amines (p$K_b \leq 4$ [21, 22]), but its nucleophilicity suffices to participate in this reaction. The corresponding product dimethylphosphinoylmethyl-iminobis(methanephosphonic acid) (**1**) was isolated in good yield (76 %; Table 1).

3-Aminopropyl-dimethylphosphine oxide is a stronger nucleophile than the aminomethyl-dimethylphosphine oxide, since its amino group is more remote from the electronegative phosphinoyl group. Hence the corresponding acid **2** was obtained in higher yield (83 %; Table 1).

The secondary amine *N*-benzylaminomethyl-dimethylphosphine oxide is less nucleophilic than the parent aminomethyl-dimethylphosphine oxide as a result of the influence of the benzene ring, and hence the yield of **3** · **HCl** is slightly lower.

Some preparative and analytical data for the novel acids are given in Table 1. The crystalline, colorless compounds melt at relatively high temperatures. The acids **1** and **2** have zwitterionic structures. The amine nitrogen atoms in these acids are protonated by the acidic phosphonate OH groups (see the discussion of the IR and X-ray data). The nitrogen atom in **3** · **HCl** is protonated by HCl. It was not possible to eliminate HCl even after repeated dissolution in water and subsequent evaporation. This phenomenon is due to the higher basicity of the nitrogen atom in disubstituted aminomethanephosphonic acids RR′N-CH_2-PO_3H_2 compared to monosubstituted imino-bis(methanephosphonic acids) RN[CH_2-PO_3H_2]$_2$ [19].

Table 1. Preparative and analytical data of *N*-phosphinoyl-substituted aminomethanephosphonic acids **1**, **2** and **3** · **HCl**.

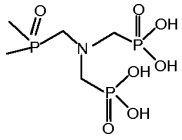
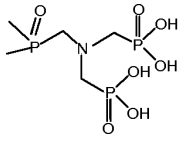
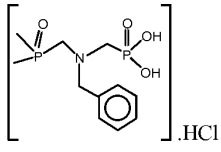
	Structure	Yield (%)	M. p., °C, (Solvent)	Molecular formula (Mol. mass)	Elemental analysis (%) Carbon found	Carbon calcd.	Hydrogen found	Hydrogen calcd.	Phosphorus found	Phosphorus calcd.	Nitrogen found	Nitrogen calcd.
1		76	187 – 189 (ethanol-water)	$C_5H_{16}NO_7P_3$ (295.11)	20.21	20.35	5.38	5.46	31.25	31.49	4.64	4.75
2		83	237 – 238 (ethanol-water)	$C_7H_{20}NO_7P_3$ (323.16)	25.93	26.02	6.23	6.24	28.91	28.75	4.42	4.33
3 · **HCl**		58	158 – 159 (ethanol-*i*-PrOH)	$C_{11}H_{20}ClNO_4P_2$ (327.68)	40.06	40.32	6.01	6.15	18.75	18.90	4.11	4.27

Table 2. IR spectral data (cm^{-1}) of the *N*-dimethylphosphinoyl-substituted aminomethanephosphonic acids **1**, **2** and **3** · **HCl**[a].

Acids **1**	Acids **2**	Acids **3** · **HCl**	Assignments	Molecular fragment
3500 – 3300 (b)	3500 – 3300 (b)	3500 – 3270 (b)	ν(O–H)	(OH···O-H)
3000 – 2800 (m)	3000 – 2800 (m)	3000 – 2800 (w)		(P=O···H-O) (non-cyclic)
2340 (b, s)	2560 – 2332 (m)	2542 (m, b)	ν(R–N^+)	(R_3N^+H)
			ν(O–H)	(P=O···H-O) (cyclic)
		1622 (s) 1501 (w)	ν(C_{Ar}–C_{Ar})	(Ar)
1320 – 1260 (m)	1304 (w)	1305 (w)	δ(P–C-H)	(P-CH_3)
1184 (vs)	1201 (vs)	1184 (vs)	ν(P=O)	(CH_3-P=O) and (HO-P=O)
1153 (vs)	1153 (vs) 1120 (vs)	1112 (vs)		
–	–	1104 (vs)	ν(C_{Ar}–C)	(Ph-CH_2)
948 (vs)	957 – 933 (vs)	962 – 938 (s)	ν(P–O)	(P-O-H)
768 (w)	758(m)	772 (m)	δ(C–P–C)	(CH_3-P-CH_3)
736 (w)	737 (m)	735 (m)	δ(O–P–O)	(HO-P-OH)
715 (w)	721 (m)			
586 – 538 (m)	520 (w)	542 (m)	δ(P=O)	(HO–P=O)

[a] s strong, vs very strong, m middle, w week, b broad.

The acids are easily dissolved in water, methanol and aqueous ethanol, sparingly soluble in hot DMFA and DMSO, and insoluble in less polar solvents like dichloromethane, chloroform, diethyl ether, dioxane, ethyl acetate, tetrahydrofurane, and aliphatic and aromatic hydrocarbons. The structures of **1**, **2** and **3** · **HCl** were confirmed by elemental analyses, IR and NMR spectroscopy, and electrospray ionization mass spectrometry. In addition, the molecular structures of the acids were determined by single crystal X-ray diffraction.

The IR spectral data are presented in Table 2. The bands characteristic for P=O groups in tertiary phosphine oxide and phosphonic acid fragments were observed in the region 1200 – 1110 cm^{-1}. The corresponding deformation frequencies appear at about 590 – 520 cm^{-1}. There are two frequency regions which characterize the stretching vibrations of the acidic P-OH engaged in hydrogen bonding. These units take part in cyclic P=O···HO (2600 – 2330 cm^{-1}) and non-cyclic (at about 3000 – 2800 cm^{-1} and 3500 – 3270 cm^{-1}) O-H·OH or

Table 3. ^{1}H and ^{31}P{^{1}H} NMR data for anions **1A** – **3A** of *N*-dimethylphosphinoyl-substituted aminomethanephosphonic acids **1**, **2** and **3** · **HCl** obtained at 500 and 202.4 MHz, respectively (δ in ppm, J in Hz)[a].

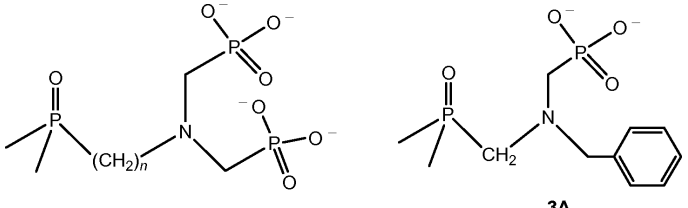
	^{1}H NMR							^{31}P{^{1}H} NMR		
	$(CH_3)_2$P(O)		P(O)-CH_2-N		Ph-CH_2-N	N-CH_2-PO_3^{2-}		$(CH_3)_2P$(O)	CH_2-PO_3^{2-}	
	δ_H	$^2J_{PH}$	δ_H	$^2J_{PH}$	δ_H	δ_H	$^2J_{PH}$	δ_P	δ_P	$^nJ_{PP}$
1A	1.65 (d)	−13.0	3.39 (d)	−6.3	–	2.79(d)	−11.5	56.35 (s)[b]	17.14 (s)[b]	n. r.[b]
2A[c]	1.57 (d)	−13.1	2.89 (t)	[c]	–	2.70 (d)	−11.6	57.53 (s)	17.93 (s)	n. r.
3A[d]	1.46 (d)	−13.0	3.18 (d)	−6.1	3.94 (s)	2.76 (d)	−11.0	55.31 (d)[e]	16.68 (d)[e]	1.4[e]

[a] Abbreviations: d doublet, m multiplet, s singlet, t triplet, n. r. not resolved. Only absolute values of $^nJ_{PP}$ are given; [b] J_{PP} resolved at 81 MHz to 1.4 Hz; [c] complex [ABC]$_2$X spin system for the *P*(O)-CH_2-CH_2-CH_2-N skeleton. P(O)-CH_2-C-C-N protons: deceptively simple triplet at 2.89 ppm, $N_{HH} = {}^3J_{HH} + {}^3J_{HH'} = 14.4$ Hz; P(O)-C-CH_2-C-N and P(O)-C-C-CH_2-N protons: signals overlap, broad multiplet at 1.65 – 1.95 ppm; [d] C_6H_5 protons: broadened, almost deceptively simple [AB]$_2$C multiplet. Repeated simulation of the corresponding 500 MHz ^{1}H NMR spectrum using WINDAYSY lead to the following data (not iterated): $\delta_H(H_o) = 7.48$ (d), $\delta_H(H_m) = 7.41$ (t), $\delta_H(H_p) = 7.35$ (t); $^3J_{HH} = 7.2$ Hz, $^4J_{HH} = 0.6 – 1.0$ Hz, $^5J_{HH} = 0.3$ Hz; [e] J_{PP} resolved at 81 MHz to 1.5 Hz.

Table 4. ^{13}C{^{1}H} NMR data for anions **1A** – **3A** of *N*-dimethylphosphinoyl-substituted aminomethanephosphonic acids **1**, **2** and **3** · **HCl** obtained at 125.7 MHz (δ in ppm, J in Hz)[a].

	$(CH_3)_2$P(O)		P(O)-CH_2-N		N-CH_2-PO_3^{2-}	
	δ_C	$^1J_{PC}$	δ_C	$^nJ_{PC}$	δ_C	$^nJ_{PC}$
1A	16.88 (d)	67.4	59.11 (dt)	$^1J_{PC} = 83.4$	60.17 (dt)	$^1J_{PC} = 144.8$
				$^3J_{PC} = 8.4$		$^3J_{PC} = 8.4$
2A[b]	14.39 (d)	68.3	27.90 (d)	$^1J_{PC} = 69.4$	54.97 (dd)	$^1J_{PC} = 143.6$
						$^5J_{PC} = 9.6$
3A[c]	16.20 (d)	67.8	56.39 (dd)	$^1J_{PC} = 85.2$	57.89 (dd)	$^1J_{PC} = 139.6$
				$^3J_{PC} = 7.6$		$^3J_{PC} = 6.5$

[a] Abbreviations: d doublet, dd doublet of doublets, dt doublet of triplets. Only absolute values of $^nJ_{PC}$ are given; [b] resonance signals for the P(O)-C_α-C_β-C_γ-N skeleton: $\delta(C_\alpha)$: the data are shown in the table, $\delta(C_\beta) = 17.51$ (d), $^2J_{PC} = 3.2$ Hz; $\delta(C_\gamma) = 56.69$ (dt), $^3J_{PCNC} = 6.4$ Hz, $^3J_{PCCC} = 17.6$ Hz; [c] Ph-CH_2-N: $\delta = 63.60$ (dd), $^3J_{PC} = 6.1$ Hz, $^3J_{PC} = 7.2$ Hz; C_6H_5: $\delta(C_1) = 141.45$, $\delta(C_2) = 132.55$; $\delta(C_3) = 131.11$; $\delta(C_4) = 130.07$.



Scheme 2.

P=O···H-O intermolecular hydrogen bonds. The $^+HNR_3$ stretching frequencies are observed in the region 2560 and 2300 cm^{-1} in the spectra of the three acids confirming their protonation.

The NMR data of the acids are in agreement with the proposed structures. The assignments are corroborated by data of structurally related molecules [5a, b, 7, 9, 14, 23, 24]. Spectral halfwidths of the NMR spectra of aminoalkanephosphonic acids depend strongly on the protonation state in solution. Anions exhibit sharper spectral lines than acidic forms involving P-OH functions. Hence the ^{1}H, ^{31}P{^{1}H}, and ^{13}C{^{1}H} NMR data were recorded for the fully deprotonated phosphonate anions **1A**, **2A** and **3A** (Scheme 2) by dissolving the corresponding acids in excess 1 M NaOD/D_2O (see Tables 3 and 4 and the Experimental Section).

In the ^{1}H NMR spectra of the three phosphonate anions the $(CH_3)_2$P(O) groups are doublets. The methylene protons of phosphine oxide groups P(O)CH_2 in **1A** and **3A** are doublets as well. The proton spectrum of **2A** is more complex. The unit P(O)CH_2CH_2CH_2-N gives rise to an [ABC]$_2$X spin system. The signal for methylene protons close to the phosphorus atom is registered as a deceptively simple triplet in the same region as the methylene protons of the P(O)-CH_2 group in **1A** and **3A**. The resonance signal for the two other methylene protons is a broad overlapping multiplet. The protons of the phenyl group in **3A** give a characteristic (AB)$_2$C system.The recorded and simulated

Table 5. Crystal data and details of the data collection and structure determination for **1**, **2** and **3** · **HCl**.

	1	**2**	**3** · **HCl**
Empirical formula	$C_5H_{16}NO_7P_3$	$C_7H_{20}NO_7P_3$	$C_{11}H_{20}ClNO_4P_2$
Formular weight	295.10	323.15	327.67
Crystal color; habit	colorless, prism	colorless, prism	colorless, plate
Crystal size, mm^3	0.06 × 0.12 × 0.52	0.05 × 0.12 × 0.45	0.02 × 0.08 × 0.10
Crystal system	monoclinic	triclinic	triclinic
Space group	$P2_1/c$	$P\bar{1}$	$P\bar{1}$
a, Å	11.6423(8)	5.9886(9)	8.1483(10)
b, Å	5.8058(2)	9.4468(14)	9.9302(13)
c, Å	17.3581(13)	12.5394(19)	9.9809(11)
α, deg	90	102.536(18)	67.383(13)
β, deg	102.813(8)	93.860(18)	87.749(14)
γ, deg	90	99.494(17)	88.033(15)
Volume, Å^3	1144.07(12)	679.07(18)	744.75(16)
Z	4	2	2
Density (calcd.), g cm^{-3}	1.71	1.58	1.46
Temperature (K)	291(2)	173(2)	173(2)
Radiation; wavelength, Å	MoK_α; 0.71073	MoK_α; 0.71073	MoK_α; 0.71073
Absorption coefficient, mm^{-1}	0.5	0.5	0.5
F(000), e	616	340	344
Scan mode	φ	φ	φ
θ range, deg	$2.41 \leq \theta \leq 25.00$	$2.25 \leq \theta \leq 24.99$	$2.21 \leq \theta \leq 25.00$
Index ranges *hkl*	±13, ±6, ±20	±7, ±11, ±14	±9, ±11, ±11
Refl. collected / unique / R_{int}	14147 / 2010 / 0.079	10013 / 2306 / 0.093	9733 / 2457 / 0.164)
Observed reflections [$I \geq 2\,\sigma(I)$]	1437	1233	831
Data / ref. parameters	2010 / 161	2306 / 178	2457 / 182
Goodness of fit on F^2	1.005	0.873	0.871
Final $R1$ / $wR2$ [$I \geq 2\,\sigma(I)$]	0.039 / 0.089	0.040 / 0.077	0.040 / 0.077
$R1$ / $wR2$ (all data)	0.056 / 0.092	0.082 / 0.082	0.139 / 0.073
Largest diff. peak / hole, e Å^{-3}	0.509 / −0.255	0.388 / −0.255	0.229 / −0.203

(using the programme WINDAYSY) NMR parameters of these protons are in good agreement.

The $^{31}P\{^1H\}$ NMR spectra (see Table 3) of **1A** – **3A** gave only two signals for the tertiary phosphine oxide and phosphonate phosphorus atoms.

In the $^{13}C\{^1H\}$ NMR spectra of anions **1A** – **3A** (Table 4) the methyl carbons of the $(CH_3)_2P(O)$-CH_2 fragment are isochronous and give rise to typical doublets centered at 14 – 17 ppm exhibiting coupling constants $^1J_{PC}$ of around 68 Hz. The signals of methylene carbons of the same fragment are observed as a doublet of triplets in **1A** and as a doublet of doublets in **3A** with characteristic data for $^1J_{PC}$ and $^3J_{PC}$. Again, the resonances for the P(O)-CH_2-CH_2-CH_2-N skeleton in **2A** are slightly more complex with resonance signals for $\delta(C_\alpha)$, $\delta(C_\beta)$, $\delta(C_\gamma)$ and corresponding coupling constants. The resonances of the methylene carbon atoms N-CH_2-PO_3^{2-} in **2A** and **3A** are doublets of doublets, while in **1A** they appear as a doublet of triplets.

The acids **1**, **2** and **3** were further identified by electrospray ionization (ESI) mass spectrometry without further derivatization in both the positive and negative ion mode. The ESI mass spectra obtained in the positive ion mode show most intense signals for $[M+H]^+$ (**1**: *m/z* = 296; **2**: *m/z* = 324; **3**: *m/z* = 292). Peaks for the protonated dimers $[2M+H]^+$ and trimers $[3M+H]^+$ have been detected as well. In the negative ion mode, the ESI mass spectra exhibit strong signals for $[M-H]^-$ (**1**: *m/z* = 294; **2**: *m/z* = 322; **3**: *m/z* = 290), $[2M-H]^-$ and $[3M-H]^-$ ions. It should be mentioned that other ionization methods like EI, CI or FAB failed due to proceeding dehydration reactions.

The solid-state structures of **1**, **2** and **3** · **HCl** were determined by X-ray diffraction. Crystal data and details of the data collection and structure determination are compiled in Table 5. Selected bond lengths and angles are listed in Table 6, geometrical details of the hydrogen bonds are given in Table 7. The structure determinations have shown that in the crystals of **1** and **2** the *N*-protonated betainic forms of the bisphosphonic acids are present, *i. e.*, the solids of these compounds might be described as ammonio-methane hydrogenphosphonates. *N*-protonation is also obvious for the cationic species in the solid of **3** · **HCl**. Even when subtle differences originating from the different strengths of the hydrogen bonding interactions, are

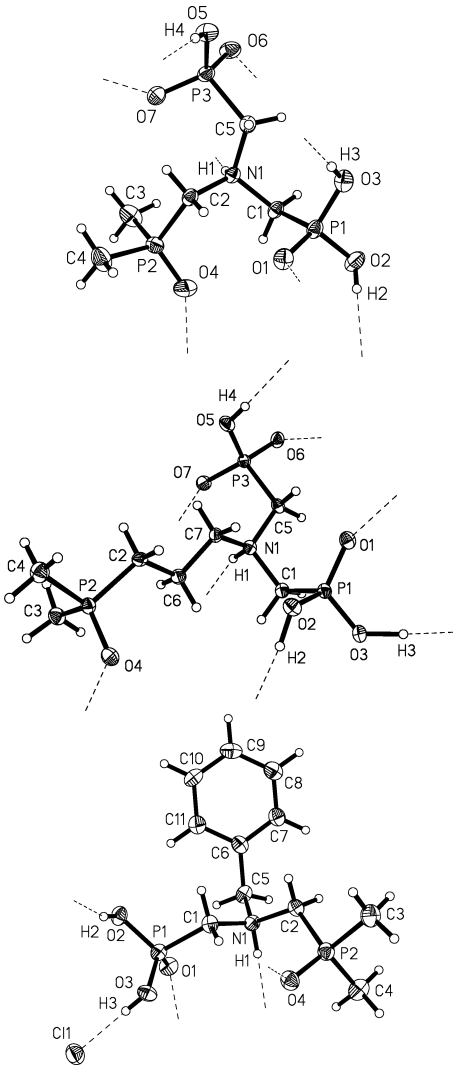


Fig. 1. Diagrams of the molecular structures of **1** (top) and **2** (middle) in the crystal and of the asymmetric unit of the crystal structure of **3** · **HCl** (bottom). Displacement ellipsoids are drawn at the 40 % probability level, radii of the hydrogen atoms are chosen arbitrarily, and most of the hydrogen atom labels are omitted for clarity. Dashed lines are indicating the directions of intermolecular hydrogen bonding.

considered in which the terminal or O–H group oxygen atoms are involved, all the bond lengths observed for the components of **1**, **2** and **3** · **HCl** are as expected. As can be seen from Table 7, all the O–H···O and N–H···O hydrogen bonds are intermolecular ones. In the case of **1** and **2**, three-dimensional supramolecular networks result, while in **3** · **HCl** a coordination-polymeric chain of aminophosphonic acid molecules is formed which is protonated at the nitrogen atoms

Table 6. Selected bond lengths (Å) and angles (deg) for **1**, **2**, and **3** · **HCl**.

	1	**2**	**3** · **HCl**
Bond lengths			
P1–O1	1.481(2)	1.479(3)	1.476(3)
P1–O2	1.545(3)	1.542(3)	1.537(3)
P1–C1	1.827(3)	1.830(4)	1.816(5)
Bond angles			
O1–P1–O2	114.52(14)	111.22(17)	110.7(2)
O2–P1–O3	106.64(15)	109.53(16)	109.4(2)
O1–P1–C1	111.27(14)	110.58(16)	111.8(2)
O2–P1–C1	100.05(14)	106.01(18)	106.2(2)
O4–P2–C2	112.97(15)	111.03(16)	111.9(2)
O4–P2–C3	112.76(19)	112.85(18)	114.0(2)
C2–P2–C3	106.61(16)	107.51(19)	104.0(3)
C3–P2–C4	106.3(2)	106.1(2)	107.6(2)
C1–N1–C2	113.5(2)	–	110.6(4)
C1–N1–C5	113.3(2)	110.8(3)	112.5(4)
C1–N1–C7	–	115.0(3)	–
N1–C1–P1	117.4(2)	117.5(3)	115.9(3)
N1–C5–C6	–	–	115.5(4)

Table 7. Hydrogen bond geometries (Å and deg) for **1**, **2**, and **3** · **HCl**[a].

Acid	D–H···A	D–H	H···A	Angle	D···A
1	N1–H1···O1*a*	0.82(4)	1.86(4)	174(3)	2.672(3)
	O2–H2···O4*b*	0.75(4)	1.78(4)	176(5)	2.527(4)
	O3–H3···O6*c*	0.85(5)	1.62(5)	178(5)	2.472(3)
	O5–H4···O7*d*	0.78(5)	1.86(4)	174(3)	2.672(3)
2	N1–H1···O7*e*	0.88(4)	1.82(4)	165(3)	2.679(4)
	O2–H2···O4*b*	1.06(4)	1.47(4)	173(4)	2.522(4)
	O3–H3···O6*f*	1.17	1.29	168.9	2.448(4)
	O5–H4···O1*g*	0.73(5)	1.87(5)	172(6)	2.595(4)
3 · **HCl**	N1–H1···O1*a*	0.92(6)	1.82(6)	165(5)	2.718(6)
	O2–H2···O4*h*	0.84	1.72	163.9	2.536(5)
	O3–H3···Cl1	0.84	2.02	177.3	2.862(4)

[a] Symmetry transformations used to generate equivalent atoms: *a*: *x*, *y* − 1, *z*; *b*: −*x*, −*y*, −*z*; *c*: *x*, *y* + 1, *z*; *d*: −*x* − 1, *y* + 1/2, −*z* − 1/2; *e*: −*x*, −*y*, −*z* + 1; *f*: −*x*, −*y* + 1, −*z* + 1; *g*: −*x* + 1, −*y* + 1, −*z* + 1; *h*: −*x* + 1, −*y*, −*z* + 1.

and has chloride anions connected by O–H···Cl hydrogen bonds. Fig. 1 shows diagrams of the quasi-molecular components indicating the direction of the non-covalent bonding. The N-H hydrogen bond donor group is connected to the oxo function of a phosphonate group in the case of **1** and **3** · **HCl**, and to the deprotonated phosphonate group in the case of **2**. In each compound the oxo function of the phosphinoyl group is connected to one of the phosphonate OH functions by strong O···H-O bonding, as indicated by O···O distances of *ca.* 2.53 Å. Even stronger than these interactions are the electrostatically assisted O–H···O hydrogen bonds between the phosphono and the deprotonated phosphonate groups in **1** and **2** (O···O distances 2.472(3) Å and 2.448(4) Å, respectively).

Experimental Section

Starting materials

Aminomethyl-dimethylphosphine oxide and *N*-benzyl-aminomethyl-dimethylphosphine oxide were prepared according to references [2, 6]. 3-Aminopropyl-dimethyl-phosphine oxide was donated from the former Hoechst AG, Frankfurt/Main, Germany. Paraformaldehyde and phosphorous acid were commercially available products from Fluka and Aldrich, respectively, and were used without further purification. All solvents were dried by standard procedures prior to use.

Characterization of the compounds

The elemental analysis for carbon and hydrogen was performed on a Vario EL*III* instrument in CHNS mode, for phosphorus according to ref. [25]. Nitrogen was determined using Duma's method. The melting points (not corrected) were measured on a Boetius microheating plate PHMK05 (Germany). The infrared spectra (400 – 4000 cm^{-1}) were recorded on a Bruker IFS-113V spectrometer using KBr pellets.

NMR: Sample preparation: 42.0 mg (**1**), 46.7 mg (**2**) and 50.9 mg (**3** · **HCl**), were dissolved in 0.75 mL of 1 M NaOD in D_2O. Under these conditions the total deprotonation of the phosphonic acids is achieved [23, 24]. Spectrometers from Bruker Spectrospin AG, Rheinstetten, were used: a) Avance DRX 500, b) Avance DRX 200 (see text). ^1H and $^{13}C\{^1H\}$ NMR spectra were obtained at 500.13 and 125.7 MHz, respectively, with chemical shifts referenced *vs.* internal 3-(trimethylsilyl)propanesulfonic acid sodium salt. $^{31}P\{^1H\}$ NMR spectra were recorded at 202.4 MHz and 81 MHz (above) and referenced *vs.* external 85 % H_3PO_4. Spectra were processed with WINNMR (Bruker). Simulations and iterations were performed with WINDAYSY (Bruker).

Mass spectra: ESI mass spectra were obtained by flow injection of 10^{-4}–10^{-5} M solutions of the acids in methanol into the standard ES interface of a Finnigan LCQ Deca mass spectrometer. The instrument was operated in the positive and negative ion mode. A mixture of acetonitrile and water (90 : 10 %, v/v) with an additive of 0.1 % formic acid at a flow-rate of 0.4 mL min^{-1} was used as the eluent.

*Crystal structure determination of compounds **1**, **2** and **3**·**HCl***

Well shaped crystals of the compounds were selected by means of an optical microscope, sealed in thin-walled glass capillaries (Hilgenberg GmbH, Germany) and investigated on an imaging plate Stoe IPDS diffractometer, using graphite-monochromatized MoK_α radiation (λ = 0.71073 Å). Only very small crystals of **3** · **HCl** were available. Unit cell parameters were determined by least-squares refinements on the positions of 8000, 1555 and 2030 strong reflections, distributed equally in reciprocal space in the range $2.4 < \Theta$ ¡ 26.0°, $2.2 < \Theta < 25.0^\circ$, and $2.2 < \Theta < 24.0^\circ$, respectively. In the case of **1**, a monoclinic lattice was found, and space group $P2_1/c$ was uniquely determined by inspection of the systematic extinctions. In the cases of **2** and **3** · **HCl**, anorthic lattices were found compatible with space groups $P1$ and $P\bar{1}$. In the course of the structure refinements the latter type proved to be the correct one in both cases. Crystal data, as well as details of data collections and refinements are listed in Table 5. All structures were solved by Direct Methods [26] and subsequent Fourier syntheses. Approximate positions of all hydrogen atoms were found in difference Fourier syntheses. Refinements by full-matrix least-squares calculations on F^2 [27] converged (max. shift/esd: 0.000 in all cases) to the final indicators given in Table 5. Refined parameters include anisotropic displacement parameters for all atoms heavier than hydrogen, positional and isotropic displacement parameters for the H atoms bonded to nitrogen, positional and isotropic displacement parameters for the H atoms bonded to the oxygen atoms of **1**, as well as positional parameters for the H atoms bonded to the oxygen atoms of **2** with the exception of the positional parameters of H3 at O3. For the latter pair of atoms a rigid group refinement applying the O3-H3 distance found in a ΔF synthesis was used. H atoms not mentioned above were treated as riding on their parent carbon and oxygen atoms, respectively, in idealized positions. In addition, the H atoms of the CH_3 groups of **2** and **3** · **HCl**, and of the OH groups of **3** · **HCl** were allowed to rotate around the directions of neighboring C–C and P–O bonds, respectively. Isotropic displacement parameters were kept equal to 120 % of the equivalent isotropic displacement parameters of the parent secondary and 'aromatic' carbon atom, respectively, and equal to 150 % of the parent primary carbon and oxygen atom, respectively. Scattering factors, dispersion corrections and absorption coefficients were taken from International Tables for Crystallography, Vol. C (1992).

CCDC 651352, 651353, and 651354 contain the supplementary crystallographic data for this paper. These data can be obtained free of charge from The Cambridge Crystallographic Data Centre *via* www.ccdc.cam.ac.uk/data_request/cif.

Preparative studies

*Dimethylphosphinoylmethyl-imino-bis(methanephosphonic acid) (**1**)*

A mixture of 1.07 g (10 mmol) aminomethyl-dimethylphosphine oxide, 1.64 g (20 mmol) of phosphorous acid, 2 mL of water and 2 mL of concentrated hydrochloric acid

was heated to reflux. 1.20 g (40 mmol) of paraformaldehyde was then added in four portions with stirring and the mixture refluxed for 2.5 h. The water and **HCl** were removed by distillation under reduced pressure. The colorless crude solid residue melted at 179 – 187 °C. It was purified by recrystallization from aqueous ethanol. Yield 2.24 g (76 %). M. p. 187 – 189 °C.

*[3-(Dimethylphosphinoyl)propyl]imino-bis(methanephosphonic acid) (**2**)*

From 1.49 g (11 mmol) of 3-aminopropyl-dimethylphosphine oxide, 1.80 g (22 mmol) of phosphorous acid, 2 mL of water, 2 mL of concentrated hydrochloric acid, and 1.31 g (44 mmol) of paraformaldehyde, according to the previously described procedure, a light-yellow viscous crude product was obtained. It was stirred with diethyl ether, and the solid product formed was filtered, washed with diethyl ether and dried. Yield 3.10 g (83 %). M. p. 234 – 235 °C. After recrystallization from ethanol-water the colorless crystalline compound had a constant melting point 237 – 238 °C.

*N-Benzyl-N-dimethyphosphinoylmethyl-aminomethanephosphonic acid hydrochloride (**3** · **HCl**)*

From 1.18 g (6 mmol) of *N*-benzylaminomethyl-dimethylphosphine oxide, 0.49 g (6 mmol) of phosphorous acid, 2 mL of water, 1.5 mL of concentrated hydrochloric acid, and 0.36 g (12 mmol) of paraformaldehyde according to the procedure described above a colorless, transparent, viscous liquid was obtained, which was washed with ethanol. The residue was recrystallized from an ethanol/isopropananol mixture. Yield 1.15 g (58 %). M. p. 158 – 159 °C.

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