New *N*-substituted 1-hydroxy-3-aminopropylidenediphosphonic acids

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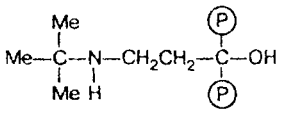
N-Substituted 1-hydroxy-3-aminopropylidenediphosphonic acids were synthesized. Their acid-base and complexation properties toward a wide series of metal cations in water were investigated.

Key words: aminoalkylidenediphosphonic acids, synthesis; zwitterion; dissociation constant, stability constant.

We have previously synthesized and studied acid-base and complexation properties of various aminomethylenediphosphonic[1] and amino-substituted hydroxypropylidenediphosphonic acids.[2] Compounds of this type are used as efficient complexons and medicinals.[3,4]

In this report, we describe the synthesis and properties of new amino-substituted hydroxypropylidenediphosphonic acids containing bulky *tert*-butyl (**1**) and cyclohexyl (**2**) substituents at the N atom as well as those of compounds in which N atoms belong to piperidine (**3**) and morpholine (**4**) cycles.



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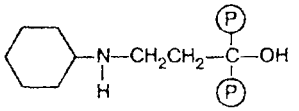

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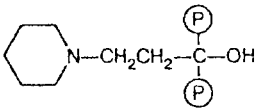

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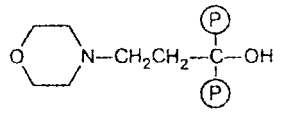

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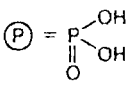
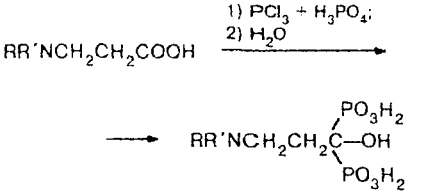


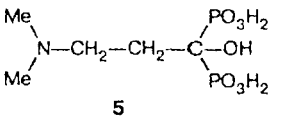
First of all, it was of interest to estimate the influence of the nitrogen-containing groups indicated on the complexation properties of the compounds synthesized. In addition, the presence of the secondary amino group in the molecules of ligands **1** and **2** allows the further modification of the structure of these complexons.

For the synthesis of compounds **1**—**4**, we used the method specially developed by us previously[5] for preparing 3-amino-1-hydroxypropylidenediphosphonic acids: the reactions of the corresponding aminopropionic acids with PCl_3 and H_3PO_4 followed by hydrolysis of the reaction mixture.



The starting aminopropionic acids were obtained according to the procedure described previously[6] by the addition of piperidine, morpholine, *tert*-butylamine or cyclohexylamine to freshly distilled methyl acrylate followed by hydrolysis of the esters that formed by water at room temperature.

We have previously studied the acid-base, complexation, and medical biological properties of ligand **5**.



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It has been established for this compound by IR spectroscopy[7] and X-ray diffraction analysis[8] that the complexon has the zwitterionic (betaine) structure in both the solution and crystalline state, and the proton bound to the N atom is the last one that dissociates (at the stage pK_4).

To elucidate the mechanism of acid dissociation of ligands **1**—**5**, we used the ^{31}P NMR method, which

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Table 1. Logarithms of acid dissociation constants (pK_a) of ligands **1**—**5** (25 °C, μ = 1.0 (KNO_3))

Ligand	pK_1	pK_2	pK_3	pK_4
1	2.28±0.04	5.95±0.01	10.12±0.04	12.4±0.10
2*	2.37±0.04	6.10±0.01	10.65±0.04	11.8±0.10
3	<1	5.74±0.01	9.99±0.03	12.3±0.10
4*	<2	5.69±0.01	9.38±0.03	11.5±0.10
5	<2	5.44±0.02	9.28±0.03	11.7±0.10

* μ = 0.1 (KNO_3).

previously proved to be successful for other aminophosphonic acids. We showed for ligands **3** and **5** the absence of the jump of chemical shift, which is characteristic of aminophosphonic acids[9] containing the amino group in the α-position relative to the P atom. Perhaps, its absence is due to the great removal of the N atom from the P atoms in molecules of ligands **3** and **5**. In addition, the mechanism of dissociation of these acids is strongly affected by the presence of hydrogen bonds between the nitrogen atoms and hydroxyphosphoryl groups: the formation of a great number of these bonds is typical of ligand **5**.[7,8] Table 1 presents the data on dissociation of compounds **1**—**5**. The pK_a values of compounds **1**—**4** and **5** are close, which suggests that in complexons **1**—**4**, the betaine proton, as in ligand **5**, also dissociates at the stage pK_4.

For studying the composition of the complexes of the ligands synthesized, we chose the Cu^{2+} cation, which is characterized by the formation of binuclear and polynuclear complexes with different complexons in an aqueous solution. The compositions of the complexes were determined by the conductometric method.

The measurement of electroconductivity in the L^{4-}—$Cu(NO_3)_2$ system (L^{4-} is the ligand neutralized by a solution of KOH) for complexes **2** and **4** shows that Cu^{2+} : L^{4-} = 1 : 1 complexes are formed in the solution (Fig. 1). It can be assumed that complexes of the other cations studied with both these and other ligands under study also have the M : L = 1 : 1 composition in an aqueous solution (see Experimental), although the possibility of formation of binuclear complexes cannot be ruled out.

Substituents at the N atom of ligands **1**—**5** affect slightly both the stability of the complexes formed (Table 2) and the selectivity of complexation. The values of efficiency (A) and selectivity (S) of complexation calculated by the previously described procedure[9] change insignificantly in the series of ligands **1**, **3**—**5**. The introduction of various alkyl substituents to the N atom change considerably the solubility of these ligands and their complexes in water. Ligand **4** with the highly hydrophilic morpholine substituent in the molecule is the most soluble. Unlike other diphosphonic acids, this ligand forms water-soluble complexes with rare-earth element (REE) ions.

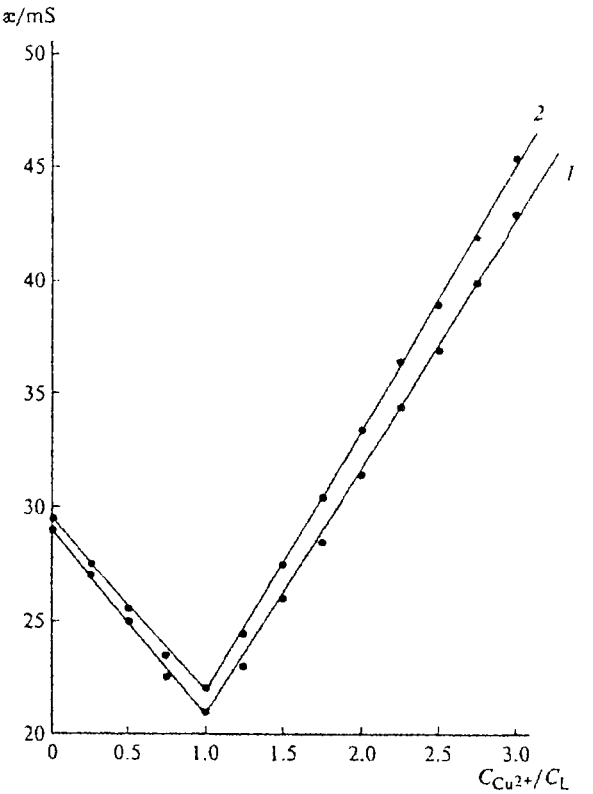

Fig. 1. Changes in electroconductivity (æ) of ligands **2** (*1*) and **4** (*2*) (neutralized by 4 equiv. alkali) on the concentration of the Cu^{2+} ion. Concentration of ligands C_L = 0.002 mol L^{-1}.

The data on the stability of ML, MHL, and MH_2L complexes of REE cations with ligand **4** (K_{ML} = [ML]/([M][L]), K_{MHL} = [MHL]/([M][HL]), K_{MH_2L} = [MH_2L]/([M][H_2L])) are presented in Table 3.

It is noteworthy that the stability constants (K_{st}) of the complexes of Sm^{3+}, Eu^{3+}, and Gd^{3+} (rare-earth elements that are neighbors in the Periodic system) differ greatly. The difference in the K_{st} values of the yttrium and REE complexes (see Table 3) is also significant.

Experimental

^{31}P-{^1H} NMR spectra were recorded on a Bruker CXP-200 instrument relative to 85% H_3PO_4 (external standard), and the concentration in the solutions was 0.05—0.10 mol L^{-1}.

pH-Potentiometric titration was carried out on an OP-208 instrument (Hungary) with accuracy 0.01 pH units in water at 25 °C and the ratio M : L = 1 : 1. The concentration of ligands (**1**, **3**, and **5**) was 0.005 mol L^{-1}, and that of ligands **2** and **4** was 0.002 mol L^{-1}, the ionic strength of solutions for the first of them was μ = 1.0 (KNO_3), and for the second ligands, μ = 0.1 (KNO_3). Electrodes were calibrated by standard buffer solutions with pH 1.68, 4.01, and 9.18. For these experimental conditions, the activity coefficients of hydrogen ions and hydroxyl groups were $p\gamma_{H^+}$ = 0.16 [13] and 0.11,[12] $p\gamma_{OH^-}$ = 0.04 [13] and 0.11,[12] respectively. The pK_a values of

Table 2. Logarithms of stability constants ($\log K_{st}$) of MH_jL complexes (j = 0—2), efficiency (A) and selectivity (S) of complex formation (25 °C, μ = 1.0 (KNO_3))[a]

L	Complex	Be^{2+}	Mg^{2+}	Ca^{2+}	Mn^{2+}	Co^{2+}	Ni^{2+}	Cu^{2+}	Zn^{2+}	Cd^{2+}	Pb^{2+}	REE	A	S
1	MH_2L	[b]	[c]	2.02	5.02	5.04	6.01	7.02	4.99	3.93	[c]	[c]		
	MHL	[b]	[c]	5.45	8.55	8.53	8.71	11.21	10.21	9.50	[c]	[c]		
	ML	[b]	[c]	6.05	9.00	9.01	9.20	12.43	10.67	9.97	[c]	[c]	9.47	2.88
2[d]	MH_2L	6.4	[c]	—	[c]	[c]	[c]	5.50	4.68	3.41	[c]	[c]		
	MHL	13.0	[c]	2.30	[c]	[c]	[c]	11.38	10.42	8.87	[c]	[c]		
	ML	14.7	[c]	6.29	[c]	[c]	[c]	12.79	11.48	10.14	[c]	[c]		
3	MH_2L	[b]	2.66	1.93	4.93	4.98	5.96	6.97	4.99	4.00	[c]	[b]		
	MHL	[b]	5.83	5.31	8.82	8.80	9.11	11.03	10.19	9.70	[c]	[b]		
	ML	[b]	6.31	5.82	9.20	9.28	9.60	12.91	10.70	10.18	[c]	[c]	9.66	3.12
4[d]	MH_2L	6.8	3.07	2.22	[b]	4.82	3.56	5.64	4.35	4.69	[b]	Soluble		
	MHL	12.3	5.68	5.03	[b]	8.45	7.20	10.58	9.13	9.10	[b]	comp-		
	ML	14.9	6.42	6.33	[b]	10.28	9.11	13.29	11.21	10.70	[b]	lexes	10.04	3.20
5	MH_2L	—	2.55	1.87	4.30	3.87	3.15	4.84	—	[b]	[b]	[b]		
	MHL	13.0	5.78	5.24	8.17	8.08	7.25	10.33	8.90[d]	[b]	[b]	[b]		
	ML	—	6.29	5.79	9.33	9.93	9.58	13.18	10.24[d]	[b]	[b]	[b]	9.74	3.09

[a] Errors in $\log K_{st}$ values of the complexes were determined as described[10] and were ±0.01—0.10 logarithmic units. If these errors exceeded 0.05 logarithmic units, in Tables 1—3 the $\log K_{st}$ values were approximated to decimals. Cation base for ligands **1**, **3**, and **5** for the calculation of A and S values: Ca^{2+}, Co^{2+}, Ni^{2+}, Cu^{2+}, and Zn^{2+}.

[b] Complexation with this cation was not studied.

[c] Water-insoluble complex.

[d] μ = 0.1 (KNO_3 or KCl).

Table 3. Logarithms of stability constants ($\log K_{st}$) of MH_jL complexes (j = 0—2) of REE cations with ligand **4**, efficiency (A) and selectivity (S) of complexation (25 °C, μ = 1.0 (KNO_3 or KCl))

Complex	Ga^{3+}	Y^{3+}	La^{3+}	Nd^{3+}	Sm^{3+}	Eu^{3+}	Gd^{3+}	Ho^{3+}	Er^{3+}	Yb^{3+}	A[a]	S[a]
MH_2L	—	—	5.6	6.5	6.4	7.0	4.5	5.7	5.7	6.4		
MHL	14.0	12.7	11.8	12.4	12.7	12.1	12.1	12.5	12.7	12.6		
ML	21.4	16.8	13.8	14.1	15.1	13.6	15.0	14.7	15.3	14.0	14.6	0.8

[a] The A and S values were calculated as described previously[9] for the REE cation base: Nd^{3+}, Sm^{3+}, Gd^{3+}, Ho^{3+}, and Er^{3+}.

acids and $\log K_{st}$ of complexes were calculated by the special program[14] on a PC AT-386. Electroconductivity was measured on an OK-101/2 (Hungary) at the concentration of ligands C_L = 0.002 mol L^{-1}.

β-Piperidinopropionic acid. Freshly distilled methyl acrylate (8.6 g, 0.1 mol) was added dropwise with stirring and cooling to piperidine (8.5 g, 0.1 mol) in such a way that the temperature of the reaction mixture was not higher than 20 °C. The mixture was let to stand at this temperature over 48 h and then stored in a vacuum of a water jet pump. Water (150 mL) was added to the residue, and the mixture was stirred at 20 °C for 48 h. After the excess water was removed in the vacuum of a water jet pump, the residue was recrystallized from an ethanol—acetone mixture. Piperidinopropionic acid (13.4 g, 85%) with m.p. 106—109 °C was obtained in 85% yield (13.4 g); Ref. 12: m.p. 105—110 °C.

β-Morpholinopropionic acid. Morpholinopropionic acid with m.p. 121—123 °C was obtained in 82% yield (6.5 g) similarly to the procedure described above from morpholine (4.3 g, 0.05 mol) and methyl acrylate (4.3 g, 0.05 mol). Found (%): C, 47.8; H, 8.8; N, 7.9. $C_7H_{13}NO_3 \cdot H_2O$. Calculated (%): C, 47.5; H, 8.5; N, 7.9.

β-*tert*-Butylaminopropionic acid. *tert*-Butylaminopropionic acid with m.p. 115—117 °C (with decomp.) was obtained in 79% yield (5.7 g) similarly to the procedure described above from *tert*-butylamine (7.3 g, 0.1 mol) and methyl acrylate (4.3 g, 0.05 mol). Found (%): C, 57.8; H, 10.3; N, 9.5. $C_7H_{15}NO_2$. Calculated (%): C, 57.9; H, 10.3; N, 9.7.

β-Cyclohexylaminopropionic acid. Cyclohexylaminopropionic acid with m.p. 152—154 °C was obtained similarly in 68% yield (5.7 g) from cyclohexylamine (7.4 g, 0.075 mol) and methyl acrylate (4.3 g, 0.05 mol). Found (%): C, 63.4; H, 10.2; N, 8.1. $C_{19}H_{17}NO_2$. Calculated (%): C, 63.2; H, 9.9; N, 8.2.

1-Hydroxy-3-*tert*-butylaminopropylidenephosphonic acid (1). A mixture of β-*tert*-butylaminopropionic acid (3.6 g, 0.25 mol), 85% H_3PO_4 (4 mL), and chlorobenzene (13 mL) was heated in a flask with a stirrer, reflux condenser, and a dropping funnel on an oily bath at 100—105 °C. PCl_3 (6.2 mL, 0.07 mol) was added dropwise with stirring at this temperature, the mixture was heated for 3 h at the same temperature, then water (15 mL) was added carefully dropwise, and the mixture was heated for 1 h. The aqueous layer was separated, and the excess water was removed *in vacuo*. After precipitation with ethanol, acid **1** (3.3 g, 46%) was obtained with m.p. 243—245 °C (with decomp.) from a water—ethanol mixture). $^{31}P\{H\}$ NMR (H_2O): δ 17.62. Found (%): C, 27.1; H, 6.9; N, 4.3. $C_7H_{19}NO_7P_2 \cdot H_2O$. Calculated (%): C, 27.2; H, 6.8; N, 4.3.

1-Hydroxy-3-cyclohexylaminopropylidenediphosphonic acid (2). Acid **2** with m.p. 175—178 °C (with decomp.) (from

H_2O) was obtained similarly in 40% yield (3.2 g) from β-cyclohexylaminopropionic acid (4.3 g, 0.025 mol), 85% H_3PO_4 (4 mL), and PCl_3 (6.2 mL, 0.07 mol) in chlorobenzene (13 mL) after hydrolysis with water. ^{31}P-{H} NMR (H_2O): δ 17.59. Found (%): C, 32.3; H, 6.9; N, 4.0. $C_9H_{21}NO_7P_2$. Calculated (%): C, 32.3; H, 6.9; N, 4.2.

1-Hydroxy-3-piperidinopropylidenediphosphonic acid (3). Acid **3** with m.p. 243—245 °C (with decomp.) (from H_2O) was obtained similarly in 41% yield (6.2 g) from β-piperidinopropionic acid (7.8 g, 0.05 mol), 85% H_3PO_4 (9 mL), and PCl_3 (12.5 mL, 0.14 mol) in chlorobenzene (25 mL) after hydrolysis with water. ^{31}P-{H} NMR (H_2O): δ 17.44. Found (%): C, 31.8; H, 6.2; P, 20.5. $C_8H_{19}NO_7P_2$. Calculated (%): C, 31.7; H, 6.3; P, 20.5.

1-Hydroxy-3-morpholinopropylidenediphosphonic acid (4). Acid **4** with m.p. 207—210 °C (with decomp.) (from H_2O) was obtained similarly in 42% yield (3.2 g) from β-morpholinopropionic acid (4.0 g, 0.025 mol), 85% H_3PO_4 (4 mL), and PCl_3 (6.2 mL, 0.07 mol) in chlorobenzene (13 mL) after hydrolysis with water. ^{31}P-{H} NMR (H_2O): δ 17.44. Found (%): C, 27.4; H, 5.5; P, 20.6. $C_7H_{17}NO_7P_2$. Calculated (%): C, 27.5; H, 5.6; P, 20.3.

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