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Amino-substituted *gem*-diphosphonic acids: structures of complexes with divalent metal cations in aqueous solutions

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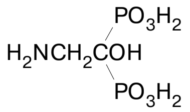
A comparative study of complexation of acids $R_2N(CH_2)_nCR'(PO_3H_2)_2$ (R = H or Me; R′ = OH or H; n = 1 or 2) with the Ca^{2+}, Mg^{2+}, Zn^{2+}, and Cu^{2+} cations in aqueous solutions was carried out by vibrational (IR and Raman) and electronic spectroscopy using the data of ESR spectroscopy and conformational analysis (molecular mechanics). The MOPCPO chelate ring is formed in all ML and MHL complexes. The involvement of the N atom in coordination was found only in the Cu^{2+} complexes and is determined by the structure of the ligand. The relationship between the stability constants and the structures of the complexes in aqueous solutions is analyzed.

Key words: ω-aminoalkylidenediphosphonic acids, *gem*-diphosphonates, Cu^{2+}, Ca^{2+}, Mg^{2+}, and Zn^{2+} complexes, IR spectroscopy, Raman spectroscopy, UV spectroscopy, complexation in aqueous solutions.

In recent years, considerable attention has been given to the synthesis and investigation of *gem*-diphosphonic acids due to their use in medicine[1] and agricultural chemistry.[2] *gem*-Diphosphonates form complexes with different metals owing to their high chelating ability.[3,4] These compounds are active with respect to a wide range of cations because of the geminal arrangement of the phosphonate groups involved in a single acid unit due to which they can be readily "adjusted" to ions of different radii.[4,5] The introduction of the amino group bound to the diphosphonic unit of the alkylidene chain of variable length into the acid molecule (the formation of amino-substituted *gem*-diphosphonic acids) influences the donor ability of the phosphonate groups, extends the pH range of complex formation, changes their solubility, and opens up possibilities for additional chelation involving the nitrogen atom.[3,6] Pharmacological assays demonstrated that the therapeutic activity of the synthesized compounds depends substantially on the structure of the aminoalkylidene fragment.[1,7] In studies of the complex-forming ability of amino-substituted *gem*-diphosphonates (AGDP), the question of whether the N atom is involved in coordination is of great importance. According to the spectral data,[6,8,9] the N atom in MH_nL complexes is protonated and the metal atom is coordinated only by the O atoms of the phosphonate groups. In the ML complexes with cations possessing the affinity for the N atom, the M←N coordination bond can occur, but it is not necessarily the case,[6,8] the mode of coordination being dependent on both the structure of the ligand and the nature of the cation.

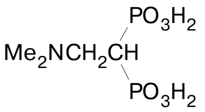
In the potentiometric studies[10] of amino-substituted *gem*-diphosphonates $R_2N(CH_2)_nCR'(PO_3H_2)_2$ (R = H or Me; R′ = H or OH; n = 0, 1, 2, or 3), we have examined the effect of the structure of the aminoalkylidene fragment on the formation constants of their complexes with a series of divalent metal cations.

The present study was aimed at determining the structures of metal complexes that are formed in aqueous solutions of AGDP **1—4**, which differ from each other by the length of the alkylidene chain and/or by the substituents at the N atom.



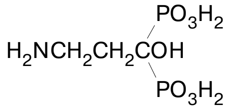
$H_2NCH_2C(OH)(PO_3H_2)_2$

1



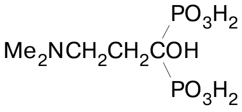
$Me_2NCH_2CH(PO_3H_2)_2$

2



$H_2NCH_2CH_2C(OH)(PO_3H_2)_2$

3



$Me_2NCH_2CH_2C(OH)(PO_3H_2)_2$

4

With the aim of revealing the effect of the structure of the aminoalkylidene fragment on the coordination environment of the cation, we studied complexation of ligands **1—4** with the same cation, *viz.*, with Cu^{2+}. The influence of the nature of the metal atom on the mode of coordination of the ligand was examined using compound **4** and the Ca^{2+}, Mg^{2+}, Zn^{2+}, and Cu^{2+} cations.

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Experimental

The synthesis and purification of 2-amino-1-hydroxyethylidenediphosphonic (**1**), 2-dimethylaminoethylidenediphosphonic (**2**), 3-amino-1-hydroxypropylidenediphosphonic (**3**), and 3-dimethylamino-1-hydroxypropylidenediphosphonic (**4**) acids have been reported previously.[10,11] Commercial 1-hydroxyethylidenediphosphonic acid (HEDP) (**5**) of reagent grade purity was purified by reprecipitation with chloroform from a solution in ethanol. The melting points, neutralization equivalents, and the IR and NMR spectra are consistent with the published data.

Twice-distilled water and D_2O (the content of the major isotope was 99.8%, the specific conductivity was $2 \cdot 10^{-6}$ S, TU 95.7046-73) were used as the solvents. Potassium hydroxide of reagent grade and metallic potassium (reagent grade; glass ampules with 100-mg weighed samples, TU 48-03-53-75), and a solution of DCl in D_2O (the concentration was 32.4%, the content of the major isomer was 99.6%, TU 95.7046-73) were used. A carbonate-free aqueous solution of KOH was prepared by dilution of a saturated solution of KOH. A solutions of KOD was prepared by dissolution of metallic potassium in D_2O. The concentrations of the solutions were determined by titration with adipic acid or potassium biphthalate. The solutions of the acids under study were prepared by the weight method.

The $CaCl_2$, $MgCl_2 \cdot 6H_2O$, $CuCl_2 \cdot 2H_2O$, and $ZnCl_2$ salts (chemically pure and analytical grade) were purified and dried according to known procedures.[12] The concentrations of the salts in solutions were controlled by chelatometric titration with EDTA.

Preparation of solutions for spectral studies. A calculated amount of a solution of KOH (KOD) and that of a solution of a particular salt in the corresponding solvent were successively added to a solution of the acid with the required concentration or a calculated amount of a solution of metal chloride and that of a solution of HCl or DCl in usual or heavy water, respectively, were successively added to a neutralized solution of a chelating agent using a microsyringe or a micropipette. The pH values of the solutions were determined potentiometrically or with the use of a pH-test-paper set (Aldrich, the measurement were carried out at intervals of 0.2 unit of pH).

IR spectra of solutions of the chelating agents in H_2O (in the region of 950—1300 cm^{-1}) and D_2O (in the regions of 850—1200 and 2700—3100 cm^{-1}) with the concentrations of 0.2—0.5 mol L^{-1} were recorded on a UR-20 spectrophotometer using Krs-5, BaF_2, and CaF_2 cells with the optical length of 0.025—0.050 mm.

Raman spectra of the solutions of the complexes with the concentrations used in the IR spectral studies were measured on a Coderg PH0 instrument equipped with a He—Ne laser ($\lambda = 632.8$ nm).

Electronic spectra in the visible and UV regions were recorded on Specord M-40 or Hitachi (solutions of the complexes of acid **4**) spectrometers. The spectra in the visible and UV regions were measured using solutions with the concentrations of 0.3 and 0.001 mol L^{-1}, respectively, in 1- and 0.1-cm cells, respectively.

ESR spectra of aqueous solutions of the complexes with the concentration of 0.1 mol L^{-1} were measured at 77 and 293 K on a Varian F-12 spectrometer equipped with a temperature-controlled attachment.

Conformational analysis. The energies of the molecular conformations in the region of the global minimum were calculated by molecular mechanics (MM) with the use of the MM2 (QCPE 395) and MMP1 (QCPE 318) force fields. The conformational energy of the ligand was calculated on the assumption that a six-coordinate complex is formed assigning the spatial structure of the polyhedron with typical distances between the metal cation and the coordinated atoms of the ligand.[13] The strain energy of the molecule (ΔE) was estimated as the difference between the energy of the conformer adopting the complex-forming conformation and that of the conformer in the region of the global minimum.

Results and Discussion

According to the results of potentiometric titration,[10] all acids under study are tetrabasic (H_4L) in aqueous solutions and form the ML^{2-}, MHL^{-}, and MH_2L complexes with divalent metal cations if the metal to ligand ratio is 1 : 1. The formation of complexes of more complicated composition under these conditions was not considered because the experimental data on the conductivity for *N*-substituted 1-hydroxypropylidenediphosphonic acids[14] are indicative of the preferential formation of mononuclear complexes with these ligands. The conductivity measurements in the chelating agent **4**—$CuCl_2$ system performed under the same conditions depending on the M : L ratio revealed an analogous regularity.[14] The existence region of the complexes of the same composition can be determined from distributions plots of the ionic forms of the complexes *versus* pH of the solution (Fig. 1). These plots demonstrate that the ML^{2-} and MHL^{-} complexes prevail in a rather wide pH range, whereas the MH_2L complexes exist as the minor component. In accordance with this fact, the spectra of solutions in the presence of two equivalents of KOH represent superpositions of bands corresponding to different ions. In some cases, precipitates were formed in this pH range. Hence, in the present study, we considered the structures of the ML^{2-} and MHL^{-} complexes.

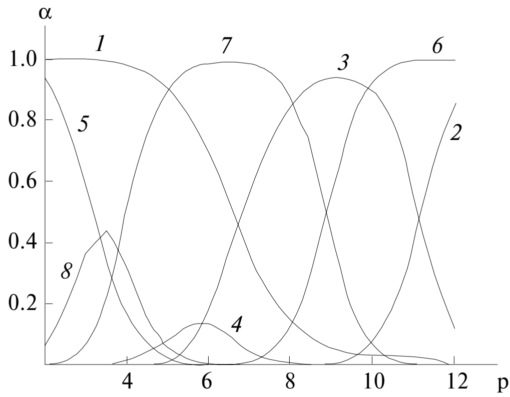


Fig. 1. Distribution of the ionic forms of the complexes depending on pH of the solution in the 1 : 1 ligand **4**—M^{2+} system according to the published data[10] at $c = 5 \cdot 10^{-3}$ mol L^{-1}: Ca^{2+} (*1*), CaL^{2-} (*2*), $CaHL^{-}$ (*3*), CaH_2L (*4*), Cu^{2+} (*5*), CuL^{2-} (*6*), $CuHL^{-}$ (*7*), and CuH_2L (*8*); α is the ratio between the concentration of the particular form and the initial concentration of the ligand.

Since no dissociation of the proton of the alcoholic group was observed in the pH range under study,[10] the possibility of its coordination in complexes with the divalent metal cations was not considered. The deprotonated L^{4-} anions of acids **1—4** are potentially heptadentate (N + 3 O +3 O′), but the maximum dentation is not generally realized.[3,4,6] Either the N atom and the O atoms of two phosphonate groups (N + O + O′) or only the O atoms of the phosphonate groups (O + O′), each being able to act as a bidentate ligand (2 O), can be involved in chelation. However, in the latter case the resulting four-membered ring is energetically unfavorable and the phosphonate groups in crystalline complexes are generally chelate-bridging.[3] The dentation of the chelating agent decreases upon protonation of the donor centers.

Complexes of ligand 4 with the Ca^{2+}, Mg^{2+}, Zn^{2+}, and Cu^{2+} cations. In the diphosphonate unit of the free deprotonated L^{4-} anion, the vibrations of each PO_3^{2-} group obey the local symmetry C_{3v} and are classified into in-phase and antiphase vibrations with respect to the plane passing through the central C atom. Consequently, the spectra have bands of antiphase symmetrical ($\nu''_s(PO_3)_2$ = 950 cm $^{-1}$), in-phase symmetrical ($\nu'_s(PO_3)_2$ = 998 cm^{-1}), and doubly degenerate ($\nu_e(PO_3)$ = 1090 cm^{-1}) vibrations. It should be noted that the $\nu_e(PO_3)$ and $\nu''_s(PO_3)_2$ vibrations are observed only in the IR spectra, whereas the $\nu'_s(PO_3)_2$ vibration gives an intense polarized line in the Raman spectra, but it is almost completely forbidden in the IR spectra[5] (Table 1).

The regular changes[15] indicative of the involvement of the PO_3^{2-} groups in coordination are observed in the spectra of the ML^{2-} complexes (see Table 1). First, the frequencies of the in-phase $\nu'_s(PO_3)_2$ and antiphase $\nu''_s(PO_3)_2$ symmetrical vibrations are increased by 10—20 cm^{-1}. Second, the intensities of the corresponding IR bands and the Raman lines are redistributed, *viz.*, the in-phase $\nu'_s(PO_3)_2$ vibration (~1010 cm^{-1}) whose intensity is comparable with the intensity of the $\nu''_s(PO_3)_2$ band is observed in the IR spectra of the complexes. Meanwhile, the antiphase $\nu''_s(PO_3)_2$ vibration gives a noticeable line in the Raman spectra of the CaL^{2-} and ZnL^{2-} complexes (~960 cm^{-1}). The third indication is the splitting of the band of the doubly degenerate $\nu_e(PO_3)$ vibration in the IR spectra of the CuL^{2-} ($\Delta\nu$ = 65 cm^{-1}) and ZnL^{2-} ($\Delta\nu$ = 50 cm^{-1}) complexes. This removal of degeneration results from the lowering of the symmetry of the PO_3 group due to formation of the directed $M \leftarrow O$ bond. However, splitting of the $\nu_e(PO_3)$ band in the IR spectra of the CaL^{2-} and MgL^{2-} complexes is not evidenced and only broadening of this band (in the IR spectrum of MgL^{2-}) or distortion of its shape (in the IR spectrum of CaL^{2-}) is observed. It should be noted that the Raman spectrum of the CaL^{2-} complex has a weak band at ~1110 cm^{-1}. Therefore, splitting is at most 20 cm^{-1} if ever occurs. An analogous dependence of splitting on the nature of the cation has been noted previously in studies of complex formation of different phosphonates[16—18] and phosphates,[19] and hence, the degree of splitting of the $\nu_e(PO_3)$ band can be considered as a measure of covalence of the $M \leftarrow O$ coordination bond.[18]

The involvement of the N atom in coordination can be revealed from a change in the frequencies of vibrations of the CH_3 and CH_2 groups bound to the N

Table 1. Data of vibrational spectroscopy (ν/cm^{-1}) of the normal CaL^{2-}, MgL^{2-}, ZnL^{2-}, and CuL^{2-} complexes and of the free L^{4-} anion of acid **4**

Assignment	L^{4-}		CaL^{2-}		MgL^{2-}, IR[a]	ZnL^{2-}		CuL^{2-}, IR[b]
	IR	Raman spectrum	IR	Raman spectrum		IR	Raman spectrum	
$\nu''_s(PO_3)_2$	950 m	—	970 m	968 m.dp	970 m	960 m	960 m.dp	960 m
$\nu'_s(PO_3)_2$	1000 v.w	998 s.p	1010 m	1008 s.p	1010 m	1010 m	1012 s.p	1010 sh
$\nu_e(PO_3)$	1090 v.s	—	1080 sh, 1090 s, 1110 sh	1110 w	1095 v.s.br	1065 s,[c] 1115 s [c]	1065 w, 1112 w	1045 s,[c] 1110 s [c]
$\nu(CH)$	**2800**, 2850, 2880, 2945, $\underline{2960}$, 2990 —	**2800**, 2850, 2880, $\underline{2968}$, — —	**2800**, 2850, 2880, 2940, $\underline{2960}$, 2985 —	**2800**, 2850, 2875, $\underline{2950}$, 2968 — —	**2800**, 2840, 2880, 2930, $\underline{2960}$, 2990 —	**2800**, 2840, 2880, 2930, $\underline{2960}$, 2990 —	**2800**, 2850, 2880, 2940, $\underline{2970}$, — —	— 2850, 2880, $\underline{2930}$, 2970, 2990, **3010** sh

Note. Bands (lines) with the maximum intensity in the region of CH vibrations are underlined; bands (lines) characterizing the state of the N atom are printed in bold type.

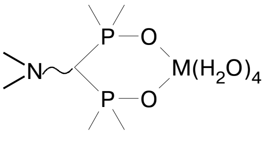
[a] The Raman spectra were not recorded.

[b] Attempts to measure the Raman spectra failed due to an intense color of the solutions.

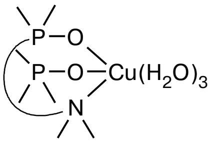
[c] The doublet, the maxima with similar intensities.

atom.[18] The regions of 2700—3100 cm^{-1} in the spectra of solutions of the $\mathrm{CaL^{2-}}$ and $\mathrm{MgL^{2-}}$ complexes and of a freshly prepared solution of $\mathrm{ZnL^{2-}}$ are identical with that of the free $\mathrm{L^{4-}}$ anion, which indicates that the N atom is not involved in complexation (see Table 1). The IR spectrum of the $\mathrm{CuL^{2-}}$ complex provides evidence for the M←N coordination. Thus, the maximum at 2800 cm^{-1} disappears and the intensities of the absorption bands are redistributed throughout the region of CH vibrations (see Table 1). As in the studies[5] of dissociation of acid **4**, the band at 2800 cm^{-1} appeared to be the most informative. This band is characteristic of both the methyl[20] (presumably, it belongs[20] to an overtone of the deformation vibrations of CH groups) and methylene[21] bonds in the amino group, but it is absent in the spectra of coordination compounds of amines with metals[20,21] as well as in other cases of delocalization of the free electron pair at the N atom.[20]

Therefore, it can be concluded that the $\mathrm{CaL^{2-}}$, $\mathrm{MgL^{2-}}$, and $\mathrm{ZnL^{2-}}$ complexes in freshly prepared solutions have structure **A**, whereas the $\mathrm{CuL^{2-}}$ complex has structure **B** (on the assumption that the free $\mathrm{M^{2+}}$ cation is coordinated by six $\mathrm{H_2O}$ molecules).



A

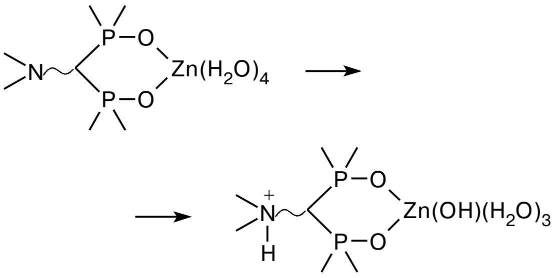


B

M = $\mathrm{Ca^{2+}}$, $\mathrm{Mg^{2+}}$, $\mathrm{Zn^{2+}}$

Solutions of the $\mathrm{ZnL^{2-}}$ complexes change with time. The spectra of the freshly prepared solutions containing equimolar amounts of acid **4** and $\mathrm{ZnCl_2}$ and 4 equiv. of KOH (pH ~9—11) are indicative of the formation of complex **A**. Meanwhile, the spectra measured after several hours provide evidence for protonation of the nitrogen atom,[5] *viz.*, the band (line) at 2800 cm^{-1} disappears and the band (line) at 3030 cm^{-1} appears. Then bands of the protonated phosphonate groups appear.[5] After 15—20 h, pH of the solution decreases to ~3—4. Based on these changes and taking into account the fact that the zinc cation tends to form hydroxo complexes, we assumed that the acidity of the solution increases due to hydrolysis of the complex. Its initial stage is shown in Scheme 1.

Scheme 1



In the $\mathrm{MHL^-}$ complexes of all cations under study with ligand **4**, the N atom is protonated, which was established based on the fact that the regions of CH vibrations in the spectra of the $\mathrm{MHL^-}$ complexes (Table 2) are identical with that of the free $\mathrm{HL^{3-}}$ anion (*cf.* Ref. 5), *i.e.*, the cations can be coordinated only by the O atoms of the $\mathrm{PO_3{}^{2-}}$ groups (structure **C**).

Table 2. Data of vibrational spectroscopy (ν/cm^{-1}) of the $\mathrm{CaHL^-}$, $\mathrm{MgHL^-}$, $\mathrm{ZnHL^-}$, and $\mathrm{CuHL^-}$ complexes and of the free $\mathrm{HL^{3-}}$ anion of acid **4**

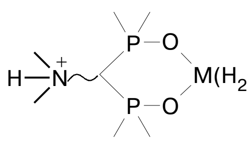
Assignment	$\mathrm{HL^{3-}}$		$\mathrm{CaHL^-}$		$\mathrm{MgHL^-}$, IR^a	$\mathrm{ZnHL^-}$		$\mathrm{CuHL^-}$, IR^b
	IR	Raman spectrum	IR	Raman spectrum		IR	Raman spectrum	
$\nu''_s(\mathrm{PO_3})_2$	950 m	950 sh	970 m	—	970 m	970 sh	970 sh	970 m
$\nu'_s(\mathrm{PO_3})_2$	—	982 s.p	—	1010 s.p	990 sh	990 m, 1020 sh, 1060 sh	995 s.p, 1020 sh	990 w, 1030 sh, 1050 sh
$\nu_e(\mathrm{PO_3})$	1100 s.br	—	1100 s.br	1080 w	1100 v.s	1100 s.br	—	1100 s.br
$\nu(\mathrm{CH})$	2850, 2880, — $\underline{2970}$, **3030**	2820, 2880, 2945, $\underline{2968}$, **3030**	^{c} $\underline{2970}$, **3030**	2825, 2880, 2940, $\underline{2970}$, **3030**	^{c} 2940, $\underline{2970}$, **3030**	2940 sh, $\underline{2970}$, **3030**	^{c} $\underline{2970}$, **3030**	^{c} 2940, $\underline{2970}$, **3030**

Note. Bands (lines) with the maximum intensity in the region of CH vibrations are underlined; bands (lines) characterizing the state of the N atom are printed in bold type.

[a] The Raman spectra were not recorded.

[b] Attempts to measure the Raman spectra failed due to an intense color of the solutions.

[c] Unresolved absorption in the region of 2800—2970 cm^{-1}.



C

M = Ca^{2+}, Mg^{2+}, Zn^{2+}, Cu^{2+}

The positions and intensities of the bands in the regions of PO vibrations in the spectra of the $CaHL^-$ and $MgHL^-$ complexes are slightly changed compared to those of the corresponding normal ML^{2-} complexes and of the free HL^{3-} anion, which is consistent with the ionic type of coordination (see Tables 1 and 2). In the spectra of the $CuHL^-$ and $ZnHL^-$ complexes, new bands are observed in the region of 1010—1030 cm^{-1}. Their relative intensities, including the intensity of the $\nu'_s(PO_3)_2$ band at ~990—995 cm^{-1}, can be redistributed upon small changes of pH of the solution. The broad structured $\nu_e(PO_3)$ band has no pronounced splitting. This spectral pattern can be explained by several reasons: first, by the formation of a hydrogen bond between the noncoordinated O atoms and the betaine proton resulting in violation of the correlation between the degree of splitting and the strength of the M←O bond;[15] second, by the bidentate coordination of one of the phosphonate groups (conformational analysis of ligand **5** by the MM method demonstrated that this coordination can occur); third, by the conformational inhomogeniety of the MHL^- complexes due to the fact that the O atoms of the ligand and of the H_2O molecules can change places in the coordination polyhedron. For the Cu^{2+} cation, the latter fact is most evident because its environment cannot be strictly octahedral due to the Jahn—Teller effect (see also the results of studies by ESR spectroscopy). In other words, solutions contain several forms of the MHL^- complex characterized by similar but not identical spectral parameters.

Therefore, the modes of coordination of ligand **4** in the normal and monoprotonated complexes with the Ca^{2+}, Mg^{2+}, Zn^{2+}, and Cu^{2+} cations were established based on the vibrational spectra. In the CaL^{2-}, MgL^{2-}, and ZnL^{2-} complexes, the metal cations are coordinated by the phosphonate groups (structure **A**). In the CuL^{2-} complex, both the phosphonate groups and the N atom are involved in coordination (structure **B**). In all MHL^- complexes, the N atom is protonated (structure **C**) and intramolecular NH...OP hydrogen bonds can exist.

The structure of the coordination polyhedron in the Cu^{2+} complexes was established by ESR spectroscopy. The parameters of the CuL^{2-} complex ($g_{\|} = 2.23$, $g_{\perp} = 2.09$*, $g = 2.17$, $A_{Cu} = 54.5 \cdot 10^{-4}$ cm^{-1}) are characteristic[22] of the tetragonal-pyramidal environment about the cation with the unpaired electron on the $d_{x^2-y^2}$ orbital ($g_{\|} > g_{\perp}$). The N atom is most probably located in the equatorial plane.[22] The degree of covalence of the coordination bonds is estimated at ~20%. The signal in the ESR spectrum of the $CuHL^-$ complex is isotropic ($g = 2.18$) and is virtually identical to the signal in the spectrum of the copper aqua complex due, apparently, to the equilibrium between the conformers of the complex, which differ by the arrangement of the O atoms of the ligand and the coordinated H_2O molecules, and to the fact that the parameters of the resulting polyhedron are similar to those of the copper hexaaqua complex.

In the visible region of the absorption spectrum of the CuL^{2-} complex, the d—d transition band is observed at ~720 nm. The spectrum of the $CuHL^-$ complex shows the absorption maximum at 800 nm along with a weak band at ~970 nm, which is analogous to the d—d band of the free hydrated Cu^{2+} ion (820 and 970 nm).

The UV spectrum of a solution of the CuL^{2-} complex (Fig. 2, curve *4*) has two absorption maxima at ~235 and ~270 nm, whereas no absorption bands are present in this region of the spectrum of the free ligand. Previously,[23] we have observed analogous bands in the spectra of the copper complexes of aminophosphonic acids adopting different structures and these bands have been interpreted as the O←Cu and N←Cu charge-transfer bands (at ~240 and ~270 nm, respectively). The spectrum of the protonated $CuHL^-$ complex has only one maximum at ~240 nm (see Fig. 2, curve *4′*) and it is

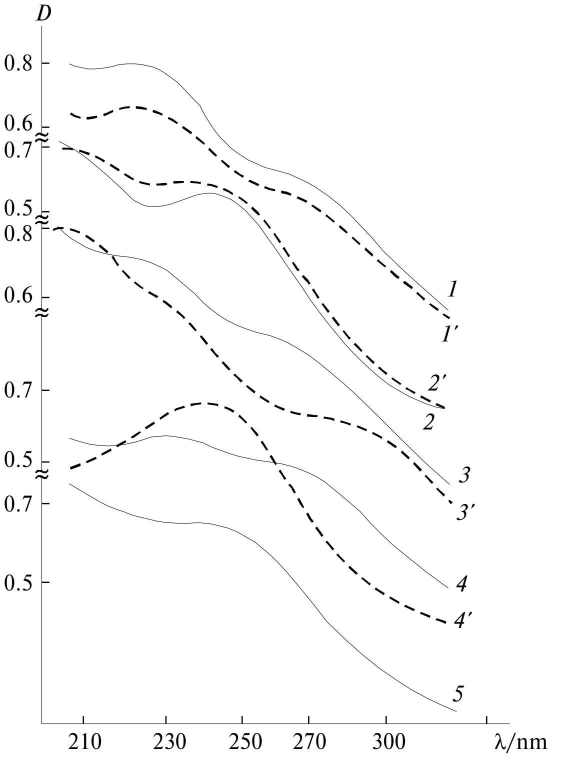


Fig. 2. UV spectra of the CuL^{2-} and $CuHL^-$ complexes (numbers for the latters are primed) with ligands **1—4** and the CuL^{2-} complex with ligand **5** ($c = 0.001$ mol L^{-1}, $d = 0.1$ cm); the numbering of the curves corresponds to the numbering of the ligands.

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[*] The $g_{\perp}$ value was calculated by the formula $g = 1/3(g_{\|} + 2\,g_{\perp})$.

similar to that of the CuL^{2-} complex with ligand **5** (see Fig. 2, curve *5*) in which the O atoms of the PO$_3$ groups are involved in coordination. Consequently, the O atoms of the phosphonate groups and the N atom are involved in coordination in the CuL^{2-} complex with ligand **4**, whereas only O atoms are involved in coordination in the CuHL$^-$ complex.

The data obtained for ligand **4** demonstrated that the O atoms of the phosphonate groups and the N atom in the nonprotonated CuL^{2-} complex form the axially extended tetragonal polyhedron [CuNOO′(H$_2$O)$_3$]. In the protonated CuHL$^-$ complex, the O atoms form the conformationally labile octahedron [MOO′(H$_2$O)$_4$].

Complexation of ligands 1—3 with the Cu^{2+} cation. Studies of the complexes of the Cu^{2+} cation with acid **4** demonstrated that the involvement of the N atom in coordination can be revealed from UV spectra.

The UV spectra of the CuL^{2-} complexes with acids **1** or **3** containing the unsubstituted amino group have two maxima identical with those observed in the spectrum of the normal complex with acid **4** (see Fig. 2, curves *1*, *3*, and *4*, respectively), which is indicative of the formation of the Cu←O (the maximum at ~230 nm) and Cu←N bonds (the maximum at ~270 nm). Unlike the above-mentioned spectra, the spectrum of the CuL^{2-} complex with acid **2** has one maximum at ~245 nm and it is analogous to the spectra of the CuL^{2-} complex with diphosphonate **5** and of the CuHL$^-$ complex with ligand **4** (see Fig. 2, curves *2*, *5*, and *4′*, respectively), which is indicative of the presence of Cu←O coordination and the absence of Cu←N coordination. The CuHL$^-$ complex with ligand **2** is characterized by an analogous spectrum (see Fig. 2, curve *2′*). The Cu←N charge-transfer band at 270—280 nm is retained in the spectra of the monoprotonated CuHL$^-$ complexes with ligands **1** and **3** (see Fig. 2, curves *1′* and *3′*, respectively). A decrease in its intensity and (in the case of ligand **3**) the shift of this band to the long-wavelength region occur near the pH boundary of the existence region of the CuHL$^-$ complex.

In the IR spectra of the CuL^{2-} complexes with ligands **1—3** (Table 3), the $\nu_e(PO_3)$ band splits, which is indicative of the formation of the Cu←O coordination bond. In the case of ligand **2**, splitting is the least pronounced, the low-frequency component is unresolved, but a shoulder is observed at ~1130 cm^{-1} (see Table 3). The latter may appear due to the bidentate coordination of one of the phosphonate groups, which is more probable in the absence of Cu←N coordination. On the whole, the IR spectrum of the CuHL$^-$ complex with acid **2** is similar to that of the nonprotonated complex with **2** and to the spectrum of the CuHL$^-$ complex with ligand **4** (the $\nu_e(PO_3)$ band is structured, but no pronounced splitting is observed), which is evidence for the structural similarity of these complexes.

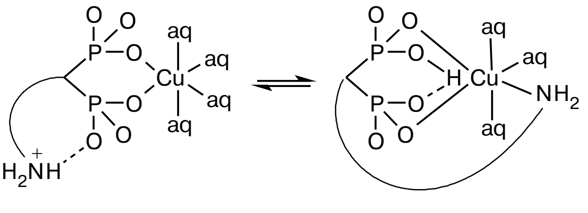
The characteristic spectral feature of the copper complexes with ligands **1** and **3** is the retention of splitting of the $\nu_e(PO_3)$ band in the IR spectra of the CuHL$^-$ complexes (see Table 3). Throughout the existence region of the CuL^{2-}—CuHL$^-$ complexes, the relative intensities of the components of the doublet depend on pH of the solution. Thus, the intensity of the high-frequency component (1100 cm^{-1}) increases as the acidity of the solution increases and the spectrum of a solution of the CuHL$^-$ complex near the pH boundary of its existence region becomes similar to the spectra of the CuHL$^-$ complexes with acids **4** and **2** in which the labile polyhedron is formed only by O atoms. The retention of the coordination of the N atom in the CuHL$^-$ complex should lead to the formation of the PO$_3$H$^-$ group, which is characterized by absorption bands at ~1160 ($\nu_{as}(PO_2)$), ~1060 ($\nu_s(PO_2)$), and 920 cm^{-1} (ν(P—OH)).[5] Actually, the IR spectra of the CuHL$^-$ complexes with ligands **1** and **3** (see Table 3) have a shoulder at ~1160 cm^{-1}, but its intensity is very low, which is inconsistent with the almost unchanged Cu←N charge-transfer band. Apparently, this inconsistency is attributable to O...HO hydrogen bonding within the diphosphonate unit, *i.e.*, to proton withdraw from the "own" O atom due to which the phosphonate groups become spectrally indistinguishable. Unlike the spectra of the complexes with ligand **4**, the spectra of the CuL^{2-} and CuHL$^-$ complexes with ligands **1** and **3** are complicated (splitting or broadening of bands is observed; for example, a shoulder at 930 cm^{-1} in the spectrum of CuL^{2-}) due, apparently, to the formation of the intramolecular O...HO and NH...O hydrogen bonds.

Table 3. Absorption bands in the IR spectra (ν) and in the spectra in the visible region (λ) of the CuL^{2-} and CuHL$^-$ complexes with ligands **1—4**

Ligand	ν/cm^{-1}				λ/nm, d—d-band
	$\nu''_s(PO_3)_2$	$\nu'_s(PO_3)_2$	$\nu_e(PO_3)$	$\nu_{as}(PO_3H)$	
1	930 w.sh 950 m	1000 m 1030 sh	1060 s 1115 sh		720
2	960 m	1000 w	1050 sh 1100 s 1130 sh		730
3	960 m	1010 sh	1050 s* 1110 s*		720
4	960 m	1010 sh	1045 s* 1110 s*		720
	Complex CuHL$^-$				
1	930 w.sh 960 m	1020 sh	1065 m 1115 s	1160 sh	750
2	960 m	1000 sh	1060 sh 1100 s		750
3	960 m	1000 sh	1050 m 1110 s	1160 sh	750
4	970 m	990 w 1030 sh	1050 sh 1100 s.br		780

* The doublet, the maxima with similar intensities.

The results obtained for ligands **1** and **3** are attributable to the fact that the solutions contain two tautomers of the $CuHL^-$ complex existing in the equilibrium. One of these tautomers (**D**) is analogous to the complex with ligand **4** (**C**), *i.e.*, it contains the protonated N atom and the coordinated phosphonate groups. Another tautomer (**E**) is characterized by the protonated phosphonate groups and by the retention of the coordination of the N atom. The equilibrium is shifted to tautomer **D** as the acidity of the solution increases.



D **E**

The existence of the tautomeric equilibrium is confirmed by a change in the position of the d—d-transition band in the region of formation of the CuL^{2-} and $CuHL^-$ complexes with ligands **1** and **3** (see Table 3). Thus, the maximum of the band belonging to the CuL^{2-} complex (4 equiv. of KOH in solution) is observed at 720 nm, which corresponds to the $[CuNOO'(H_2O)_3]$ chromophore. The spectrum of the solution containing 3 equiv. of KOH shows the maximum at ~750 nm, and this maximum is gradually shifted to 780 nm, which corresponds to the $[CuOO'(H_2O)_4]$ chromophore, as the acidity of the solution increases. The intermediate position of the maximum is attributable to superposition of the bands of these chromophores.

In spite of the fact that the N atom in the CuL^{2-} complex with ligand **2** is not involved in coordination, the position of the d—d-transition band in the spectrum of this complex is similar to the positions of the d—d band in the spectra of the CuL^{2-} complexes with other ligands. Apparently, the differences between the Cu←N and Cu←O bond lengths in the coordination polyhedra are small. The spectrum of the $CuHL^-$ complex with acid **2** has the maximum of the d—d band at ~750—760 nm (see Table 3).

Therefore, ligands **1** and **3** containing the unsubstituted amino group are coordinated through the N atom not only in the CuL^{2-} complex, but also in the $CuHL^-$ complex, whereas ligand **2** containing the substituted amino group and the short alkylidene chain is not coordinated through the N atom even in the CuL^{2-} complex.

Apparently, the $CuHL^-$ complexes characterized by the involvement of the N atom in coordination, which were found in the case of acids **1** and **3**, occurred due to formation of intramolecular hydrogen bonds between the coordinated NH_2 and PO_3 groups (chelate H,M-rings[3]), which stabilize the $[CuNOO'(H_2O)_3]$ coordination polyhedron. An analogous difference between acids **1** and **3**, on the one hand, and the acids containing the dimethylamino group, on the other hand, was observed in the studies of their dissociation. Thus, two species, *viz.*, species protonated at the N atom and at the O atom of the phosphonate group, existing in the equilibrium were detected in the solution at the stage of formation of the HL^{3-} ion.[5]

The fact that the N atom in the CuL^{2-} complex with ligand **2** is not involved in coordination may be associated with steric hindrances.[6] Hence, we performed theoretical conformational analysis of ligands **1—4**. Calculations by the MM method demonstrated that the strain energies (ΔE) in the case of the complex-forming conformation corresponding to the $[CuNOO'(H_2O)_3]$ coordination polyhedron have close values for ligands **1**, **2**, **3**, and **4** (6.7, 10.4, 6.3, and 9.2 kcal mol^{-1}, respectively). Although ligand **2** in this series is characterized by the largest value ΔE (10.4 kcal mol^{-1}), the difference between these values for ligands **2** and **4** (1.2 kcal mol^{-1}) gives no grounds to explain the fact that the N atom is not involved in coordination by steric reasons. Therefore, the difference in the spatial structure of AGDP is not, apparently, the only factor determining the possibility of the involvement of the N atom in coordination.

Stability and structures of the complexes. The relationship between the stability of the complexes and the structure of the ligand was analyzed using the complexes of AGDP with Ca^{2+} and Cu^{2+} as an example. In Table 4, the stability constants of the complexes with

Table 4. Logarithms of the stability constants (log*K*) of the ML^{2-} and MHL^- complexes of the Ca^{2+} and Cu^{2+} cations with ligands **1—5** (25 °C; μ = 0.1 (0.1 *M* KCl)) based on the published data[3,10]

Acid	log*K*[a]		Δlog*K*[b]
	ML^{2-}	MHL^-	
	M = Ca^{2+}		
1	undis.[c]	undis.[c]	—
2	5.7[d]	5.6[d]	0.1[d]
3	5.8	5.7	0.1
4	5.7	5.6	0.1
6	6.1	6.0	0.1
5	6.0	3.5	2.5
	M = Cu^{2+}		
1	14.6[b]	(9.6)[c]	5.0[c]
2	12.7[b]	11.4[c]	1.3[c]
3	13.6	(10.9)	2.7
4	13.0	10.8	2.2
6	12.9	11.3	1.6
5	12.5	6.3	6.2

[a] The values of log*K* for ligands **1**, **2**, and **4—6** [3,10] are rounded off to the first decimal place; log*K* given in parentheses are effective values and describe the equilibrium for a mixture of the tautomeric forms of the $CuHL^-$ complexes.

[b] $\Delta\log K = \log K_{ML} - \log_{MHL}$, $K_{MHL} = [MHL]/([M][HL])$.

[c] Undissolved.

[d] Calculated with the inclusion of the empirical correction for $\log K_{MHL}$, which was experimentally determined at a different ionic strength.

ligands **1—4** and with the $H_2N(CH_2)_3C(OH)(PO_3H_2)_2$ ligand (**6**) (in the Cu^{2+} complexes with **6**, the N atom is noncoordinated)[9] are compared with the data for *gem*-diphosphonate **5**, which does not contain the N atom. In all Ca^{2+} complexes with AGDP, the metal cation is coordinated only by the phosphonate groups and, consequently, the coordination is analogous to that of ligand **5** in the CaL^{2-} complex (structure **A**). If this coordination is realized, the inductive effect of the R_2N and R_2HN^+ substituents on the stability of the complex is insignificant. Thus, the stability constants of the CaL^{2-} and $CaHL^-$ complexes with ligands **1—4** and **6** ($\log K = 5.6—6.1$) are close to that of the CaL^{2-} complex with *gem*-diphosphonate **5** ($\log K = 6.0$). The stability constants approximate the latter one as the alkylidene chain becomes longer. The CuL^{2-} complexes with ligands **2** and **6**[9] are structurally similar and show the same regularities. However, the inductive effect of the R_2HN^+ substituent in the $CuHL^-$ complexes is somewhat more substantial than that in the $CaHL^-$ complexes, which is attributable to a substantial degree of covalence of the Cu←O bond compared to the purely ionic Ca←O bond ($\log K_{CuHL}$ are 11.4 and 11.3 for ligands **2** and **6**, respectively; these values are lower than $\log K_{CuL} = 12.5$ for ligand **5**). Noteworthy is also stabilization of the complexes through the intramolecular N—H...O—P hydrogen bond and the N^+—H...O—P bond in the coordinated ligand. This effect depends on the length of the alkylidene chain. It is more pronounced in copper complexes than in calcium complexes and, what is more important, is manifested regardless of the involvement of the N atom in coordination (see, for example, $\log K$ for the CaL^{2-}, $CaHL^-$, and CuL^{2-} complexes with ligands **3** and **4**).

If the N atom is involved in chelation of the cation in the CuL^{2-} complexes with AGDP **1**, **3**, or **4** (structure **B**), the stability of the complexes increases compared to the complexes in which only phosphonate groups are involved in coordination. As expected, the degree of strengthening depends on the length of the alkylidene chain. Thus, the stability of the complex increases by approximately two orders of magnitude (see $\log K_{CuL}$ for ligands **1** and **5**) upon closure of the additional six-membered N-chelate ring, whereas the closure of the less favorable seven-membered ring leads to an increase in stability by only 0.5—1 orders of magnitude (see $\log K_{CuL}$ for ligands **3**, **4**, and **5**). It should be noted that an increase in stability of the complex due to the closure of the seven-membered ring is comparable with an increase in stability due to the formation of intramolecular hydrogen bonds (0.6 log. un.).

A comparison of the stability constants of the CuL^{2-} and $CuHL^-$ complexes demonstrated that their difference ($\Delta\log K$, see Table 4) cannot be used as a reliable criterion for the involvement of the N atom in coordination in nonprotonated complexes as sometimes suggested.[6] For example, the stability constants corresponding to the $CuHL^-$ complexes with acids **1** and **3** are effective values and do not characterize the complexes with particular structures, because different tautomeric forms of this complex are present in solution.

Therefore, the stability of the complexes with AGDP **1—4** and **6** in the absence of coordination of the cation by the N atom is virtually independent of the structure of the aminoalkylidene fragment, *viz.*, both the inductive effect of the substituent, which results in a decrease in stability of the complex, and the influence of the formation of intramolecular hydrogen bonds in the coordinated ligand, which stabilize the complex, are small. If the N atom is involved in coordination, the enhancement of stability of the complexes depends primarily on the length of the alkylidene chain of AGDP, which determines the size of the additional chelate ring. The stability of the complex is affected to a lesser degree by the ability of the substituent at the N atom to form hydrogen bonds stabilizing the complex.

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