Amino-substituted *gem*-diphosphonic acids: dissociation mechanism and the structure of species in aqueous solutions

A. G. Matveeva, M. P. Pasechnik, P. V. Petrovskii, S. V. Matveev, and S. A. Pisareva*

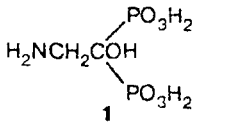
A. N. Nesmeyanov Institute of Organoelement Compounds, Russian Academy of Sciences, 28 ul. Vavilova, 117813 Moscow, Russian Federation.
Fax: +7 (095) 135 5085. E-mail: smatveev@ineos.ac.ru

The mechanism of dissociation of amino-substituted *gem*-diphosphonic acids $R_2N(CH_2)_nCR'(PO_3H_2)_2$ with different lengths of the alkylidene chain and different substituents at the N atom was studied by vibrational (IR, Raman) and NMR (^1H, ^{14}N, ^{31}P) spectroscopy using data of conformational analysis (molecular mechanical) data. The important role of intramolecular H-bonds and cyclic solvates for the stabilization of various conformations and tautomeric forms of ions was demonstrated. The spectral data that allow one to consider the *gem*-diphosphonate group as a single acidic center were found.

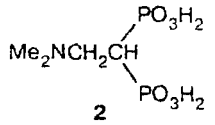
Key words: ω-aminoalkylidenediphosphonic acids, *gem*-diphosphonates, dissociation mechanism, IR, Raman, and ^1H, ^{14}N, and ^{31}P NMR spectra, conformational analysis, hydrogen bonds.

The interest in amino-substituted *gem*-diphosphonic acids (AGDP), $R_2N(CH_2)_nCR'(PO_3H_2)_2$, containing a physiologically stable P—C bond, which arose about 20 years ago, has initiated synthesis of numerous AGDP with various structures of the aminoalkylidene fragment. The recent screening tests demonstrated that a number of compounds of this class show unique therapeutic activity in treating bone tissue diseases.[1] Compounds with herbicide and fungicide properties have also been found among AGDP.[2] An appropriate step in elucidating the "structure—activity" correlations is the examination of the natures of species in solution aimed at understanding the "structure—nature of species in solution—activity" relationship. Therefore, the possible difference between the structures of species (ions and molecules) in the series of closely related compounds becomes a significant point.

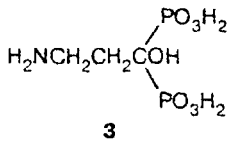
In this work, we study the order of dissociation and the nature of dissolved species in aqueous solutions of AGDP **1**—**4**, differing in the length of the alkylidene chain and in substituents at the N atom.



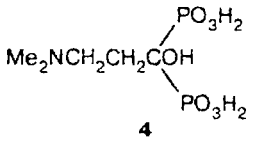
1



2



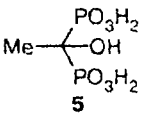
3



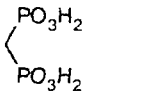
4

Compounds **3** and **4** are known[3,4] to exhibit biomedical activity; no data on the biological activity of compounds **1** and **2** are available. However, according to the potentiometric titration data, the acid—base and chelating properties of these complexones are similar.[5]

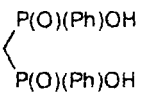
Model compounds **5**—**14**, whose structures are close to the structures of the compounds under study and whose dissociation mechanism is known, were used in the study.



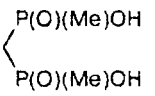
5



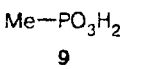
6



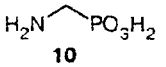
7



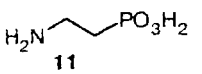
8



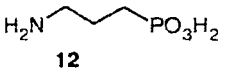
9



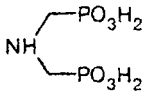
10



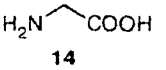
11



12



13



14

Experimental

Objects of investigation. The methods for 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 were described previously.[5—7] The melting points, neutralization equivalents, and the data of elemental analysis and NMR and IR spectroscopy correspond to published data.

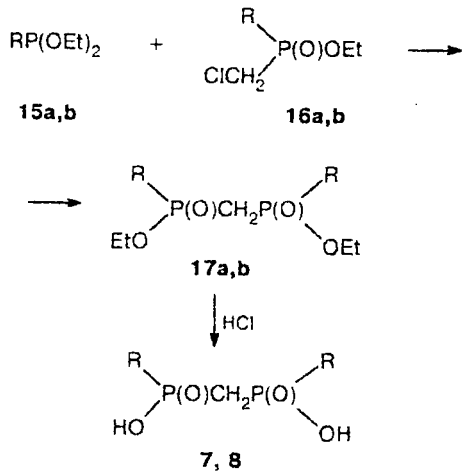
Model compounds. 1-Hydroxyethylidenediphosphonic acid (HEDP) (**5**) and methylenediphosphonic acid (**6**) (commercial

Translated from *Izvestiya Akademii Nauk. Seriya Khimicheskaya*, No. 6, pp. 1051—1064, June, 2000.

preparations) were purified by recrystallization. Characteristics of the samples correspond to the published data.

Model bisphosphinic acids **7** and **8** were synthesized according to Scheme 1.

Scheme 1



R = Ph (**7**,**15a**—**17a**); Me (**8**, **15b**—**17b**)

Bis(ethoxyphenylphosphoryl)methane (17a) was prepared[8] by the reaction of ester **16a** (7.2 g, 0.032 *M*), synthesized by a known procedure,[9] with ester **15a** (7.2 g, 0.039 *M*), prepared by a known procedure.[10] This gave 6.3 g (54.5%) of ester **17a**, b.p. 236 °C (1 Torr), n_D^{20} 1.557. Found (%): C, 58.00; H, 6.30; P, 17.54. $C_{17}H_{22}P_2O_4$. Calculated (%): C, 57.95; H, 6.25; P, 17.61.

Bis(ethoxymethylphosphoryl)methane (17b) was synthesized similarly to **17a** from ester **16b** (11.5 g, 0.07 *M*), synthesized by a known procedure,[11] and ester **15b** (12.5 g, 0.08 *M*), synthesized by a procedure reported previously.[10] This gave 7.2 g (42%) of compound **17b**: b.p. 177 °C (1 Torr), n_D^{20} 1.467. Found (%): C, 36.99; H, 7.96; P, 26.87. $C_7H_{18}O_4P_2$. Calculated (%): C, 36.84; H, 7.89; P, 27.19.

Bis(hydroxyphenylphosphoryl)methane (7). A mixture of ester **17a** (4.6 g) and 20 mL of conc. HCl was refluxed for 4.5 h. The precipitate formed overnight was recrystallized from ethanol to give 3.4 g (85%) of colorless crystals, m.p. 233—234 °C. Found (%): C, 52.74; H, 4.76; P, 21.10. $C_{13}H_{14}P_2O_4$. Calculated (%): C, 52.70; H, 4.73; P, 20.94. Neutralization equivalent (Found/calculated) 148.0/148.0, $pK_1 < 1$, $pK_2 = 3.71 \pm 0.02$.

Bis(hydroxymethylphosphoryl)methane (8) was prepared similarly to **7** by refluxing **17b** (4.4 g) with 15 mL of conc. HCl. This gave 3.1 g (95%) of acid **8**: m.p. 139—140 °C (from ethanol). Found (%): C, 20.89; H, 5.84; P, 36.00. $C_3H_{10}O_4P_2$. Calculated (%): C, 20.93; H, 5.81; P, 36.04. Neutralization equivalent (Found/calculated) 86.0/86.0, $pK_1 < 1$, $pK_2 = 3.61 \pm 0.02$.

Reagents and materials. Doubly distilled water and D_2O (content of D 99.8%, specific electrical conductivity $2 \cdot 10^{-6}$ Ω^{-1} cm^{-1}, TU 95.7046-73) and "pure" grade methyl alcohol, purified by the standard procedure, were used as solvents.

"Chemically pure" grade KOH and "chemically pure" grade potassium metal (glass tubes with 100-mg samples, TU 48-03-53-75), and a solution of DCl in D_2O (concentration 32.4%, content of D 99.6 %, TU 95.7046-73) were used.

Carbonate-free aqueous solutions of KOH were prepared by dilution of a saturated solution of KOH; solutions of KOD were prepared by dissolution of potassium metal in D_2O. The concentration was determined by indicator titration using adipic acid and potassium hydrogen phthalate. The alkali concentration normally used in spectral studies was 10—11 mol L^{-1}; that used in potentiometric titration was 0.3 mol L^{-1}. Solutions of the acids to be studied were prepared by the weight method.

Preparation of solutions for spectral studies. A calculated amount of KOH or KOD in the appropriate solvent was added in portions to a solution of an acid with a required concentration using a microsyringe or micropipette, or a calculated amount of a solution of HCl or DCl in ordinary or heavy water was added to a neutralized solution of a complexone. The pH values of solutions were checked by potentiometry or using indicator paper sets (Aldrich, with sensitivity of 0.2 pH units).

When using KOH (KOD) as the titrating agent, the possible complex formation with the potassium cation or hydrolysis of the resulting salts were not taken into account. The validity of this assumption was confirmed in relation to AGDP **4**. It is known that acid **4** either forms[7b] very weak ($\log K_{KL} = 0.78$) complexes with potassium cations or does not form them at all[7a]; the composition of solutions of this acid after the addition of 1, 2, 3, or 4 equivalents of KOH corresponds to the predominant amount of one particular ionic form of the acid.[7c] Since the acid-base and complexing properties of AGDP **1**—**4** are close,[5] this assumption must be valid for all the studied compounds.

IR spectra of solutions of the compounds in H_2O and D_2O with concentrations of 0.2—0.5 mol L^{-1} were measured on a UR-20 spectrophotometer using KRS-5, BaF_2, and CaF_2 0.025—0.050-mm-thick cells.

Raman spectra were recorded on a Coderg PH-0 instrument with a He—Ne laser.

^{31}P NMR spectra were recorded on a Bruker WR-200 SY instrument operating at 81.01 MHz using 85% H_3PO_4 as the external standard at 303 K. The concentration of the substance studied was 0.03, 0.1, and 0.3 mol L^{-1} in D_2O. Standard tubes 10 mm in diameter were used; the external standard was placed in a coaxial capillary tube. The error of measurements of δ values was ±0.1 ppm.

^{14}N NMR spectra were recorded on a Bruker AMX-400 spectrometer operating at 28.90 MHz at 298 and 383 K using $MeNO_2$ as the external standard. Standard tubes 5 mm in diameter were used; the external standard was placed in a coaxial capillary tube. The concentration of solutions of acids in D_2O was 0.5 or 0.15 mol L^{-1}.

^1H NMR spectra were recorded on a Bruker AMX-400 instrument operating at 400.13 MHz at 298 K using HMDS as the external standard. The concentration of solutions of the acids in D_2O was 0.03 mol L^{-1}. Standard tubes 5 mm in diameter were used; the external standard was placed in a coaxial capillary. The error of measurements of δ values was ±0.005 ppm.

The downfield shifts of signals were taken to be positive for all isotopes. The ^{31}P and ^{14}N NMR spectra were recorded with noise proton decoupling for the corresponding nuclei.

Potentiometric titration was carried out on an OP-208 pH-meter (Hungary) with an accuracy of ±0.01 pH units in water at 298.0±0.1 K in an argon atmosphere. The electrode pair was calibrated against standard buffer solutions with pH 1.68, 4.01, and 9.18.

The required ionic strength was produced using "chemically pure" grade KNO_3 additionally purified by recrystallization.

The concentrations of acids **7** and **8** were 0.005 mol L^{-1}, ionic strength μ = 0.1 (0.1 mol L^{-1} KNO_3). The activity coefficients for these conditions $\gamma_{H^+} = \gamma_{OH^-} = 0.7719$.[12] The

volume of the titrated solution was 25 mL; for titrant (KOH) concentration of 0.3 mol L^{-1}, the titration curve had 30—40 points in the pH 2—12 range. The pK_a values of the acids were calculated by the known program.[13] The error of the determination of the constants was found as the half-sum of deviations found by shifting the experimental titration curve by the possible error of the pH-meter (±0.01 pH units); this corresponded to ±0.01 log units for pK_a.

Conformation analysis. The energy of the conformation of the molecule in the region of the global minimum was found by molecular mechanics calculations (PC Model, Serena Soft Ware, MM2 (QCPE 395) and MMP1 (QCPE 318) force fields). The conformation energy of the structure was calculated assuming the formation of H-bonds by specifying distances between the corresponding oxygen atoms (2.63 Å) or between nitrogen and oxygen atoms (2.88 Å) typical[14] of this type of bonds; otherwise the conformations of the local minima allowing the formation of H-bonds were found. The strain energy of a conformation (ΔE) was estimated as the difference between the energy of the given conformer and the conformer corresponding to the global minimum.

Results and Discussion

Complexones **1**—**4** are tetrabasic acids H_4L in aqueous solutions. The pK values for each step are of the same order for different acids[5] (Table 1). Since there are several types of centers available for proton addition in AGDP (the N atom and the O atoms of the phosphonate groups), several tautomeric forms with different combinations of protonated centers can exist at each dissociation step (except for the completely deprotonated anion L^{4-}). The degree of protonation of the PO_3 group can be determined by methods of vibrational spectroscopy. Monitoring the state of the N atom by IR spectroscopy is methodically a more difficult task. The site of proton attachment can also be detected reliably by studying the ^{14}N and ^{31}P resonance and ^{1}H resonance for the methylene and methyl groups in the complexone. Comparison of the data obtained by different methods makes it possible to identify fine distinctions in the structure of the anions, in particular, to distinguish between the protonated atom and the atom involved in a strong intramolecular H-bond.

Table 1. The pK_a values of AGDP **1**—**4** (298 K, μ = 1.0; 1.0 *M* KNO_3)[a]

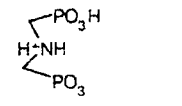
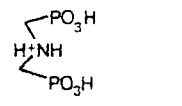
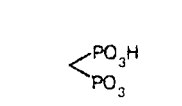
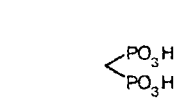
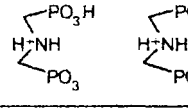
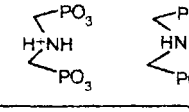
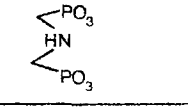
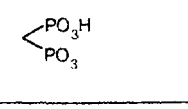
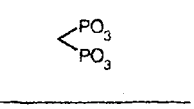
Acid	pK_1[b]	pK_2[b]	pK_3[b]	pK_4[b]
1	1.8	5.72	9.36	>12.0
2	<1.0	5.75	8.98	≥12.0
3[c]	2.55	5.85	9.90	10.8
4[c]	2.35	5.89	9.70	10.8
4	<2.0	5.44	9.28	11.7

[a] According to the data of Ref. 5 and works cited therein. [b] The stepwise dissociation constants (K_a) describe the following equilibria: $H_4L \leftrightarrow H_3L^- + H^+$, K_1; $H_3L^- \leftrightarrow H_2L_2^- + H^+$, K_2; $H_2L^{2-} \leftrightarrow HL^{3-} + H^+$, K_3; $HL^{3-} \leftrightarrow L^{4-} + H^+$, K_4. [c] μ = 0.1 (0.1 *M* KCl).

Vibrational spectroscopy

Dissociation sequence. In order to study the mechanism of dissociation, IR spectra of aqueous solutions of acids **1**—**4** at different neutralization steps and the Raman spectra of aqueous solutions of acid **4** were recorded. The results obtained for acid **4** were used as reference data in the interpretation of the IR spectra of acids **1**—**3**, which are insufficiently soluble in the region of existence of the H_4L—H_3L^- forms. The vibration frequencies of *gem*-diphosphonates **5**[15] and **6**[16] and iminodiphosphonate **13**[17] with non-geminal arrangement of the phosphonate groups were also used for comparison (Table 2).

Table 2. Stretching frequencies (ν/cm^{-1}) of the PO_3H^- and PO_3^{2-} groups in monophosphonic[a] ($-PO_3H_2$) and some model diphosphonic (**5**, **6**, **13**) acids

Vibration	$-PO_3H^a$				
		Acid **13**[17]		**6**[b]	**5**[15]	**6**[b]	**5**[15]
$\nu_{as}(PO_2)$	1150	1180	1190	*1170*, 1150	1155	*1190*, 1170	1170
$\nu_s(PO_2)$	1060	1090	1080	1070	1050	1060	1060
ν(P—OH)	920	930	920	905	895	920, *900*	895
	$-PO_3^{2-}$						
$\nu_e(PO_3)$	1060	1100	1100	1080	1080, *1105*	1075, *1095*	1080	1080
$\nu'_s((PO_3)_2)$					*1028*	—	*998*	*990*
$\nu_s(PO_3)$	950	980	980	970	975	975		
$\nu''_s((PO_3)_2)$							945	945

Note. Frequencies specific to *gem*-phosphonates are marked by an italic typeface.
[a] Frequencies typical of monophosphonic acids and their salts are given (see, for, example, Ref. 18).
[b] IR and Raman spectra recorded in this work and taken from the literature.[16]

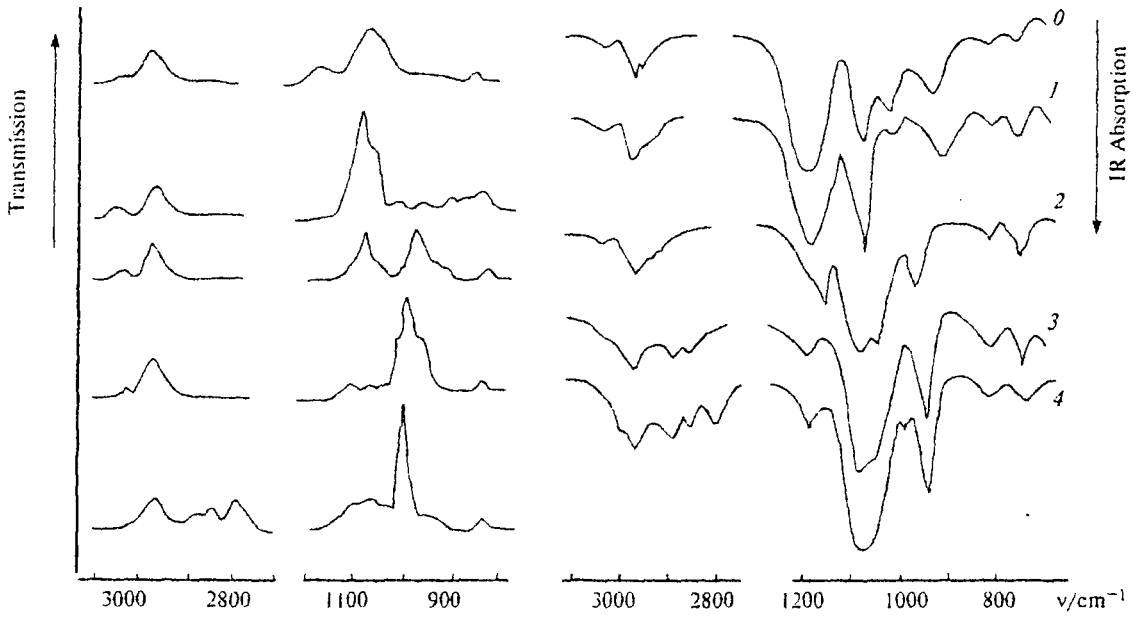
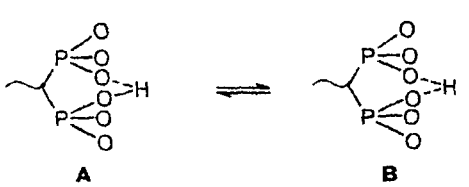


Fig. 1. Raman and IR spectra of solutions of acid **4** at different neutralization steps. Raman spectra were recorded in H_2O, $C = 0.5$ *M*. IR spectra were recorded in D_2O or in H_2O, $C = 0.5$ *M*. The numbers of spectra correspond to the numbers of equivalents of KOH.

The vibrations of the PO_3 group in monophosphonic acids and their anions are characteristic and obey the local group symmetry (see Table 2). Similar frequencies were observed upon dissociation of polyphosphonic acids with non-geminal phosphonic groups.[18] In the case of *gem*-diphosphonates, the attachment of two PO_3 groups to the same C atom results in the coupling of these vibrations. Therefore, in the spectra of the L^{4-} anions derived from acids **5** and **6**, the band for the symmetrical $\nu_s(PO_3)$ mode is split into bands for synphase (~1000 cm^{-1}) and antiphase (~950 cm^{-1}) vibrations; the synphase vibration of the free anion gives an intense polarized line in the Raman spectrum and is nearly forbidden in the IR spectrum. An increase in the intensity of this IR band is indicative of a change in the symmetry of the mutual arrangement of the phosphonate groups and/or of the dipole moment.

Band splitting ("additional" frequencies are marked by italics in Table 2) is also observed in the spectra of the HL^{3-} anions of *gem*-diphosphonic acids **5** and **6**, in which the proton is bound predominantly to one phosphonate group (the presence of bands due to the PO_3H^- group). In this case, band splitting can be explained by assuming the formation of an H-bond in anions with different proton localization and the existence of the following equilibrium shifted to the left:



A **B**

The formation of type **B** H-bonds has been assumed in interpretation of the abnormally high fourth dissociation constants in *gem*-diphosphonic acids.[19]

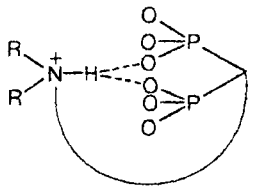
The band splitting in the case of the $H_2L_2^{2-}$ anion (see Table 2) can be due either to the formation of an H-bond or to the coupling of vibrations of the two equivalent PO_3H^- groups.

The IR and Raman spectra of acid **4** and its anions in the region of stretching PO and CH modes are shown in Fig. 1. The change in the bands due to the CH_3 and CH_2 vibrations provides information on the state of the N atom; its protonation results in higher vibration frequencies of the CH_3 and CH_2 groups attached to it.[20] In the case of acid **4**, the Raman lines at 3030 and 2800 cm^{-1} were the most informative. Their analogs can also be observed in the IR spectra of solutions of the acids in D_2O. The higher-frequency band is typical of Me groups linked to a positively charged ammonium nitrogen atom.[21a] It is observed in the spectra of acid H_4L and the H_3L^-, H_2L^{2-}, and HL^{3-} anions and vanishes upon elimination of the last proton. This points to a zwitter ion structure of acid **4**, which liberates the betaine proton in the last dissociation step. In the spectra of the completely deprotonated L^{4-} anion, a band at 2800 cm^{-1} appears, typical of CH_3 groups linked to a tricoordinated nitrogen atom.[21b,c] Thus, the appearance of this Raman line (as well as the IR band) on passing from the L^{4-} anion to HL^{3-} points to the protonation of the N atom. Other vibration frequencies of the CH_3 and CH_2 groups (in the 2800—3000 cm^{-1} range) change gradually following the transition $H_2L^{2-} \rightarrow HL^{3-} \rightarrow L^{4-}$, which can be explained by partial "pulling off" of the betaine proton from the N atom in

the HL^{3-} anion due to the formation of an H-bond with the phosphonate groups.

The region of PO vibrations in the spectra of the L^{4-} anion of acid **4** exhibits bands typical of completely deprotonated *gem*-diphosphonates. The only intense polarized line in the Raman spectrum (998 cm^{-1}) corresponds to a synphase symmetrical mode, $\nu'_s(PO_3)$; its analog (a weak band) is displayed in the IR spectrum, in which the intense bands at 950 and 1090 cm^{-1} are due to the symmetrical antiphase $\nu''_s(PO_3)$ and degenerate $\nu_e(PO_3)$ modes.

The attachment of a proton to the N atom is accompanied by displacement of the maximum of the synphase symmetrical mode to 982 cm^{-1} and by splitting of the band corresponding to the degenerate vibration, giving rise to a high-frequency component. An increase in the frequency of the degenerate mode on passing from the L^{4-} anion to HL^{3-} is observed for acid **13** (see Table 2); it has been interpreted[17] as being due to the protonation of the N atom. These changes can be accounted for by the formation of an H-bond between the O atoms of the phosphonate groups and the betaine proton: apparently, this is a bifurcate bond because the spectra comply with the vibrations of equivalent PO_3^{2-} groups (structure **C**).



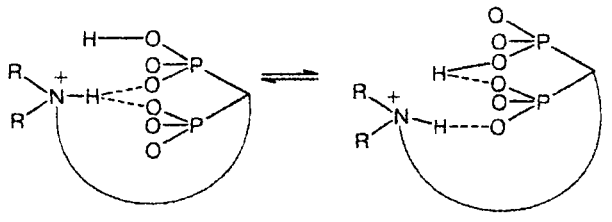
C

R = Me

Thus, the addition of the first proton does not change the spectral pattern in the region of PO vibrations, which proves indirectly that the proton belongs to the N atom in the HL^{3-} anion of acid **4**.

The second proton adds to one of the phosphonate groups, as indicated by the presence of two polarized lines at 1070 and 965 cm^{-1} in the Raman spectrum of the H_2L^{2-} anion, which belong to the symmetrical $\nu_s(PO_2)$ and $\nu_s(PO_3)$ modes of the PO_3H^- and PO_3^{2-} groups, respectively. In the IR spectrum, the PO_3H^- group is responsible for bands at 1160 cm^{-1} ($\nu_{as}(PO_2)$) and 1060 cm^{-1} ($\nu_s(PO_2)$). The ν(P—OH) absorption band is absent from the expected region (920 cm^{-1}) and all the observed bands are either broadened or split. This may be due to the existence of several forms stabilized by different competing H-bonds (Scheme 2).

Scheme 2



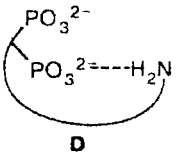
R = Me

The spectra of the H_3L^- anion exhibit bands corresponding to vibrations of the PO_3H^- groups at 1190 cm^{-1} (IR), $\nu_{as}(PO_2)$; 1070 cm^{-1} (IR, Raman), $\nu_s(PO_2)$; and 918 cm^{-1} (IR), ν(P—OH); the shoulder observed at the Raman line (at 1050 cm^{-1}), similar to the splitting in the spectrum of compound **5**, can be due to the formation of H-bonds.

The spectra of the zwitter ion H_4L are superpositions of bands typical of the PO_3H_2 and PO_3H^- groups.

Thus, acid **4** has a zwitter ion structure and the betaine proton is the last to split off. The results of the study of acid **4** were invoked in interpreting the IR spectra of AGDP **1**—**3**.

The absorption bands of the L^{4-} anions derived from AGDP **1**—**3** (Table 3) fully conform to the vibrations of geminal PO_3^{2-} groups. However, the intensities of the band for the synphase symmetrical mode are substantially different. In the case of acids **1** and **2** with a short alkylidene chain, this mode is not manifested at all in the IR spectrum; in the spectrum of acid **4**, it is weak, while in the spectrum of acid **3**, it has a substantial intensity. This indicates that in the anion derived from acid **3**, the symmetry of the mutual arrangement of the phosphonate groups is violated. Apparently, the combination of the unsubstituted amino group with the long chain is favorable for the formation of an H-bond between the protons of the NH_2 group and one of the PO_3^{2-} groups, which accounts for the violation of symmetry (structure **D**).



D

The spectra of the HL^{3-}anions reveal the difference between the order of protonation of the anions of acids with unsubstituted and substituted amino groups. In the case of unsubstituted acids **1** and **3**, weak bands due to the protonated phosphonate group appear in the spectra of HL^{3-} (they are in a boldface font in Table 3). Thus, at this dissociation step, solutions of acids **1** and **3** contain two equilibrated forms of the HL^{3-} anion; in one of them, the protonated site is the N atom and in the other, it is the phosphonate group.

Scheme 3

For simplicity, Scheme 3 does not show the H-bonds.

It follows from a comparison of band intensities that the equilibrium is shifted toward the betaine form for both acids (for acid **1**, to a greater extent).

The spectrum of the HL^{3-} anion derived from acid **2** does not point to protonation of the phosphonate groups; hence, as in the case of acid **4**, the only proton is attached to the N atom.

The dependence of the site of single protonation on the substituents at nitrogen is not apparently due to the

Table 3. Variation of the PO vibration frequencies during dissociation of acids **1**—**4** (solutions in H_2O, D_2O, C = 0.3—0.5 *M*)

Anion	Acid				Assignment	Group
	1	**2**	**3**	**4**		
L^{4-}	1090 s.br	1100 s.br	1090 s.br	1090 s.br	$\nu_e(PO_3)$	PO_3^{2-}
	—	—	1000 m	998 w	$\nu'_s(PO_3)$	
	950 m	950 m	950 m	950 m	$\nu''_s(PO_3)$	
HL^{3-}	**1160 sh**	—	**1160 sh**	—	$\nu_{as}(PO_2)$	PO_3H^-
	1080 sh	—	**1060 sh**	—	$\nu_s(PO_2)$	
	1105 s.br	1100 s.br	1100 s.br	1100 s.br	$\nu_e(PO_3)$	PO_3^{2-}
	990 w	990 w	1000 w	982 w	$\nu'_s(PO_3)$	
	960 m	960 m	960 m	950 m	$\nu''_s(PO_3)$	
H_2L^{2-}	1170 m	1160 m	1160 m	1160 m	$\nu_{as}(PO_2)$	PO_3H^-
	1060 sh	1060 sh	1060 sh	1060 sh	$\nu_s(PO_2)$	
	1090 s	1100 s	1090 s	1100 s	$\nu_e(PO_3)$	PO_3^{2-}
	1020 sh	—	*1010*,	*990* w.sh		
	950 w	960 w	950 w	965 m	$\nu_s(PO_3)$	

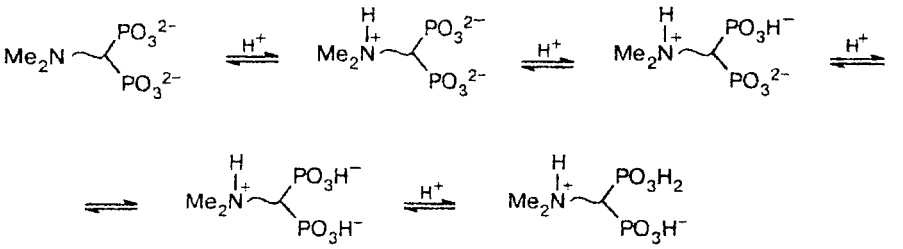
Note. Frequencies of protonated phosphonate groups are marked by a bold typeface; those specific to *gem*-phosphonates are marked by italics (see the text).

lower basicity of the NH_2 group compared to the NMe_2 group but rather to the formation of an $NH_2...O_3P$ hydrogen bond (structure **D**) in the L^{4-} anion, promoting the transfer of the proton from the amino group to the phosphonate group simultaneously with nitrogen protonation.

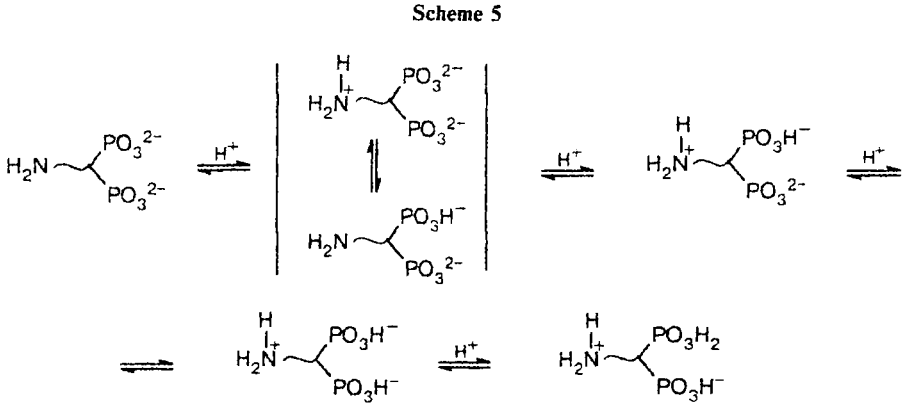
In addition to the absorption bands corresponding to the PO_3^{2-} and PO_3H^- groups, the spectra of the H_2L^{2-} anions of acids **1**—**3** also contain "intermediate" bands (marked by an italic typeface in Table 3), which cannot be assigned to canonical vibrations of the PO_3^{2-} and PO_3H^- groups and may result from "chelation" of the proton by two phosphonate groups (structure **B**).

Thus, the sequence of dissociation of acids **1**—**4** has been established based on vibrational spectroscopy. Each acid has a zwitter ion structure in aqueous solutions. In acids with substituted amino groups (**2** and **4**), the betaine proton is the last to split off (Scheme 4), whereas in acids with unsubstituted amino groups (**1** and **3**) (Scheme 5), an equlibrium between two species, one protonated at nitrogen and the other at oxygen, is

Scheme 4



Scheme 5



established when the HL^{3-} anion has been formed; the equilibrium is shifted toward the betaine form.

In both cases, equilibria between the anion forms with different H-bonds are possible at each dissociation step; this accounts for the complicated spectral pattern observed.

^{31}P NMR spectroscopy

The gem-diphosphonate acid center. The phosphorus chemical shift is fairly sensitive to the degree of protonation of the phosphonate group. The abstraction of a proton from a phosphonate group is normally manifested as a decrease in the chemical shift (an upfield shift). For example, the changes in the chemical shift (δ_P) for the first and second dissociation steps of acid **9** and ethylphosphonic acid are 7.0, 3.8 ppm and 6.0, 4.0 ppm, respectively[22] (see Fig. 2). For model aminoalkylidenephosphonic acids (AAP) **10**—**12**, which exist in aqueous solutions as zwitter ions, the abstraction of a proton from a phosphonate group is also accompanied by a decrease, while the abstraction of a betaine proton from the N atom induces a sharp increase, in the phosphorus chemical shift[22] (see Fig. 2). Presumably, this increase is due to the destruction of cyclic species with closely spaced amino and phosphonate groups, in which both direct Coulomb interactions and H-bonding are possible. These features are also typical of acid **13**, which is similar to AGDP in the number of phosphonate groups but differs by a non-geminal arrangement of these groups[23] (see Fig. 2).

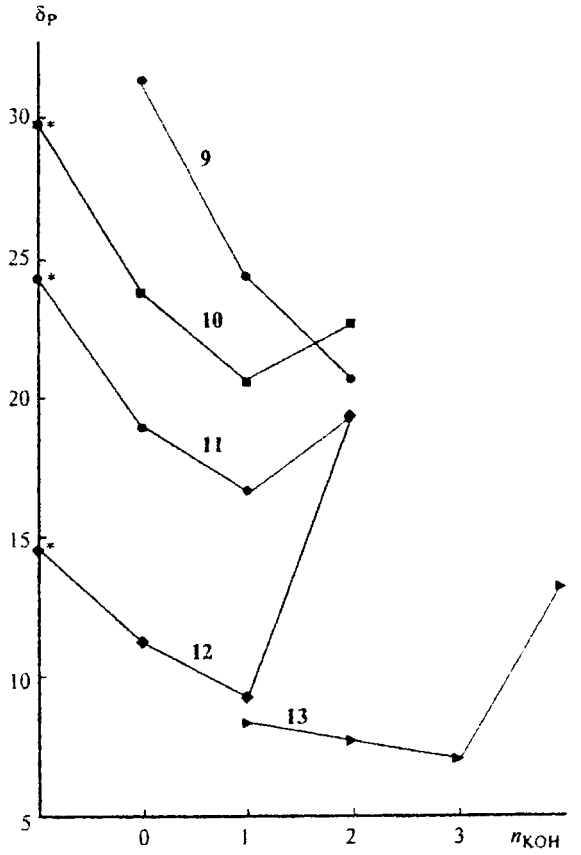


Fig. 2. Dependence of δ_P of compounds **9**—**13** on the number of neutralization equivalents (n_{KOH}) in aqueous solutions according to Refs. 22 and 23 (C = 0.5 M for **9**—**12** and 0.3 M for **13**). The asterisks refer to the acids in the cationic form H_3L^+.

Similar v-shaped plots were also obtained for diverse nitrogen-containing phosphonic and phosphinic acids,[23,24] $(H_2NCH_2)_2PO_2H$, $R_2NCHR^1PO_3H_2$, $H_2NCH(R)PO_3H_2$, $N(CH_2PO_3H_2)_3$, and $RN(CH_2PO_3H_2)_2$; this corresponds to the elimination of a betaine proton from the N atom at the last dissociation step. It should be noted that this series does not contain structures with a geminal arrangement of phosphorus atoms.

To study the mechanism of dissociation of acids **1**—**4**, the ^{31}P NMR spectra of their solutions in D_2O at different dissociation steps were recorded (Table 4). The results of measurements in 0.03, 0.1, and 0.3 M aqueous solutions were qualitatively similar; therefore, intermolecular interactions were excluded from consideration.

It was found that the ^{31}P chemical shift in the spectra of acids **1**—**4**, unlike that for model compounds **9**—**13**, virtually does not depend on the extent of neutralization (Fig. 3), *i.e.* deprotonation of acids **1**—**4** in aqueous solutions barely changes the magnetic shielding of the ^{31}P nuclei. Plots of the same type can be constructed for *gem*-diphosphonic acids **5** and **6** (Fig. 4).

Analysis of published data indicates that slight dependence of δ_P on the extent of neutralization of the complexone is peculiar to the whole class of diphosphonic acids with a geminal arrangement of phosphonic groups. Thus in the case of $R^1R^2C(PO_3H_2)_2$ (R^1R^2 = MeMe, HMe, Me(OH), HH, H(OH), ClCl), the chemical shifts of acids and di-, tri-, and tetra-tetraalkylammonium salts in 0.5 M aqueous solutions vary over a range of 1.6 ppm.[25] However, on passing from methylenediphosphonic *gem*-acid **6** to polymethylenediphosphonic acids $H_2O_3P(CH_2)_nPO_3H_2$ (n = 2—6), the expected dependence of the chemical shift on the number of neutralization equivalents can again be followed[26]: the changes in the δ_P values of solutions of acid **6** and its

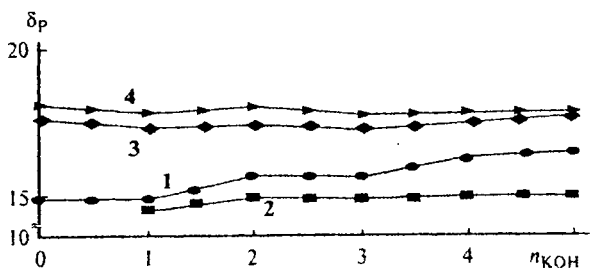


Fig. 3. Dependence of δ_P of acids **1**—**4** on the number of neutralization equivalents (n_{KOH}) in aqueous solutions (C = 0.03 and 0.1 M, see note to Table 4).

Table 4. Data of the ^{31}P NMR spectroscopy (δ_P) of aqueous solutions of acids **1**—**5**, **7**, **8** for different neutralization steps (D_2O, 85% H_3PO_4 as the external standard, 303 K, $C = 0.03$ mol L^{-1}, titration by KOH)

n_{KOH}	Acid						
	1 [a]	**2** [a]	**3**	**4**	**5** [a]	**7**	**8** [b]
0	14.9	—[c]	17.6	18.1	19.7	44.7	31.3
1	14.8	14.5	17.3	17.8	19.6	40.6	26.9
2	15.6	14.9	17.4	18.0	19.0	35.2	23.4
3	15.6	14.8	17.2	17.7	19.2		
4	16.2	14.9	17.4	17.8	18.8		
5	16.4	14.9	17.7	17.8	18.8		

Note. The accuracy of measurement of δ_P is ±0.1 ppm; n_{KOH} is the number of equivalents of KOH.

[a] The acid concentration was 0.1 mol L^{-1}.

[b] In MeOH (the acid was poorly soluble in water).

[c] Poorly soluble in water.

sodium salts (with an accuracy of measurements of ±1 ppm) amount to ~3 ppm, whereas in the case of polymethylenediphosphonic acids $H_2O_3P(CH_2)_nPO_3H_2$ ($n = 2$—6), they are 6—8 ppm.[26]

Thus, the structure of the *gem*-diphosphonate group remains roughly the same when protons are either eliminated or added; thus it can be regarded as a single unit rather than a combination of two monophosphonate groups. In our opinion, the specificity of the *gem*-diphosphonate group manifests itself not only in the HL^{3-} anion,[19,25] in which the formation of an intramolecular H-bond is assumed, but also at other pH values, including those corresponding to the L^{4-} anion. The structural invariance of a *gem*-diphosphonate unit in aqueous solutions may be due to the formation of cyclic solvates and intramolecular hydrogen bonds (IntraHB) both in the neutral molecule and in the anions. The substantial ordering of water molecules caused by the hydration of HEDP is also indicated by the data on the entropy effects in complexing reactions.[27] The hypothesis of formation of cyclic solvates was used previously in a study of aqueous solutions of dicarboxylic[28] and aminocarboxylic[29] acids.

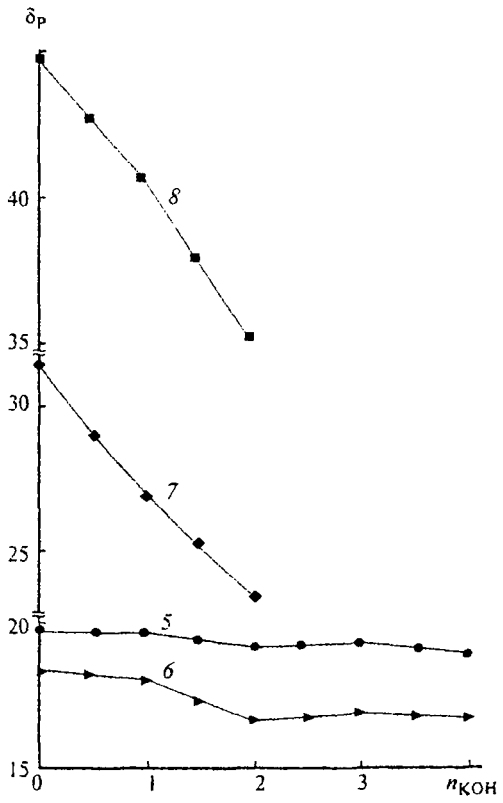


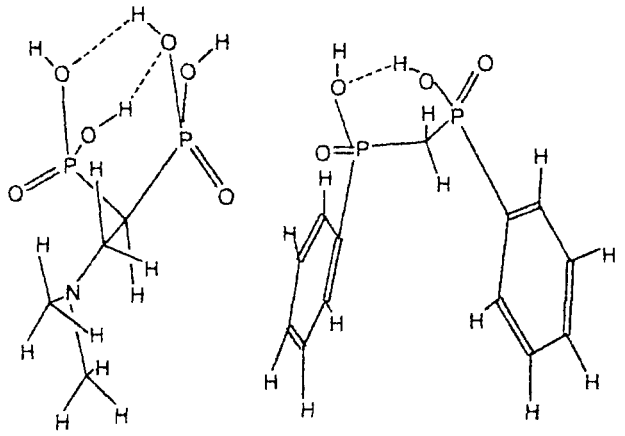
Fig. 4. Dependence of δ_P of model compounds **5**—**8** on the number of neutralization equivalents (n_{KOH}) in aqueous solutions according to this study (for acids **5**, **7**, **8**) and published data[35] (for **6**).

The replacement of an OH group in the *gem*-diphosphonate unit by an alkyl or aryl group is expected to decrease the chance of formation of an IntraHB or cyclic hydrates*; hence, the acids would exhibit a normal pattern of dependence of the phosphorus chemical shift on the extent of neutralization. To verify this assumption, *gem*-diphosphinic acids **7** and **8** were studied.

Molecular mechanics calculations showed that two H-bonds can be formed in the geminal unit of diphosphonic acids **4** and **6** and only one bond is possible in complexones **7** and **8** (see, for example, Fig. 5). The energies of conformations involving IntraHB differ from the energy of the global minimum by 2 and 7 kcal mol^{-1}, respectively.

gem-Diphosphinic acids **7** and **8** were found to display the classical type of dependence of δ_P on the number of neutralization equivalents (see Fig. 4). Thus, the formation of IntraHB is one of the factors accounting for the structural invariance of the *gem*-diphosphonate unit during acid neutralization.

* We were unable to verify experimentally the role of cyclic hydrates in the stabilization of the *gem*-diphosphonate unit due to the very low solubility of *gem*-diphosphonates **1**—**4** and their K salts in polar organic solvents. Acid **5**, HEDP, has a sufficient solubility in nonaqueous media but its K salts are also poorly soluble.



4 7

Fig. 5. Conformations of acids **4** and **7**, allowing for the formation of H bonds in the *gem*-diphosphonate unit.

Thus, it follows from the analysis of the ^{31}P NMR spectra of AGDP and a number of model compounds that the *gem*-diphosphonate group in these compounds acts as a single acid center stabilized by an IntraHB and cyclic hydrates. The structural invariance of the center during titration of the acid accounts for the low utility of the ^{31}P NMR spectra in the study of the sequence of dissociation of *gem*-diphosphonic acids.

The low sensitivity of the phosphorus chemical shift to titration of diphosphonic acids in water can serve as a spectral indication of the geminal arrangement of two phosphonic groups.

^{14}N NMR spectroscopy

Betaine structure of AGDP in solution. Cyclic conformations. Since, according to IR spectroscopy, the differences between the mechanisms of dissociation of AGDP **1**—**4** are determined by the substituents at the N atom, acids **3** and **4** containing unsubstituted and substituted amino groups were compared by ^{14}N and ^{1}H NMR spectroscopy.

The nitrogen chemical shifts in systems with saturated bonds such as alkylamines usually change upon protonation[30] by about 10 ppm (downfield shift), while those in aminocarboxylic acids change upon elimination of the betaine proton[30] by ~8 ppm. However, elimination of the betaine proton in nitrilotrimethylphosphonic acid, $N(CH_2PO_3H_2)_3$, changes the ^{14}N chemical shift by 40 ppm.[31]

The ^{14}N signals in the spectra of acids **3** and **4** are located in the expected region[30] and have different widths (Table 5). For identical concentrations, the signals in the spectra of acid **4** are normally broader than those in the spectra of acid **3**. In both cases, the signal width increases after addition of every subsequent equivalent of KOH; upon addition of 4 and 6 equiv. of KOH to acids **4** and **3**, respectively, the corresponding signal disappears due to strong broadening.

One of the main reasons for line broadening in the ^{14}N NMR spectra is quadrupole relaxation, caused by coupling of the quadrupole moment of the nucleus with the gradient of the electric field of the species. If the species is symmetrical, the electric field gradient is relatively low and the quadrupole line broadening is also insignificant. Broad (20—50 ppm) resonance lines due to the ^{14}N nuclei are displayed in the spectra of amines and nonsymmetrical ammonium salts, whereas in the spectra of the NH_4^+ and Me_4N^+ ions, these lines are narrow (1—2 ppm).[32]

The solvation and association, which distort the symmetry of the electric field of ions, and high viscosity of solutions result in line broadening due to the enhancement of quadrupole coupling.

Raising the temperature, which suppresses quadrupole relaxation, made it possible to record the signal in the spectrum of acid **3** after the addition of 6 equiv. of KOH. However, in the case of compound **4**, we were unable to record the signal from the L^{4-} anion by varying experimental conditions (see Table 5). Apparently, in the L^{4-} anion of acid **4**, the electric field gradient, which induces the quadrupole broadening of the resonance line, is much greater than those in other species derived from acids **3** and **4**.

Table 5. Data of ^{14}N NMR spectroscopy (δ and line width $\Delta_{1/2}$) of aqueous solutions of acids **4** and **3** for different neutralization steps (D_2O, external $MeNO_2$, titration by KOH)

n_{KOH}	δ ($\Delta_{1/2}$)				
	4			**3**	
	A	B	C	A	B
1	−349 (12)	−345 (12)	−343 (3)	−349.5 (6)	−348 (1)
2	−349 (12)	−345 (15)	—	−349.4 (6)	—
3	−355 (20)	−351 (25—30)	—	−354 (25)	—
4	—*	—*	—*	−356 (50)	—
6	—*	—*	—	—*	−355 (15)

Note. n_{KOH} is the number of equivalents of KOH. A, C = 0.15 mol L^{-1}, 298 K; B, C = 0.5 mol L^{-1}, 298 K; C, C = 0.5 mol L^{-1}, 353 K.

* The signal is not recordable.

By analogy with aminocarboxylic[33] and AAP[22] acids, it can be suggested that zwitter ionic and ionic species derived from acids **3** and **4** occur in aqueous solutions mainly in the cyclic form with closely spaced amino and phosphonate groups. An exception is the completely deprotonated L^{4-} anion of acid **4**, which should exist predominantly in an acyclic conformation, in which the amine—phosphonate interaction, which is possible only *via* a solvation water molecule, would be the least pronounced. The conformations of AGDP **3** and **4** according to the data of ^{14}N NMR spectroscopy of aqueous solutions are presented in Scheme 6.

Evidently, the electric field gradient should be much greater in the uncoiled linear conformations bearing a negative charge on the phosphonate end of the flexible alkylidene chain than in cyclic conformations.

In strongly alkaline media (K_4L + 2 KOH), solvation conditions change and the equilibrium between cyclic and acyclic conformations in the case of acid **3** shifts toward linear forms.

The change in the signal width during titration of acids **3** and **4** is also explained by the existence of cyclic conformations with different stabilities.

By comparing the ^{14}N chemical shifts observed on titration of acids **3** and **4** (see Table 5) with the ^{15}N NMR data for model compounds, protonation of the N atom in all the H_nL^{4-n} species (at n = 2—4) is evident. The nitrogen chemical shifts in the H_3L^- and H_2L^{2-} anions are the same (−349 ppm at C = 0.15 mol L^{-1} and −345 ppm at C = 0.5 mol L^{-1}) and are about the same as that of the betaine nitrogen in glycine (−345.7 ppm at C = 1.6—2.1 mol L^{-1}, scaled in relation to $MeNO_2$[33]). The abstraction of the betaine proton from glycine is accompanied by a change in the chemical shift, $\Delta\delta_N$ = 12 (the scaled chemical shift of the anion is −358 ppm[33]). The signal of the amine nitrogen in the L^{4-} anion of acid **3** occurs at δ −356 and $\Delta\delta_N$ = 7. The absence of a signal of L^{4-} in the spectrum from acid **4** due to its substantial broadening (see above) is also consistent with the abstraction of the betaine proton. The chemical shifts of HL^{3-} are intermediate (−354 and −355 ppm for acids **3** and **4**, respectively). This can be due either to the occurrence of an equilibrium between tautomeric forms protonated at both the N atom and the phosphonate group or to a strong IntraHB between the betaine proton and the phosphonate end of the HL^{3-} ion. Since, according to IR spectroscopy, a tautomeric equilibrium is observed only for acid **3**, the assumption that a strong IntraHB is formed is preferred. It should be noted that similar "intermediate" values of nitrogen chemical shifts were found in a study of dissociation of the diaminocarboxylic acid $RHN(CH_2)_4CH(NHR)COOH$ with R = H and were absent for the acid with R = CH_2OH, in which the formation of an IntraHB should be sterically hindered.[34]

Thus, all the proton-containing species derived from AGDP exist in solutions as zwitter ions, predominantly, in cyclic configurations. The IntraHB formed in the monoprotonated anion HL^{3-} is stronger than that in the aminocarboxylic prototype; in the case of HL^{3-}, the betaine proton, being still linked to the N atom, is substantially displaced toward the negatively charged terminal group of the zwitter ion. In the case of acid with the unsubstituted amino group, cyclic conformations predominate even for the completely deprotonated anion.

The changes in the ^{14}N chemical shift are insensitive to tautomeric equilibria. The substantial quadrupole broadening of resonance signals does not allow one to rule out completely the contribution of other tautomeric forms and to establish reliably the structure of the ionic species.

^1H NMR spectroscopy

Amino-phosphonate interactions; H-bonds. The data of the ^1H NMR spectra of aqueous solutions of acids **3** and **4** at different neutralization steps were analyzed in comparison with the data for model acid **12** with the same length of the alkylidene chain (Table 6).

Acid **12** exists in water as a zwitter ion and the betaine proton is the last to split off.[22] The pres-

Scheme 6

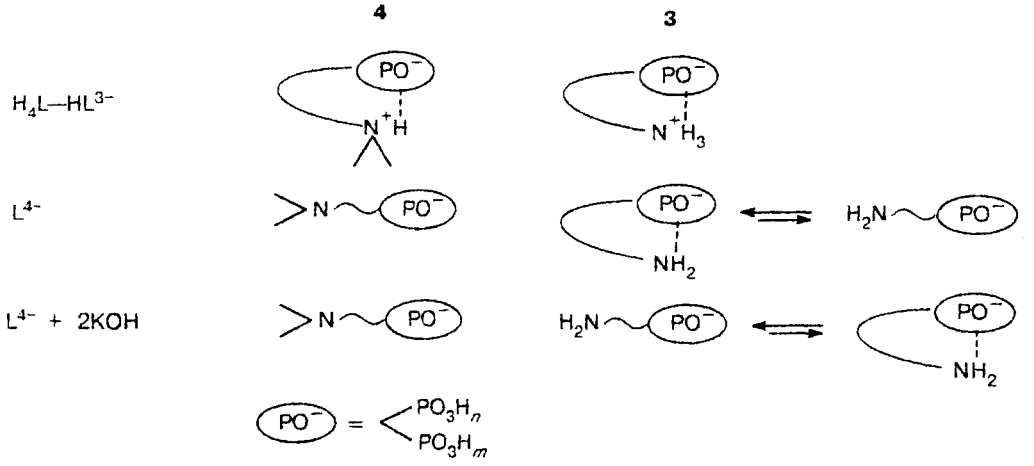


Table 6. Data of the ^{1}H NMR spectroscopy (δ, J/Hz) of aqueous solutions of acids **3**, **4**, and **12** for different neutralization steps (D_2O, external HMDS, 303 K, C = 0.03 mol L^{-1}, titration by KOH)

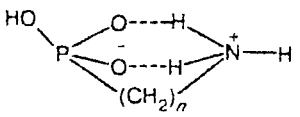
n_{KOH}	**12** [a]	**3**		**4**		
	H(3)	H(3)	H(2)	H(3)	H(2)	H(Me)
	(m)	t ($^3J_{H-H}$)	tt ($^3J_{H-H}$, $^3J_{H-P}$)	t ($^3J_{H-H}$)	tt ($^3J_{H-H}$, $^3J_{H-P}$)	(s)
—[b]	3.10					
0	3.07	3.16 (7.0)	2.13 (7.0, 13.5)	3.23 (6.8)	2.13 (6.8, 13.5)	2.66
1	3.01	3.14 (6.8)	2.09 (6.7, 12.8)	3.19 (6.5)	2.09 (6.6, 13.1)	2.64
2	2.59	3.11 (6.5)	2.04 (6.4, 12.4)	3.11 (6.1)	2.04 (6.2, 12.9)	2.59
3		2.96 [c]	1.94 [c] (6.6,[c] 13.4 [c])	2.97 (5.8)	1.99 (5.8, 14.0)	2.46
4		2.87 [c]	1.90 [c] (6.9,[c] 13.6 [c])	2.80 (6.5)	1.92 (6.6, 13.5)	2.30
6		2.81 (7.1)	1.86 (7.1, 13.6)			

Note. The error of measurement of δ_H was ±0.005; the error of measurement of J was ±0.25 Hz; n_{KOH} is the number of equivalents of KOH.

[a] According to Ref. 22, C = 0.5 mol L^{-1}. [b] pH = −0.4, the acid exists as the cation.[22]

[c] Overlap of two (or several) close, qualitatively similar multiplets (see Fig. 6). The average values are given.

ence of cyclic conformations of type **E** with closely located amino and phosphonate groups, which allow for both direct Coulomb interactions and H-bonds, is assumed for each species from H_3L^+ to L^{2-}.

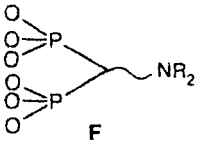


E

The elimination of the last two protons from the phosphonate group (transition from H_3L^+ to H_2L and then to HL^-) in these conformations changes only slightly the magnetic environment of both the phosphorus nuclei (see above) and the nuclei of the hydrogen atoms of the γ-methylene group; therefore, the NMR signals of these nuclei shift insignificantly. The chemical shifts change substantially upon abstraction of the last, betaine proton ($\Delta\delta_H$ = 0.42).

In the ^{1}H NMR spectra of acids **3** and **4**, the signals of the protons of the methylene group located in the γ-position relative to the phosphonate groups are displayed as a triplet and the protons of a β-methylene group are responsible for a triplet of triplets. The positions of signals and the spin-spin coupling constants correspond to the expected values (see Table 6). The protons of the Me group in complexone **4** account for a singlet.

Upon the addition of 3 and 4 equivalents of KOH, the spectra of acid **3** with the unsubstituted amino group exhibits a superposition of several sets of close (the difference between the chemical shifts is ~0.01 ppm), qualitatively similar multiplets, whereas after the addition of 6 equivalents, only one set of signals is again present (Fig. 6). In the spectra of acid **4**, one set of signals is preserved during titration.



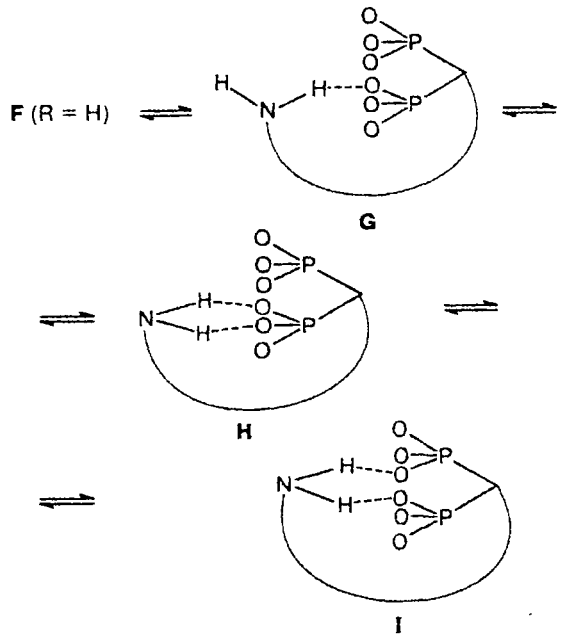
F

R = H, Me

In accordance with the data of conformation analysis and ^{14}N NMR and IR spectroscopy, we believe that the L^{4-} anion of acid **4** mostly exists in a strongly alkaline medium as the uncoiled acyclic conformer **F**, whereas the L^{4-} anion derived from acid **3** can exist in both cyclic and linear forms (Scheme 7).

Scheme 7 shows the cyclic structures (G, H, and I) that are most likely from the molecular mechanics viewpoint. Structure **G** corresponds to the conformation of the global minimum; for conformers **H** and **I**, the strain energies ΔE are 2 and 4.5 kcal mol^{-1}, respectively. Evidently, the chemical shifts of the methylene protons in these conformers should not differ much. When 6 equivalents of KOH have been added, linear conformer **F** predominates in the solution (one set of signals in the proton spectrum, the absence of a ^{14}N NMR signal). After the addition of 4 equivalents of KOH, the fraction of conformer **F** is insignificant; the solution contains

Scheme 7



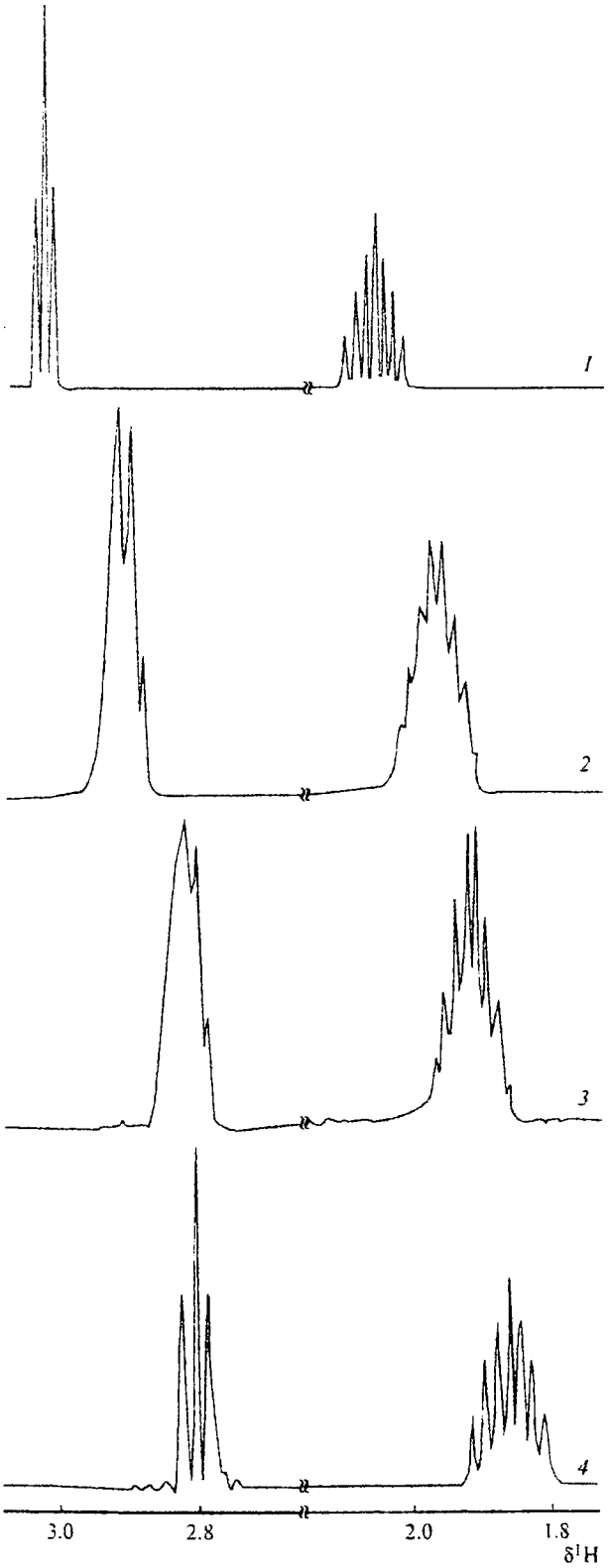
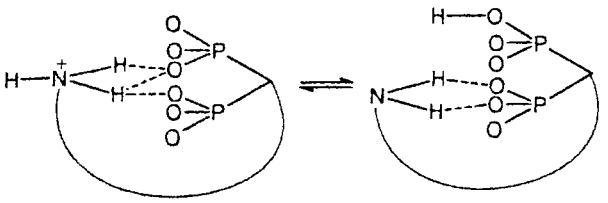


Fig. 6. Evolution of ^{1}H NMR spectra of acid **3** during titration. The number of equivalents of KOH: 2 (*1*), 3 (*2*), 4 (*3*), 6 (*4*). Experimental conditions are given in Table 6.

mainly cyclic conformers **G** and **H** (two sets of signals of methylene protons, one signal of the nitrogen nucleus, and a clear-cut band for the synphase symmetrical vibration of the PO_3^{2-} group in the IR spectrum).

The HL^{3-} anion from acid **4** forms presumably one cyclic conformer (one set of signals in the ^{1}H NMR spectrum, one signal in the ^{14}N NMR spectrum). Apparently, this is conformer **C** stabilized by a strong bifurcate H-bond. The strain energy of this conformer is only 2.5 kcal mol^{-1}.

In the case of the monoprotonated HL^{3-} anion formed from acid **3**, an equilibrium is assumed between cyclic conformers of two tautomeric forms in one of which the protonated site (**J**) is nitrogen and in the other it is the phosphonate group (**K**)

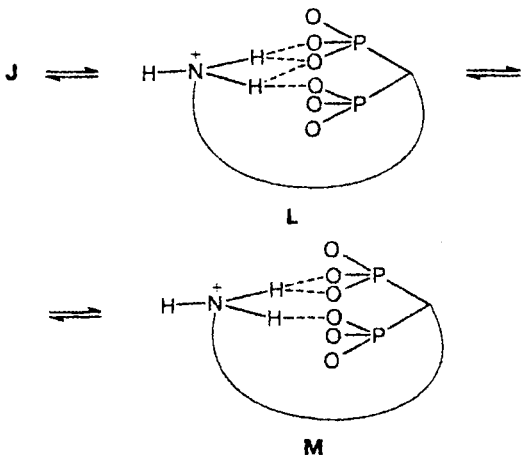


J **K**

For both tautomers, several cyclic conformations with close energies are possible. In particular, tautomer **J** can exist as three conformations (Scheme 8)

The energies of the three conformers are virtually equal (ΔE = 0 and 2.5 kcal mol^{-1} for **L** and **M**, respectively, and **J** is the conformation corresponding to the global minimum (Fig. 7)). Each conformation allows for the formation of several, including bifurcate, IntraHB. In line with this fact, the proton spectrum displays overlap of several sets of signals with close chemical shifts; the ^{14}N spectrum has one signal; the IR spectrum demonstrates equilibrium of two tautomeric forms one of which is protonated at the N atom and the other of which is protonated at the phosphonate group.

Scheme 8



L

M

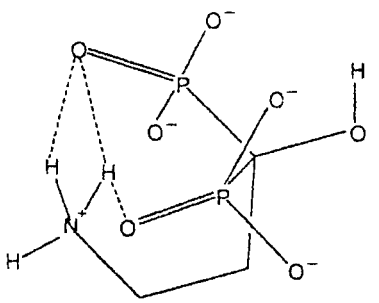


Fig. 7. Conformation of the HL^{3-} anion of acid **3** in the region of global minimum.

On further protonation, the resulting zwitter ions for both acids apparently exist in solution mainly as one cyclic conformer stabilized by an intramolecular H-bond (bonds) between the ammonium and phosphonate groups and additional O—H...O bonds complementing the *gem*-diphosphonate unit.

Analysis of the ^1H NMR spectra recorded during titration of acids **3** and **4** (see Table 6) shows that, as in the case of model acid **12**, the spectra exhibit a nonmonotonic decrease in the δ_H value of the protons of methylene and methyl groups (upfield shifts of signals). The signals of the protons of the β-methylene groups of both acids, unlike the signals of other groups, vary almost monotonically (see Table 6); this precludes using them for determining the site of proton attachment in the anions.

The signals of methyl and γ-methylene protons of acid **4** vary in parallel upon variation of the extent of neutralization (Fig. 8). The substantial (0.16 and 0.17 ppm) and simultaneous displacement of signals of these protons on passing from L^{4-} to HL^{3-} implies that

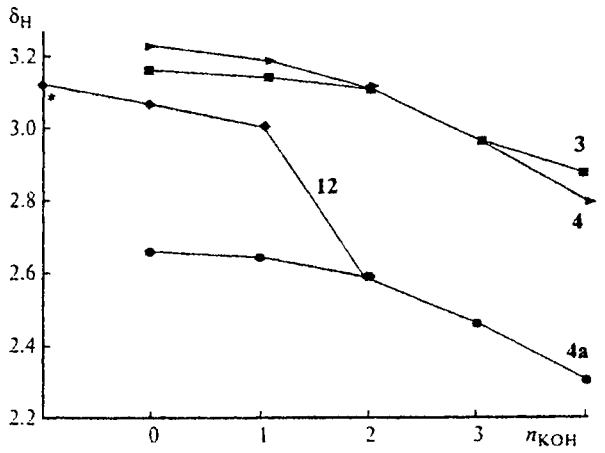


Fig. 8. Dependence of the chemical shift of the γ-methylene protons (δ_H) of compounds **3**, **4**, and **12** on the number of neutralization equivalents (n_{KOH}) in aqueous solutions according to the data of Table 6. The numbers of curves correspond to the numbers of compounds; **4a** is the same plot for the methyl protons of acid **4**. The asterisk represents results for the acid in the cationic form H_5L^+.

the first proton adds to the N atom, and that is consistent with the data of IR spectroscopy. However, transition from HL^{3-} to H_2L^{2-} is accompanied by a signal displacement of the same order (0.13 and 0.14 ppm). Further protonation has a slight influence on the position of signals, which smoothly move downfield ($\Delta\delta$ = 0.02—0.08 ppm). According to the data of IR spectra, the betaine structure is retained when H_2L^{2-}, H_3L^-, and H_4L are formed and protonation involves the phosphonate groups. By analogy with model acid **12**, these changes in the proton spectra of acid **4** can be explained by assuming the existence of cyclic structures stabilized by amino—phosphonate IntraHB. Obviously, in the monoprotonated anion (HL^{3-}) of acid **4** (structure **C**), the betaine proton should be displaced to a greater extent toward the phosphonate groups than in the monoprotonated anion (HL^-) of acid **12** (structure **A**) even due to the Coulomb forces alone. On further protonation (the formation of H_2L^{2-}, H_3L^-, and H_4L), the stability of cyclic structures formed by complexone **4** becomes roughly equal to that for AAP and the signals of the γ-methylene protons in the spectra AGDP **4** and AAP **12** are nearly identical ($\Delta\delta$ = 0.04, 0.08 and 0.03, 0.06, see Table 6).

The change in the chemical shifts of the γ-methylene protons during titration of acids **3** and **4** is virtually the same (see Table 6 and Fig. 8), although according to IR spectra, in the case of acid **3**, the HL^{3-} anion exists as two equilibrated tautomers protonated at the N atom and at the phosphonate group (see above).

Thus, the sequence of dissociation and the structures of species formed from acids **3** and **4**, determined from the proton spectra, are consistent with the conclusions based on ^{14}N NMR and IR spectroscopy. The ^1H NMR spectra of AGDP are less sensitive to tautomeric equilibria than IR spectra. However, ^1H NMR spectra provide more precise data on the structures of ionic and betaine species formed from acids with substituted and unsubstituted amino groups.

***

In aqueous solutions, AGDP exist as zwitter ions and as ions characterized by IntraHB, Coulomb interactions between the amine and phosphonate moieties, and specific solvation, namely, the formation of cyclic hydrates. These factors determine the following main properties and behavior of AGDP in aqueous solutions: formation of a single *gem*-diphosphonate acid center, which accounts for the special place of *gem*-diphosphonates in the series of bisphosphonic acids; establishing of a tautomeric equilibrium due to stabilization of some species; the formation of cyclic conformations capable of chelating a cation; and either hydrophobicity or hydrophilicity of species, a property important for adsorption or transport through a membrane.

The sequence of dissociation in the series of compounds studied does not depend on the length of the alkylidene chain in AGDP but is governed by the ability

of the substituent at the N atom to participate in the formation of H-bonds.

The limitations of the applicability of spectral methods to the study of the mechanism of dissociation of AGDP are outlined.

The authors are grateful to E. I. Goryunov for fruitful discussion of the results.

This work was supported by the Russian Foundation for Basic Research (Project No. 96-15-97298).

References

1. F. H. Ebetino, *Abstracts, XIVth Intern. Conference on Phosphorus Chem. (XIVth-ICPC)*, Cincinnati, Ohio, 1998, B. 1, p. LM1-1; G. Russell, *Ibid.*, p. LMA; L. Widler, K. A. Jaeggi, J. R. Green, and F. H. Ebetino, *Ibid.*, p. LM1-3; H. Blum, *Ibid.*, p. LF1-3; O. Aleksiuk, D. Z. Gabriel, D. Kantoci, W. J. Wechter, D. Borchardt, and F. H. Ebetino, *Ibid.*, p. PO5.
2. M. O. Lozinsky, A. L. Chuiko, P. Kafarski, I. Jasicka-Misiak, L. P. Filonenko, and A. N. Borisevich, *Abstracts. XIVth Intern. Conference on Phosphorus Chem. (XIVth-ICPC)*, Cincinnati, Ohio, 1998, B. 2, p. P148; P. Kafarski, B. Lejczak, G. Forlani, A. L. Chuiko, M. O. Lozinsky, I. Jasicka-Misiak, K. Czekala, and J. Lipok, *Ibid.*, p. LH5-4.
3. E. I. Sinyavskaya, *Koord. Khim.*, 1992, **18**, 899 [*Sov. J. Coord. Chem.*, 1992, **18** (Engl. Transl.)].
4. *Calcium Disorders*, Eds. D. Heath and S. J. Marx, Butterworth Scientific, London—Boston—Sydney—Wellington—Durban—Toronto, 1982.
5. S. V. Matveev, F. I. Bel'skii, A. G. Matveeva, A. Yu. Gukasova, Yu. M. Polikarpov, and M. I. Kabachnik, *Izv. Akad. Nauk. Ser. Khim.*, 1998, 1784 [*Russ. Chem. Bull.*, 1998, **47**, 1736 ((Engl. Transl.)].
6. M. I. Kabachnik, T. Ya. Medved', N. M. Dyatlova, Yu. M. Polikarpov, B. K. Shcherbakov, and F. I. Bel'skii, *Izv. Akad. Nauk SSSR, Ser. Khim.*, 1978, 433 [*Bull. Acad. Sci. USSR, Div. Chem. Sci.*, 1978, **27**, 374 (Engl. Transl.)].
7. a) M. I. Kabachnik, F. I. Bel'skii, M. P. Komarova, B. K. Shcherbakov, E. I. Matrosov, Yu. M. Polikarpov, N. M. Dyatlova, and T. Ya. Medved', *Izv. Akad. Nauk SSSR, Ser. Khim.*, 1979, 1726 [*Bull. Acad. Sci. USSR, Div. Chem. Sci.*, 1979, **28** (Engl. Transl.)]; b) T. A. Matkovskaya, L. S. Nikolaeva, B. K. Shcherbakov, A. M. Evseev, and N. M. Dyatlova, *Zh. Neorg. Khim.*, 1987, **32**, 295 [*J. Inorg. Chem. (USSR)*, 1987, **32** (Engl. Transl.)]; c) K. B. Yatsimirskii, M. I. Kabachnik, E. I. Sinyavskaya, M. A. Konstantinovskaya, T. Ya. Medved', Yu. M. Polikarpov, and B. K. Shcherbakov, *Zh. Neorg. Khim.*, 1980, **25**, 3326 [*J. Inorg. Chem. (USSR)*, 1980, **25** (Engl. Transl.)].
8. M. I. Kabachnik and T. Ya. Medved', *Izv. Akad. Nauk SSSR, Otd. Khim. Nauk*, 1962, 2103 [*Bull. Acad. Sci. USSR, Div. Chem. Sci.*, 1962, **11** (Engl. Transl.)].
9. M. I. Kabachnik and E. S. Shepeleva, *Izv. Akad. Nauk SSSR, Otd. Khim. Nauk*, 1953, 862 [*Bull. Acad. Sci. USSR, Div. Chem. Sci.*, 1953, **2** (Engl. Transl.)].
10. J. Dodonow and H. Medox, *Chem. Ber.*, 1928, **61**, 907.
11. K. A. Petrov, F. L. Maklyaev, and N. K. Bliznyuk, *Zh. Obshch. Khim.*, 1960, **30**, 1602 [*J. Gen. Chem. USSR*, 1960, **30** (Engl. Transl.)].
12. T. Shedlovsky and D. A. MacInnes, *J. Am. Chem. Soc.*, 1937, **59**, 503.
13. N. I. Voronezheva, Yu. V. Rudyak, N. M. Dyatlova, and A. I. Grigor'ev, *Koord. Khim.*, 1980, **6**, 991 [*Sov. J. Coord. Chem.*, 1980, **6** (Engl. Transl.)].
14. G. C. Pimentel and A. L. McClellan, *The Hydrogen Bond*, San-Francisco—London, 1960.
15. A. Yu. Kireeva, B. V. Zhadanov, and B. I. Bikhman, *Trudy IREA [Collection of Works of IREA]*, 1972, **34**, 12 (in Russian)
16. E. Steger and J. Rehar, *Z. Anorg. Allg. Chem.*, 1965, **336**, 156.
17. B. V. Zhadanov, I. A. Polyakova, N. V. Tsirul'nikov, T. M. Sushitskaya, and V. Ya. Temkina, *Koord. Khim.*, 1979, **5**, 1614 [*Sov. J. Coord. Chem.*, 1979, **5** (Engl. Transl.)].
18. L. V. Nikitina, A. I. Grigor'ev, and N. M. Dyatlova, *Zh. Obshch. Khim.*, 1974, **44**, 1598 [*J. Gen. Chem. USSR*, 1974, **44** (Engl. Transl.)].
19. E. N. Rizkalla, *Rev. Inorg. Chem.*, 1983, **5**, 223.
20. A. I. Grigor'ev, *Dokl. Akad. Nauk SSSR*, 1966, **171**, 136 [*Dokl. Chem.*, 1966 (Engl. Transl.)].
21. (a) K. W. F. Kohlrausch, *Ramanspectren*, Leipzig, 1943; (b) L. J. Bellamy, *Advances. in Infrared Group Frequencies*, Methuen & Co., Suffolk, 1968; (c) B. Schrader, *Raman/Infrared Atlas of Organic Compounds*, 2 ed., VCH-Verl.-Ges., Weinheim, 1989.
22. T. G. Appleton, J. R. Hall, A. D. Harris, H. A. Kimlin, and I. J. McMahon, *Aust. J. Chem.*, 1984, **37**, 1833.
23. F. I. Bel'skii, I. B. Goryunova, P. V. Petrovskii, M. I. Kabachnik, and T. Ya. Medved', *Izv. Akad. Nauk SSSR, Ser. Khim.*, 1982, 103 [*Bull. Acad. Sci. USSR, Div. Chem. Sci.*, 1982, **31** (Engl. Transl.)].
24. L. Maier, *J. Organomet. Chem.*, 1979, **178**, 157; G. Hagele, M. Grzonka, H.-W. Kropp, J. Ollig, and H. Spiegl, *Phosphorus, Sulfur, and Silicon*, 1993, **77**, 85; Z. H. Kudzin, G. Andrijewski, and J. Drabowicz, *Heteroatom Chem.*, 1994, **5**, 1; T. G. Appleton, J. R. Hall, and I. J. McMahon, *Inorg. Chem.*, 1986, **25**, 726.
25. R. J. Grabenstetter, O. T. Quimby, and T. J. Flautt, *J. Phys. Chem.*, 1967, **71**, 4194.
26. K. Moedritzer and R. R. Irani, *J. Inorg. and Nucl. Chem.*, 1961, **22**, 297.
27. G. Anderegg, *Helv. Chim. Acta*, 1965, **48**, 1712.
28. E. N. Tsvetkov, *Zh. Obshch. Khim.*, 1976, **46**, 2763 [*J. Gen. Chem. USSR*, 1976, **46** (Engl. Transl.)].
29. I. G. Orlov, V. S. Markin, Yu. V. Moiseev, and U. I. Khurgin, *Zh. Strukt. Khim. SSSR*, 1966, **7**, 796 [*J. Struct. Chem. USSR*, 1966 (Engl. Transl.)].
30. *Annual Reports on NMR Spectroscopy*, V. **18**, Ed. G. A. Webb, Academic press, London, 1986, 761 p.
31. N. M. Dyatlova, V. Ya. Temkina, and K. I. Popov, *Kompleksony i kompleksonaty metallov [Complexones and Metal Complexonates]*, Khimiya, Moscow, 1988, 422, 544.
32. (a) J. W. Emsley, J. Feeney, and L. H. Sutcliffe, *High Resolution Nuclear Magnetic Resonance Spectroscopy*, V. 2, Pergamon Press, Oxford—London—Edinburgh—New York—Paris—Frankfurt, 1966; (b) V. 1
33. T. K. Leipert and J. H. Noggle, *J. Am. Chem. Soc.*, 1975, **97**, 269.
34. N. Naulet, D. Tome, and G. J. Martin, *Org. Magnetic Res.*, 1983, **21**, 564.
35. G. Gross, B. Kostizella, K. Shvarts, M. I. Kabachnik, F. I. Bel'skii, and M. Yu. Polikarpov, *Zh. Obshch. Khim.*, 1990, **60**, 749 [*J. Gen. Chem. USSR*, 1990, **60** (Engl. Transl.)].

Received October 18, 1999