Protonation Behavior and Intramolecular Interactions of α,ω-Alkanediaminepolymethylenepolyphosphonates

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The protonation equilibria of two types of aminopolyphosphonates ($((CH_3)_{2-p}(CH_2PO_3)_pN(CH_2)_mN(CH_2PO_3)_{p'}(CH_3)_{2-p'}$) in aqueous solution were investigated by means of potentiometry and ^{31}P NMR spectroscopy. The protonation behavior of diaminotetramethylenetetraphosphonate ($p=p'=2$) is significantly altered by a change in the number of methylene chains ($m=2$, 3, 6). The protonations of the imino fragments of hdtmp, which is connected with a six methylene chain ($m=6$), are essentially independent of each other, whereas edtmp, which is connected with a two methylene chain ($m=2$), forms a hydrogen bond between both nitrogen atoms ($NH^+\cdots N$) in the mono protonated species. The ethylenediaminepolyphosphonates ($m=2$), having an iminodiphosphonate group ($p=2$, $p'=0$—2), show a peculiar ^{31}P NMR behavior in which the signal shows a downfield shift at higher protonated species. However, eddmp (*N*,*N*′), having one methylenephosphonate group at each imino fragment ($p=p'=1$), does not show such an anomaly. These results indicate the existence of an intramolecular interaction between both fragments, such as a hydrogen bond of a protonated nitrogen atom with unprotonated phosphonates of another imino fragment, where two methylenephosphonate groups in one imino fragment are required to operate such an interaction.

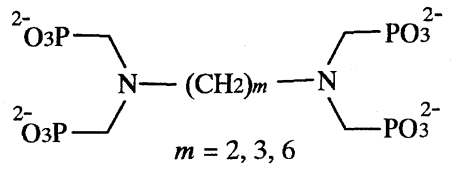
Various kinds of aminopolyacids have been synthesized, and the reactions and structures of these compounds have been intensively studied. Aminopolycarboxylates (APC) represented by ethylenediamine-*N*,*N*,*N*′,*N*′-tetraacetate (edta) are the most characterized aminopolyacid with respect to analytical and coordination chemistry. The aminopolyphosphonates (APP) were synthesized for the first time by Scwarzenbach,[1—3] and have been used for industrial purposes, such as a scale inhibitor for oil drilling and geothermal power plants.[4—7] Nevertheless, their properties are not so well understood compared with those of APC.[8—13] We had studied the complex formation behavior of APP, such as nitrilotrismethylenephosphonate ($ntmp^{6-}$) and *N*-methyliminodimethylenephosphonate ($midmp^{4-}$), and reported on the formation of eight-membered chelate-ring complexes with alkaline earth metals[14,15] and transition metals.[15] The eight-membered chelate-ring complexes of APP of inert Co^{III} polyamine complexes were isolated and characterized.[16]

These APP have large first-protonation constants relative to those of corresponding APC. The first protonation on the nitrogen atom of APP causes a large upfield shift of the ^{31}P NMR signal ($\Delta\delta\approx10$ ppm). The succeeding protonations occur on the phosphonate oxygen atoms, and show only a small change in the ^{31}P NMR chemical shift. On the other hand, in the case of ethylenediamine-*N*,*N*,*N*′,*N*′-tetramethylenetetraphosphonate ($edtmp^{8-}$), thermodynamic[17] and ^{31}P NMR spectroscopic studies[17,18] revealed that the protonation equilibria are rather complicated; that is, the first protonation occurs on the nitrogen atom and forms a hydrogen bond between both nitrogen atoms ($NH^+\cdots N$). Because of the decrease in the bascity of an unprotonated nitrogen atom due to the formation of a hydrogen bond, the second protonation predominantly occurs on the phosphonate oxygen atom, and both of the nitrogen atoms are protonated at the third protonation. Furthermore, the ^{31}P NMR signal of edtmp shows a peculiar behavior, i.e., the ^{31}P NMR signal shifts downfield, even due to the protonation of phosphonate oxygen atoms at higher protonated species. This fact suggests an intramolecular interaction between both fragments other than the hydrogen bond between the nitrogen atoms. This behavior was also observed in APP complexes of Co^{III}(polyamine).[19]

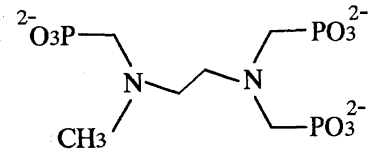
In the present study, in order to elucidate this intramolecular interaction, various kinds of α,ω-alkanepolymethylenepolyphosphonates having various lengths of the methylene chains and number of methylenephosphonate groups were synthesized (Scheme 1), and the prorotonation behavior of these ligands was investigated by means of potentiometry and ^{31}P NMR spectroscopy.

Experimental

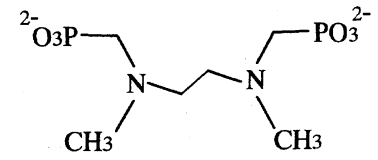
Reagents. Ethylenediamine-*N*,*N*,*N*′,*N*′-tetramethylenetetrakis(phosphonic acid) (H_8edtmp) (Dojin Chemicals) and hexamethylenediamine-*N*,*N*,*N*′,*N*′-tetramethylenetetrakis(phosphonic acid) (H_8hdtmp) (Mitubishi Monsanto) were purified by recrystallization. Trimethylenediamine-*N*,*N*,*N*′,*N*′-tetramethylenetetrakis(phosphonic acid) (H_8tdtmp) was synthesized by a reaction of 1,3-propanediamine (37 g) and phosphorous acid (164 g) with 40%-formaldehyde (320 cm^3) in 5 mol dm^{-3} HCl (500 cm^3) according to methods of Moedritzer and Irani.[20] The hydrogen chloride and excess formaldehyde were removed by evaporation. After dissolving in water, the barium salt of the ligand was precipitated by $Ba(OH)_2$ at pH 3.8. The barium salt was converted to free acid by a reaction



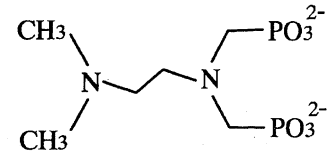
edtmp^{8-}, tdtmp^{8-}, hdtmp^{8-}



medtmp^{6-}



eddmp *(N,N')*$^{4-}$



eddmp *(N,N)*$^{4-}$

Scheme 1.

with sulfuric acid. Condensation of the solution yielded crystals. The crystals were dissolved in 1 mol dm^{-3} HCl and recrystallized by the addition of ethanol. *N*-methylethylenediamine-*N*,*N*′,*N*′-trimethylenetri(phosphonate) (H_5medtmp) was synthesized from *N*-methylethylenediamine (21 g), phosphorus acid (71 g), and 40% formaldehyde (130 cm^3) in 5 mol dm^{-3} HCl (500 cm^3) and purified by the same method as that of tdtmp; a viscous liquid was obtained instead of crystals. *N*,*N*′-dimethylethylenediamine-*N*,*N*′-dimethylenebis(phosphonic acid) (H_4eddmp (*N*,*N*′)) and *N*,*N*-dimethylethylenediamine-*N*′,*N*′-dimethylenebis(phosphonic acid) (H_4eddmp (*N*,*N*)) were synthesized by reactions of dimethylethylenediamine ($CH_3NHCH_2CH_2NHCH_3$ and $(CH_3)_2NCH_2CH_2NH_2$) (21 g) with phosphorous acid (38 g) and formaldehyde (80 cm^3). In the case of H_4eddmp (*N*,*N*′), after evaporating the reaction mixture, the products were dissolved in 1 mol dm^{-3} HCl (100 cm^3) and crystallized by the addition of hot ethanol (200 cm^3). The crystals were dried at 100 °C under vacuum. In the case of H_4eddmp (*N*,*N*), a viscous ligand was obtained by evaporation. The products were washed with hot 90% ethanol three times and with 50% ethanol, and then dried at 100 °C under vacuum. The purities of the ligands were determined by ^{31}P, ^{13}C, and ^{1}H NMR and pH titration. Those were more than 99%, except for H_4eddmp (*N*,*N*) (97%).

Potentiometric Measurements. The pH titration was carried out with an Ion Analyzer C-130 Corning Research Model under a nitrogen stream. The electromotive force (emf) of the glass electrode (Iwaki, glass electrode IW002 and calomel electrode IW 022) was calibrated by titration with nitric acid or potassium hydroxide at 25.0±0.1 °C (I = 0.1 mol dm^{-3} KNO_3, pK_w = 13.82). The pH, logarithm of reciprocal of the hydrogen ion concentration, was evaluated from the emf by using the calibration curve. The solution of free acid, H_rL (r is the number of protons of free acid, c_L = 1—5×10^{-3} mol dm^{-3}) was titrated in a water jacket cell (25.0±0.1 °C) with 0.01 mol dm^{-3} KOH at I = 0.1 mol dm^{-3} (KNO_3).

NMR Measurements. The ^{31}P NMR spectra of the ligands (c_L = 5×10^{-3} mol dm^{-3}) were measured by a Varian Unity 500 FT-NMR spectrometer (202.35 MHz for ^{31}P) with a 10 mm diameter sample tube at 25.0±0.5 °C (I=0.1 mol dm^{-3} KNO_3). The external standard, which was served by a 5 mm diameter concentric tube, was 0.5% H_3PO_4 in D_2O. The observed chemical shifts were converted to the values of an aqueous 85% H_3PO_4 reference.

Results

Protonation Constants. The results of pH titration of the ligands are shown in Fig. 1. The mean number of protons bound to the ligand ($\bar{n}$), is obtained from the pH using

$$\bar{n}_{obs} = (rc_L - c_{OH} - [H^+] + [OH^-])/c_L, \quad (1)$$

where c_{OH} and c_L are the total concentrations of KOH titrated and ligand H_rL, respectively. The calculated values of the mean number of protons bound to the ligand, ($\bar{n}_{calc}$) are given by Eq. 2 using the protonation constants of the ligand, $\boldsymbol{K}_n$= $[H_nL]/[H^+][H_{n-1}L]$, where $\beta_n = \Pi \boldsymbol{K}_n$.

$$\bar{n}_{calc} = \sum n[H_nL]/c_L = \sum n\beta_n[H^+]^n/(1+\sum \beta_n[H^+]^n). \quad (2)$$

The charges of the chemical species are omitted for simplicity. The values of $\boldsymbol{K}_n$ were evaluated with our original com-

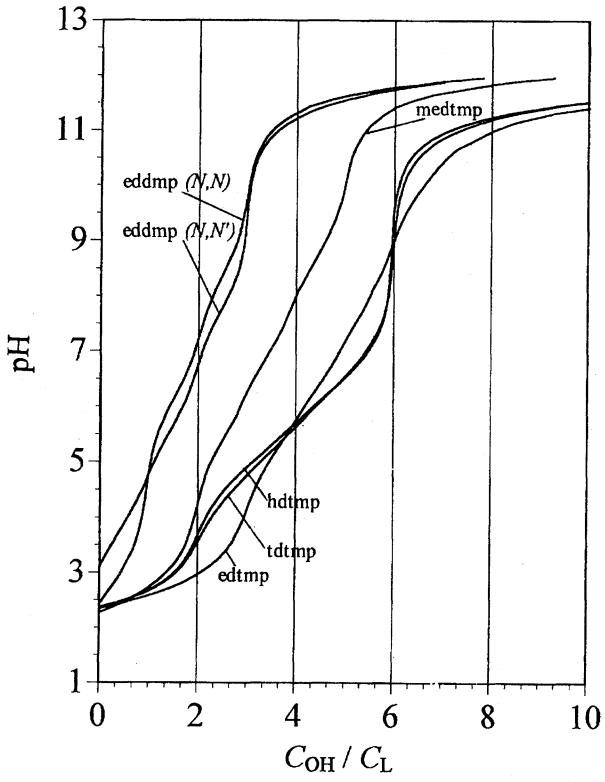


Fig. 1. pH titration curves of edtmp, tdtmp, hdtmp, medtmp, eddmp (*N*,*N*′), and eddmp (*N*,*N*) at 25.0±0.1 °C. Ionic strength I = 0.1 (KNO_3).

puter program.[14] A set of K_n giving the minimum sum of the squares of the deviations [$=\sum(\bar{n}_{obs}-\bar{n}_{calc})^2$] was obtained by a non-linear regression. The values of the protonation constants obtained from 30—40 data points are listed in Table 1. Because of the quite high values of the first protonation constants, the protonation constants of the $\log K_1$ values have large errors (about ±0.3). The first protonation constants listed in the Table 1 are values obtained by an analysis of the change in the chemical shift with pH, as mentioned below. The constants obtained by potentiometry agree with those determined by the NMR measurements within the experimental errors.

The values of the first protonation constants of edtmp, tdtmp, and hdtmp, having four methylenephosphonates, do not differ very much from each other. On the other hand, the second protonation constants decrease due to a decrease in the number of methylene chains ($\log K_2$=13.0, 11.15, and 9.85 for hdtmp, tdtmp, and edtmp, respectively, Table 1). The constants of higher protonation steps ($\log K_3$—$\log K_6$) for tdtmp and hdtmp are close to each other, whereas the constants of the third and sixth protonations for edtmp differ significantly from the constants of the corresponding steps of the other ligands.

The protonation constants of the ethylenediamine-type ligands (edtmp, medtmp, eddmp (*N*,*N*′), and eddmp (*N*,*N*)) decrease due to a decrease in the number of methylenephosphonate groups for each protonation step. The protonation constants of eddmp (*N*,*N*) are larger than those of eddmp (*N*,*N*′), except for the fourth protonation step ($\log K_4$=2.80 and 3.85 for eddmp (*N*,*N*) and eddmp (*N*,*N*′), Table 1).

Chemical Shifts. The ^{31}P NMR spectra of any ligand solutions show triplet peaks with an intensity ratio of 1 : 2 : 1, arising from coupling with the two protons of the adjacent methylene group. The proton decoupled $^{31}P\{^1H\}$ NMR spectra show one singlet peak, except for that of medtmp, which consists of two signals with a peak area-ratio of 2 : 1, corresponding to the $-N(CH_2PO_3^{2-})_2$ (A) and $-N(CH_3)(CH_2PO_3^{2-})$ (B) groups. In spite of the presence of many kinds of protonated species (H_nL), only a sharp singlet peak is observed in the $^{31}P\{^1H\}$ NMR spectra over the whole pH range. The ^{31}P NMR chemical shifts are plotted as a function of pH in Figs. 2 and 3. These results indicate that the proton exchanges of the ligand are very fast, and that the chemical shifts of the phosphorous atoms are averaged. Thus, the chemical shift is given by a liner combination of each protonated species as

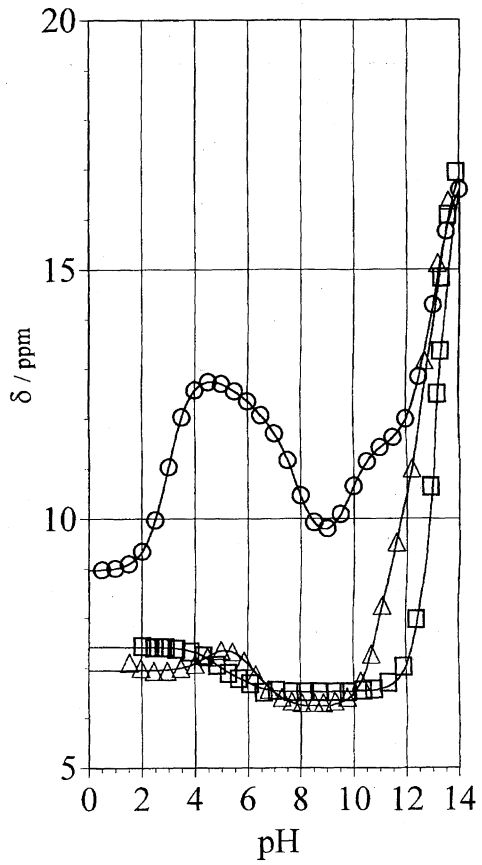


Fig. 2. ^{31}P NMR chemical shifts of edtmp, tdmp, and hdtmp as a function of pH. ○, edtmp; △, tdtmp, and □, hdtmp. Solid lines are calculated curves, see text.

$$\delta_{calc} = \sum \delta_n X_{HnL}, \quad (3)$$

where δ_n and X_{H_nL} are the chemical shift and proportion of each protonated and unprotonated species H_nL. The proportions of the chemical species (X_{H_nL}) at a given pH were calculated using the protonation constants (K_n). A set of chemical shifts for each species (δ_n) minimizing the sum of squares of deviations between the observed and calculated chemical shifts [$=\sum(\delta_{obs}-\delta_{calc})^2$] was evaluated by a non-linear regression.[14,15] The values of K_1 were evaluated by this fitting. The thus-obtained chemical shifts of protonated and unprotonated species are listed in Table 2. The calcu-

Table 1. Logarithmic Protonation Constants ($\log K_n$) of Diaminopolyphosphonates[a]

	edtmp	tdtmp	hdtmp	medtmp	eddmp (*N*,*N*)	eddmp (*N*,*N*′)
$\log K_1$	13.0±0.2[b]	13.0±0.2[b]	13.3±0.2[b]	12.6±0.2[b]	12.5±0.2[b]	11.46±0.07
$\log K_2$	9.85±0.03	11.15±0.06	13.0±0.2[b]	8.94±0.03	8.40±0.03	7.83±0.03
$\log K_3$	7.87±0.03	6.99±0.03	6.88±0.03	7.06±0.02	6.15±0.03	5.68±0.03
$\log K_4$	6.40±0.03	6.07±0.03	6.13±0.03	5.45±0.03	2.80±0.05	3.85±0.03
$\log K_5$	5.12±0.03	5.18±0.03	5.29±0.03	2.89±0.05		
$\log K_6$	2.96±0.06	4.37±0.03	4.61±0.03	<1		
$\log K_7$	<1	<1	<1			

a) $K_n=[H_nL]/[H^+][H_{n-1}L]$, I=0.1 (KNO_3). b) Evaluated by ^{31}P NMR spectroscopy.

Table 2. ^{31}P NMR Chemical Shifts (δ_{H_nL}/ppm) of Diaminopolyphosphonates

	edtmp	tdtmp	hdtmp	medtmp (A)[a)]	medtmp (B)[b)]	eddmp (*N*,*N*)	eddmp (*N*,*N*′)
δ_L	17.15	17.54	17.70	16.63	15.96	16.46	15.08
δ_{HL}	11.50	10.40	11.75	15.54	8.12	16.15	11.17
δ_{H_2L}	9.42	6.21	6.52	14.67	6.74	17.86	8.72
δ_{H_3L}	11.83	6.70	6.53	17.89	6.67	19.75	8.67
δ_{H_4L}	12.54	7.44	6.81	18.77	7.64	11.63	6.71
δ_{H_5L}	12.94	7.40	6.95	10.65	7.03		
δ_{H_6L}	8.96	6.95	7.41				

a) medtmp (A): ^{31}P of iminodiphosphonate group. b) medtmp (B): ^{31}P of iminomonophosphonate group.

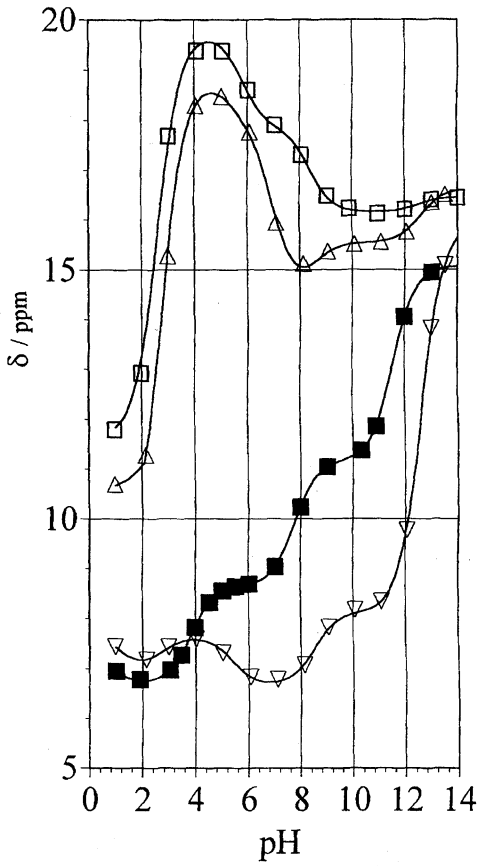


Fig. 3. ^{31}P NMR chemical shifts of medtmp, eddmp (*N*,*N*), and eddmp (*N*,*N*′) as a function of pH. △, medtmp (A); ▽, medtmp (B); □, eddmp (*N*,*N*), and ■, eddmp (*N*,*N*′). Solid lines are calculated curves, see text.

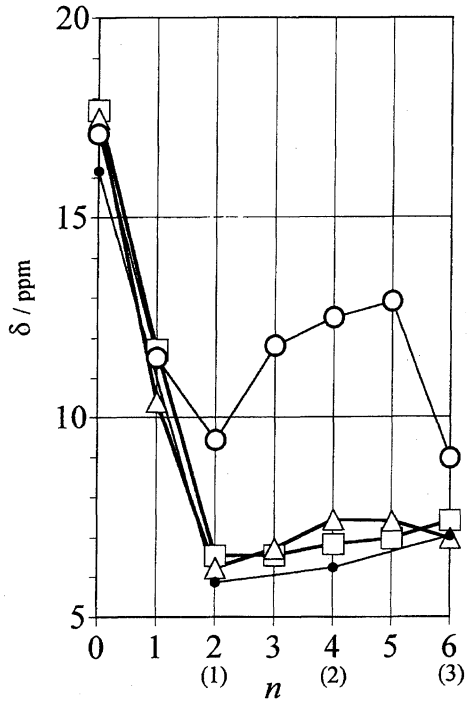


Fig. 4. ^{31}P NMR chemical shifts of protonated species of edtmp, tdtmp, hdtmp, and midmp as a function of the number of proton bound to ligand, *n*. The number of the proton bound to midmp is shown by (*n*). ○, edtmp; △, tdtmp; □, hdtmp, and ●, midmp.

lated curves of the chemical-shift changes obtained by using these constants are shown in Fig. 2 by solid lines.

The chemical shifts of each species (δ_n) of the ligands (edtmp, tdtmp, and hdtmp) are plotted as a function of the number of proton bound to the ligands (*n*) in Fig. 4, where the chemical-shift change of midmp[15] is also depicted. The change in the chemical shift due protonation is very similar between tdtmp and hdtmp. The chemical shift shows a large upfield shift due to the first and second protonations. The changes in the chemical shifts due to the succeeding protonations are very small. On the other hand, edtmp shows a quite different behavior compared with that of tdtmp and hdtmp. The change in the chemical shift of edtmp due to the second protonation is smaller than that of tdtmp and hdtmp, and the chemical shifts of higher protonated species of edtmp show a large downfield shift.

The results of the chemical shift of edtmp, medtmp, eddmp (*N*,*N*), and eddmp (*N*,*N*′) are shown in Fig. 5. The chemical shifts of medtmp show a quite interesting behavior. The ^{31}P NMR of the imino fragment (B), having one methylenephosphonate, shows a large upfield shift due to the first protonation, and small changes due to the succeeding protonations in a similar manner as that of hdtmp. Whereas that of the imino fragment, having two methylenephosphonate groups (A), does not show upfield shifts up to H_4medtmp, and the fifth protonation (H_5medtmp) causes a steep upfield shift. In the case of eddmp, two kinds of eddmp show totally different NMR behaviors from each other. The change in the chemical shift of eddmp (*N*,*N*′) shows the same behavior as

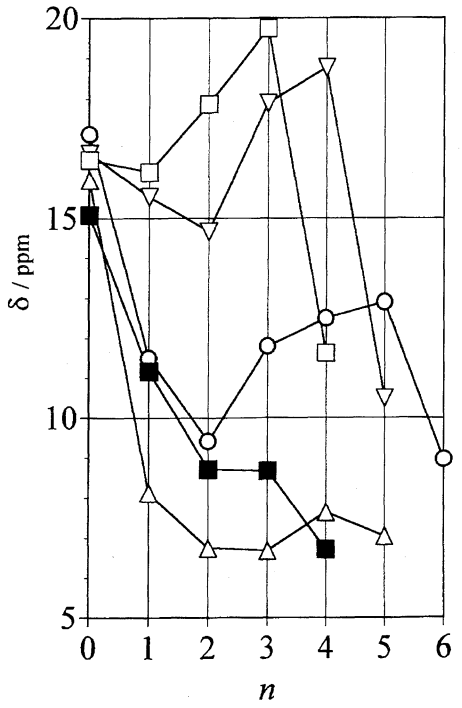


Fig. 5. ^{31}P NMR chemical shifts of protonated species of edtmp, medtmp, eddmp (N,N'), and eddmp (N,N) as a function of number of proton bound to ligand, n. ○, edtmp; ▽, medtmp (A); △, medtmp (B); ■, eddmp (N,N'), and □, eddmp (N,N).

that of the fragment (B) of medtmp, whereas the change for eddmp (N,N) is similar to that of the fragment (A) of medtmp. These results concerning the chemical-shift change indicate that the phosphonate in the imino fragment having only one methylenephosphonate group shows an ordinary behavior, while phosphonates in the fragment, having two methylenephosphonate groups, show a peculiar behavior.

Discussion

α,ω-Alkanediaminetetramethylenetetraphosphonates ($p=p'=2$). The quite large first protonation constants and the upfield shift of ^{31}P NMR signals due to the first protonation indicate that this protonation occurs on the imino nitrogen atom in any ligands. The second protonation constants are lowered due to a decrease in the number of methylene chains connecting two imino nitrogen atoms (m). In the case of hdtmp, the second protonation constant ($\log K_2=13.0$) is comparable to that of first protonation ($\log K_1=13.3$), and the second protonation again causes a large upfield shift. The change in the chemical shift due to succeeding protonations ($n\geq3$) is small. Thus, the chemical shift of hdtmp changes in the same manner as that of midmp. These results suggest that the second protonation of hdtmp occurs at another imino nitrogen atom, and that the first protonation scarcely affects to the second protonation. The succeeding protonations occur onto phosphonate oxygen atoms.

On the other hand, the second protonation constant of edtmp is significantly smaller than that of the first protonation, and the change in the chemical shift for the second protonation is much smaller than that of hdtmp. These results indicate that the basicity of an unprotonated nitrogen atom of edtmp is lowered by the formation of a hydrogen bond between both imino nitrogen atoms ($NH^+\cdots N$) (Chart 1), and that the second protonation predominantly occurs on the phosphonate oxygen atom. The third protonation occurs at the unprotonated imino nitrogen, i.e., both nitrogen atoms are protonated in the triprotonated species, H_3edtmp, which is supported by the large value of $\log K_3$ (=7.87) relative to that of hdtmp ($\log K_3=6.88$). These protonation processes are supported by thermodynamic studies of aminopolyphosphonates.[17] In the same manner as the protonations of aminopolycarboxylates, the protonations of the amino nitrogen and the phosphonate oxygen are exothermic and slightly endothermic, respectively. The large exothermic reaction of the first protonation of edtmp is followed by small exothermic ones of second and third protonations. These results indicate that the first protonation occurs on the imino nitrogen, and that the second one is dominantly on the phosphonate oxygen, although partially on the imino nitrogen. The endothermic reactions of the fourth and fifth protonations suggest protonation on the phosphonate oxygen. Thus, both nitrogen atoms of the triprotonated species, H_3edtmp, are completely protonated.

The chemical shifts of the higher protonated species of edtmp ($n\geq3$) show a peculiar behavior compared with those of hdtmp and tdtmp, i.e., the ^{31}P NMR signals of $H_n$edtmp are located downfield. These results indicate that there is some intramolecular interaction, such as a hydrogen bond between the protonated imino nitrogen and phosphonates of another imino fragment. The chemical shifts show a large upfield shift due to the sixth protonation. Consequently, this intramolecular interaction is absent in this species (H_6edtmp) in which all phosphonate groups are protonated. The small value of this protonation ($\log K_6=2.96$) supports this argument. The details of this interaction are discussed below.

The changes in the chemical shift and the protonation constants of tdtmp are quite similar to those of hdtmp, except for the second protonation constant ($\log K_2=11.15$) being relatively small compared with that of hdtmp. These results indicate that although the structures of the protonated species of tdtmp are essentially the same as that of the corresponding species of hdtmp, the interaction between two nitrogen atoms ($NH^+\cdots N$) is also operated in the monoprotonated species, Htdtmp. However, the intramolecular interaction between

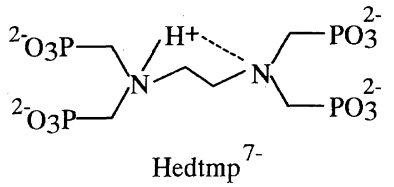


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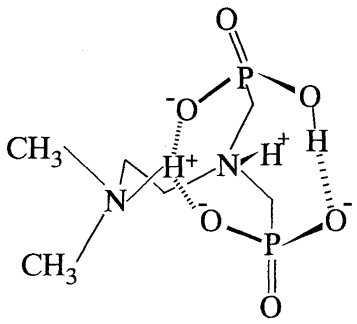
Chart 1.

two iminodimethylenediphosphonate fragments in the higher protonated species no longer takes place.

Ethylenediaminepolymethylenepolyphosphonates (*m*=2). The large first protonation constants of these ligands indicate protonation on the imino nitrogen atom. The difference between the first and second protonation constants ($\log K_1 - \log K_2$=3.7, 3.6, and 4.1 for medtmp, eddmp (*N*,*N*′), and eddmp (*N*,*N*), respectively) are quite large. Thus, it is anticipated that the basicities of the unprotonated nitrogen atom are weakened due to the hydrogen bond between the nitrogen atoms ($NH^+\cdots N$) in the same manner as that of edtmp (Chart 1) in the HL species. The small values of $\log K_2$ and the small change in the chemical shift indicate that the second protonation predominantly occurs on the phosphonate oxygen atom. The small difference between the second and third protonation constants indicates that the third protonation occurs on the unprotonated imino nitrogen atom. Consequently, both of the imino nitrogen atoms are protonated, and the hydrogen bond between two nitrogen atoms is disrupted in the H_3L species.

The chemical-shift change due to protonations is quite different between eddmp (*N*,*N*) and eddmp (*N*,*N*′). In the case of eddmp (*N*,*N*′), in which both of the imino fragments have one methylenephosphonate group, the ^{31}P NMR signal shows a large upfield shift due to the first protonation, indicating protonation on the imino nitrogen atom. The second protonation shows a small upfield shift, and the succeeding protonations do not cause a downfield shift. These results indicate that there is no special intramolecular interaction in the higher protonated species, $H_n$eddmp (*N*,*N*′), ($n \geq 3$).

On the other hand, the chemical shift of eddmp (*N*,*N*), in which one fragment has two methylenephosphonates, scarcely changes due to the first protonation. Consequently, the first protonation would occur on the imino nitrogen atom of the fragment having two methyl groups. Since the second protonation occurs on the phosphonate oxygen, it is a reasonable result that the ^{31}P NMR signal does not show an upfield shift. As can be seen from the protonation constants, both of the imino nitrogen atoms are protonated at the third protonation step. Nevertheless, the ^{31}P NMR signal of eddmp (*N*,*N*) does not show an upfield shift due to the third protonation. Thus, an intramolecular interaction in the H_3eddmp (*N*,*N*) is anticipated, i.e., the hydrogen bonds between the protonated imino nitrogen and the phosphonate groups of the other imino fragment as shown in Chart 2. On the other hand, in the case of eddmp (*N*,*N*′), such a peculiar behavior (the downfield shift of higher protonates species H_3L) is not observed. These results indicate that two hydrogen bonds are required for an intramolecular interaction. The chemical shift of the H_4eddmp (*N*,*N*) species, in which all of the phosphonate is protonated, shows a normal value. Consequently, the protonation of phosphonate ruptures the intramolecular hydrogen bonds. Nevertheless, in spite of the protonation of one phosphonate, the hydrogen-bonding structure is maintained for the H_3L species. This might be interpreted as being due to the hydrogen bond between the phosphonate groups ($PO\text{–}H^+\cdots{}^-OP$), as shown in Chart 2. A relatively small

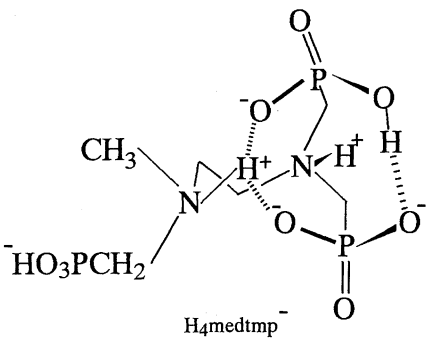


2

Chart 2.

value of $\log K_4$ (=2.8) of eddmp (*N*,*N*) compared with that of eddmp (*N*,*N*′) ($\log K_4$=3.85) supports the idea that the H_3L species is stabilized by the hydrogen bonds. A molecular-mechanics calculation performed with the CAChe® program support the idea that the Chart 2 is a stable conformation.

In the case of medtmp, each ^{31}P NMR signal of iminodiphosphonate (A) and iminomonophosphonate (B) is observed separately. The changes in the chemical shifts of fragments (A) and (B) show different behaviors from each other (Fig. 5, ▽ and △). The first protonation causes a large upfield shift of fragment (B), whereas the signal of fragment (A) scarcely changes. These changes indicate protonation on the imino nitrogen of fragment (B). A relatively small chemical-shift change of both fragments due to the second protonation supports the idea that this protonation occurs mainly on the phosphonate oxygen atom. Fragment (B) shows only a small change in chemical shift due to the succeeding protonations, whereas the fragment (A) shows downfield shift at the steps of third and fourth protonations although both of the nitrogen atoms are protonated. These results indicate that although the imino fragment (A), having two phosphonates, participates in the intramolecular interaction, fragment (B), having only one phosphonate, does not. Consequently, it is confirmed that two hydrogen bonds are required to operate the intramolecular interaction, as shown in Chart 3. The fact that the behavior of the fifth protonation



3

Chart 3.

of medtmp is quite similar to that of the fourth protonation of eddmp (*N,N*) supports the rupturing of the intramolecular interaction. That is, signal (A) shows a large upfield shift and the protonation constant of medtmp ($\log K_5$=2.89) is almost the same as that of eddmp (*N,N*) ($\log K_4$=2.80).

In the case of edtmp, since both of the imino fragments have diphosphonate groups, they can participate with the intramolecular hydrogen bond. The fact that the ^{31}P NMR spectra show only one signal indicates a fast proton exchange. Consequently, the signals of the iminodiphosphonate groups forming the intramolecular hydrogen bond and not forming at higher protonated species must be averaged. Thus, it is quite reasonable that the values of the chemical shifts of higher protonated species of edtmp are very close to the average values of the corresponding chemical shifts of signals (A) and (B) of medtmp (Fig. 5).

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