Inorg. Chem. **1993,** *32,* 2821-2826

Complexation of Indium(III), Gallium(III), Iron(III), Gadolinium(III), and Neodymium(III) Ions with Amino Diphosphonic Acids in Aqueous Solution

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Received June 10, 1992

The compounds $(Me_2N)CH(PO_3H_2)_2$ (MAMDP) and $MeC(NH_2)(PO_3H_2)_2$ (AEDP) have been synthesized. These compounds have been titrated with base and the protonation constants determined. Titration data of pH against added acid or base show that AEDP acts as a ligand toward In^{3+} and that MAMDP binds as a ligand to In^{3+}, Ga^{3+}, Fe^{3+}, Gd^{3+}, and Nd^{3+}. From a least-squares fit of the pH titration curves, the stability and protonation constants have been obtained for solutions containing these ligands and these trivalent metal ions. The ligands bind to the trivalent metal ions *via* the phosphonate oxygens, although it is likely that hydrogen bonding occurs between water and the phosphonate ligand. For the ions In^{3+}, Ga^{3+}, and Fe^{3+}, the logarithms of the stability constants $\log K_{101}$ and $\log K_{102}$ (where $K_{101} = [ML^-]/[M^{3+}][L^{4-}]$ and $K_{102} = [ML_2^{5-}]/[M^{3+}][L^{4-}]^2$) have the respective values of 30.0, 25.8, 28.8 and 35.8, 33.7, 34.3. For the lanthanide ions Nd^{3+} and Gd^{3+} the values are lower at 16.0, 17.6 and 20.4, 20.7, respectively. This pattern of stability constants follows the trend for the complexation of EDTA with these trivalent metal ions. The compound MAMDP remains coordinated to the metal ions in solutions of low acidity because protonation occurs at the free rather than the complexed phosphonate oxygens.

Introduction

As medical technology continues to develop, there is an increasing need for metal complexes to become available for use as clinical *in vivo* imaging agents. Two imaging techniques that use metal complexes and are becoming widely used in clinical practice are magnetic resonance imaging (MRI) and single photon emission computed tomography (SPECT).[1,2] A further imaging technique that is beginning to receive increased attention is positron emission tomography (PET). This method uses computational data analysis to develop the image created from the pair of γ rays generated 180° apart that result from the annihilation of the emitted positron. In the MRI technique, lanthanide complexes are commonly used as image enhancement agents, with those of gadolinium being the ones of choice. For SPECT imaging, much of the development has been carried out using technetium complexes containing the ^{99m}Tc isotope. Other metal ions can, however, be used for imaging applications. Two such ions are Ga^{3+} and In^{3+}, and as a result there is an increasing interest in the synthesis and use of new complexes of gallium and indium as radiopharmaceuticals. These two metal ions can be used in clinical applications as the radioactive isotopes ^{67}Ga, ^{68}Ga, ^{111}In, and ^{113}In. Complexes of ^{68}Ga, which is a positron emittor, can be used for PET imaging. The other isotopes of gallium and indium are γ-ray emittors that can be used in standard imaging techniques.[3]

In order for a metal complex to be useful in imaging applications, a critically important feature is that it have a high stability constant for binding between the metal ion and the ligand. In order to achieve these high metal–ligand binding constants, it is usually necessary that the ligand can complex to the metal ion *via* several coordination positions as a multidentate chelate ligand. A feature of the complexes of gallium and indium, as well as those of the lanthanide ions, is that they exist in solution primarily in their trivalent (3+) states. Two differences between metals having partially filled p or f electron shells are found in the ionic radii and the coordination number. The lanthanide ions have both larger ionic radii and coordination numbers than do the ions of gallium and indium. Thus, whereas the coordination numbers of Ga^{3+} and In^{3+} are usually 6, the coordination numbers of the trivalent lanthanide ions are commonly larger, and they frequently have up to 9 ligands bound.[4] Each group of metal ions are similar, however, in that they each form strong complexes with oxygen donor ligands. This property makes the complexation properties of these metal ions analogous to that of the ferric ion, another trivalent metal center. This ion is particularly significant because it is a competitor for binding to the ligands used for imaging purposes in an *in vivo* environment.

The majority of ligands used for synthesizing imaging agents containing metal ions are chelate compounds of the EDTA type which have both nitrogen and oxygen donor atoms complexed to the metal ion. However, macrocylic compounds are being increasingly considered, and this is especially true for complexing agents that have nitrogen donor atoms as the ligating atoms in the macrocycle.[5] These ligands yield complexes that have high stability constants for lanthanide ions as well as for gallium and indium in their trivalent oxidation states.[6] Nevertheless, an additional factor that must be considered when ligands are designed for imaging applications is the stability of the complex in the regions of the body where the solution pH is low. This feature can be potentially problematic for imaging agents that use EDTA-type ligands, because the relatively high pK_a values of the carboxylato arms of the ligand can result in their preference for a proton rather than for the metal ion under low pH conditions. As a result of this protonation of a ligating carboxylate group, the metal can become decomplexed from the ligand and transferred into the blood stream as a potentially toxic free metal ion. In order to evaluate one possible approach to circumvent

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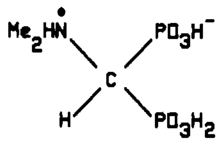
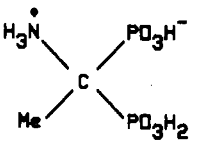
this problem, we have chosen to investigate the complexation of amino phosphonate anions as ligands.[7] These compounds are chosen because the lower pK_a of the hydrogen phosphate moiety can yield metal complexes that have higher stabilities in acid media than do the analogous carboxylate complexes. Phosphonates with amino substituents are chosen because the nitrogen heteroatom can be incorporated into a range of multidentate chelate ligands or used as a point of attachment to a protein. The particular compounds chosen are (dimethylamino)methylenediphosphonic acid (MAMDP) and (aminoethylene)diphosphonic acid (AEDP).[8] In addition, these compounds can serve as model compounds for investigating the selectivity of these ligands toward complexation of the metal ions *via* either the amine or the phosphonate moieties. If, as we anticipate, the amino group does not coordinate to the metal ion, the ligand can then have this nitrogen functionality available for binding the ligand periphery to proteins or other biopolymers. The metal ions that we have chosen to study are In^{3+}, Ga^{3+}, Fe^{3+}, Gd^{3+}, and Nd^{3+}. These ions are chosen because they are some of the more important ions that are used for imaging applications, the lanthanide and iron for MRI and gallium and indium for γ-ray imaging. The ferric ion is also chosen because its high *in vivo* concentration makes it a competitive complexing agent for any new ligands used in imaging applications.



MAMDP



AEDP

This study of the complexation of MAMDP represents one of the first detailed comparisons of a single phosphonate ligand with all five of these trivalent metal ions.

Experimental Section

The compounds MAMDP and AEDP were prepared using published procedures.[8] Gallium chloride, neodymium and indium perchlorates, and neodymium nitrate were purchased from Aesar. Gadolinium nitrate was purchased from Aldrich and ferric nitrate from Baker. All metal salts had a purity of greater than 99.99%. Dimethylformamide, phosphorus trichloride, phosphorous acid, acetonitrile, and glacial acetic acid were reagent grade and were used without prior purification. Microanalyses were carried out by Galbraith Inc., Knoxville, TN. Melting points were obtained on a hot-stage apparatus. ^{1}H and ^{31}P{^{1}H} NMR spectra were obtained on a Bruker AC200 spectrometer as solutions in D_2O.

(Dimethylamino)methylenediphosphonic Acid (MAMDP). Dimethylformamide (14 g, 0.2 mol) was added dropwise with stirring to a mixture of phosphorous acid (17 g, 0.2 mol) and phosphorus trichloride (80 g, 0.6 mol) contained in a round-bottomed flask at ambient temperature. The mixture was warmed to 70 °C and stirred for 1 h, and then water (75 mL) was added carefully to the reaction mixture. After standing for 12 h, the solution was reduced to an oil using a rotary evaporator. Addition of ethyl alcohol to this oil gave a colorless solid. Filtration and recrystallization of the solid from dilute hydrochloric acid gave the compound as colorless crystals. Yield: 30.5 g (70%). Anal. Calcd for $C_3H_{11}NO_6P_2$: C, 16.5; H, 5.07. Found: C, 16.7; H, 5.22. ^{1}H NMR: δ 3.25 (s, 6H), 3.78 (t, 1H; ^2J(PH) = 20 Hz). ^{31}P{^{1}H} NMR: δ 7.33 (s). Mp: 247–250 °C dec.

Aminoethylenediphosphonic Acid (AEDP). Acetonitrile (10 g, 0.24 mol) was added dropwise with stirring to phosphorus trichloride (55 g, 0.4 mol) at 0 °C. The mixture was then stirred at ambient temperature for 20 h. At this time, glacial acetic acid (65 g) was added, and the reaction mixture was stirred at ambient temperature for a further 20 h. The two-phase mixture was allowed to stand without stirring for 1 h; then the top layer was decanted to leave a thick oil. Water (10–20 mL) was added, and the solvent was removed on a rotary evaporator. Addition of absolute ethyl alcohol (50–100 mL) to the residue gave a colorless solid. Filtration followed by recrystallization from dilute hydrochloric acid gave the compound as colorless crystals. Yield: 25 g (51%). Anal. Calcd for $C_2H_9NO_6P_2$: C, 11.7; H, 4.33. Found: C, 11.7; H, 4.60. ^{1}H NMR: δ 1.67 (t, 3H; ^3J(PH) = 14 Hz). ^{31}P{^{1}H} NMR: δ 13.8 (s). Mp: 250–255 °C dec.

Potentiometric Methods. Potentiometric titrations were typically carried out using the solution (50–60 mL) contained in a 150-mL airtight vessel, fitted with inlet and outlet tubes for high-purity nitrogen, glass and reference electrodes, and a buret tip extending below the surface of the solution. Titrations were carried out at 24 ± 0.2 °C, with the temperature monitored by an automatic temperature compensated (ATC) probe. The solutions contained sodium nitrate, sodium perchlorate, or tetramethylammonium perchlorate as the electrolyte at a constant ionic strength of 0.2 M. The solution pH was measured on an Orion Model 720A pH meter which was calibrated by the titration of strong acid (0.20 M) with strong base (0.20 M) in a solution containing sodium nitrate (0.20 M), such that hydrogen ion concentrations were accurately known. The pK_w values that were used in the data fitting were compatible with the ionic strengths of the solution used. The nitrate and perchlorate salts were used because literature data show that they form very weak complexes with trivalent metals used in this study.[9] Protonation constants were determined directly from standard and back-titration data using 0.200 M sodium hydroxide and perchloric acid standardized solutions. Solutions of the ligands were typically 0.5 mM, and the titrant solutions were delivered from a 10-mL buret calibrated with 0.05-mL graduations. The titration data typically contained between 50 and 75 data points which were collected over the pH range 2–12. Stability constants for the gallium and ferric ions were determined by titration with standard base (0.2 M) at the temperature and ionic strength conditions described for the calibration and protonation constant determinations. The ligand concentrations were again approximately 0.5 mM, and the concentrations of the metal nitrate solutions were in the 0.1–0.4 mM range.

Stability constants with neodymium, gadolinium, and indium ions were determined by back-titration with acid. For the back-titrations, solutions containing the ligand, metal ion, and electrolyte were brought to a pH of approximately 12 by the addition of 0.2 M base solution. The resulting solution was then titrated to pH 2 by addition of aliquots of 0.2 M acid solution. This method was used because it enabled the metal complex to remain dissolved in solution throughout the pH range used for the titration. These solutions which are supersaturated in the metal complex still yield valid equilibrium constants even though the system is metastable (see ref 10, p 119). The metal ions as their nitrate or perchlorate salts were dissolved in 0.20 M sodium nitrate solution, and their concentrations were adjusted to yield ligand:metal ion ratios in the region of 2:1 or 3:1. For the case of In^{3+}/MAMDP, the occurrence of a slow equilibrium, as evidenced by slow pH changes, caused the back-titration method to be too slow to be practical at ambient temperature. This titration was therefore carried out at an elevated temperature. A 150-mL airtight vessel was fitted with a nitrogen inlet tube, an outlet condenser to preserve the solution volume, a stir bar, a buret, and an ATC probe. This vessel assembly was placed in a hot water bath maintained at 72–73 °C. Data were collected on an Orion Model 720A pH meter calibrated at 72 °C with a Model 81-02 Ross combination electrode.

Data Fitting

The data were analyzed using the Fortran program BEST by following the published procedures available with the software.[10] The program uses an iterative least-squares-fit algorithm to obtain numerical values from the experimental data. The software package was installed on both an IBM-PC computer and a DEC 3100 workstation, and the experimental data was analyzed using either computer. The data-fitting routine required proposing the presence of both mono- and bischelated species, along with proton-transfer reactions occurring at the peripheral ligand sites to give an array of complexes that differ in the number of protonated sites. The metal hydrolysis constants for the species $M(OH)_n$ (n = 1–4) were taken

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into account for all the different metal ions, with the numerical values for each individual metal ion being taken from ref 11. Polynuclear hydrolysis products such as the cluster compound $Ga_{26}(OH)_{65}^{13+}$ were not included in the calculations because the low concentrations of the uncomplexed metal ions over the entire pH ranges of the titrations preclude their being formed in significant quantity. However, the hydrolysis of a coordinated water ligand in a metal complex that is also ligated with the phosphonate cannot be disregarded in the calculations and cannot be unambiguously distinguished from a proton transfer occurring at a ligand ancillary site. We propose a model, therefore, whereby the chelated complexes contain water molecules that are acidic due to binding to the metal ions or the phosphonate oxygens. Molecular models indicate that in the bis chelate there can be considerable hydrogen bonding between a complexed water molecule and the oxygens of the coordinated phosphonates.

Results and Discussion

Ligand Syntheses and Protonation Equilibria. The compounds MAMDP and AEDP have been prepared by the single-step procedures shown in eqs 1 and 2.[8]

$$Me_2NCHO + 2H_3PO_3 \rightarrow \underset{\text{MAMDP}}{(Me_2N)CH(PO_3H_2)_2} + H_2O \quad (1)$$

$$MeCN + 2H_3PO_3 \rightarrow \underset{\text{AEDP}}{MeC(NH_2)(PO_3H_2)_2} + H_2O \quad (2)$$

In each case the compound can be obtained in pure form in high yield. The combination of an amino acid and a phosphonate moiety results in the compounds existing as the zwitterionic forms $(Me_2HN^+)CH(PO_3H_2)(PO_3H^-)$ and $(MeC(^+NH_3)(PO_3H_2)(PO_3H^-)$. At low solution pH conditions these compounds can only bind to the metal ions *via* the phosphonate oxygen, but as the solution pH is raised, the alkylammonium group is deprotonated and it can act as a ligand through its lone electron pair. For MAMDP in these more basic solutions, it is unlikely that the tertiary amine formed will form stable complexes, because such compounds do not bind strongly to metal ions. For AEDP, however, where the deprotonated alkylammonium ion is a primary amine, such complexation cannot be disregarded. Acid–base titrations of MAMDP and AEDP have identified four species which are present in different pH regions of the solution. These species are $(R_2N)CR'(PO_3^{2-})_2(L)$, $(R_2N^+H)CR'(PO_3^{2-})_2$ (LH), $(R_2N^+H)CR'(PO_3^{2-})(PO_3H^-)$ (LH_2), $(R_2N^+H)CR'(PO_3H^-)_2$ (LH_3), and $(R_2N^+H)CR'(PO_3H^-)(PO_3H_2)$ (LH_4). The interconversions between these species in acid or base solution are shown in Scheme I. The protonation constants K_1, K_2, K_3, and K_4 for MAMDP (R = Me, R′ = H) and AEDP (R = H, R′ = Me) have been measured using potentiometric titration methods. These equilibrium data are collected in Table I as the log K values. The value of log K_1 for MAMDP is 13.4, which is significantly greater than the value of 11.5 found for AEDP. This difference is due to the fact that the methyl groups on nitrogen in MAMDP confer a higher basicity on the nitrogen atom than do the hydrogens on nitrogen in AEDP. The high value of log K_1 for MAMDP (13.4), also likely, reflects both the electron-donating properties of the methyl groups and the electrostatic stabilizing effect that protonation has on the small tetraanion. It should be noted, however, that this numerical value of log K_1 is somewhat inaccurate because the fully deprotonated ligand is present in only 2% at the titration limit (pH 12). The differences in the log K values for K_2, K_3, and K_4 between MAMDP and AEDP are smaller. For log K_2, the values of MAMDP (8.55) and AEDP (8.58) are essentially identical, but for log K_3 and log K_4 the values for AEDP are greater than those for MAMDP by approximately 0.5. This difference in log K values can again be explained by the presence of a methyl group on the carbon atom in MAMDP which results in a slightly lowered acidity at the phosphonate group of this ligand.

Scheme I

$$\underset{\text{L}}{(R_2N)CR'(PO_3^{2-})_2} \overset{K_1}{\rightleftarrows} \underset{\text{LH}}{(R_2N^+H)CR'(PO_3^{2-})_2} \overset{K_2}{\rightleftarrows}$$

$$\underset{\text{LH}_2}{(R_2N^+H)CR'(PO_3^{2-})(PO_3H^-)} \overset{K_3}{\rightleftarrows}$$

$$\underset{\text{LH}_3}{(R_2N^+H)CR'(PO_3H^-)_2} \overset{K_4}{\rightleftarrows} \underset{\text{LH}_4}{(R_2N^+H)CR'(PO_3H^-)(PO_3H_2)}$$

Table I. Protonation Constants ($-pK_a$) for MAMDP and AEDP

	log K_1	log K_2	log K_3	log K_4
MAMDP	13.4	8.55	4.86	1.06
AEDP	11.5	8.58	5.37	1.50
EIDMP	12.4	5.92	4.70	<2

For comparative purposes, the protonation constants for $EtN(CH_2PO_3H_2)_2$ (EIDMP) are included in Table I.[12] Except for the value of log K_2, the protonation constants of EIDMP closely match those of MAMDP. The similarity between the log K_1 values supports our proposal that this step involves proton transfer at the nitrogen, which was shown to be the case for EIDMP. Nevertheless, the protonation constants are not sufficiently close to provide conclusive proof of such a structure, and we cannot disregard the possibility that this step involves proton transfer at a phosphonate oxygen.

Complexation of Metal Ions with MAMDP. Acid–base titrations of MAMDP and AEDP have also been carried out in the presence of trivalent indium, gallium, iron, gadolinum, and neodymium. These metal ions are introduced into the solution as their perchlorate salts. Other than for indium, no quantitative data could be obtained for solutions of the other metal ions with AEDP because of the immediate precipitation of insoluble complexes. No attempt was made to identify these precipitates. The titration data for the metal–ligand combinations of In^{3+}, Ga^{3+}, Fe^{3+}, Gd^{3+}, and Nd^{3+} with MAMDP have been carried out over as a wide pH range as possible. These experimental data have been fitted using the program BEST. The data-fitting routine has required using an iterative fit to equilibrium expressions that require including the presence of the complexes ML^-, MLH, MLH_2^+, ML_2^{5-}, ML_2H^{4-}, $ML_2H_2^{3-}$, $ML_2H_3^{2-}$, $ML_2H_4^-$, ML_2H_5, and $ML_2H_6^+$. In the successive protonations of ML and ML_2 complexes, the method of analysis does not, as we have noted earlier, unambiguously distinguish between proton transfer occurring to and from a coordinated hydroxide site or an ancillary acidic site on the ligand. We find that the respective values of log K_{101} for the complex ML^- with MAMDP are 30.0, 16.0, 28.8, 17.6, and 25.8 for complexation with In^{3+}, Nd^{3+}, Fe^{3+}, Gd^{3+}, and Ga^{3+}. The respective values of log K_{102} for ML_2^{5-} are 35.8, 20.4, 34.3, 20.7, and 33.7 for the same respective metal ions. These data show that, for the diphosphonate ligand MAMDP, the stability constants for complexation with Nd^{3+} and Gd^{3+} are significantly smaller than are those for In^{3+}, Fe^{3+}, and Ga^{3+}.

By comparison, europium(III) complexes of substituted alkanediphosphonic acids have somewhat smaller stability constants than do these complexes of substituted amino diphosphonic acids.[13] Similarly, the respective log K_{101} and log K_{102} complexation between In^{3+} and the ligand $MeP(O)(CH_2P(O)(OH)_2)_2$ to give

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Table II. Logarithms of the Protonation and Stability Constants for the Complexation of Amino Diphosphonates with In^{3+}, Nd^{3+}, Fe^{3+}, Gd^{3+}, and Ga^{3+} [a]

quotient		MAMDP					AEDP
		In^{3+}	Nd^{3+}	Fe^{3+}	Gd^{3+}	Ga^{3+}	In^{3+}
$[ML^-]/[M^{3+}][L^{4-}]$	log K_{101}[b]	30.0	16.0	28.8	17.6	25.8	27.7
$[MLH]/[ML^-][H^+]$	log K_{111}	9.5	>13	6.5	12.9	1.5	3.7
$[MLH_2^+]/[MLH][H^+]$	log K_{121}	<1	2.9	1.4	3.0	1.5	<1
$[ML_2^{5-}]/[M^{3+}][L^{4-}]^2$	log K_{102}	35.8	20.4	34.3	20.7	33.7	32.7
$[ML_2H^{4-}]/[ML_2^{5-}][H^+]$	log K_{112}	10.8	>13	10.3	>13	17.6[c]	9.6
$[ML_2H_2^{3-}]/[ML_2H^{4-}][H^+]$	log K_{122}	9.9	10.8	9.6	10.5		8.4
$[ML_2H_3^{2-}]/[ML_2H_2^{3-}][H^+]$	log K_{132}	6.0	12.6[d]	5.5	7.0	5.4	4.8
$[ML_2H_4^-]/[ML_3H_3^{2-}][H^+]$	log K_{142}	4.9		3.9	3.7	4.0	1.0
$[ML_2H_5]/[ML_2H_4^-][H^+]$	log K_{152}	1.7	2.1	1.6	1.2	2.0	<1
$[ML_2H_6^+]/[ML_2H_5][H^+]$	log K_{162}	<1		1.5		2.0	<1

[a] The errors in the values which are given to one decimal place are ±0.3. [b] The designation uses MHL as 111. [c] The composite value of log K_{112} + log K_{122}. [d] The composite value of log K_{132} + log K_{142}.

ML and ML_2 species are 15.4 and 18.7, although these values have been subsequently considered to be doubtful.[14] Our data also indicate that the stability constants for complexation between In^{3+} and these substituted amino diphosphonic acids are comparable to or larger than those found for carboxylato ligands. The respective binding constants for EDTA and the ions In^{3+}, Nd^{3+}, Fe^{3+}, Gd^{3+}, and Ga^{3+} are 24.95, 16.48, 25.1, 17.37, and 20.25.[15] The trends between MAMDP and EDTA are very similar, with the highest binding constants being found for In^{3+} and Fe^{3+} and the lowest being found for Nd^{3+} and Gd^{3+}. Carboxylates with fewer binding sites for chelation have significantly smaller binding constants than does MAMDP since the stability constants for In^{3+} binding of glycine and nitriloacetic acid are 8.22 and 8.02, respectively.[14] Values similar to those for In^{3+}/EDTA have also been found for a series of phenolic ligands related to *N,N'*-bis(2-hydroxybenzyl)ethylenediamine-*N,N'*-diacetic acid.[16]

From Table II it is apparent that there are no large differences between the stability constants of MAMDP/In^{3+} and AEDP/In^{3+}, which indicates that the amino group of AEDP does not complex to indium. Nevertheless, it is difficult from these data to precisely deduce whether the phosphonate groups are monodentate or bidentate or whether one or more water molecules are complexed to the trivalent metal ions. The values of log K_{111} and log K_{112} for the complexes are decreased from those found for free MAMDP. This decrease may be due to the inductive effect caused by complexation of the phosphonate oxygen to the metal ion. For the case of Fe^{3+}, however, the value of log K_{111} in the complex is 6.5, as compared to a value of 13.7 in the absence of a metal ion. This large decrease in log K_{111} caused by the addition of Fe^{3+} to solutions of MAMDP is suggestive of complexation of the amine nitrogen to the metal ion.

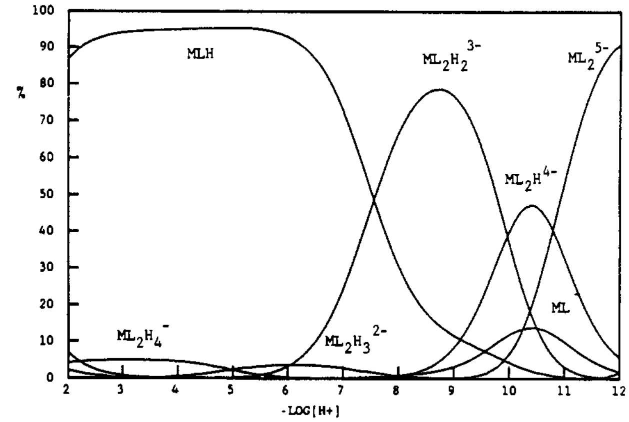

Figure 1. Species distribution plot for aqueous solutions of MAMDP and In^{3+} at a 2:1 ligand:metal ion ratio.

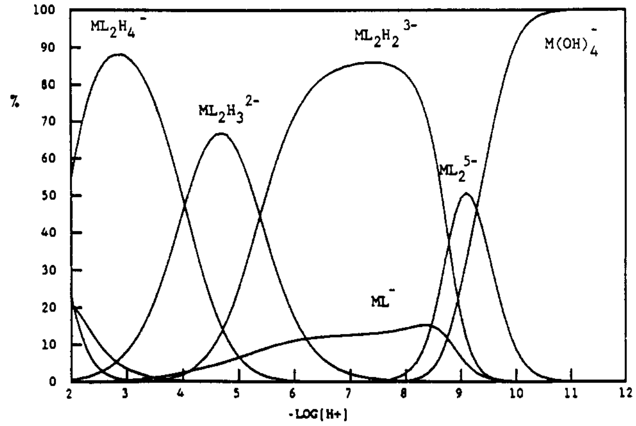

Figure 2. Species distribution plot for aqueous solutions of MAMDP and Ga^{3+} at a 2:1 ligand:metal ion ratio.

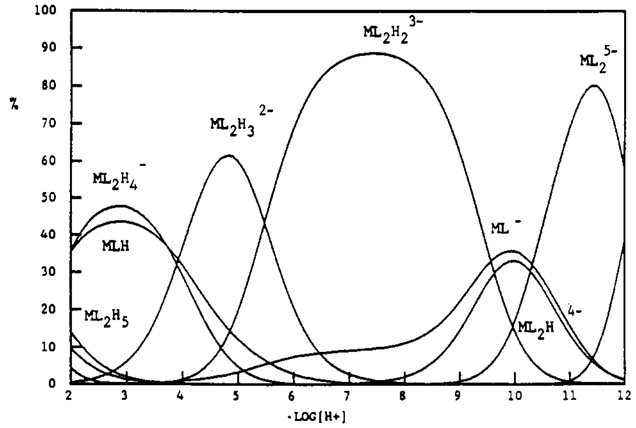

Figure 3. Species distribution plot for aqueous solutions of MAMDP and Fe^{3+} at a 2:1 ligand:metal ion ratio.

Species distribution curves (Figures 1–5) derived from the stability and protonation constant data show that a variety of species are present in solution throughout virtually the entire pH range. The concentrations of the ions present in these solutions reflect those values used in the respective titrations. For Ga^{3+} and Fe^{3+}, the major species present in solutions at low pH have the formulas $ML_2H_3^{2-}$ and $ML_2H_4^-$ although, for Fe^{3+}, the species MLH is a significant contributor in the pH 2.0–3.5 range. For Nd^{3+}, the species MLH is the major contributor down to pH 4, but in the region down to pH 2 the species MLH_2^+ becomes the dominant complex in solution. For In^{3+} and Gd^{3+}, acidic solutions consist of one dominant complex, which in each case is MLH. Thus all the solutions show complexation of the metal ions with MAMDP down to low pH values. By contrast, the anionic complexes of EDTA or DTPA can be readily protonated.[17] The difference between MAMDP and the EDTA-type ligands is due

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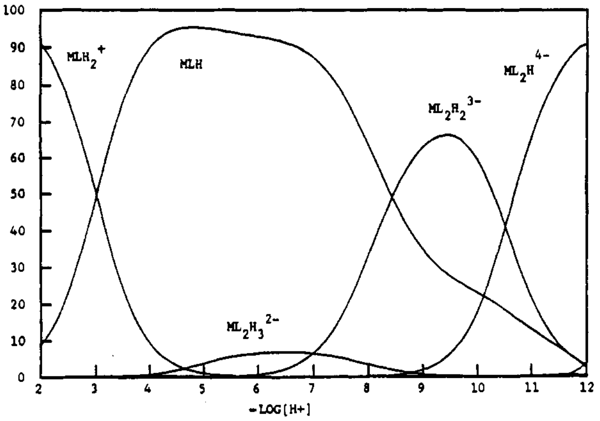

Figure 4. Species distribution plot for aqueous solutions of MAMDP and Gd^{3+} at a 2:1 ligand:metal ion ratio.

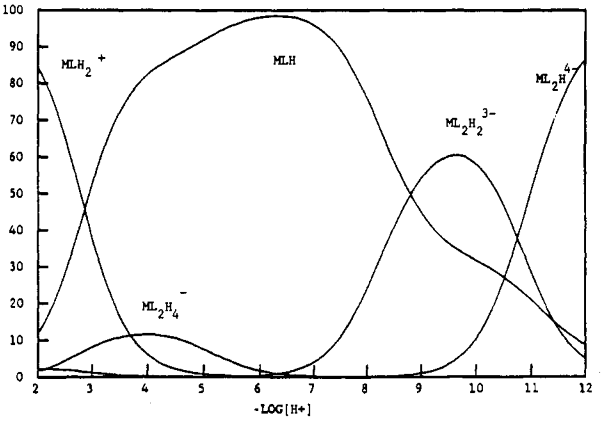

Figure 5. Species distribution plot for aqueous solutions of MAMDP and Nd^{3+} at a 2:1 ligand:metal ion ratio.

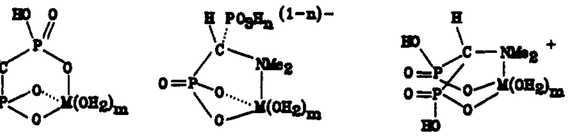

Figure 6. Proposed structures for complexes having a metal ion:ligand ratio of 1:1.

to the facts that MAMDP has a smaller pK_1 value than does a carboxylic acid and also that the complexes containing MAMDP have uncoordinated ancillary oxygens that can be protonated in preference to the oxygen anions that coordinate to the metal ion. It is possible that at higher pH's the amino group coordinates to the metal ion, accompanied by subsequent deprotonation at this site. It is likely that such amino-coordinated complexes, if present, exist specifically in the forms ML_2H^{4-} and ML_2^{5-}, and possibly ML. If this is the case, a difference in acid dissociation constants will be observed between the coordinated and uncoordinated ligand amino sites, corresponding the stabilization of this site by complexation to the metal center. Such a coordination may also be accompanied by a conformational change within the ring and the loss of any stabilization contribution from the hydrogen bonding. In Figure 6 are shown some of the possible coordination modes between MAMDP and the trivalent metal ions when complexed in a 1:1 stoichiometry. These proposed structures are based on precedence found in the structures of phosphonate complexes with similar metal ions.[18]

Three types of ligating mode are shown, one where the amine group is uncoordinated and two where it is bonded to the metal ion. For cases where log K_{111} of the complex is close to log K_1 of the ligand, we propose that the structure of the complex resembles that with the amine group uncoordinated. Such a case is likely for In^{3+}, Nd^{3+}, and Gd^{3+} with MAMDP. For cases such as Fe^{3+} and Ga^{3+}, where the respective log K_1 and log K_{101} values are widely different between the free and complexed MAMDP, coordination of the amine group is likely with the other coordination sites complexed with the oxygens of either one or both of the phosphonate groups. In Figure 7 are shown the possible coordination modes when the complexes have a 1:2 (M:L) stoichiometry. Again, structures are proposed where the nitrogen is either coordinated or free. In this figure we also propose a structural modification that explains how a coordinated water molecule can also be associated with the phosphonate oxygens.

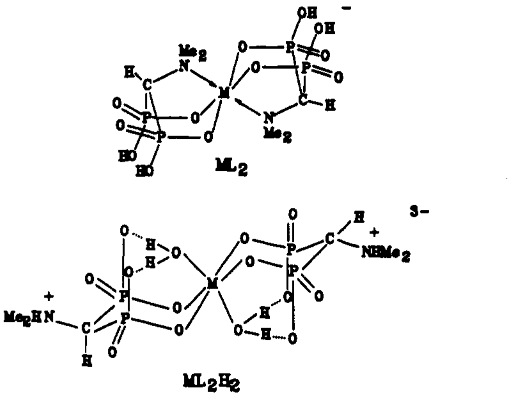

Figure 7. Proposed structures for complexes having a metal ion:ligand ratio of 1:2.

Hydrogen-bonded structures such as these are likely to interconvert between several forms. Also it is to be expected that the removal or addition of protons will cause structural and conformational changes within the various solution species. In each instance, a slow drift in the solution pH was observed upon addition of aliquots of acid or base during the titration. No precipitate was observed, however, during the establishment of equilibrium in these solutions. In cases where these protonation reactions occurred too slowly for efficient titration of the solutions at ambient temperature, elevated temperatures were used. The species distribution curves suggest that at low pH values the slow equilibrium is represented by eq 3 and at high pH values by the reverse (eq 4). These observations of the slow establishment of

$$MLH + LH^{3-} \rightarrow ML_2H_2^{3-} \tag{3}$$

$$ML_2H_2^{3-} \rightarrow ML_2H^{4-} + H^+ \tag{4}$$

equilibrium between the different solution species supports our premise that coordinative changes occur within the metal complex during these proton-transfer steps. This system is not unique, however, since similar slow equilibria for complexation reactions with trivalent metal ions have been reported previously.[19]

The literature on the binding of phosphonates to lanthanide ions is quite extensive, and several studies have been published which include data for Nd^{3+} and Gd^{3+}.[20] The stability constant data for ethylenebis((iminomethylene)phosphonic acid) (EIMPA), ethylenebis((iminoisopropyl)propylenephosphonic acid) (EIPPA), and ethylenedinitrilo-*N,N'*-diacetic-*N,N'*-bis(methylenephosphonic acid) (EDDMPA) with these ions are compared in Table III with the analogous stability constant data for MAMDP.

In conclusion, it is apparent that diphosphonate ligands meet many of the criteria required of a ligand to be useful for the synthesis of imaging agents using radioactive gallium and indium.

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Table III. Comparative Stability Constant Data for the Binding of Gd^{3+} and Nd^{3+} with MAMDP, EIMPA, EIPPA, and EDDMPA[a]

	Gd^{3+}		Nd^{3+}	
	log K_{101}	log K_{102}	log K_{101}	log K_{102}
MAMDP	17.6	20.7	16.0	20.4
EIMPA		26.80		26.80
EIPPA	12.27	26.39	11.60	26.05
EDDMPA	17.35	27.92	17.56	28.15

[a] Comparative data taken from ref 20.

The metal to ligand binding constants are high, and there is no evidence for the precipitation of the metal hydroxide, even at high pH values. Furthermore, the presence of ancillary oxygens on the complexed diphosphonate allows the ligand to remain bound to the metal ion even in solutions of high acidity. The binding constant for Fe^{3+} is closely similar to those found for Ga^{3+} and In^{3+}, thereby making the latter two ions competitive binders for the diphosphonate ligand in the presence of ferric ion in the solution. For the lanthanide ions Gd^{3+} and Nd^{3+}, the binding constants for MAMDP are much smaller, thereby making these diphosphonate ligand systems less favorable for use with a lanthanide ion as a MRI enhancement agent.

Acknowledgment. We thank R. J. Motekaitis for many helpful discussions concerning the use of the program BEST and the Center for Bioenvironmental Research for financial support.