creasing acidity of the solutions—with the instrument settings remaining constant—greatly improved multiplet resolution, and, in the alkaline systems, perfectly resolved multiplets were seen. This effect was first observed[3] for the triplet in the ^{31}P spectrum of methylenediphosphonate. Even the salt of phenylphosphinic acid, $C_6H_5P(O)(H)OH$ (which in acid solution exhibits the P–H doublet with no fine structure), showed a triplet fine structure in both of the doublet peaks. These triplets are attributable to coupling of the phosphorus atoms with the *ortho* hydrogens of the phenyl group and the over-all phenomenon probably is due to exchange processes involving the protons in the solution. A similar effect was observed for the salt of phenylphosphonic acid, $C_6H_5P(O)(OH)_2$.

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Nitrilotri(methylenephosphonic acid), Ethyliminodi(methylenephosphonic acid), and Diethylaminomethylphosphonic Acid: Acidity and Calcium(II) and Magnesium(II) Complexing

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The acidity constants for nitrilotri(methylenephosphonic acid), ethyliminodi(methylenephosphonic acid), and diethylaminomethylphosphonic acid are reported. The available information, including measurements of p*K* and ^{1}H and ^{31}P nmr chemical shifts as a function of the number of bound protons per ligand, indicates that these ligands exist as dipolar ions in solution. Complexing of alkaline earth metal ions by nitrilotri(methylenephosphonic acid) is shown to be principally due to interaction with the phosphonate part, with little interaction by the nitrogen. The contrast with ligands containing the acetate moiety is discussed. Complexing data show that successive replacement of methylenephosphonic groups by ethyl groups results in weaker Ca^{2+} and Mg^{2+} complexes.

Introduction

Considerable interest has developed during recent years in the complexing properties of molecules containing N-acetate moieties. In particular, the literature dealing with nitrilotriacetic acid (NTA) is quite extensive. The effect of the substitution of acetate by methylenephosphonate on the nitrogen has been of interest also. It has been shown[1] that the replacement of one acetate by a methylenephosphonate group resulted in a significant increase in the Ca^{2+} and Mg^{2+} stability constants, while replacement by two methylenephosphonate groups resulted in a slight decrease in the Ca^{2+} stability constant.[2]

With the development of a new synthetic route for preparing α-aminomethylphosphonic acids,[3] it was of interest to measure the acidity and Ca^{2+} and Mg^{2+} stability constants for molecules containing one, two, and three methylenephosphonates attached to nitrogen.

In order to define more clearly the individual deprotonation steps of the α-aminomethylphosphonic acids, ^{1}H and ^{31}P nmr chemical shifts were obtained as a function of the number of bound protons per molecule. This approach has been beneficial in confirming the existence of NTA and related N-acetates as dipolar ions in solution.[4]

Experimental Section

Chemicals.—Nitrilotri(methylenephosphonic acid) (NTMTP), ethyliminodi(methylenephosphonic acid) (EIDMP), and diethylaminomethylphosphonic acid (DEAMP), isolated as the monopotassium sesquihydrate salt, were prepared according to known methods.[3] *Anal.* Calcd for $N(CH_2PO_3H_2)_3$: C, 12.05; N, 4.68; P, 31.08. Found: C, 12.14; N, 4.61; P, 31.35. Calcd for $CH_3CH_2N(CH_2PO_3H_2)_2$: C, 20.60; N, 6.01; P, 26.61. Found: C, 20.54; N, 5.90; P, 26.80. Calcd for $(CH_3CH_2)_2N(CH_2PO_3HK)\cdot 1.5\,H_2O$: C, 25.85; N, 6.03; P, 13.33. Found: C, 26.07; N, 5.90; P, 13.40.

Potentiometric Measurements.—The potentiometric titrations for determination of acidity and metal complexing constants employed a Beckman Expandomatic pH meter with a Sargent S-30050-15 glass electrode. The pH meter was calibrated with Fisher buffers at pH values of 2, 4, 6, 7, 9, 10, and 11. The pH meter was calibrated several times during a titration using the buffer in the pH region of the titration. Also the buffers checked with each other within ±0.03 pH unit. The distilled water used to make up the solutions was boiled to remove any residual CO_2 that may interfere in the titration. All experiments were conducted in a nitrogen atmosphere.

Acidity Constants.—Acidity constants were determined at 25.0° in 1 *M* KNO_3. Primary standard grade KNO_3 was used in all experiments.

In a typical experiment, *y* ml of a solution that is C_l molar in H_aL (where H_aL represents the completely protonated ligand)

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[1] G. Schwarzenbach, H. Ackermann, and P. Ruckstuhl, *Helv. Chim. Acta*, **32**, 1175 (1949).

[2] S. Westerback, K. S. Rajan, and A. E. Martell, *J. Am. Chem. Soc.*, **87**, 2567 (1965).

[3] K. Moedritzer and R. R. Irani, *J. Org. Chem.*, **31**, 1603 (1966).

[4] D. Chapman, D. R. Lloyd, and R. H. Prince, *J. Chem. Soc.*, 3645 (1963).

and C_2 molar in KOH are added to b ml of a solution with a molarity of C_1 in H_aL, both solutions being at the same ionic strength. The material balances for the system and the ensuing calculations, correcting for ligand hydrolysis at high pH, are[5]

$$C_1 = \sum_{i=0}^{i=a} \mathrm{H}_i\mathrm{L}^{(-a+i)} \tag{1}$$

$$\bar{a} = a + \frac{K_w^0}{C_1(\mathrm{H}^+)\gamma_{\mathrm{OH}^-}} - \frac{(\mathrm{H}^+)}{C_1\gamma_{\mathrm{H}^+}} - \frac{yC_2}{C_1(b+y)} \tag{2}$$

where (H^+) is antilog (−pH) and

$$\gamma_{\mathrm{H}^+} = \frac{\text{antilog}\,(-\mathrm{pH})}{[\mathrm{H}^+]} \tag{3}$$

$$\gamma_{\mathrm{OH}^-} = \frac{K_w^0}{[\mathrm{OH}^-]\,\text{antilog}\,(-\mathrm{pH})} \tag{4}$$

where brackets indicate concentration.

In 1 M KNO_3, the values of γ_{H^+} and γ_{OH^-} were found to be 0.691 and 0.911. A value of 1.008×10^{-14} was used for K_w^0.

Experimental values of (H^+), y, b, C_2, C_1, γ_{OH^-}, and γ_{H^+} were used to calculate $\bar{a}$ from eq 2. These values of $\bar{a}$ were then used to calculate constants from eq 5 where

$$\bar{a} = \frac{\displaystyle\sum_{i=1}^{i=a} \frac{i(\mathrm{H}^+)^i}{K_1K_2\cdots K_a}}{1 + \displaystyle\sum_{i=1}^{i=a} \frac{(\mathrm{H}^+)^i}{K_1K_2\cdots K_a}} \tag{5}$$

$$K_i = \frac{(\mathrm{H}^+)[\mathrm{H}_{a-i}\mathrm{L}]}{[\mathrm{H}_{a-i+1}\mathrm{L}]} \tag{6}$$

All computations of the equilibrium constants were made using an IBM 7044 computer and a minimum of 30 data points.

Calcium and Magnesium Stability Constants.—The calcium and magnesium stability constants also were determined in 1 M KNO_3. The experimental procedure was as follows: Standardized $Ca(NO_3)_2$ or $Mg(NO_3)_2$ solution was added in about 15 increments to a solution with a known concentration of ligand and 1 M in KNO_3, with the pH of the solution adjusted to a value where the ratio of the concentrations of H_iL and $H_{i-1}L$ was near 1. After each addition of metal ion solution, the pH of the solution was recorded. The concentration of the solution containing the metal ion was always much greater than the concentration of the ligand solution to minimize changes in the ionic medium.

The general mass balance equations for the total metal, ligand, and proton concentrations were used to calculate the formation constant

$$\beta_{\mathrm{MH}_i\mathrm{L}} = \frac{[\mathrm{MH}_i\mathrm{L}]}{[\mathrm{M}][\mathrm{H}_i\mathrm{L}]} \tag{7}$$

In all computations, only two forms of the ligand were assumed to co-exist at a specific pH, *i.e.*, H_iL and $H_{i-1}L$. Overlap by a third species was minimized where possible; for example, β_{MHL} for NTMTP was determined in the region where the ratio of total acidity to ligand was below 1 to take advantage of the large difference between K_5 and K_6 as compared to the difference between K_4 and K_5. Such a technique was not applicable to β_{MH_2L} for NTMTP, and larger errors are shown in Table II.

Nuclear Magnetic Resonance Spectra.—The ^{31}P nmr measurements were obtained with a Varian high-resolution spectrometer operating at 24.288 Mc and are reported relative to 85% H_3PO_4 as an external reference. A Varian A-60 spectrometer was used to obtain ^1H data, and chemical shifts are reported relative to the methyl groups of the sodium salt of 3-(trimethylsilyl)-1-propanesulfonic acid, present as an internal reference. Solutions for nmr measurements were prepared quantitatively in order to maintain constant concentration for each ligand. Solutions for ^1H measurements on EIDMP and DEAMP were prepared in D_2O and the pH adjusted with DCl or NaOD in order to eliminate interference from the ^1H resonance due to H_2O protons.

Results and Discussion

The potentiometric titration data are deposited with the American Documentation Institute.[6]

Acidity Constants.—Like other phosphonic acids, α-aminomethylphosphonic acids are expected to form complexes with K^+. In the absence of K^+, the dissociation constants of the weakest proton[7] of all the ligands studied are estimated to be less than 10^{-13} and hence are not accurately measurable from potentiometric titrations.

The successive acidity constants for NTMTP, EIDMP, and DEAMP are tabulated in Table I. The pK values for the strong protons of NTMTP and EIDMP are small and cannot be measured accurately using conventional pH titration procedures.

TABLE I

ACIDITY CONSTANTS, 1 M KNO_3, 25.0°

	$N(CH_2PO_3H_2)_3$	CH_3CH_2N- $(CH_2PO_3H_2)_2$	$(CH_3CH_2)_2$- $NCH_2PO_3H_2$
pK_a[a]	12.34 ± 0.14	12.42 ± 0.10	12.32 ± 0.19
pK_{a-1}	6.66 ± 0.04	5.92 ± 0.04	5.79 ± 0.11
pK_{a-2}	5.46 ± 0.05	4.70 ± 0.04	. . .
pK_{a-3}	4.30 ± 0.05	<2	. . .
pK_{a-4}	<2	. . .	. . .
pK_{a-5}	<2	. . .	. . .

[a] a equals the number of protons on the completely protonated ligand.

As will be evident from the following arguments, the pK data indicate that α-aminomethylphosphonic acids and partial salts exist as dipolar ions in solution. It is known[8] that phosphonic acid groups possess a strong proton in molecules where formation of a dipolar ion is not possible. However, the three phosphonic acids described in this paper have one less strong proton than would be predicted. For example, DEAMP would be expected to have a strong and a weak proton due to its single phosphonic acid group, yet it actually has two weak protons. Likewise, EIDMP and NTMTP have, respectively, only one and two strongly acidic protons.

Also, another result supporting the existence of a dipolar ion in solution for these anions is the fact that values for pK_a are essentially identical within the experimental error. This would indicate that the deprotonation of the last proton is independent of the charge of the anion. The difference in charge for the extreme case, *i.e.*, NTMTP and DEAMP, is 4 units. In addition, the large difference between pK_a and

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[5] R. R. Irani and C. F. Callis, *J. Phys. Chem.*, **65**, 934 (1961).

[6] Material supplementary to this article has been deposited as Document No. 9376 with the ADI Auxiliary Publications Project, Photoduplication Service, Library of Congress, Washington 25, D. C. A copy may be secured by citing the document number and by remitting $2.50 for photoprints or $1.75 for 35-mm microfilm in advance by check or money order payable to: Chief, Photoduplication Service, Library of Congress.

[7] Throughout the remainder of this discussion the terms "weak proton" and "strong proton" are used for brevity to distinguish weakly acidic and strongly acidic hydrogen atoms for a specific molecular structure, respectively.

[8] R. R. Irani and K. Moedritzer, *J. Phys. Chem.*, **66**, 1349 (1962), and other references therein.

pK_{a-1} for the three ligands is consistent with the dipolar ion assignment. Simple electrostatic arguments would not predict such a large difference. The difference between pK_5 and pK_6 (5.68) for NTMTP may be contrasted to that for tetraphosphoric acid (1.71 in 1 *M* tetramethylammonium nitrate),[9] a similarly charged species incapable of existing as a dipolar ion in solution.

Consistent with the above, a complete single crystal X-ray structure determination,[10] where all twelve hydrogen atoms were located, has shown that NTMTP does exist as a dipolar ion in the solid state.

The similarity of pK_a for the ligands deserves additional comment. While the replacement of a methylenephosphonate by the less electronegative ethyl group would be expected to result in higher pK values, the charge effect contributing to multiple bonding would have an opposite contribution to that of the alkyl group. Moreover, the statistical factor for proton dissociation would cause major differences in the values of pK_a for the three acids studied if the weakest proton was associated with a phosphonate group. Additional evidence for the dipolar ion assignment will be given in the nmr section.

Nmr Measurements.—The changes in ^{31}P and ^{1}H chemical shifts for the ligands as a function of the number of equivalents of added base are presented in Figures 1 and 2.

A large change in the ^{31}P nmr chemical shift results upon removal of the final proton for each of these ligands, which is consistent with a final deprotonation step involving N, *i.e.*

$$[(CH_3CH_2)_{3-n}NH^+(CH_2PO_3{}^{2-})_n] \rightleftharpoons [(CH_3CH_2)_{3-n}N(CH_2PO_3{}^{2-})_n] + H^+ \quad (8)$$

where $n = 1$, 2, or 3. Except for the removal of the weakest proton, the ^{31}P chemical shift behavior of the ligands is typical of simple phosphonates.[11] The change in the ^{31}P nmr chemical shift for NTMTP upon removal of the final proton has been attributed[8] to the change in the extent of nitrogen hybridization and its effect upon the shielding of the phosphorus atom. Similar effects occur upon removal of the final proton from EIDMP and DEAMP. The formalism employed in eq 8 is not meant to emphasize formal zwitterion formation as opposed to a multiple bonded structure.

The ^{1}H nmr data offer strong evidence for the involvement of nitrogen in the final deprotonation step. For example, the removal of the intermediately acidic protons by dissociation from the distant phosphonic acid group results in negligible changes in the CH_3CH$_2$ chemical shift for DEAMP and EIDMP, while a large change in CH_3CH$_2$ chemical shift occurs upon removal of the least acidic proton. Similar results are observed for the shift of the CH$_3$CH_2 protons for DEAMP. At the concentrations employed, it was not possible to obtain reliable data for the ^{1}H chemical shifts of the CH$_3$CH_2 protons for EIDMP due to overlap with the CH_2PO$_3$ signal. These large changes in the nmr chemical shifts of the ethyl protons would not be anticipated if the final deprotonation step involved only the distant phosphonate moiety. However, the change in nitrogen hybridization upon removal of the least acidic proton would be expected to cause a noticeable change in the ethyl proton chemical shifts.

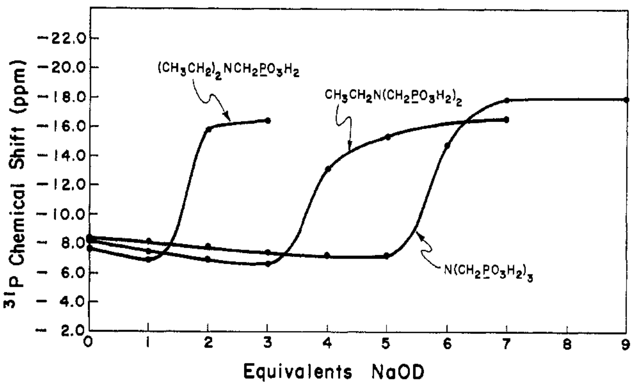

Figure 1.—Variation of ^{31}P nmr chemical shifts with equivalents of NaOD added for NTMTP (0.33 *M*), EIDMP (0.15 *M*), and DEAMP (0.25 *M*) at 25° in D$_2$O.

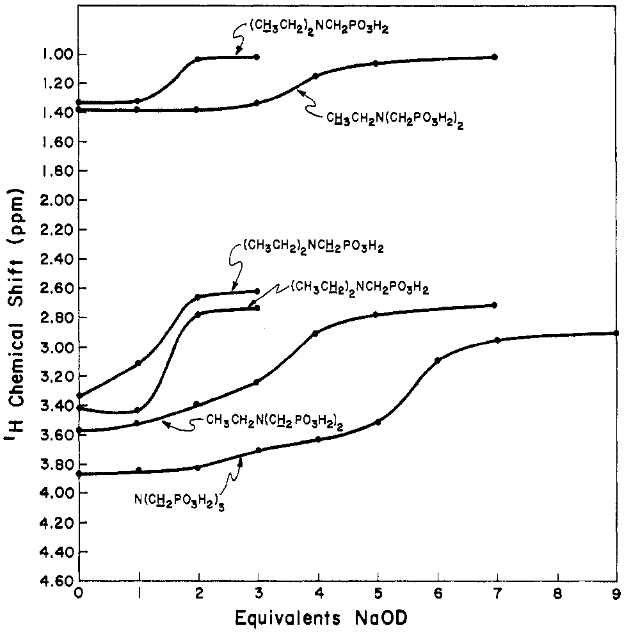

Figure 2.—Variation of ^{1}H nmr chemical shifts with equivalents of NaOD added for NTMTP (0.10 *M*), EIDMP (0.15 *M*); and DEAMP (0.25 *M*) at 25° in D$_2$O.

The change in nitrogen hybridization would also affect the CH_2PO$_3$ protons, and a large change in their chemical shift is observed upon removal of the least acidic proton. Smaller changes in the chemical shift of the CH_2PO$_3$ protons result during the deprotonation of the phosphonic acid groups.

The removal of the least acidic methylenephosphonic acid proton causes +0.26 ± 0.03 change in the CH_2PO$_3$ chemical shift, *i.e.*, removal of the least acidic proton on the phosphonic acid group from DEAMP causes a +0.23 shift, while the removal of the two least acidic protons from the two phosphonic acid groups of

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[9] J. I. Watters, P. E. Sturrock, and R. E. Simonaitis, *Inorg. Chem.*, **2**, 765 (1963).

[10] J. J. Daly and P. J. Wheatley, *J. Chem. Soc., Sect. A.*, 212 (1967).

[11] K. Moedritzer, *Inorg. Chem.*, **6**, 936 (1967).

EIDMP causes a +0.28 shift and removal of the three least acidic protons from the three phosphonic acid groups of NTMTP causes a +0.26 shift. These results are in agreement for the removal of the intermediately acidic protons from the phosphonic acid group. Thus, it follows that the large change in the CH_2PO_3 chemical shift for the removal of the last proton is the result of rehybridization of nitrogen and not due to the removal of a proton from a phosphonate site. The proton resonances for the CH_2PO_3 protons are shifted upfield upon substitution of ethyl for methylenephosphonate groups, in agreement with simple electronegativity considerations.

Complexing of Ca^{2+} and Mg^{2+}.—The complexing results for Ca^{2+} and Mg^{2+} with NTMTP, EIDMP, and DEAMP are tabulated in Table II. The average value for β was determined from at least eight data points. The estimated errors are reported in terms of statistical 95% confidence limits. Values for the logarithms of the stability constants β_{ML} for various N-acetates and N-methylenephosphonates are included in Table III.

TABLE II

Ca^{2+} AND Mg^{2+} STABILITY CONSTANTS FOR NTMTP, EIDMP, AND DEAMP, 1 *M* KNO_3, 25°

	log β_{CaH_iL}	log β_{MgH_iL}
	$L^{6-} = N(CH_2PO_3)_3^{6-}$	
L^{6-}	6.68 ± 0.10	6.49 ± 0.10
HL^{5-}	2.85 ± 0.10	3.24 ± 0.09
H_2L^{4-}	2.27 ± 0.3	2.65 ± 0.3
H_3L^{3-}	1.79 ± 0.18	1.85 ± 0.18
	$L^{4-} = CH_2CH_2N(CH_3PO_3)_2^{4-}$	
L^{4-}	3.36 ± 0.05	4.42 ± 0.09
HL^{3-}	1.29 ± 0.08	2.33 ± 0.07
H_2L^{2-}	<<1	1.88 ± 0.26
	$L^{2-} = (CH_3CH_2)_2NCH_2PO_3^{2-}$	
L^{2-}	1.28 ± 0.18	*Ca.* 2[a]
HL^{-}	<<1	1.25 ± 0.16

[a] Estimate. Precipitation prevented precise measurements.

TABLE III

LOGARITHM OF THE STABILITY CONSTANT β_{ML}

	Mg^{2+}	Ca^{2+}
$N(CH_2PO_3)_3^{6-}$	6.49[a]	6.68[a]
$N(CH_2CO_2)(CH_2PO_3)_2^{5-}$	. . .	6.17[b]
$N(CH_2CO_2)_2(CH_2PO_3)^{4-}$	6.28[c]	7.18[c]
$N(CH_2CO_2)_3^{3-}$	5.41[c]	6.41[c]
$CH_3N(CH_2CO_2)_2^{2-}$	3.44[c]	3.75[c]
$CH_3CH_2N(CH_2PO_3)_2^{4-}$	4.42[a]	3.36[a]
$(CH_3CH_2)_2NCH_2PO_3^{2-}$	*Ca.* 2[d]	1.28[a]

[a] 1 *M* KNO_3, 25°, this work. [b] 0.1 *M* KNO_3, 25°, ref 2. [c] 0.1 *M* KCl, 20°, ref 1. [d] Estimated.

Since K^+ forms complexes with the N-methylenephosphonates, the stability constants listed in Table III are expected to be smaller than those determined in a noncomplexing medium. No definitive evidence for the formation of 2:1 complexes (M_2L) was obtained for NTMTP, EIDMP, and DEAMP.

The complexing data, as expected from results reported on the analogous N-acetates,[1] show that the stability constants increase with increase in the number of methylenephosphonic acid groups, which leads to an increase in charge per molecule. Moreover, salts of the weaker acids show higher stability constants for Ca^{2+} and Mg^{2+}. The complexing of Ca^{2+} by EIDMP is comparable with the results obtained for methyliminodiacetate,[1] whereas EIDMP is considerably better than methyliminodiacetate for Mg^{2+}. The β_{ML} values for methyliminodiacetate for Ca^{2+} and Mg^{2+} in 0.1 *M* KCl at 25° are 3.75 and 3.44, respectively.

It is of interest to compare the complexing properties of NTMTP with nitrilotriacetic acid, nitrilodiaceticmethylenephosphonic acid, and nitriloaceticdimethylenephosphonic acid. These compounds represent the complete series for the stepwise replacement of the acetate moiety in NTA by the methylenephosphonate moiety. The log β_{CaL} values on proceeding from NTA to NTMTP are 6.41,[1] 7.18,[1] 6.17,[2] and 6.68, respectively. Considering the compounds in this series other than NTMTP, this nonlinear behavior has been interpreted[2] in terms of the electrostatic repulsion of the larger negatively charged methylenephosphonate groups, which prevents the interaction at any time of the three functional groups about the same divalent calcium ion. In view of the results for NTMTP, where the three acetate groups have been replaced by three methylenephosphonate groups, this interpretation does not appear to be adequate. It would seem that the explanation is much more complicated, involving the relative degree of interaction of the acetate and phosphonate moieties, as well as the configuration of the anion. Also, as will be evident from the following discussion, the role of nitrogen interaction is an important factor in molecules containing only the N-acetate moiety.

The role of nitrogen participation in binding of Ca^{2+} and Mg^{2+} can best be illustrated by considering the N-oxides of NTA and NTMTP.[12] Unlike NTA, there is no large decrease in binding of Ca^{2+} and Mg^{2+} in going from NTMTP to its N-oxide. This suggests that binding of Ca^{2+} and Mg^{2+} in compounds containing the $NCH_2PO_3^{2-}$ moiety is principally by the phosphonate group with little or no interaction by the tertiary nitrogen.

Thus, it would appear that the two principal effects controlling the interaction of Ca^{2+} and Mg^{2+} upon the stepwise replacement of acetate by a methylenephosphonate group are the decreased interaction of the metal ion with $:N \lessdot$ and a corresponding increase in the electrostatic interaction resulting from the higher charge density on the phosphonate group(s). Detailed comparison of the alkaline earth metal binding behavior of mixed aminoacetate–methylenephosphonates should include an evaluation of the contributions of charge, the central nitrogen, and structural effects. These contributions are not quantitatively understood at present.

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(12) R. P. Carter, M. M. Crutchfield, and R. R. Irani, *Inorg. Chem.*, **6**, 943 (1967).