

Complexation Properties of the Di-, Tri-, and Tetraacetate Derivatives of Bis(aminomethyl)phosphinic Acid

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Four ligands, which can be considered as di- [both symmetric (L^1) and asymmetric (L^2)], tri- (L^3), and tetraacetate (L^4) derivatives of bis(aminomethyl)phosphinic acid (L^0) have been synthesized and their complexation equilibria involving Mg^{2+} , Ca^{2+} , Ni^{2+} , Cu^{2+} , Zn^{2+} , Cd^{2+} , and Pb^{2+} have been studied by pH potentiometry. The first two protonation constants of the ligands are lower than those of the analogous diaminopolycarboxylates due to the electron-withdrawing effect of the phosphinate group. The asymmetric ligands L^2 and L^3 and their complexes are protonated first at the primary (NH_2) and secondary (NH) amine groups, respectively. The ligands L^0 , L^1 , L^2 , and L^3 form the species ML , MLH , ML_2 , and ML_2H whereas heptadentate L^4 forms very stable ML complexes, protonated (MLH and MLH_2) species and, unlike the other ligands, it also forms dinuclear M_2L complexes. The stability constants of the complexes of L^0 , L^1 , L^2 , and L^3 are generally lower, while those of the L^4 are similar or higher, than those of the analogous diaminocarboxylate

derivatives. The phosphinate group is not directly coordinated to the metal ions but may contribute to the stability by increasing the electrostatic interaction, which is significant for the complexes of L^4 . The 1H NMR spectra of complexes ZnL^2 , ZnL^3 , and ZnL^4 show an AB multiplet pattern for the protons of the iminodiacetate moiety of the ligands, which indicates the long half-life of the Zn^{2+} -N bond and the rigid structure of this segment of the complexes. The solid-state structure of the ligand $[H_5L^3]Cl$ and complex $K[CuL^1] \cdot H_2O$ have been determined by X-ray diffraction techniques. The arrangement of the ligand L^1 is square planar around Cu^{2+} with two nitrogen and carboxylate oxygen donor atoms, although the axial proximity of a carboxylate and a phosphinate oxygen atom in two neighboring molecules results in a distorted octahedral coordination.

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Introduction

Due to their biological importance there has been a growing interest in recent years in the coordination chemistry of ligands containing phosphinate functional groups.^[1] The charge of the phosphinate group, PO_2^- , is minus one, similar to that of the carboxylate, and thus the complexation properties of aminoalkylphosphinate ligands are similar to those of aminocarboxylates in many respects. However, as phosphinate groups are less basic than carboxylates, the stability constants of the complexes formed with aminoalkylphosphinates are lower than those of aminocarboxylates.^[2–8]

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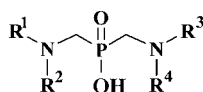
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The successful use of some tri- and tetraacetate derivatives of cyclen in medical diagnosis and therapy has drawn attention to the tetramethylenephosphinates of cyclen, and a number of cyclen derivatives have been synthesized with different phosphinate functional groups. The Gd^{3+} complexes of these ligands have been proposed as contrast enhancing agents in magnetic resonance imaging.^[9–15] Since the methylenephosphinate groups $[CH_2P(R)O_2^-]$, where R is H, alkyl, or aryl in these cyclen derivatives are attached to the ring nitrogens, the phosphinate groups are in terminal position, similar to open-chain ligands. However, in contrast to the carboxylate and phosphonate groups, phosphinate groups may also occupy an “in-chain” position and some multidentate aminocarboxylate ligands that contain PO_2^- groups as linkers have attracted considerable interest in recent years.^[16–26] Phosphinic acid peptides are specific inhibitors of peptide hydrolytic enzymes (e.g. Zn metalloproteinases and aspartic acid proteinases) because the non-hydrolyzable $>PO_2^-$ moiety resembles the transition state of the hydrolyzable peptides.^[18,19]

The complexation properties of bis(aminomethyl)phosphinic acid and some of its derivatives have already been investigated. Complex formation between the ligands bis(aminomethyl)-, bis(*N*-methylsarcozinato)-, bis(*N*-methyl-

prolinato)-, and bis(*N*-methyliminodiacetato)phosphinate and some divalent metal (Co^{2+} , Cu^{2+} , Zn^{2+} , Cd^{2+} , Pb^{2+}) and lanthanide(III) (Ln^{3+}) ions has been studied in solution by pH potentiometry and ^1H NMR and EPR spectroscopy.^[20–24] Although the coordination of the phosphinate group to M^{2+} ions has been detected in some cases, it is more important in the formation of complexes with Ln^{3+} ions.^[21,22] The PO_2^- group has also been incorporated into macrocyclic rings. Eight- and fourteen-membered functionalized bis(aminomethyl)phosphinate macrocycles have recently been synthesized by Aime et al. and Song et al., respectively.^[25,26] The stability constant of the Gd^{3+} complex formed with the eight-membered diphosphinate ligand was found to be relatively high ($\log K_{\text{GdL}} = 17.6$).^[25] The fourteen-membered ligand does not form highly stable complexes.^[26]

The ligand HL^0 (Scheme 1) was first synthesized by Maier and somewhat later by Natchev.^[27,28] More recently, Kubiček et al. have published a new procedure for the synthesis of HL^0 and they also studied its Co^{II} , Ni^{II} , Cu^{II} , and Zn^{II} complexes in solution and in the solid state.^[24] The ligand H_3L^1 was also prepared by Maier but its complexation was studied only with Ni^{II} .^[29] The same author prepared the ligand H_5L^4 from the reaction of iminodiacetic acid (H_2imda) and paraformaldehyde in the presence of hypophosphorus acid.^[30] Similar conditions were used previously in our laboratory by Varga to obtain some bis(aminomethyl)phosphinic acid derivatives from various imino-(di)acids.^[20] The experimental conditions were found to have a great influence on these reactions. Thus, high concentrations of the reactants at reflux temperature led to the formation of a number of by-products and purification of the final products was difficult.^[20]



R^1	R^2	R^3	R^4	Ligand
H	H	H	H	HL^0
H	CH_2COOH	H	CH_2COOH	H_3L^1
H	H	CH_2COOH	CH_2COOH	H_3L^2
H	CH_2COOH	CH_2COOH	CH_2COOH	H_4L^3
CH_2COOH	CH_2COOH	CH_2COOH	CH_2COOH	H_5L^4

Scheme 1. Structure of the ligands synthesized and investigated in this work.

One of our goals was to find a procedure which would allow the large-scale preparation of bis(aminomethyl)phosphinic acid derivatives from readily available, inexpensive starting materials without expensive instrumental purification methods. Similarly, the bis(aminomethyl)phosphinic acid itself can be considered as a building block for the synthesis of macrocycles containing linker phosphinate group(s) when the macrocycle itself has a negative charge. By dividing the Mannich-type synthesis into two consecu-

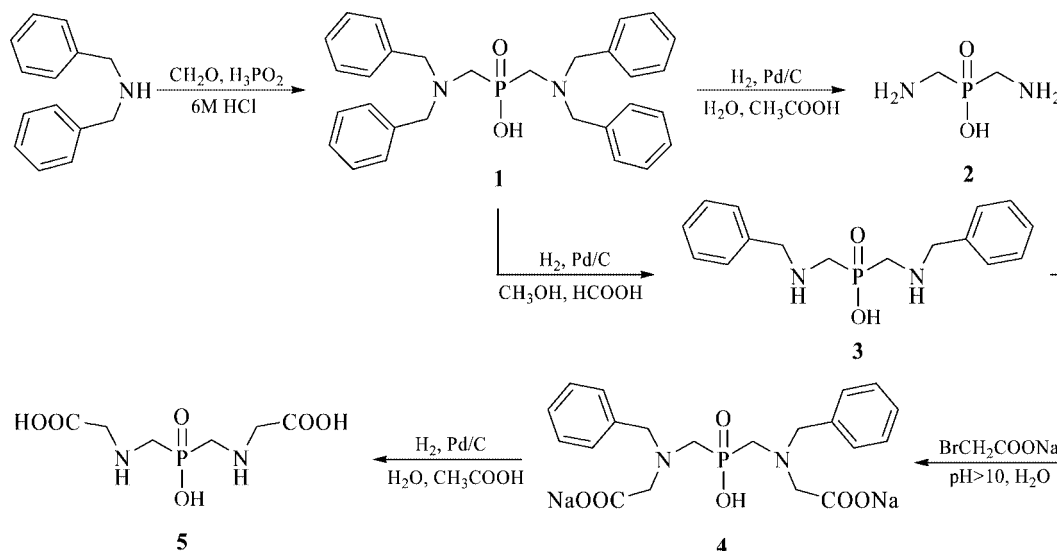
tive steps we have successfully synthesized the ligands H_3L^1 , H_3L^2 , and H_3L^3 (Scheme 1). These compounds can be regarded as fragments of the edta analog H_5L^4 , which was reported earlier.^[21,22] In the present study, the stability constants of the complexes formed between some endogenous (Mg^{2+} , Ca^{2+} , Cu^{2+} , and Zn^{2+}) and toxic (Ni^{2+} , Cd^{2+} , and Pb^{2+}) divalent metal ions and bis(aminomethyl)phosphinic acid derivatives are examined by pH potentiometry. The structures of the ligand $[\text{H}_3\text{L}^3]\text{Cl}$ and the complex $\text{K}[\text{CuL}^1] \cdot \text{H}_2\text{O}$ have been determined in the solid state by X-ray diffraction methods and the Zn^{2+} complexes studied by ^1H and ^{31}P NMR spectroscopy in solution.

Results and Discussion

Synthesis of the Ligands

Synthesis of the symmetric bis(aminomethyl)phosphinic acid derivatives was achieved in a multi-step reaction starting from *N,N*-dibenzylamine according to Scheme 2. The monohydrochloride of the intermediate **1** was obtained in high yields by a Mannich reaction in 6 M HCl. The debenzylation of this key intermediate by catalytic hydrogenolysis can be carried out in different ways depending on the solvent selected. Using acetic acid/water as a solvent in the presence of EtOH with slight heating to achieve complete dissolution of the starting material the bis(aminomethyl)phosphinic acid hydrochloride **2** could be prepared in very high yields. Another advantage of this synthesis is that it does not use expensive materials or instrumentation and can be scaled up easily. The debenzylation of **1** in MeOH in the presence of formic acid was found to be controlled by solubility and the hydrochloride salt of the selectively protected bis(benzylaminomethyl)phosphinic acid **3** crystallized out quantitatively from the reaction mixture during the reduction process. An analytical sample of **3** was obtained by recrystallization of crude **3** from hot water. Compound **3** proved to be a valuable intermediate for the synthesis of new carboxy- or phosphonomethyl derivatives of bis(aminomethyl)phosphinic acid. Alkylation of **3** with bromoacetic acid in the presence of NaOH afforded the trisodium salt of **4**. The monohydrochloride salt of the free acid was prepared by crystallizing **4** from fairly acidic solutions ($\text{pH} < 2$). Debenzylation of **4** in a water/acetic acid mixture afforded compound **5** (H_3L^1).

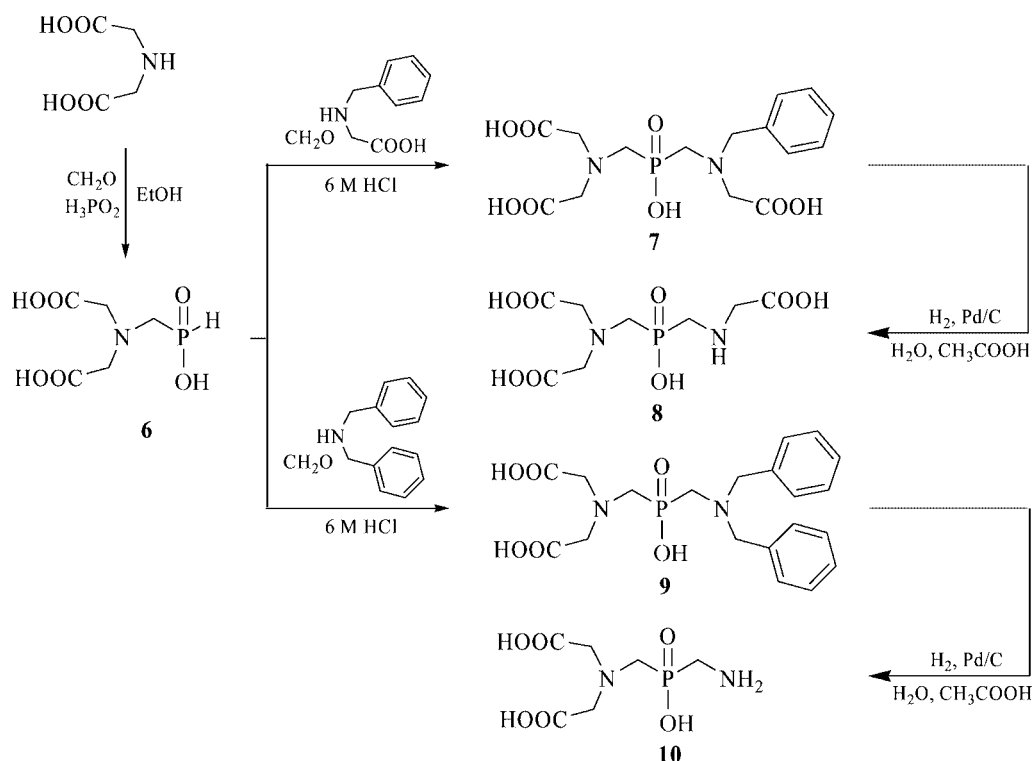
The synthesis of the asymmetric bis(aminomethyl)phosphinic acid derivatives **7–10** is presented in Scheme 3. They are all new compounds that have not been published previously. The intermediate **6** was obtained from the reaction of iminodicarboxylic acid with paraformaldehyde in a Mannich-type reaction in ethanol in the presence of excess hypophosphorus acid, which also acts as an acid catalyst. In this particular case (when H_2imda was used as starting material), the reaction was found to be solubility controlled and at the end of the reaction the product crystallized out from the reaction mixture. The remaining P–H bond in the molecule can be reacted further in a second Mannich-type reaction in 6 M HCl to replace the H with another aminomethyl



Scheme 2. Synthesis of the symmetric bis(aminomethyl)phosphinic acid derivatives studied in this work.

segment. This process allowed us to synthesize hitherto unknown asymmetric bis(aminomethyl)phosphinic acid derivatives (Scheme 3). The best yields for this reaction were obtained when short reaction times (about 1.5 h) were used as the number of by-products in the reaction mixture increased with an increase of the reaction time while the amount of desired products (**7** and **9**) decreased. When longer reaction times (up to 6 h) were used the reaction

mixtures yielded compounds **4** and H_5L^4 , respectively, after the workup and separation procedure. The formation of these compounds is evidence that the phosphorus-carbon bond [$\text{CH}_2\text{P}(\text{O})(\text{OH})\text{H}$] is not stable under Mannich conditions and *trans*-aminomethylation occurs. The debenzoylation of **7** and **9** to **8** (H_4L^3) and **10** (H_3L^2), respectively, was achieved by catalytic hydrogenation under similar conditions to those described for compound **2**.



Scheme 3. Synthesis of the asymmetric bis(aminomethyl)phosphinic acid derivatives studied in this work.

X-ray Crystal Structure of $[\text{H}_5\text{L}^3]\text{Cl}$ and $\text{K}[\text{CuL}^1]\cdot\text{H}_2\text{O}$

The structures of $[\text{H}_5\text{L}^3]\text{Cl}$ and $\text{K}[\text{CuL}^1]\cdot\text{H}_2\text{O}$ were established by single-crystal X-ray diffraction studies (see Figures 1 and 2, Tables 1 and 2, and the Supporting Information). The most important feature of the structure of the protonated ligand of $[\text{H}_5\text{L}^3]\text{Cl}$ is the extensive H-bonding network (Table S1) and the related disordered position of the chloride ions (see below). The compound crystallizes in the noncentrosymmetric space group $Pn2_1a$ (no. 33). It is important to note that the position of the carboxylate hydrogen atoms as well as the protons at the nitrogen atoms could be found in the difference electron density maps of both structures. However, these hydrogen atoms were placed in geometric positions in the final refinement cycle. The C–O bond length data (Table 3) of $[\text{H}_5\text{L}^3]\text{Cl}$ show C3–O4, C6–O6, and C8–O8 bond lengths of 1.298(10), 1.316(9), and 1.310(10) Å, respectively, which also indicate the sites of protonation. Besides the electronic and steric factors of the phosphinate moiety, the higher values of the P–C bond lengths compared to C–C bonds as well as the slightly different bond angles are another tool for the fine tuning of the ligand that could be important in applications. For example, the water exchange rate and thereby the relaxivity of Gd^{III} complexes formed with poly(amino)carboxylates depends on the steric crowding in the complex.^[31] In our case, the significant difference between the P1–C1 and P1–C4 distances [1.803(7) and 1.821(8) Å, respectively] also shows the electronic and steric effects of the mono- and bis(diacetate) arms on the N1 and N2 nitrogen atoms, respectively as these bond lengths are the same in the analogous symmetric bis(aminomethyl)phosphinate hydrochloride structure.^[24]

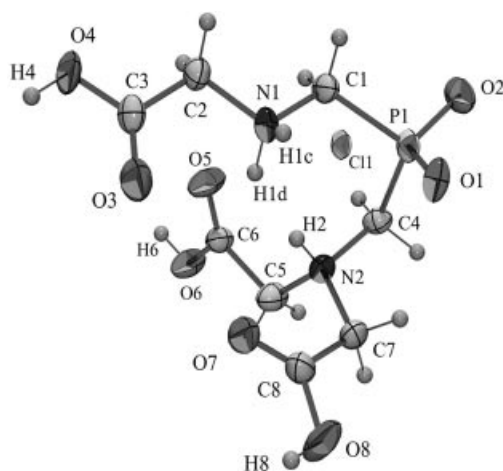


Figure 1. ORTEP view of the asymmetric unit in the structure of $[\text{H}_5\text{L}^3]\text{Cl}$ with thermal ellipsoids at the 50% probability level, with atom-numbering scheme.

The packing of $[\text{H}_5\text{L}^3]\text{Cl}$ is shown in Figure S1 and the data of the H-bonding network are listed in Table S1 (see Supporting Information). The high max/min atomic displacement parameter ratio of the chloride ions in the structure of $[\text{H}_5\text{L}^3]\text{Cl}$ can be explained by the fact that the chloride ion is not fixed in the lattice but loosely occupies a

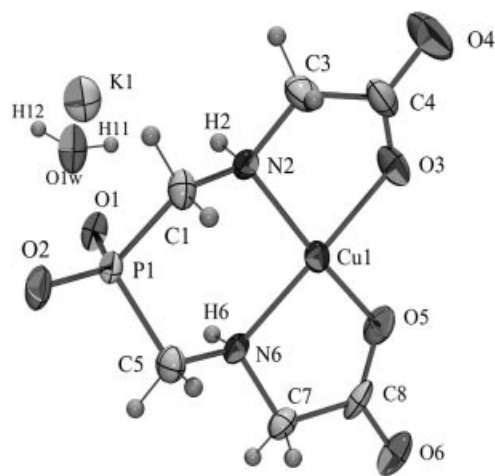


Figure 2. ORTEP view of the asymmetric unit in the structure of $\text{K}[\text{CuL}^1]\cdot\text{H}_2\text{O}$ with thermal ellipsoids at the 50% probability level, with atom-numbering scheme.

Table 1. Selected bond lengths [Å] and angles [°] for $[\text{H}_5\text{L}^3]\text{Cl}$.^[a]

P1–O1	1.503(6)	P1–C1	1.821(8)
P1–O2	1.493(5)	P1–C4	1.803(7)
C3–O3	1.204(10)	C8–O7	1.188(10)
C3–O4	1.298(10)	C8–O8	1.310(10)
C6–O5	1.188(9)	C1–N1	1.477(9)
C6–O6	1.316(9)	C4–N2	1.469(8)
O1–P1–O2	115.7(4)	C2–C3–O3	123.7(7)
C1–P1–C4	103.7(4)	C5–C6–O5	125.7(7)
C5–N2–C4	112.8(6)	C7–C8–O7	125.5(7)
C4–N2–C7	111.8(6)	C1–N1–C2	111.8(6)

[a] See Figure 1 for numbering scheme.

Table 2. Selected bond lengths [Å] and angles [°] for $\text{K}[\text{CuL}^1]\cdot\text{H}_2\text{O}$.^[a]

Cu1–N2	2.008(6)	O1–P1	1.504(6)
Cu1–N6	2.013(6)	O2–P1	1.491(5)
Cu1–O3	1.940(6)	C1–P1	1.811(8)
Cu1–O5	1.961(5)	C5–P1	1.799(8)
Cu1–O2 ⁱ	2.249(5)	O1–K1	2.648(6)
Cu1–O5 ⁱⁱ	2.945(5)	O1w–K1	2.714(7)
O1w–K1 ⁱⁱⁱ	2.731(8)	O6–K1 ⁱ	3.012(7)
O4–K1	2.726(8)	O6–K1	2.780(7)
O3–Cu1–O5	90.1(3)	O2–P1–O1	119.8(3)
O5–Cu1–N2	166.0(2)	O2–P1–C5	108.8(3)
N2–Cu1–N6	99.4(2)	O1–K1–O1w	107.9(2)
N2–Cu1–O2 ⁱ	89.7(2)	C5–P1–C1	104.6(4)
O5–Cu1–N6	83.5(2)	C1–N2–C3	111.2(6)

[a] See Figure 2 for numbering scheme. Symmetry transformations used to generate equivalent atoms: i: $1/3 + y, 2/3 - x + y, 2/3 - z$; ii: $-x, -y, -z$; iii: $4/3 - x + y, 2/3 - x, z - 1/3$.

polar channel. Strong N–H···Cl hydrogen bonds fix the anion in the analogous layered structure of bis(aminomethyl)phosphinate hydrochloride, although the long range Cl–Cl distances are similar in the two structures (approx. 3.96 Å). In our case, however, the three strong hydrogen bonds with the participation of carboxylate donors and P1–O1 or P1–O2 as acceptors as well as the steric restraints prevent the formation of N–H···Cl hydrogen bonds (Table S1).

K[CuL¹] $\cdot$ H₂O crystallizes in the trigonal centrosymmetric space group $R\bar{3}$ (no. 148). The configuration of the nitrogen atoms N2 and N6 is mixed, and the complex exists as a racemate with equal amounts of (*R,S*) and (*S,R*) enantiomers present in the lattice. Selected bond lengths and angles are summarized in Table 2. The coordination of the Cu²⁺ in K[CuL¹] $\cdot$ H₂O is best described as elongated distorted octahedral. N2, N6, O3, and O5 form the basal square-planar coordination and the copper is positioned out of this plane by 0.211 Å. The carboxylate oxygen atom O5ⁱ and phosphinate oxygen atom O2ⁱⁱ of symmetry-related molecules (i: $-x, -y, -z$; ii: $y + 1/3, -x + y + 2/3, -z + 2/3$) are coordinated in the axial positions with Cu–O distances of 2.945 and 2.249 Å, respectively. In this way, two O5 atoms serve as bridging ligands that hold together two copper complexes with a Cu–Cu distance of 3.827 Å and give rise to a supramolecular polymer structure. This bridging role of O5 also supports an octahedral rather than a square-pyramidal coordination. The coordination of O2 of the next complex in the lattice can be attributed to the electron-withdrawing properties of the phosphinate group as well as the increase in the length of the side arm due to the P–C bonds.

The hydrogen-bond data are summarized in the Supporting Information (Table S2). In this web, the H2 and H6 participate in bifurcating hydrogen bonds while O1 is a bifurcating acceptor. However, the N2–H2 $\cdots$ O1 hydrogen bond has an unfavorable angle of 107°.

Tetradentate ligands analogous to 1,3-propanediamine-*N,N'*-diacetate can form square-pyramidal copper(II) complexes.^[32] However, a search in the Cambridge Structural Database (version 5.27, November 2005; update May 2006) revealed that octahedral coordination may also occur in similar compounds.^[33] This is especially important in the case of a Cu^{II} complex containing a small, sterically undemanding ligand such as in (3-hydroxy-1,5-diazacycloheptane-*N,N'*-diacetato)copper(II), where the coordination is N2O4.^[34] Here, the hydroxyl oxygen and a water molecule complete the octahedral coordination with Cu–O distances of 2.456 and 2.564 Å, respectively. The deposited data do not contain hydrogen atoms, which may indicate some ambiguity, but similar octahedral coordination has also been observed in another case where an axial water molecule and another axial carboxylate oxygen complete the coordination sphere of the copper ion with Cu–O distances of 2.275 and 2.780 Å, respectively.^[35]

The coordination of potassium is also octahedral, with carboxylate, phosphinate, and water oxygen atoms (O6ⁱ, O6ⁱⁱⁱ, O4, O1, O1w, and O1w^{iv}; i: $-x, -y, -z$; iii: $x - y + 1/3, -x + 2/3, -z + 2/3$; iv: $-y + 2/3, x - y + 1/3, z + 1/3$) with K $\cdots$ O distances in the range 0.265–3.01 Å. O6 and O1w serve as bridges between the potassium ions and the K $\cdots$ K distance is 4.046 Å. Altogether, the complicated supramolecular structure of K[CuL¹] $\cdot$ H₂O is stabilized by interpenetrating ionic and coordination interactions as well as a strong hydrogen bond network. In the polymer there are hexagonal channels with a diameter of approximately 8.5 Å (Figure S2, Supporting Information), which are filled with disordered water molecules.

Protonation Constants and Protonation Sites of the Ligands

The protonation equilibria of the ligands, L⁰, L¹, L², L³, and L⁴ were studied by pH-potentiometry and ¹H (in some cases ³¹P) NMR spectroscopy (Figures S3–S7 in the Supporting Information). The titrations were performed in the pH range of about 1.8–11.5 in the presence of 1.0 M Me₄NCl. The protonation constants, defined as $K_i^H = [H_iL]/[H_{i-1}L][H^+]$, were also determined in 1.0 M KNO₃ since the complexation with Cd²⁺ and Pb²⁺ was studied in KNO₃ solution in order to avoid the formation of chloro complexes. For the calculation of the protonation constants of the ligands, the number of data points was between 160 and 250. The log K_i^H values obtained are presented in Table 3, where the standard deviations are shown in parentheses. The protonation constants of the ligands L⁰ and L⁴, which have been determined previously (Table 3),^[22–24] are comparable with the ones obtained in this work when the different experimental conditions are taken into account.

As was expected, we found by ¹H (and ³¹P) NMR studies that the most basic donor atoms in all derivatives of L⁰ are the two nitrogens, which are protonated first (Figures S4 and S5).^[21,22,24] The protonation of these nitrogens is followed by protonation of the carboxylates, while the strongly acidic phosphinate group is protonated only in strongly acidic solution.^[22,24] The protonation constants of L⁰ are lower than those of 1,3-diaminopropane (log K_1^H = 10.52 and log K_2^H = 8.74), in which the two nitrogen donors are also separated from each other by three atoms. The behavior of the derivatives of L⁰ is similar. The first two protonation constants of L⁴ (Table 3) are significantly lower than those of 1,3-diaminopropane-*N,N',N'',N'''*-tetraacetic acid (10.41 and 8.02).^[36] Similarly, the log K_1^H and log K_2^H values of L¹ are lower than the first two protonation constants of ethylenediamine-*N,N'*-diacetic acid (L⁶; 9.69 and 6.72).^[36] The lower basicity of the nitrogen atoms of the phosphinate ligands is probably due to the electron-withdrawing effect of the phosphinate group.

Table 3. Protonation constants of the ligands L⁰, L¹, L², L³, and L⁴ (25 °C).

L	log K_1^H	log K_2^H	log K_3^H	log K_4^H
L ⁰ [a, f]	8.73 (0.01)	7.35 (0.01)	–	–
L ⁰ [b]	8.74 (0.01)	7.38 (0.01)	0.91 (0.08)	–
L ⁰ [c]	8.51	7.07	0.77	–
L ¹ [a]	9.00	6.53	2.53	1.66
L ¹ [b]	8.93 (0.02)	6.80 (0.03)	2.65 (0.05)	1.77 (0.05)
L ² [a]	9.97 (0.01)	5.62 (0.02)	2.42 (0.02)	–
L ² [b]	9.94 (0.01)	5.68 (0.01)	2.23 (0.01)	–
L ³ [a]	10.17 (0.01)	5.52 (0.01)	2.49 (0.02)	2.03 (0.04)
L ³ [b]	9.79 (0.01)	5.67 (0.02)	2.68 (0.03)	1.43 (0.04)
L ⁴ [a]	10.01	6.50	2.68	2.17
L ⁴ [b]	9.44 (0.01)	6.56 (0.01)	2.54 (0.01)	1.98 (0.01)
L ⁴ [d]	8.87 (0.01)	6.41 (0.01)	2.49 (0.01)	1.69 (0.05)
L ⁴ [e]	9.27	6.56	2.84	2.32

[a] 1.0 M Me₄NCl. [b] 1.0 M KNO₃. [c] 0.1 M KNO₃. [d] 1.0 M NaCl. [e] 0.16 M NaCl.^[22] [f] Redetermined in the present study (I = 1.0 M Me₄NCl).

A comparison of the data in Table 3 reveals that the difference between the protonation constants $\log K_1^H$ and $\log K_2^H$ is lower for the symmetric ligands L^0 , L^1 , and L^4 than for asymmetric L^2 and L^3 , which show a larger difference in the basicity of the nitrogen atoms. Parallel with this finding, the question arises regarding the protonation order of the nitrogens in the asymmetric ligands L^2 and L^3 . The protonation scheme of L^2 and L^3 was determined by ^1H NMR titrations in the pH range of about 1–12. The ^1H NMR titration curves of ligands L^2 and L^3 are shown in Figures 3 and 4, respectively. In Figure 3, the chemical shift of the $-\text{CH}_2\text{NH}_2$ methylene protons (the center of the doublet) increases with a decrease of pH from about 12 to 8.5, while the signals of both the phosphinate and acetate methylene protons $[-\text{CH}_2\text{N}(\text{CH}_2\text{COO}^-)_2]$ are practically not shifted. This finding indicates that the first proton is attached to the NH_2 group of L^2 . In the pH range of about 4 to 7 the signals of both the phosphinate and acetate methylene protons $[-\text{CH}_2\text{N}(\text{CH}_2\text{COO}^-)_2]$ are strongly shifted to higher frequencies due to the protonation of the imda nitrogen. A further decrease of pH below about 3 results in a shift of the signal of the acetate methylene protons to higher frequencies, which indicates the protonation of the carboxylate groups.

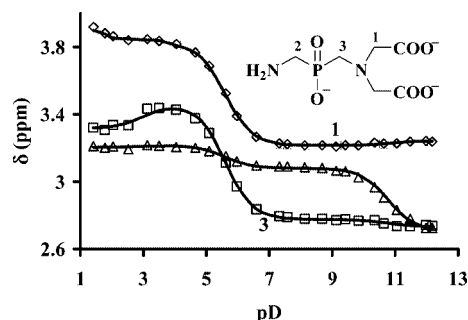


Figure 3. ^1H NMR titration curves of ligand L^2 ($C_L = 0.05\text{ M}$, 25°C) showing the change in the chemical shifts of the protons indicated in the figure.

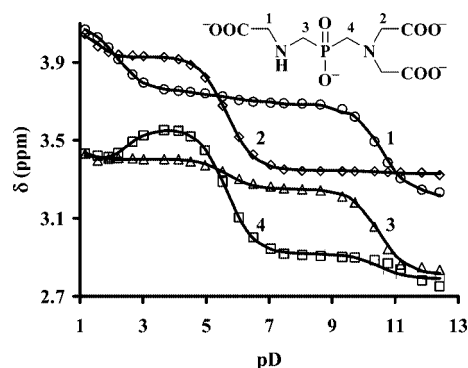


Figure 4. ^1H NMR titration curves of ligand L^3 ($C_L = 0.05\text{ M}$, 25°C) showing the change in the chemical shifts of the protons indicated in the figure.

In Figure 4, a decrease of the pH from about 12 to 8 leads to a significant change in the chemical shifts of the glycinate and phosphinate methylene protons ($-\text{CH}_2\text{NHCH}_2\text{COOH}$), which indicates the protonation of the glycinate nitrogen of L^3 . In the pH range 4–7 a strong change can be observed in the chemical shifts of the imda and phosphinate methylene protons, which shows that the second proton is attached to the nitrogen of the imda group. At a pH of around 3.5 the signal of the glycinate methylene protons starts to move to higher frequencies due to the protonation of the glycinate carboxylate.

The protonation constants $\log K_1^H$ determined in KNO_3 solution are generally lower than those obtained in Me_4NCl solution, and the $\log K_1^H$ value of L^4 determined in NaCl solution is even lower. These results indicate that at higher pH values the ligands form very poorly stable complexes with K^+ and somewhat more stable complexes with Na^+ ions.

Stability Constants of the Complexes

To characterize the complexation properties of L^0 , L^1 , L^2 , L^3 , and L^4 the formation equilibria between these ligands and the metal ions Mg^{2+} , Ca^{2+} , Ni^{2+} , Cu^{2+} , Zn^{2+} , Cd^{2+} , and Pb^{2+} were studied by pH potentiometry. The titrations were performed at three or four different metal-to-ligand concentration ratios. The number of data points for the calculations were usually between 250 and 500. Some typical titration curves are presented in Figure 5, which shows the formation of complexes with L^1 . The equilibrium models used for the calculation of the stability constants were selected on the basis of the properties of the metal ions and the ligands by taking into consideration the quality and number of the donor atoms. The results of the EPR study of the Cu^{2+} complexes with L^0 , L^1 , and L^4 were also used to assume the species formed in these systems.^[23] For characterizing the solution equilibria, the formation of the following complexes was considered: MLH_2 , MLH , ML , $\text{M}(\text{OH})\text{L}$, ML_2H , ML_2 , and M_2L . The stability constants that describe the equilibria were defined as follows (the charges of the species have been omitted for simplicity):

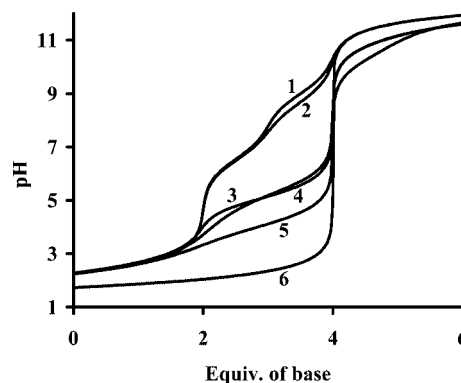


Figure 5. Titration curves of a $5 \times 10^{-3}\text{ M}$ solution of L^1 in the absence of metal ions (1) and in the presence of one equivalent of Ca^{2+} (2), Pb^{2+} (3), Cd^{2+} (4), Zn^{2+} (5), and Cu^{2+} (6).

$$K_{ML} = \frac{[ML]}{[M][L]} ; K_{ML}^H = \frac{[MLH]}{[ML][H]}$$

$$K_{MLH}^H = \frac{[MLH_2]}{[MLH][H]} ; K_{M(OH)L} = \frac{[M(OH)L][H]}{[ML]}$$

$$K_{ML_2} = \frac{[ML_2]}{[ML][L]} ; K_{ML_2}^H = \frac{[ML_2H]}{[ML_2][H]}$$

$$K_{M_2L} = \frac{[M_2L]}{[ML][M]}$$

The equilibrium constants $\beta_{pqr} = [M_pH_qL_r]/[M]^p[H]^q[L]^r$ were calculated with the program PSEQUAD.^[37] Tables 4, 5, 6, and 7 present the stepwise stability constants related to the formation of ML, ML₂ and M₂L complexes as calculated from the β_{pqr} values. We also calculated the protonation constants of the complexes, K_{ML}^H , K_{MLH}^H , and $K_{ML_2}^H$ because these values give some information about the site of protonation (nitrogen or carboxylate oxygen). By fitting the titration data to the assumed equilibrium model we obtained the equilibrium constants β_{pqr} and also the standard deviation values (given in parentheses in Tables 4–7).

Complexes of L⁰

The formation of complexes between the L⁰ and Mg²⁺ or Ca²⁺ could not be detected by pH potentiometry up to a pH of around 10. This is probably due to the fact that the nitrogens of the two NH₂ groups do not coordinate to Mg²⁺ or Ca²⁺ and the binding of the phosphinate oxygen is very weak. The titration curves obtained in the presence of Ni²⁺, Cu²⁺, Zn²⁺, Cd²⁺, and Pb²⁺ can be interpreted by assuming the formation of complexes ML and ML₂ and the protonated species MLH and ML₂H. The possible formation of hydroxo complexes was taken into consideration when calculating the stability constants by using the equilibrium constants known for the species M(OH)⁺.^[38] The stability constants of the complexes of Ni²⁺, Cu²⁺, and Zn²⁺ determined by Kubiček et al. and in our laboratory are similar (Table 4). The log K_{ML} and log K_{ML_2} values are lower than those of the complexes formed with 1,3-diaminopropane (L⁵). The stability constants (log K) of the species ML, ML₂, and ML₃ formed, for example, between Ni²⁺ and Cd²⁺ and L⁵ are 6.47, 4.43, and 1.2 and 4.50, 2.70, and 0.8, respectively.^[36] The lower stabilities of the complexes of L⁰ indicate that the phosphinate group does not play a role in the complexation. It is more probable that L⁰ is coordinated to the two N donor atoms to form a six-membered chelate ring.^[24] However, the ligand L⁵ forms ML₃ species and the absence of the formation of 1:3 complexes with L⁰ shows that some weak interaction may exist between the metal ion and the phosphinate group and the steric requirement of the L⁰ is larger than that of L⁵, which hinders the coordination of a third L⁰ ligand.

Table 4. Stability constants of the complexes formed between L⁰ and Ni²⁺, Cu²⁺, Zn²⁺ (25 °C, 1.0 M Me₄NCl), Cd²⁺, and Pb²⁺ (25 °C, 1.0 M KNO₃).

	log K_{ML}	log K_{ML}^H	log K_{ML_2}	log $K_{ML_2}^H$
Ni ²⁺	5.63 (0.01)	6.12 (0.06)	3.99 (0.03)	7.46 (0.05)
Ni ²⁺ [a]	5.58	5.4	3.83	—
Cu ²⁺ [b]	8.30	5.01	6.35	6.59
Cu ²⁺ [a]	7.64	5.07	5.41	6.74
Zn ²⁺	4.28 (0.02)	6.59 (0.04)	2.97 (0.02)	7.95 (0.05)
Zn ²⁺ [a]	4.12	6.5	3.41	—
Cd ²⁺	4.25 (0.04)	7.52 (0.02)	3.73 (0.02)	7.79 (0.03)
Pb ²⁺	4.20 (0.04)	7.46 (0.03)	3.01 (0.04)	8.02 (0.08)

[a] $I = 0.1$ M KNO₃.^[24] [b] $I = 1.0$ M Me₄NCl.^[23]

The K_{ML}^H and $K_{ML_2}^H$ protonation constants of the complexes are relatively large (Table 4), which suggests that the protonation occurs at one of the two NH₂ groups while the ligand L⁰ is coordinated only through its other NH₂ group. The negatively charged phosphinate group may contribute to the stability of the protonated complex.

Complexes of L¹ and L²

The ligands L¹ and L² possess two amine nitrogens, two carboxylate oxygens, and one phosphinate oxygen as donor atoms. The structure of L¹ and the asymmetric L² resemble the structure of ethylenediamine-*N,N'*-diacetate (L⁶) and ethylenediamine-*N,N*-diacetate (L⁷), with the difference that the latter do not contain a phosphinate moiety. For comparison, therefore, the diacetate derivatives of 1,3-diaminopropane would be more suitable, but unfortunately these ligands have not been studied to date. The titration data obtained for L¹ in the presence of Mg²⁺, Ca²⁺, Ni²⁺, and Cu²⁺ can be interpreted by assuming the formation of the species ML only, while Zn²⁺, Cd²⁺, and Pb²⁺ form hydroxo complexes M(OH)L and very weak ML₂ complexes as well at a pH above 9. The stability constants are shown in Table 5. Ligand L¹ has been prepared earlier and the stability constant of its Ni²⁺ complex, log $K_{NiL} = 12.24$, agrees well with the value found by us (Table 5).^[17] The stability constants of the ML complexes formed with L¹ are somewhat lower than those formed with L⁶ (the log K_{ML} values for the complexes of L⁶ formed with Mg²⁺, Ni²⁺, Zn²⁺, and Cd²⁺ are 3.95, 13.65, 11.22, and 8.99, respectively).^[36] The lower log K_{ML} values of the complexes can be interpreted as being due to the lower protonation constants of the ligand L¹ (the protonation constants for L⁶ are 9.69, 6.72, 2.37, and 1.66).^[36] Considering these findings, it is surprising that the stability constant log K_{ML} of the Cu²⁺ complex of L¹ is higher than that of CuL⁶ (log $K_{CuL} = 16.2$).^[36] This unexpected result can not be interpreted by assuming participation of the phosphinate group in the complexation. It is more likely that the formation of two five-membered (>NCH₂COO[−]) and a six-membered (>NCH₂PO₂−CH₂N<) chelate ring around the Cu²⁺ ion leads to a more stable square-planar arrangement than the coordination of L⁶, which involves the formation of three five-membered chelate rings. Similar results are known for the formation

Table 5. Stability constants of the complexes formed between the ligands L¹ and L² and Mg²⁺, Ca²⁺, Cu²⁺, Zn²⁺ (25 °C, 1.0 M Me₄NCl), Cd²⁺, and Pb²⁺ (25 °C, 0.1 M KNO₃).

M ²⁺	L ¹			L ²		
	log <i>K</i> _{ML}	log <i>K</i> _{M(OH)L}	log <i>K</i> _{ML}	log <i>K</i> _{ML} ^H	log <i>K</i> _{M(OH)L}	log <i>K</i> _{ML₂}
Mg ²⁺	2.50 (0.05)	–	3.98 (0.06)	8.44 (0.05)	–	3.00 (0.07)
Ca ²⁺	2.61 (0.02)	–	4.62 (0.04)	8.00 (0.03)	–	2.69 (0.08)
Ni ²⁺	12.22 (0.03)	–	12.89 (0.05)	4.44 (0.09)	–	2.80 (0.08)
Cu ²⁺	17.40 ^[a]	–	13.76 (0.07)	5.21 (0.01)	–9.63 (0.07)	–
Zn ²⁺ ^[b]	9.82 (0.01)	–10.27 (0.02)	10.37 (0.04)	5.80 (0.01)	–10.80 (0.04)	–
Cd ²⁺ ^[b,c]	7.82 (0.01)	–11.40 (0.05)	9.00 (0.04)	6.50 (0.03)	–10.51 (0.05)	3.61 (0.06)
Pb ²⁺ ^[b,c]	8.19 (0.03)	–10.87 (0.07)	9.59 (0.03)	7.32 (0.02)	–11.27 (0.03)	2.87 (0.05)

[a] Ref.^[23] [b] The stability constants of ML₂ complexes formed with L¹ are as follows: log *K*_{ZnL₂} = 1.94 (0.06), log *K*_{CdL₂} = 2.47 (0.05), log *K*_{PbL₂} = 2.95 (0.04). [c] The studies with Cd²⁺ and Pb²⁺ were performed in 1.0 M KNO₃.

of Cu²⁺ complexes with *N,N'*-bis(2-aminoethyl)dimethylenediamine (log *K*_{CuL} = 23.9) and triethylenetetramine (log *K*_{CuL} = 20.1).^[36]

The structure and donor atoms of ligand L¹ and those of bis(*N*-methylsarcosinato)phosphinic acid, which was synthesized previously in our laboratory, are similar, although the stability constants of the complexes formed with L¹ are higher.^[20,21] This difference is probably a result of the steric hindrance caused by the two methyl groups attached to the nitrogen donor atoms of the bis(*N*-methylsarcosinato)phosphinate ligand.

The titration data obtained for L² in the presence of the metal ions were interpreted by assuming the formation of the species ML, MLH, ML₂, and M(OH)L. The stability constants of ML complexes are generally higher than those of the complexes of L¹. The only exception is complex CuL², which exhibits much lower stability than CuL¹. This difference in the behavior of Cu²⁺ complexes is understandable if we take into account the propensity Cu²⁺ to form square-planar complexes. The other metal ions studied prefer octahedral (or some other) geometry. Due to its linear structure, L¹ forms a high stability square-planar complex with Cu²⁺. The ligand L² can not occupy four coordination sites in one plane if the phosphinate is not involved in complexation. For metal ions other than Cu²⁺, the coordination of the two nitrogen and two carboxylate oxygen donor atoms of L² is possible at four apices of an octahedron, which results in relatively high log *K*_{ML} values. The fourth coordination site of CuL² in the equatorial position is probably occupied by a water molecule as, in contrast to CuL¹, CuL² starts to hydrolyze at about pH 8.

All the metal ions except Cu²⁺ and Zn²⁺ form ML₂ complexes with L². The log *K*_{ML₂} values are much lower than those for ligand L⁷ (the log *K*_{ML₂} values for the ML₂ complexes of Ni²⁺ and Cd²⁺ are 5.91 and 6.01, respectively).^[36] The low log *K*_{ML₂} values indicate that the first ligand probably coordinates in the equatorial plane and hinders the coordination of the second ligand. As a result, the second ligand is coordinated through only two donor atoms for steric reasons.

Complexes of L³ and L⁴

Ligands L³ and L⁴ are structurally similar. While the symmetric L⁴ possesses two nitrogen, four carboxylate, and

one phosphinate oxygen donor atoms, the asymmetric L³ contains only three carboxylate groups. Because of its heptadentate nature, L⁴ does not form ML₂ complexes, and the ML₂ species formed with hexadentate L³ have very low stability (Cu²⁺ does not even form such a complex). The L³ ligands in the ML₂ complexes are probably coordinated through their imda groups and the coordination of two imda groups is more favorable than formation of the ML complex.

The titration data obtained for the ligand L³ in the presence of metal ions can be interpreted by the formation of the complexes MLH, ML, M(OH)L, ML₂, and ML₂H. The calculated stability constants are presented in Table 6. The log *K*_{ML} values are significantly lower than those of the hexadentate edta (ethylenediamine-*N,N,N',N'*-tetraacetate). The only exception is CuL³, whose stability constant is similar to that of Cu(edta)^{2–} (log *K*_{CuL} = 18.80).^[36]

The log *K*_{ML} values of the complexes CuL³ and CuL¹ are practically identical, which suggests that L³ is coordinated to Cu²⁺ through two nitrogen and two carboxylate oxygen donor atoms and that the third carboxylate (and phosphinate) group does not participate in the complexation. The protonation constant of the complex CuL³ is very low, which indicates protonation of the free carboxylate. The protonation constants of the other complexes of L³ are higher (particularly those of MgL³ and CaL³) as in these species the nitrogen atom of the glycinate is most likely protonated.

In an earlier study of complexes of the ligand L⁴ with some divalent metal ions the formation of ML and MLH species was assumed.^[21] The results of a recent, more detailed pH potentiometric titration study were interpreted by the formation of ML, MLH, MLH₂, and M₂L species. The number of data points used for the calculations, which were obtained at three or four metal-to-ligand ratios, are given in parenthesis for the respective metals as follows: Mg²⁺ (338), Ca²⁺ (355), Ni²⁺ (347), Cu²⁺ (665), Zn²⁺ (513), Cd²⁺ (476), and Pb²⁺ (493). The calculated stability constants as well as the data reported for the analogous propylenediamine-*N,N,N',N'*-tetraacetate (L⁸) are shown in Table 7. We have also determined the protonation constants of L⁸ and found that at 25 °C in 1.0 M KCl the log *K*_i^H values are 10.50 (0.03), 8.17 (0.04), 2.78 (0.05), and 1.96 (0.05). These log *K*_i^H values are significantly higher than those of L⁴

Table 6. Stability constants of the complexes formed between L^3 and Mg^{2+} , Ca^{2+} , Cu^{2+} , Zn^{2+} (25 °C, 1.0 M Me_4NCl), Cd^{2+} , and Pb^{2+} (25 °C, 0.1 M KNO_3).

	$\log K_{ML}$	$\log K_{ML}^H$	$\log K_{M(OH)L}$	$\log K_{ML_2}$	$\log K_{ML_2}^H$
Mg^{2+}	4.83 (0.04)	7.40 (0.05)	—	3.63 (0.04)	8.97 (0.07)
Ca^{2+}	5.35 (0.04)	7.66 (0.03)	—	3.80 (0.05)	9.02 (0.08)
Cu^{2+}	18.32 (0.25)	1.75 (0.09)	—	—	—
Zn^{2+}	12.66 (0.01)	3.47 (0.01)	−12.16 (0.04)	1.90 (0.16)	—
Cd^{2+}	10.04 (0.03)	5.11 (0.03)	−11.47 (0.04)	2.44 (0.09)	—
Pb^{2+}	10.34 (0.03)	5.60 (0.02)	−10.92 (0.04)	2.77 (0.06)	—

Table 7. Stability constants of the complexes of the ligands L^4 and $L^{8[a]}$ formed with Mg^{2+} , Ca^{2+} , Ni^{2+} , Cu^{2+} , Zn^{2+} , Cd^{2+} , and Pb^{2+} . The data for L^4 were obtained at 25 °C, in 1.0 M $Me_4NCl^{[b]}$ and for L^8 at 20 °C, in 0.1 M Me_4NCl .

	L^4				$L^{8[a]}$	
	$\log K_{ML}$	$\log K_{ML}^H$	$\log K_{MLH}^H$	$\log K_{M_2L}$	$\log K_{ML}$	$\log K_{ML}^H$
Mg^{2+}	7.65 (0.03)	6.42 (0.04)	4.28 (0.02)	3.23 (0.03)	6.21	7.30
Ca^{2+}	7.66 (0.03)	6.41 (0.02)	4.28 (0.02)	3.23 (0.03)	7.28	6.34
Ni^{2+}	17.77 (0.05)	2.64 (0.07)	—	3.30 (0.09)	18.15	2.20
$Cu^{2+ [b]}$	19.30	2.80	—	3.70	18.92	2.20
Zn^{2+}	15.94 (0.01)	2.14 (0.01)	1.96 (0.02)	1.61 (0.05)	15.26	2.50
$Cd^{2+ [c]}$	13.07 (0.01)	3.16 (0.01)	2.53 (0.02)	3.00 (0.02)	13.90	3.06
$Pb^{2+ [c]}$	11.29 (0.04)	5.66 (0.05)	2.26 (0.09)	6.31 (0.04)	13.78	3.86

[a] Propylenediamine-*N,N,N',N'*-tetraacetate.^[36] [b] Ref.^[23] [c] The studies with Cd^{2+} and Pb^{2+} were performed in 1.0 M KNO_3 .

(Table 3). In spite of the lower protonation constants, the stability constants of the complexes of L^4 are very similar or higher than those of L^8 . The phosphinate oxygen is not coordinated directly to the metal ion and the high stability constants probably result from the higher negative charge of the ligand and the two coordinated imda groups, which pull the phosphinate closer to the metal ion. However, the complexes of smaller and larger metal ions (Ni^{2+} , Cu^{2+} , and Zn^{2+} vs. Cd^{2+} and Pb^{2+}) behave differently, which is particularly evident when the stability constants are compared with those of the edta complexes. The $\log K_{ML}$ values for the edta complexes of Zn^{2+} and Pb^{2+} are 16.50 and 18.04, respectively, while ligand L^4 shows an unexpectedly high selectivity for Zn^{2+} over Pb^{2+} ($\log K_{ML}$ values of 15.94 and 11.29, respectively; Table 7). These results can be interpreted according to Hancock, who found that larger metal ions prefer five-membered chelate rings while smaller metal ions form high stability complexes with both five- and six-membered chelate rings.^[39] In the dinuclear complexes formed with L^4 both metal ions are attached to an iminodiacetate group of the ligand, as was found for the Cu^{2+} complexes by EPR spectroscopy.^[23] The formation of dinuclear complexes was also unambiguously detected by pH potentiometry. Typical titration curves obtained in the presence of one and two equivalents of Pb^{2+} are shown in Figure 6. Because of the strong competition between protons and Pb^{2+} in the presence of one extra equivalent of Pb^{2+} , the buffer region observed at a 1:1 metal-to-ligand ratio disappears completely, which indicates the formation of dinuclear species in solution. The K_{ML}^H protonation constants imply the protonation of the acetate group in the complexes of Ni^{2+} , Cu^{2+} , Zn^{2+} , and Cd^{2+} while the protonation is more probable at a nitrogen in the complexes of Mg^{2+} , Ca^{2+} , and Pb^{2+} .

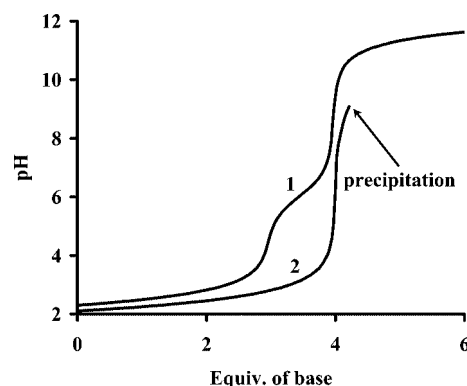


Figure 6. Titration curves of 5×10^{-3} M solutions of L^4 in the presence of one (1) and two equivalents (2) of Pb^{2+} ions ($I = 1.0$ M KNO_3 , $T = 25$ °C).

1H NMR Spectra of the Zn^{2+} Complexes

The formation of complexes between Zn^{2+} and the ligands L^1 , L^2 , L^3 , and L^4 results in a significant change in the 1H NMR spectra. The doublet signals of the phosphinate ($-[CH_2]_2PO_2^-$) methylene protons are shifted slightly to low field but their multiplicity does not change. The shift of the signals of the methylene protons is due to the inductive effect of the Zn^{2+} ion. Upon formation of ZnL^1 the signal of the glycinate methylene protons is shifted to $\delta = 3.48$ ppm but is not split. With a decrease of temperature from 50 °C to close to 0 °C the signals broaden significantly, however an AB multiplet pattern could not be observed even at this temperatures (Figure S8). Similarly, the signal of the glycinate methylene protons for ZnL^3 is not split by the formation of the complex and it appears at about $\delta = 3.30$ ppm (pH 7.05) as a broad signal (Figure 8). The shift of the signals for the acetate methylene protons

of the iminodiacetate groups are usually larger and often appear in the form of AB multiplets (Figures 7 and 8). The formation of an AB multiplet indicates the inequivalence of the acetate methylene protons of the imda group, which is the result of the relatively long lifetime of the Zn^{2+} -N bond on the NMR timescale.^[40] The chemical shifts of the non-equivalent A and B protons of ZnL^2 at pH 7.02 (Figure 7) are $\delta = 3.62$ and 3.23 ppm, respectively. The exceptionally large H-C-H geminal coupling constant between these protons ($^2J_{\text{H,H}} = 17.3$ Hz) suggests a dihedral angle of about 180° for the coordinated acetate arms (positions of the CH_2 H atoms towards the p_z orbital of the carbon atom of COO^-).^[41] The signals of the phosphinate methylene protons give a "pseudo-triplet" consisting of two overlapping doublets centered at $\delta = 2.99$ and 2.96 ppm ($^2J_{\text{P,H}} = 8.6$ and $^2J_{\text{P,H}} = 11.5$ Hz). Since these signals are doublets due to coupling with phosphorus, the value of the geminal coupling constants for the CH_2 protons ($^2J_{\text{H,H}}$) can not be determined from the spectra (the values appear to be less than 0.8 Hz), which indicates a very weak interaction between the phosphinate oxygen and Zn^{2+} in these complexes (presumably of an electrostatic nature). Figure 8 shows the ^1H NMR spectrum of ZnL^3 recorded at pH 7.05. The AB multiplet pattern of the iminodiacetate methylene protons appears at $\delta = 3.57$ and 3.19 ppm (the geminal coupling constant is $^2J_{\text{H,H}} = 17.3$ Hz), and the broad singlet at $\delta = 3.30$ ppm is due to the glycinate methylene protons, while the doublets of the phosphinate methylene protons are cen-

tered at $\delta = 2.95$ and 2.93 ppm ($^2J_{\text{P,H}} = 12.6$ and $^2J_{\text{P,H}} = 13.3$ Hz). For ZnL^4 the imda methylene protons appear as an AB multiplet ($^2J_{\text{H,H}} = 17.5$ Hz), which shows the rigid structure of the complex (Figure S9). These carboxymethyl groups may occupy equivalent positions on the coordination polyhedron around Zn^{2+} . In summary, we can state that in complexes ZnL^2 , ZnL^3 , and ZnL^4 the Zn^{2+} -N bond of the coordinated imda fragment has a long lifetime while the Zn^{2+} -N bonds formed by the coordination of the $-\text{NHCH}_2\text{COO}^-$ group in ZnL^1 and ZnL^3 and the $-\text{CH}_2\text{NH}_2$ group in ZnL^2 appear to be more labile. These findings demonstrate that the lifetime of the Zn^{2+} -N bond is long on the NMR timescale as the coordination of the two carboxylate groups keeps the N atom in the vicinity of the Zn^{2+} ion.

Conclusions

A new synthetic method has been developed that starts from inexpensive materials and gives reasonable yields of bis(aminomethyl)phosphinic acid as well as its derivatives containing the phosphinate group in a linker position. In addition, two consecutive Mannich reactions afford asymmetric bis(aminomethyl)phosphinic acids. These procedures can easily be scaled up and do not require inert atmosphere techniques. This synthetic method will likely be applicable to the synthesis of macrocyclic ligands that incorporate a bis(aminomethyl)phosphinic acid moiety in the macrocycle.

The basicities of the nitrogen atoms of the symmetric and asymmetric diacetate (L^1 and L^2) and tri- (L^3) and tetraacetate (L^4) derivatives of bis(aminomethyl)phosphinic acid (L^0) are lower than those of the analogous diaminopolycarboxylates mainly due to the electron-withdrawing effect of the phosphinate group. For a given ligand, the basicity of the nitrogen atoms decreases in the order primary > secondary > tertiary.

The stability constant of complexes formed between L^0 , L^1 , L^2 , L^3 , and L^4 and the metal ions Mg^{2+} , Ca^{2+} , Ni^{2+} , Cu^{2+} , Zn^{2+} , Cd^{2+} , and Pb^{2+} increase with an increasing number of carboxylate groups of the ligands. The complexes formed with ligands L^0 , L^1 , L^2 , and L^3 generally have lower stability constants than those of the analogous diaminopolycarboxylates, which indicates the unimportant role of the phosphinate group in the complexation. On the other hand, the presence of the phosphinate group has a significant effect on the complexation properties of L^4 . In spite of the lower basicities of the two nitrogen atoms of L^4 , it forms complexes of similar or higher stability with the smaller metal ions than the analogous 1,3-diaminopropane- N,N,N',N' -tetraacetate (L^8). L^4 also shows an unusually high selectivity for Zn^{2+} over Pb^{2+} , unlike edta or L^8 . Its stability constants are higher probably because of the higher charge of the ligand, and there is a strong electrostatic interaction between the phosphinate and the metal ion due to the coordination of both imda groups. Furthermore, L^4 shows a strong propensity for the formation of dinuclear M_2L complexes, which indicates that in the presence of the

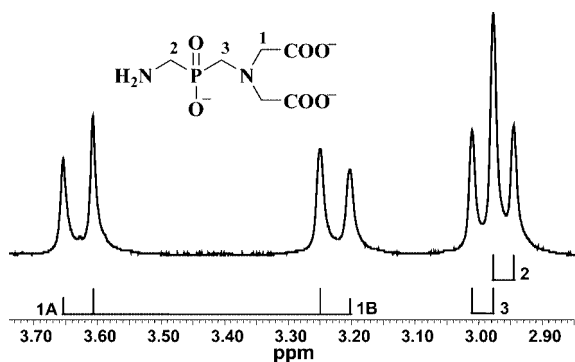


Figure 7. ^1H NMR spectrum of a 0.05 M ZnL^2 solution at 25 $^\circ\text{C}$ (pH 7.02).

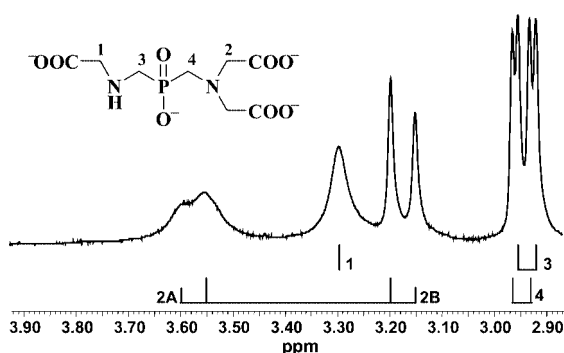


Figure 8. ^1H NMR spectrum of a 0.05 M ZnL^3 solution at 25 $^\circ\text{C}$ (pH 7.05).

phosphinate group the two imda groups behave more independently than in the case of edta or L⁸.

Of the two diacetate derivatives the asymmetric L² forms complexes of higher stability with the metal ions that prefer octahedral coordination. However, the metal ions that prefer square-planar coordination, like Cu²⁺, form more stable complexes with the symmetric ligand L¹. The equatorial coordination of L¹ to Cu²⁺ has been confirmed by X-ray crystallography in the solid state for K[CuL¹]·H₂O, which has a polymer structure with hexagonal channels.

The ligands L² and L³ form ML and ML₂ complexes but the stability constants of the ML₂ species are relatively low, probably due to the larger steric requirement of the phosphinate-containing ligands.

In the ¹H NMR spectra of the complexes of Zn²⁺ formed with L¹, L², L³, and L⁴ the acetate methylene protons of the coordinated imda groups appear as an AB multiplet, thus indicating the long lifetime of the Zn²⁺–N bond on the NMR timescale, while the signal of the glycinate methylene protons is a singlet.

Experimental Section

Synthesis of the Ligands: All reagents and solvents used in this paper were commercially available and used without further purification, unless noted otherwise. The synthesis of ligands L⁰, L¹, L², and L³ is outlined in Schemes 1 and 2. Ligand L⁴ was prepared following a previously published procedure.^[20] A detailed description of the synthetic procedures for compounds 1–10 is included in the Supporting Information (SI). The purity of the ligands was controlled by multinuclear (¹H, ¹³C, and ³¹P) NMR spectroscopy; the spectra obtained together with the results of pH potentiometric studies indicated the suitable purity of the ligands (higher than 99%).

X-ray Diffraction Studies: Large crystals of approx. 1 cm × 5 mm × 3 mm were obtained from saturated solution after the purification of L³. Equivalent amounts (0.3 mmol) of H₃L¹ and CuCl₂ stock solutions were mixed and the pH of the mixture was increased to about pH 7.5 by addition of KOH solution. The solution was evaporated to dryness and a weighed amount (0.1 mmol) of the dried complex was redissolved in doubly distilled water (0.5 mL) and placed into a narrow tube. Anhydrous ethanol was carefully layered on the aqueous phase and the tube was placed in a refrigerator at around 4 °C. Navy blue crystals suitable for X-ray crystallography grew in three weeks.

X-ray quality crystals of [H₅L³]Cl and K[CuL¹]·H₂O were mounted on a glass fiber using epoxy resin. Data were collected at 293(1) K with an Enraf Nonius MACH3 diffractometer using monochromated Mo-K_α radiation (λ = 0.71073 Å) in the ω–2θ mode. The absorption correction was made using psi scans. The structure was solved by direct methods with the SIR-92 software and refined on F² by full-matrix least-squares methods with the program SHELX-97.^[42,43] All non-hydrogen atoms were refined anisotropically. Hydrogen atoms were included using a riding model. Some of the water hydrogen atoms were found in the difference electron density map while others were placed in calculated positions for strong hydrogen bonds. For the final refinement the O–H bond lengths were restrained at 0.85 Å but otherwise the coordinates of O–H hydrogen atoms were refined. Publication material was prepared with the WINGX-97 suite.^[44] Some other details of data collection and structure determination are shown in Table 8.

Table 8. X-ray crystallographic data and structure refinement for [H₅L³]Cl and [K(CuL¹)]·H₂O.

	[H ₅ L ³]Cl	K[CuL ¹]·H ₂ O
Chemical formula	C ₈ H ₁₆ ClN ₂ O ₈ P	C ₆ H ₁₂ CuKN ₂ O ₇ P
Molecular weight	334.65	357.79
Crystal color and habit	colorless block	blue block
Crystal size [mm]	0.45 × 0.4 × 0.36	0.55 × 0.35 × 0.27
Crystal system	orthorhombic	trigonal
Space group	<i>Pn</i> 2 ₁ <i>a</i> (no. 33)	<i>R</i> 3 (no. 148)
<i>a</i> [Å]	7.877(3)	28.477(2)
<i>b</i> [Å]	13.564(3)	28.477(2)
<i>c</i> [Å]	13.837(5)	8.681(2)
<i>α</i> [°]	90.00	90.00
<i>β</i> [°]	90.00	90.00
<i>γ</i> [°]	90.00	120.00
<i>V</i> [Å ³]	1478.4(8)	6096.6(15)
<i>Z</i>	4	18
Temperature [K]	293	293
<i>D</i> _{calcd.} [g cm ^{−3}]	1.504	1.754
<i>μ</i> [mm ^{−1}]	0.403	2.062
<i>F</i> (000)	696	3257
2θ _{max} [°]	50.4	52
Index ranges	−4 ≤ <i>h</i> ≤ 9 −2 ≤ <i>k</i> ≤ 15 0 ≤ <i>l</i> ≤ 15	−35 ≤ <i>h</i> ≤ 30 −15 ≤ <i>k</i> ≤ 35 −10 ≤ <i>l</i> ≤ 5
Reflections collected	1391	4275
Unique reflections with <i>I</i> > 2σ(<i>I</i>)	1244	1731
Completeness of data	97.5	95.4
Decay [%]	2	0
Parameters	181	169
Refinement method	Full-matrix least-squares on <i>F</i> ²	
<i>R</i> _[a]	0.053	0.057
<i>R</i> _w (all data) ^[b]	0.154	0.193
GOF on <i>F</i> ²	1.292	1.082
Largest diff. peak/hole [e Å ^{−3}]	0.583/−0.587	0.994/−0.924

[a] $R = \sum |F_o - F_c| / \sum F_o$. [b] $R_w = \{\sum [w(F_o^2 - F_c^2)^2] / \sum [w(F_o^2)^2]\}^{1/2}$, where $w = 1/[\sigma^2(F_o^2) + (aP)^2 + bP]$, $P = (F_o^2 + F_c^2)/3$; *a* and *b* are given in the Supporting Information.

CCDC-616444 (for [H₅L³]Cl) and -616445 (for K[CuL¹]·H₂O) contain the supplementary crystallographic data for this paper. These data can be obtained free of charge from The Cambridge Crystallographic Data Centre via www.ccdc.cam.ac.uk/data_request/cif.

Materials and Preparation of Solutions: Stock solutions of MgCl₂, CaCl₂, NiCl₂, CuCl₂, ZnCl₂, Cd(NO₃)₂, Pb(NO₃)₂, Me₄NOH, and KOH were prepared with the highest analytical grade reagents. The concentrations of the metal-ion solutions were determined by complexometric titration with standardized Na₂H₂edta solution using eriochrome black T, murexide or xylenol orange indicator. Aqueous solutions of the ligands were prepared by weight and the concentrations were determined by pH potentiometric titrations.

Equilibrium Studies: The protonation constants of the ligands and stability constants of complexes were determined by pH potentiometric titration in vessels thermostatted at 25 °C. The ionic strength of the solutions was kept constant at 1.0 M Me₄NCl or, in the case of Cd²⁺ and Pb²⁺, at 1.0 M KNO₃. Titration experiments were performed at two to four different metal-to-ligand ratios (1:1, 1:2, 1:3, and 2:1) by varying the ligand concentration in the range 0.0025–0.006 M. The titrations were performed with a Radiometer pHM 85 pH-meter equipped with pHG 211 glass and REF 201 Ag/AgCl electrodes and a Radiometer ABU 80 autoburette. The

samples (in general 15 mL) were stirred and argon was bubbled through the solutions. KH-phthalate (pH = 4.005) and borax (pH = 9.180) buffers were used to calibrate the pH meter. The H^+ ion concentration was obtained from the measured pH data by the method suggested by Irving et al. A 0.01 M HCl solution was titrated in 1.0 M Me_4NCl (or 1.0 M KNO_3) with the Me_4NOH (or KOH) solution used for the titrations.^[45] The difference between the calculated and measured pH values was used to obtain the H^+ ion concentrations from the pH values measured in the titration experiments.^[45] The ionic product of water (pK_w) was also calculated from the data obtained in the titration of the 0.01 M HCl solution. The pK_w values obtained in 1.0 M Me_4NCl and 1.0 M KNO_3 are 13.99 and 13.88, respectively. The protonation constants of the ligands and stability constants of the complexes were calculated from the titration data with the computer program PSE-QUAD.^[37]

NMR Measurements: The solutions of complexes were prepared by mixing equivalent amounts of the ligands and $ZnCl_2$ solutions. After evaporation of the H_2O the solid material was dissolved in D_2O . The pD of the solutions was monitored by the addition of KOD or DCl (Cambridge Isotope Laboratories, Inc.) solutions and the readings were corrected for the deuterium isotope effect using the relationship $pH = 0.4 + pD$. Both one- and two-dimensional NMR spectra were recorded on a Bruker Avance DRX-360 spectrometer operating at 360.0 and at 90.5 MHz for 1H and ^{13}C , respectively. A Bruker DRX-500 spectrometer equipped with a Eurotherm variable temperature unit (± 0.1 K), which was calibrated by the methanol method,^[46] was used for variable-temperature measurements. Two-dimensional 1H - 1H correlation spectra (COSY-45, DQF-COSY, NOESY, EXSY) were recorded using standard pulse sequences in direct mode with a 5-mm QNP probehead. ^{13}C NMR spectra were recorded in J -modulated or inverse gated decoupling mode. Data processing was performed with the Bruker WinNMR software package.

Supporting Information (see footnote on the first page of this article): Description of the synthetic procedures for compounds **1–10**; H-bond network in $[H_5L^3]Cl$ (Figure S1); data of the H-bond network in $[H_5L]Cl$ (Table S1); the H-bond network and long-range packing in $K[CuL^1] \cdot H_2O$ (Figure S2); the H-bond network in $K[CuL^1] \cdot H_2O$ (Table S2); 1H and ^{31}P NMR titration curves for the ligands L^0 , L^1 , and L^4 (Figures S3–S7); temperature dependence of the 1H NMR spectra of ZnL^1 (Figure S8); 1H - 1H COSY spectrum of ZnL^4 (Figure S9).

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