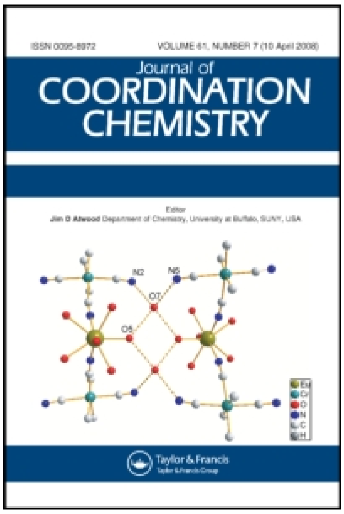

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TRANSITION METAL COMPLEXES OF AMINOPHOSPHONIC ACID ANALOGUES OF METHIONINE AND ALANINE IN AQUEOUS SOLUTION

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The stoichiometries and stability constants of the nickel(II), copper(II) and zinc(II) complexes of 1-amino-3-methylthiopropanephosphonic acid (MetP) and 1-amino-ethanephosphonic acid (α-AlaP) have been determined pH-metrically at 25°C at an ionic strength of 0.2 mol dm^{-3} (KCl). From the stability data and the absorption spectra of the complexes it has been established that simple aminophosphonic acids coordinate to the nickel(II) and copper(II) ions forming chelate complexes in which the metal binding mode is bidentate with the $\{NH_2, PO_3^{2-}\}$ donor set. ^{31}P and ^{1}H NMR measurements showed that MetP and α-AlaP exhibit similar properties in the presence of zinc(II) ions, but the ligand reacts to form a cyclic phosphonoamidate in neutral and slightly alkaline solution in the Zn(II)-α-AlaP system and at slightly acidic conditions in the Zn(II)-MetP system. This difference reveals that the latter ligand at pH > 7 prefers Zn(II) coordination involving all possible (amino, phosphonate and thioether sulfur) donor groups.

Keywords: potentiometry, ^{31}P and ^{1}H NMR spectra, electronic spectra, complexes, stability constants, aminoacids, phosphonic acids, first-row metals

INTRODUCTION

Aminophosphonic acids are analogues of aminocarboxylic acids in which a -COOH group is replaced by a -PO_3H_2 group. The chemistry and, in particular, biochemistry of aminophosphonic acids is of increasing interest owing to the fact that the -PO_3H_2 group is present in a number of substances including neuroactive compounds, antibiotics and herbicides [1]. Some are potent inhibitors of metalloproteases [2, 3] and some display biological activities with possible application from medicine to agriculture. [1]

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Phosphonic and carboxylic groups differ substantially in many aspects including size (phosphonic function is considerably larger), shape (flat carboxylic *versus* tetrahedral phosphonic group), basicity and electron-releasing effects. These differences may play important roles in enzyme-substrate interactions. Thus, investigation of the interactions of this class of compounds with various metal ions may contribute to a better understanding of their powerful metalloenzyme inhibitory effects and biological activity. Although metal complexes of aminophosphonic acids have been studied fairly extensively in solution [4], their solution chemistry is still not well understood. Recently we showed for the first time that 4-amino-4-phosphonobutanoic acid underwent chemical transformation upon reaction with zinc(II) ions under neutral and slightly alkaline solution [5].

In the present work, the study has been extended to 1-amino-3-methylthiopropanephosphonic acid (MetP) and 1-amino-ethanephosphonic acid (α-AlaP). Stoichiometries, stability constants and bonding modes of the complexes formed with nickel(II), copper(II) and zinc(II) are presented below.

EXPERIMENTAL

Materials

The phosphonic acid ligands were prepared by the method of Tam *et al.* [6] and used in racemic form. Zinc nitrate hexahydrate was obtained from Aldrich. The purities and exact concentrations of solutions of the ligands used for potentiometric studies were determined pH-metrically by the Gran method [7]. Metal chloride solutions were purchased from Merck. The concentrations of the metal(II) chloride stock solutions for potentiometry were standardized by complexometric (edta) titration. Carbonate-free potassium hydroxide was prepared and standardized against a standard potassium hydrogen phtalate solution. The concentration of the KOH solution was *ca* 0.2 mol dm^{-3}.

Potentiometry

Stability constants for H^+ and metal(II) complexes were calculated from titration curves carried out at 25 ± 0.1°C using a total volume of 5 cm^{-3}. The ligand concentration was 4×10^{-3} mol dm^{-3} and metal: ligand ratio were 1:1, 1:2 and 1:4. Ionic strength was adjusted to 0.2 mol dm^{-3} with KCl. Titrations were performed over the range pH 3-11 with KOH solution of known concentration (*ca* 0.3 mol dm^{-3}). In the case of complexes with zinc(II), reliable titration curves were not obtained for higher pH values because of precipitation of complex and/or metal hydroxide.

The pH was measured with a MOLSPIN automatic titration system using a micro combination pH electrode (Mettler-Toledo, U402-M6-S7/100). The electrode system was calibrated by periodic titrations of an HCl solution (5×10^{-2} mol dm^{-3} in KCl) against a standard KOH solution. Resulting titration data were used to calculate standard potentials, E^0, and the dissociation constant for H_2O. These were then used to calculate the hydrogen ion concentration [H^+] from potential readings [8]; number of titrations was 3 and the method of calculation employed SUPERQUAD [9]. Standard deviations (σ values) quoted were computed by SUPERQUAD and refer to random errors only. They are, however, a good indication of the importance of the particular species in the equilibrium [10].

For the sake of clarity, charges on the complexes are omitted in the text and the Table. It has to be mentioned, however, that depending on the type of ligands, the fully deprotonated forms have different charges; *i.e.*, L^{-2} refers to aminophosphonic acids, L^- to amino acid. Hence, species with the same stoichiometric composition may have different charges.

Spectroscopic Measurements

EPR spectra were measured on a Bruker ESP 300E spectrometer at the X-band frequency (9.45 GHz) at 120K in frozen ethylene glycol-water (1:1 v/v) solutions. The ligand concentration was 1.6×10^{-2} mol dm^{-3} and the metal:ligand ratio was 1:4. Visible absorption spectra were obtained at 278K on a Beckman DU-68 spectrophotometer. The spectra were recorded digitally (with 0.5 nm steps) in the 900-350 nm range in a 5.0 cm quartz cuvette.

The ligand concentration and metal:ligand ratio for the copper(II)-ligand system was the same as used in the EPR. For the nickel(II)-ligand system the ligand concentration was 2.0×10^{-2} mol dm^{-3} and the ratio 1:3. The pH of the final solution was adjusted with HCl or KOH.

Phosphorus and proton NMR spectra were recorded on a Bruker DRX 300 MHz spectrometer at 300 K and are given relative to 85% H_3PO_4 and $SiMe_4$, respectively. Samples for NMR studies were prepared in deuteriated water with a ligand concentration of 0.01 mol dm^{-3}. A zinc(II) to ligand mol ratio of 1:2 was applied using zinc nitrate hexahydrate as a source of Zn(II) ions. The pH of the samples was measured using a Radiometer pHM 83 instrument equipped with a 2401c combined electrode and are given as meter readings without correction for pD.

TABLE I Protonation constants of free ligands ($\log\beta_n{}^H$) and formation constants of Ni(II), Cu(II) and Zn(II) complexes ($\log\beta_n$) of some aminophosphonic acids (MetP and α-AlaP) and an amino acid (α-Met) at 25°C and I = 0.2 mol dm^{-3} (KCl).

Ligand	Species	H^+	Ni(II)		Cu(II)		Zn(II)	
			this work	ref. [8]	this work	ref. [8]	this work	ref. [8]
MetP	[HL]	9.58(1)						
	[H_2L]	15.12(2)						
	[M(HL)]	12.40(8)						
	[ML]			5.15(1)	8.21(1)	4.81(4)		
	[ML_2]			8.94(5)	14.89(3)	9.46(5)		
	[ML_2H_{-1}]	4.1(1)						
α-AlaP	[HL]	9.97(1)	10.11					
	[H_2L]	15.57(1)	15.66					
	[M(HL)]			11.98	12.92(4)	12.29	12.93(2)	11.79
	[ML]			5.42	8.26(1)	8.29	5.66(3)	5.99
	[ML_2]			9.31	14.66(3)	14.94		
	[ML_3]			12.20				
	[ML_2H_{-1}]	3.97(6)						
α-Met	[HL]	9.12(1)						
	[H_2L]	11.34(2)						
	[ML]			5.26(1)	7.76(1)	4.32(1)		
	[ML_2]			9.74(2)	14.27(2)	8.18(1)		
	[ML_2H_{-1}]	3.05(4)						

RESULTS AND DISCUSSION

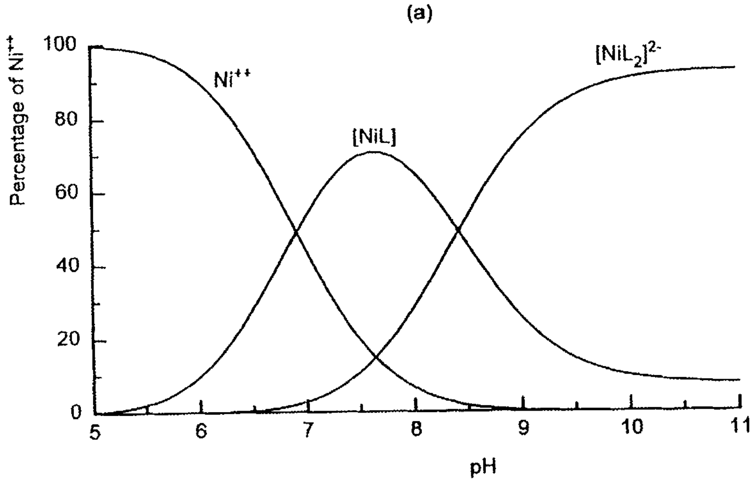
The pH-metrically determined proton dissociation and the metal(II) complex formation constants of MetP, together with those of 1-aminoethanephosphonic acid (α-AlaP) and methionine are given in Table I. In the pH range studied (pH 3-11) MetP contains two dissociable protons. These are involved in the dissociation of the $-PO_3H^-$ and $NH_3{}^+$ groups, respectively. The pK characteristic of the dissociation of $-PO_3H_2$ is ≈ 1.0 [11, 12] and this group does not take part in metal co-ordination equilibria.

It seen from Table I that the methionine $NH_3{}^+$ group is more acidic (≈0.5 log units) than that of the phosphonic acid analogue. This change was recorded for other aminophosphonic acids [13]. The more acidic character of the $-NH_3{}^+$ group of MetP than of α-AlaP ($\log \Delta K_{NH_3{}^+} = 0.53$) can be explained by the slight electron-withdrawing effects of the CH_3-S-CH_2-group.

Stability constants of the complexes formed, together with derived equilibrium constants are listed in Table I. Although, data for metal ion—Met complexes can be found in the literature [14], for comparison we decided to determine all of the data under the same experimental conditions.

Ni(II)—MetP System

A species distribution for the nickel(II)—MetP system (Figure 1a), indicates the formation of the two complexes above pH 5. [NiL] at pH *ca* 8 reaches 70%; at pH 10.5 [NiL_2] reaches 92% of the total. The lack of the [Ni(HL)] species in the



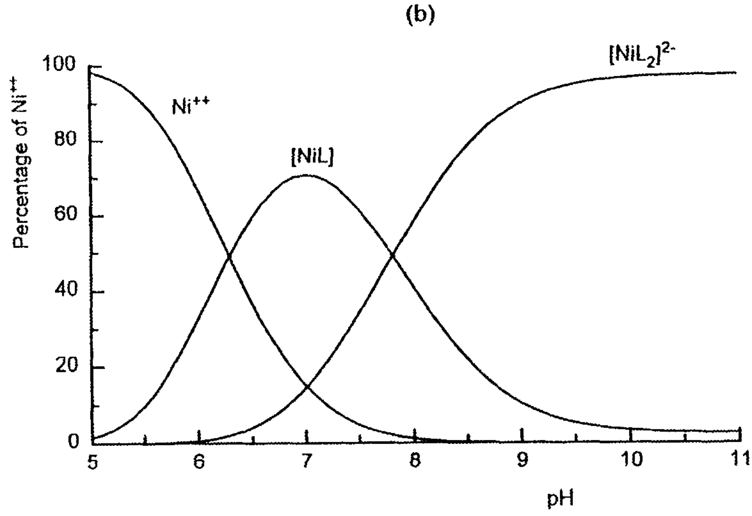


FIGURE 1 Species distribution for the nickel(II)-MetP system as a function of pH: (a) $c_M = 1.0 \times 10^{-3}$, $c_L = 4.0 \times 10^{-3}$ mol dm^{-3}; (b) $c_M = 7.0 \times 10^{-3}$, $c_L = 2.0 \times 10^{-2}$ mol dm^{-3}.

system studied suggests bidentate coordination with the {NH_2, PO_3^{2-}} donor set.

The absorption spectra of the Ni(II)—MetP system (Figure 2) were obtained under appropriate conditions. At pH 7 the maximum at 645 nm corresponds to the predominant concentration of [NiL]. At pH 9.4 a shift in the spectrum was observed, giving a maximum at 640 nm (Figure 2). This coincides with the formation of [NiL_2]. The very weak absorption spectra in the d-d region clearly indicate octahedral or pseudooctahedral geometries around the metal ions. The d-

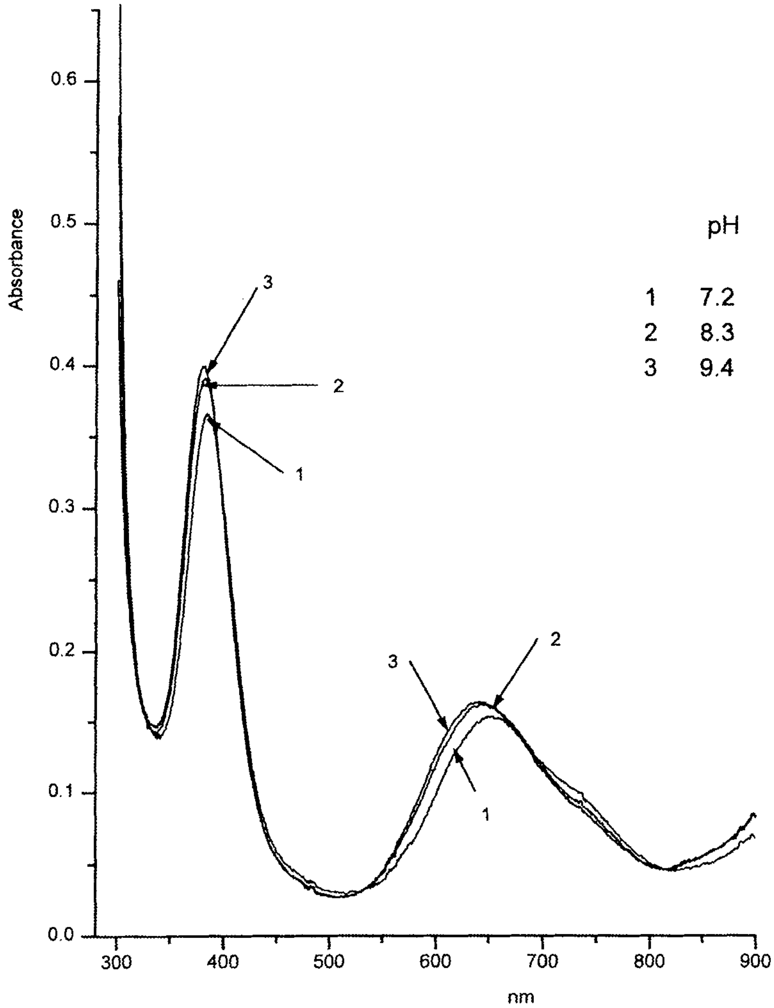


FIGURE 2 Changes of d-d absorption bands in the nickel(II)-MetP system as a function of pH for $c_M = 7.0 \times 10^{-3}$, $c_L = 2.0 \times 10^{-3}$ mol dm^{-3}, l = 5.0 cm.

d transition energy found for $[Ni(MetP)_2]$ is very similar to that of $[Ni(\alpha\text{-AlaP})_2]$ (pH = 9.4; λ_{max} = 640 nm, ϵ = 5 M cm^{-1} and λ_{max} = 640 nm, ϵ = 6 M cm^{-1}, respectively).

Cu(II)—MetP System

As shown in the species diagram (Figure 3), at lower pH [Cu(HL)] is formed. In this complex only the phosphonate group is coordinated to the metal ion and the amino group is protonated. The stability constant for this complex agrees well with the stability constant obtained for the Cu(II)-HPO_4^{2-} system ($\log K_{[Cu(HL)]}$ = 2.82 and $\log K_{[CuHPO_4]}$ = 3.2 [13]), which confirms the assumed bonding mode in [Cu(HL)]. At higher pH, MetP coordinates in a similar way to α-AlaP [13] forming chelate species [CuL] and $[CuL_2]$, in which the ligands are bound to the metal ions *via* the amino and PO_3^{2-} groups. The overall stability constant of [Cu(HL)] for MetP is considerably lower than for α-AlaP system (Table I). The difference is probably due to the difference in basicity of the NH_2 groups. [CuL] and $[CuL_2]$ complexes of MetP are more stable than the methionine complexes. This can be explained by the difference in basicity of the -PO_3^{2-} and the COO^- groups.

Electronic spectra parameters confirm 2N coordination in the complex $[CuL_2]$. Typical absorption spectra for the Cu^{2+}—MetP system are plotted in Figure 4, in the pH range 2.8-12. This spectra in the d-d region at pH < 3 exhibit a transition

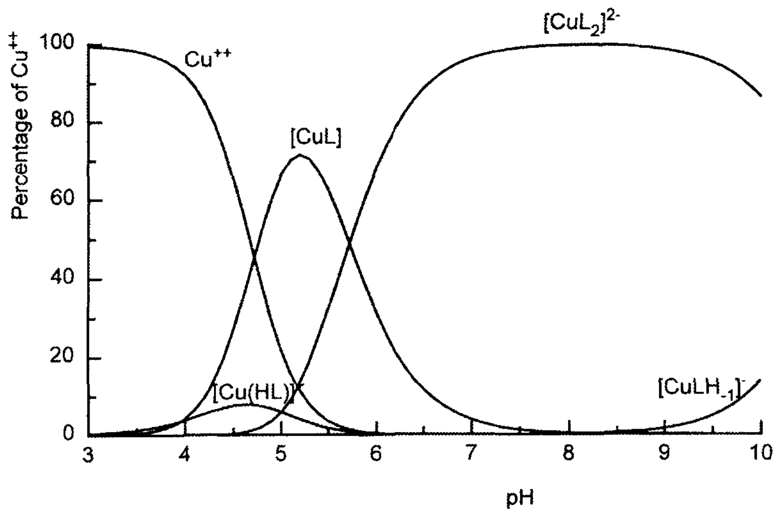


FIGURE 3 Simulated species distribution for the copper(II)-MetP system as a function of pH for conditions used in the visible studies ($c_M = 4.0 \times 10^{-3}$, $c_L = 1.6 \times 10^{-2}$ mol dm^{-3}).

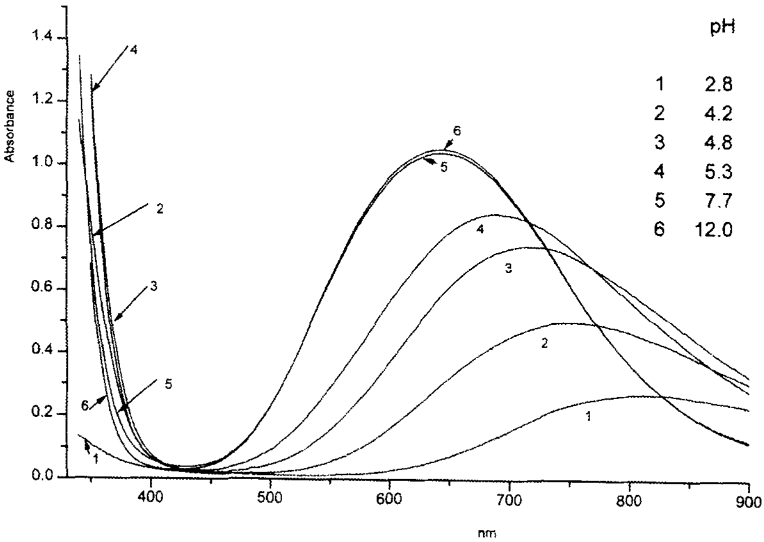


FIGURE 4 Changes of d-d absorption bands in the copper(II)-MetP system as a function of pH for $c_M = 4.0 \times 10^{-3}$, $c_L = 1.6 \times 10^{-2}$ mol dm^{-3}, l = 5.0 cm.

around 820 nm characteristic of the copper(II) aqua ion. An increase in pH above 3 leads to the appearance of a new d-d band and its maximum shifts towards the visible region indicating greater extent of complexation.

At pH 5.3 the λ_{max} at 680 nm corresponds to the maximum concentration (*ca* 68%) of [CuL]. The maximum at 650 nm does not change position in pH range of 7.7 to 8.5, which corresponds to the predominance of [CuL_2]. The next shift of the maximum with further increase in pH above 9.5 is consistent with the formation of the new complex [CuL_2H_{-1}] (Table I and Figure 4). Spectroscopic parameters of the corresponding complexes of MetP, α-AlaP and α-Ala are (for pH = 8) λ_{max} = 650 (ϵ = 53 M cm^{-1}) and 645 (ϵ = 56 M cm^{-1}) nm for the Cu(N,O)$_2$—chromophore involving *N*-amino and *O*-phosphonate donors and 615 nm (ϵ = 50 M cm^{-1}) for *N*-amino and *O*-carboxylate coordination, respectively. From these parameters we conclude that MetP and α-AlaP coordinate to copper(II) in a similar way to α-Ala, *i.e.*, involving C_α-bonded donor groups [13].

In addition to the pH-metric and spectrophotometric studies, EPR measurements were also performed in the copper(II)—MetP system. Parameters of $g_{\parallel}$ = 2.271 and $A_{\parallel}$ = 159 G for [Cu(MetP)$_2$] also seem to indicate that two nitrogens are bound to copper(II) in this species. The bonding parameters (AOM) of [Cu(MetP)$_2$] in aqueous solution suggest that the σ—bonding effect of the *O*-ligator (from the phosphonate group) with isotropic π bonding is considerably greater than that of the *N*-ligator (amine group) [15].

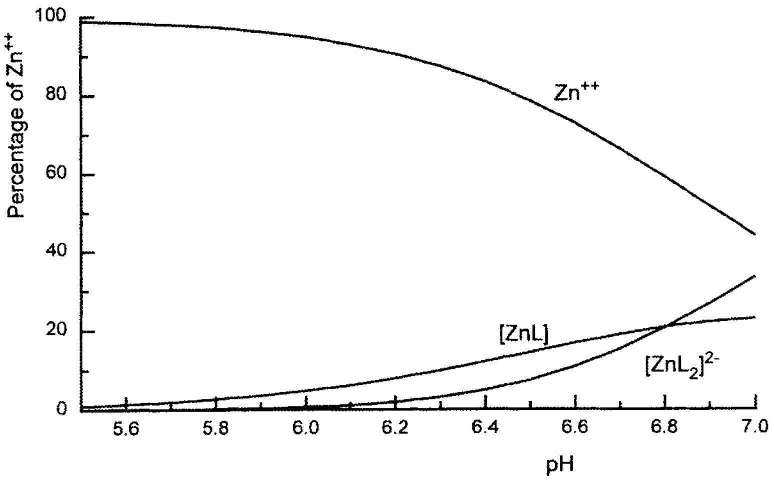
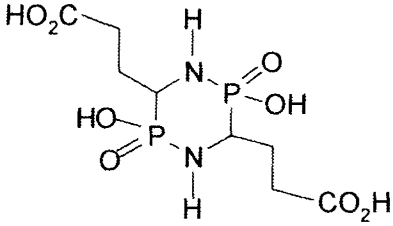


FIGURE 5 Species distribution for the zinc(II)-MetP system as a function of pH for $c_M = 1.0 \times 10^{-3}$, $c_L = 4.0 \times 10^{-3}$ mol dm^{-3}.

Zn(II)—MetP System

Recently, we showed that 4-amino-4-phosphonobutanoic acid (α-GluP) underwent chemical transformation upon reaction with zinc(II) ions in neutral and slightly alkaline solution [16]. This process was manifested in ^{31}P, ^{13}C and ^{1}H (C$_\alpha$H region) NMR spectra where two sets of resonances (pH-independent and pH-dependent *versus* temperature) were observed. The effect of rising temperature was the apparent narrowing of the upfield, pH-dependent signal. The first set we ascribed to a new compound whereas the second is due to a fast equilibrium involving both α-GluP and its Zn(II) complex(es). Release of the ligand observed at pH > 9.5 was manifested in ^{31}P NMR spectra by a narrowing of the downfield resonance. Simultaneous formation of a fine suspension of hydroxide or hydroxo complexes was observed. Further analysis showed that some other α-aminophosphonic acids also react with zinc(II) in a manner similar to that observed for α-GluP. Finally, by elimination of several possible products of ligand rearrangement, we proposed the formation of the cyclic phosphonamidate (see below) whose chemical shift (26.06 ppm for the compound derived from α-GluP) is characteristic of phosphonamidates [17-19].

^{31}P and ^{1}H (C$_\alpha$H region) NMR measurements confirmed that α-AlaP exhibits similar properties to α-GluP in the presence of the zinc(II) ions. Additional species were detected at a pH range *ca* 6.5-8.5 (Figure 6). Meanwhile, analogous measurements for the Zn(II)-MetP system clearly indicated the presence of the cyclic phosphonamidate in solution at pH 5.8-7 (Figure 7). It should be noted, 9



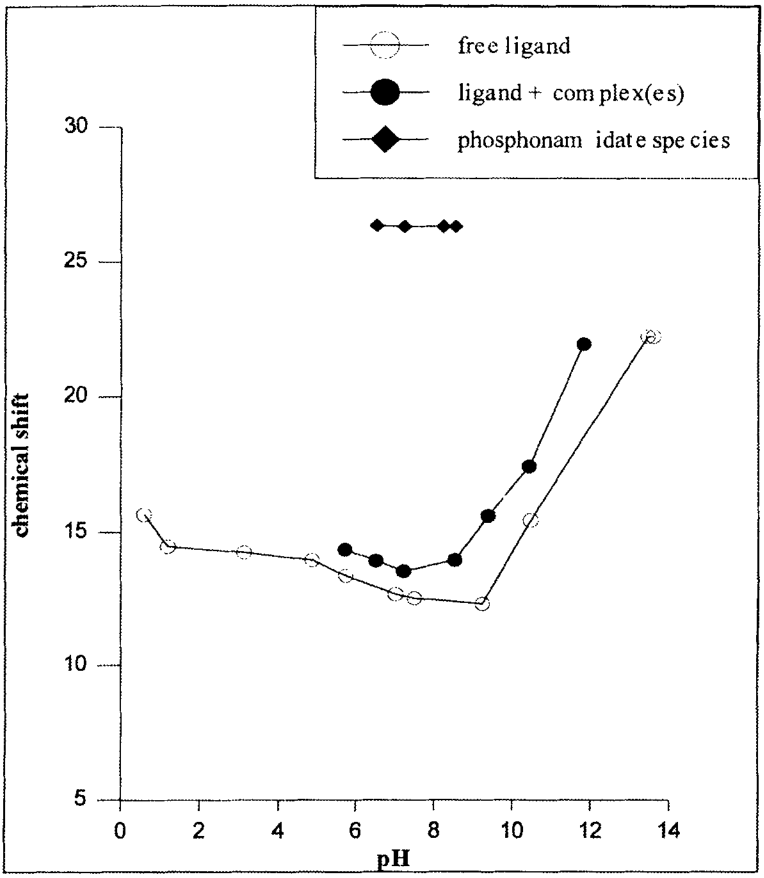


FIGURE 6 Phosphorus-31 NMR chemical shifts as a function of pH for α-AlaP and Zn(II)-α-AlaP solutions (1:2 mol ratio).

however, that at pH above *ca* 6.5 the measurements were carried out on solutions containing some amount of precipitate.

Since recent results obtained for zinc(II)-aminophosphonic acid systems indicated that the formation of the cyclic phosphonamidate generally improves solubility, it seems obvious that the precipitate could be attributed to Zn(II)-MetP

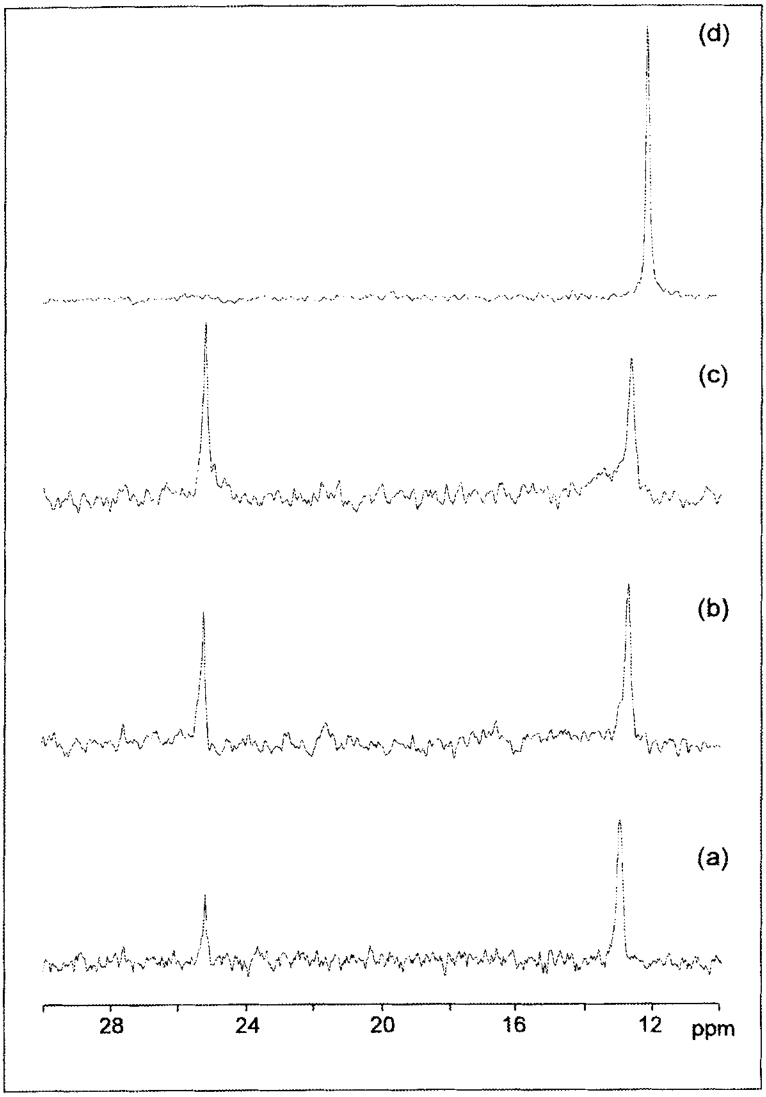


FIGURE 7 ^{31}P NMR spectra for Zn(II)-MetP solutions (1:2 mol ratio) *versus* pH (pH = 5.80 (a); pH = 6.41 (b); pH = 6.99 (c); pH = 7.31 (d)).

complex(es), different to those of α-AlaP. The lack of a low field resonance in the ^{31}P spectra at pH > 7 indicates that in alkaline solution, equilibrium shifts towards more stable, poorly soluble species involving thioether sulfur donors besides amino and phosphonate groups.

In the case Zn(II), reliable titration curves were obtained up to pH *ca* 6.5, prior to any precipitation. This pH is practically the same for different metal-ligand ratios. This suggests that precipitation is caused primarily by the poor solubility of complex(es) and not by hydrolysis. Zn(II) complexes in solutions of MetP and their stabilities are listed in Table I. Figure 5 shows as an example the pH-dependent Zn(II)-species distribution in the solutions with Zn(II):MetP = 1:4. The species distribution shows only two complexes, [ZnL] and [ZnL_2]. The protonated ligand and hydrolysed metal species had to be taken into account to fit the data.

A comparison of the zinc complexes of MetP and α-AlaP shows significant differences (see Table I). Thus, [Zn(MetP)] complex is *ca* one order of magnitude less stable than [Zn(α-AlaP)]. It can be calculated from the complex stabilities (Table I) that the formation of [Zn(MetP)] is unfavourable ($\log K_{ZnL}/K_{ZnL_2}$ value is near zero). Equilibrium constants ($\log K_n$) derived for $Zn + H_2L = ZnL + 2H^+$ and $ZnL + H_2L = ZnL_2 + 2H^+$, which take into account the difference in basicity of the coordinating donor groups ($-PO_3^{2-}$ and $-NH_2$) of MetP and α-AlaP are $\log K_1 - pK_1 - pK_2 = -10.31, -9.91$, respectively and $\log K_2 - pK_1 - pK_2 = -10.47$ for MetP. Taking this into account, comparison of [Zn(MetP)] and [Zn(α-AlaP)] complexes still reveals a difference in stabilities of about 0.4 log units, suggesting some kind of interaction between zinc(II) and the sulfur atom.

Acknowledgements

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