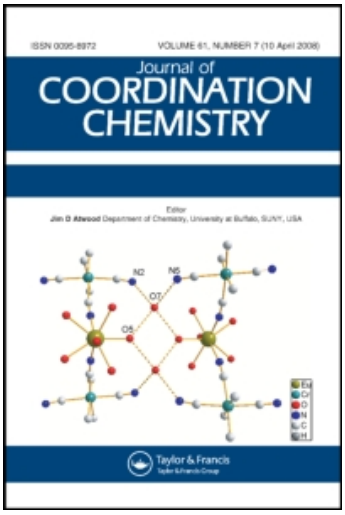

Journal of Coordination Chemistry
Publication details, including instructions for authors and subscription information:
http://www.informaworld.com/smpp/title~content=t713455674

COMPLEXES OF AMINOPHOSPHONATES PART 9.[1] COPPER(II) COMPLEXES OF CIT RIC ACID DERIVATIVES

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To cite this Article Kiss, Erzs Ébet , Jezowska-Bojczuk, Malgorzata and Kiss, Tamas(1996) 'COMPLEXES OF AMINOPHOSPHONATES PART 9.[1] COPPER(II) COMPLEXES OF CIT RIC ACID DERIVATIVES', Journal of Coordination Chemistry, 40: 1, 157 — 166
To link to this Article: DOI: 10.1080/00958979608022854
URL: http://dx.doi.org/10.1080/00958979608022854

J. Coord. Chem., 1996, Vol. 40, pp. 157–166
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COMPLEXES OF AMINOPHOSPHONATES PART 9.[1] COPPER(II) COMPLEXES OF CITRIC ACID DERIVATIVES

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(Received 11 January 1996)

Complex formation between copper(II) and 3-amino-3-phosphonoglutaric acid (Apga), an ambidentate aminophosphonate or citric acid derivative, was studied in aqueous solution by pH-potentiometry and EPR and electronic spectroscopy. Complexation with the parent molecules citric acid and tricarballylic acid was reinvestigated. The stoichiometries and stability constants of the complexes formed in these systems were determined at 25°C at an ionic strength of 0.20 mol dm^{-3} (KCl). Stability constant data and spectroscopic results revealed that in the acidic pH range Apga behaves as a citric acid derivative, forming the phosphonate-bridged dimeric species $Cu_2A_2H_2$, while in the basic pH range, with decreasing proton competition at the amino binding site, it rearranges to yield mononuclear complexes involving aminophosphonate-like (NH_2, PO_3^{2-}, CO_2) coordination.

Keywords: copper(II); complexes; aminophosphonic acids; citric acid; tricarballylic acid; potentiometry; spectroscopy; stability constants

INTRODUCTION

The structures and chemical properties of aminophosphonates endow them with versatile biological activities. As structural analogues of amino acids, aminophosponic acids can act as their antimetabolites and compete with their carboxylic counterparts for the active sites of (metallo)enzymes and other cellular receptors.[2] As inhibitors of metabolic processes, they can exert antibacterial, neuromodulator and plant growth regulator activities among others.[3] Phosphonic derivatives of iminodiacetate and nitrilotriacetate, such as Roundup® and Polaris®,

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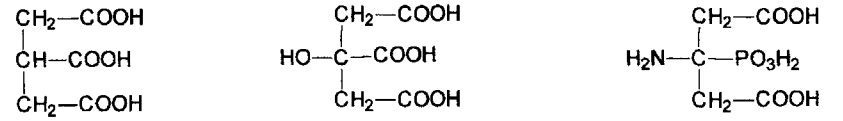
are well-known herbicides [4–5] and it is assumed that their interactions with soil and plant tissue metal ions may be involved in their activity[6]. 3-Amino-3-phosphonoglutaric acid has been synthetized and tested for herbicide activity. This compound can be regarded as an aminophosphonic derivative of citric acid or tricarballylic acid in which the central donors are replaced by amino and phosphonic functions (see Scheme 1).



Scheme 1

Complexation of citric acid by copper(II) is well established as regards its solution speciation and also its structural aspects.[7–17] Both pH-metric [8–11] and magnetic measurements[8,14] have unambiguously demonstrated the predominant formation of alcoholate-bridged dinuclear species in the pH range 5–11. The importance of the central alcoholic-OH group in the metal ion binding is clearly revealed by the fact that tricarballylic acid, which does not contain the central OH group, binds to copper(II) much more weakly and cannot hinder hydrolysis of the metal ion at pH > 7 even at high excess of ligand.[9]

We report here the coordination properties of 3-amino-3-phosphonoglutaric acid, a potentially tetradentate ligand, with copper(II); this complexation was studied in a wide pH range by means of pH-potentiometry, electron spin resonance and electronic spectroscopy. For purposes of comparison, the copper(II)-complexation processes of citric acid and tricarballylic acid were also reinvestigated.

EXPERIMENTAL

Citric acid and tricarballylic acid were Fluka products of *puriss.* quality. 3-Amino-3-phosphonoglutaric acid was synthetized as in Ref. 18. Its purity was checked and the exact concentrations of its solutions were determined by the Gran method.[19] The concentration of the metal chloride stock solution was measured gravimetrically *via* precipitation of the oxinate.

The stability constants of the proton and copper(II) complexes of the ligands were determined by pH-metric titration of 25.0 cm^3 samples (5.00 cm^3 in the case of Apga due to the small amount of ligand available). The concentration of the

ligand in each sample was 0.004 or 0.006 mol dm^{-3} (0.002 mol dm^{-3} in the case of Apga) and the metal ion to ligand ratio was 0:1, 1:1, 1:2 or 1:4 (besides 2:1, 1:6 and 1:8 in the case of tricarballylic acid). The ionic strength was adjusted to 0.20 mol dm^{-3} with KCl in each case. The titrations were performed over the pH range 3–11 (up to only pH 6–7 with tricarballylic acid because of precipitation), with a carbonate-free KOH solution of known concentration (*ca* 0.2 mol dm^{-3}).

The pH was measured with a Radiometer PHM 84 instrument with a GK 2322 combined glass electrode, calibrated for hydrogen ion concentration according to Irving *et al.*[20] The value of pK_w determined from strong acid-strong base titration was 13.76. In all cases the temperature was 25.0 ± 0.1°C. The concentration stability constants $\beta_{pqr} = [M_pA_qH_r]/[M]^p[A]^p[H]^p$ were calculated with the aid of the PSEQUAD computer program.[21]

To establish the bonding modes in the complexes formed, spectroscopic measurements were carried out. Absorption spectra were recorded on a Varian DMS-100S and a Cary 5 spectrophotometer. ESR spectral measurements were performed on a Radiopan SE/X spectrometer at the X-band (9.3 GHz) at 120 K in ethylene glycolwater (1:2 v/v) solutions.

RESULTS AND DISCUSSION

The protonation constants and the copper(II) complex formation constants of citric acid, tricarballylic acid and 3-amino-3-phosphonoglutaric acid, obtained by joint evaluation of the titration curves of the proton-ligand systems at different ligand concentrations and of the copper(II)-ligand systems at different metal ion to ligand ratios, are listed in the Table I (as discussed later, for Apga the results of two different speciation models are given).

TABLE I Protonation constants (log K) and copper(II) complex formation constants (log β) of the ligands studied, at 25 ± 0.1 °C and I = 0.20 mol dm^{-3} (Kcl)

	Citric acid	*Tricarballylic acid*	*Apga*	
			Model 1	*Model 2*
HA	5.57(2)	5.73(2)	10.15(3)	
H_2A	4.27(2)	4.44(2)	9.05(4)	
H_3A	2.87(3)	3.45(2)	6.53(6)	
H_4A			2.03(7)	
H_5A			<1	
$CuAH_2$		11.53(15)	24.96(3)	24.87(3)
CuAH	9.29(1)	8.03(3)		20.03(4)
CuA		3.35(2)	11.53(5)	11.42(5)
$CUAH_{-1}$		−3.34(5)	1.83(5)	1.70(5)

TABLE I *(Continued)*

	Citric acid	*Tricarballylic acid*	*Apga*	
			Model 1	*Model 2*
$Cu_2A_2H_2$			43.20(7)	
Cu_2A_2H			34.73(14)	
Cu_2A_2	14.10(1)			
$Cu_2A_2H_{-2}$	10.43(1)			
$Cu_2A_2H_{-2}$	5.71(1)			
Cu_2A		4.87(22)		
fitting[a]	0.00748	0.00668	0.00853	0.00856
No. of points	317	257	368	368

[a] The average difference in the calculated and experimental titration curves expressed in cm^3 of the titrant.

Complexes of Citric Acid

Citric acid contains three dissociable protons on the three carboxylic functions; the alcoholic-OH group is so weakly acidic (pK > 15) that it does not dissociate in the measurable pH range. When the difference in ionic strength is taken into account the protonation constants of citric acid listed in the Table are in reasonably good agreement with those reported in previous papers at 0.1 mol dm^{-3} (KNO_3) ionic strength.[8–11]

In accordance with the model proposed by Daniele *et al.*,[10–11] the copper(II)-citric acid system can be described best by a speciation model involving mostly dinuclear species (see Table I). The concentration distribution curves for the complexes formed as a function of pH are depicted in Figure 1. The complex CuAH starts to form at pH~2.5 and is presumably a dicarboxylate chelate, although (because of the low stability of a seven-membered chelate) monodentate carboxylate coordination cannot be excluded. In this pH range EPR spectra indicate the formation of a single complex besides $Cu(H_2O)_6$; its EPR parameters ($g_{||}$ = 2.39, $A_{||}$=127G) differ only slightly from those of the aquaion, which lends support to the abovementioned weak mono- or dicarboxylate coordination. As the pH is increased, the EPR signals broaden and their intensities decrease, and by pH~4-4.5 (almost independently of the metal ion to ligand ratio) the samples become EPR silent, indicating the formation of spin-coupled Cu(II) dimers. The exclusive formation of dinuclear species was checked spectrophotometrically; samples with the constituents at 1:1 ratio at pH~7 obeyed the Beer-Lambert law in the copper(II) concentration range 0.001–0.04 mol dm^{-3}. As shown in Figure 2 formation of the dinuclear species is accompanied by a significant shift in the d-d transition to 735 nm, which remains unchanged in the pH range 5–12. The speciation curves depicted in Figure 1 indicate that this is the pH range for formation of the dinuclear species. Hence, it is justified to assume the same bonding mode for all three dinuclear species Cu_2A_2, $Cu_2A_2H_{-1}$ and $Cu_2A_2H_{-2}$

(see Scheme 2); coordination of two carboxylate-O^- atoms and one alcoholate O^- atom through alkoxo bridges *via* the formation of 5 + 6-membered (if one of the terminal carboxylates and the central carboxylate are involved in the coordination), or 6 + 6-membered (if the two terminal carboxylates coordinate)joint chelate systems. As the pH is increased stepwise deprotonation $Cu_2A_2 \leftrightarrows Cu_2A_2H_{t-1} \leftrightarrows Cu_2A_2H_{-2}$ of the third carboxylic group takes place. The data do not support axial coordination of the third carboxylate groups, as was assumed earlier.[15] Such axial coordination should result in a slight, but well-detectable red shift of the d-d transition,[22] but this cannot be observed in this system (see Figure 2).

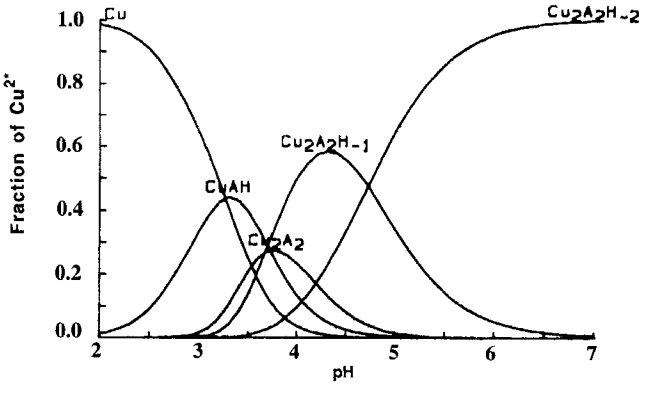


FIGURE 1 Species distribution diagram for the Cu(II)-citric acid system; $c_{cu} = 0.002$ mol dm^{-3}, $c_{ligand} = 0.004$mol dm^{-3}.

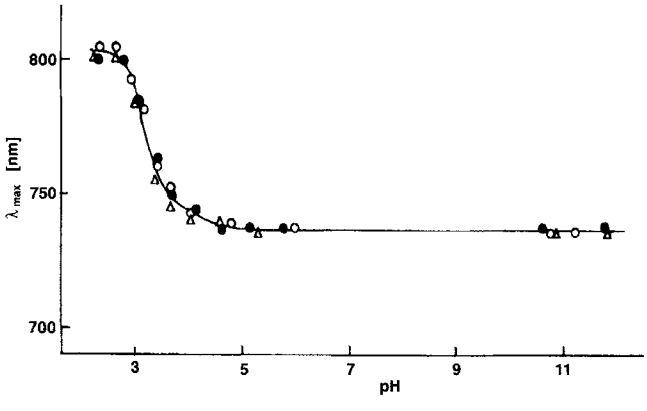
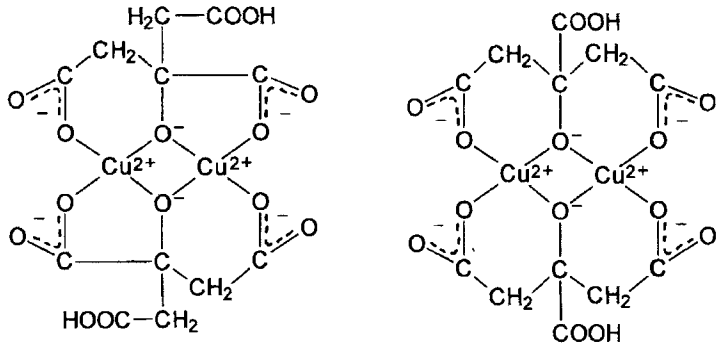


FIGURE 2 Changes of d-d transition position (λ_{max}) in the copper(II)-citric acid system as a function of pH at different metal ion to ligand ratios: 1:1 (•); 1:2 (•); 1:4 (o).



Scheme 2

Complexes of Tricarballylic Acid

The lack of the central alcoholic-OH group leads to the copper (II) binding ability of tricarballylic acid being dramatically lower. Only weakly coordinated monodentate ($CuAH_2$, a minor species) or bidentate (CuAH and CuA, the third carboxylic group is in protonated or in deprotonated form) carboxylato complexes could be detected in the pH range 4–6; a mixed hydroxo species $CuAH_{-1}$ (or more precisely CuA(OH)) is subsequently formed before the metal starts to precipitate. EPR spectra recorded in the pH range 2–5 reveal the presence of two coexisting species, the free $Cu(H_2O)_6$ ion ($g_{||}$ = 2.41, $A_{||}$ = 120G) and the carboxylate-chelated complexes CuAH or CuA ($g_{||}$ = 2.38, $A_{||}$ = 138G). EPR parameters of the latter species are in good agreement with those of the CuAH complex of citric acid, which has the same binding mode (*vide supra*).

The fitting of the pH-metric titration curves obtained at a metal excess improved slightly, when a dinuclear species Cu_2A^{11} was also assumed. Its formation, however, is very uncertain; if it is formed at all, it overlaps strongly with the beginning of precipitation. The binding mode of this complex could be expected to involve a 7 + 7-membered joint chelate system *via* a carboxylate bridge.

Complexes of 3-Amino-3-phosphonoglutaric Acid

Four protons are liberated from the ligand in the pH range 2–11, as the first proton of the phosphonic function is very acidic (log $K_{H5A} < 1$) and it is in the deprotonated $-PO_3H^-$ form in the pH range studied. The most likely assignments of the deprotonation constants are given in Figure 3. The significant decreases in acidity of the phosphonic and carboxylic groups can be attributed to the formation of intramolecular hydrogen bonding. The difference in the values of

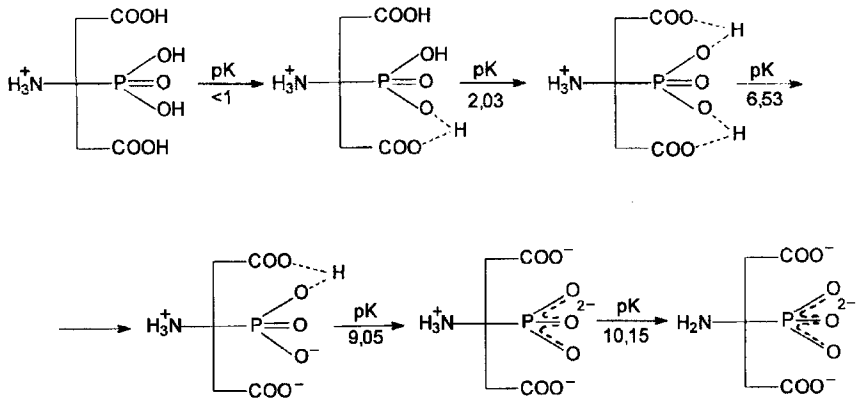


FIGURE 3 Stepwise deprotonation processes of 3-amino-3-phosphonoglutaric acid.

log K_{HA} and log K_{H2A} (see Table and Figure 3) is so small that the parallel overlapping deprotonation of the central -NH_3^+ and PO_3H^- groups (*via* the formation of isomeric microspecies) cannot be excluded.

From the stability constant data listed in the Table, it can be seen that the copper(II)-Apga system could be described equally well by two different speciation models: (i) involving only mononuclear 1:1 complexes in different protonation states, $CuAH_2$, CuAH, CuA, and $CuAH_{-1}$; (ii) including dinuclear complexes $Cu_2A_2H_2$ and Cu_2A_2H instead of CuAH. *Bis* complexes (CuA_2H_2, CuA_2H and CuA_2) were rejected by the computer program. The EPR results strongly suggest the dimeric model; in the pH range 5–8 a broad, low intensity spectrum is observed (see Figure 4), indicating a significant copper(II)-copper(II) interaction, though somewhat weaker than that in the copper(II)-citric acid system, where it led to complete spin pairing. The proposed binding mode of the dimer $Cu_2A_2H_2$, shown in Scheme 3 is in accordance with the EPR behaviour. The central phosphonate moiety acts as a bridging group between the two copper(II) centres, but in contrast with the copper(II) dimer of citric acid, the significantly weaker interaction *via* the Cu(II)-O-P-O-Cu(II) chain does not lead to complete spin coupling. A molecular model suggests that the axial Cu(II)-Cu(II) distance in the complex is ~5 Å. This interaction should result in EPR behaviour similar to that reflected by the middle spectrum in Figure 4. Deprotonation of one of the non-coordinating -NH_3^+ groups yields the complex Cu_2A_2H. The species distribution diagram calculated with the species included in Model 2 is shown in Figure 5. The first complex formed at around pH 4 is $CuAH_2$. Its high stability constant as compared with that of the α-phosphonic derivative of aspartic acid (which differs from Apga by a -CH_2COOH moiety), log β_{CuAH2} = 18.01,[23] suggests bidentate coordination through the phosphonate and one of the two carboxylates. The amino group and the other

carboxylate group are in protonated form. The derived equilibrium constant for the reaction $Cu^{2+} + H_2Apga^{2-} = Cu(H_2Apga)$ is log $K_{CuAH2} = 5.67$, which is two orders of magnitude higher than that for Asp-α-P; this latter ligand is capable only of monodentate phosphonate coordination in the corresponding $CuAH_2$ complex.[23] The bidentate coordination of Apga is supported by its EPR parameters ($g_{||} = 2.39$, $A_{||} = 131G$), which are comparable with those of the corresponding complex CuAH formed in the copper(II)-citric acid system. Then, in the wide pH range of $5 < pH < 8$, the dimeric species $Cu_2A_2H_2$ and Cu_2A_2H predominate, as discussed above. As the pH is raised above pH > 8, proton competition at the more basic central amino group decreases and deprotonation of the dimeric complex Cu_2A_2H is accompanied by rearrangement to a mononuclear aminophosphonate-type CuA complex (see Scheme 3). This change in coordination is indicated by the spectroscopic parameters as well (UV-VIS: $\lambda_{max} = 690$ nm, $\varepsilon = 35$ M^{-1} cm^{-1}; ESR: $g_{||} = 2.33$, $A_{||} = 145G$), which are in good agreement with those of the CuA complex formed in the Cu(II)-Asp-α-P system.[23] Although log K_{CuA}=11.42 for Apga is two log units larger than the corresponding log $K_{CuA} = 9.34$ for Asp-α-P,[23] this difference can be explained by the difference in basicity of the coordinating donor groups. Accordingly, terdentate (NH_2, PO_3^{2-}, CO_2^-) coordination of Apga is highly probable in the complex CuA. Deprotonation of this complex ($pK_{CuA} = 9.70$) can be ascribed to the ionization of the water molecule located at the fourth equatorial coordination site of the complex (see Scheme 3).

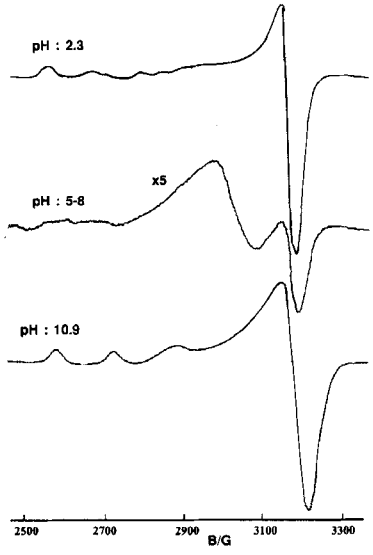


FIGURE 4 Characteristic EPR spectrum of the Cu(II)-Apga system at different pH values at 120 K.

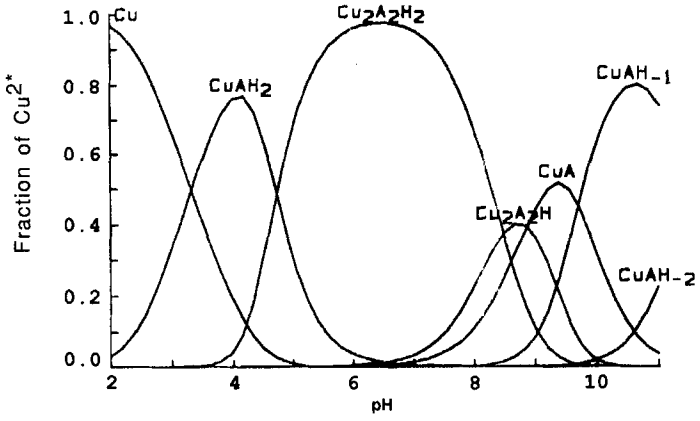
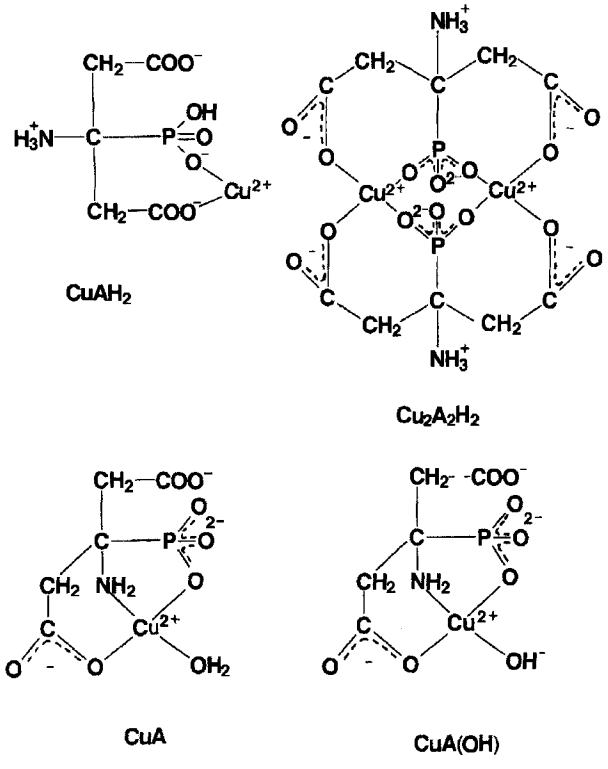


FIGURE 5 Species distribution diagram for the Cu(II)-Apga system; c_{cu} = 0.002 mol dm^{-3}, c_{ligand} = 0.004 mol dm^{-3}.



Scheme 3

3-Amino-3-phosphonoglutaric acid can be regarded either as a derivative of citric acid or as a tetradentate aminophosphonic acid derivative. Its copper(II)-binding behaviour is determined by the ambidentate character of the ligand. At low pH, when proton competition at the amino binding site is high, it behaves as a citric acid analogue and forms the phosphonate-bridged dimeric species $Cu_2A_2H_2$ and Cu_2A_2H. With increasing pH, the binding mode rearranges and the ligand behaves as an aminophosphonate derivative, coordinating as a terdentate *via* the (NH_2, PO_3^{2-}, CO_2^-) donor set. This change in binding mode is a convincing example of how pH can affect the binding ability and mode of ambidentate ligands.

Acknowledgments

The authors wish to thank Dr. M. Soroka for providing 3-amino-3-phosphonoglutaric acid. This work was carried out as part of the project COST D4 0009 and was supported financially by the Hungarian Academy of Sciences (Project OTKA 7458) and by the Polish State Committee for Scientific Research.

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