DALTON COMMUNICATION

Insertion of oximic and hydroxamic functions into one simple amino acid creates a new family of powerful chelating agents

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2-(Hydroxyimino)propanohydroxamic acid, a derivative of alanine in which the amino group has been transformed into oxime and the carboxylic group into a hydroxamic function, is a more powerful chelating agent for Cu^{2+} and Ni^{2+} ions than alanine itself, its oximic or hydroxamic analogues.

Simple amino acid molecules may be modified both at the carboxylic and amino terminals enabling them to bind metal ions. The most effective modification of the carboxylic group is its transformation into an hydroxamic function.[1] Even simple amino–hydroxamic acids have two pairs of very effective donor sets: amino and hydroxamic nitrogens $\{N_{amine},N_{hydrox}\}$ and two hydroxamic group oxygens $\{O,O^-\}$. Both sets of donor atoms form, when co-ordinated, very stable five-membered rings. Amino–hydroxamic ligands, having different affinities to metal ions (oxygen being a harder base and nitrogen being a borderline base), are very effective chelators for a variety of metal ions from very hard Al^{3+} and Fe^{3+} to softer Cu^{2+} and Ni^{2+}.[1,2]

Amino nitrogen is usually an anchoring binding site of many metal ions both in amino acids and peptides. The pK of the protonation of NH_3^+ group ranges usually between 7 and 9 and metal ions bind to amino nitrogen usually around pH 4–5 (*e.g.* Cu^{2+} or Ni^{2+}). Modification of the amino group into the oxime function (HON=) results in a very acidic nitrogen and rather basic oxygen (log $K \approx 11.0$, Table 1). This oxime nitrogen binds metal ions at very low pH acting as an even more efficient anchoring site than that of the amino group. The hydroxyl moiety, when protonated may be involved in a very effective and specific hydrogen bond, or when deprotonated may act as a bridge between different metal ions in oligomeric species.[3–5] Thus, both hydroxamic and oximic analogues of amino acids are much more efficient in metal-ion binding than their parent amino acid. In this work we have synthesised and studied the binding ability of the new ligand: 2-(hydroxyimino)-propanohydroxamic acid (HPH)‡ containing both oximic and hydroxamic functions as two potential co-ordination sites in one ligand molecule.

2-(Hydroxyimino)propanohydroxamic acid has two protonation constants§ (Table 1). The first, starting at high pH, corresponds to protonation of the hydroxyimino group ($C{=}NO^-$ with pK = 11.00) and the other corresponds to protonation of the hydroxamic group (pK 8.16). Potentiomeric data calculations show that HPH forms very stable dimeric species with Cu^{2+} below pH 3. The formation of this species is clearly seen in the EPR spectra, but vanishes around pH 4 when the Cu_2L_2 species is dominant in solution (Figs. 1 and 2). Above pH 6 the EPR spectrum of the Cu^{2+} species reappears with very clear hyperfine splitting suggesting that all four nitrogen atoms are co-ordinating, $2 \times \{N_{ox},N_{hydrox}^-\}$, in all monomeric species formed above this pH: $CuHL_2$, CuL_2 and $CuH_{-1}L_2$ (Fig. 1). The comparison of the stability constants of Cu^{2+} complexes with HPH with those of L-α-alaninehydroxamic acid (AHA) clearly shows that HPH is a much more effective chelating agent for Cu^{2+} ions than AHA (Table 1) and that the free-metal concentration vanishes at distinctly lower pH in the case of HPH when compared with AHA (Fig. 2). The metal binding in the dimeric species in both HPH and AHA ligands is hydroxamic in

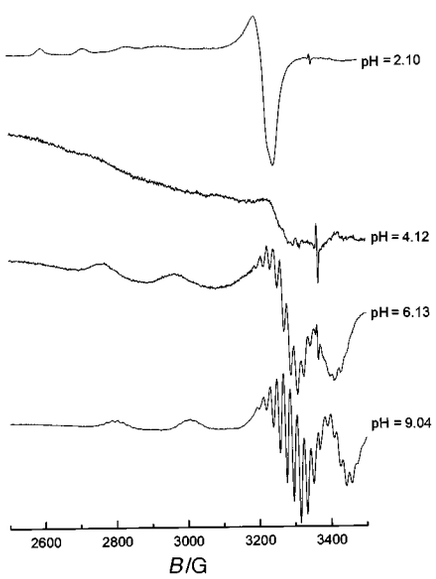

Fig. 1 The EPR spectra of the Cu^{2+}–HPH solutions at varying pH; Cu^{II} concentration 5 mmol dm^{-3} and metal-to-ligand ratio 1 : 5 at 120 K in 1 : 5 ethane-1,2-diol–water solutions; G = 10^{-4} T

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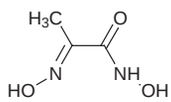
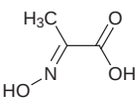
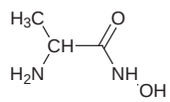
‡ Characterisation of HPH (Found: C, 30.39; H, 5.20; N, 23.93. Calc. for $C_3H_6N_2O_3$ (118.09): C, 30.51; H, 5.12; N, 23.72%). ^{1}H NMR [$(CD_3)_2SO$, 300 MHz]: δ 1.864 (s, 3 H, CH_3), 8.957 (br s, 1 H, NH), 10.672 (br s, 1 H, OH), 11.568 (s, 1 H, C=NOH).

§ Titrations involved an ionic background of 0.1 mol dm^{-3} KNO_3, a pro-ligand concentration of 3×10^{-3} mol dm^{-3} and metal-to-pro-ligand ratios of 1 : 2, 1 : 3, 1 : 5 (for Cu^{2+}) and 1 : 5 (for Ni^{2+}). Stability constants for the complexes of H^+, Cu^{2+} and Ni^{2+} were calculated from titrations carried out using total volumes of 2 cm^3. Alkali was added from a 0.250 cm^3 micrometer syringe which had been calibrated by weight titrations and the titration of standard materials. The pH-metric titrations were performed at 25 °C using a MOLSPIN automatic titration system with a microcombined glass-calomel electrode calibrated daily in hydrogen-ion concentration using HNO_3.[6] Titrations were performed in triplicate and the SUPERQUAD computer program was used for the calculations of the stability constants ($\beta_{pqr} = [M_pH_rL_q]/[M]^p[H]^r[L]^q$).[7] Standard deviations quoted refer to random errors only.

Table 1 Protonation constants and complex formation constants (log β) of 2-(hydroxyimino)propanohydroxamic acid (HPH), 2-(hydroxyimino)propanoic acid (HPA) and L-α-alaninehydroxamic acid (AHA) at 25 °C and $I = 0.1$ mol dm^{-3} KNO_3

	HPH	HPA[a]	AHA[b]
			
Species			
HL	11.00 (=NOH)	11.61 (=NOH)	9.16 (NHOH)
H_2L	19.16	14.86	16.50
log K (H_2L)	8.16 (NHOH)	3.25 (COOH)	7.34 (NH_2)
Nickel(II) complexes			
NiL	—	—	6.76(1)
NiH_2L_2	32.71(2)	28.86(1)	—
$NiHL_2$	27.48(1)	23.66(5)	—
NiL_2	22.16(1)	13.49(5)	14.13(1)
$NiH_{-1}L_2$	10.56(3)	—	5.47(1)
Copper(II) complexes			
CuL	—	—	10.89(2)
CuH_2L_2	—	31.76(6)	—
$CuHL_2$	29.91(6)	29.00(5)	—
CuL_2	22.65(5)	18.84(14)	19.87(1)
$CuH_{-1}L_2$	12.16(5)	—	9.98(2)
Cu_2HL_2	37.13(3)	—	—
Cu_2L_2	31.84(8)	27.15(7)	—
$Cu_2H_{-1}L_2$	26.66(6)	21.64(7)	20.89(2)
$Cu_2H_{-2}L_2$	—	11.67(8)	—

[a] Refs. 3 and 4. [b] Ref. 2.

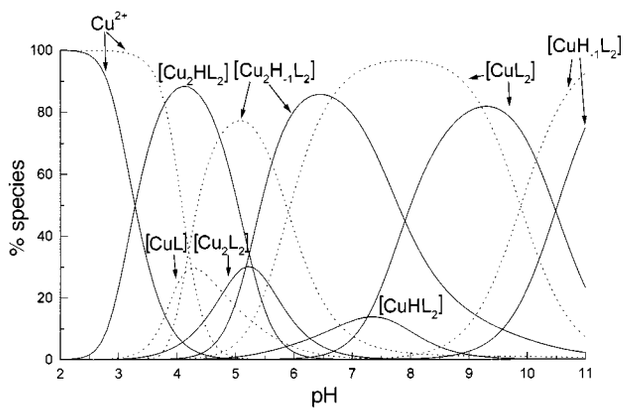


Fig. 2 Species distribution curves for Cu^{2+}–HPH (solid line) and Cu^{2+}–AHA (dotted line) complexes (2:1), $c_L = 3 \times 10^{-3}$ mol dm^{-3}

nature as it was earlier shown to be for the AHA ligand.[2] The co-ordination equilibria in Cu^{2+}–HPH solutions are also considerably different than those found for Cu^{2+}–HPA (Table 1).

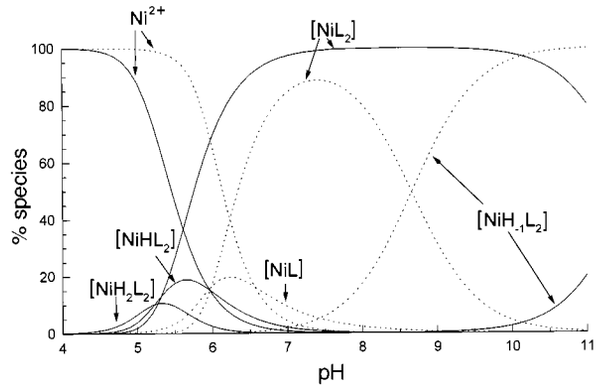


Fig. 3 Species distribution curves for Ni^{2+}–HPH (solid line) and Ni^{2+}–AHA (dotted line) complexes (2:1), $c_L = 3 \times 10^{-3}$ mol dm^{-3}

2-(Hydroxyimino)propanohydroxamic acid also forms very stable complexes with Ni^{2+} ions (Table 1). Four monomeric bis-complexes are observed: NiH_2L_2, $NiHL_2$, NiL_2 and $NiH_{-1}L_2$. The stability constants are distinctly higher than those of AHA and HPA (Table 1). The species distribution *vs.* pH plot clearly indicates that free-metal concentration vanishes at distinctly lower pH for HPH than for AHA (Fig. 3). The absorption spectra of the bis-complexes formed above pH 5 indicate that all of them are the square-planar species with a $2 \times \{\mathbf{N_{ox}}, \mathbf{N_{hydrox}}^-\}$ binding mode.

Acknowledgements

I. O. F. wishes to thank Kasa J. Mianowskiego for financial support and to the International Soros Science Education Program (grant No. APU073113). This work was performed within the COST action D8.

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Received 29*th January* 1998; *Communication* 8/00784E