

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 Cu²⁺ and Ni²⁺ 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 Al³⁺ and Fe³⁺ to softer Cu²⁺ and Ni²⁺.^{1,2}

Amino nitrogen is usually an anchoring binding site of many metal ions both in amino acids and peptides. The p*K* of the protonation of NH₃⁺ group ranges usually between 7 and 9 and metal ions bind to amino nitrogen usually around pH 4–5 (*e.g.* Cu²⁺ or Ni²⁺). Modification of the amino group into the oxime function (HON=) results in a very acidic nitrogen and rather basic oxygen (log *K* ≈ 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 p*K* = 11.00) and the other corresponds to protonation of the hydroxamic group (p*K* 8.16). Potentiometric data calculations show that HPH forms very stable dimeric species with

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‡ Characterisation of HPH (Found: C, 30.39; H, 5.20; N, 23.93. Calc. for C₃H₆N₂O₃ (118.09): C, 30.51; H, 5.12; N, 23.72%). ¹H NMR [(CD₃)₂SO, 300 MHz]: δ 1.864 (s, 3 H, CH₃), 8.957 (br s, 1 H, NH), 10.672 (br s, 1 H, OH), 11.568 (s, 1 H, C=NOH).

Cu²⁺ below pH 3. The formation of this species is clearly seen in the EPR spectra, but vanishes around pH 4 when the Cu₂L₂ species is dominant in solution (Figs. 1 and 2). Above pH 6 the EPR spectrum of the Cu²⁺ species reappears with very clear hyperfine splitting suggesting that all four nitrogen atoms are co-ordinating, 2 × {N_{ox}, N_{hydrox}⁻}, in all monomeric species formed above this pH: CuHL₂, CuL₂ and CuH₋₁L₂ (Fig. 1). The comparison of the stability constants of Cu²⁺ complexes with HPH with those of L-α-alaninehydroxamic acid (AHA) clearly shows that HPH is a much more effective chelating agent for Cu²⁺ 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

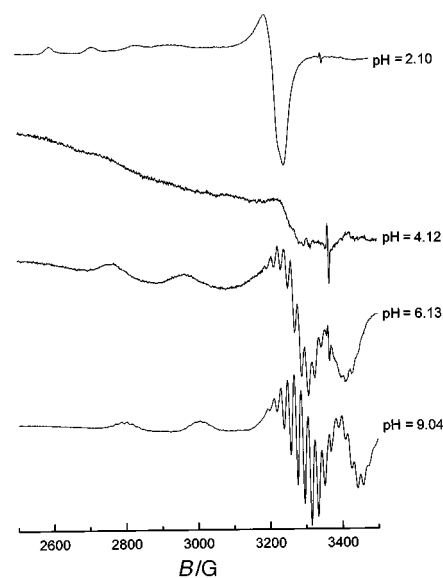


Fig. 1 The EPR spectra of the Cu²⁺–HPH solutions at varying pH; Cu^{II} concentration 5 mmol dm⁻³ and metal-to-ligand ratio 1:5 at 120 K in 1:5 ethane-1,2-diol–water solutions; G = 10⁻⁴ T

§ Titrations involved an ionic background of 0.1 mol dm⁻³ KNO₃, a pro-ligand concentration of 3 × 10⁻³ mol dm⁻³ and metal-to-proligand ratios of 1:2, 1:3, 1:5 (for Cu²⁺) and 1:5 (for Ni²⁺). Stability constants for the complexes of H⁺, Cu²⁺ and Ni²⁺ were calculated from titrations carried out using total volumes of 2 cm³. Alkali was added from a 0.250 cm³ 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 HNO₃.⁶ Titrations were performed in triplicate and the SUPERQUAD computer program was used for the calculations of the stability constants (β_{pyr} = [M_pH_qL_q]/[M]^p[H]^q[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 $I = 0.1 \text{ mol dm}^{-3} \text{ KNO}_3$

	HPH	HPA ^a	AHA ^b
<chem>C=C(O)C(=O)N(O)O</chem> <chem>C=C(O)C(=O)O</chem> <chem>C=C(O)C(=O)N</chem>			
Species			
HL	11.00 (=NOH)	11.61 (=NOH)	9.16 (NHOH)
H ₂ L	19.16	14.86	16.50
log K (H ₂ L)	8.16 (NHOH)	3.25 (COOH)	7.34 (NH ₂)
Nickel(II) complexes			
NiL	—	—	6.76(1)
NiH ₂ L 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 ₂ L 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 ₂ HL ₂	37.13(3)	—	—
Cu ₂ L ₂	31.84(8)	27.15(7)	—
Cu ₂ H ₋₁ L ₂	26.66(6)	21.64(7)	20.89(2)
Cu ₂ H ₋₂ L ₂	—	11.67(8)	—

^a Refs. 3 and 4. ^b Ref. 2.

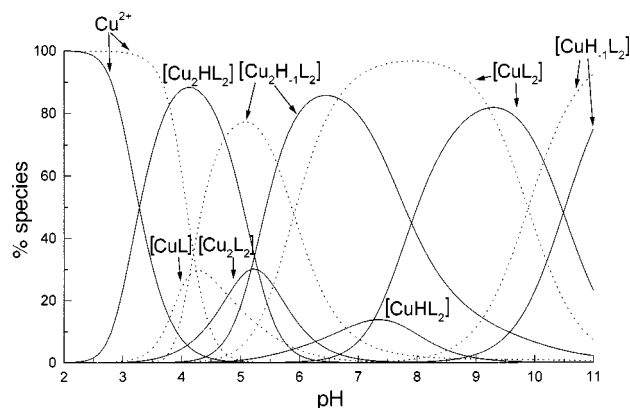


Fig. 2 Species distribution curves for Cu²⁺–HPH (solid line) and Cu²⁺–AHA (dotted line) complexes (2:1), $c_L = 3 \times 10^{-3} \text{ mol dm}^{-3}$

nature as it was earlier shown to be for the AHA ligand.² The co-ordination equilibria in Cu²⁺–HPH solutions are also considerably different than those found for Cu²⁺–HPA (Table 1).

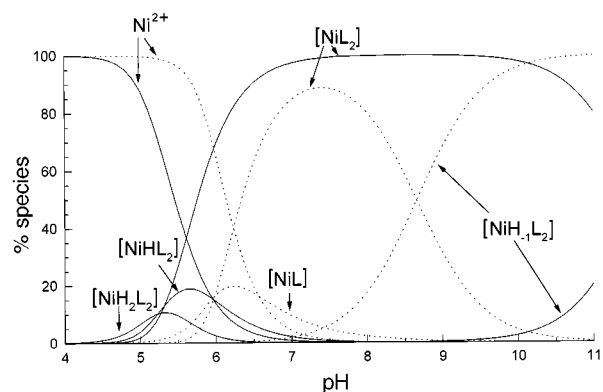


Fig. 3 Species distribution curves for Ni²⁺–HPH (solid line) and Ni²⁺–AHA (dotted line) complexes (2:1), $c_L = 3 \times 10^{-3} \text{ mol dm}^{-3}$

2-(Hydroxyimino)propanohydroxamic acid also forms very stable complexes with Ni²⁺ ions (Table 1). Four monomeric bis-complexes are observed: NiH₂L₂, NiHL₂, NiL₂ and NiH₋₁L₂. 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 $2 \times \{N_{ox}, N_{hydrox}^-\}$ binding mode.

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