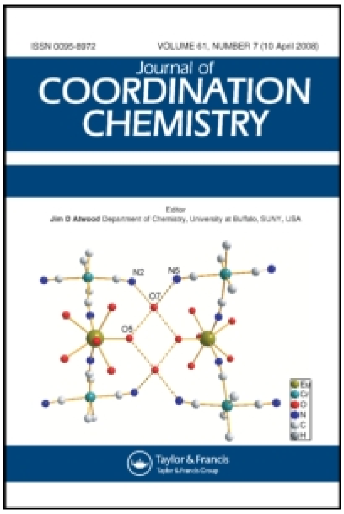

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COPPER(II), NICKEL(II) AND ZINC(II) COORDINATION BY DIHYDROXAMIC ACIDS

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COPPER(II), NICKEL(II) AND ZINC(II) COORDINATION BY DIHYDROXAMIC ACIDS

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Potentiometric titrations, absorption and e.p.r. spectra were used to establish coordination equilibria in Cu(II), Ni(II) and Zn(II) solutions with tetramethylenodihydroxamic acid and hexamethyleno-*N*,*N*′-diethylodihydroxamic acid. Results have shown that in all systems the major complexes formed at basic pH are dinuclear species. The complexes formed by dihydroxamic acids were found to be distinctly more stable than those of monohydroxamic acids.

Keywords: dihydroxamic acids, complexes, stability constants, e.s.r.

INTRODUCTION

Microbial siderophores belong to an important class of metal sequestering agents which are widely used in medical treatment, biotechnology, industry and analytical chemistry.[1] The commercially available siderophore, deferriferioxamine, a trihydroxamic acid, is used for the treatment of iron overload and aluminum intoxication.[2]

Iron(III) complexes with acetohydroxamate and glycinehydroxamate were shown to be reasonably effective[3,4] but none of the monohydroxamic ligands may be competitive enough with existing oral preparations to justify their practical use. This has directed further studies of complexes of dihydroxamic acids,[5,6] including naturally occurring rhodotorulic acid.[7]

The hydroxamic group is a potentially very effective donor system for the majority of metal ions due to the specific properties of the strongly delocalized π-bond system with the CONHOH group and the possibility of the $\{O, O^-\}$ 5-membered chelate ring formation.[7–10]

This paper presents results of a potentiometric and spectroscopic study of the binding ability of dihydroxamic acid ligands in which two donor systems are separated by four and six methylene groups. The metal ions chosen were Cu(II), Ni(II) and Zn(II) since these have been shown to be strongly bound to monohydroxamic amino acid ligands[1,8–10] and have been rarely studied precisely enough with this group of ligands. Brown *et al.*[5] have presented some results concerning dihydroxamic acid complexation by Ni(II) ions but no convincing evidence for coordination equilibria was presented. Evers *et al.*[11] have presented the potentiometric results for several dihydroxamic acids but proposed models for complex equilibria are neither well documented nor sterically realistic (*vide infra*).

Hexamethyleno-*N*,*N*′-diethylodihydroxamic acid (C_6DEDHA) was chosen in order to avoid any involvement of the nitrogen donors in direct binding to metal ions, while tetramethylenodihydroxamic acid (C_4DHA) was selected as a ligand unable to coordinate to one metal ion simultaneously *via* two hydroxamic groups due to steric reasons. The tetramethylene chain is too short to allow the formation of monomeric species involving two hydroxamic groups of the same ligand molecule.

EXPERIMENTAL

Hexamethyleno-*N*,*N*′-diethylodihydroxamic acid (C_6DEDHA), $H_2L = CH_3CH_2N(OH)CO(CH_2)_6CON(OH)CH_2CH_3$, was prepared by a method described earlier.[12] Tetramethylenedihydroxamic acid (C_4DHA) was synthesized by a modification of the method of Hanser and Renfrow,[13] starting from the diethylester of the dicarboxyl acid (0.1 mol) and hydroxylamine hydrochloric acid (0.4 mol) and adding of 0.6 mol of KOH. Synthesis was performed under nitrogen in methanol at room temperature during 72 h. The final product was recrystallized from ethanol.

Potentiometric measurements

Ligand concentration and purity was determined potentiometrically. Ionic strength was maintained at 0.2 mol dm^{-3} by KCl. The measuring system was kept at 25°C. The titrations were carried out with carbonate-free KOH solution of known concentration (*ca* 0.2 mol dm^{-3}). Small amounts of base were added with a micropipette. The pH-metric titrations were performed over the pH range 2.0–11.0 using 20.0 cm^{-3} samples. The concentration of ligand was 1×10^{-2} mol dm^{-3}. Metal to ligand molar ratios were adjusted in the range of 1:1–1:3. The pH-metric measurements were carried out using an OP-208/1 pH-meter (Radelkis) equipped with OP 7183 glass and OP 830 saturated calomel electrodes; the electrode system was calibrated by the method of Molina *et al.*[14] Resulting titration data were used to calculate hydrogen ion concentrations from potential readings. Formation constants were calculated using the SUPERQUAD computer program.[15]

Spectroscopic measurements

Absorption spectra in the 900–300 nm region were recorded on a SPECORD M-40 (C. Zeiss, Jena) and solutions were scanned at a series of pH values from pH 2 to 10 using quartz cells. The metal ion concentration in solutions used in the spectroscopic measurements was 4.2×10^{-3} mol dm^{-3} for Cu(II) and 7.4×10^{-3}

mol dm^{-3} for the ligand, while for Ni(II)-containing solutions these values were 8.5×10^{-4} mol dm^{-3} and 2.1×10^{-3} mol dm^{-3}, respectively. The pH was adjusted by adding 1.0 M NaOH solution.

E.p.r. measurements

E.p.r. spectra were recorded with a RADIOPAN SE/X spectrometer in the X-band (9.3 GHz) at 120 K in an ethyleneglycol:water (1:2) mixture. The samples contained 3×10^{-3} mol dm^{-3} Cu(II) and 6×10^{-3} mol dm^{-3} dihydroxamic acid.

RESULTS AND DISCUSSION

The two protonation constants of C_6DEDHA are close to those obtained for the similar *N*-unsubstituted dihydroxamic acids *i.e.*, C_4DHA, C_5DHA, C_6DHA, C_7DHA and C_8DHA (Table I).[5,11] Both hydroxamic groups dissociate over a similar pH range and both groups may act as competitive binding sites for metal ion.

Recent studies by Evers *et al.*[11] have suggested that dihydroxamates, C_nDHA, $n = 4, 6, 7, 8$, (LH_2), are tetradentate ligands forming with most metal ions, including Cu(II), Ni(II) and Zn(II), monomeric MLH and ML species. Molecular model considerations show, however, that the chelation of two hydroxamic groups of C_4DHA to the same metal ion (monomeric species) is sterically unlikely. In order to solve this problem more reliably we have performed a potentiometric and spectroscopic study of two systems with $n = 4$ and 6. For the latter ligand the formation of the monomeric species with a tetradentate mode of coordination is also hardly possible even if two chelates were in a less hindered *cis* position to each other.

The calculations based on the potentiometric titration data indicate that all three metal ions, Cu(II), Ni(II) and Zn(II) may form monomeric, MLH, and dimeric, M_2L_2, complexes (Table I, Fig. 1) with one or two hydroxamic groups involved in metal ion binding. Each hydroxamic group is chelated to metal ion *via* its two oxygens. The M_2L species was found only for the Cu(II)–C_6DEDHA system, for which measurements could be performed for solutions with metal ion excess.

Spectroscopic data obtained for Cu(II) with both ligands show that the *d–d* transition energy for solutions at a pH where CuLH is the major species (Fig. 1), is centred at around 745 nm ($\varepsilon = 30$ m^{-1} cm^{-1}, Table II), while the aquaion absorbs at 840 nm ($\varepsilon = 10$). The shift of the *d–d* transition energy towards higher values clearly indicates the substitution of water-bound oxygens by the stronger hydroxamic oxygen donors.[9,16–18] Binding to hydroxamic oxygens is also seen in the UV region of the absorption spectra; at 370 nm ($\varepsilon \sim 800$), hydroxamic oxygen to Cu(II) charge-transfer[9] is observed.

At a pH above 4, the major complex is Cu_2L_2. The *d–d* transition shifts to 640 nm ($\varepsilon = 35$), remaining the same to pH 10.5. An isosbestic point observed at 680 nm supports constant stoichiometry between two species, CuLH and Cu_2L_2. The charge-transfer band is shifted to 350 nm and its intensity increases about three-fold as compared to the spectrum characteristic of the CuLH species (Table II). This clearly indicates the involvement of the second hydroxamic group in metal ion binding. E.p.r. spectra show two different tetragonal complexes formed in Cu(II)–C_6DEDHA solutions. The major species at pH ~ 4, CuLH, gives $g_{\|} = 2.339$ and $A_{\|} = 150$ Gs while the second, Cu_2L_2, is characterized by $g_{\|} = 2.274$ and $A_{\|} = 173$ Gs. In both

TABLE I

Stability constants (log β_n) for proton and metal complexes of C_6DEDHA in 0.2 KCl at 25°C. Standard deviations are given in parentheses. The data obtained earlier[11] for C_4DHA and C_6DHA are also shown for comparison.

Species	log β C_4DHA	log β C_4DHA[11]	log β C_6DEDHA	log β C_6DHA[11]
HL	9.67 (2)	9.38	9.83 (2)	9.61
H_2L	18.69 (1)	18.19	18.60 (3)	18.53
CuLH[a]			17.80 (1)	
Cu_2L[a]			16.31 (1)	
CuLH	17.24 (1)	17.06	17.76 (1)[b]	17.53
CuL		13.11		13.40
Cu_2L_2	28.19 (1)		28.22 (5)[b]	
NiLH	14.60 (2)	14.43	14.54 (2)	
NiL		7.63		
Ni_2L_2	17.85 (5)		17.92 (5)	
ZnLH	14.67 (10)	14.51	14.64 (5)	14.92
ZnL		7.76		8.05
Zn_2L_2	18.04 (4)		19.00 (4)	

Stabilities for copper(II) complexes were calculated from the potentiometric data obtained from a solution containing 2:1 ([a]), and 1:1–1:6 ([b]) metal to ligand ratios.

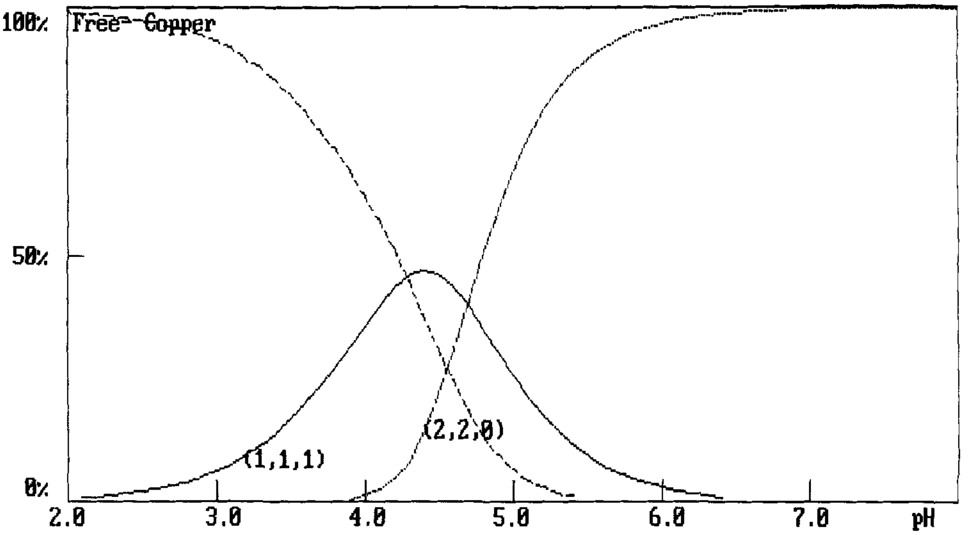

FIGURE 1 Species distribution curves for the Cu(II)–C_4DHA system in terms of pH; $C_M = 5 \times 10^{-3}$ mol dm^{-3}; M:L = 1:2.

cases the single spectrum obtained is well resolved and this indicates that both cupric ions in the dinuclear complex lie in the same tetragonal environment (*i.e.*, they are bound to the same donor set (2 × {O^-, O}) in equatorial positions).

The pH dependence of the e.p.r. and absorption spectra follows very closely the species distribution curves obtained from the potentiometric data (Fig. 1). Thus, the

TABLE II
Spectroscopic parameters for Cu(II) complexes with C_4DHA and C_6DEDHA.

Complex	λ [nm] (ε, $m^{-1} cm^{-1}$)	$g_{\parallel}$	$A_{\parallel} \times 10^{-4} cm^{-1}$
C_4DHA			
CuLH	757 (25) 370 (40)	2.340	151.0
Cu_2L_2*	658 (25) 364 (120)	2.275	175.0
C_6DEDHA			
CuLH	745 (30) 370 (80)	2.239	150.0
Cu_2L_2	640 (35) 350 (240)	2.274	173.0

* The ε parameters for this species could be doubtful due to the precipitation observed several minutes after adjusting the pH (6.77).

spectroscopic data strongly support the model obtained from the potentiometric titrations. Spectroscopic data obtained for the Cu(II)–C_4DHA system are very similar to those discussed above (Table II).

The potentiometric titration study performed by Evers *et al.*[11] has suggested two mononuclear species, MHL and ML to be formed in Cu(II)–C_nDHA systems ($n = 4$, 6, 7, 8). From the stability constants of CuL presented in that work it is clear that both groups should be involved in metal ion coordination. The pK^{CuL}_{CuHL} values, being about 4, are much lower than the pK values of the second hydroxamic group which is close to 9 (Table I). Promotion of deprotonation of this group by five orders when compared to the free ligand can be only caused by coordination. This is clear from the spectroscopic data presented above.

As mentioned, even simple molecular model considerations indicate that coordination of both hydroxamic groups in the tetragonal CuL complex is sterically unlikely both for C_4DHA and C_6DEDHA. Almost the same spectroscopic behaviour of the complexes formed with the two ligands (Table II) indicates the same coordination pattern. The absorption and e.p.r. spectra agree well with equatorial binding of both hydroxamic groups. Thus the severe steric hindrance expected for *cis* coordination of both groups of C_6DEDHA excludes the formation of monomeric species with tetradentate ligate binding in both cases.

It should also be mentioned that tetradentate coordination of C_8DHA leads to severe steric hindrance when equatorial binding sites are assumed. Thus, the binding model assumed earlier on the basis of the simple potentiometric data is sterically unlikely. This is especially evident for the ligands with short $\{(CH_2)_n\}$ chains. For the same reasons, the assumption of a monomeric species for Fe(III) complexes (FeL^{11}), is doubtful. Iron ion, which is very strongly bound to hydroxamic acid oxygens,[7,9,20] can not form an FeL complex with C_4DHA or C_6DHA ligand with coordination of two hydroxamic groups. The earlier assumption of the Fe_2L_3 complex by Raymond[20] seems to be much more realistic. Also, X-ray structures of Fe(III) complex C_5DHA derivatives indicates formation of oligomeric structures in which two hydroxamic groups are bound to a different metal ion.[7] Thus, the similarities of the β values reported by Evers *et al.*[11] for all studied C_nDHA ligands suggest that dimer formation is important in all cases.

The potentiometric results obtained for two other studied metal ions are similar to those of Cu(II) (Table I). According to the absorption spectra, the two Ni(II)-C_6DEDHA complexes are octahedral or *pseudo*-octahedral. The ν_3 *d–d* transition at 390 nm ($\varepsilon = 17$) observed for NiLH splits into two bands at 380 ($\varepsilon = 17$) and 395 nm ($\varepsilon = 18$) when Ni_2L_2 is the major complex. This indicates some distortion of octahedral symmetry around the metal ion when the dimer is formed.

Comparison of the coordination ability of dihydroxamic and monohydroxamic acids indicates that dihydroxamic acid ligands are distinctly better chelating agents and they coordinate metal ions at a pH more than one log unit lower (pH 4 for Cu(II) and pH 7 for Ni(II) and Zn(II) and conditions given in Fig. 1) than the monohydroxamic acids (pH $\sim$ 5 and 8, respectively). It is interesting to note that the zinc complexes are more stable than the respective nickel complexes. This is usually found, however, for hydroxamic acid complexes with oxygen coordination.[1,4]

The other characteristic feature found for the systems reported here is that unusually high stability constants for the dinuclear copper(II) complexes are found, as compared to the species formed by Ni(II) or Zn(II) ions. This was previously noted for M_2L_2 species with some amino acid ligands.[19]

The binding modes discussed above are considerably different to those proposed earlier.[5,11] Molecular models clearly indicate that the involvement of both hydroxamic donor functions should lead to the formation of dimeric complexes which can be easily fitted to the data obtained from the potentiometric and spectroscopic measurements.

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