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The Formation Constants and Structures of Copper(II)–Glycinehydroxamic Acid Complexes

E. B. PANIAGO and S. CARVALHO

Universidade Federal de Minas Gerais, Departamento de Química do ICEx, Pampulha, 30000, Belo Horizonte, Brazil

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Formation constants for the complexes formed between copper(II) and glycinehydroxamic acid ($H_2NCH_2CONHOH$) have been measured potentiometrically at 25.0 °C and I = 0.10 M ($NaClO_4$). The existence of a dimeric copper(II) species has been shown from the line broadening of the epr spectrum of a solution at room temperature. The structures of the complexes are discussed and conclusions are drawn based on absorption and epr spectra.

Introduction

There is an important biochemical interest in the hydroxamic acids, as a result of the finding of the oxidized peptide (amide) group, –CON(OH)–, in a number of natural products, especially in antibiotics and bacterial growth factors [1].

Apart from porphyrins, hydroxamic acids are the other major class of naturally occurring iron complexing agents. While Fe(III) hydroxamate complexes are all very stable, the corresponding Fe(II) complexes are relatively unstable. This is incompatible with an oxido–reduction mechanism for the iron but is, on the other hand, ideally suited for the biological role the hydroxamate is supposed to play, *i.e.* metal transport [2]. Ferric glycinehydroxamate has been considered as a suitable source of iron as a trace element in animal nutrition [3].

Recent X-ray crystallographic [4], IR and potentiometric [5] studies have reported the structure and the formation constants of nickel(II) complexes of glycinehydroxamic acid.

The hydroxamic acid group as a typical bidentate donor behaves very much like acetylacetone towards various metals ions [6, 7]. However, in the presence of another donor group in the same molecule, the hydroxamate group has been shown to behave as a monodentate group, coordination to Ni(II) and Cu(II) ions taking place through its nitrogen atom, after an induced deprotonation takes place [4, 7].

In this paper we present our results concerning the formation constants of copper(II) complexes of glycinehydroxamic acid ($HL = H_2NCH_2CONHOH$). Complexes of this acid with Cu(II) have already been isolated and their stoichiometric composition determined [8]. However, spectrophotometric measurements demonstrate a rather complex equilibrium in solution [9].

Our results suggest the existence of four different complex copper(II) species in solution, one of which is a dimeric one. The formation constants of these species were determined from potentiometric titrations. Attempts to isolate this dimeric species were unfruitful but experimental evidence, based on visible spectra and epr measurements, confirms its existence in solution.

Experimental

Reagents and Materials

Copper(II) and sodium perchlorates were prepared from the corresponding carbonates and perchloric acid. The concentration of the copper stock solution was determined complexometrically using a Metrohm copper selective electrode. The sodium perchlorate solution was analysed using a cation-exchange resin. Carbonate-free sodium hydroxide solution was prepared and standardized by titration with potassium hydrogen phthalate. The concentration of the perchloric acid solution was determined by potentiometric titration. Glycinehydroxamic acid was prepared as described by Safir [10]. *Anal.* Calc.: C, 26.67%; H, 6.71%; N, 31.10%. Found: C, 26.83%; H, 6.57%; N, 31.00%. Fresh aqueous ligand solutions were prepared daily, adding excess perchloric acid.

Potentiometric Titrations

Potentiometric titrations were performed using a Metrohm E636 Titroprocessor equipped with Metrohm EA 109 glass and EA 404 calomel (containing 0.1 *M* NaCl) electrodes. The electrode system was calibrated by periodic titrations of perchloric acid (or sodium hydroxide) solution (0.1 *M* in $NaClO_4$) with standard sodium hydroxide (or perchloric acid) solution. The resulting titration data was used to calculate the standard electrode potential E^0 and

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the dissociation constant for water. These values were then used in the calculation of hydrogen ion concentration ($p[H^+] = -\log[H^+]$) from potential readings [11].

All measurements were made at 25.0 °C under a purified nitrogen atmosphere and at an ionic strength of 0.1 *M* $NaClO_4$. Test solutions were prepared by dilution with bidistilled water of stock ligand and copper standard solutions. Ligand titrations were performed in the absence and in the presence of copper ions (in this case, the concentration ratios of ligand to metal ions varied in the range of 2.4:1 to 9.6:1). Formation constants were calculated using a modified version of the computer program SCOGS [12]. Species distribution as a function of $p[H^+]$ was determined with the COMICS [13] computer program. Calculations were carried out with the aid of an electronic computer Burroughs B6700.

Spectrophotometric Measurements

Absorbance spectra were recorded on a CARY 17D spectrophotometer using 10 cm quartz cells thermostatted at 25.0 °C. Measurements of potential were done with the system used in the potentiometric titrations, calibrated in the same way. The stock solution (0.1 *M* in $NaClO_4$ 1.0×10^{-3} *M* in Cu(II) and 2.0×10^{-3} *M* in glycenehydroxamic acid) was maintained under a nitrogen atmosphere and was adjusted by adding 1.0 *M* NaOH solution.

EPR Measurements

The electron paramagnetic resonance solutions spectra were obtained at room temperature on a X-band (9 GHz) spectrometer, operating at 100 KHz. The samples were prepared from a stock solution containing 5.0×10^{-3} *M* copper(II) ions and 1.0×10^{-2} *M* glycinehydroxamic acid in bidistilled water. The appropriate $p[H^+]$ was adjusted with sodium hydroxide solution, under a nitrogen atmosphere.

Results

Titrations

The glycinehydroxamic acid (HL) contains one ionizable proton in its hydroxamic acid group (pK_a = 9.12) and is able to coordinate an additional proton to the amino group (pK = 7.37).

Titrations of protonated glycinehydroxamic acid (H_2L^+, 9.6×10^{-3} *M*) in the presence of copper(II) ions ($1.0–4.0 \times 10^{-3}$ *M*) show three inflection points corresponding to the release of 2.5, 4 and 5 protons per copper respectively, which can be related to the following reactions:

$$2Cu^{2+} + 2H_2L^+ = Cu_2H_{-1}L_2^+ + 5H^+$$

$$Cu^{2+} + 2H_2L^+ = CuL_2 + 4H^+$$

$$Cu^{2+} + 2H_2L^+ = CuH_{-1}L_2^- + 5H^+$$

These reactions, together with the protonation reactions of the glycinehydroxamate ligand (L^-) can be represented by eqn. 1, the formation constant for this generalised reaction being β_{pqr}.

$$pL^- + qCu^{2+} + rH^+ = ((L^-)_p(Cu^{2+})_q(H^+)_r)^{2q+r-p} \quad (1)$$

Evaluation of the β_{pqr} constants, using the computer program SCOGS, led us to include a fourth copper(II) species, CuL^+, as a result of graphical comparisons between experimental and simulated titration curves. The results are shown in Table I.

TABLE I. Log β_{pqr} for the Species $L_pM_qH_r$ (25.0 °C and I = 0.1 *M* $NaClO_4$). Standard Deviations Given in Parentheses.

p	q	r	log β
1	0	1	9.118(2)
1	0	2	16.491(3)
1	1	0	10.83(4)
2	2	−1	20.91(3)
2	1	0	19.89(2)
2	1	−1	9.95(3)

The calculated concentrations of these four copper(II) complex species, as a function of $p[H^+]$, in a solution containing 1.0×10^{-3} *M* Cu(II) and 2.0×10^{-3} *M* glycinehydroxamic acid (shown in Fig. 1) indicate that under these conditions the CuL^+ species is not more than 25% of the total copper content in solution, while the dimeric species, at

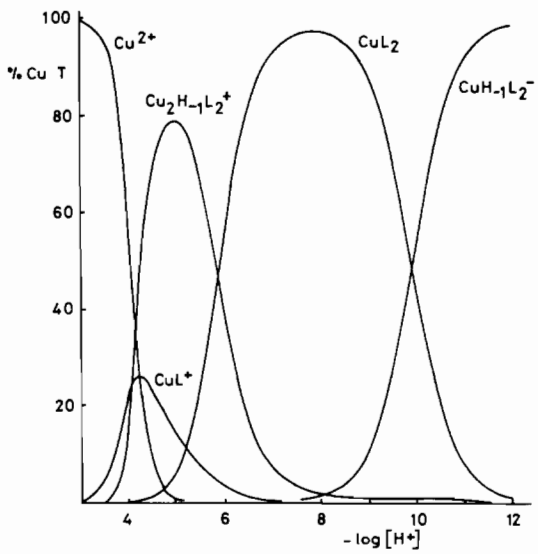


Fig. 1. The $-\log[H^+]$ dependence of the computed distribution of Cu(II) species in the presence of glycinehydroxamic acid (HL). $[Cu^{2+}]_T = 1.0 \times 10^{-3}$ *M*; $[HL]_T = 2.0 \times 10^{-3}$ *M*.

$p[H^+] = 5$, almost reaches 80%. The species CuL_2, from $p[H^+] = 7$ to 9, corresponds to over 90%, with a maximum of 97% at $p[H^+] \sim 8$.

Absorption Spectra

Formation of the different copper(II)–glycinehydroxamate complexes with increasing $p[H^+]$ can be followed by absorption spectroscopy in the 350–800 nm range. The spectra in Fig. 2 were obtained under exactly the same conditions used in the calculation of the species concentrations shown in Fig. 1. At low $p[H^+]$ the absorption presents a broad spectrum near the infrared region, its maximum shifting progressively into the visible region as the $p[H^+]$ is increased. A maximum at 650 nm is reached at $p[H^+] = 4.93$, which corresponds to the maximum in the concentration of the complex species $Cu_2H_{-1}L_2^+$ at about this same $p[H^+]$. Calculation of ϵ at this wavelength, based on the calculated species concentration, gives, for $Cu_2H_{-1}L_2^+$, $\epsilon = 200\ M^{-1}\ cm^{-1}$.

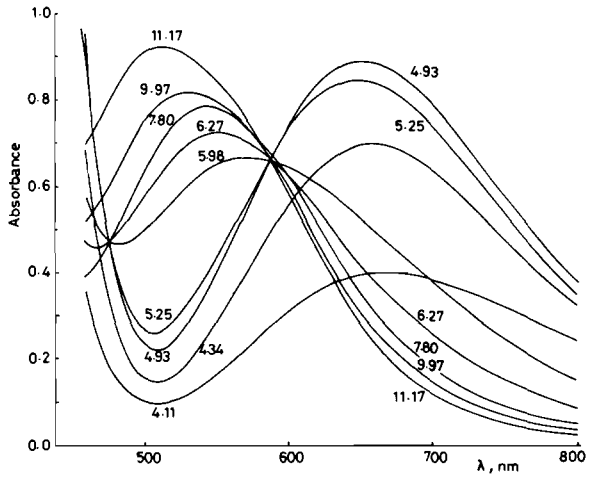


Fig. 2. Absorption spectra of Cu(II)-glycinehydroxamic acid as function of $-\log[H^+]$. Conditions: $[Cu^{2+}]_T = 1.0 \times 10^{-3}$ M; $[HL]_T = 2.0 \times 10^{-3}$ M; $I = 0.1$ M ($NaClO_4$); 25.0 °C (10 cm cells).

As the $p[H^+]$ increases above 5, a simultaneous decrease in the absorption occurs with a maximum at 650 nm and an increase in the absorption with a maximum at 545 nm. A distinctive isosbestic point appears at 465 nm. This corresponds to an equilibrium between the species $Cu_2H_{-1}L_2^+$ and CuL_2 which are the prevailing species from $p[H^+] = 6$ to 8, according to Fig. 1. The maximum at 545 nm thus corresponds to CuL_2, with $\epsilon = 80\ M^{-1}\ cm^{-1}$.

As the $p[H^+]$ increases further, above $p[H^+]$ 9, a new shift in the spectrum is observed with a maximum occurring at 510 nm. This coincides with the formation of the species $CuH_{-1}L_2^-$ shown in Fig. 1, for which the calculated ϵ at this wavelength is 95 $M^{-1}\ cm^{-1}$.

EPR Spectra

The electron paramagnetic resonance spectra of solutions containing copper(II) perchlorate (5.0×10^{-3} M) and glycinehydroxamic acid (1.0×10^{-2} M) as a function of $p[H^+]$ are shown in Fig. 3. The spectra may be divided into four types, depending on the $p[H^+]$ of the solution. These different spectra can also be related to the appearance of different copper(II) species in solution.

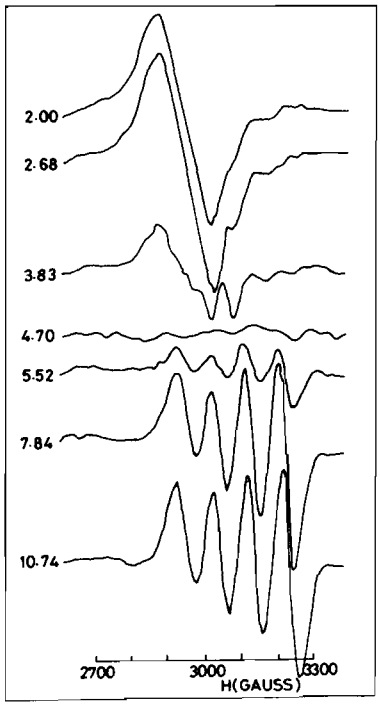


Fig. 3. EPR spectra of Cu(II)-glycinehydroxamic acid as a function of $-\log[H^+]$. Conditions: $[Cu^{2+}]_T = 5.0 \times 10^{-3}$ M; $[HL]_T = 1.0 \times 10^{-2}$ M; aqueous solution at room temperature.

At the lowest $p[H^+]$ (2.00), before any complexation takes place, the spectrum is characteristic of copper(II) ions in solution. The two following spectra ($p[H^+] = 2.68$ and 3.83), while still showing the characteristics of the copper(II) ions spectrum in the background, also shows the structure characteristic of a copper(II) complex. These spectra correspond to a mixture of Cu(II) and CuL^+ ions in equilibrium, the concentration of the latter corresponding, in the two solutions, to 1 and 20% of the total copper content respectively. In the measurements made at $p[H^+] = 4.70$, the spectrum has disappeared, which is considered the result of the transformation of over 80% of the total copper content in the dimeric species $Cu_2H_{-1}L_2^+$. With further increase in $p[H^+]$, the spectrum reappears at $p[H^+]$ 5.52 and acquires a well resolved structure starting at $p[H^+]$ 7.84. This corresponds to the appearance of the species CuL_2, starting at $p[H^+]$ 5 and representing

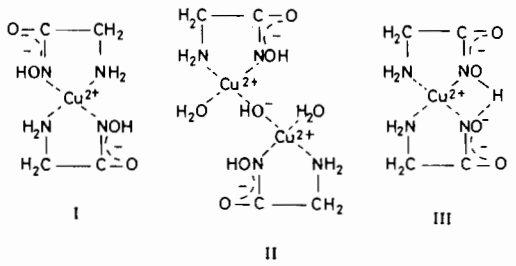
almost 100% of the total copper content at $p[H^+]$ = 7.84.

With further increase in $p[H^+]$, the spectrum does not change its structure significantly, in spite of the appearance of the species $CuH_{-1}L_2^-$, which is well characterized by the absorption spectra.

Discussion

Attempts to isolate from solution the dimeric copper(II) species, by adjusting the hydrogen ion concentration, were unfruitful. In all cases, a green solid of undefined composition was obtained.

The bis(glycinehydroxamate)copper(II) complex, CuL_2, was isolated as violet crystals from solutions with $p[H^+] \sim 8$. Its X-ray crystal structure has been determined [14] and found to be similar to the corresponding nickel(II) complex [4]. This means that the coordination about the central Cu(II) atom is strongly tetragonally-distorted. The nitrogen atoms of the two glycinehydroxamate ligands which occupy the four coordination sites with *trans* geometry, together with Cu, define the square plane, as shown in structure I.



I II III

It is significant in these Ni(II) and Cu(II) complexes with glycinehydroxamic acid that the coordination by the hydroxamic acid side of the molecule, after deprotonation, occurs *via* the nitrogen atom of the –CONHOH group rather than through the oxygen atom. This property is reflected in the absorption spectrum of the CuL_2 complex with λ_{max} = 545 nm, characteristic of copper(II) coordination by four nitrogen donor groups [15], two N(amino) and two N(hydroxamate) in this case.

According to Billo [15] the ligand-field contribution of each N(amino) is equal to 4.53 kK, which means that the contribution of the nitrogens of the two hydroxamate groups in the CuL_2 complex with ν_{max} = 18.35 kK corresponds to: (18.35–9.06)/2 = 4.65 kK.

For the dinuclear complex $Cu_2H_{-1}L_2^+$, with λ_{max} = 650 nm, if we suppose coordination of one glycinehydroxamate group to each copper atom *via* the nitrogens of the amino and hydroxamate groups, this would result in a contribution of 9.18 kK to the energy of the d–d transition. The two remaining groups would have to contribute 3.1 kK each, in order to arrive at the observed ν_{max} (15.4 kK) for the complex. This value agrees well with the predicted contribution of OH^- or H_2O groups, which is 3.01 kK. It is, therefore, reasonable to suppose the coordination of these two groups to each copper atom, since the equilibrium results indicate the presence of an OH^- group (or the absence of an H^+) in the dinuclear species. This implies the existence of one OH^- bridging group, and could mean that an OH^- ligand bridges two $[CuL]^+$ units equatorially, the fourth position in each copper atom being occupied by an H_2O molecule as shown in structure II. This structure, except for the fourth coordination position, corresponds to the structure proposed for dinuclear complexes of copper(II) and simple aliphatic dipeptides [16]. The only difference being that, in these, the fourth position is occupied by a –COO– group.

The structure of the $CuH_{-1}L_2^-$ complex has not been determined, however it is reasonable to assume it to be similar to the corresponding Ni(II) complex, as shown in structure III. $NiH_{-1}L_2^-$ is known to maintain the square-planar structure of NiL_2 with the four nitrogen atoms occupying the coordination sites [17]. The significant difference is the geometry of the ligand which is *trans* in the NiL_2 and CuL_2 complexes and *cis* in $NiH_{-1}L_2^-$. To form $NiH_{-1}L_2^-$, one of the protons of the two $-CONOH^-$ groups is lost and a strong intramolecular H bond is established between the oxygen atoms of the two groups.

One additional aspect to be mentioned is that, as expected, the complex CuL_2, according to its formation constant, is 2.5×10^3 times more stable than NiL_2 ($\log \beta_2$ = 13.495 [5]). However, considering these two complexes as acids, according to the equilibrium:

$$ML_2 \rightleftharpoons MH_{-1}L_2^- + H^+,$$

NiL_2 (pK_a = 8.4 [18]) is an acid 35 times stronger than CuL_2 (pK_a = 19.89–9.95 = 9.94).

This is certainly related to the change in the geometry of the ligands which occurs during deprotonation and would mean that the *cis* geometry is more stable for the Ni(II) complex than for the Cu(II) one.

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