



# Formation studies of binary and ternary complexes of copper(II) with an oxazol derivative of nicotinic acid and some amino acids



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## ARTICLE INFO

### Article history:

Received 3 October 2016

Received in revised form 2 December 2016

Accepted 3 December 2016

Available online 10 December 2016

### Keywords:

Copper(II) complexes

Amino acids

Potentiometric studies

Speciation

Ternary complexes

## ABSTRACT

Binary and ternary complexes of copper(II) with the 2-(benzo[d]oxazol-2-yl)nicotinic acid (Ligand HL) and the amino acids Glycine (HGly, HB), Proline (HPro),  $\alpha$ -Alanine (H $\alpha$ -Ala, HB),  $\beta$ -Alanine (H $\beta$ -Ala, HB) were studied in aqueous solution at 25 °C, using 1.0 mol · dm<sup>-3</sup> KNO<sub>3</sub> as the ionic medium. The types of complexes formed and their overall stability constants were established on the basis of the computer analysis of the potentiometric data, using a version of the program LETAGROP. It was inferred that the aromatic oxazol Ligand L<sup>-1</sup> acts as a primary ligand in the ternary complexes, while the oxygen and nitrogen donor-containing amino acids are the secondary ligands. The analysis showed the formation of five complexes: [Cu(L)(HB)]<sup>+</sup>, Cu(L)(B), [Cu(L)(B)(OH)]<sup>-</sup>, [Cu(L)<sub>2</sub>(B)]<sup>-</sup> and [Cu(L)(B)<sub>2</sub>]<sup>-</sup> in the Cu(II)-L<sup>-</sup>-Gly and Cu(II)-L<sup>-</sup>- $\beta$ -Ala systems, for the Cu(II)-L<sup>-</sup>-Pro system, the complexes [Cu(L)(HB)]<sup>+</sup>, Cu(L)(B), [Cu(L)(B)(OH)]<sup>-</sup> and [Cu(L)(B)<sub>2</sub>]<sup>-</sup> were detected and, finally, in the Cu(II)-L<sup>-</sup>- $\alpha$ -Ala system, only the complexes [Cu(L)(HB)]<sup>+</sup>, Cu(L)(B) and [Cu(L)(B)(OH)]<sup>-</sup> were observed. The concentration distributions of various species formed in aqueous solution were also evaluated as a function of pH.

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## 1. Introduction

Low-molecular-weight copper (II) complexes have been studied as potential chemotherapeutic agents for several diseases, such as tuberculosis, rheumatoid arthritis, gastric ulcers and different cancer lines. In these previous investigations, remarkable pharmacological effects have been described for some copper (II) complexes. These activities have not been observed when the parent ligands or inorganic forms of copper were used [1], thus confirming the importance of the coordination compound. Additionally, the reactions between amino acids and metal ions are considered as models of the processes that take place at the molecular level in the metal/protein system. Mixed ligand complexes have a key role in biological chemistry, since mixed chelation commonly occurs in biological fluids as a consequence of the competition among potential ligands for metal ions *in vivo*. This type of compounds originates specific structures that might be involved in significant biological functions [2].

Chemical speciation studies of biologically relevant metal complexes are essential for an understanding of their distributions, mobility, toxicity, bioavailability and, for setting environmental quality standards. The knowledge of the equilibrium constants of such compounds is

necessary for the calculation of the concentration of each ionized species at any pH, which is important for the complete understanding of their physicochemical behavior [2]. Until now, to the best of our knowledge, there are no reports on the speciation of ternary complexes of Cu(II)-2-(benzo[d]oxazol-2-yl) nicotinic acid (Ligand HL) and the amino acids Glycine (HGly), Proline (HPro),  $\alpha$ -Alanine (H $\alpha$ -Ala),  $\beta$ -Alanine (H $\beta$ -Ala) [3,4]. Therefore, it seems of considerable interest to conduct investigations of binary and ternary complexes of copper (II) with the Ligand HL and some selected bidentate amino acids. In the present investigation we report the complex formation equilibria and speciation studies for the interaction of copper(II) with the 2-(benzo[d]oxazol-2-yl)nicotinic acid (Ligand HL) and the amino acids Glycine (HGly), Proline (HPro),  $\alpha$ -Alanine (H $\alpha$ -Ala),  $\beta$ -Alanine (H $\beta$ -Ala). This work represents a contribution to the understanding of chemical speciation of binary and ternary Cu (II) complexes in aqueous solution.

## 2. Experimental

### 2.1. General information

Cu(NO<sub>3</sub>)<sub>2</sub> · 3H<sub>2</sub>O (Merck p.a.) and the amino acids: glycine (HGly), proline (HPro),  $\alpha$ -alanine (H $\alpha$ -Ala),  $\beta$ -Alanine (H $\beta$ -Ala) (Merck p.a.) are all commercial products which were used without further

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**Table 1**  
Values of  $\log \beta_{pr}$  for the ligands studied (25 °C,  $I = 1.0 \text{ mol} \cdot \text{dm}^{-3} \text{ KNO}_3$  ionic medium).

Equilibria	$\log \beta_{pr}$				
	Ligand L <sup>-</sup>	HPro	HGly	H $\alpha$ -Ala	H $\beta$ -Ala
L <sup>-</sup> + H <sup>+</sup> $\rightleftharpoons$ HL	9.46(5)				
L <sup>-</sup> + 2H <sup>+</sup> $\rightleftharpoons$ H <sub>2</sub> L <sup>+</sup>	17.4(1)				
HL + H <sup>+</sup> $\rightleftharpoons$ H <sub>2</sub> L <sup>+</sup>		2.10(1)	2.46(2)	2.49(2)	3.70(1)
HL $\rightleftharpoons$ L <sup>-</sup> + H <sup>+</sup>		-10.54 (2)	-9.65(2)	-9.60(5)	-10.15(1)
Dispersion ( )	0.044	0.010	0.013	0.019	0.009

Values in parentheses represent 3 times the standard deviations [3 ( $\log \beta_{pr}$ )] on the last significant figure.

purification. The HNO<sub>3</sub> and KOH solutions were prepared using 100.0 mmoldm<sup>-3</sup> Titrisol Merck ampoules. The KOH solution was standardized against potassium hydrogen phthalate (Merck p.a.) using phenolphthalein as indicator, and the HNO<sub>3</sub> solution was standardized with the KOH solution of known concentration [5]. The solutions were prepared using triply glass-distilled water, boiled before preparation of the solutions in order to remove dissolved CO<sub>2</sub>. The Cu(II) stock solution was standardized using a Na<sub>2</sub>EDTA·2H<sub>2</sub>O (Merck p.a.) solution (0.01 mol · dm<sup>-3</sup>) in a buffer media (pH = 10) using murexide (Merck p.a.) as indicator [6]. Potentiometric measurements were carried out in aqueous solution using 1.0 mol · dm<sup>-3</sup> KNO<sub>3</sub> as ionic medium and, nitrogen free of O<sub>2</sub> and CO<sub>2</sub> were used. Solution <sup>1</sup>H and <sup>13</sup>C{<sup>1</sup>H} NMR spectra were recorded on a Bruker Avance 300 MHz spectrometer at Laboratorio Nacional de Resonancia Magnética Nuclear, Instituto Venezolano de Investigaciones Científicas (IVIC). Peak positions are relative to tetramethylsilane for <sup>1</sup>H and <sup>13</sup>C{<sup>1</sup>H} NMR. The chemical shifts ( $\delta$ ) are measured according to IUPAC [7], expressed in parts per million (ppm) and were calibrated against the residual solvent resonance (<sup>1</sup>H) or the deuterated solvent multiplet (<sup>13</sup>C). Coupling constants J are given in Hertz (Hz) as absolute values. The multiplicity of the signals is indicated as d, t, or m for doublets, triplets, or multiplets, respectively. Quaternary carbon atoms are indicated as C<sup>quat</sup> and aromatic units as CH<sup>ar</sup>. All the NMR spectra were recorded at room temperature (25 °C) unless otherwise stated.

## 2.2. Synthesis and characterization of the ligand 2-(benzo[d]oxazol-2-yl)nicotinic acid

The ligand 2-(benzo[d]oxazol-2-yl)nicotinic acid (Ligand HL) was synthesized using a modification of the method reported in the literature [8]. However, its characterization by <sup>13</sup>C{<sup>1</sup>H} NMR was not included in the previous work [8], and corrections were made to the reported melting point. 2,3-pyridinedicarboxylic acid anhydride (0.5 g; 3.35 mmol) and o-aminophenol (0.365 g; 3.35 mmol) were dissolved in acetic acid (10 mL) and stirred at room temperature. The yellow precipitate was filtered and washed with toluene. Yield: 0.610 g; 93.7%. m.p.: 184 °C. <sup>1</sup>H NMR (300.1 MHz; dms<sub>o</sub>-d<sub>6</sub>):  $\delta = 9.31$  (d, <sup>3</sup>J<sub>HH</sub> = 3.3 Hz, 1H), 8.85 (d, <sup>3</sup>J<sub>HH</sub> = 7.7 Hz, 1H), 8.19 (t, <sup>3</sup>J<sub>HH</sub> = 5.8 Hz, 1H), 7.25 (m, 2H), 7.16 (m, 1H), 7.07 (m, 1H). <sup>13</sup>C{<sup>1</sup>H} NMR (75.5 MHz; dms<sub>o</sub>-d<sub>6</sub>):  $\delta = 168.1$  (C<sup>quat</sup>), 166.7 (C<sup>quat</sup>), 152.7 (C<sup>quat</sup>), 151.8 (CH<sup>ar</sup>),

**Table 2**  
Equilibrium constants ( $\log \beta_{pqr}$ ) for the Cu(II)-Ligand L<sup>-</sup> system (25 °C,  $I = 1.0 \text{ mol} \cdot \text{dm}^{-3} \text{ KNO}_3$  ionic medium).

Equilibria	Ligand L <sup>-</sup> $\log \beta_{pqr}$	Bipy <sup>a</sup> $\log \beta_{pqr}$
Cu <sup>2+</sup> + L <sup>-</sup> $\rightleftharpoons$ CuL <sup>+</sup>	9.0(2)	7.69
Cu <sup>2+</sup> + 2 L <sup>-</sup> $\rightleftharpoons$ CuL <sub>2</sub>	15.33(6)	13.40
Cu <sup>2+</sup> + 3 L <sup>-</sup> $\rightleftharpoons$ CuL <sub>3</sub> <sup>-</sup>	16.6 max 17.3	16.75
Cu <sup>2+</sup> + L <sup>-</sup> + H <sub>2</sub> O $\rightleftharpoons$ Cu(OH)L + H <sup>+</sup>	2.5(1)	0.7
Cu <sup>2+</sup> + L <sup>-</sup> + 2H <sub>2</sub> O $\rightleftharpoons$ Cu(OH) <sub>2</sub> L <sup>-</sup> + 2H <sup>+</sup>	-6.66(3)	-9.94
2Cu <sup>2+</sup> + 2 L <sup>-</sup> + 2H <sub>2</sub> O $\rightleftharpoons$ Cu <sub>2</sub> (OH) <sub>2</sub> L <sub>2</sub> + 2H <sup>+</sup>	7.8(1)	4.7
Dispersion ( )	0.052	

Values in parentheses 3 times the standard deviations [3 ( $\log \beta_{pqr}$ )] on the last significant figure.

<sup>a</sup> Bipy = 2,2'-Bipyridine [15].

145.1 (C<sup>quat</sup>), 138.4 (CH<sup>ar</sup>), 135.2 (C<sup>quat</sup>), 126.6 (C<sup>quat</sup>), 125.2 (CH<sup>ar</sup>), 120.0 (CH<sup>ar</sup>), 118.2 (CH<sup>ar</sup>), 115.9 (CH<sup>ar</sup>), 115.1 (CH<sup>ar</sup>).

## 2.3. Potentiometric methods

The potentiometric measurements were done using the following instruments: Thermo Orion model 520A pH meter, Metrohm EA 876–20 titration vessel, Lauda Brikmann RM6 thermostatic bath. The sealed 100 mL thermostated double-walled glass titration vessel with a titrant inlet, magnetic stirrer, and an inert nitrogen atmosphere inlet with outlet tubes was fitted with a combined Orion Ross 8102BN pH electrode. The temperature was maintained at (25.0 ± 0.1) °C by constant circulation of water from the thermostatic bath.

The emf (H) measurements were carried out by means of the REF//S/GE cell, where REF = Ag/AgCl/3.0 mol · dm<sup>-3</sup> KCl; S = equilibrium solution and GE = glass electrode. At 25 °C the emf (mV) of this cell follows the Nernst equation,  $E = E^0 + jh + 59.16 \log h$ , where  $h$  represents the free hydrogen ion concentration,  $E^0$  is the standard potential and  $j$ , represents a constant which takes into account the liquid junction potential [9]. The experiments were carried out as follows: a fixed volume of 0.100 mol · dm<sup>-3</sup> HNO<sub>3</sub> was titrated with successive additions of 0.100 mol · dm<sup>-3</sup> KOH until near neutrality in order to get the parameters  $E^0$  and  $j$ . Then, aliquots of the Ligand HL and the amino acid under study were added and finally an aliquot of the copper (II) stock solution was sequentially added. The titration was continued with 0.100 mol · dm<sup>-3</sup> KOH. The measurements were performed using a total metal concentration,  $M_T = 2\text{--}3 \text{ mmol} \cdot \text{dm}^{-3}$  and molar ratios  $R = 1, 2$  and  $4$  for the Cu(II)-Ligand HL system and for the Cu(II)-Ligand HL-amino acids systems the molar ratios  $R = 1:1:1, 1:1:2$  and  $1:2:1$  were used.

The Cu(II)-Ligand L<sup>-</sup> system was studied according to the reaction scheme:



The Cu<sup>2+</sup>-Ligand L<sup>-</sup>-Amino Acids (B<sup>-</sup>) systems were studied according to the reaction scheme:



where B<sup>-</sup> represents the amino acids: glycine (Gly), proline (Pro),  $\alpha$ -alanine ( $\alpha$ -Ala),  $\beta$ -Alanine ( $\beta$ -Ala), [Cuq(OH)p(L)r] and [Cuq(OH)p(L)r(B)s], are the binary (p, q, r) and the ternary (p, q, r, s) complexes (the charges were omitted), where  $\beta_{pqr}$  and  $\beta_{pqr\text{s}}$  are the respective stability constants.

The potentiometric data was analyzed using the program LETAGROP [10,11], in order to minimize the function  $Z_B = (H-h)/M_T$ , where  $Z_B$  is the average number of moles of H<sup>+</sup> associated per moles of metal,  $H$  is the total (analytical) concentration of H<sup>+</sup>,  $h$  is the concentration in equilibrium of H<sup>+</sup> and,  $M_T$  represents the total (analytical) concentration of Cu(II).

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