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Potentiometric and DFT studies of Cu(II) complexes with glycylglycine and methionine of interest for the brain chemistry

Felipe S. Vilhena [a, b, *], Judith Felcman [b], Bruno Szpoganicz [c], Fabio S. Miranda [a]

[a] Department of Inorganic Chemistry, Universidade Federal Fluminense – UFF, 24020-141, Niterói, Brazil
[b] Department of Chemistry, Pontifícia Universidade Católica do Rio de Janeiro – PUC-Rio, 22453-900, Rio de Janeiro, Brazil
[c] Department of Chemistry, Universidade Federal de Santa Catarina – UFSC, 88040-900, Florianópolis, Brazil

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ABSTRACT

A large number of copper (II) complexes have been used as mimetic models for metalloproteins and metalloenzymes. Due to the lack of structural information about copper (II) complexes in aqueous solution, the coordination environment of this metal is not well established. In this work, pK_a values of the complexes in the Cu:GlyGly, Cu:Met and Cu:GlyGly:Met systems were calculated by potentiometric titration at 25 °C and ionic strength of 0.1 mol L^{-1}. The coordination modes of the ligands were explored for the main hydrolytic species throught RI-PBE/def2-SVP/COSMO level. In the Cu:GlyGly system, DFT results indicated that the $N_{amine}N_{pept}$ coordination of dipeptide is 2.1 kcal mol^{-1} more stable than the tridentate $N_{amine}N_{pept}O_{carboxy}$ coordination moiety. The deprotonation of the peptide nitrogen is 13.7 kcal mol^{-1} more favorable than the hydrolysis of the water molecule coordinated to the metal. In the Cu:GlyGly:Met system, the sulfur atom does not belong to the copper (II) coordination sphere. Once the copper ion is incorporated into peptides, another ligand as methionine could bind to this system and carry an antioxidant site to different brain regions.

1. Introduction

The knowledge of the coordination modes of biological ligands to copper (II) ion in aqueous solution is essential to understand the structures and functions of copper in these biological systems [1–7]. Despite the structural information of many Cu(II) complexes in the solid state is available in literature [6–14] the geometry of complexes in aqueous solution has been a topic for many discussions [13–20].

The Cu(II) ion is strongly solvated in aqueous solution and it is a classic example of a transition metal with a 6-fold hydration shell [14,15,20,21]. The d^9 electronic configuration of Cu(II) ($t_{2g}^6 e_g^3$) is subject to the Jahn-Teller effect [14–22] which is generally assumed as the elongation of two axial bonds in the octahedral geometry. *Ab initio* and DFT calculations [23–27] have been shown that the Cu(II) complexes lose one or two axial ligands and they tend to form four or five-coordinate complexes. The Cu(II) complexes exhibit a high flexibility in their coordination geometries in both the crystalline and aqueous solution phases.

The complexes formed by copper (II) and the dipeptide glycylglycine (GlyGly), have been studied over fifty years as models of copper coordination for many proteins and enzymes [1–7]. Due to the lack of structural information about complexes in aqueous solution, the geometry and the coordination modes of the glycylglycine are not well established.

Neurodegenerative diseases are characterized, in part, by the deposition of protein plaques in several regions of the brain. There are evidences that transition metal ions such as copper, zinc and iron play an important role in the neurotoxicity of protein [28,29]. The interaction of Cu(II) with peptides and proteins could induce the aggregation.

It is known that methionine presents antioxidant properties in several models of oxidative stress. It has been shown that it acts as a powerful endogenous antioxidant agent, leading to the reduction of lipid peroxidation in membranes [30].

In this work, the formation constants of the main hydrolytic species present in biological systems between copper (II) with glycylglycine and methionine (Cu:GlyGly, Cu:Met and Cu:GlyGly:Met) were obtained by potentiometric titration at 25 °C with ionic strength of 0.1 mol L^{-1}. The coordination modes for ligands in the species were explored through DFT calculations at RI-PBE/def2-

* Corresponding author.Department of Inorganic Chemistry, Universidade Federal Fluminense – UFF, 24020-141, Niterói, Brazil.
E-mail address: fs_vilhena@id.uff.br (F.S. Vilhena).

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SVP/COSMO level.

2. Experimental

2.1. Materials

$Cu(NO_3)_2.3H_2O$, standard solutions of potassium hydroxide 0.1 mol L^{-1} and the buffer solutions of pH 4.0 and 7.0 were from Merck. Glycylglycine and methionine were purchased from Sigma-Aldrich. Co. All the solutions were prepared with distillate water.

2.2. Apparatus

The titrimetric data were obtained using an 809 Methrom automatic burette, a B375 Micronal pH meter and a combined glass electrode. All titrations were performed at 25.0 ± 0.1 °C by coupling the titration cell with a thermostatic bath set at this temperature and under argon atmosphere.

2.3. Procedure

For the determination of the protonation constants of the glycylglycine and methionine, aqueous solution (1×10^{-3} mol L^{-1}) of the protonated ligand was titrated with 0.1 mol L^{-1} KOH at 25 °C, under ionic strength of 0.1 mol L^{-1} using a 1.2 mol L^{-1} of KNO_3 solution under argon atmosphere. For the determination of the formation constants of the binary systems, solutions containing ligands and copper (II) ion were titrated at the ratio 1:1. For the determination of the formation constants for the ternary system solutions containing Cu(II), GlyGly and Met were titrated at the ratio 1:1:1. All the constants were redetermined using the BEST7 program and the species distribution diagrams using the program Species [31].

2.4. Computational methods

DFT calculations were performed using the TURBOMOLE 6.1 program [32,33]. The geometry optimizations were carried out using the resolution of identity (RI-J) method [34] with the PBE functional [35] and the def2-SVP basis set [36]. The harmonic frequencies were calculated for all the studied complexes to confirm the nature of stationary points, no imaginary or negative frequencies were found. The calculation were performed without any symmetry constraints using a grid size of 4 and the SCF convergence criterion of 10^{-8} hartree. The solvation effects were taken into consideration by using the Conductor-like Screening Model (COSMO) method [37] with a dielectric constant for water of $\varepsilon = 78.3553$.

3. Results and discussion

3.1. Potentiometric studies

The potentiometric curves of GlyGly, Met, Cu:GlyGly, Cu:Met and Cu:GlyGly:Met systems are shown in Fig. 1. The potentiometric curves were performed by adding 1.0 mL of HCl 0.100 mol L^{-1} with the aim of the protonation of the ligands. The titration curve for GlyGly (a), showed two inflections in 1.0 and 2.0 mL of KOH, attributed to the deprotonation of carboxylic and amino groups, respectively [7,38,39]. In the absence of metal in aqueous solution, the dipeptides do not lose the hydrogen of the amide peptide group [7]. In the potentiometric titration curve for the Met (b), only one inflection in 1.0 mL of KOH was observed, which was attributed to the deprotonation of the carboxylate group. For the Cu:GlyGly binary system (c), the titration curve presents one inflection at

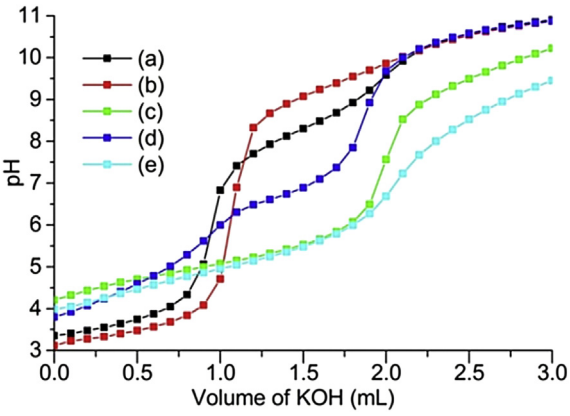

Fig. 1. Potentiometric equilibrium curves for GlyGly, Met, Cu:GlyGly, Cu:Met and Cu:GlyGly:Met at 25 °C and μ = 0.1 mol L^{-1} (KNO_3). (a) 0.098 mmol of GlyGly in 100.00 mL of solution with 1.0 mL HCl 0.1000 mol L^{-1}; (b) 0.105 mol of Met in 100.00 mL of solution with 1.0 mL HCl 0.1000 mol L^{-1}; (c) 0.102 mmol of GlyGly and 0.101 mmol of Cu(II) in 100.00 mL of solution; (d) 0.097 mmol of Met and 0.105 mmol of Cu(II) in 100.00 mL of solution and (e) 0.108 mL of GlyGly, 0.103 mmol of Met and 0.118 mmol of Cu(II) in 100.00 mL of solution.

2.0 mL, assigned to the simultaneous deprotonations of the amino and peptide groups [7,38,39]. In the Cu:Met system (d), two inflections were observed, attributed to the deprotonation of the amino group and the water molecule coordinated to metal, respectively. The titration curve of the Cu:GlyGly:Met ternary system (e) shows a similar profile to Cu:GlyGly, but the first system shows lower pH values after the inflection region. Using data of the potentiometric titration curves, the formation constants and the pKa_1 and pKa_2 values were redetermined using the program BEST 7 (Table 1) [31].

The formation constants are shown in Table 1. These constants were used to generate the species distribution diagrams through the SPECIES program [31]. Considering the Cu:GlyGly system, the distribution diagram reveals that the $Cu(H_{-1}GlyGly)$ species arises at pH close to 4.5 ($pKa_1 = 4.28$) and prevails until the pH of 9.5 ($pKa_2 = 9.79$). For the Cu:Met system, the CuMet species exists until pH (pKa_1) 6.72, in which the hydrolytic species $CuMetH_{-1}$ arise in high concentrations and prevail until high pH values ($pKa_2 = 10.02$). In the ternary system, the $Cu(H_{-1}GlyGly)$Met species is formed at pH 4.42. This species prevails until pH 7.65 (pKa_2) (Fig. 2).

Table 1
Stability constants and pKa values for Cu:GlyGly, Cu:Met and Cu:GlyGly:Met systems.

$pKa_1 = -\log Ka_1 = -(\log\beta_{CuL} - \log\beta_{CuLH-1})$

$pKa_2 = -\log Ka_2 = -(\log\beta_{CuLH-2} - \log\beta_{CuLH-1})$

Systems	Species	logβ	pKa_1	pKa_2
Cu:GlyGly	CuGlyGly	5.42	4.28	9.79
	$Cu(H_{-1}GlyGly)$	1.14		
	$Cu(H_{-1}GlyGly)H_{-1}$	−8.65		
Cu:Met	CuMet	7.92	6.72	10.02
	$CuMetH_{-1}$	1.20		
	$CuMetH_{-2}$	−8.82		
Cu:GlyGly:Met	CuGlyGlyMet	16.20	4.42	7.65
	$Cu(H_{-1}GlyGly)$Met	20.62		
	$Cu(H_{-1}GlyGly)MetH_{-1}$	8.55		