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A desamidination process forming a novel guanidine derivative during the complexation between copper(II) and guanidinoacetic acid

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Abstract

A novel trianionic disubstituted guanidine, ([1]*N*-carboxymethylguanidino)hydroxyacetic acid-$C_5H_6N_3O_5$), oag^{3-}, has been formed through a desamidination process occurred during copper(II) complexation with guanidinoacetic acid, $C_3H_7N_3O_2$ (Gaa), which produced $[Cu_2(oag)(Gaa)(H_2O)]NO_3\cdot 2H_2O$ (**1**). A proposal mechanism of formation of **1** is presented based on the low temperature electron paramagnetic resonance and previous potentiometric studies, which have indicated the presence of CuH_2Gaa as the precursor species.

Keywords: Guanidinoacetic acid; Copper(II); Transamidination

Transamidination reactions are known to play an important biological role due to their participation in several processes such as the creatine synthesis [1] and antibiotic biosynthesis [2], both catalyzed by amidinotransferase. These reactions have produced several neuroactive guanidino compounds [3]. The inhibition of these reactions is related with some dysfunctions in our organisms as the gyrate atrophy of the choroids and the retina [4]. Guanidinoacetic acid (Gaa), precursor of creatine, may be a possible amidino donor for transamination reactions, which was already observed in 2-guanidinoethanol formation [5]. Gaa is also important because of its participation in several biological processes [6,7].

Previously, we have reported the study of Gaa complexes [7] and its guanidino–carboxylate interactions with glutamic and aspartic acid in solution [8], in addition to some synthesized complexes with chromium(III), cobalt(II), nickel(II), zinc(II), and copper(II) [9–11]. We report herein the formation of a new guanidine derivative (oag), formed after a transamidination reaction that took place during the complexation process between Cu(II) and Gaa. Hence, we propose the mechanism of oag formation supported by low temperature EPR data (X-band, 5.0 Gauss modulation amplitude and microwave power of 2.21×10^2 mW, using DPPH as standard, $g = 2.0037$ on a Bruker ESP 380 FT-CW spectrometer).

The complex $[Cu_2(oag)(Gaa)(H_2O)]\ NO_3\cdot 2H_2O$ was synthesized by slowly adding an aqueous solution of

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copper(II) nitrate trihydrate (3 mmol) to Gaa(aq) (3 mmmol) (solution 1, pH 3). Afterwards, the mixture was heated at 60 °C, with stirring, for 3 h and KOH (1 mol l^{-1}) was slowly added for 10 h. After 24 h, the mixture was filtered and the filtrate was cooled at 4 °C for 24 h. The resultant solution (solution 2, pH 6.0) was slowly evaporated at room temperature until the formation of blue crystals of **1**. A second route of synthesis of **I** was previously described [11].

The crystal structure of **1** is shown in Fig. 1 [11], where it can be observed that oag^{3-} is coordinated to two copper(II) ions through three oxygen atoms (O3, O5 and O6) and one nitrogen atom (N4). Gaa is also coordinated to both copper(II) ions through two oxygen atoms (O2 and O1) from a carboxylate bridge group. There is also coordinated water to Cu1.

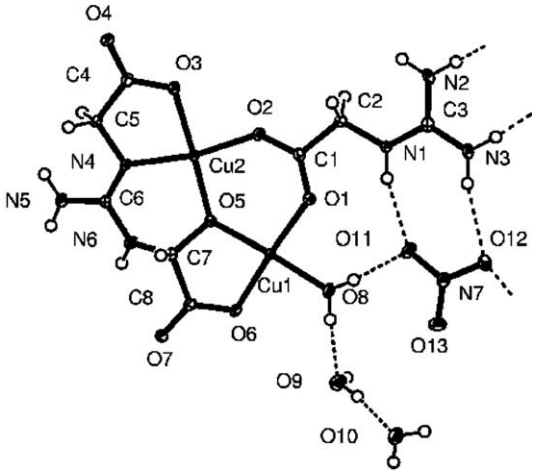

Fig. 1. Crystal structure of $[Cu_2(oag)(Gaa)(H_2O)]\ NO_3\cdots 2H_2O$ (**1**).

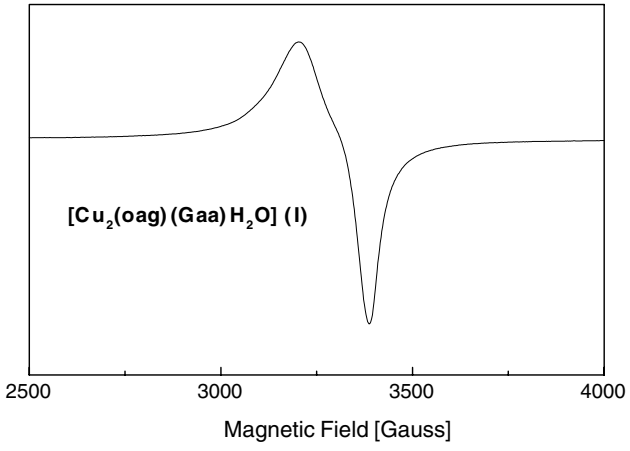

Fig. 2. Powder EPR spectrum of complex **1** measured at 77 K.

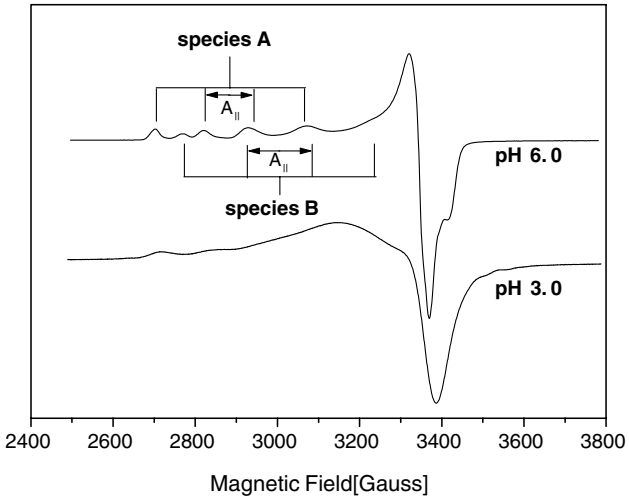

Fig. 3. EPR spectra of the frozen solutions at 150 K: lower spectrum – solution 1, upper spectrum – solution 2.

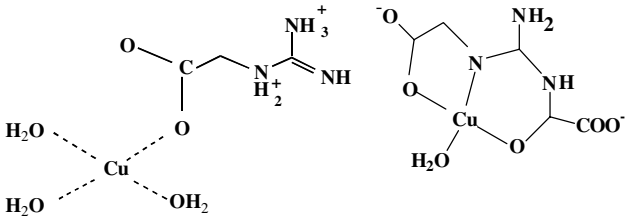

Fig. 4. Proposal structures of species A (left) and B (right).

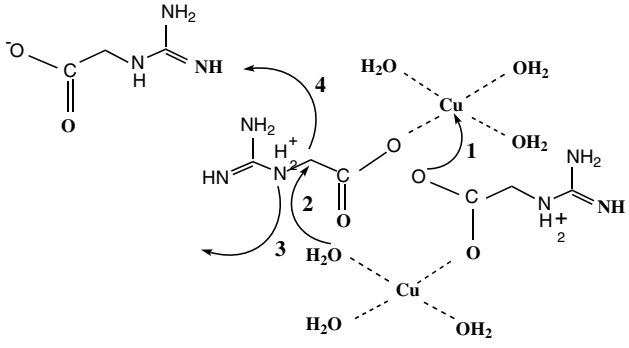

Fig. 5. Proposed mechanism of formation of oag.

Table 1
Experimental and simulated EPR parameters of $[Cu_2(gaa)(oag)H_2O]NO_3\cdot 2H_2O$ and its precursors

Sample	$A_{\|}$[G]	$g_{\|}$	$A_{\perp}$[G]	$g_{\perp}$	g_{iso}	T (K)	Coordination
$[Cu_2(gaa)(oag)H_2O]$	–	2.18	–	2.09	2.12	77	two centres 1N3O; 4O
CuH_2Gaa	121.0	2.40	–	2.08	2.18	77	4O
Solution 1	142.8	2.38	9	2.07	2.12	150	4O
Species A	120.0	2.41	9	2.08	2.19	150	4O
Species B	152.2	2.32	9	2.06	2.15	150	1N3O

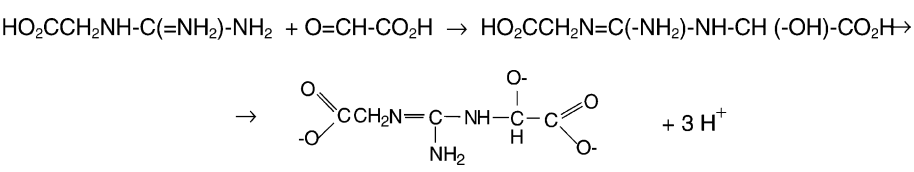

Fig. 6.

In order to investigate the process of formation of oag as well of its possible precursors, the EPR spectra of **1** and of the former solutions of its synthesis in several stages were recorded.

The powder EPR spectra of complex **1** (Fig. 2) measured both at room temperature and at 77 K, presented a broad asymmetrical line with unresolved hyperfine splitting, typical of Cu(II) in a tetragonal environment. Due to the large line widths, the only measurable parameters were the *g*-factors, listed in Table 1. The EPR spectrum of **1** has been analyzed following the classification proposed by Vängard [12], from which it can be related to Type 2 copper species due to its hyperfine splitting parameters, typical of ordinary copper(II) complexes.

The EPR spectrum of the frozen initial solution of Gaa and Cu(II) (solution 1, pH 3.0, 150 K) also presented a broad line (Fig. 3, lower spectrum) in consequence of dipolar interaction of neighbor Cu^{2+} species. However, as solution 1 presented the $A_{\|}$(Cu) = 142.8 G and $g_{\|} = 2.38$ values, we can assume that the observed species is Cu^{2+}(aq) [13].

On the other hand, the EPR spectrum of the frozen solution 2 at pH 6.0 showed the presence of two copper species, A and B (Fig. 3, upper spectrum, 150 K).

Species A presents $A_{\|}$(Cu) = 120.0 G and $g_{\|} = 2.41$ values, corresponding to a four-oxygen coordination site on the basis of the method of Peisach and Blumberg [13]. However, as its EPR parameters are fairly different from those of hexaquocopper(II), species A cannot be related to it (Table 1). Thus, species A should present at least one oxygen–carboxylate-coordination. By comparison with the previous potentiometric study on 1:1 Cu(II):Gaa solution [7], we can correlate species A with CuH_2Gaa species (Table 1).

Still according to Peisach and Blumberg [13], species B should present one nitrogen and three oxygen atoms as the coordination sites. This is in agreement with the increasing $A_{\|}$ and decreasing $g_{\|}$ values observed from solution 1 (four-oxygen-coordination) to species B, which is expected due to the strengthening ligand field.

Considering that both species A and B are present in the solution of formation of **1** and according to their coordination sites, it can be concluded that they are precursor monomers of **1**. Since at this stage they are still separated species, it is reasonable that EPR parameters may not be equal to those measured for **1**, as reflected by the g_{iso} values. However, based on the coordination sites of species A and B, it can be presumed that oag derivative has already been formed. As species A has been attributed to CuH_2Gaa, we propose that species B may be Cu(oag)H_2O (Fig. 4).

The presence of CuH_2Gaa species, predominant (up to pH 4–5) in equilibrium solutions with Gaa and Cu(II) even in the presence of glutamic acid or aspartic acid [8], strongly suggests its importance in complexation process of Gaa. This fact associated with its presence in the former solution 2 indicates its role in oag synthesis. Following these data, we propose a mechanism of oag formation (Fig. 5), based on a reaction between two CuH_2Gaa species, through a nucleophilic attack of the oxygen atom from carboxylate group of one species into the Cu(II) ion of the second one (1 in Fig. 5). Then, the neighbor coordinated water attacks the α-carbon (2 in Fig. 5) of Gaa, causing its desamidination (3 in Fig. 5). The residual moiety of Gaa, O═CH─CO_2H, reacts with a non-coordinated Gaa, resulting in the oag synthesis (4 in Fig. 5) as stated in Fig. 6.

The proposed mechanism for oag synthesis can be helpful in the understanding of transamidination reactions as well as the alternative pathways of Gaa metabolism, especially important in the creatine phosphate synthesis [14] and in the guanidinomethyltransferase deficiency [15].

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