



Research paper

An EPR and voltammetric study of simple and mixed copper(II) complexes with L- or D-glutamate and L-arginate in aqueous solution



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ARTICLE INFO

Article history:

Received 13 April 2016

Received in revised form 15 July 2016

Accepted 18 July 2016

Available online 19 July 2016

Keywords:

CW EPR

Cu(II) complexes

Aminoacidate ligands

cis/trans copper conformers

Electrostatic interactions

SWV formal redox potentials

ABSTRACT

EPR CW measurements at room and low temperature have been carried out on the systems containing ⁶³copper(II) nitrate, L-Arg and L- or D-Glu or DL- racemic mixtures of both amino acids in aqueous solution or in mixed solvents. For these copper(II) bis and ternary complexes, RT EPR spectra revealed that mixtures of *cis* and *trans* conformers are really present in aqueous solution. In most cases, for these systems, the *cis* conformer is more abundant at the lowest temperature (275 K). Increasing gradually the temperature from 275 K to 305 K the *cis/trans* ratio tends towards the *trans* conformer. This latter is less abundant in the case of [Cu(L-Glu)₂], because of the possible interaction of negative side chain carboxylate anions with the water molecules axially bound, and for [Cu(L-Arg)(D-Glu)], probably owing to a possible electrostatic interaction between the two opposite charged side chains which are on the same side of the CuN₂O₂ coordination plane. Low temperature frozen solution EPR spectra run on these systems show the presence of only one absorbing specie thus giving reason to the stabilization of one conformer over the other, in particular, the *cis* conformer. There are no evident differences in the anisotropic Spin Hamiltonian parameters derived from the frozen EPR solution spectra of these systems, which are characterized by a tetragonally elongated octahedral stereochemistry. SWV measurements confirmed the EPR spectroscopic data, actually giving rise to the observation of slightly asymmetrical peaks, which revealed two near formal redox potentials assigned to the two conformers.

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1. Introduction

The discovery of the involvement of arginine in Alzheimer's disease (AD) dates back to about a year ago [1]. However, there has been also increasing evidences which support an important role of metals in neurobiology. In particular, copper(II) is an essential trace element that may damage cells and tissues due to its redox reactivity, as reported for copper-dependent disorders such as Menkes' and Wilson's diseases. It is well known that copper is present in a large amount in human brain and it could play a key role in neurodegenerative diseases such as Alzheimer's, Parkinson's or "prion" diseases [2–6].

This is the reason why we decided to reconsider the complex formation between copper(II) with arginine and glutamate, which

is known to be an important neurotransmitter [7]. In particular, we analyzed the formation of the copper(II) bis complex with the two aminoacidate anions carrying a positive or negative charge in their side chains and of their copper(II) mixed complex. The stereoselectivity in the copper(II) complex formation with D- or L- aminoacidates or with DL- or LL- dipeptides has long been a major topic of research in the 80's. It is well known that aminoacidate ligands coordinate copper(II) giving rise to CuN₂O₂ chromophore in which the two nitrogen atoms could be in a *trans* or in a *cis* conformation. The groups of L.D. Pettit [8] in England and O. Yamauchi [9] in Japan were greatly involved in giving reason of the extra-stability of complexes of copper(II) with aminoacidates having side chain charged groups, which could exert intramolecular electrostatic interactions. They stressed the influence of these non-covalent interactions on the ratio between *cis* and *trans* conformers. Moreover, one of the present authors was previously involved in a study of copper(II) dipeptide complexes with aliphatic or aromatic side chains which could give hydrophobic, stacking or *d-π* interactions [10].

Abbreviations: AD, Alzheimer's disease; Arg, Arginate; EPR, Eletron Paramagnetic Resonance; CV, Cyclic Voltammetry; Glu, Glutamate; RT, Room Temperature; shf, Superhyperfine; SWV, Square Wave Voltammetry.

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Thermodynamic parameters for the formation process of these copper(II) complexes as well as their spectroscopic features are well known in the literature [11–15].

Therefore, EPR CW measurements at room and low temperature have been carried out on the systems containing ^{63}Cu (II) nitrate, L-arginine and L- or D-glutamate or DL- racemic mixtures of both in aqueous solution or in mixed solvent, in order to re-consider the type of coordination for these copper(II) bis and ternary complexes and their *cis/trans* ratio. Moreover, SWV (square wave voltammetry) measurements have been carried out on the same solutions containing the bis and ternary complexes to check for slightly different formal redox potentials ascribable to the two *cis* and *trans* conformers.

2. Materials and methods

2.1. Copper complexes preparation

L-Arginine and L- or D-Glutamic Acid were purchased from Sigma-Aldrich.

Copper(II) complexes (charges were omitted for the sake of simplicity) were prepared by addition of the appropriate amount of isotopically pure $^{63}\text{Cu}(\text{NO}_3)_2$ 50 mM to the pertinent aminoacide [L-Arg] = [L- or D-Glu] or [DL-Arg] = [DL-Glu] = 10 mM, with metal-to-ligand ratios ranging from 1:2 up to 1:10 and with absolute copper concentrations ranging from about 1 to 3 mM. Ternary metal complexes were prepared by adding Glu to the aqueous solutions of the copper(II) complex with Arg or viceversa, in a metal to ligand ratio 1:5:5, with absolute copper concentrations ranging from about 1 to 3 mM. The final solution pH was adjusted to about 7.5 by using concentrated NaOH or HNO_3 as required and stirring the solution for at least ten minutes in order to favour the copper simple or mixed species formation.

2.2. CW EPR measurements

A Bruker Elexsys E500 CW-EPR spectrometer driven by a PC running XEpr program under Linux and equipped with a Super-X microwave bridge operating at 9.3–9.9 GHz and a SHQE cavity, was used throughout this work. All the EPR spectra of frozen solution of copper(II) complexes were recorded in quartz tubes at 150 K by means of a ER4131VT variable temperature apparatus, also controlling all the experiments in the fluid aqueous solution at variable temperature which were carried out by using a glass capillary inserted into a quartz tube. The measurements at room temperature were also recorded by means of a WG-812-H flat quartz cell. Methanol or glycerin up to 10% was added to the aqueous solution to increase resolution of the LT frozen solution spectra. The anisotropic magnetic parameters were obtained directly from the experimental EPR spectra of frozen solution, considering the 2nd and the 3rd copper line to get rid of second order effects [16]. In the case of RT EPR spectra, the isotropic magnetic parameters were calculated from the average distances among the peaks of the experimental EPR spectra recorded in the 2nd derivative mode.

In these experimental conditions, copper(II) bis complexes completely form starting from pH = 6. For copper(II) ternary complexes, according with their species distribution diagrams (see Fig. 1), we considered EPR difference spectra, subtracting both spectra of $\text{Cu}(\text{L-Glu})_2$ and $\text{Cu}(\text{L-Arg})_2$ and giving them a weight of 25% from those associated with the ternary species after a normalization. This procedure was applied to both RT and LT frozen solution spectra. Stability constants of binary and ternary complexes were taken by literature data [17].

Instrumental settings of frozen solution EPR spectra recording were as following: number of scans 1–3; microwave frequency

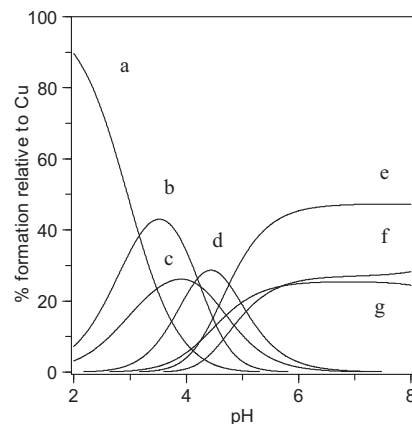


Fig. 1. Diagram of species distribution in the case of the formation of ternary $[\text{Cu}(\text{L-Arg})(\text{L-Glu})]$ complex: $[\text{Cu}] = 3 \text{ mM}$, $[\text{L-Glu}] = [\text{L-Arg}] = 15 \text{ mM}$. a. $\text{Cu}(\text{II})$ free ion; b. $[\text{Cu}(\text{L-GluH})]$; c. $[\text{Cu}(\text{L-ArgH})]$; d. $[\text{Cu}(\text{L-Glu})_2]$; e. $[\text{Cu}(\text{L-Arg})(\text{L-Glu})]$; f. $[\text{Cu}(\text{L-Glu})_2]$; g. $[\text{Cu}(\text{L-Arg})_2]$. Charges were omitted for clarity. The distribution diagram for the formation of the ternary $[\text{Cu}(\text{L-Arg})(\text{D-Glu})]$ complex is practically identical.

9.44–9.48 GHz; modulation frequency 100 kHz; modulation amplitude 0.2–0.6 mT; time constant 164–327 ms; sweep time 3–6 min; microwave power 10–15 mW; linear receiver gain 1×10^4 – 1×10^5 . Instrumental settings of room temperature solution EPR spectra were substantially the same except for the value of microwave frequency which was in the range 9.70–9.80 GHz, when using the flat quartz cell.

2.3. Voltammetric measurements

Cyclic voltammograms (CVs) of the $\text{Cu}(\text{II})$ complexes in solution (1–3 mM in copper and three or fivefold in ligand concentration, 0.1 M KNO_3 as ground electrolyte) were recorded by means of a Metrohm Autolab PGSTAT 128N potentiostat-galvanostat driven by a standard PC. These solutions were analyzed by using a Metrohm glass cell with a three electrodes assembly: a working glassy carbon electrode (2 mm diameter), a platinum rod as auxiliary electrode and an Ag/AgCl reference electrode. All electrodes and parts were manufactured by Metrohm. The cell was also hosting a combined 3-mm Metrohm Biotrode micro pH glass electrode which was connected with a titrator Metrohm Titrando 905 dispensing KOH 0.1 M directly in the cell. The PGSTAT 128N and Titrando 905 are coupled by programming the communications of the two driving software (i.e. Tiamo 2.4 and Nova 1.11.2) released by Metrohm. Complex solutions were degassed by using ultrapure argon. Electrochemical measurements were generally acquired in the region from +0.500 to –0.700 V. The square wave voltammetry (SWV) experiments were carried out a 15 Hz frequency and a 25–35 mV applied pulse value, avoiding more intense pulses which can cause broadening of the current peak. Cyclic voltammetry (CV) measurements with sweep rate of 50 mV s^{-1} were run in the same potential range of SWV experiments and all runs were carried out at 25 °C. All potentials in the paper are referred to Ag/AgCl reference electrode, +0.215 V vs. Normal Hydrogen Electrode (NHE), unless otherwise stated. The Ag/AgCl electrode potential was checked by using methylviologen redox couple ($\text{MV}^{2+}/\text{MV}^+$) –0.446 V vs. NHE [18].

3. Results and discussion

It is well known that copper(II) bis complexes with L- or D- aminoacide ligands show their bulky charged side chains on the same side, when the *trans* conformation is obtained, viceversa,

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