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Structure, stability, and ligand exchange of copper(II) complexes with oxidized glutathione

Valery G. Shtyrlin ^{*}, Yulia I. Zyavkina, Vladislav S. Ilakin,
Ruslan R. Garipov, Alexey V. Zakharov

Department of Inorganic Chemistry, Kazan State University, Kremlevskaya st. 18, Kazan 420008, Russian Federation

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Abstract

Formation constants and structures of copper(II) complexes with oxidized glutathione (L) have been determined by computer modelling of spectrophotometric and NMR relaxation measurements data over a wide range of pH (1–13) and metal and ligand concentrations in aqueous KNO₃ (1 M) at 298 K. Among 11 found complexes, four forms were characterized for the first time. Based on a comparison of thermodynamic, relaxation, and optical and EPR spectroscopy parameters the structural conclusions were made. In particular, the CuLH₂ and CuLH[−] complexes both contain two isomers which are similar to mono- and bis-amino-acid copper(II) complexes. In the Cu₂L and Cu₃L₂^{2−} species one of the copper atoms is bound only with the carboxylate or carbonyl groups and the others are coordinated similarly to aminoacid chelates. Along with the last, in Cu₂LH₂^{2−} two bridging OH[−] groups in one isomer or two chelate rings including deprotonated peptide nitrogen and glycyl carboxylate oxygen in another are also present. In Cu₃L₂H₄^{6−} the mixed variant of coordination between CuL^{2−} (CuN₂O₂) and Cu₂LH₄^{4−} (CuN₃O) is realized. The structures of polynuclear complexes have been optimized in density functional theory computations. Rate constants of ligand exchange reactions of Cu(LH)₂^{4−} and CuL₂^{6−} with participation of the LH^{3−} and L^{4−} forms were determined for the first time. Factors determining rates of these processes have been revealed and their proceeding by associative substitution mechanism shown.

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1. Introduction

The copper(II) oligopeptide complexes serve as models of copper-containing peptides and enzymes (oxydases and oxygenases), mediators, and transport forms of copper in living organisms. In the previous work [1] we have studied the structures of coordination compounds, their formation thermodynamics, and kinetics of the chemical exchange processes in aqueous solutions of copper(II) with elementary tripeptide, triglycine. In the present work similar investigation of copper(II)

complexes with oxidized form of natural tripeptide, glutathione (γ -L-glutamyl-L-cysteinylglycine), containing disulfide bond (GSSG, **Scheme 1**), was carried out.

Glutathione in the reduced (GSH) and oxidized (GSSG) forms is main intracellular non-protein thiol which performs the important biological functions involving in active transport of amino acids (γ -glutamyl cycle), operating of enzymes (glutathione S-transferase, glutathione peroxidase, and glutathione reductase), complex formation with microelements (Zn^{II}), functioning of redox couple Cu^{II}–Cu^I, etc. [2,3]. The copper(I)/(II)-glutathione systems are of particular importance for bioinorganic chemistry.

The literature data [4–8] on thermodynamics of complex formation between copper(II) and GSSG are

^{*} Corresponding author. Tel.: +7 8432 315392; fax: +7 8432 315416.
E-mail address: valery.shtyrlin@ksu.ru (V.G. Shtyrlin).