XXI Brazilian Meeting on Inorganic Chemistry
X Brazilian Meeting on Rare Earths
III Workshop on Theoretical Bioinorganic Chemistry
Belo Horizonte, September 12 - 15th 2024

A hybrid metallophore binds copper(II) ions and dephosphorylates L-serine: dual approach for multifactorial neurodegenerative diseases

Elisa S. Tardem[1,2], **Talis U. Silva**[3], **Sérgio P. Machado**[3],
Nicolás A. Rey[4] **and Daphne S. Cukierman**[2]

[1]Faculty of Pharmacy, Federal University of Rio de Janeiro, Brazil
[2]Department of General and Inorganic Chemistry, Rio de Janeiro State University, Brazil
[3]Institute of Chemistry, Federal University of Rio de Janeiro, Brazil
[4] Department of Chemistry, Pontifical Catholic University of Rio de Janeiro, Brazil

E-mail: elisatardemlab@gmail.com

Thematic Area: Biological Inorganic Chemistry

Keywords: neurodegeneration, metallophores, dephosphorylation.

Some neurodegenerative conditions such as Alzheimer's and Parkinson's diseases are characterized by protein misfolding and aggregation.[1] Many factors seem to contribute to protein structure instability, including metal interactions and post-translational modifications.[2] Although copper is an endogenous biometal involved in a variety of physiological processes, its dyshomeostasis can lead to abnormal interaction with amyloidogenic proteins, increasing aggregation, toxicity and oxidative stress.[3] Another important hallmark of neurodegeneration is the increase in protein phosphorylation.[4] In this context, we propose a hybrid approach with the BPMAMFF-ox ligand: a compound that is able to bind physiological metal ions such as copper(II) coupled with an oximic moiety that presents well-known dephosphorylating abilities. The ligand was synthesized and characterized in the solid state through mid-IR and thermogravimetry, and in solution using ^{1}H NMR and UV-Vis. The method of continuous variations demonstrated a 1:1 stoichiometry interaction between BPMAMFF-ox and copper(II) in pseudo-physiological conditions. The ML complex was also obtained in the solid state, although in the form of the $[Cu_2(BPMAMFF\text{-}ox)_2Cl_2]Cl_2$ bis(chloro-bridged) dimer. Its structure was optimized by DFT calculations [WB97XD/6-311g(d,p)], presenting good agreement with the experimental data. It is important to note that the oxime does not take part in metal coordination, which confirms the potential for the dual action proposed for the compound. The dephosphorylation activity of the ligand was demonstrated through ^{1}H NMR experiments using phospho-L-serine as a model since the Ser-129 residue of α-Synuclein, the amyloidogenic protein related to Parkinson's disease, is the major site for pathological phosphorylation. The ligand was also evaluated regarding its ability to scavenge electrochemically generated superoxide radicals, demonstrating a statistically significant reduction in the reoxidation process at –695 mV from 400 µmol L^{-1} on. Dephosphorylation studies of BPMAMFF-ox in the presence of copper are underway in order to determine whether such activity will be preserved, or even increased under these conditions.

Acknowledgments: FAPERJ and CNPq.

References

[1] C. A. Ross and M. A. Poirier, Nature Medicine, **10,** S10 (2004).
[2] N. González *et al*., Journal of Neurochemistry, **150(5)**, 507 (2019).
[3] K. Acevedo *et al*., Journal of Biological Inorganic Chemistry, **24**, 1141 (2019).
[4] S. Tenreiro, K. Eckermann, T. F. Outeiro, Mol Neurosci, **7**, 19(2014).