



Predicting the redox potential of tetra-aza macrocycle copper complexes

Minh T. N. Ho, Donatus A. Agbaglo, Benjamin G. Janesko*

Department of Chemistry and Biochemistry, Texas Christian University, TX 76129

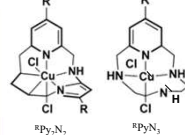
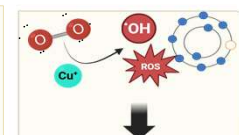
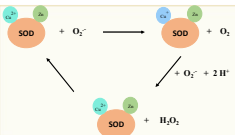


Introduction

Superoxide dismutase (SOD) enzymes are a major defense against superoxide

Misregulating of reactive oxygen species is the hallmarks of neurodegenerative disease

Tetra-aza macrocyclic Cu complexes



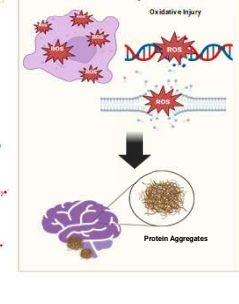
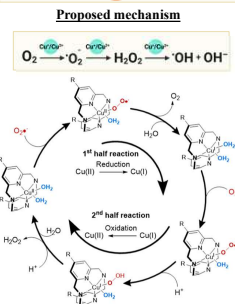
R = CF₃, OMe, Cl, H, I, CN, NMe₂

Objectives:

Performing computational simulations to predict the redox potential of un-synthesized tetra-aza macrocycles.

Long Term Goal:

Helping to identify the most promising candidates for further study.



Redox potential calculations and corrections

- All calculations are carried out in solvated state, using Density Functional Theory (DFT) workflow.
- Redox potential were derived from the Gibbs free energy change associated with the redox reaction
- The redox potential of the copper complex is obtained using the equation below, referenced to the standard hydrogen electrode (SHE) and reported against the measured ferrocene (Fc) reference:

$$E_{\text{redox}} = E_{\text{ox}} - E_{\text{red}} - E_{\text{SHE}}$$

where: E_{ox} and E_{red} are the electronic energies of the oxidized and reduced forms in electron volts ($1 \text{ eV} = 27.2114 \text{ eV}$)

Results and Discussion

Ligand	Experimental	Compt. Eo
OMePy ₂ N ₂ Cl ₂	-803	-1025.8
CF ₃ Py ₂ N ₂ Cl ₂	-914	-1129.6
ClPy ₂ N ₂ Cl ₂	-929	-1157
NMe ₂ Py ₂ N ₂ Cl ₂	-1088	-1313.6
HPy ₂ N ₂ Cl ₂	-740	-997
CNPy ₂ N ₂ Cl ₂	-920	-1106.7
CF ₃ Py ₂ N ₂ Cl ₂	-716	-868.7
HPy ₂ N ₂ Cl ₂	-948	-1215
OMePy ₂ N ₂ Cl ₂	-988	-1257.6
ClPy ₂ N ₂ Cl ₂	-652	-897
IPy ₂ N ₂ Cl ₂	-687	-922.4
IPy ₂ N ₂ Cl ₂	-859	-1167.5

Table 1: Experimental and computational redox potentials for Cu complexes with chlorine ligands

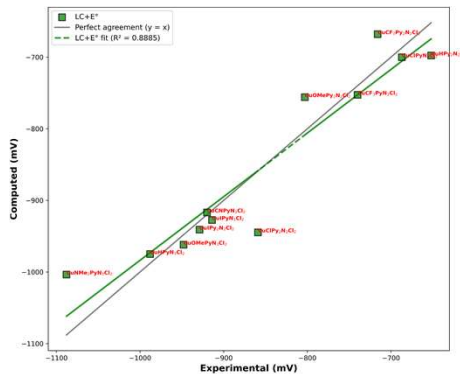


Figure 1: Correlation between experimental measurements and computed redox potential (LC+E°) of Cu complexes with chlorine ligands

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Table 2: Experimental and computational redox potentials for Cu complexes without chlorine ligands

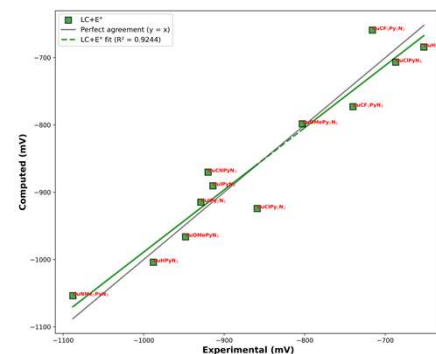
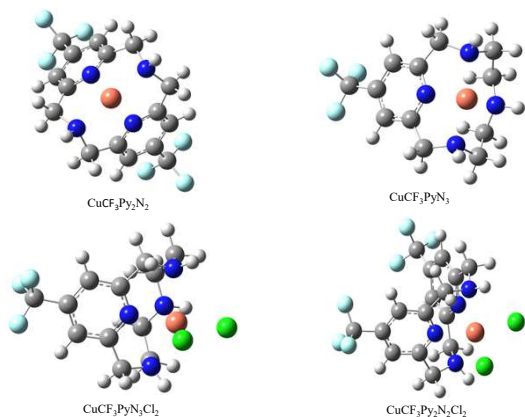


Figure 2: Correlation between experimental measurements and computed redox potential (LC+E°) of Cu complexes without chlorine ligands

Method and Theory

Refine Geometry of Each Copper Complex using CREST



Conclusion and Further Steps

- The strongest performance was observed for without chloride complexes, while chloride-bound models also showed good agreement after linear correction
- These results demonstrate that this workflow is a practical and transferable framework for estimating redox potential of copper-based, redox-active systems relevant to biomimetic and medicinal chemistry.
- Further research on predicting the intermediates' structure can be conducted in order to achieve the goal of successfully mimicking SOD enzymes.

References

- Smith, K. J.; Schwartz, T. M.; Freire, D. M.; Bowers, C. J.; Dann, S. K.; Bonnell, J. F.; Mekhail, M. A.; Akkaraju, G.; Green, K. N. *Inorg. Chem.* **2024**, *63*, 23544–23553.
- Mekhail, M. A.; Smith, K. J.; Freire, D. M.; Pota, K.; Nguyen, N.; Burnett, M. E.; Green, K. N. *Inorg. Chem.* **2023**, *62*, 5415–5425.

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