Copper Macrocycles as Mimics of SOD1

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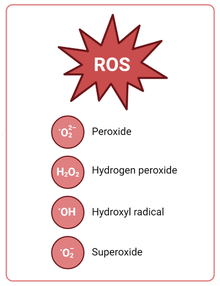
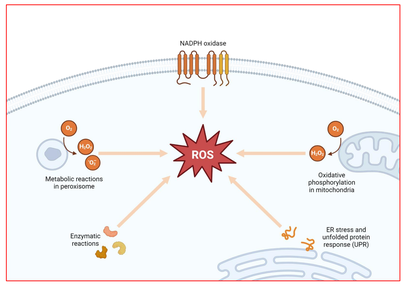
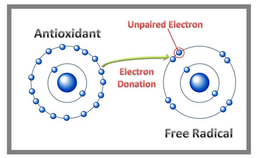
Introduction





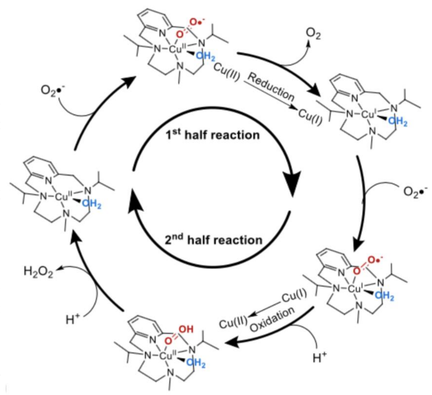
- **Reactive oxygen species (ROS):** Atoms/molecules that contain unpaired valence electrons and at least one oxygen atom within the structure.
- **ROS is necessary:** Natural metabolic byproduct that serves important functions in cellular processes, including immune system and homeostasis.

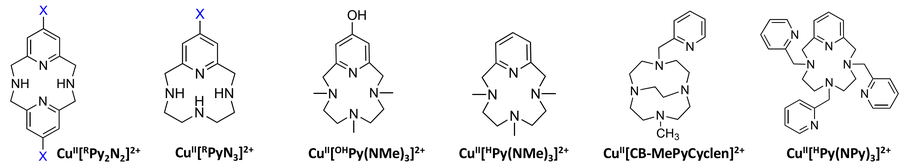


- **ROS mis-regulation:** Severe damage to cells and membranes, can lead to neurological diseases like Alzheimer's Disease (AD).
- **Radical scavengers:** Substances that react with ROS to neutralize them and make them less reactive.
- Natural Antioxidant Sources Include:

Impact of Metal Coordination on SOD Activity

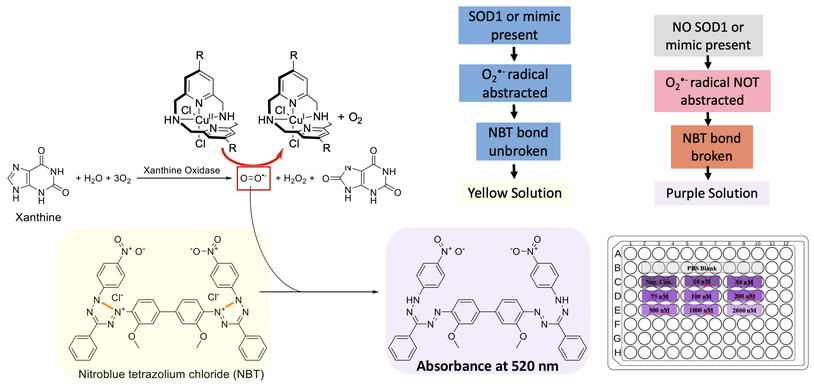
- **Metal Coordination in SOD**: SOD enzymes use Cu, Mn, Fe, or Zn active sites to catalyze superoxide dismutation
- **Small Molecule Mimics**: Catalytic mechanisms are largely unexplored for copper macrocyclic complexes
- **Insufficient Coordination Sites**: Fewer binding residues reduce metal stability and redox cycling, impairing enzymatic activity.
- **Steric Hindrance by Large R Groups**: Bulky side chains block substrate access, distort coordination geometry, and destabilize the enzyme.
- **SOD Mimics and Design Considerations**: Synthetic complexes must balance metal accessibility, redox potential, and steric effects for optimal function.
- How does the coordination chemistry around the copper center impact reactivity?





Measurement of SOD Activity

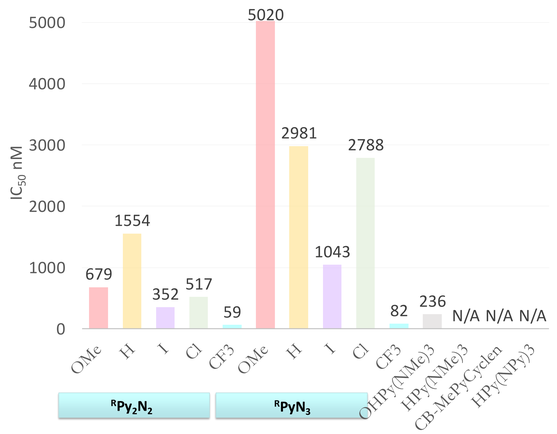
- Used to predict antioxidant activity through consumption of superoxide.
- Xanthine/Xanthine Oxidase used to generate superoxide.



McCord, J. M.; Fridovich, I. Superoxide dismutase: an enzymic function for erythrocuprein (hemocuprein). *J. Biol. Chem.* **1969**, *244*(22), 6049– 6055, DOI: 10.1016/S0021-9258(18)63504-5

SOD Assay Results

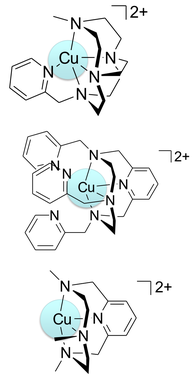
		IC_{50} (μM)	k_{cat}
$^{R}Py_2N_2$	$Cu^{II}[^{OMe}Py_2N_2]^{2+}$	0.679(1)	3.94
	$Cu^{II}[^{H}Py_2N_2]^{2+}$	1.554(1)	1.72
	$Cu^{II}[^{I}Py_2N_2]^{2+}$	0.352(1)	7.58
	$Cu^{II}[^{Cl}Py_2N_2]^{2+}$	0.517(1)	5.16
	$Cu^{II}[^{CF3}Py_2N_2]^{2+}$	0.059(1)	45.36
$^{R}PyN_3$	$Cu^{II}[^{OMe}PyN_3]^{2+}$	5.020(1)	1.58
	$Cu^{II}[^{H}PyN_3]^{2+}$	2.981(1)	0.53
	$Cu^{II}[^{I}PyN_3]^{2+}$	1.043(1)	0.90
	$Cu^{II}[^{Cl}PyN_3]^{2+}$	2.788(1)	0.96
	$Cu^{II}[^{CF3}PyN_3]^{2+}$	0.082(1)	32.87
	$Cu^{II}[^{OH}Py(NMe)_3]^{2+}$	0.236 (69)	7.05
	$Cu^{II}[^{H}Py(NMe)_3]^{2+}$	-	-
	Cu^{II}[CB-MePyCyclen]$^{2+}$	-	-
	$Cu^{II}[^{H}Py(NPy)_3]^{2+}$	-	-



Mekhail, M. A.; Smith, K. J.; Freire, D. M.; Pota, K.; Nguyen, N.; Burnett, M. E.; Green, K. N. Increased Efficiency of a Functional SOD Mimic Achieved with Pyridine Modification on a Pyclen-Based Copper(II) Complex. *Inorganic Chemistry* **2023**, *62* (14), 5415–5425. https://doi.org/10.1021/acs.inorgchem.2c04327.

Conclusions

- Cu^{II}[CB-MePyCyclen]$^{2+}$ had poor activity because steric hindrance blocked key coordination sites.
- $Cu^{II}[^{H}Py(NPy)_3]^{2+}$ was ineffective due to an insufficient number of coordination sites for stable metal binding.
- $Cu^{II}[^{OH}Py(NMe)_3]^{2+}$ had good activity due to the open and strong coordination sites
- Results highlight the importance of ligand design in optimizing metal coordination for enzymatic function.



Future Directions

- Analyze ligands with varying coordination sites to confirm the impact on metal binding and enzymatic function.
- Investigate how steric and electronic effects influence catalytic efficiency in SOD mimics.
- Test manganese-containing compounds to compare their activity with copper-containing molecules
- Optimize ligand design to improve accessibility and stability for enhanced activity.

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