Copper-Dioxygen Coordination Chemistry Relevant to Copper Proteins

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Copper ion is a vital constituent of metalloprotein active sites, those supporting the aerobic organisms. Biological roles include electron shuttling/trafficking and the processing of the critical small molecule nitrogen oxides NO, NO_2^- and N_2O, as well as O_2 (dioxygen). For the latter, copper proteins participate in O_2-transport, oxygenase activity (i.e., O-atom(s) insertion) and O_2-reduction to H_2O_2 or water accompanied by substrate dehydrogenation. Functions include pigment production, neurotransmitter and hormone generation, conversion of methane to methanol, oxidative cleavage of recalcitrant polysaccharides as well as scavenging of reactive oxygen species (ROS). Copper biochemistry encompasses one-electron (e^-) redox shuttling within the Cu^{II}/Cu^{I} oxidation states.

A major theme of our long-term research program has focused on ligand (L) design, systematic ligand variation and the use of cryogenic solution handling, enabling the generation and investigation of $(L)Cu^{I}_n/O_{2(g)}$ (n = 1, 2) derived species. Through such approaches, one may identify factors such as donor atom type or number, coordination geometry, metal complex redox potential, and second coordination sphere composition, those which significantly contribute to Cu-protein active site structure & generation of reactive intermediates, all providing insights into reaction mechanism(s).

Prior to our research efforts, no synthetically derived well-characterized Cu^{I}_n-$(O_{2(g)})$ species existed. Success in this area has come from carefully considered ligand design and application of cryogenic solution handling. Use of tripodal tetradentate N_4 ligands leads to the generation of superoxo-copper(II) $\{(ligand)Cu^{II}(O_2^{\bullet-})\}$ complexes and/or peroxo-dicopper(II) analogs which have been characterized structurally/spectroscopically and have been examined with respect to scope of reaction. Binucleating ligands hold two copper(I) ions may undergo reversible $O_{2(g)}$-binding and/or 'activation' of the bound peroxo (O_2^{2-}) ligand leading to hydroxylation of unactivated arene C–H bonds, chemistry which has relevance to the tyrosinase enzyme reaction mechanism. Study of phenolato-bridged dicopper complexes leads to new kinds of superoxo, peroxo or hydroperoxo dicopper(II) complexes which can be reversibly interconverted with oxidants/reductants and/or acids-bases, thus leading us to elucidate thermodynamic interrelationships. Most recently we described peroxo-dicopper(II) complex nucleophilic oxidative aldehyde deformylation chemistry, a dioxygenase reaction.

Results obtained from the present research presented provides insights into biological copper ion mediated O_2-processing and thus also possibly can apply to practical organic oxidation chemistry and/or energy related fuel-cell technologies.

Recent relevant publications:

Karlin, Kenneth D.; Hota, Pradip Kumar; Kim, Bohee; Panda, Sanjib; Phan, Hai "Synthetic Copper-(Di)oxygen Complex Generation and Reactivity Relevant to Copper Protein O_2-Processing" *Bull. Jpn. Soc. Coord. Chem.* **2024**, *83*, 16-27.

Kim, Bohee.; Karlin, Kenneth D. "Ligand–Copper(I) Primary O_2-Adducts: Design, Characterization, and Biological Significance of Cupric–Superoxides" *Acc. Chem. Res.* **2023**, *56*, 2197-2212.

Quist, David. A.; Ehudin, Melanie A.; Schaefer, A. W.; Schneider, G. L.; Solomon, Edward I.; Karlin, Kenneth D. "Ligand Identity-Induced Generation of Enhanced Oxidative Hydrogen Atom Transfer Reactivity for a $Cu^{II}_2(O_2^{\bullet-})$ Complex Driven by Formation of a $Cu^{II}_2(^-OOH)$ Compound with a Strong O−H Bond". *J. Am. Chem. Soc*. **2019**, *141*, 12682.

Quist, David A.; Diaz, Daniel E.; Liu, Jeffrey J.; Karlin, Kenneth D. Activation of dioxygen by copper metalloproteins and insights from model complexes. *J. Biol. Inorg. Chem.* **2017**, *22*, 253-288.