N_2S_2 Donor Sets as Models for Metalloenzyme Active Sites

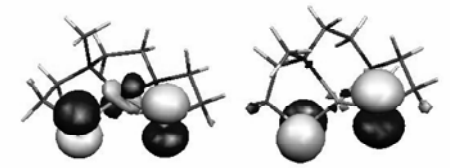
Christopher S. Mullins, Craig A. Grapperhaus, Mark S. Mashuta, Pawel M. Kozlowski

University of Louisville, Department of Chemistry

The nucleophilicity of transition metal thiolates is well-documented. Biologically relevant electrophilic substrates include oxygen or oxygen-transfer agents (such as H_2O_2) and alkylation agents (such as CH_3I). Nature makes use of the latter with Zn-containing de-alkylation proteins such as the Ada repair mechanism and the former in the case of the post-translationally modified active form of Nitrile Hydratase.

The reactivity of Ni thiolate systems towards alkylation has been known for nearly a half-century, whereas recent work has elucidated the realm of sulfur-based oxygenation. Zinc thiolate systems are known to be alkylated as well; however, many reports show a loss of Zn-S bonding upon alkylation. Prior to our work in this area, there were no reports of Zn thiolate sulfur-based oxygenation. In a side-by-side study with the same chelating ligand both alkylation and oxygenation of Ni and Zn thiolates was accomplished.

Through DFT calculations the difference in Ni versus Zn reactivity is attributable to energetic overlap of metal d orbitals with the thiolate ligand p orbitals. As shown below, the HOMO of Ni(bme-dmed) (left) has good mixing of these orbitals whereas Zn(bme-dmed) (right) is predominantly sulfur p in character.



Recently the crystallographic analysis of Ni-containing form of Superoxide Dismutase (NiSOD) was shown to contain an N_2S_2 donor environment in its reduced (Ni^{II}) state. The process of converting two molecules of superoxide anion ($O_2^{\cdot -}$) to a mole of dioxygen and one mole of hydrogen peroxide is achieved by the redox cycling of Ni between its +2 to +3 oxidation states. As nickel thiolates are prone to sulfur oxygenation, their innocence in this catalytic cycle is of interest. A DFT study was utilized to compare a group of related NiN_2S_2 systems in order to understand this reactivity.