Ni Superoxide Dismutase: Insights into Electronic Structure and Catalytic Mechanism Obtained Using a Combined Spectroscopic/ Computational Approach

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Superoxide dismutases (SODs) are metalloenzymes that detoxify superoxide ($O_2^{\bullet-}$) via its disproportionation to H_2O_2 and O_2. While Fe, Mn, and Cu/Zn superoxide dismutases (SODs) have been studied extensively for years, an additional class of Ni-containing SODs (NiSODs) has emerged within the past decade. Recent crystallographic studies (Barondeau et al. *Biochemistry* **2004**, *43*, 8038) have revealed that oxidized NiSOD features a Ni^{3+} center ($S = 1/2$) with a $[S_2N_3]$ ligand set in a square-pyramidal coordination geometry. Upon reduction, the axial imidazole ligand of the His1 residue dissociates to yield a diamagnetic Ni^{2+} center with square-planar geometry. The four equatorial ligands include two thiolates in a *cis* arrangement, a deprotonated amide from the protein backbone, and the N-terminal amine.

We have engaged in detailed investigations of the electronic structure of the NiSOD active site using a combination of spectroscopic and computational methods (Fiedler et al. *J. Am. Chem Soc.* **2005**, *127*, 5449). Electronic absorption, circular dichroism (CD), and magnetic circular dichroism (MCD) spectroscopies were used to explore the numerous charge-transfer and ligand-field transitions exhibited by NiSOD, and resonance Raman spectroscopy probed the Ni-S bonding interactions. By using these results in conjunction with density functional theory (DFT), we have succeeded in generating an experimentally-validated electronic structure description of the NiSOD active site that elucidates the role of its unique ligand set in tuning the metal redox potential. Comparison of the spectral and electronic properties of NiSOD to those reported for other metalloproteins with metal-thiolate ligation have yielded significant insights into how M-S_{Cys} bonding is used to optimize active sites for catalytic activity. Moreover, our studies of NiSOD in the presence of small-molecule inhibitors point to the importance of second-sphere residues in substrate binding, with implications for the catalytic mechanism

In addition, we have pursued parallel studies of synthetic Ni complexes with S/N ligation that model the active sites of numerous Ni-containing metalloenzymes, including NiSOD. These well-defined model complexes provide a useful starting point the development of a better understanding of Ni-ligand bonding interactions in biological systems.