Synthetic models of Nickel Superoxide Dismutase

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Superoxide dismutases (SODs) are metalloenzymes that catalyze the conversion of superoxide to hydrogen peroxide and dioxygen. This process requires a one-electron redox potential of approximately 200 mV, and two protons. The nickel containing SOD differs from other SODs (Mn-, Fe-, and Cu/Zn-) in both metal coordination and amino acid sequence. Studies of the nickel site in NiSOD by XAS[1] and crystallography[2,3] reveal a nickel site with thiolate ligation that is unique among SODs. In the oxidized protein, the nickel center is five coordinate with the ligands provided by the N-terminal H1 residue via the amino terminus and the Im side chain, two cysteine S-donors, and an amidate ligand provided by the C2 residue. Upon reduction, the apical H1 Im ligand is lost, forming a planar, four-coordinate nickel site. Using synthetic models, we are probing the mechanism of catalysis to explore the details of NiSOD function. Synthetic tridentate ligands of formula $RN(CH_2CH_2SH)_2$ provide examples of nickel thiolate complexes with potentials appropriate for SOD catalysis. The NiSOD crystal structure also reveals a tyrosine located proximal to the nickel site. This tyrosine may be involved in a redox process and/or the source of protons for the disproportionation reaction. Models designed with a phenol moiety in the R group were used to assess the role of the Y residues in catalysis. These models also provide systems where the S-donors can be protonated, as suggested for the reduction product of NiSOD produced by reaction hydrogen peroxide using S K-edge XAS.[4]

[1] Choudhury, S. B. et al. Biochemistry. 1999, 38(12), 3744-3752
[2] Barondeau, D. et al. Biochemistry. 2004, 43(25), 8038-47.
[3] Wuerges J. et al. PNAS. 2004, 101(23), 8569-74.
[4] R.K. Szilagyi, et al. 2004. JACS. 126: 3018-3019.