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XAS Probes of Structure/Function in Ni Metallobiochemistry

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Ni K-edge XAS is being used to examine the structure of Ni containing sites in enzymes and proteins with the goal of elucidating the role of Ni in the relevant biological functions and structure/functional trends. These studies included a study of the Ni site in *E. coli* glyoxalase I, a Ni containing glyoxalase, that provided a number of structural details regarding the reaction mechanism including features of the enzyme-substrate complex.

One of the strong trends to emerge from the study of Ni enzymes is the relationship between Ni sites involved in redox catalysis and polycysteinate ligation of the Ni, raising the possibility that Nature utilizes Ni not as a redox center, but to control redox chemistry that is inherently sulfur-based. During the last period, we have used this trend to determine aspects of the reaction mechanism of acireductone dioxygenase (Ni-ARD), the only known Ni containing dioxygenase, which was cloned and expressed by the Brandeis group. There are two limiting mechanisms exhibited by dioxygenases. The first involves a redox metal to activate O₂, the second utilizes the Lewis acidity of a metal center to activate the substrate to attack by O₂ upon binding to the metal. The structure determined for the resting enzyme reveals a six-coordinate Ni center with a ligand environment composed of O,N-donor ligands including ca. three His ligands. The lack of polycysteinate ligation indicates a role in substrate activation, however, the six-coordinate geometry was puzzling in this regard. Subsequent studies of the enzyme-substrate complex prepared anaerobically to prevent turnover revealed that substrate binds to the Ni center in a bidentate fashion with the displacement of at least one His ligand, which may serve as a base to deprotonate the substrate.

Other studies were directed toward understanding the structure of a putative Ni complex formed between histone H4 and nickel that has been implicated in Ni carcinogenesis. Studies of the structure of Ni sites in peptide models and initial studies of the Ni-H4 complex are consistent with ligation of the Ni by a His residue in the N-terminal domain of the histone near Lys residues that are involved in acetylation and gene expression. The Ni K-edge XAS results provide the first structural data to support this model.