Advances in Ligand Design for Bioinorganic Chemistry Applications

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The interaction between metal ions, ligands, and biomolecules play a fundamental role in bioinorganic chemistry, from metalloenzymes to medicine. In addition to balancing charge, ligands can tune stability and associated reactivity via diverse interaction pathways and redox activation. Recent developments show that ligands serving as electron reservoirs can offer new reactivity pathways, and we are currently investigating the spectroscopic signatures of ligand radical systems to better understand the associated electronic structure and reactivity pathways. The first part of this talk will discuss our recent results exploring how ligand design can influence radical localization and reactivity in metal-phenoxide systems containing nitrides.[1,2,3] The second part of the talk will focus on the development of multifunctional ligands that target mutant p53 protein misfolding and aggregation in cancer. One destabilizing p53 mutation, Y220C, causes local protein unfolding and ultimately results in loss of Zn in the DNA-binding domain. The Y220C mutation also creates a druggable surface that many aim to stabilize using small molecules.[4] We are developing small molecule stabilizers of p53 Y220C that feature Zn-binding fragments to chaperone Zn to the metal depleted site and restore wild-type function. This presentation describes the design and synthesis of a series of ligands containing phenols for interaction and stabilization of the p53-Y220C surface cavity, and Zn-binding fragments for metallochaperone activity.[5,6,7] Recent results will be presented, including inhibition of mutant p53 aggregation.

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