Thermodynamics of Metal-Protein Interactions

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The thermodynamics of metal ions binding to proteins underlies important areas of bioinorganic chemistry, ranging from essential metal uptake, transport and storage to chaperone-assisted maturation of metalloenzymes to mechanisms of metal toxicity. Isothermal titration calorimetry (ITC) has emerged as the key method for quantifying the thermodynamics of metal-protein interactions, and three studies with this technique will be described.

First, in certain cases there is a significant discrepancy between metal binding enthalpies determined by van't Hoff analysis of the temperature dependence of the stability constant and metal binding enthalpies determined directly by calorimetry. Using our own data and data from the literature, these discrepancies are quantitatively understood to originate from the enthalpy of (de)protonation events that are coupled to metal binding.

Second, the thermodynamics of Zn^{+2} binding to DNA-binding motifs (e.g. zinc fingers) of transcription factors have been investigated. ITC studies of peptides corresponding to Zn-binding sequences with Cys_2His_2, $Cys_2HisCys$ and Cys_4 Zn^{+2} coordination reveal significantly different enthalpic and entropic components of the free energy of Zn-peptide complex formation. These results provide insight about the relative protein and metal contributions to the stability of the metal-protein structure.

Finally, the toxic elements As and Hg both have biologically-important inorganic and organic forms (e.g. arsenite and monomethylarsenite) that have different chemical properties and toxicological profiles. ITC studies have quantified the thermodynamics of formation of their complexes with glutathione, lipoic acid and other biologically-relevant thiols, thereby providing quantitative insight relevant to their interaction with Cys residues in proteins and the chemical basis for their toxicity.