

Chapter 9: Learning Objectives

- * In hydrolytic enzymes, the metal generally acts as a Lewis acid for two reasons: to make the substrate more electrophilic, and to make a water/hydroxide deprotonated and hence more nucleophilic. This enables some of the greatest enzymatic enhancements of activity known (factor of $\sim 10^9$ in rate or more).
- * Zn^{2+} and Mg^{2+} are especially common in hydrolytic enzymes, and they are held by very different amino acids (soft vs. hard). Zn^{2+} is less labile than Mg^{2+} , and is a stronger Lewis acid. Therefore, Zn^{2+} is used for more difficult tasks (peptide, carboxylate cleavage) than Mg^{2+} (phosphate cleavage, enolate additions).
- * Transition metals (Mn^{2+} , Fe^{3+}) are sometimes used for catalytic hydrolysis. Mn^{2+} is also substituted into metalloenzymes by inorganic chemists who use the distinctive EPR signatures to learn about the binding site. Co^{2+} is used in this capacity for its distinctive UV-vis signatures. However, substitution of a transition metal into a non-transition-metal site assumes that the binding is the same.
- * The active sites of metallohydrolases usually feature a hydrophobic pocket (for substrate binding and recognition) with a localized hydrophilic site (for the metal and associated water molecules). The recognition aspects are exceptionally important in the site-specific hydrolysis ("nuclease") and formation ("polymerase") of nucleic acid polymers (DNA and RNA), and in the site-specific phosphorylation and dephosphorylation of proteins and small molecules.
- * Urease is one of the most studied hydrolases, and its dinickel active site is well-characterized. However, the mechanism of this enzyme is still under debate.
- * Inhibitors of hydrolases are often sought for medicinal purposes. Hydroxamic acids are often excellent inhibitors of the enzymes, because they are strong, "hard" bases.
- * Aconitase is part of the TCA (tricarboxylic acid) cycle through which carbohydrates and proteins are metabolized. It is one of the few examples of an iron-sulfur cluster that is used as a catalyst rather than as an electron-transfer site. The chemistry happens at a labile iron atom that is part of an [4Fe-4S] cluster.
- * "Ribozymes," "DNAzymes" and other catalytic nucleic acids usually use Mg^{2+} for catalysis. These are widely speculated to be the earliest biological catalysts.