Glenn T. Seaborg Center Postdoctoral Candidate Seminar

New Water Soluble Porphyrins for the Decomposition of Peroxynitrite and for Use in Heme Model Compounds

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Enzymatic catalysis continues to inspire synthetic chemists because of the ease and efficiency with which Nature facilitates such challenging transformations. The heme moiety is a commonly found structural motif in enzymes and plays a major role in their catalytic activity. Taking a cue from Nature, a major research effort has been devoted to the development of synthetic metalloporphyrins. These have largely been used as model compounds for various heme enzymes, in order to help elucidate enzyme mechanism. In many cases the insight gained has led to the development of catalysts for industrial and therapeutic applications. Our group has demonstrated that synthetic metalloporphyrins can catalytically decompose the reactive nitrogen species peroxynitrite, which has been correlated with metalloprotein nitration in such diseases as diabetes, arthritis, and colitis. In a peroxidase-like mechanism, peroxynitrite is converted to the benign isomer nitrate. The iron porphyrins developed in our group comprise the most reactive catalysts reported to date, exhibiting rate constants exceeding 10^6 M^{-1} s^{-1} in reaction with peroxynitrite. The high reactivity seen in the laboratory translates into such *in vivo* effects as amelioration of protein tyrosine nitration in rodent models of diabetes. The current "world record" catalyst, FP15, was developed in our group, and it continues to be studied in animal models of numerous diseases. We have recently developed a next-generation compound, FP23, which kinetically outperforms FP15 and has the added benefit of a synthesis that is green, more facile, and amenable to scaleup. In the course of this work, we have also identified a novel intramolecular structural motif in this class of porphyrins. Research efforts focused on high-valent metal complexes of this unique ligand may help elucidate enzyme mechanism and function.

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