Structural Insight into Antibiotic Fosfomycin Biosynthesis by a Mononuclear Iron Enzyme

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The biosynthetic pathway of the clinically important antibiotic fosfomycin uses enzymes that catalyze reactions without precedent in biology. Among these is hydroxypropylphosphonic acid epoxidase, which represents a new subfamily of non-heme mononuclear iron enzymes. We have determined a series of X-ray structures of this enzyme, both alone and in complex with substrates. These structural data suggest how this enzyme is able to recognize its substrate and respond with a conformational change that protects the radical-based intermediates formed during catalysis. Comparisons with other family members suggest why substrate binding is able to prime iron for dioxygen binding in the absence of α-ketoglutarate (a co-substrate required by a majority of mononuclear iron enzymes), and how the unique epoxidation reaction of hydroxypropylphosphonic acid epoxidase may occur.