Synthetic Models of Peptide Deformylase

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Peptide deformylase (PDF) is a non-heme iron enzyme that contains a mononuclear iron(II) center bound by two histidines, one cysteine, and a catalytically active water/hydroxide ligand. This enzyme catalyzes the deformylation of the N-terminus of newly formed polypeptides, and is found mostly in bacteria. It has come under scrutiny as a target for new antibiotics, and therefore its mechanism of action is of interest from a practical as well as fundamental perspective. Examination of the primary sequence, structure, and function of PDF suggest that this enzyme belongs to the mononuclear zinc enzyme family, yet there is strong evidence that the metal ion in vivo is iron(II), not zinc(II). Moreover, the zinc(II) form of the protein, Zn(II)-PDF, is much less active than Fe(II)-PDF. In order to understand the role of the metal ion in the mechanism of PDF, and in particular, the unusual metal dependence of the reactivity of this enzyme, we have synthesized a series of model complexes of the active site.

The hydrolytic reactivity of one of these complexes, (PATH)ZnOH, will be presented in regard to carboxylic ester (4-nitrophenylacetate) and phosphate ester (tris(4-nitrophenyl)phosphate) substrates. Detailed kinetic analyses, including pH-rate profiles and activation parameters, point to different mechanisms of hydrolysis for the different substrates, and demonstrate the flexible nature of zinc(II) in a tetrahedral, NNS(thiolate) environment. The synthesis and structural characterization of zinc(II)-formate and iron(II)-formate complexes will also be described along with theoretical calculations on these and related complexes. A rationale regarding the low reactivity of Zn(II)-PDF as compared to Fe(II)-PDF is proposed based on a combination of the kinetic and structural results described above and recent data on the enzyme.

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