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STUDIES ON COORDINATION CHEMISTRY OF HYDROXAMIC ACID COMPLEXES

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ABSTRACT

The present paper process the coordination of monohydroxamic acids to several Zn(II)- or Ni(II)-containing metalloenzymes has been studied by X-ray crystallography. Hydroxamic acids have been long known to inhibit urease, a dinuclear Ni(II)-containing enzyme, which catalyses the hydrolysis of urea to ammonia and carbamate. In the X-ray crystal structure of ahaH (1−)-bound urease from Bacillus pasteurii, the amidohydroxylato group of the acetohydroxamato ligand bridges between the two Ni(II) atoms in the dinuclear active site, which replaces a bridging hydroxyl group in native urease.

Key-Words: Hydroxamic acids, Ligands

1. INTRODUCTION

The rich coordination chemistry of hydroxamic acids,in terms of the number of complexes characterized by X-ray crystallography and the solution chemistry suggests that these ligands may also coordinate active site metal ions in metalloproteins. The coordination of monohydroxamic acids to several Zn(II)- or Ni(II)-containing metalloenzymes has been studied by X-ray crystallography. The enzymes studied include urease (binuclear Ni(II)-containing) and Zn(II)-containing enzymes, including matrix metalloproteinases (MMPs), aminopeptidases, anthrax lethal factor, botulinium neurotoxin and carbonic anhydrase. X-ray crystallography has also proven a useful tool for examining the binding between Fe(III)-loaded polyhydroxamic acids and cognate binding proteins that are integral to prokaryotic Fe(III)-uptake mechanisms.

2. NI(II)-DEPENDENT SYSTEMS

Hydroxamic acids have been long known to inhibit urease, a dinuclear Ni(II)-containing enzyme, which catalyses the hydrolysis of urea to ammonia and carbamate [1]. In the X-ray crystal structure of ahaH (1−)-bound urease from Bacillus pasteurii, the amidohydroxylato group of the acetohydroxamato ligand bridges between the two Ni(II) atoms in the dinuclear active site [16] which replace s a bridging hydroxyl group in native urease. Donation from four histidine residues (two per Ni(II)), a bridging carbamylated lysine residue and a mondentate carboxylate (Ni2) or the CO group from ahaH(1−) (Ni1) gives a five-coordinate geometry at each Ni(II). The trigonal-distortion parameters, τ(Ni1) = 0.363 and τ(Ni2) = 0.365, indicate greater trigonal bipyramidal character [2] relative to the geometry of the active-site Ni(II) ions in B. pasteurii urease bound to diamidophosphate or β-mercaptoethanol. A hydrogen bond (2.6A°) exists between the NH group of ahaH(1−) and the non-coordinated O atom of the Asp group. A similar coordination environment is observed at the dinuclear Ni(II) centre in the X-ray crystal structure of ahaH(1−) bound to a recombinant mutant of urease from Klebsiella aerogenes [3].

3. ZN(II)-DEPENDENT SYSTEMS

Many X-ray crystal structures report the coordination of hydroxamic acids to the catalytic Zn(II) site in matrix metalloproteinases (MMPs). Matrix metalloproteinases are a family of Zn(II)-containing endopeptidases which play roles in the regulation of the structures of extracellular matrices. The overexpression and/or misregulation of MMPs (collagenase, gelatinase, stromelysin, matrilysin, metalloelastase) has pathological implications in diseases including rheumatoid and osteoarthritis, metastasis and emphysema. Hydroxamic acids inhibit MMPs by binding to the catalytic Zn(II) site which has fueled research into the design of hydroxamic acid-based drugs with superior zinc-binding groups (ZBG) for the treatment of MMP-related diseases. There is a characteristic binding motif between hydroxamic acids and the catalytic Zn(II) site of MMPs. First, the ahaH_2 or C-substituted analogue (**1**: R_C = alkyl/aryl, R_N =H) coordinates to the catalytic Zn(II) ion in a O,O'-bidentate fashion as a neutral donor with three histidine-derived nitrogen atoms from the zinc-binding sequence motif (HExxHxxGxxH) saturating the overall Zn(II) trigonal-bipyramidal active-site geometry. Second, there is a hydrogen bond formed between the NO-H hydrogen atom of the coordinated hydroxamic acid and the O atom(s) of a proximal glutamic acid residue of a distance ranging between 2.4 °A and 3.1A° . Third, in many (but not all) of the structures, there is an additional hydrogen bond interaction between the hydroxamic acid NH group and the amide O atom of a distal alanine residue. Structurally complex hydroxamic acid-based inhibitors, such as batimastat, show many additional hydrogen bonds and hydrophobic interactions upon binding to Zn(II) in MMP-12 [4]. The structures of ternary ahaH_2-MMP-12-inhibitor (non-hydroxamato-based) complexes have also been described in which the binary ahaH_2- MMP-12 complex directs the solubility and IC_{50} properties of the ternary complex [5].

4. RESULTS AND DISCUSSION

The X-ray crystal structure of gallichrome (apoferrichrome $((Gly)_3$-(N-δ-acetyl-N-δ-hydroxy-L-ornithine$)_3$) metallated with Ga(III)) bound to the periplasmic binding protein huD from E. coli has been solved to 1.9 °A resolution [6]. The Ga(III) O bond lengths in gallichrome range between 2.15 °A and 2.28 ° A, which are 0.1 °A longer than in gallichrome in the absence of the cognate binding protein [7]. The strength of conclusions drawn in relation to the metal-O bond lengths is tempered somewhat by the limits of the resolution of the protein crystal structures. It is surprising that although the ferrichrome–FhuD binding constant is 0.1 μM [8], only 45% of gallichrome is buried in the complex. The interaction between Arg84 and two carbonyl oxygen atoms of the hydroxamato moiety are thought to be essential to the complex formation, inaddition to the third carbonyl oxygen atom and Tyr 106. The X-ray crystal structure of ferrichrome bound to FhuA from E. coli (2.7 °A resolution) shows a significant conformational change in FhuA upon binding ferrichrome in a tyrosine-rich binding pocket [9]. (Figure. 1).

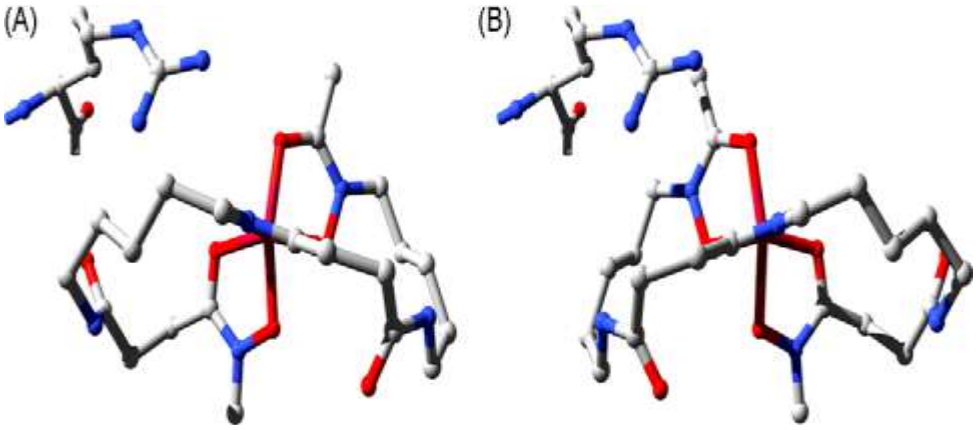

Figure. 1. X-ray crystal structure (2.0 °A resolution) of Λ-C-trans, cis-FOB (A) or the superposed enantiomer (Δ-C-trans, cis-FOB) (B) complexed with the periplasmic transport protein FhuD. Figure generated using Swiss-PdbViewer v3.7 [4] and POV-Ray v3.6 [5].

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