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Review

Coordinating properties of peptides containing histidyl residues

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ABSTRACT

Numerous studies have demonstrated the high metal binding capacity and selectivity of peptide molecules. The terminal amino group, deprotonated amide nitrogens, and various side chain donor functions are the most common metal binding sites in these complexes. Imidazole-N donors of histidyl residues are especially important for complex formation because their complexes exhibit outstanding thermodynamic stability and high structural variation. Complex formation reactions with simple oligopeptides containing one histidyl residue have already been clarified satisfactorily and the results have been reviewed. However, the coordination chemistry of multihistidine peptides is understood less well, although the relevant molecules have major biological significance. These systems include peptide fragments of prion protein, amyloid-β and various copper(II) or zinc(II) transporter proteins. Recently, much data have been reported about these complexes and the most important results are summarized in this review. The second part of this review describes complex formation by peptides that contain another strongly coordinating side chain (e.g., carboxylates of Asp and Glu, and thiolates of Cys residues) in addition to the histidyl sites.

1. Introduction

Proteins are the most common and efficient metal binding sites in all living systems. They are built from amino acids via an amide (or peptide) bond between adjacent amino acids. The number of natural amino acids is rather limited (around 20 in native proteins) and their coordination chemistry is relatively simple. The terminal amino-N and carboxylate-O donors are the primary ligation sites of these molecules, but the donor atoms in the side chains can also make significant contributions to the overall stability of their metal complexes. Numerous critical reviews and book chapters have reported various aspects of complex formation with amino acids. These studies are indispensable for understanding the metal ion affinities of various proteins, but amino acids are not appropriate models for the structural characterization of metalloproteins.

Peptides built from several amino acids are a better approach for mimicking the binding modes of proteins because the terminal functions are well separated and they also contain amide bond. Moreover, the number of possible peptide molecules is almost infinite, thereby facilitating systematic studies of the roles of specific

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side chains in complex formation. Quantitative studies of the metal complexes of peptides began in the 1960s and the first comprehensive review of this subject was published in 1982 [1]. Subsequently, many studies have summarized the most important general observations related to metallopeptide chemistry [2–5], most of which have demonstrated the stabilizing role of histidyl residues in metal complexes of peptides, in agreement with the high frequency presence of the M–N_{im} bond in the active centers of metalloproteins. Recently, the possible roles of metal ions in the development and/or onset of neurodegenerative disorders have motivated studies of peptide complexes. Many of the relevant proteins and peptides (such as prion protein and amyloid-β) are rich in histidyl residues with remarkable metal ion affinities. A survey of metal ion–peptide complexes unambiguously demonstrated that peptides containing histidyl residues are among the most widely studied molecules in coordination chemistry, where the peptide complexes containing a single histidyl site are the best characterized [3,4] and they exhibit significant differences in their coordination behavior depending on the location of the histidyl residues and the nature of the metal ion. The binding modes of these peptide molecules can be estimated well, although most studies have focused on copper(II), nickel(II), and zinc(II) complexes, whereas other metal ions have been studied only rarely. Moreover, the biologically important proteins and their peptide fragments generally contain two or more histidines and some other amino acids with specific coordinating side chains (such as Asp, Glu, or Met). In the last two decades, due to the development of solid phase peptide synthesis, there have been many studies of the complexes of multihistidine peptides. However, the high diversity of the sequences of these substances results in highly variable complex formation processes, although the complex formation processes have many common features. In this review, we survey the complex formation processes of peptides containing multiple histidyl sites and/or additional donor functions. Some general characteristics of these complex formation reactions are highlighted and the complexes of biologically relevant metal ions other than copper(II) are also discussed. Many of these studies were performed in our laboratories in Debrecen (Hungary) and by the research group of Prof. H. Kozlowski at the University of Wroclaw (Poland), but the most important studies are also evaluated.

2. Metal complexes of small peptides with one histidine in the sequence

The great diversity of the complex formation processes by peptides has been discussed in several previous reviews [3,4]. Thus, we only provide a short summary of these observations to understand the metal binding properties of the more complicated ligands discussed in the following. The most important binding modes formed with the one-histidine peptides are as follows.

- For peptides with a histidine in position-1 (or N-terminal His), the terminal amino and the imidazole nitrogen donors can form a six-membered chelate, thereby generating the so-called histamine-like coordination mode. In the presence of excess ligand, this leads to bis(ligand) complex formation and the metal binding affinities of these peptides are enhanced compared with those of simple oligoglycines and related ligands [6–10]. This type of reaction can occur with a wide range of metal ions, including most divalent transition metals. However, the bidentate coordination mode cannot saturate the coordination sphere of the metal ions in equimolar samples, thereby resulting in the hydrolysis of the complexes or the formation of imidazole bridged dinuclear complexes by increasing the pH. The latter reactions can occur only with metal ions, which are able to promote the ionization of amide groups. The copper(II)–HisGly system is the simplest example of this reaction, where the formation of the complex starts with the formation of the (NH_2,N_{im}) chelate in slightly acidic samples, which is followed by the tridentate (NH_2,N^-,COO^-) coordination mode and the imidazole side chains link these units in a dinuclear complex [4,7].
- For peptides containing histidine in position-2 (X-His-Y… sequences), the formation of (NH_2,N^-,N_{im}) (5,6)-membered fused chelates is the major coordination mode. Many solution studies [7,11–13] and the X-ray structures of the corresponding copper(II) complexes [14–16] support the outstanding thermodynamic stability of these species. Moreover, these peptide complexes have two interesting and very specific properties: (i) the aforementioned tridentate binding mode does not saturate the coordination sphere of the metal ions and imidazolato-bridged tetranuclear complexes can be formed in alkaline samples (pH 9–10). The formation of these species was first proposed for the reactions between copper(II), nickel(II), and palladium(II) ions with GlyHis [17], and proved later by X-ray crystallography of the corresponding gold(III) complexes [18]; (ii) a general feature of the coordination chemistry of peptides is that only a few metal ions are able to promote the ionization and metal ion coordination of peptide amide bonds. For glycylglycine this reaction occurs around pH 2.0, 4.0–5.0, and 7.0–9.0 in the corresponding palladium(II), copper(II), and nickel(II) complexes, respectively. However, in the case of GlyHis and related substances, this reaction also occurs in the zinc(II) and cobalt(II) complexes [19,20].
- The peptides containing histidine in position-3 (X-Y-His- … sequences) probably form the most thermodynamically stable peptide complexes with metal ions. The outstanding copper(II) and nickel(II) binding affinities of albumin are also related to this sequence, which is often called the amino terminal CuNi binding site motif (ATCUN-motif). The remarkable stability of these species is explained by the cooperative deprotonation of two adjacent amide nitrogen atoms between the terminal amino and imidazole-N donors, thereby yielding the (NH_2,N^-,N^-,N_{im}) coordination mode [21–24]. Similar species are also formed easily with palladium(II) and gold(III) ions [25], but in contrast to the results mentioned earlier, zinc(II) and cobalt(II) ions cannot induce deprotonation of the amide groups of peptides containing this sequence [26].
- The separation of the terminal amino and internal histidyl sites by three or more amino acid residues (Xaa-Yaa-Zaa-His … sequences) increases the complexity of the coordination chemistry of these peptides. Both terminal amino and internal histidines can be anchoring sites for the coordination of copper(II) ions, but various macrochelates can also exist in these systems, depending on the specific sequences [4,27,28]. Moreover, these peptides can easily bind two metal ions if the anchoring amino and histidyl sites are present in more distant locations [29].
- Protection of the amino terminus significantly reduces the metal binding affinity of peptide molecules. However, in histidine-containing ligands, the imidazole-N can be an effective anchoring site for the subsequent deprotonation and coordination of the neighboring peptide amide bonds. If the histidyl residue is far from the amino terminus, this deprotonation occurs preferentially at the amino terminus in the form of (6,5,5)-membered chelates. However, in peptides where the histidyl residue is preceded by the secondary amine proline or sarcosine, deprotonation is blocked in this direction, but it can occur toward the C-termini of the molecule. The corresponding chelates are (7,5,5)-membered, thereby decreasing the metal binding affinity of these peptides. Peptide fragments of prion protein are the best examples of these coordination modes, as discussed in Section 3.2.