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Review

Metal complexes of synthetic cyclic peptides

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ABSTRACT

The marine and terrestrial environments offer many opportunities for natural product isolation and study. Many of the naturally occurring compounds offer potential as therapeutic agents and in some cases their activity is moderated or enhanced by complexation with metal ions, both the alkali and alkaline earths and transition metal ions. Thus, many naturally occurring ionophores have become powerful experimental tools for investigating the roles of metal ions in regulating complex biological phenomena. Cyclic peptides from the terrestrial and marine environments have proven to be a rich source of inspiration for synthetic endeavors given their stability to hydrolysis and preorganization for receptor, that is, metal ion binding. Here, we review the metal ion chemistry of synthetic cyclic peptides, from relatively simple cyclic dipeptides, through cyclic octapeptides inspired by examples from the marine environment and beyond to cyclic dodecapeptides, bicyclic peptides and bridged cyclic peptides.

Contents

1. Introduction

Naturally occurring cyclic peptides, isolated from both terrestrial and marine sources, have been the focus of extensive research, with particular interest in their potential use as antibiotic, antifungal, cytotoxic and anticancer agents [1–4]. The stability of peptides to hydrolysis when in a cyclic form has also led researchers to synthesise cycles that incorporate biologically active linear peptide sequences [5–7]. Furthermore, the constraining effect of cyclising a linear peptide leads to further advantages in that the molecule can be pre-organised for receptor-binding, there being reduced conformational entropy associated with preorganisation [5].

What is apparent is that cyclic peptides are involved in numerous, sometimes as yet undefined, biological roles in living organisms. In many cases metal ion coordination is inherent in the activities displayed by these cyclic peptides and copper(II)

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chemistry is often involved in these activities, although not exclusively, with Ca(II), Mg(II) and Ba(II) chemistry featuring prominently [8,9]. Any discussion of cyclic peptides, and peptides in general, invariably involves discussion of the typical donors involved in coordination chemistry and in terms of peptide ligands these donors include imidazole (often from Histidine) and amide nitrogen donors, as well as thiolate/thioether and carboxylate donors from their respective amino acids. Many synthetic analogues of bioactive cyclic peptides have been prepared to investigate metal ion coordination and selectivity, and the influences of conformational constraints [10–25]. In this review the focus is on the metal ion binding characteristics of synthetic cyclic peptides, encompassing examples from the cyclic dipeptides through to the cyclic dodecapeptides. Although conformational aspects are included briefly, as appropriate, this is not the focus of the review. In the majority of cases included herein reference to the metal complexes of naturally occurring cyclic peptides will not be included; exceptions are made, for example, in the discussion of hexa-, octa- and dodeca-peptides where the chemistry of the naturally occurring peptide has led to extensive examination of the transition metal complexes of synthetic analogues.

Comments concerning nomenclature are important at this point. The abbreviation employed to indicate a cyclic peptide is *c*-(L-AA-L-BB)$_m$ where the "*c*" indicates "cyclic", the "L" indicating chirality, the symbols AA and BB following established nomenclature for the amino acids [26], and the subscripted "m" indicating the repeat sequence, where present. In many cases, the terminology cyclic "n"-peptide (n = di-, tri-, tetra-, etc) would imply that the cyclic peptide contains "n"-peptide bonds, but this is not always the case and thus, technically the nomenclature is incorrect. A case in point is some examples of the cyclic octapeptides discussed in Section 2.6. These cyclic structures do not exhibit eight peptide bonds but historically they are called octapeptides or pseudo octapeptides based on the belief that the heterocyclic rings present in the peptides are derived from amino acid precursors. Throughout this work, no distinction will be made between pseudo and non-pseudo cyclic peptides. Data for the structural representations included herein were sourced from the Cambridge Structural Database (CCDC) [27], through the Mercury CSD software [28] and visualized with CYLview [29,30].

Finally, the omission of reference to published examples of the metal complexes of both naturally occurring and synthetic cyclic peptide ligands in this review does not reflect a lack of importance or interest; as many examples as have been possible have been included. There are numerous reviews on the topic of cyclic peptides, for example [4,10,31–38].

2. Metal complexes of cyclic peptides

2.1. Cyclic dipeptides

Substituted diketopiperazines, cyclic dipeptides, have been extensively utilized as protein model systems because they permit studies of metal ion interactions with side chain substituents and the amide linkage whilst excluding effects of terminal functional moieties [39]. Typical cyclic dipeptides are shown in Fig. 1. Numerous studies of the structures of substituted diketopiperazines as well as their metal complexes have been reported; in addition, infrared and UV–Vis and electron paramagnetic resonance (EPR) and nuclear magnetic resonance spectroscopy (NMR) as well as potentiometric methods, have been employed in their characterisation.

In His-containing cyclic dipeptides, such as *c*-(L-Asp-L-His) and *c*-(L-His-L-Leu) the diketopiperazine ring is usually substantially planar [40], the former having the folded imidazole group facing the aspartic acid side-chain. For *c*-(L-His-L-Leu) the apolar Leu

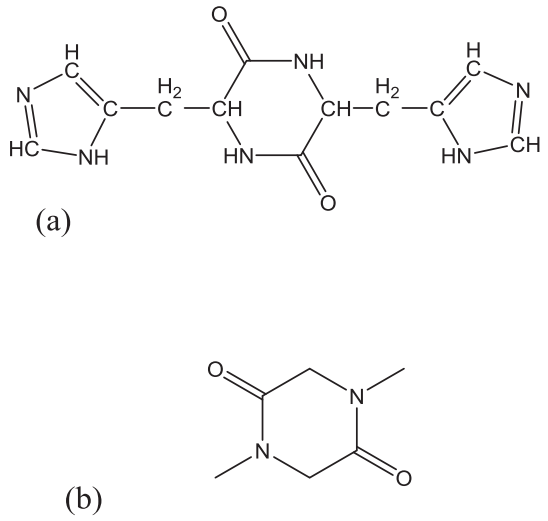

Fig. 1. Cyclic dipeptides (a) 3,6-bis((1H-imidazol-5-yl)methyl)piperazine-2,5-dione; (b) 1,4-dimethylpiperazine-2,5-dione.

residue is in the opposite direction of the folded His moiety [41]. Examples of non-planar diketopiperazine rings include *c*-(L-His-L-Thr) [42], in which the ring exhibits a flattened twist-boat form, the two side-chains interacting through a water molecule. *c*-(L-His-L-Met) displays a buckled diketopiperazine ring, with four of the six atoms lying on the same plane, with the two methionine carbon atoms positioned 0.06 Å out of the least squares plane. The side-chains are stabilised in the folded conformation, the Met group by a significantly short intramolecular contact between the sulfur and its carbonyl carbon atom and the His residue by interaction between the aromatic ring and the amide group [43]. The X-ray structure of *c*-(L-Met-Gly) exhibits a nearly planar arrangement of the diketopiperazine moiety, with the thioether involved in a short contact with the methionine carbonyl [44].

A study of the copper(II) complex with 1,4-dimethyl-2,5-piperazinedione *c*-(disarcosyl) suggested that, based on the infrared spectrum, the metal ion was coordinated to the carbonyl groups of the dipeptide and, using X-ray analysis, a 2:1 sandwich structure was proposed for the Cu(II) complex [45]. The X-ray crystal structure of the Cu(II) complex with *c*-(disarcosyl) was subsequently described as Cu(H_2O)$_6$.(ClO_4)$_2$.(*c*-disarcosyl)$_2$, the six water molecules coordinated to the Cu(II) with four independent halves of the *c*-(disarcosyl) molecules lying on centres of symmetry [46]. The Ag(I) complex with *c*-(disarcosyl) was also reported [46].

An extensive study by Brubaker et al. reported the Cu(II) complexes of *c*-(Gly-L-His), *c*-(Gly-L-Asn), *c*-(Gly-L-Gln), *c*-(Gly-L-Asp), *c*-(Gly-L-Glu), and *c*-(Gly-L-Ser) [39]. They reported the synthesis of the ligands and complexes, characterisation with visible spectroscopy and EPR, and attempted to obtain stability constants through potentiometric methods [39]. All complexes exhibited λ_{max} in the range 650–660 nm at pH 6. The EPR spectra of the Cu(II) complexes showed hyperfine splitting in solution above pH 6 and, based on these hyperfine lines, the number of coordinated N donors was determined to be two. The authors reported that they were unable to obtain stability constants due to the presence of multiple equilibria and the precipitation of copper hydroxide at pH 8 [39].

Using NMR studies of *c*-(Gly-L-His) and *c*-(L-Met-L-His) in the presence of Cu(II) and Ni(II) (the ligand in 5000- and 1000-fold excess, respectively) Kojima et al. showed that, based on broadening of the respective NMR resonance, the metal ions were bound to the imidazole moieties and the sulfur atom, the amide groups