Chemistry

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Conformational Preferences of Short Peptide Fragments

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Introduction

In contrast to the numerous studies on peptide folding in protein structures, there are few reports about the folding of short peptide fragments, as they normally adopt random-coil conformations in water. Therefore, examining the latent folding propensity of short peptides is important for understanding how they interact with proteins. In aprotic environments where peptide fragments are protected from water, hydrogen bonding between amide groups is effectively induced and equilibrium should favor a folded structure. To study the latent propensity of short peptides to adopt folded conformations, alanine-rich tri- to hexapeptides **2**–**5** were placed in the cavity of self-assembled host **1** (Figure 1). We found that these peptide fragments adopted specific helical conformations within the protected cavity. In all cases, hybrid β-turn (3_{10})/α-helix (4_{13}) conformations were found instead of pure α-helix conformations. Thus, we propose that in the absence of solvent interference, short peptide fragments—effective protein termini mimics—adopt mixed $3_{10}/4_{13}$ conformations.

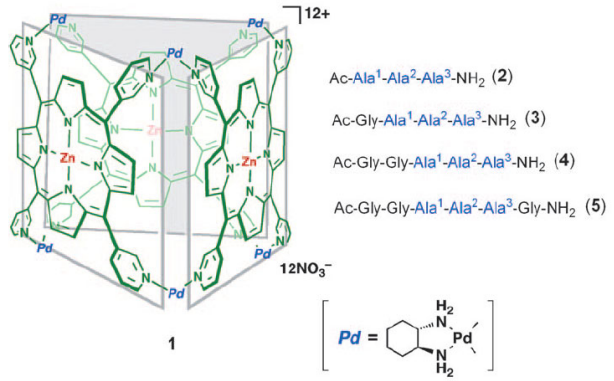

Figure 1. Self-assembled host **1** and alanine-rich tri- to hexapeptides **2**–**5**.

Results

The porphyrin-prism host **1** was prepared from self-assembly of zinc(II) tetrakis(3-pyridyl)porphyrin with [Pd(chxn)(NO_3)$_2$] (chxn=(*S*,*S*)-1,2-diaminocyclohexane) in aqueous solvents. The enclathration of peptides **2**–**5** was accomplished by simply mixing **1** (2.0 μmol) and the desired peptide (2.0–4.0 μmol) in D_2O (2.0 mL) at 70 °C for 3 h.

In all cases, single crystals suitable for crystallographic analysis were obtained by slow evaporation. The chiral Pd^{II} end cap ((*S*,*S*)-1,2-diaminocyclohexane) forces the inclusion complex to crystallize in a chiral space group, thus avoiding false symmetry issues and simplifying the crystallographic analysis of the entrapped chiral guests. The hydrogen-bonding distances determined from the crystal and NMR structure analysis are quite similar (*e.g.* 3.1 Å (**2**⊂**1**) and 3.4 Å (ethylenediamine **2**⊂**1'**), respectively), and thus we believe that the solid and solution-state structures of peptides **3**–**5** in the cavity should also be similar.

A hybrid 3_{10}-/4_{13}-helix conformation was formed by hexapeptide **5**. The crystal structure determined by synchrotron radiation at AR-NW2A (Figure 2) revealed that the central alanine sequences formed α-helices in both **4**⊂**1** and **5**⊂**1**, and 3_{10}-helix domains were found at the flexible termini. The crystallographic observations strongly suggest that rigid α–helix conformations are not favored at peptide termini and engenders the hypothesis that 3_{10}- and α–helix conformations exist in equilibrium in the peripheral regions of protein structures.

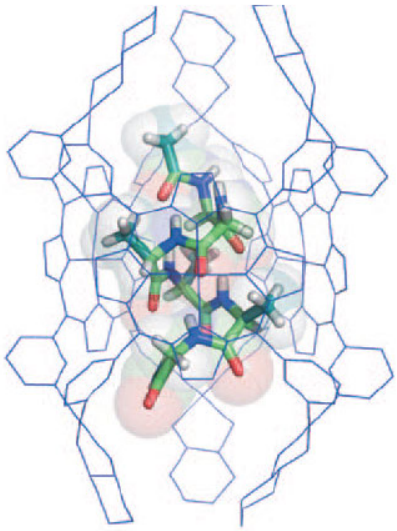

Figure 2. The X-ray crystal structure of **5**⊂**1**.

In summary, we have successfully obtained the crystal structures of short peptide fragments by confining them in the cavity of a self-assembled host. Short peptide fragments **3**–**5** adopted hybrid 3_{10}-/4_{13}-helix conformations rather than a pure α-helix conformation. The present study thus imparts useful insights into the conformational behavior of small biomolecules relevant to the folding processes of oligopeptides in hydrophobic protein pockets.

Reference

[1] Y. Hatakeyama *et al.*, *Angew. Chem. Int. Ed.* **48**, 8695 (2009).

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