Chemistry

NW2/2005G153

Sequence-Selective Recognition of Peptides within the Single Binding Pocket of a Self-Assembled Coordination Cage

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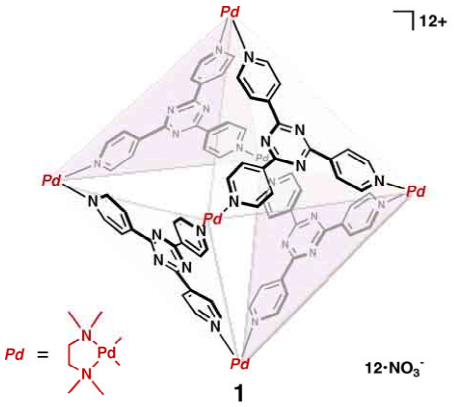
Introduction

Sequence-selective recognition of peptides is expected to be an essential process for the site-specific recognition of protein surfaces, which leads to the control of protein functions and to the understanding of biological events at protein surfaces such as protein-protein or protein-oligopeptide interactions. Although a few groups have reported artificial receptors for sequence-selective peptide recognition, the highly designed receptors are in their early stages. Here, we report that the single binding pocket of self-assembled coordination cage **1** can accommodate oligopeptides in a highly sequence-selective fashion. Having a large hydrophobic cavity, cage **1** binds as many as three amino acid residues. X-ray analyses reveal that the sequence-selective recognition is ascribed to cooperative multiple interactions between the residues and the cavity.[1]



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Results

We found that cage **1** bound Ac-Trp-Trp-Ala-NH_2 (**2**) very strongly (K_a >10^6 M^{-1}). Strong binding was specific to the Trp-Trp-Ala sequence because the binding of tripeptides possessing those same residues in different sequences, such as Ac-Trp-Ala-Trp-NH_2 (**3**) and Ac-Ala-Trp-Trp-NH_2 (**4**), was much less effective (K_a = 2.5 x 10^5 and 2.1 x 10^4 M^{-1}, respectively). Even singly mutated tripeptides, such as Ac-Trp-Trp-Gly-NH_2 (**5**) and Ac-Trp-Tyr-Ala-NH_2 (**6**), showed poorer affinity (K_a = 7.4 x 10^4 and 5.3 x 10^4 M^{-1}, respectively) although they have very similar aromatic-aromatic-aliphatic sequences. These results suggest that the two indole rings and the Ala methyl group in **2** should cooperatively interact with the cage in the **1**•**2** complex.

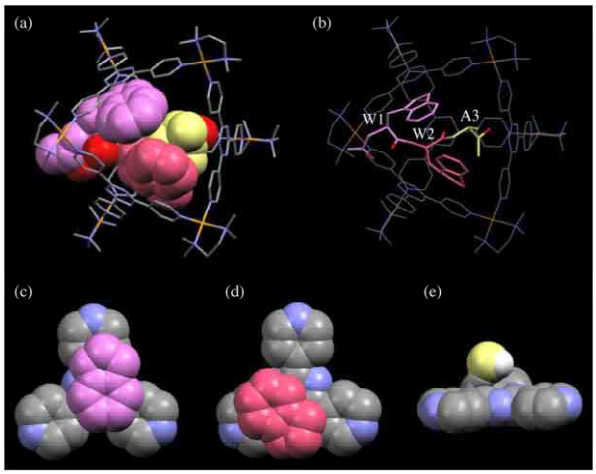

Figure1. Crystal structure of **1**•**2**. Peptide **2** in the cavity is represented by (a) space-filling and (b) cylindrical model. The π–π interactions of **1** with indole rings of (c) W1 and (d) W2. (e) The CH-π interaction between **1** and methyl group of A3.

In fact, the multiple interactions of the methyl and indole groups with the cage were revealed by X-ray crystallographic analysis. Single crystals were obtained after an aqueous solution of **1**•**2** complex stood at room temperature for 4 d. The diffraction data were collected by synchrotron X-ray irradiation. The crystallographic analysis showed that tripeptide **2** is fully encapsulated in the cavity of **1** (Figure 1a,b). As predicted, all residues interact very efficiently with cage **1**. Namely, two indole rings are stacked on the triazine ligand by π–π interaction (3.4-3.5 Å), while the Ala methyl group interacts with another ligand by CH-π contact (2.5 Å) (Figure 1c-e). Despite the enclathration within the restricted cavity, the peptide backbone is fixed in an extended conformation.

References

[1] S. Tashiro et. al. *J. Am. Chem. Soc.,* 127, 4546 (2005).

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