Chemistry

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Endohedral Peptide Coating of a Self-Assembled Spherical Complex to Generate Chirality-Confined Hollows

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Introduction

Enzyme pockets are chiral cavities consisting of amino acid residues, where specific molecular recognition and chemical reactions take place. Although there are many reports on the design and control of peptide 3D-structures, the artificial construction of chiral pockets has been never achieved. Herein peptide fragments are anchored to the interior of a self-assembled $M_{12}L_{24}$ nano-sized spherical complex to generate peptide-coated chiral cavities (Figure 1). In the way, we succeeded in coating the interior surface of the 4 nm shell with 24–96 amino acid residues. As the ligand synthesis is modular, we expect that the combinatorial replacement of peptide residues enable the artificial evolution of enzyme-like pockets.

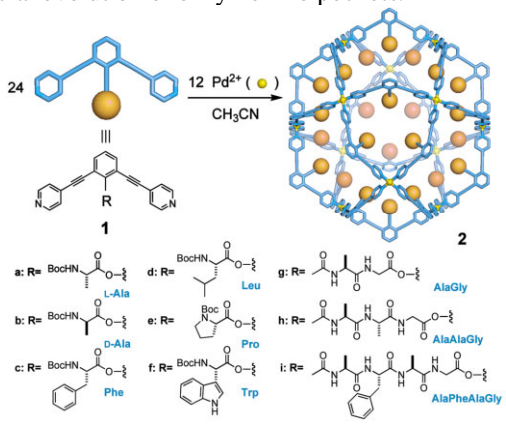

Figure 1. Self-assembly of endohedrally peptide-coated $M_{12}L_{24}$.

Results

When a mixture of **1a** and $Pd(CF_3SO_3)_2$ in acetonitrile-d_3 was heated at 50 °C for 4 h, the endohedrally functionalized $M_{12}L_{24}$ complex **2a** was quantitatively obtained as indicated by NMR and CSI-MS. Complexes **2b**-**i** were prepared in the same way. These complexes contain 24- (**2a**–**f**), 48- (**2g**), 72- (**2h**), and 96- (**2i**) amino acid residues, respectively. When the 5-residue peptide was introduced, the spherical complex was not formed as a single product, due to the size limitation of the cavity. These results reveal that the complex can contain up to ca. 100 amino acid residues, corresponding to small proteins in size and the number of amino acid residues.

The structure of complex **2a** was unambiguously determined by single crystal X-ray diffraction. Despite the severe disorder of solvent molecules and counterions, synchrotron X-ray irradiation using KEK AR-NW2 beamline with high flux and low divergence provided high quality data, from which the structure of $M_{12}L_{24}$ spherical complex with a diameter of 4.6 nm was revealed (Figure 2). The locations of the 24 L-alanine moieties on the interior surface were precisely determined. The positions of the *t*-Boc protection groups, however, could not be clearly observed due to disorder.

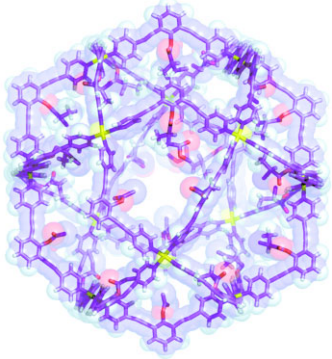

Figure 2. The X-ray crystal structure of the shell framework of **2a**. Counter ions and solvent molecules are omitted for clarity.

The accumulation of 24 asymmetrical amino acid moieties generates a chiral environment within the spherical shell. The intensity of the circular dichromism (CD) spectra of ligands **1a** (L-Ala) and **1b** (D-Ala) was very weak (Figure 3). However, complex **2a** showed thirty times higher Cotton effects in the absorptive region of the complex framework. Mirror image Cotton effects were exhibited for **2a** and **2b**, reflecting the absolute configurations of L- and D-alanine moieties. The chirality of 24-amino acids was transferred to the backbone of the spherical complex, resulting in twisting of the coordinated ligands in solution.

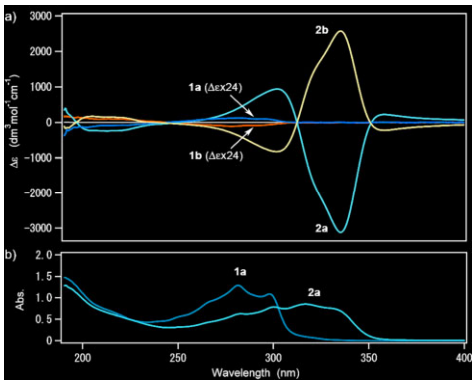

Figure 3. (a) CD and (b) UV spectra of ligand **1a** (L-Ala, 24 μM), **1b** (D-Ala, 24 μM) and complex **2a**, **b** (1 μM). The CD spectra of **la**, **b** was multiplied by a factor of 24 for comparison.

References

[1] K. Suzuki *et al.*, *J. Am. Chem. Soc.*, 129, 10652 (2007).

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