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Ni(II)-Mediated Self-Assembly of Artificial β -Dipeptides Forming a Macrocyclic Tetranuclear Complex with Interior Spaces for In-Line Molecular Arrangement

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Metal-mediated self-assembly has been recognized as an excellent strategy to build up well-defined molecular architectures with an isolated, functional nanospace.^{1,2} To date, a large number of excellent examples of self-assembled macrocyclic molecules have been reported.^{2–5} Internal spaces of these molecules have their unique shape and volume and thereby provide a variety of functions such as molecular recognition⁴ and specific chemical reactions.⁵ However, to construct more sophisticated molecular functions, systematically, chemically easy-to-modify building blocks are required. In this respect, our group has focused on biorelated molecular building blocks such as amino acids and nucleosides because they can be easily modified in a way that their structure, number, and sequence are controlled.⁶ For instance, amino acids that have a metal binding site at the side chains⁷ could provide functional oligopeptides bearing a repeated sequence of metal-ligand and amide functionalities. Therefore, metal-mediated assemblage of such functional building blocks would generate unique structural frameworks and spaces. Herein, we report a well-defined macrocyclic tetranuclear Ni(II) complex with four artificial β -dipeptides 1 (Figure 1). The unique twisted-boat structure allows the formation of interior spaces for in-line arrangement of water and anion molecules.

The β -dipeptide **1** consists of two artificial β -amino acids with a propanediamine ligand at the side chain, thereby providing two tridentate ligands with two amide carbonyl groups. The dipeptide **1** was prepared starting from N-protected 2,2bis(*tert*-butoxycarbonylaminomethyl)-3-phthalimidopropanoic acid⁸ as its trifluoroacetic acid salts. The subsequent coupling reaction of this building block was carried out under microwave irradiation to obtain the dipeptide **1** ·(CF₃CO₂H)₄ in 36% overall yield (for the details, see Supporting Information).

The reaction of dipeptide $1 \cdot (CF_3CO_2H)_4$ with Ni(ClO₄)₂ · 6H₂O in a 1:1 ratio in the presence of 4 equiv of diisopropylethylamine in EtOH at 50 °C for 3 h produced a pale purple powder, which was recrystallized from water to obtain Ni₄1₄(ClO₄)₈(H₂O)₁₀ in 38% yield as purple block crystals suitable for X-ray diffraction analysis.⁹ In the resulting molecular structure, four Ni(II) ions and four dipeptides 1 are connected in a head-to-tail manner. An N-terminal tridentate ligand of one dipeptide is connected with a C-terminal tridentate ligand of another dipeptide to complete an octahedral Ni(II) center, and the two oxygen donor atoms of their amide groups are placed in the *cis* position (Figure 1). The cyclic structure of the Ni(II)

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Figure 1. Schematic representation of the formation of a macrocyclic tetranuclear complex, Ni₄1₄(ClO₄)₈(H₂O)₁₀, from a β -dipeptide 1 and Ni(ClO₄)₂·6H₂O. Metal binding sites of the N-terminal and the C-terminal sides of the β -dipeptide 1 are colored blue and red, respectively. In the center circle, the coordination mode of the Ni(II) center is indicated. The figure in the circle shows a Λ -fac configuration.



Figure 2. (a) Molecular structure of $[Ni_41_4]^{8^+}$ with 50% thermal ellipsoids viewed from the side of the top groove. Only one enantiomer is shown: Λ - Δ - Λ - Δ for Ni(1)–Ni(2)–Ni(1')–Ni(2'). It is notable that the peptide direction from the N- to the C-terminal portions is counterclockwise in this view. The dashed lines represent hydrogen bonds. (b) An outline drawing showing a twisted-boat structure with a hole and two grooves. A dashed red circle and two gray half-cylinders represent a hole and two grooves, respectively.

complex has a crystallographically imposed C_2 symmetry with one-half of the molecule being in the asymmetric unit (Figure 2a). As shown in the conceptual diagram of the Ni(II) complex with a twisted-boat structure (Figure 2b), four Ni(II) centers are positioned at the apexes of a distorted tetrahedron. There are two crystallographically different Ni(II) centers, Ni(1) and Ni(2), due to different coordination bond lengths around each Ni(II) center (see Supporting Information), and each Ni(II) center adopts a different configuration (Λ -fac or Δ -fac).¹⁰ Therefore, this complex is chiral, and one set of enantiomeric tetranuclear Ni(II) complexes coexists in the crystal to form a racemate. When viewed from the top groove side of an enantiomer shown in Figure 2a, the direction of the peptide framework from the N- to the C-terminal portions is counter-

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Figure 3. Encapsulated H_2O and ClO_4^- molecules in the hole and the two grooves. (a) In-line arrangement of H₂O and ClO₄⁻ molecules along the central hole with a side view of the packing structure of the macrocyclic Ni(II) complex. Some $\mathrm{H_2O}$ and $\mathrm{ClO_4^-}$ molecules included in the two grooves are omitted for clarity. (b) In-line arrangement of H₂O and ClO₄ molecules within the top and bottom grooves. H₂O molecules are shown without hydrogen atoms.

clockwise. The distances of the neighboring Ni(II) ···· Ni(II) ions are 8.14 Å (Ni(1)-Ni(2)) and 7.90 Å (Ni(2)-Ni(1')). In the peptide framework, amide groups support the macrocyclic structure by six hydrogen bonds in the internal space of the macrocyclic structure in the Ni(II) complex (Figure 2a).

The uniquely folded, twisted-boat structure allows the space formation of two half-cylinder-shaped grooves and a central hole along the c axis with a diameter of ca. 2 Å within the Ni(II) complex, as drawn in Figure 2b. Four H₂O molecules and five ClO₄⁻ anions are encapsulated into these internal spaces. Of these included guest molecules, two H₂O and one ClO₄⁻ molecules are aligned in the order of H₂O-H₂O-ClO₄⁻ along the 2-fold axis through the central hole (Figure 3a).¹¹ The central H₂O molecule is doubly hydrogen bonded with the macrocyclic framework (Table S1). It is also notable that the central H₂O molecule is very close to the terminal H₂O molecule with an extremely short O····O distance of 2.58 Å, which is shorter than that seen in the I_h type of ice crystal (ca. 2.7 Å).¹² In the crystal packing structure, the holes of macrocyclic Ni(II) complexes are stacked on top of each other¹³ along the 2-fold axis to form a channel, and therefore, the encapsulated molecules $(2H_2O \text{ and } ClO_4^-)$ within the hole are repeatedly aligned to form a channel and the ClO₄⁻ anion is intermolecularly hydrogen bonded with one terminal H₂O molecule of the neighboring Ni(II) complex (Figure 3a). Such an in-line molecular arrangement of H2O and ClO4- molecules was also found in the top and bottom grooves, which are nearly vertical to the hole forming the channel (Figure 2b). In the top groove, one H₂O and two ClO_4^- molecules are aligned in the order of $ClO_4^--H_2O-ClO_4^-$, while in the bottom groove, two H_2O and three ClO_4^- molecules are aligned in the order of $ClO_4^--H_2O-ClO_4^--H_2O-ClO_4^-$. The terminal H₂O and ClO₄⁻ molecules in the central hole are identical to the central H₂O molecule in the top groove and the central ClO₄⁻ molecule in the bottom groove, respectively.

The electrospray ionization time-of-flight (ESI-TOF) mass spectrum of the macrocyclic Ni(II) complex in CH₃CN showed prominent signals of Ni₄ $\mathbf{1}_4$ species at m/z 474.1 ([Ni₄ $\mathbf{1}_4$ - $(ClO_4)_4]^{4+}$ and 665.0 ($[Ni_41_4(ClO_4)_5]^{3+}$) (Figure S8), indicating that the macrocyclic tetranuclear Ni(II) complex exists in solution.

In summary, we synthesized a macrocyclic tetranuclear Ni(II) complex of an artificial β -dipeptide 1 which possesses two sets of tridendate ligands. Its cyclic twisted-boat structure provides well-defined isolated spaces for in-line molecular arrangement of water and anion molecules. Such an approach would open a new way of a precise molecular arrangement within isolated spaces. In a preliminary study, we found that the β -dipeptide 1 forms a cyclic trinuclear Zn(II) complex. In addition to the type of metals, controlling the number, sequence, and structural frameworks of amino acid residues in the peptide ligand would develop new approaches to designable peptide-based molecular architectures with novel functions directed toward molecular recognition, transport, and transformation.

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Supporting Information Available: Experimental procedures, additional structural data, and spectral data of Ni₄1₄(ClO₄)₈(H₂O)₁₀ complex. This material is available free of charge via the Internet at http://pubs.acs.org.

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- (10) The assignment of the absolute configurations was determined based on the arrangement of the two sets of propanediamine units at each Ni(II) center.
- (11) In a preliminary study, the kind of counteranions (BF₄⁻, PF₆⁻, CF₃SO₃⁻) was not found to affect the macrocyclic structure. However, for instance, in the crystal which was obtained from a mixture of Ni₄1₄(ClO₄)₈(H₂O)₁₀ and NaBF4 salts in water, three H2O molecules were found aligned in the hole. The effects of counteranion will be reported elsewhere.
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