Molecular recognition by multiple metal coordination inside wavy-stacked macrocycles

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Most biological and synthetic receptors for small organic molecules employ a combination of relatively weak intermolecular interactions such as hydrogen bonds. A host compound that utilizes stronger yet reversible bonding in a synergistic manner could realize precise recognition, but the regulation and spatial arrangement of such reactive interaction moieties have been a challenge. Here, we show a multinuclear zinc complex synthesized from a macrocyclic ligand hexapap, which inwardly arranges labile metal coordination sites for external molecules. The metallomacrocycle forms a unique wavy-stacked structure upon binding a suitable length of dicarboxylic acids via multipoint coordination bonding. The saddle-shaped deformation and dimerization realize the differentiation of the interaction moieties, and change of guest-binding modes at specific metal coordination sites among the many present have been achieved utilizing acid/base as external stimuli.

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Precise recognition of small molecules plays a vital role in nature. It serves as a basis for sophisticated functions such as signal transduction. Molecular recognition in biological systems is usually realized by the combination of relatively weak intermolecular interactions, such as hydrogen bonds (typically 10–40 kJ/mol), aromatic–aromatic interactions (~5 kJ/mol), and van der Waals interactions (~1 kJ/mol). Many artificial synthetic receptors utilizing these interactions have already been developed, but they are still not optimized in terms of specificity. To achieve sophisticated recognition events, it is required to properly and three-dimensionally incorporate multiple interactions in a synergistic manner. It is required to properly and three-dimensionally incorporate multiple interactions in a synergistic manner could create a sophisticated artificial host. That is, a host that utilizes multiple coordination sites on the metal centers should be spatially arranged in the binding pocket. External small molecules bind to multiple metals in place of the exchangeable ligands. In this context, utilization of stronger and more directional interactions could be beneficial. Thus, in this study, we create a rigid macrocyclic ligand hexapap H₆, and embed the metals in its cavity, with their labile coordination sites directed toward the center of the pore.

**Fig. 1** Synthesis and characterization of hexapap ligand and Zn-hexapap. a Formation of an N,N,O-type tridentate ligand Hpap and its metal complex. b Synthesis of hexapap H₆ from the bifunctional monomer 2 by a one-pot reaction. c Chemical structure and schematic representation of a metallomacrocycle, Zn-hexapap [1Zn₆X₆], with inwardly arranged coordination sites. d–f 1H NMR spectra (600 MHz, 298 K). See b, c for the assignment of NMR signals. d 2 (CDCl₃). e H₆ (CDCl₃/CD₃OD = 10/1 (v/v)). f [1Zn₆(acac)₆] (CDCl₃/CD₃OD = 10/1 (v/v)). g A MALDI TOF mass spectrum of H₆ (positive, matrix: 2,5-dihydroxybenzoic acid). The simulated and observed isotope patterns of [H₆] are shown in the inset. h Absorbance spectra of H₆ (green) and [1Zn₆(acac)₆] (purple) and emission spectrum of [1Zn₆(acac)₆] (red, λₑₓ = 546 nm) (5 μM, CHCl₃/CH₃OH = 10/1 (v/v), 298 K, l = 1.0 cm)
The complexation of \( \text{H}_6\text{I} \) with \( \text{Zn}^{\text{II}} \) produces a hexanuclear complex, \( \text{Zn-hexapap [1Zn}_n\text{X}_m \] (X = exchangeable labile ligands). Interestingly, the dicarboxylic acids with suitable chain lengths induce the formation of a uniquely-shaped wavy-stacked dimer of the Zn-hexapap via multiple coordination bonds between the carboxylate groups and Zn. Although the monomeric Zn-hexapap \([1\text{Zn}_n\text{X}_m]\) has six chemically equivalent metal centers, the saddle-shaped deformation and dimerization of the macrocycles realize the differentiation of the Zn(pap) units. This desymmetrized dimeric macrocycle achieves the regulation and change of the guest-binding modes at specific metal coordination sites among the many available utilizing acid/base as external stimuli.

**Results**

**Synthesis of hexapap ligand and Zn-hexapap complex.** \( \text{H}_6\text{I} \) possesses six inward Hpap \((2\{\text{pyridin-2-ylmethylene}\text{amino}\}\text{phenol}) \) chelate-binding units\(^5, 18\) (Fig. 1a). Pap is a negatively-charged tridentate ligand. Upon binding of a metal, labile coordination sites not occupied by pap are available for guest binding. Meanwhile, the tridentate chelation of the metal is strong enough to prevent its removal by external guests.

Reversible imine bonds are often utilized for the construction of thermodynamically stable target products\(^19\text{–}21\), and most of them were constructed by mixing aldehyde and amine building blocks\(^22\text{–}24\). Here, \( \text{H}_6\text{I} \) was synthesized from a bifunctional monomer \( 3 \) possessing both o-aminophenol and 2-formylpyridine moieties (Fig. 1b). The compound 2, a derivative of \( 3 \), was designed whose formyl group was protected by dimethyl acetal to prevent spontaneous self-oligomerization\(^25\). \( 2 \) was prepared as an isolable cyclization precursor \((1\text{H nuclear magnetic resonance (NMR), Fig. 1d})\) (see Supplementary Figs. 1–10 for the synthesis of \( 2 \) and its synthetic intermediates).

The angle between the formyl group and the amino group of \( \text{H}_6\text{I} \) was about 120°. This geometrical feature realized the formation of \( \text{H}_6\text{I} \) as a cyclic hexamer (Fig. 1c). Changes in the chemical shifts of \( 1\text{H} \) NMR spectrum upon the complexation of Zn, and the \( 1\text{H} \) NMR signals of the complex were also not shifted depending on the concentrations \((0.15\text{–}1.2 \text{mM})\) (see Supplementary Figs. 12 and 13). These results indicated that stacking of the macrocycles did not occur under these conditions.

**Wavy-stacked dimer of Zn-hexapap with dicarboxylic acids.** Carboxylic acids were investigated as guest molecules in this study, for their ubiquity in nature and coordination ability of

![Image](image-url)

**Fig. 2** Binding of dicarboxylic acids by Zn-hexapap and the formation of the wavy-stacked dimer. a–i Interaction of dicarboxylic acids \( \text{H}_2\text{m} \)–\( \text{H}_2\text{m} \) and Zn-hexapap \([1\text{Zn}_n\text{acac}]_n \) (\( n = 6 \)). M(\( 1\text{H} \)) NMR, 600 MHz, CDCl\(_3/\text{CD}_3\text{OD} = 10/1 \)(v/v), 298 K. \( [1\text{Zn}_n\text{acac}]_n = 2.5 \text{mM} \).

- a Malonic acid \( \text{H}_2\text{m} (m = 1) \).
- b Succinic acid \( \text{H}_2\text{m} (m = 2) \).
- c Adipic acid \( \text{H}_2\text{m} (m = 4) \).
- d Pimelic acid \( \text{H}_2\text{m} (m = 5) \).
- e Sebacic acid \( \text{H}_2\text{m} (m = 6) \).
- f Azelaic acid \( \text{H}_2\text{m} (m = 7) \).
- g Suberic acid \( \text{H}_2\text{m} (m = 8) \).
- h Malonate \( \text{H}_2\text{m} (m = 9) \).
- i Pimelate \( \text{H}_2\text{m} (m = 10) \).

\( ^1\text{H} \) ROESY (rotating-frame Overhauser effect spectroscopy) NMR spectrum of the complex with two pimelates \( 4\text{e}^2\text{m} \), \([1\text{Zn}_2\text{acac}X_m]_2 \) (X = labile coordinating ligand) (600 MHz, CDCl\(_3/\text{CD}_3\text{OD} = 10/1 \)(v/v), 323 K). Yellow circles indicate ROE cross peaks between the top and bottom macrocycles.

- **k** Chemical structure of \([1\text{Zn}_2\text{acac}X_m]_2 \). Red arrows indicate the pairs of \( ^1\text{H} \)–\( ^1\text{H} \) between which the ROE cross peaks were observed (see Supplementary Fig. 18). See also Fig. 3d for the crystal structure of \([1\text{Zn}_2\text{acac}X_m]_2 \) colored in the same manner. Emissions from Zn-hexapap during UV irradiation \((365 \text{nm}) \) upon binding of a series of dicarboxylic acids \( \text{H}_2\text{m} \)–\( \text{H}_2\text{m} \) \((10 \mu\text{M}, \text{CHCl}_3/\text{CH}_3\text{OH} = 10/1 \)(v/v), 298 K).

- **m** A schematic representation of the recognition of dicarboxylic acids in the cavity of the wavy-stacked dimer of the Zn-hexapap.
their carboxylate groups to labile coordinating sites of metal centers. The recognition experiments of aliphatic dicarboxylic acids HOOC-(CH$_2$)$_m$-COOH ($m = 1–8$, 10) by Zn-hexapap [1Zn$_6$(acac)$_6$] are shown in Fig. 2. A series of $^1$H NMR spectra (Fig. 2a–i) suggest that only adipic acid H$_2$4d ($m = 4$) and pimelic acid H$_2$4e ($m = 5$) led to the formation of a single species. In other words, a clear dependence of the molecular length was observed in this coordination-driven recognition event. The formation of a certain host–guest complex was also supported by the change in emission, where the samples in which H$_2$4f was desymmetrized and six different pap moieties were present was recognized though multipoint coordinative interaction bonding with the metallomacrocycles. The two terminal carboxylate groups of 4e$^{2-}$ both bridged two Zn atoms. One of the Zn atoms belonged to the top macrocycle, while the other to the bottom one (Fig. 3a, d). All the Zn centers adopted a five-coordinate trigonal-bipyramidal geometry, but they can be categorized into three types in terms of the coordinating ligands at the inner exchangeable coordination sites (Fig. 3e). The first type of Zn (depicted in red in Fig. 3d, e) was coordinated by a carboxylate oxygen atom of 4e$^{2-}$ and a phenoxo oxygen atom of the pap$^-$. The coordination bond between the Zn (type1) and phenoxo oxygen bridged the two Zn-hexapap macrocycles. The second type (depicted in blue) was bound by another carboxylate oxygen atom of 4e$^{2-}$ and a Cl$^-$. The third type (depicted in green) was bound by a Cl$^-$ and a water. Thus, Zn (type 3) was free from the guest molecule 4e$^{2-}$ (Cl$^-$ probably derived from the decomposition of 1,1,2,2-tetrachloroethane used as the crystallization solvent. We assumed that the slow generation of Cl$^-$ helped to grow single crystals with good qualities). From the structural analysis described above, the following three main factors are considered to be the driving forces for the formation of the dimeric structure [1Zn$_{12}$4e$_n$X$_n$]: (i) Inter-macrocycle coordination bonds between the Zn (type 1) and phenoxo oxygen; (ii) Coordination of the carboxylate groups of 4e$^{2-}$ bridging two Zn atoms (types 1 and 2); and iii) π–π stacking between the hexapap aromatic frameworks.

The top and bottom macrocycles were in a different environment as the result of the binding of 4e$^{2-}$. The overall structure of [1Zn$_{12}$4e$_n$(H$_2$O)$_4$Cl$_8$] had a pseudo C$_2$ symmetry (Fig. 3d), which is consistent with the $^1$H NMR observation in the solution state. All the $^1$H NMR signals of [1Zn$_{12}$4e$_n$X$_n$] were successfully assigned based on the $^1$H–$^1$H COSY and $^1$H–$^1$H ROESY measurements (Fig. 2e, j, Supplementary Figs. 17, 18). Several characteristic ROE crosspeaks confirmed that the wavy...
Regulation of guest binding at specific coordination sites. In the wavy-stacked dimer of the Zn-hexapap, four coordination bonds were used to connect the two stacked macrocycles, while 20 coordination sites in total were unoccupied by the N,N-O-chelating moieties of the hexapap ligand and arranged inward (Fig. 3f). Despite possessing many possible coordinating sites, the addition of more than two molar amounts of the pimelic acids H$_4$4e against the wavy-stacked dimer [1:Zn$_{12}$X$_n$] did not change a binding mode, but the host-guest complex stably existed in a bimolecular recognition mode [1:Zn$_{12}$4eX$_n$] (see Supplementary Fig. 19). Interestingly, however, an acid stimulus (CF$_3$SO$_3$H) triggered further incorporation of two more 4e$^{2-}$'s and led to a tetramolecular recognition mode [1:Zn$_{12}$4eX$_n$] (Fig. 4a, Supplementary Fig. 20). The conversion and the resulting complex were examined by $^1$H NMR (Supplementary Figs. 20–22), ESI-TOF mass (Supplementary Fig. 23), and X-ray crystallographic analysis (vide infra). Three different [Zn(pap)X$_n$] moieties were observed in the $^1$H NMR spectrum of [1:Zn$_{12}$4eX$_n$], which suggested a change in the binding mode from [1:Zn$_{12}$4eX$_n$] (C$_2$ symmetry, six different [Zn(pap)X$_n$]) units (Supplementary Fig. 20). The molecular structure of [1:Zn$_{12}$4e(H$_2$O)$_4$Cl$_4$] was revealed by the X-ray crystallographic analysis (Fig. 4b, c and Supplementary Fig. 24; recrystallized from 1,1,2,2-tetrachloroethane/MeOH). The curvature of the wavy dimeric frameworks of [1:Zn$_{12}$X$_n$] was slightly less bent for the complex with four 4e$^{2-}$'s than the one with two 4e$^{2-}$'s, although the frameworks were basically the same for the two complexes (see Supplementary Fig. 25). The binding mode of the 4e$^{2-}$'s in the structure of [1:Zn$_{12}$4e(H$_2$O)$_4$Cl$_4$] showed an interesting difference compared to the complex with two 4e$^{2-}$'s (Fig. 4c). One carboxylate group of 4e$^{2-}$'s bridged two Zn atoms in a μ$_2$–η$_1$ coordination mode, while the carboxylate group at the other end of 4e$^{2-}$'s was bound to Zn in a monodentate mode (μ$_1$ mode). In terms of the Zn centers, there are three types of [Zn(pap)X$_n$] moieties as in the case with the complex with two 4e$^{2-}$'s. The entire structure of [1:Zn$_{12}$4e(H$_2$O)$_4$Cl$_4$] had an S$_4$ symmetry, which is consistent with the $^1$H NMR observation in solution (see Supplementary Fig. 20).

The acid-triggered binding of H$_4$4e was explained by the protonation and following release of HO$^-$ or MeO$^-$ coordinating to the [Zn(pap)] units. In solution, water and/or methanol molecules were bound to the labile coordination sites of [1:Zn$_{12}$4eX$_n$] (mainly water-bound complexes were observed in ESI-TOF mass and X-ray measurements). It is considered that the water/methanol molecules at the inner labile coordination sites initially exist as deprotonated HO$^-$/MeO$^-$ forms. The weak carboxylic acid H$_4$4e failed to protonate those ligands, but only the strong acid CF$_3$SO$_3$H was able to protonate them. This is consistent with the fact that the pK$_a$ values of H$_2$O bound to a Zn complex are in the range of 6–9, i.e., neutral pH. This protonation weakened the coordination strength of the H$_2$O/MeOH coordinating to Zn (type 2) in [1:Zn$_{12}$4eX$_n$], resulting in the replacement of them with the additional pimelates 4e$^{2-}$ to produce [1:Zn$_{12}$4eX$_n$]. Furthermore, the strategy to use acid/base stimuli to control the coordination strength can be applied to the release of guest molecules. That is, the addition of the Me$_4$NOH base to the solution of [1:Zn$_{12}$4eX$_n$] released the guest 4e$^{2-}$ and produced the guest-free Zn-hexapap [1Zn$_{12}$X$_n$] (Fig. 4a, Supplementary Fig. 20). Here, HO$^-$ or MeO$^-$ worked as relatively strong ligands under basic conditions, and dissociated the host–guest complex into [1Zn$_{12}$X$_n$], whose inner coordinating sites were occupied by HO$^-$/MeO$^-$. To summarize, the unique property of the wavy-stacked macrocycles Zn-hexapap to express multiple modes of molecular recognition via coordination bonds was demonstrated.

**Discussion**

To summarize, we have designed and synthesized a hexapap ligand H$_4$1, and its Zn complex Zn-hexapap [1Zn$_{12}$X$_n$] that...
The inner cavity in which labile coordination bonds are spatially arranged. Zn-hexapap recognized the dicarboxylic acid 4e–2 though multiple coordination bonding to form the unique wavy-stacked dimeric structure. Furthermore, the clear control and change of the binding modes of the guest was achieved, although the metallcocyclic dimer \([1\text{Zn}_6\text{X}_4]\) possesses as many as 20 available labile coordination sites. Thus, hexapap is shown to be an artificial host molecule that achieves the binding and the control of small molecules via multiple coordination bonds in solution. Metal complexes of the hexapap are promising control of small molecules via multiple coordination bonds.

**Methods**

**General.** Unless otherwise noted, solvents and reagents were purchased from TCI Co., Ltd., Wako Pure Chemical Industries, Ltd., Kanto Chemical Co., Inc., Nacalai Tesque, Inc. or Sigma-Aldrich Co., and used without further purification. THF was purified by Nikko Hansen Ultimate Solvent System 3S-TCN 1.

Measurements were performed at 298 K unless otherwise noted. \(^1\)H, \(^13\)C, and other 2D NMR spectra were recorded on a Bruker AVANCE III-600 (600 MHz) spectrometer or a Bruker AVANCE III-400 (400 MHz) spectrometer. Tetramethylsilane was used as an internal standard (0.00 ppm) for \(^1\)H and \(^13\)C NMR measurements when CDCl\(_3\) or a mixed solvent with CDCl\(_3\) was used as a solvent. MALDI-TOF mass data were recorded on an AB SCIEX TOF/TOF 5800 system. ESI-TOF mass data were recorded on a Waters SYNAPT G2 HDMS system or an AB SCIEX TriTOF 4600 system. Ultraviolet (UV) spectrometer and ESI-TOF-MS measurements. To the solution was added Me\(_4\)NOH for air-saturation. IR spectra were recorded on a JASCO FT/IR-480Plus spectrometer. Elemental analysis was performed on a Yanaco MT-6 analyzer with a Yanaco MT-6 analyzer. 

**General**

The inner cavity in which labile coordination bonds are spatially arranged. Zn-hexapap recognized the dicarboxylic acid 4e–2 though multiple coordination bonding to form the unique wavy-stacked dimeric structure. Furthermore, the clear control and change of the binding modes of the guest was achieved, although the metallcocyclic dimer \([1\text{Zn}_6\text{X}_4]\) possesses as many as 20 available labile coordination sites. Thus, hexapap is shown to be an artificial host molecule that achieves the binding and the control of small molecules via multiple coordination bonds in solution. Metal complexes of the hexapap are promising control of small molecules via multiple coordination bonds.

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**Control of binding of a dicarboxylic acid by acid/base stimulus.** Experimental procedure (Fig. 4a, Supplementary Fig. 20): Hexapap \(\text{H}_6\text{L}\) (1.96 mg, 1.29 \(\mu\)mol, 1.0 eq.) was weighed in an NMR tube. To the tube were added Zn(acac)\(_2\) (2.13 mg, 8.08 \(\mu\)mol, 6.7 eq.) in a CDCl\(_3\)/CD\(_3\)OD/CD\(_2\)Cl\(_2\)/CH\(_2\)Cl\(_2\) (1:10/1 mixed solvent (550 \(\mu\)l) and pimelic acid \(\text{H}_2\text{E}\) (2.6 \(\mu\)mol, 2 eq.) in a CDCl\(_3\)/CD\(_3\)OD/CD\(_2\)Cl\(_2\)/CH\(_2\)Cl\(_2\) (10/1/1 mixed solvent (6.0 \(\mu\)l)). The mixture was stirred at 55 °C for 2 days. The solution was filtered through a membrane filter, and to the filtrate was diffused the vapor of isopentane at 4°C. The resultant precipitate was collected by filtration and dried to yield a purple solid (31.9 mg). The obtained complex \(\text{Zn}_6\text{H}_4\text{L}_4\text{E}_4\text{Cl}_4\text{C}_4\text{H}_6\text{Cl}_4\) was neutralized with sat. NaHCO\(_3\) aq. (5.0 mL), and the precipitation was collected by filtration. The solid was washed with H\(_2\)O, CH\(_3\)CN, and MeOH, and dried in vacuo to give \(\text{H}_6\text{L}_4\text{E}_4\text{Cl}_4\text{C}_4\text{H}_6\text{Cl}_4\) (7.9 mg, 49 \(\mu\)mol, 49 \(\mu\)mol, 1 eq.). The mixture was stirred at 55 °C for 2 days. The reaction mixture was heated at 50 °C for 3.5 h to produce \([1\text{Zn}_6\text{E}_4\text{X}_4\text{L}_4]\). To the solution was added CF\(_3\)SO\(_2\)H (4.0 \(\mu\)mol, 3 eq.) for \(\text{H}_6\text{L}\) in a CDCl\(_3\)/CD\(_3\)OD/CD\(_2\)Cl\(_2\)/CH\(_2\)Cl\(_2\) (10/1 mixed solvent (6.0 \(\mu\)l)). The conversion of the host–guest complexes from \([1\text{Zn}_6\text{E}_4\text{X}_4\text{L}_4]\) to \([1\text{Zn}_6\text{E}_4\text{X}_4\text{L}_4]\) was characterized by \(^1\)H NMR and ESI-TOF-MS measurements. The solution was added Me\(_2\)NOH•\(\text{H}_2\text{O}\) (18.1 \(\mu\)l, 14 eq. for \(\text{H}_6\text{L}\) in CDCl\(_3\) (28 \(\mu\)l), which released the host-guest complex free of \(\text{Zn}_6\text{H}_4\text{L}_4\text{E}_4\text{Cl}_4\text{C}_4\text{H}_6\text{Cl}_4\). The control data up to 0.9 \(\AA\) was used for the structure refinement.

**Crystal data** for [1\text{Zn}_6\text{E}_4\text{X}_4\text{L}_4\text{Cl}_4\text{H}_6\text{Cl}_4] • 2\text{CH}_2\text{Cl}_2.

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Author contributions
T. Nakamura and T. Nabeshima conceived the project. T. Nakamura and Y.K. designed and analyzed the experiments. Y.K. carried out the experimental work. E.N. performed X-ray measurement and analysis. T. Nakamura and T. Nabeshima conceived the project. T. Nakamura and T. Nabeshima conceived the project. T. Nakamura and T. Nabeshima conceived the project.

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