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Self-assembly and binding properties of a metallomacrocycle having two interactive binding subcavities†

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A metallomacrocycle containing two topologically discrete binding subcavities is self-assembled and shows a positive homotropic cooperative binding behavior.

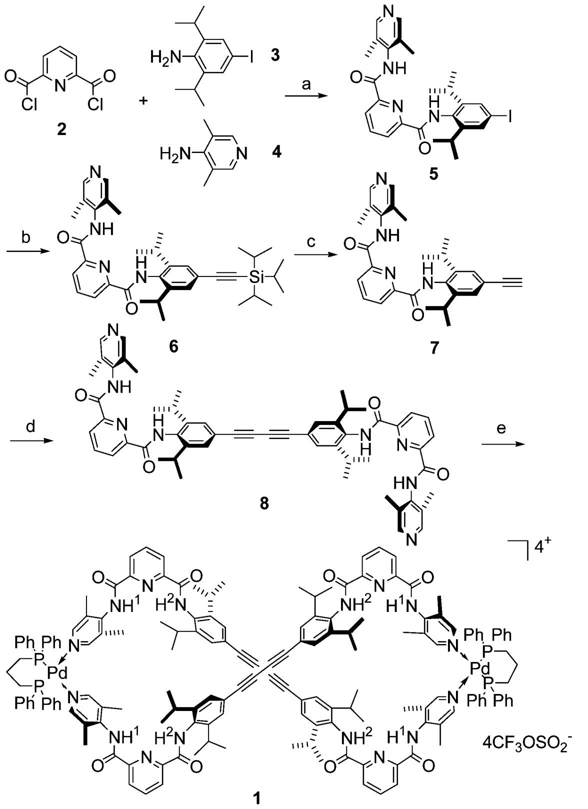
A large number of the coordinate bond-mediated macrocycles such as triangles, squares, rectangles and higher polygons have been prepared in the last decade.[1] These metallomacrocycles have rigid cavities of single binding domain that potentially accommodate small molecules.[2] Herein we report a new class of the metallomacrocycle **1** that folds to generate two homotropic binding subcavities and therefore gives an opportunity to investigate allosteric binding events.[3] On the guest binding, two identical subcavities of **1** strongly interact with each other and show a positive homotropic cooperativity.

The ligand **8** designed here consists of three functional parts; the pyridyl end for metal coordination, the pyridine-dicarboxamido corner for hydrogen bonding site, and the butadiynyl unit for the connection. Especially, the butadiynyl unit in the middle has been chosen to minimize possible steric congestion around the crossing point of two ligand strands on the self-assembly of the metallomacrocycle. Furthermore, its rigidity prevents the formation of mononuclear macrocycles by 1 : 1 (ligand : metal) assembly. The synthesis of **8** is outlined in Scheme 1. Reaction of **8** with the metallic moiety Pd(dppp)OTf$_2$[4] provided the corresponding metallomacrocycle **1** in 95% isolated yield.

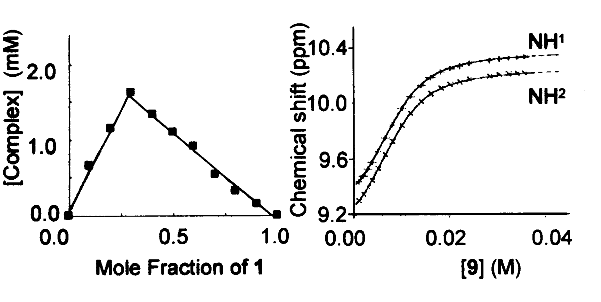
Elemental analysis was consistent with the molecular formula of **1**. The ^{1}H NMR signal for the terminal pyridines was downfield shifted by 0.3 ppm relative to that of free ligand **8**, as expected on the coordination of the pyridyl nitrogen to the Pd(II) center. Furthermore, the ^{1}H NMR spectra of **1** were found to be concentration-independent over a wide range of 0.5–20 mM, suggesting that no aggregation or dissociation occurs. The mass spectral analysis provided definitive evidence for the formation of **1**. For example, the ESI-mass spectrum of **1** in 1 : 1 CHCl$_3$–CH$_3$CN showed characteristic peaks of [M − 2OTf]$^{2+}$, [M − 3OTf]$^{3+}$ and [M − 4OTf]$^{4+}$ at m/z = 1574 (100%), 1000 (65%) and 712 (70%), respectively. The observed isotope distribution patterns of the fragments are consistent with the calculated ones based on the dinuclear macrocycle. The molecular weight of **1** in solution was measured by vapor pressure osmometry (VPO)[5] and found to be 3650 ± 250 in the range of concentrations between 3.6 and 13 g kg^{-1} (sample/CH$_2$Cl$_2$), which is very close to the calculated one (3448 for **1**).

Despite being a monocyclic compound, **1** is designed to possess two topologically discrete binding subcavities, like giant porphyrinoids.[6] Consequently, each subcavity can accommodate in a cooperative manner a guest molecule with complementary size, shape and functionality.[7]

On the basis of computer modeling[8] and our previous studies,[9] *N*,*N*,*N*′,*N*′-tetramethylterephthalamide (**9**) was chosen as the guest molecule. Job's plots[10] confirmed 1 : 2 (**1** : **9**) stoichiometry of the complex, showing the maximal complex formation at ~0.33 mol fraction of the metallomacrocycle **1** (Fig. 1a) in 3% (v/v) CD$_3$CN–CDCl$_3$. The ESI-mass experiments also support the formation of 1 : 2 (**1** : **9**) complex. For example, in 3% (v/v) CH$_3$CN–CHCl$_3$, the ESI-mass spectrum of **1** in the presence of excess **9** (~10 equiv) showed characteristic peaks corresponding to 1 : 2 complex; [MG$_2$ −



Scheme 1 *Reagents and conditions*: (a) *i*-Pr$_2$NEt, CH$_2$Cl$_2$, 0 °C to rt (65%); (b) PPh$_3$, CuI, triisopropylsilylacetylene, Pd(dba)$_2$, THF, Et$_3$N, 60–70 °C (85%); (c) Bu$_4$NF, THF, H$_2$O, 70–72 °C (85%); (d) Cu(OAc)$_2$, pyridine, 60–65 °C (85%); (e) Pd(dppp)OTf$_2$, CH$_2$Cl$_2$, rt (95%).



(a) (b)

Fig. 1 (a) Job's plot between metallomacrocycle **1** (NH^1) and guest **9**. (b) ^{1}H NMR titration plots: Chemical shift changes (×) of NH^1 and NH^2 in **1** on the gradual increase of **9** in 3% CD$_3$CN–CDCl$_3$. Solid lines are theoretical ones generated by HOSTEST program.[12]

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† Electronic supplementary information (ESI) available: synthesis, ESI-mass data, binding studies, concentration-dependent ^{1}H NMR spectra, modeling structure and VPO experiments of **1**. See http://www.rsc.org/suppdata/cc/b3/b306497b/

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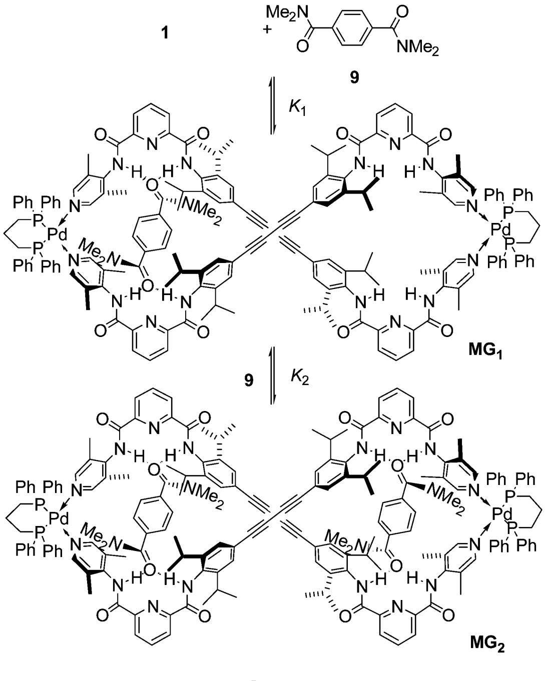
2OTf]$^{2+}$, [MG$_2$ − 3OTf]$^{3+}$ and [MG$_2$ − 4OTf]$^{4+}$ at m/z = 1794 (7%), 1146 (25%) and 823 (32%), respectively.[11]

To determine the binding affinities, the ^{1}H NMR titration experiments were performed in 3% (v/v) $CD_3CN–CDCl_3$ at 23 ± 1 °C, and time-averaged resonances for the free and the complexed species were observed under the titration conditions. As the guest **9** was added, two NH signals of **1** were gradually downfield shifted from 9.44 and 9.31 ppm to 10.35 and 10.22 ppm (Fig. 1b), indicative of hydrogen bond formation. In contrast, the chemical shift changes were negligible ($\Delta\delta < 0.1$ ppm) when a monoamide, *N*,*N*-dimethylbenzamide, was added under the same conditions. It is also worthwhile noting that the aryl signal of the bound **9** was considerably upfield-shifted ($\Delta\delta > 1.0$ ppm) relative to that of the free **9**. These observations are consistent with the proposed structure of the complex shown in Scheme 2, where **9** is diagonally located inside the binding subcavities by the formation of four hydrogen bonds.

The titration curves were slightly sigmoid in the initial stage and analyzed with the HOSTEST program[12] of a 1 : 2 (host : guest) binding isotherm (Fig. 1b). Both titration curves from NH^1 and NH^2 gave identical association constants within experimental error (< 5%), indicating that two NH's are participated in the same binding event. The macroscopic association constants of K_1 (= [**MG$_1$**]/[**1**][**9**]) and K_2 (= [**MG$_2$**]/[**MG$_1$**][**9**]) were found to be 180 ± 5 M^{-1} and 450 ± 20 M^{-1}, respectively.[13] Considering the relationship of $K_2 = 1/4\ K_1$ for noncooperative binding,[10] the magnitude of the association constants obtained here reflects a high positive cooperativity between two binding sites. Hill plots[10] also support the positive cooperative bindings. The Hill coefficient h was determined to be approximately 1.8 for this system. One plausible explanation for this positive cooperativity is that the first **9** binding to one subcavity possibly optimizes the distance between two diagonally positioned pyridinedicarboxamide units in the other subcavity to form stronger hydrogen bonds with the second **9**.



Scheme 2

In conclusion, the metallomacrocycle having two interactive binding sites has been prepared for the first time by the coordination-mediated self-assembly. The macrocycle shows high homotropic cooperativity and is considered to be a new type of artificial homotropic allosteric model.

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