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# Self-assembly and characterization of a giant metallocycle

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**Abstract**—A giant, 100-membered metallocycle **3** was prepared via coordination bond-based self-assembly from W-shaped ligand **9** and a palladium complex. Metallocycle **3** may create three topologically discrete subcavities, thus capable of binding up to three molecules of a diamide guest by hydrogen-bonding interactions. Elemental analysis, $^1$H NMR, and the ESI-mass spectra, and vapor pressure osmometry (VPO) data were all consistent with the structure of **3**. *N*,*N*,*N′*,*N′*-tetramethylterephthalamide **G** was used as a guest for the binding study, and ESI-mass spectrum clearly displayed a characteristic, intense peak at *m*/*z* 1542 (41%), attributed to the fragment $[\mathbf{3}\cdot\mathbf{G}_3\text{-}3CF_3SO_3]^{3+}$ of 1:3 (host/guest) complex. The $^1$H NMR titration experiments gave association constants of 2300 ± 300 and 1200 ± 200 $M^{-1}$ in $CDCl_3$ at 25 °C for two identical outer cavities, with weak positive cooperativity (Hill coefficient $h = 1.3$).

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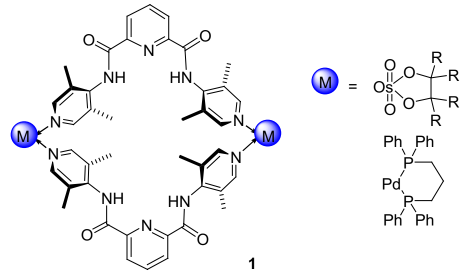
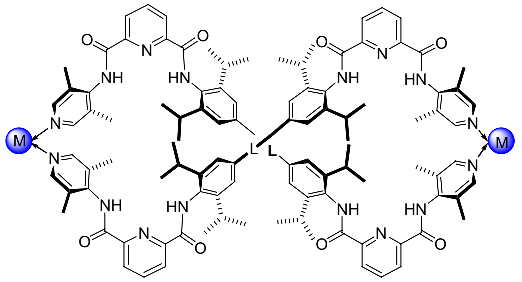
Reversible coordinative bonds between transition metals and ligands have been widely used for self-assembly of discrete supramolecular entities such as molecular squares, polygons, and cages under thermodynamic conditions over the past decade.[1] Several transition metals have been employed for this purpose, and Pd(II) and Pt(II) have been proven to be highly versatile because of reasonable strength of the coordination bonds and of their suitability in both organic and aqueous solutions. In early days, researches in this field were mainly focused on the creation of two- or three-dimensional structures, not available by conventional covalent synthesis, but recently it has shifted to the construction of more functional entities that can serve as artificial receptors and that may have potentials as molecular materials, machines, and devices.[2]

We previously described self-assembly of metallocycles **1** and **2** that contain hydrogen-bonding sites inside the cavities, thus functioning as artificial receptors for organic molecules with complementary sizes, shapes, and functional groups. For example, macrocycle **1** binds strongly and selectively terephthalamide or adipamide derivatives by hydrogen-bonding interactions in solution.[3] More recently, we reported the self-assembly of metallocycle **2**, which folded to generate two binding sites using S-shaped bispyridyl ligands and a palladium compound.[4] Metallocycle **2** can bind two molecules of a diamide guest, one in each cavity, with a positive homotropic cooperative manner, and it can therefore be considered as a new kind of artificial allosteric model.[5]

Self-assembly of receptors that have well-defined, multiple binding domains are extremely challenging and only a few examples are known to date.[5b,6] Herein, we describe the self-assembly and binding properties of a



**1**



**2**

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giant metallocycle **3**, a 100-membered monocycle, that can generate three topologically discrete subcavities. Each of them possesses inside four amido NHs, and therefore **3** can bind up to three molecules of a guest by hydrogen-bonding interactions.

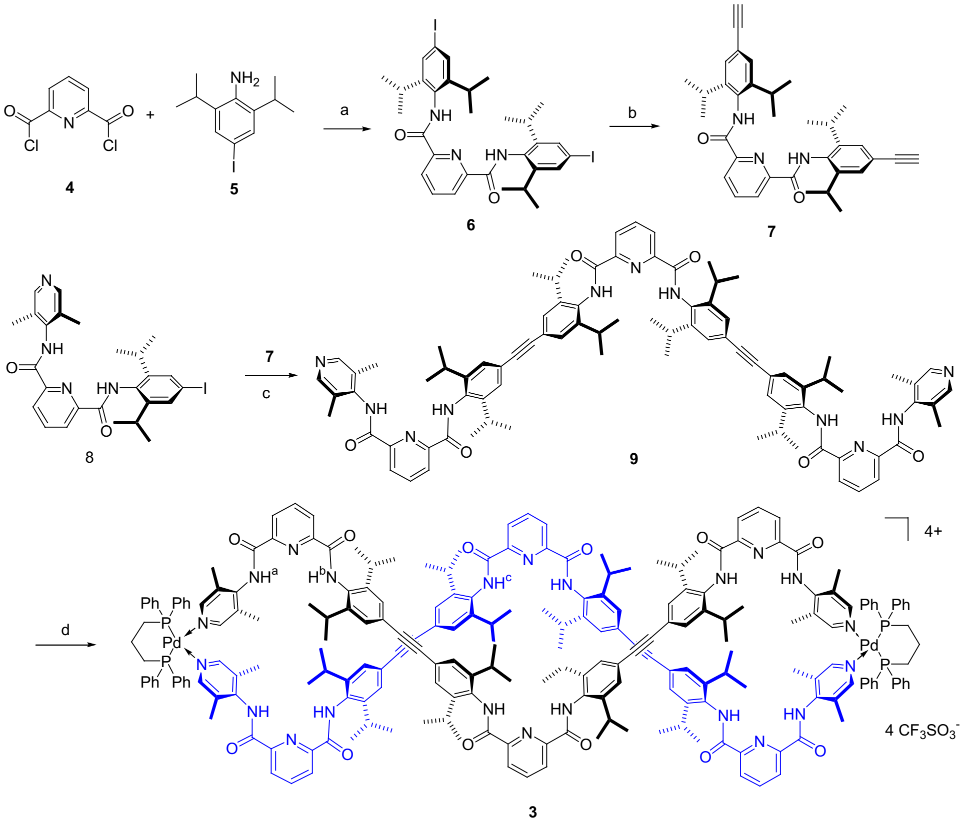
Syntheses of metallocycle **3** are summarized in Scheme 1. A W-shaped ligand **9** consists of three pyridine-2,6-carboxamide units, which are connected with ethynyl linkers by palladium-catalyzed reaction[7] of compounds **7** and **8**.[4] The ethynyl group has been chosen as a linker to minimize steric crowding around crossing points of two ligand strands on the formation of metallocycle **3**.

In addition, the methyl and isopropyl substituents on the aryl rings greatly increase the solubility of **3**, otherwise insoluble, in less competitive solvents such as $CH_2Cl_2$ and $CHCl_3$. Ligand **9** smoothly self-assembled into metallocycle **3** in the presence of a palladium complex $Pd(dppp)OTf_2$[8] in 10% (v/v) $CH_3CN/CHCl_3$ at room temperature. The reaction proceeded quantitatively within 30 min but the isolated yield was 91%. It is worthwhile noting that presence of $CH_3CN$ (5–10%) is critical for clean reaction, otherwise yielding a complicated mixture.

Elemental analyses, NMR and ESI-mass spectra, and vapor pressure osmometry (VPO) experiments support the structure of **3**, a dinuclear metallocycle resulting from 2:2 (ligand/metal) assembly. Elemental analysis and $^1H$ NMR integration indicate a 1:1 molar composition of the ligand and metal components. The pyridyl C–H signals at both ends are downfield shifted ($\delta = 0.22$ ppm) in the $^1H$ NMR spectroscopy relative to free ligand **9**, as expected on the coordination of the pyridyl nitrogen on the $Pd^{II}$ center. The mass spectrum of **3** in 50% (v/v) $CH_3CN/CHCl_3$ shows the fragments of $[\mathbf{3}{-}3CF_3SO_3]^{3+}$ (*m*/*z* 1321, 4%) and $[\mathbf{3}{-}4CF_3SO_3]^{4+}$ (*m*/*z* 954, 15%), along with the fragments corresponding to its complexes (Table 1) in the presence of *N*,*N*,*N*′,*N*′-tetramethylterephthalamide (**G**) as a guest. In addition, the VPO experiment[9] with **3** in $CHCl_3$ (benzil as a standard, 40 °C) gave a molecular weight of 4430 ± 620 in the range of concentrations between 11 and 29 $g\,kg^{-1}$

**Table 1.** ESI-mass data of **3** in the presence of excess **G** (~10 equiv) in 50% (v/v) $CH_3CN/CHCl_3$

| Complex | Fragment | *m*/*z* (intensity (%)) |
|---|---|---|
| $\mathbf{3}{\cdot}\mathbf{G}_3$ (1:3 complex) | $[\mathbf{3}{\cdot}G_3\text{-}3CF_3SO_3]^{3+}$ | 1542 (41) |
| $\mathbf{3}{\cdot}\mathbf{G}_2$ (1:2 complex) | $[\mathbf{3}{\cdot}G_2\text{-}2CF_3SO_3]^{2+}$ | 2277 (20) |
| | $[\mathbf{3}{\cdot}G_2\text{-}3CF_3SO_3]^{3+}$ | 1468 (49) |
| | $[\mathbf{3}{\cdot}G_2\text{-}4CF_3SO_3]^{4+}$ | 1064 (27) |
| $\mathbf{3}{\cdot}\mathbf{G}_1$ (1:1 complex) | $[\mathbf{3}{\cdot}G_1\text{-}3CF_3SO_3]^{3+}$ | 1394 (18) |
| | $[\mathbf{3}{\cdot}G_1\text{-}4CF_3SO_3]^{4+}$ | 1008 (13) |
| **3** (unbound) | $[\mathbf{3}\text{-}3CF_3SO_3]^{3+}$ | 1321 (4) |
| | $[\mathbf{3}\text{-}4CF_3SO_3]^{4+}$ | 954 (15) |



**Scheme 1.** Synthesis of metallocycle **3**. Reagents and conditions: (a) *i*-$Pr_2NEt$, $CH_2Cl_2$, 0 °C to room temperature (97%); (b) $Pd(PPh_3)_2Cl_2$, CuI, triisopropylsilylethyne, THF, $Et_3N$, 60–65 °C (75%), then $Bu_4NF$, THF, 50–60 °C (97%); (c) $Pd(PPh_3)_4$, CuI, $Et_3N$, THF, 60–65 °C (64%); (d) $Pd(dppp)OTf_2$, 10% $CH_3CN/CHCl_3$, room temperature (91%).

(sample/$CHCl_3$), close to the calculated one (4415.4) for **3**.

The energy-minimized structure[10] of **3** presents three topologically discrete subcavities[11] resulting from zigzag folding. Each of them contains four conversing NH groups capable of forming hydrogen bonds with an appropriate dicarbonyl guest such as *N*,*N*,*N*′,*N*′-tetramethylterephthalamide (**G**). The binding property of **3** with **G** was first revealed with ESI-mass spectrometry. The mass spectrum was taken with a mixture of **3** and excess **G** (~10 equiv) in 50% $CH_3CN/CHCl_3$ and gave a characteristic, intense peak at *m*/*z* 1542 which is attributed to the fragment $[\mathbf{3}\cdot\mathbf{G}_3\text{-}3CF_3SO_3]^{3+}$ of the 1:3 complex. In addition, the fragments corresponding to the 1:2 complex $\mathbf{3}\cdot\mathbf{G}_2$ and the 1:1 complex $\mathbf{3}\cdot\mathbf{G}_1$ are also seen with reasonably strong intensities as summarized in Table 1. This result implies that metallocycle **3** can bind three molecules of the guest **G** in the gas phase. It should be noted that the observed isotopic distributions for all the fragments shown in Table 1, regardless of stoichiometries of the complexes, are in accordance with the theoretical ones calculated on the basis of metallocycle **3**. (see Supplementary Material).

The binding properties in solution between **3** and **G** were investigated in the $^1H$ NMR spectroscopy. In metallocycle **3**, two cavities at both ends are identical but one in the middle is different. As a result, **3** shows three different $^1H$ NMR signals for amide protons, $NH^a$, $NH^b$ and $NH^c$. Addition of **G** to a $CDCl_3$ solution of **3** induced all three NH signals downfield shifted, but magnitudes of the chemical shift changes were different. For example, when **G** (5 mM) was added in a small portion to a solution of **3** (0.5 mM) at 25 °C, the $NH^a$ and $NH^b$ signals in the outer cavities were gradually shifted from 9.00 and 8.73 ppm to 10.32 and 10.18 ppm, respectively (see Fig. 1). Under the same conditions, the chemical shift change in the inner cavity $NH^c$ was much smaller, from 8.88 to 9.03 ppm, implying that **G** binds much more weakly to the inner cavity than to the outer cavities. The reduced binding affinity of the inner cavity may be attributed to two factors, steric effects and hydrogen donor ability. That is, the inner cavity is surrounded by four bulky isopropyl groups and thus sterically more hindered, compared to the outer cavities bearing two methyl and two isopropyl substituents. Furthermore, the transition metal coordination on the terminal pyridines increases the hydrogen donor ability of the amide $NH^a$ protons in the outer cavities.

The association constants for two outer cavities were determined by nonlinear curve fitting methods using the HOSTEST program developed by Wilcox,[12] and were found to be 2300 ± 300 and 1200 ± 200 $M^{-1}$ for $K_1$ ($=[\mathbf{3}\cdot\mathbf{G}_1]/[\mathbf{3}][\mathbf{G}]$) and $K_2$ ($=[\mathbf{3}\cdot\mathbf{G}_2]/[\mathbf{3}\cdot\mathbf{G}_1][\mathbf{G}]$), respectively. Considering the relationship of $K_2 = 1/4K_1$ for non-cooperative binding, these values reflect slightly positive cooperativity, which was confirmed by the Hill coefficient $h = 1.3$.[13] In addition, Job's plots[13] also support a 1:2 (**3**/**G**) binding mode, showing the highest concentration of the complex at approximately 0.33 mol fraction of **3** in $CDCl_3$ (see Fig. 1, inset). On the other hand, the chemical shift changes of the inner cavity $NH^c$ are too small ($\Delta\delta = 0.15$ ppm) to determine reliably the association constant ($K_a < 20$ $M^{-1}$).

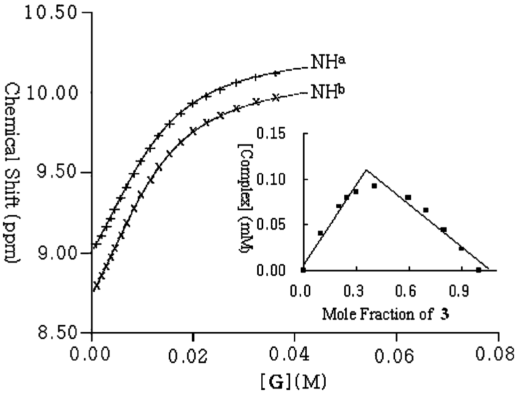


**Figure 1.** $^1H$ NMR titration curves plotting NH chemical shift changes of **3** by increasing [**G**] and Job plot (inset) showing the maximum complexation at ~0.34 mol fraction of **3**.

In conclusion, it has been demonstrated that the self-assembly based on coordination bonds is highly efficient for the preparation of a giant metallocycle with multiple polar binding sites. The binding studies have proved that the metallocycle binds up to three molecule of a diamide guest, one to each cavity, by hydrogen-bonding interactions.

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## Supplementary data

Synthesis, binding studies, VPO and ESI-mass experiments of metallocycle **3**. Supplementary data associated with this article can be found, in the online version, at doi:10.1016/j.tetlet.2005.02.048.

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