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Synthesis and binding properties of a macrocycle with two binding subcavities

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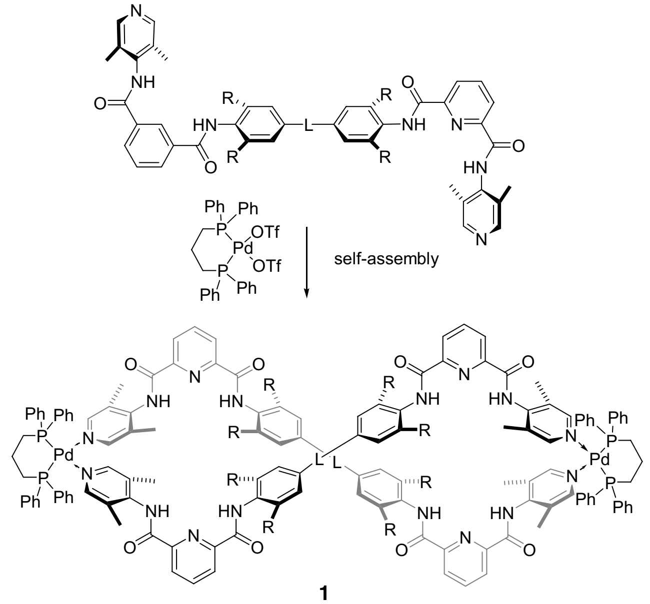
Abstract—A large, covalent macrocycle that can be served as an artificial allosteric model was prepared in a reasonable yield (36%) through the template-directed synthesis. The macrocycle contains two topologically discrete subcavities, each of which consists of four amide NHs of pyridine-2,6-dicarboxamide units. The macrocycle strongly binds two molecules of *N*,*N*,*N*′,*N*′-tetramethylterephthalamide in positive cooperative manner by hydrogen-bonding interactions. The association constants were calculated to be $K_1 = 1480 \pm 90$ and $K_2 = 5580 \pm 150\ \mathrm{M}^{-1}$ with the Hill coefficient (h) of 1.6 at 25 °C in $CDCl_3$.

The design and synthesis of an artificial receptor is at the heart of supramolecular chemistry to understand fundamental principles of molecular recognition. The receptor needs to have a geometrically well-defined binding cavity of complementary size, shape and functional group to a guest. In particular, the receptor that contains multiple binding cavities has attracted much attention because it provides an opportunity not only to study allosteric phenomena frequently found in the biological system, but also to create artificial counterparts capable of nonlinear amplification of binding affinities, reporting signals and catalytic activities. A large number of allosteric models have been developed for the last two decades,[1] but there are a limited number of artificial receptors that show positive homotropic cooperativity on the binding event.[2]

Utilizing coordination bond-driven self-assembly, we previously described the preparation of metallocycles **1** from S-shaped bispyridyl ligands and a palladium compound (Scheme 1).[3] The metallocycles fold to generate two binding subcavities, thus binding two molecules of a diamide guest by hydrogen-bonding interactions in a positive homotropic cooperative manner.The Hill coefficients (h), a measure of the cooperativity, depend on the nature of the linkers (L) in between two cavities, ranging from 1.4 to 1.8. We extended the self-assembly approach to prepare even larger metallocycle containing three binding subcavities.[4]



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Scheme 1. Coordination-driven self-assembly of metallocycles containing two binding subcavities.

Despite a great advantage in the synthesis, these metallocycles are kinetically and thermodynamically labile owing to the presence of weak covalent bonds, which

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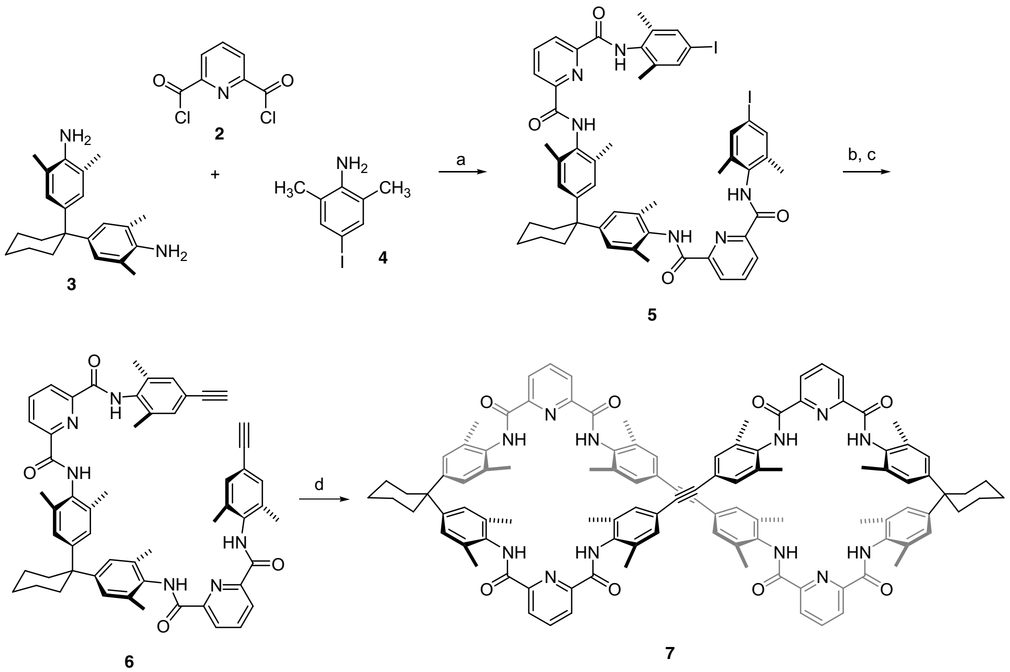

Scheme 2. Synthesis of macrocycle **7**. Reagents and conditions: (a) *i*-Pr_2NEt, CH_2Cl_2, 0 °C to room temperature (75%); (b) $Pd(PPh_3)_2Cl_2$, CuI, triisopropylsilylethyne, THF, Et_3N, 60–65 °C (85%); (c) Bu_4NF, THF, 50–60 °C (97%); (d) **5**, *N*,*N*,*N*′,*N*′-tetramethylterephthalamide (10 equiv), $Pd(dba)_2$, CuI, PPh_3, Et_3N, toluene/CH_3CN, 3 d, room temperature (36%).

leads to many drawbacks in the purification, characterization, and application. Therefore, we here prepared a much more stable covalent analogue **7** based on the template-directed synthesis. The macrocycle possesses two topologically discrete subcavities, each of which bears four hydrogen-bonding donors, amide NHs of pyridine-2,6-dicarboxamide units. The macrocycle strongly binds two molecules of a guest, *N*,*N*,*N*′,*N*′-tetramethylterephthalamide, in positive cooperative manner (Hill coefficient $h = 1.6$) by hydrogen-bonding interactions.

The synthesis of macrocycle **7** is outlined in Scheme 2. Compound **5** was prepared in 75% yield by dropwise addition of diamine **3**[5] and 4-iodo-2,6-dimethylaniline (**4**) to a CH_2Cl_2 solution of pyridine-2,6-dicarbonyl dichloride (**2**) under nitrogen. Then, **5** was converted into compound **6** by palladium/CuI-catalyzed Sonogashira coupling[6] followed by de-silylation with tetrabutylammonium fluoride. Direct coupling between **5** and **6** was first carried out to synthesize **7** under various Sonogashira reaction conditions but yields were very low (<10%) due to the formation of unidentifiable materials, possibly polymeric species. The low yield is not so surprising because the reaction requires the formation of a large, 66-membered macrocycle, via twice Sonogashira couplings.

Next, we carried out template-directed synthesis using *N*,*N*,*N*′,*N*′-tetramethylterephthalamide which was chosen as a template based on our previous studies with metallocycles **1**.[3] After several attempts under different conditions, the desired macrocycle **7** was obtained in a reasonable yield (36%) when the reaction was performed with 10 equiv of the template at room temperature in a relatively nonpolar medium (1:20, v/v, CH_3CN/toluene),[7] the conditions of which possibly optimize the hydrogen bond-mediated template effect.

The macrocycle **7** was fully characterized by elemental analysis, MALDI-mass, ^1H NMR, and ^{13}C NMR spectroscopy.[7] As seen in the energy-minimized structure[8] (Fig. 1), a monocyclic compound **7** possesses two topologically separated subcavities and its conformation resembles a figure of eight. Each cavity consists of four amide NHs, all of which are inward directed as a consequence of intramolecular NH···N (pyridine) hydrogen bond.[9]

The binding property of **7** was investigated at 25 °C with *N*,*N*,*N*′,*N*′-tetramethylterephthalamide (**G**) in the ^1H NMR spectroscopy. When **G** was gradually added up to approximately 3 equiv to a $CDCl_3$ solution of **7** (2.00 mM), two NH signals were continuously shifted

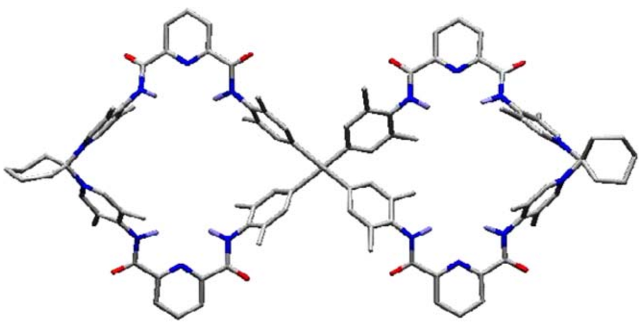

Figure 1. A side view of energy-minimized structure (MM3* force field, MacroModel version 7.1) of macrocycle **7**.

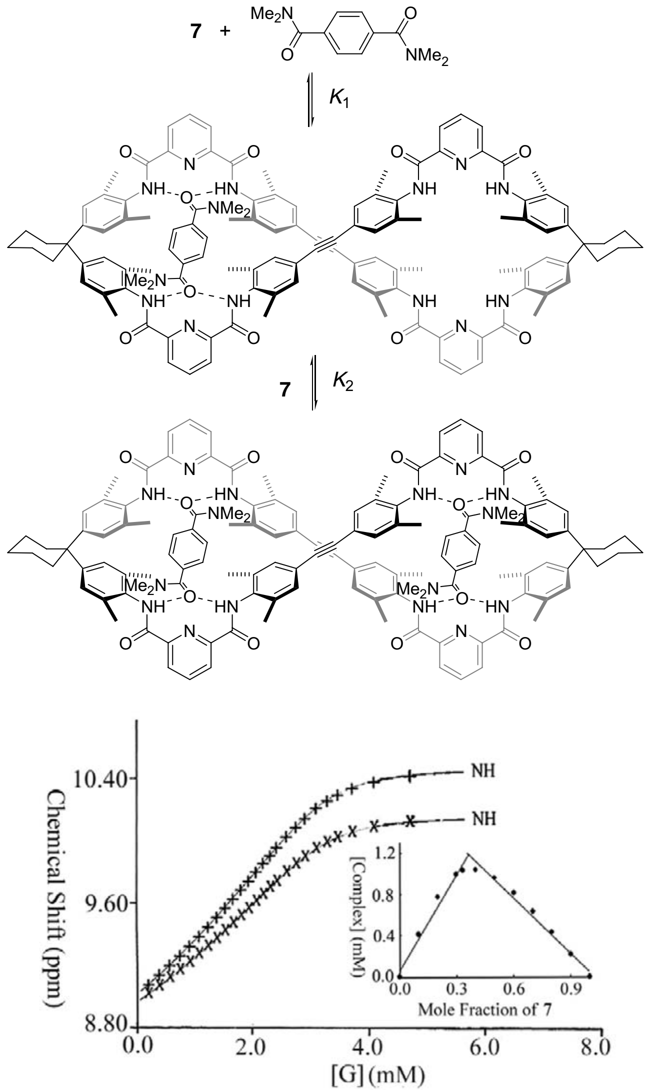

Figure 2. Proposed structure of the complex (above), experimental (×) and theoretical (line) titration curves (below), and a Job plot (below, inset) between **7** and *N*,*N*,*N*′,*N*′-tetramethylterephthalamide (**G**).

from 8.97 and 9.02 ppm to 10.12 and 10.42 ppm, respectively (Fig. 2). Nonlinear curve fitting analyses of the titration data using the HOSTEST program[10] afforded the association constants of 1480 ± 90 and $5580 \pm 150\ \mathrm{M}^{-1}$ for K_1 $(=[\mathbf{7}\cdot\mathbf{G}_1]/[\mathbf{7}][\mathbf{G}])$ and K_2 $(=[\mathbf{7}\cdot\mathbf{G}_2]/[\mathbf{7}\cdot\mathbf{G}_1][\mathbf{G}])$, respectively. The ratio of these constants implies positive homotropic cooperativity, considering the relationship of $K_2 = 1/4\ K_1$ for non-cooperative binding. The titration data were also analyzed by the Hill equation:[11] $\log(y/(1-y)) = h\log[\mathbf{G}] + \log K$, where h and K are the Hill coefficient and binding constant, respectively, and $y = K/([\mathbf{G}]^{-n} + K)$. The magnitudes of h and $\log K$ were obtained from the slope and the intercept of the linear plot of $\log(y/(1-y))$ versus $\log[\mathbf{G1}]$. The Hill coefficient was found to be $h = 1.6$, which also supports the positive cooperative binding. In addition, The continuous variation (Job) method[11] confirmed 1:2 (**7**/**G**) stoichiometry of the complex, showing the maximal complex formation at 0.33 mol fraction of **7** (Fig. 2).

The association constants between **7** and **G** are comparable or higher than those obtained from tetralactam analogues and diamide guests, the systems of which were reported to form four hydrogen bonds.[3,12] In addition, when *N*,*N*-dimethylbenzamide, was used as a monoamide guest capable of forming two hydrogen bonds, the changes in the NH chemical shifts were very small (<0.2 ppm on the addition of ~4 equiv) compared to those (1.2–1.4 ppm) induced by **G**. These observations are consistent with the formation of four simultaneous hydrogen bonds between **7** and **G**. Finally, the aromatic signal of **G** when complexed was considerably upfield-shifted ($\Delta\delta = -0.7$ ppm), suggesting that **G** inserted into the cavity was surrounded by aryl planes as shown in Figure 2.

In conclusion, a large, 66-membered macrocycle that can be served as an artificial allosteric model was prepared using the template-directed synthesis. The macrocycle possesses two topologically separated binding cavities and therefore binds two molecules of the guest, one to each cavity, in positive cooperative manner by hydrogen-bonding interactions.

Acknowledgments

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7. To a Schlenk tube were placed **5** (1.68 g, 1.55 mmol), **6** (1.36 g, 1.52 mmol), *N*,*N*,*N*′,*N*′-tetramethylterephthal-

amide (3.49 g, 15.5 mmol), CuI (65.0 mg, 0.078 mmol), [Pd(dba)$_2$] (76.0 mg, 0.078 mmol), and PPh$_3$ (120 mg, 0.155 mmol). The tube was degassed under vacuum and refilled with N$_2$, the process of which was repeated three times. Degassed toluene (200 mL), CH$_3$CN (10 mL), and triethylamine (10 mL) were added under N$_2$, and the solution was stirred at room temperature for 3 d. The reaction mixture was then filtered through Celite, and the filtrate was concentrated under reduced pressure. The residue was dissolved in CHCl$_3$ (50 mL) and washed with saturated NaHCO$_3$ aqueous solution and brine, dried over anhydrous MgSO$_4$, and concentrated. The residue was purified by column chromatography (EtOH/acetone/CHCl$_3$, 1:2:20) to give **7** as a white solid (0.97 g, 36%); mp >300 °C; IR (KBr) ν 3339 (NH), 1684 (C=O) cm^{-1}; ^{1}H NMR (500 MHz, CDCl$_3$) δ (ppm) 9.02 (s, 4H, NH), 8.97 (s, 4H, NH), 8.55–8.49 (m, 8H, pyridine-H), 8.16 (t, $J = 7.8$ Hz, 4H, pyridine-H), 7.36 (s, 8H, Ar-H), 7.06 (s, 8H, Ar-H), 2.26 (s, 48H, CH$_3$), 1.61 (m, 16H, cyclohexyl CH$_2$), 1.48 (m, 4H, cyclohexyl CH$_2$); ^{13}C NMR (126 MHz, CDCl$_3$) δ (ppm) 161.2, 148.9, 148.5, 148.1, 139.6, 135.4, 134.7, 133.5, 131.5, 130.5, 127.0, 125.8, 125.7, 122.2, 89.2, 45.3, 36.7, 29.7, 26.3, 22.8, 19,0, 18.5. Anal. Calcd for C$_{108}$H$_{104}$N$_{12}$O$_8$: C, 76.39; H, 6.17; N, 9.90. Found: C, 76.31; H, 6.13; N, 9.87; MALDI-MS (*m*/*z*) [M]$^+$ calcd for C$_{108}$H$_{104}$N$_{12}$O$_8$: 1696.81. Found: 1096.80.

8. The energy-minimized structure was generated with MM3* force field implemented in MacroModel 7.1 program on a Silicon Graphics Indigo IMPACT workstation via 1000 separated search steps in Monte Carlo conformational search.
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