A Thermally Switchable Molecular Lock. Guest-Templated Synthesis of a Kinetically Stable Nanosized Cage

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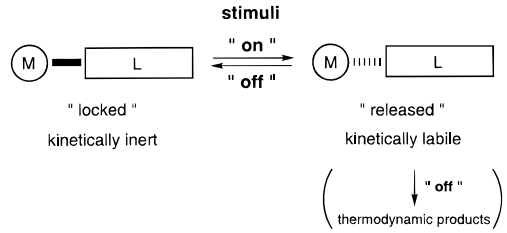
An inert coordinate bond which becomes labile by external stimuli can be termed as a "molecular lock" since a thermodynamic equilibrium structure can be trapped (or locked) to a kinetically stable form by turning off the stimuli.[1]



A thermally switchable molecular lock was recently developed by exploiting the dual character of a Pt(II)−pyridine coordinate bond which is inert but temporally becomes labile by thermal stimuli.[1,2] In this study, the thermally switchable molecular lock is incorporated into nanosized cage complex **1a**.[3,4] We found that, under thermal stimuli (i.e., heating), the molecular lock is released and the equilibrated structure of nano cage **1a** is generated from six metals (**2a**) and four ligands (**3**) with the aid of a large template guest.[5] By turning off the thermal stimuli (i.e., cooling), the cage framework was locked. Subsequently, we obtained empty cage **1a** in a high yield by removing the template (eq 1). Whereas supramolecules self-assembled through weak interactions are labile and not tolerant under forcing conditions,[6] nanocage **1a** was shown to be very stable under acidic and basic conditions since its framework is "locked".

The high-yield synthesis of **1a** was achieved with the aid of the remarkable template effect of a large guest, sodium adamantanecarboxylate (**4**). When ligand **3** (0.06 mmol) was treated with **2a** (0.09 mmol) in D_2O (18 mL), a kinetically distributed oligomer mixture was formed at first (Figure 1a). After the mixture was heated at 100 °C for 24 h, the NMR spectrum became somewhat simpler because of conversion of the components to thermodynamically stable cage structure **1a** (Figure 1b), but the conversion was too slow to give **1a** in a reasonable yield. To make the cage structure more stable, **4** (0.06 mmol, 4 equiv to **1a**), which is a suitable guest for palladium(II)-linked derivative **1b**,[3] was added and the solution was stirred at 100 °C for additional 24 h. As a result, we learned that the addition of guest **4** induced the smooth, high-yield formation of **1a** (Figure 1c). Guest signals were highly upfield-shifted due to the inclusion in the cavity ($\Delta\delta$ −0.6 to −2.1 ppm); the host−guest ratio was estimated to be 1:4 by NMR. The binding behavior is the same as that observed for palladium complex **1b**.[3]

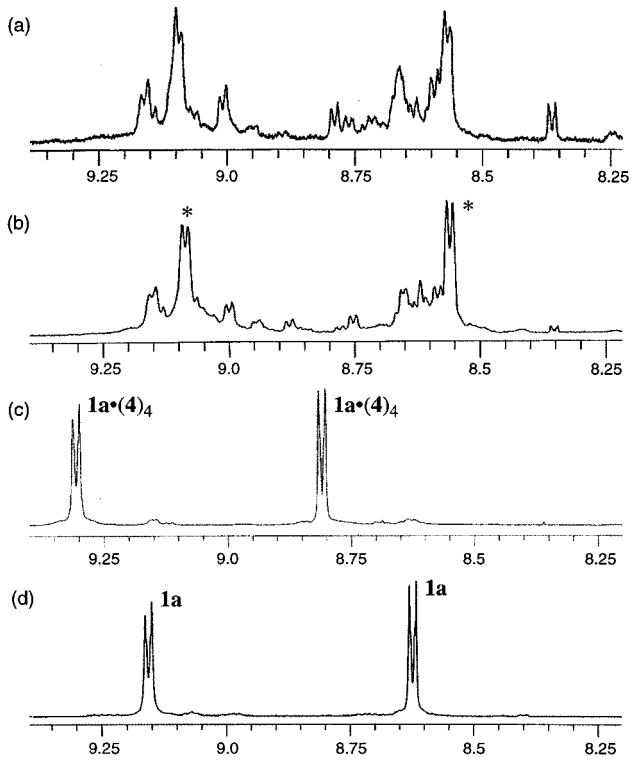


Figure 1. The ^{1}H NMR observation of the guest template synthesis of **1a** (500 MHz, D_2O, 25 °C, TMS as an external standard). (a) A kinetically distributed oligomer mixture. (b) After 24 h at 100 °C. Main peaks (*) assignable to **1a** appear at δ 9.08 and 8.56, which are slightly upfield shifted (by ∼0.05 ppm) from those of empty **1a** presumably due to some interactions with other oligomer components. (c) After 24 h at 100 °C in the presence of guest **4** (4 equiv). Signals appearing at δ 9.31 and 8.81 are assigned to **1a**−(**4**)$_4$ and slightly downfield shifted from those of empty **1a**. (d) Empty cage **1a** obtained after the removal of guest **4** (acid form) by extraction with $CHCl_3$.

The guest-templated assembly of cage **1a** is a model for induced fit since the guest induced the organization of its own receptor.[7,8]

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(8) The role of the template **4** is more clarified by the following experiments. The original mixture was heated for additional several days in the absence of **4**, but no significant change in the NMR was observed. Sodium acetate did not show any template effects, suggesting that neither sodium cation nor carboxylate ion induces the assembly of **1a**. The formation of cage **1a** was not accelerated significantly under acidic conditions (HNO_3).

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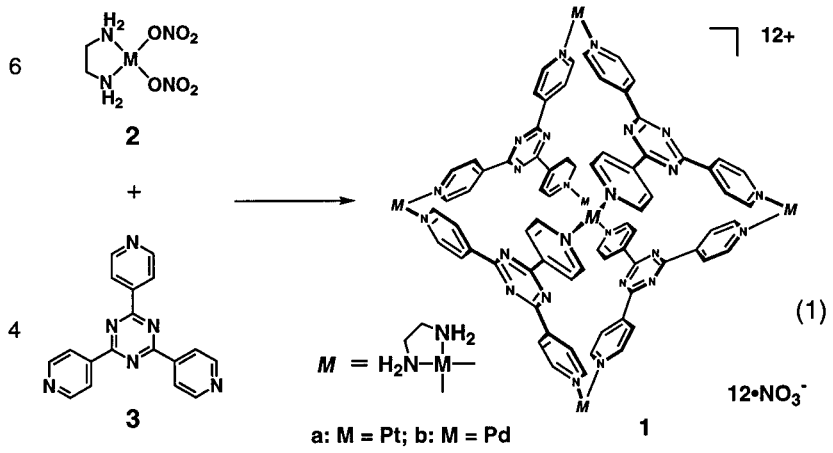
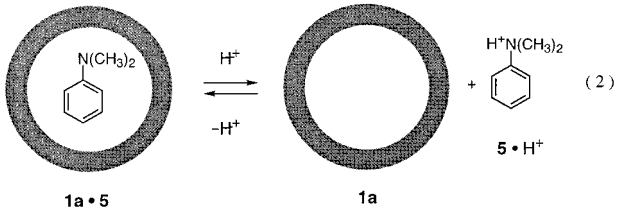


Usually, a receptor framework organized by induced fit is lost when the guest is removed. In contrast, receptor **1a** did not lose its cage structure when the guest was removed because the Pt(II)−py bond in **1a** was locked after the self-assembly event. Guest **4** included in the cavity of **1a** was easily removed as an acid form by acidification of the aqueous solution of **1a**−(**4**)$_4$ with HNO_3 followed by extraction with fresh chloroform (Figure 1d). To the resulting aqueous solution of empty cage **1a**, aqueous KPF_6 was added to precipitate pure **1a** as a PF_6 salt in 68% yield. The structure was fully assigned by ESIMS, ^{1}H and ^{13}C NMR, and elemental analysis.[9] Neutral compounds such as toluene, methoxybenzenes, and adamantane were also shown to be included by host **1b**, but they did not show any template effects for the assembly of **1a**.

The kinetic stability of **1a** deserves special attention. Nanocage **1a** is tolerant to pH <1 or pH >11 conditions at room temperature. Thus, an acid (HNO_3), a base (K_2CO_3), or even a strong nucleophile (NEt_3) did not destroy the framework of **1a**. Such a remarkable stability toward acidic and basic conditions stands in sharp contrast to that of hitherto known metal-containing supramolecules which decompose under such conditions. Actually, palladium(II) counterpart **1b** immediately decomposed when an acid (HNO_3)[10] or a nucleophilic base (NEt_3) was added.[11]

The stability of **1a** toward acid and base enabled us to design a pH-responsible host−guest system.[12] We found that *N*,*N*-dimethylaniline (**5**) was effectively bound in the cavity of **1a** in a host:guest = 1:4 ratio in D_2O. The complexation was supported by the significant upfield shift of guest protons in ^{1}H NMR ($\Delta\delta = \sim -1.0$ ppm for aromatic protons and −0.8 ppm for methyl protons). However, cage **1a** immediately liberated **5** when the solution was acidified (pH <1) with HNO_3. In NMR, the guest signals of free **5**-H$^+$ was observed upon acidification. The decapsulation of **5** from **1a** was probably due to decreased hydrophobic interaction as well as cationic repulsion between the host and the guest. The liberated guest again came back into the cavity of **1a** when the solution was treated with K_2CO_3 (pH 11).



Application of the molecular lock concept for constructing other discrete structures and the development of photo- and electrochemically switchable molecular locks are currently under investigation in our laboratory.

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Supporting Information Available: ESIMS data for **1a** and ^{1}H NMR of **1a**−(**4**)$_4$, empty **1a** after removal of **4**, **1a** violated as PF_6 salt, and **1b** and **1b**−(**4**)$_4$ as reported in ref 3 (14 pages, print/PDF). See any current masthead page for ordering information and Web access instructions.

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(9) Preparation and physical properties of **1a** (PF_6 salt): An aqueous solution of **1a** (NO_3^- salt, 0.8 mM, 16 mL) was prepared by a procedure described in the text. Addition of aqueous KPF_6 (0.27 M, 3 mL) to the resulting solution precipitated **1a** (PF_6 salt), which was filtrated and dried to give pure **1a** (PF_6 salt) in 68% yield: ESIMS (CH_3CN) *m*/*z* 1361.8 [M − $(PF_6)_3$]$^{3+}$, 984.9 [M − $(PF_6)_4$]$^{4+}$, 759.0 [M − $(PF_6)_5$]$^{5+}$; ^{1}H NMR (500 MHz, D_2O, TMS as external standard) δ 9.16 (d-like, J = 6.8 Hz, 24 H), 8.63 (d-like, J = 6.8 Hz, 24 H), 2.82 (s, 24 H); ^{13}C NMR (125 MHz, D_2O, TMS as external standard) δ 170.5 (*C*q), 153.9 (*C*H), 146.1 (*C*q), 126.7 (*C*H), 48.7 (*C*H); IR (KBr, cm^{-1}) 3401, 3060, 1622, 1575, 1527, 1377, 833, 813, 680, 559; mp 225 °C dec. Anal. Calcd for $C_{84}H_{84}F_{72}P_{12}Pt_6\cdot(H_2O)_8\cdot(C_2H_5OH)_2$: C, 22.28; H, 2.38; N, 10.63. Found: C, 22.36; H, 2.69; N, 10.34. The physical properties and binding behavior of **1a** are almost the same as those of **1b** whose structure was unambiguously determined by X-ray analysis.[3]

(10) Protonated ligand (**3**-3H$^+$) was the major product (^{1}H NMR).

(11) Upon addition of NEt_3, a fine precipitate was formed. The ^{1}H NMR measurement showed that a complex mixture was resulted.

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