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Guest-Reaction Driven Cage to Conjoined Twin-Cage Mitosis-Like Host Transformation

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Dedication

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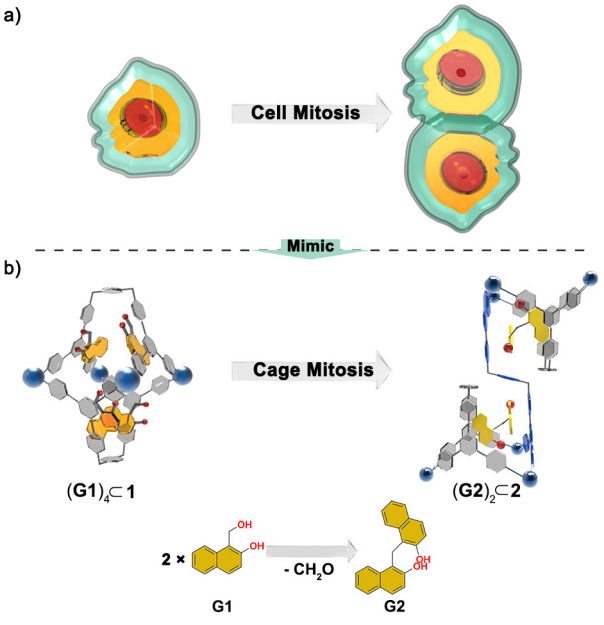
Abstract: We report here a guest-reaction induced mitosis-like host transformation from a known Pd_4L_2 cage **1** to a conjoined Pd_6L_3 twin-cage **2** featuring two separate cavities. The encapsulation of 1-hydroxymethyl-2-naphthol (**G1**), a known *ortho*-quinone methide (*o*-QMs) precursor, within the hydrophobic cavity of cage **1** is found crucial to realize the cage to twin-cage conversion. Confined **G1** molecules within the nanocavity undergo self-coupling dimerization reaction to form 2,2'-dihydroxy-1,1'-dinaphthylmethane (**G2**) which then triggers the cage to twin-cage mitosis. The same conversion also proceeds, in a much faster rate, via the direct templation of **G2**, confirming the induced-fit transformation mechanism. The structure of the (**G2**)$_2$⊂**2** host-guest complex has been established by X-ray crystallographic study, where *cis*- to *trans*- conformational switch on one bridging ligand is revealed.

Chemical-triggered structural transformations are commonly observed in biosystems.[1] Moreover, the motions of these natural systems correspond to essential biological functions, such as ATP synthase.[2] Assembled supramolecular architectures offer controllable platform at the molecular level to mimic the function of biosystems.[3] Adaptive transformations have also been widely seen in such artificial hosts with stimuli-responsiveness to anion,[4] solvent,[5] concentration,[5a,6] stoichiometric ratio of components,[5f,7] post-modification[6b,8] chemical fuel[9] and so on.[5f,10] Guided by the induced-fit mechanism, guest-templated synthesis offers an important route toward otherwise inaccessible complicated host-guest complexes.[5f,11] In this case, guest molecules with specific sizes, shapes and electrostatic interactions are usually added to the system from the beginning to drive the formation of the new complementary complexes. However, guest-reaction driven structural conversions, i.e. the new products generated in-situ from the initial added guests exert the induced-fit power to force the structural transformation of the host, are extremely rare.[11e]

o-Quinone methides (*o*-QMs) are known as a group of important intermediates in total synthesis of natural products and pharmaceutical compounds. Due to their biradical or polarized zwitterion ketene structures, *o*-QMs are highly reactive toward hetero Diels-Alder or nucleophilic additions.[12] As such, *o*-QMs precursors can be used as ideal cross-linker agents to DNAs, proteins and enzymes.[13] It is well-known that container-molecules have great potential in taming highly reactive chemicals through supramolecular encapsulation and isolation.[14] Previously, we introduced a water-soluble Pd_4L_2 cage **1** with expanded-size cavity, which can host an increased number of organic and inorganic guests for selective catalysis.[15] We then wandered whether *o*-QMs can be stabilized or new reactivity can be observed for this fleeting species within our water-soluble Pd_4L_2 cage **1**. 1-Hydroxymethyl-2-naphthol (**G1**), a known *o*-QMs precursor,[12a] was chosen as the guest in this work. Interestingly, a guest-reaction induced mitosis-like host transformation from cage **1** to an unprecedented conjoined Pd_6L_3 twin-cage **2** was observed (Scheme 1).



Scheme 1. Diagram of (a) cell mitosis and (b) mitosis-like transformation from cage (**G1**)$_4$⊂**1** to conjoined twin-cage (**G2**)$_2$⊂**2**.

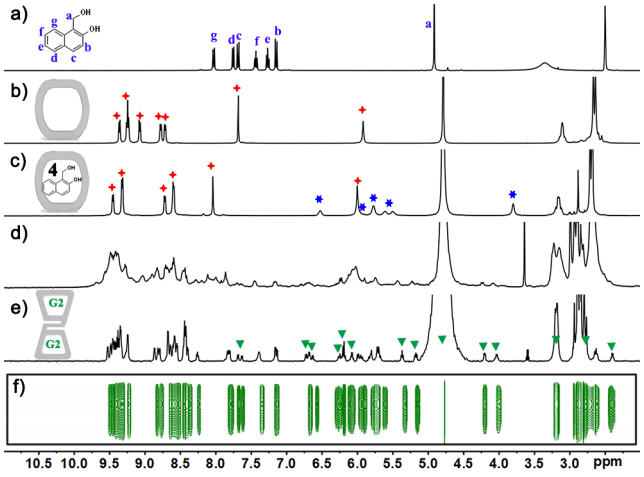


Figure 1. ^{1}H NMR (600 MHz, 298 K) spectra of (a) **G1** in DMSO-d_6, (b) Cage **1** in D_2O, (c) host-guest complex of (**G1**)$_4$⊂**1** in D_2O; (d) (**G1**)$_4$⊂**1** in D_2O after heating at 90 °C for 16 h; (e) (**G2**)$_2$⊂**2** crystal re-dissolved in D_2O and (f) its ^{1}H DOSY spectrum (✦ : Cage **1**; ✱ : **G1**; ▼ : **G2**).

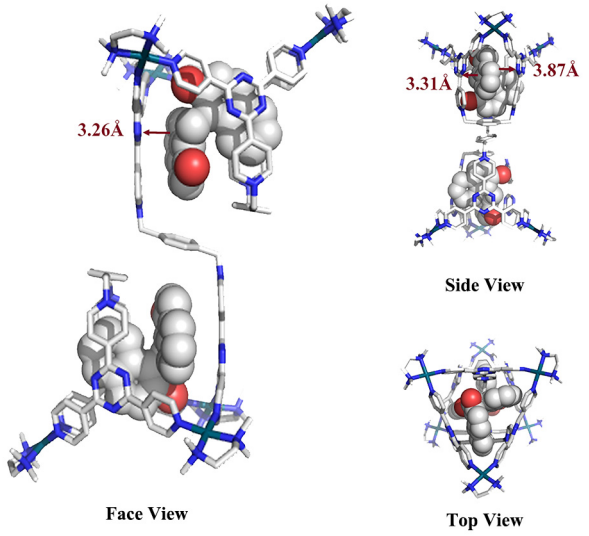


Figure 2. X-ray crystal structure of (**G2**)$_2$⊂**2**. Cage **2** and guests **G2** are displayed with stick and sphere models respectively (Color code: grey, C; blue, N; red, O; Cyan, Pd). Distances for host-guest π-π stacking interaction are indicated. Counter ions and hydrogen atoms are omitted for clarity.

According to our previous reports,[15] water-soluble cage **1** was synthesized from the *p*-xylene-bridged bis-TPT ligand and the (tmeda)Pd(NO_3)$_2$ capping unit (TPT= 2,4,6-tris(4-pyr-idyl)-1,3,5-triazine; tmeda= N,N,N',N'-tetramethyl-ethylenediamine). After different equiv. of **G1** were added to cage **1** in D_2O, formation of a (**G1**)$_4$⊂**1** host-guest complex was indicated by ^{1}H NMR spectra (Fig. 1, Fig. S10). Compared to the signals of free **G1** (Fig. 1a) and empty cage **1** (Fig. 1b), the host-guest complex shows dramatic changes. Obvious up-field shifts for the naphthalene signals on **G1** from 8.1~7.1 ppm to 6.5~5.4 ppm, and the methylene signals from 4.9 ppm to 3.7 ppm were observed, respectively (Fig. 1c). This indicates the efficient guest encapsulation within the hydrophobic cavity of cage **1**. Up to four molecules of **G1** can be encapsulated inside cage **1** based on the integral ratios from a titration experiment (Fig. S11). Diffusion-ordered ^{1}H NMR spectroscopy (^{1}H DOSY) also confirmed the formation of a stable host-guest species with a diameter of 1.59 nm estimated from the Stokes-Einstein equation (Fig. S12).

Interestingly, when the solution of host-guest complex (**G1**)$_4$⊂**1** was heated at 90 °C, dramatic changes were observed in ^{1}H NMR spectra within 16 h (Fig. 1d, Fig. S13). Characteristic signals for the encapsulated **G1** totally disappeared, along with the evolution of a new set of splitting signals spanning from 7.6 to 2.3 ppm. Meanwhile, the signature signals of host **1** also became highly asymmetric. ^{1}H DOSY confirmed that all the new signals have the same diffusion coefficient in solution (Fig. S15), with an apparent larger diameter of 3.58 nm estimated. All of those changes indicate the transformation of the original complex into another host-guest complex. The overlapping and broad nature of the signals indicates that the presence of other minor species in solution cannot be completely discounted.

Fortunately, brown-red crystals were obtained by slow evaporation of an aqueous solution of (**G1**)$_4$⊂**1** at room temperature over one month. ^{1}H and DOSY NMR measurements after re-dissolving the crystals into D_2O (Fig. 1e-f, S16-17) confirmed that it was the identical species with the same diffusion coefficient as obtained by the heating procedure described above. The crystals were of sufficient quality and X-ray crystallography finally established the structure of the new host-guest complex, which would be extremely challenging to analyze by other spectroscopic methods. According to the crystal data, the Pd_4L_2 cage **1** transformed into a brand-new Pd_6L_3 conjoined twin-cage, with two molecules of 2,2'-dihydroxy-1,1'-dinaphthylmethane (**G2**) that produced from the self-coupling of the initial **G1** guests, sitting inside two independent cavities (Fig. 2). Without concerning the guests and the peripheral capping units, cage **1** has a D_{2d} molecular point group where both ligands adopt the *cis*- conformation. In contrast, cage **2** has a low-order C_{2h} symmetry with two *cis*- and one *trans*- ligands coexisting. By one intra-ligand and two inter-ligands clipping, three TPT panels from one *cis*-ligand and half of the bridging *trans*-ligand defined each hydrophobic cavity of the twin-cage. Strong π-π stacking interactions between the naphthalene rings of two independent **G2** molecules and the TPT walls (Fig. 2) were observed, which may have served as the main driving forces for the induced-fit cage transformation. It is worth to point out that host structure transformation from one bigger cavity into two separate smaller cavities, alike the mitosis of cells, has never been observed before.

In order to confirm the induced-fit cage transformation mechanism, independently prepared **G2** was treated with cage **1** (Fig. 3). An aliquot concentrated solution of **G2** in DMSO-d_6 were thoroughly mixed with cage **1** in D_2O and the suspended free **G2** was filtered off before taking the ^{1}H NMR. Based on the integral ratios from the titration experiments, up to two molecules of **G2** can be encapsulated by cage **1** (Fig. S18-19). Compared to free **G2** (Fig. 3a) and cage **1** (Fig. 3b), the signals of this new (**G2**)$_2$⊂**1** host-guest complex (Fig. 3c) clearly changed with obvious line-broadening, suggesting the slow tumbling motion of the guests after entering the cavity of cage **1**, possibly due to the large molecular size of **G2**. Meanwhile, aromatic signals of **G2** also witnessed high up-field shifting to 6.5~5.0 ppm, confirming again a static binding mode of this host-guest complex.

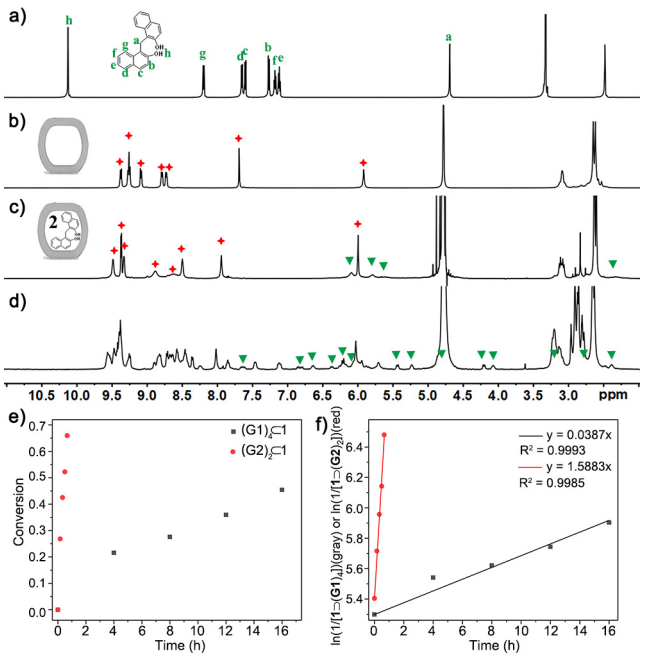


Figure 3. ^{1}H NMR (600 MHz, 298 K) spectra of (a) **G2** in DMSO-d_6, (b) cage **1** in D_2O, the host-guest complex of (**G2**)$_2$⊂**1** in before (c) and after heating at 90 °C for 40 min (d) (D_2O: DMSO-d_6 = 25:1); (e) Conversion and (f) pseudo-first-order kinetic plots for the cage transformation reaction starting from both (**G1**)$_4$⊂**1** (gray) and (**G2**)$_2$⊂**1** (red) at 90 °C. (✦ : Cage **1**; ▼ : **G2**)

Time-dependent ^{1}H NMR spectra were recorded for the (**G2**)$_2$⊂**1** complex. Even at room temperature, distinct signals assignable to (**G2**)$_2$⊂**2** can be observed after 1 h, indicating the successful induced-fit transformation of the host (Fig. S19). When heated to 90 °C, over 60% transformation from (**G2**)$_2$⊂**1** to (**G2**)$_2$⊂**2** was observed within 40 min (Fig. S21-21). Based on pseudo-first-order reaction kinetics, a 41-fold speed-up for the rate constant of the **G2**-driven transformation from cage **1** to cage **2** was estimated, compared to that of **G1** (Fig. 3 e-f; Fig. S22-23).

Hydrophobic effect has been noticed to play a key role for both the encapsulation of **G1** and the induced-fit transformation of cage **1**. In a 1:1 (volume ratio) mixed solvent of DMSO-d_6 and D_2O, ^{1}H NMR titration indicated that cage **1** has much weaker binding affinity toward **G1**, where a continuous down-field shifting of the guest signal observed (Fig. S26). Fast in and out exchange has also been clearly seen in the DOSY spectrum, with two diffusion bands observed for the both the host and the guest (Fig. S27). Moreover, no obvious change was observed in ^{1}H NMR after heating the mixture at 90 °C for 16 h (Fig. S28), indicating that the self-coupling reaction occurred slowly at this condition. Similar to **G1**, **G2** binding with cage **1** also becomes a dynamic fast-equilibrium in such mixed solvent condition (Fig. S29). However, in this case the **G2**-driven cage **1** to cage **2** transformations can still take place, though with a slower reaction rate (Fig. S30). We thus conclude that hydrophobic-driven static encapsulation of **G1** is vital for its self-coupling dimerization reaction within cage **1** (Fig. S31-32).

Due to the strong π-π interactions and the potential deprotonated anionic state of **G2** inside the highly 18$^+$ charged cage **2**, it turned out to be difficult to extract **G2** out of cage **2** by common water-immiscible organic solvents, such as chloroform and benzene. Competing guest molecules either neutral or anionic were also screened to kick **G2** out of cage **2** (Fig. S33), but without success. Finally, when the solid of (**G2**)$_2$⊂**2** was re-dissolved in DMSO-d_6, quick back-transformation to cage **1** along with severely broadened **G2** signals were observed in ^{1}H NMR (Fig. S34-36). Moreover, cage **1** could be recycled by the addition of excess amount of EtOAc to the system to force the precipitation of cage **1**, which was confirmed by ^{1}H NMR in D_2O (Fig. S37).

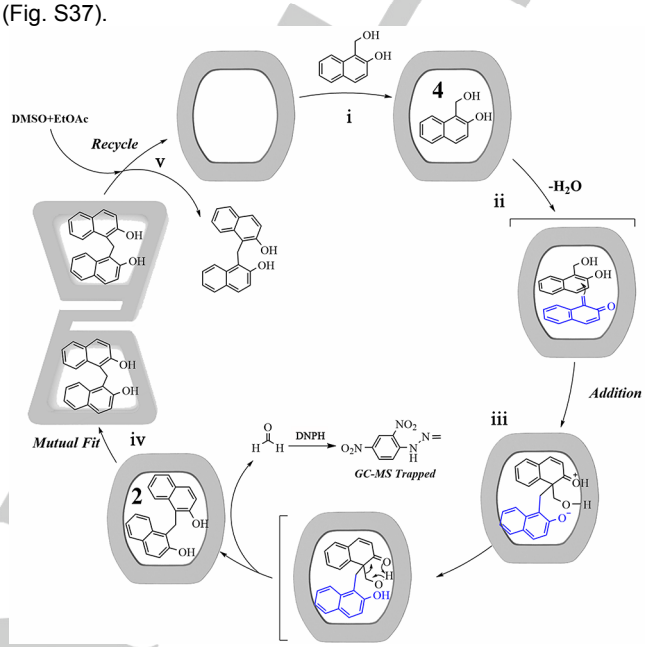


Figure 4. Proposed mechanism for the mitosis-like cage **1** to conjoined twin-cage **2** transformation.

Taken together all the above results and previous reports,[16] the following plausible mechanism (Fig. 4) is proposed for this unique guest reaction driven host transformation process: (1) In water, up to 4 molecules of **G1** were encapsulated by cage **1**, giving rise to a high local concentration of ca. 7.57 M inside the nano-cavity (Fig. S38). (2) Driven by the hydrophobic effect, encapsulated **G1** undergoes dehydration, giving rise to the *o*-QMs intermediates. (3) *o*-QMs react with another **G1** molecules nearby to form **G2**, where formaldehyde serves as a leaving group. Indeed, when DNPH (2,4-dinitrophenylhydrazine) as a formaldehyde trap was added to the reaction, presence of 2,4-dinitrophenylhydrazone signals at *m/z* 210 was clearly detected by GC-MS (Fig.S41). (4) **G2** induced cage **1** to conjoined twin-cage **2** transformation takes places quickly. (5) Solid-liquid extraction with an EtOAc/DMSO mixture leads to the recycling of cage **1** that facilitates the turn-over of the reaction. It worth to note that though this process, the self-coupling dimerization of **G1** inside cage **1** is the rate-determining step, thus (**G1**)$_4$⊂**1** is the resting-state which can be observed on the ^{1}H NMR.

In summary, an unprecedented cage to conjoined twin-cage transformation driven by a self-coupling dimerization reaction of an *o*-QMs precursor guest was discovered. To the best of our knowledge, such a reaction-driven induced-fit cage to twin-cage transformation has never been observed. This unique molecular level structural transformation is reminiscent of the cell-mitosis

and shed light on some natural phenomena such as enzyme deactivation and allosteric protein regulation.

Acknowledgements

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Keywords: Conjoined-Cage • Encapsulation • Guest Reaction • Cavity Division • Induced-Fit

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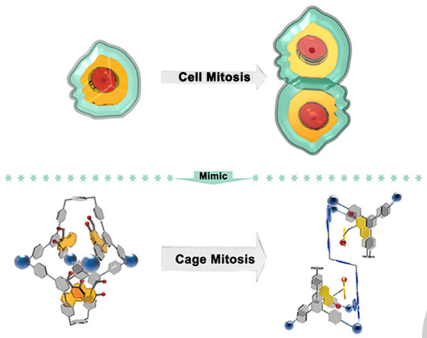

Guest-reaction induced mitosis-like host transformation from Pd_4L_2 cage **1** to an unprecedented conjoined Pd_6L_3 twin-cage **2** was observed.