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Self-assembled coordination cage as a molecular flask*

Michito Yoshizawa and Makoto Fujita‡

Department of Applied Chemistry, School of Engineering, The University of Tokyo and CREST, Japan Science and Technology Agency, 7-3-1 Hongo, Bunkyo-ku, Tokyo 113-8656, Japan

Abstract: Cavity-directed chemical transformations represent one of the most important features in 3-D host chemistry, yet they are unexplored as synthetic receptors. We are developing such functions with the large cavity of self-assembled cages, particularly an M_6L_4-type cage. The photodimerization of olefins within this cage shows remarkable rate enhancement, perfect regio- and stereoselection, and high pairwise selection (when two different olefins are used) giving only the cross [2+2] adduct. Another intriguing property of the cavity is the stabilization of labile molecules by encapsulation. We succeeded in trapping labile molecules by in situ preparation from small components coming through small portals of the cage. For example, hydrolysis and condensation of $PhSi(OMe)_3$, which ordinarily provides a sophisticated Si–O 3-D network (so-called sol-gel condensation), selectively gave a cyclic trimer, $[PhSi(OH)O]_3$, in a "ship-in-a-bottle" fashion. Cavity-sensitized photochemical oxidation of alkanes within the cage is also discussed.

Keywords: cavity-directed; three-dimensional host chemistry; self-assembled cages; photodimerization; encapsulation; sol-gel.

INTRODUCTION

Enzymatic reaction, which is the ultimate goal of synthetic organic chemistry, takes place within isolated cavities that spontaneously form through self-organization of protein molecules. The extremely high efficiency and beauty of the enzymatic reactions have fascinated and prompted chemists to develop enzyme-like reactions that proceed within restricted artificial cavities. Despite numerous attempts to utilize cyclodextrin or artificial hollow host molecules such as calixarenes, resorcinolarenes, and cavitands, however, reaction control within the cavities still remains poorly explored [1]. This is because the cavities are often too small and the host/guest association too weak to efficiently bind two or more substrates. In addition, the synthesis of artificial host is often very tedious.

Like enzymes, the creation of large cavities through spontaneous self-assembly process is an attractive and alternative approach to synthetic hosts. Hydrogen-bonded assemblies with cavities have been developed by several groups, but the size of the cavity was limited and stability in polar solvents insufficient [1,2]. As another approach, we have shown that metal-directed self-assembly provides stable nanometer-sized hollow compounds in an extremely efficient fashion [2]. Cage complex **1** possessing a roughly spherical cavity is spontaneously formed by simply mixing the metal precursors (M) and

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‡Corresponding author

the organic ligands (L) in a 3:2 ratio [3]. Despite the simple and highly symmetric structure, cage **1** possesses several unique characteristics: (1) The diagonal Pd–Pd distance measured by X-ray analysis is quite large (ca. 2 nm). (2) A procedure for large-scale production of up to 100 g scale has been established. (3) The cage is highly water-soluble due to the presence of six cationic Pd(II). (4) In contrast, the cavity provides a hydrophobic pocket that can bind as many as four neutral organic guests such as adamantane or *o*-carborane through hydrophobic interactions. (5) The molecular recognition in the cage can be easily monitored by NMR. (6) The size and shape of the cage can be modified at will by rational design of new ligands. In fact, we have constructed a variety of cavities from a family of panel-like ligands and transition metals [4].

Such facile construction of various cavities makes possible the design of a suitable "cavity" for a given "chemical reaction" rather than the reverse. In the following sections, we discuss a range of chemical transformation within the cavity of self-assembled cage **1**.

CAVITY-DIRECTED [2+2] PHOTODIMERIZATION OF OLEFINS

Selective recognition and encapsulation of molecules are some of the most attractive features of cage-like molecule **1** [3–6]. Since cage **1** can accommodate two or more guest molecules at restricted positions in the cavity, we expect the cage to act as a molecular flask for intermolecular reactions with high stereo- and regioselectivity. For example, intermolecular [2+2] photodimerization of olefins has been extensively studied in such media as micelles, zeolites, organic hosts (e.g., cyclodextrins), and crystals [7]. However, highly stereo- and regiocontrolled reactions still remain unexplored. We found that [2+2] photodimerization of acenaphthylene (**2**) proceeds within cage **1** with remarkable rate acceleration and stereocontrol to give only the *syn*-isomer **3** [8], as clearly observed by ^{1}H NMR (Fig. 1). When the encapsulated complex **1** ⊃ $(\mathbf{2})_2$ was irradiated for 0.5 h in D_2O, the signals of **2** disappeared and one set of new signals emerged. The product was identified as *syn*-dimer **3**, and the yield was estimated to be >98 % based on **2**. Within the cage, the formation of *anti*-dimer, which is concomitantly formed in organic media, was not observed. Control experiments revealed that cage **1** dramatically accelerated the reaction and strictly controlled the stereochemistry of the product.

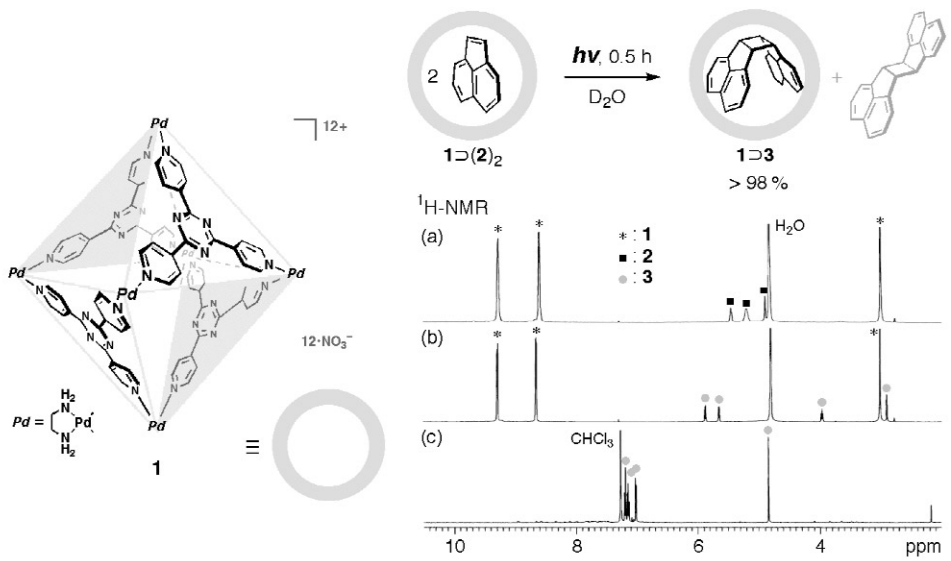


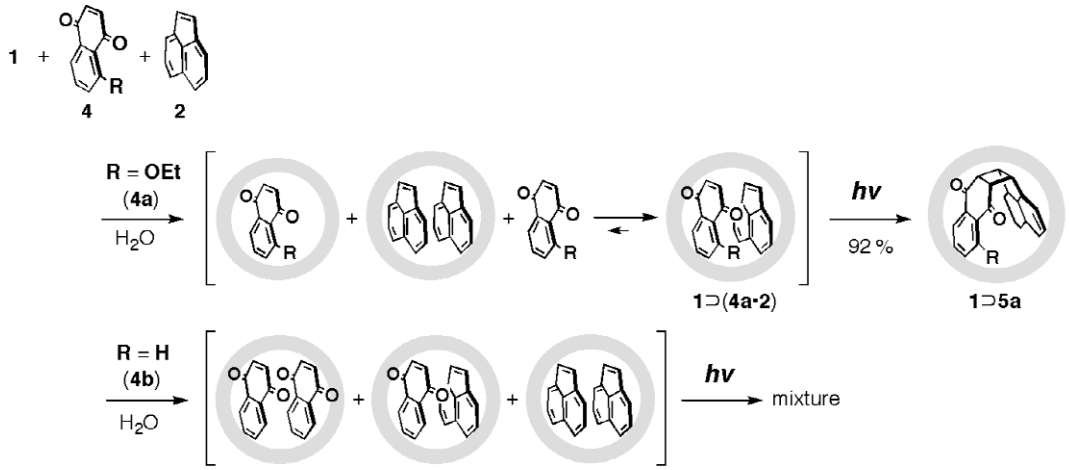
Fig. 1 Self-assembled coordination cage **1** (left) and ^{1}H NMR spectroscopic analysis (D_2O, r.t.) of the photodimerization of **2** within **1** (a: before irradiation, b: after irradiation for 0.5 h, c: after extraction with $CDCl_3$) (right).

It is worth noting that not only stereochemistry but also regiochemistry was highly controlled for the [2+2] photodimerization of 1-methylacenaphthylene (**2'**) [8]. Thus, the photoirradiation of **1** ⊃ (**2'**)$_2$ complex for 3 h gave rise to a head-to-tail *syn*-isomer in a high yield without any other regio- and stereoisomers.

PAIRWISE-SELECTIVE [2+2] CROSS-PHOTODIMERIZATION OF OLEFINS

The high stereo- and regioselectivities obtained in the photoreactions within cage **1** prompted us to examine *cross* [2+2] photodimerization of two different olefins [9,10]. In general, the pairwise selectivity of such cross-reaction is hardly controlled in solution because the two substrates must associate with suitable geometry before the reaction [7]. In contrast, the reaction within cage **1** was found to be extremely efficient in terms of reaction rate, stereoselectivity, and, most importantly, pairwise selectivity.

In expectation of observing high pairwise selectivity by the space restriction effect of the cavity, the photoaddition of acenaphthylene (**2**) and 5-ethoxynaphthoquinone (**4a**) was examined in the presence of cage **1** (**1**:**2**:**4a** = 1:1:1 ratio) (Scheme 1). When **2** and **4a** were suspended in an aqueous solution of **1** at 80 °C, the guests were efficiently accommodated in the cage and a clear solution resulted within 10 min. After irradiation of the solution for 3 h, the signals of **2** and **4a** completely disappeared and new signals appeared. Surprisingly, the product analyses (NMR and MS) showed the exclusive formation of the cross *syn*-dimer **5a**.



Scheme 1 Cross [2+2] photodimerization of **4** (R = H, OEt) and **2** within cage **1** in H_2O.

The key step of the exclusive formation of the cross-dimer is the selective formation of ternary complex **1** ⊃ (**4a**•**2**) before irradiation, which is governed by the size compatibility of the guests with the restricted space of the cavity. This finding was supported by the fact that **1** and **4a** produced only 1:1 complex (**1** ⊃ **4a**) but not 1:2 complex [**1** ⊃ (**4a**)$_2$] because of the steric bulkiness of **4a**. However, **1** ⊃ **4a** complex still has room for accommodating the less sterically demanding **2** to give **1** ⊃ (**4a**•**2**) complex. Thus, the hetero/homo equilibration in Scheme 1 shifts so that all species are complexed. When nonsubstituted **4b** was used, 1:2 complex [**1** ⊃ (**4b**)$_2$] was also formed and, upon irradiation, three products were distributed in an almost statistical ratio (hetero dimer:dimer of **4a**:dimer of **2** ≈ 2:1:1).

"SHIP-IN-A-BOTTLE" SYNTHESIS OF A SILOXANE CYCLIC TRIMER

Coordination cage **1** provides an isolated nanospace for molecules, where otherwise labile species, which are protected, can be considerably stabilized. The labile molecules are most effectively trapped in cage **1** if they are prepared in situ from smaller components coming through the small openings of the cage. Polycondensation of trialkoxysilanes (so-called sol-gel condensation) leads to the formation of siloxane networks or ladder polymers [11]. We succeeded in preparing a labile siloxane oligomer as a stable form in the cavity.

When the condensation reaction of phenyltrialkoxysilane (**6**) was carried out in the presence of cage **1**, cyclic trimer **7** was formed within the cavity of **1** in 92 % isolated yield (Fig. 2) [12,13]. In this reaction, encapsulated **6** (three molecules per cage) was hydrolyzed into **8**, which was subsequently condensed to form **7**. By detailed NMR, MS, and X-ray crystallographic analyses (Fig. 2), the observed reaction within the cage is particularly featured by the following findings. First, cyclic trimer **7** is formed in a "ship-in-a-bottle" fashion: while **6** can enter or exit through the portals of **1**, the trimer prepared in situ can no longer escape from the cage because its dimension becomes larger than the portal size. Second, the encapsulated cyclic trimer with reactive Si–OH groups, being protected by the cage, was very stable and tolerant even in acidic aqueous solution and isolable as a pure clathrate compound. Third, stereochemistry of the condensation reaction was highly controlled within the cage, giving only *cis*-isomers.

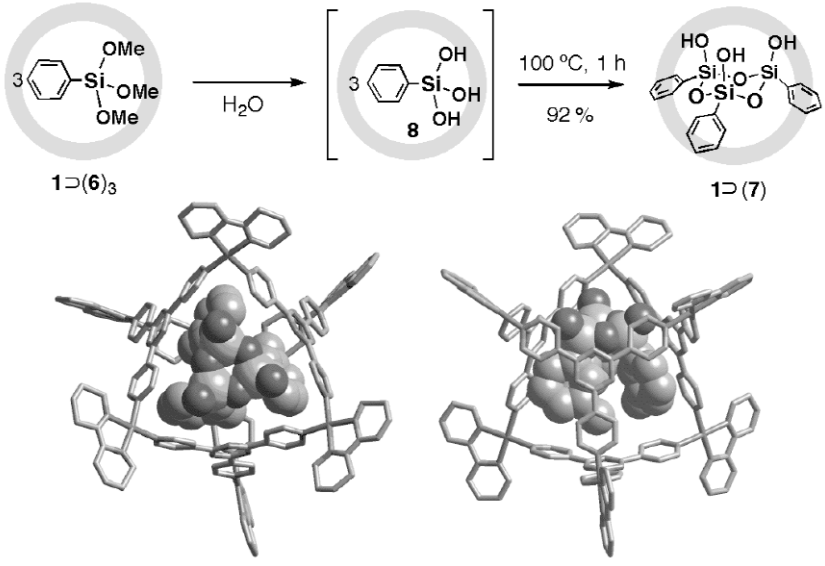


Fig. 2 Condensation reaction of phenyltrimethoxysilanes (**6**) to the cyclic trimer **7** within **1** in H_2O and X-ray crystal structure of **1'** ⊃ **7'** (**1'**, **7'**: *cis*-protection of Pd and phenyl group on Si are replaced by 2,2'-bpy and *m*-tolyl, respectively).

CAVITY-SENSITIZED PHOTOCHEMICAL OXIDATION OF ALKANES

More recently, we revealed that the photoexcitation of self-assembled cage **1** accommodating photochemically inert alkane guests led to the regioselective oxidation of the guest within the cage [14]. Interestingly, in this case, cage **1** directly participates in the photochemical processes, which is different from [2+2] photodimerization reaction where the cage does not participate in the photochemical process [8,9].

For example, when an aqueous solution of adamantane-encapsulated complex $\mathbf{1} \supset (\mathbf{9})_4$ (**9** = adamantane) was irradiated for 0.5 h under aerobic conditions, we found the regioselective oxidization of **9** at a tertiary carbon (Fig. 3). NMR analysis revealed the formation of hydroperoxide and alcohol derivatives, and the yields were estimated to be 19 and 5 %, respectively. Cyclic alkanes were also photooxidized to give the corresponding oxidized products. Control experiments revealed that such photooxidation reactions of alkanes exclusively occurred within the cage.

Under anaerobic conditions, the photooxidation is accompanied by unusual radical formation, which strongly indicated the sensitization of the reaction by the cage. When the solution of $\mathbf{1} \supset (\mathbf{2})_4$ was irradiated under argon atmosphere, the colorless solution quickly turned blue (Fig. 3A: a → b). UV–vis spectrum of the blue solution showed a new absorption band at λ_{max} = 593 nm. The blue species is stable enough under argon to remain unchanged for >3 d at room temperature. However, the solution immediately turned colorless by exposing it to oxygen (or air) (Fig. 3B: b → c). Electron spin resonance (ESR) analysis of the blue solution showed a broad signal (g = 2.002) at –170 °C (Fig. 3), indicating the generation of radical species. Detailed control experiment suggested that the radical exists on the ligand of the cage. This unusual photooxidation is characteristic to the self-assembled molecular systems since none of the components (M, L, or G) can be eliminated from the $M_6L_4 \supset G_n$ assembly for the photooxidation and the radical formation.

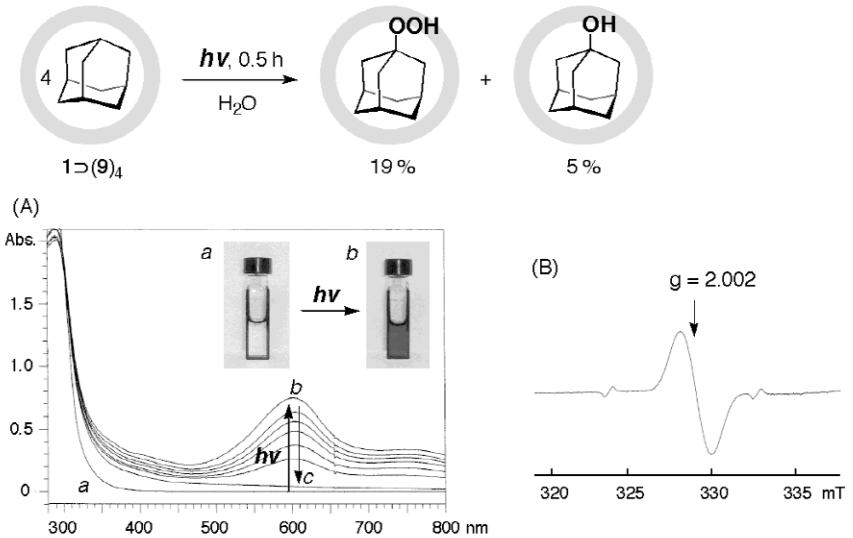


Fig 3 Photochemical oxidation of adamantane (**9**) within cage **1**. (A) UV–vis spectra of the aqueous solution of $\mathbf{1} \supset (\mathbf{9})_4$ at room temperature: (a) before photoirradiation; (b) after photoirradiation for 0.5 h under argon; color decay after the irradiation at 1, 4, 8, 18, and 24 h (each line). (c) After exposure to air. (B) ESR spectrum (H_2O, –170 °C, MnO as external standard) of $\mathbf{1} \supset (\mathbf{9})_4$ after photoirradiation for 0.5 h under argon.

CONCLUSION

We have shown chemical reactions that are controlled within the cavity of self-assembled coordination cage **1**. The reactions discussed here do not involve any catalyst or co-reagent, like transition metals or Lewis acids, which normally assist preorganization of substrates around the metal coordination sphere before the reaction. Namely, the reactions are controlled only by the spatial restriction governed by the cage. We note that the reaction control by the cavity is one of the most important essences of enzyme reactions. This essence can be achieved in laboratories only by large cavities of synthetic hosts. Metal-directed self-assembly obviously provides one of the most efficient methods to create large cavities that are capable of binding substrates in fixed orientations. We expect that potential ability of cavities can

be, in principle, infinitely expelled from the self-assembled cages. Furthermore, the creation of not only chemically but also physically and biologically interesting phenomena within the cavity is a challenging and on-going project in our laboratory.

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