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Host–Guest Systems

Highly Selective Photomediated 1,4-Radical Addition to *o*-Quinones Controlled by a Self-Assembled Cage**

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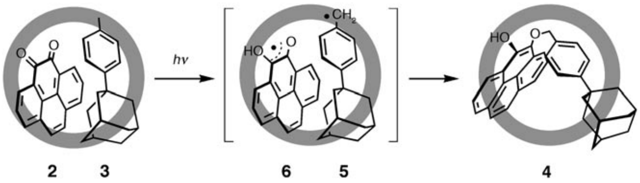
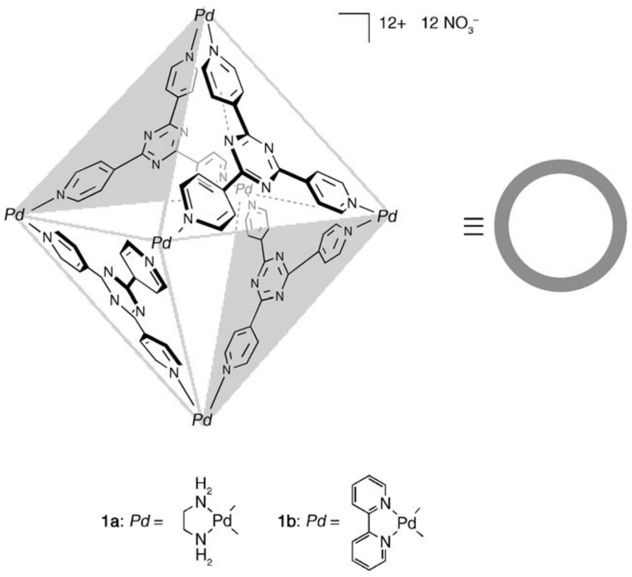
Regio- and stereoselective control in radical reactions is generally difficult, with reactions typically resulting in a complex mixture formed by various reaction pathways. Selective radical reactions can be achieved by rendering a specific pathway faster than all the other unfavorable pathways. Such control of reaction selectivity is often postulated in enzymatic reactions.[1] A substrate fixed in a specific orientation within an enzyme pocket is geometrically unable to react along common reaction pathways, thus leading to rather uncommon reaction products. In this way, radical reactions are strictly controlled by enzymes,[2] as typically observed in photosynthetic reactions.

We previously reported that self-assembled cage **1** (Scheme 1) can restrict the relative orientation of encapsulated substrates, thus leading to unusual products under thermal, photochemical, and radical conditions.[3] For example, the Diels–Alder reaction of anthracene proceeded at a terminal rather than a central benzene ring;[3b] the photoirradiation of an α-diketone gave intramolecular cyclized products, while common α-cleavage was completely suppressed.[3c] Herein we report that *o*-quinone **2** and substituted toluene **3**, coenclathrated in the cavity of **1**, are selectively transformed into an unusual 1,4-adduct **4** upon photoirradiation (Scheme 2).[4] The proposed reaction mechanism involves the 1,4-addition of benzylic radical **5**, formed by photoexcitation of quinone **2** and subsequent hydrogen abstraction from **3**.[5] We suggest that this unusual reaction takes place selectively as a consequence of unfavorable orientation of the reactant for otherwise predominant reaction pathways.



Scheme 2. Photoreaction of quinone **2** with **3** in the cavity of self-assembled coordination cage **1**.

Ternary complex **1a**·(**2**·**3**) was prepared as follows. Substrates **2** (7.0 µmol) and **3** (7.0 µmol) were suspended in an aqueous solution of cage **1a** (5 mM, 0.7 mL), and the mixture was stirred at 80 °C for 30 min. After removal of excess substrate by filtration, the ^{1}H NMR spectrum of the resulting filtrate showed desymmetrization of the host framework and highly upfield-shifted signals for **2** and **3**, thus indicating accommodation of the substrates into the cavity of **1a** (Figure 1). From the integral ratio in the NMR spectrum, the ratio of **2**/**3** in the inclusion complex was deduced to be 1:1. The ternary complex **1a**·(**2**·**3**) was formed in 70 % yield.



Scheme 1.

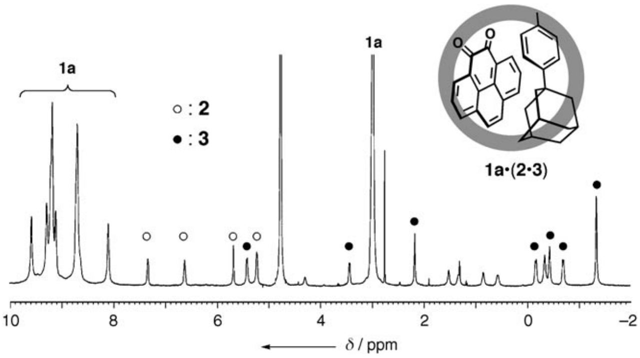


Figure 1. ^{1}H NMR spectrum of **1a**·(**2**·**3**) (500 MHz, D_2O, 300 K).

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Clear NOE correlations were observed between host and guests, suggesting the tightly fixed geometry of **2** and **3** in the cavity.[6] The coenclathration of **2** and **3** is essential for efficient inclusion: when quinone **2** alone was treated with cage **1**, formation of the inclusion complex **1**·(**2**)$_n$ was hardly observed. This finding indicates that the ternary complex is strongly stabilized by cooperative bimolecular recognition.[7]

The geometric restriction of substrates prior to reaction is particularly important for the reaction-pathway control. The geometry fixation in the **1b**·(**2**·**3**) complex was visualized by X-ray crystallography.[8] Single crystals of the **1b**·(**2**·**3**) complex suitable for diffraction study were obtained by the slow evaporation of the aqueous solution of **1b**·(**2**·**3**). Crystallographic analysis confirmed the restricted geometry of the guest molecules (Figure 2). The aromatic guest **2** is stacked with a planar ligand of **1** while substrate **3** with a bulky adamantyl group fills the remaining void. Notably, one of the carbonyl groups of **2** is in close proximity to the methyl group of **3**.

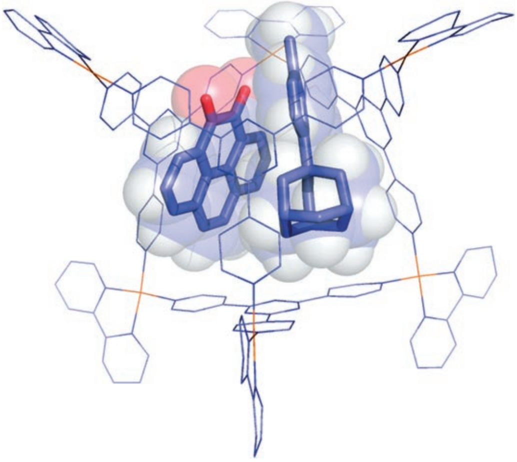

Figure 2. Crystal structure of **1b**·(**2**·**3**). For clarity, H atoms, anions and solvent molecules have been omitted. Cage **1b** is shown with thin lines, substrates **2** and **3** with thick lines. A space-filling depiction of **2** and **3** is shown in the background. C blue, O red, N black, Pd yellow.

Upon irradiation of the aqueous solution of **1a**·(**2**·**3**) (ultra-high-pressure mercury lamp, 5 min), we observed the selective formation of a single product in the cavity. From NMR spectroscopy and mass spectrometry analyses, the product was characterized as the 1,4-adduct **4**. The aromatic signals in the ^{1}H NMR spectrum showed that the pyrene framework was desymmetrized. Owing to conformational restriction within the cavity, the two methylene protons of **4** are diastereotopic and thus observed as an AB quartet, while they are observed as a singlet at $\delta = 5.3$ ppm after extraction from the cavity with an organic solvent (Figure 3). In the ESI mass spectrum, $[M+H]^+$ was observed at m/z 459. In the UV/Vis spectrum, the absorption band at $\lambda_{max} = 448$ nm (n–π* transition in **2**) disappeared after the reaction.[9] Instead, charge transfer (CT) between **1a** and **4** is clearly observed around 500 nm, owing to the increased donor ability of the aromatic moiety (see Figure S1 in the Supporting Information).

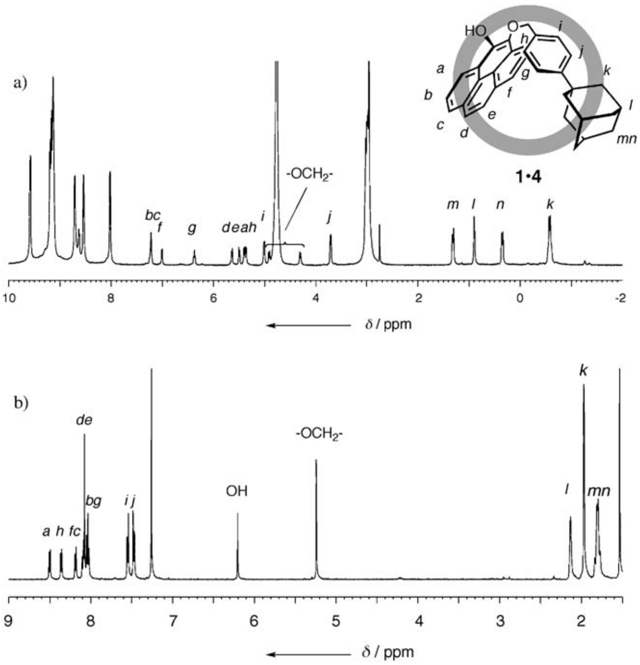

Figure 3. ^{1}H NMR spectra (500 MHz, 300 K) of a) the **1a**·**4** complex (D_2O) and b) 1,4-adduct **4** obtained after purification ($CDCl_3$).

A proposed reaction pathway involves a radical combination process (Scheme 2). The photoexcited *o*-quinone **2** abstracts hydrogen from **3** to generate benzylic radical **5** and semiquinone radical **6**, which subsequently combine at the radical centers. In general, photomediated radical coupling occurs through various reaction pathways to give a mixture of products. Since a radical center in a semiquinone is delocalized over the entire molecule, C-coupled 1,2-adduct as well as other coupling products at aromatic nuclei can be generated. Within the cage, however, the forced proximity of the reaction centers of **2** and **3** favors exclusive formation of the O-coupled 1,4-adduct **4**.

Phenanthrene-9,10-dione (**7**) was also employed for the highly selective photomediated radical addition in the cage. In this case, the formation of ternary complex **1a**·(**3**·**7**) was not exclusive. When **7** (7.0 μmol) and **3** (7.0 μmol) were suspended in the aqueous solution of **1a** (5 mM, 0.7 mL), we observed the formation of **1a**·(**3**·**7**) only in 22% yield, which was in equilibrium with inclusion complexes **1a**·(**3**)$_2$ (17%) and **1a**·**7** (22%). However, on irradiation of this equilibrium mixture for 5 min, 1,4-adduct **8** was selectively formed in 80% yield (Figure 4). This result indicated that equilibrium between the inclusion complexes is a rapid process. Once consumed by the photoaddition, **1a**·(**3**·**7**) is immediately supplied from **1a**·(**3**)$_2$ and **1a**·**7** by equilibration.

In the absence of cage **1**, we observed the formation of a complex mixture, in which the O-coupled 1,4-adduct **8** was not detected. From this control experiment, we emphasize that cage **1** accelerates only the O-coupling pathway while suppressing the others.

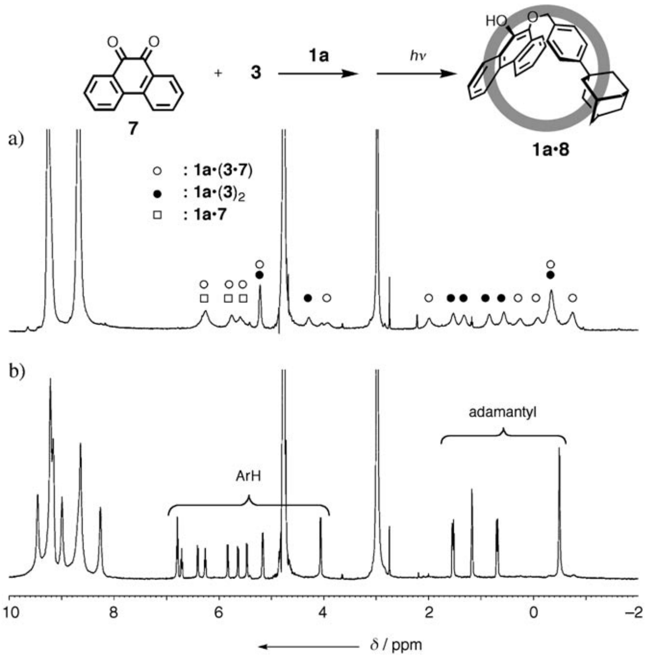

Figure 4. ^{1}H NMR spectra of the photoreaction of **7** and **3** within cage **1a** (500 MHz, D$_2$O, 300 K). a) An equilibrium mixture of **1a**·(**3**·**7**) (○), **1a**·(**3**)$_2$ (●), and **1a**·**7** (□). b) The **1a**·**8** complex obtained by photoirradiation.

In summary, we have achieved highly selective photoadditions to *o*-quinones within the cavity of **1**. Control of the relative orientation of substrates by the cavity makes a specific reaction pathway allowed while the others are forbidden, thus mimicking reaction control normally exhibited by enzymes.

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[8] Crystallographic data for **1b**·(**2**·**3**): tetragonal, space group $P4_12_12$, $T = 80(2)$ K, $a = b = 28.996(3)$ Å, $c = 30.280(6)$ Å, $V = 25459(6)$ Å^3, $Z = 4$, $\rho_{\text{calcd}} = 1.142\ \text{Mg}\,\text{m}^{-3}$, $R_1 = 0.1090$, $wR_2 = 0.3619$. CCDC-666355 contains the supplementary crystallographic data for this paper. These data can be obtained free of charge from The Cambridge Crystallographic Data Centre via www.ccdc.cam.ac.uk/data_request/cif.

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