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Unusual [2+4] and [2+2] Cycloadditions of Arenes in the Confined Cavity of Self-Assembled Cages

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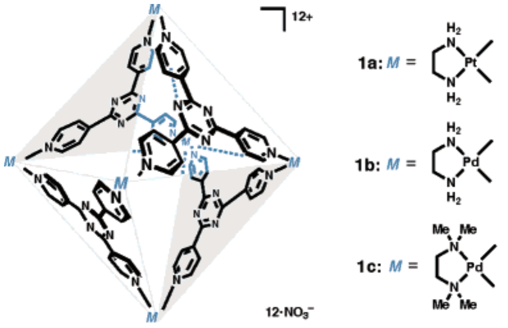
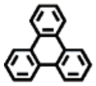
The induced proximity of reaction centers of two substrates in the confined cavity of cages reduces dramatically the entropy costs of reactions between substrates. This leads to unusual reactions between otherwise unreactive molecules. In solution, various organic hosts have provided confined cavities suitable for reactions.[1−7] However, the simultaneous recognition of two unreactive molecules followed by chemical reactions in the cavity has rarely been achieved. We have previously reported the strong binding of two or more substrates through hydrophobic forces in the cavity of self-assembled cage **1** in aqueous solution,[8] whereby two different substrates can be pairwise selectively recognized and their thermal and photochemical reactions are efficiently promoted under high regio- and stereocontrol. For example, syn-stereoselective [2+2] photoaddition of acenaphthylenes and 1,4-regioselective [2+4] (Diels−Alder) addition of anthracenes with maleimide derivatives have been reported.[7] We hereby report that highly stable arenes **2**−**6** can undergo [2+2] photo or [2+4] thermal additions cleanly inside the cavity of **1**, despite their inertness under ordinary conditions.

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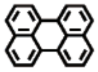
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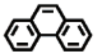
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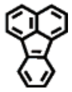
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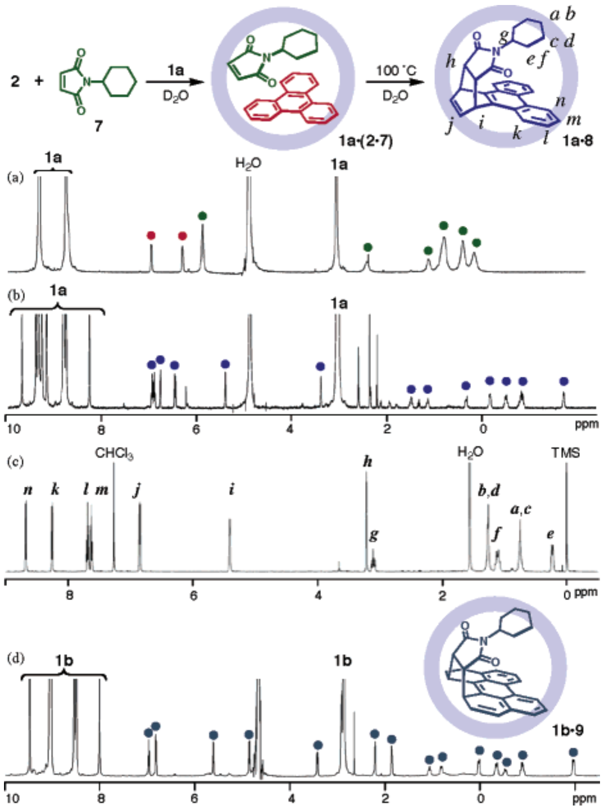

Figure 1. ^{1}H NMR observation of the Diels−Alder reactions of arenes within cage **1** (500 MHz, 27 °C): the spectra of (a) ternary complex **1a·**(**2·7**); (b) product **1a·8** (excess substrates were extracted with $CDCl_3$); (c) Diels−Alder adduct **8** obtained after purification ($CDCl_3$); (d) **1b·9** complex formed by the reaction of **3** and **7** with **1b** in D_2O. The structure of **1** is cartooned by a blue circle.

Triphenylene (**2**) is a highly stable, aromatic, compound which is expected to show very poor reactivity as an olefin or a diene. To date, pericyclic reactions involving this substrate have not been reported. We found that this inert molecule can undergo the Diels−Alder reaction with *N*-cyclohexylmaleimide (**7**) when trapped inside the cavity of cage **1**. Compounds **2** (15.0 μmol) and **7** (15.0 μmol) were suspended in the aqueous solution of **1a** (5.0 mM, 1.0 mL) containing a small amount of hexane. After stirring for 1 h at 80 °C, we observed the formation of the ternary complex **1a·**(**2·7**) in approximately 40% NMR yield based on cage **1a** (Figure 1a). When the solution was heated further (at 100 °C for 24 h), we observed the almost quantitative conversion to a single product (Figure 1b). The product was extracted with chloroform and identified by NMR and MS as compound **8**, that is, an endo Diels−Alder adduct at one of the benzene rings of **2** (Figure 1c). The syn stereochemistry of **8** was confirmed via a NOESY experiment. Molecular modeling predicts that, owing to the steric demand of *N*-cyclohexyl group on **7**, the dienophile unit can be oriented toward one of the benzene rings of **2**, thus facilitating the [2+4] pericyclic reaction.[9]

Under similar conditions, perylene (**3**) also afforded the endo Diels−Alder adduct **9** (Figure 1d). After stirring for 24 h at 80 °C in D_2O, the reaction between **3** and **7** within the cage **1b** resulted in the formation of **1b·9** complex in 90% NMR yield (based on cage **1b**). A NOESY experiment indicated the syn stereochemistry of **9**. In addition to NMR characterization, the structure of **9** was confirmed by the single-crystal X-ray diffraction of the analogous **1c·9** complex (Figure 2a).[10] Previous reports showed that the Diels−Alder adduct of **3** can be easily air-oxidized to reproduce perylene aromaticity.[11] When the guest **9** was extracted from the cage by treatment with chloroform, we observed its air-oxidation to give the aromatized compound within 30 min. When encapsulated,

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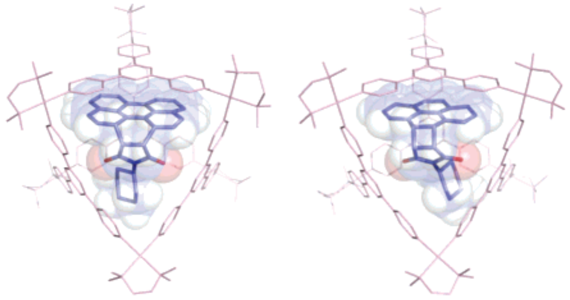


Figure 2. Crystal structures of (a) **1c·9** and (b) **1c·10**.

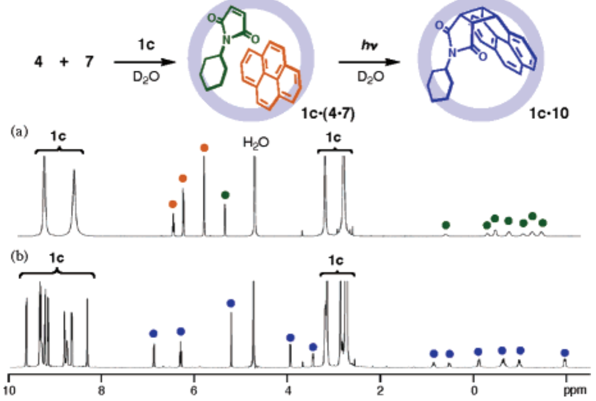


Figure 3. ^{1}H NMR observation of [2+2] photoaddition of **4** and **7** within cage **1c**. Spectra (a) before and (b) after irradiation for 6 h (500 MHz, D_2O, 27 °C) are given.

however, the adduct **9** was shown to be very stable toward oxidation even at 80 °C, suggesting the considerable stabilization of **9** inside the cavity.

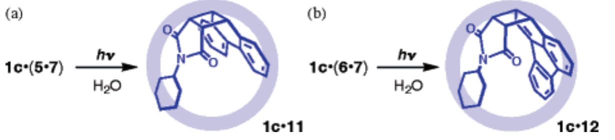
We also studied the [2+2] olefin photodimerization of polycyclic aromatic compounds, which are known to be inert under ordinary photochemical conditions.[12] Ternary complex **1c**·(**4**·**7**) was formed in 81% yield by suspending pyrene (**4**, 15.0 μmol) and **7** (15.0 μmol) in the aqueous solution of **1c** (5.0 mM, 1.0 mL; Figure 3a). After the excess substrates were removed by filtration, the aqueous solution was irradiated with a high-pressure mercury lamp (400 mW, 6 h at room temperature). NMR spectroscopy confirmed the quantitative formation of the pyrene-maleimide [2+2] cross adduct **10** (Figure 3b). The structure of **10**, indicating syn stereochemistry, was unambiguously determined by NMR spectroscopy and by the X-ray crystallographic analysis of **1c·10** (Figure 2b).[10]

We believe that the steric demand of *N*-cyclohexyl group of maleimide **7** is essential in this reaction. According to the predicted force-field optimized structure, the olefin group of **7** is in close proximity to the C4−C5 double bond of **4** prior to the reaction.[9] When a less sterically demanding group (such as Me, Et, Ph, or $PhCH_2$) was used as the N-substituent at maleimide, this substrate adopted different orientation as predicted by force-field calculation. Experimentally, these derivatives showed no reactivity in the [2+2] photoaddition with **4**.[13]

Highly efficient, syn-selective [2+2] photoaddition was also carried out in the reaction of phenanthrene (**5**) and **7** under the similar conditions to give adduct **11** in 81% yield (based on cage **1c**; Scheme 1a).

We were also intrigued by the [2+2] photoaddition of the maleimide **7** to fluoranthene (**6**). In **6**, the LUMO is equally delocalized over the molecule, rendering the reaction site unpredictable.[9] When the ternary complex **1c**·(**6**·**7**) was irradiated ($\lambda = 365$ nm) in D_2O for 5 min (room temperature), we observed eight new signals in the aromatic region of the ^{1}H NMR spectrum. The product **12** was extracted with chloroform and its solution structure was assigned by COSY and NOESY experiments. This product was formed from **6** after the [2+2] photoaddition of **7** to the C2−C3 double bond (Scheme 1b). The high regioselectivity of this reaction can presumably be ascribed to the inclusion geometry control of the substrates by the cavity of **1** rather than to orbital control.

Scheme 1. [2+2] Photoadditions of (a) **5** or (b) **6** with **7** in Cage **1**



In summary, the confined cavity of cage **1** was shown to efficiently promote the thermal [2+4] and photochemical [2+2] cycloadditions of aromatic molecules, which are relatively inert under ordinary thermal and photochemical conditions. The formation of a hydrophobic pocket in water, having the ability to bind substrates and force them into orientations that favor specific reaction paths could promote entropically unfavorable reactions. These type of processes usually take place in elaborate natural enzyme pockets. Through the present study, we have demonstrated that the hydrophobic binding pocket of the self-assembled cage **1** is also highly effective in promoting such reactions, and its behavior is reminiscent of that of enzymes' reaction pockets.

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Supporting Information Available: Experimental procedures, physical properties and crystallographic data. This material is available free of charge via the Internet at http://pubs.acs.org.

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(13) With these substituents, the thermal [2+4] reactions did not take place either. The remarkable substituent effect implies that the geometry control is important while the activation of the dienophile by Pd or Pt ions is unlikely.

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