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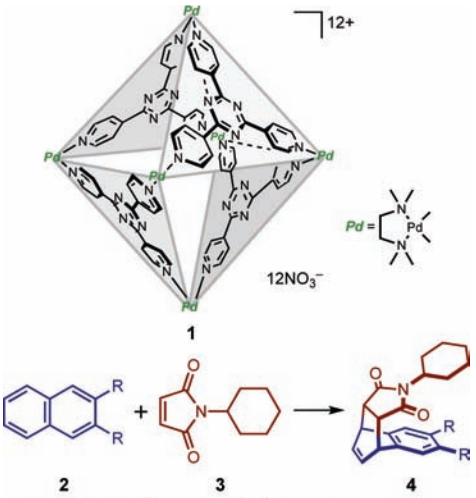
Naphthalene Diels−Alder in a Self-Assembled Molecular Flask

Takashi Murase, Shinnosuke Horiuchi, and Makoto Fujita*

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

Received December 21, 2009; E-mail: mfujita@appchem.t.u-tokyo.ac.jp

Despite their potential utility in synthetic chemistry, Diels−Alder reactions involving naphthalene are notoriously stubborn and require either electronic modulation (i.e., Lewis acid activation of dienophiles or distortion of naphthalene by peri-1,4-substitution) or harsh conditions (e.g., elevated pressures and/or neat conditions).[1] A common fallacy is the assumption that the reduction of aromatic stabilization (~250 kJ mol^{-1} for naphthalene to ~150 kJ mol^{-1} for benzene) is responsible for the lack of reactivity.[2] However, quantum-mechanical and thermochemical calculations show that the reaction is exothermic ($\Delta H \approx -30$ kJ mol^{-1}) and indicate that the entropic cost of the multicentered reaction is significant.[1f] Within molecular flasks,[3] such as self-assembled cage **1**,[4,5] the increase in the effective concentration and preorganization of the reactants greatly reduce the entropic cost and should favor an increase in the naphthalene reactivity as a diene. Expecting a reduction in entropic cost and subsequent increase in reactivity, we found that the Diels−Alder reactions of naphthalenes with maleimide **3** within cage **1** proceed smoothly under mild conditions.[6] Alkyl substituents at the naphthalene C2 and C3 positions were necessary to ensure optimal preorganization but are not electronically significant, as the Diels−Alder reaction occurred at the less electron-rich, unsubstituted ring of the naphthalene.



a: R = H; b: R = Me; c: R = Et; d: R = *n*-Pr
e: R,R = $-(CH_2)_4-$; f: R,R = $-O(CH_2)_2O-$

When 2,3-diethylnaphthalene (**2c**, 15.0 μmol) and *N*-cyclohexylmaleimide (**3**, 15.0 μmol) were suspended in an aqueous solution of cage **1** (5.0 mM, 1.0 mL) at room temperature, the ternary complex **1**·(**2c**·**3**) was formed in 71% yield, as determined by NMR analysis (Figure 1a,b). The proton signals of the guests **2c** and **3** were shifted significantly upfield upon formation of the ternary complex (Figure 1b). After the aqueous solution was heated at 100 °C for 8 h, the signals derived from **2c** and **3** disappeared, and a set of new signals appeared in the ^{1}H NMR spectrum (Figure 1c); integration indicated that 60% of the included **2c** was converted to **4c**. No side reactions were observed, but partial sublimation of the reactants under these conditions reduced the product yield. In the absence of cage **1**, the Diels−Alder reaction did not occur.

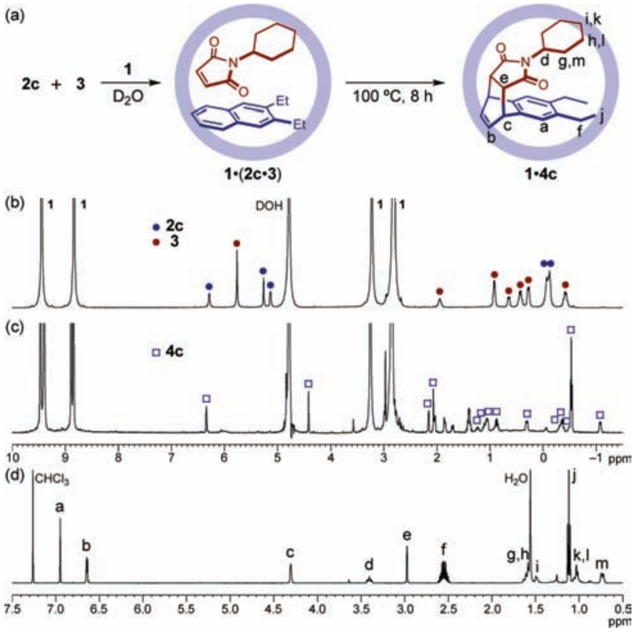


Figure 1. Diels−Alder reaction of naphthalene **2c** with maleimide **3** within cage **1**. (a) Schematic representation of pair-selective encapsulation of substrate **2c** and **3** within cage **1** and the subsequent Diels−Alder reaction leading to adduct **4c**. (b−d) ^{1}H NMR spectra (500 MHz, 300 K) of (b) ternary complex **1**·(**2c**·**3**) (in D_2O), (c) product **1**·**4c** (in D_2O), and (d) adduct **4c** obtained after purification (in $CDCl_3$).

After the product was extracted with chloroform, the structure of **4c** was determined by NMR spectroscopy (1D and 2D) and mass spectrometry. The syn stereochemistry was revealed by the shielding of the *N*-cyclohexyl protons ($H_{g-i,k-m}$: $\Delta\delta \approx 0.5$ ppm) due to the nearby benzene ring (Figure 1d). A clear nuclear Overhauser effect (NOE) correlation between the vinyl protons (H_b) and the bridgehead protons (H_e) also supported the assigned stereochemistry. The structure of **4c** was ultimately confirmed by X-ray crystallographic analysis of the inclusion complex **1**·**4c** (Figure 2).[7] The crystal structure clearly shows the syn stereochemistry and emphasizes the tight packing of **4c** in the cavity of cage **1**.

The regio- and stereoselectivity of the reaction were unusual and warrant further discussion. The diethyl substituents donate electron density to one of the two six-membered rings of **2c**, so this ring should be the more reactive one. However, the reaction occurred at the nonsubstituted ring. The syn stereoisomer **4c** arises via the transition state where, unlike common Diels−Alder reactions, dienophile **3** is oriented exo with respect to the naphthalene diene. The unusual regio- and stereoselectivity can both be explained by

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considering preorganization within the cavity of cage **1**. Within the restricted cavity, the substrates presumably adopt a conformation resembling the exo transition state, where the dienophile is in close proximity to the diene of the unsubstituted six-membered ring. The snug fit of the substrates (as implied by the X-ray structure of **1**·**4c**) precludes rearrangement, and the single regio- and stereoisomer is obtained.

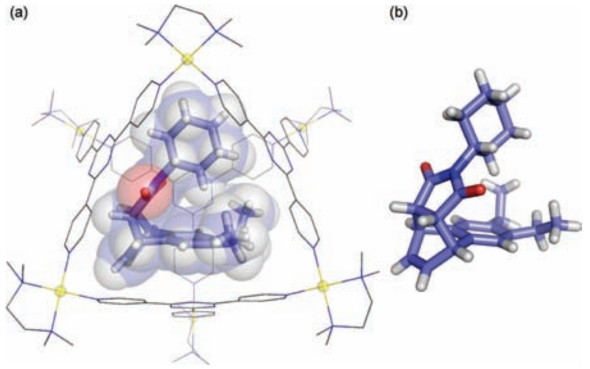
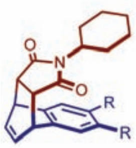


Figure 2. Crystal structures of (a) **1**·**4c** and (b) adduct **4c** only. For clarity, only one disordered position of **4c** is shown.

Table 1. Product Yields and Rate Constants for the Reactions[a]

	Product	Yield (%)[b]	Rate constant ($\times 10^{-5}$ s^{-1})
	**4a** (R = H)	0	–[c]
	4b (R = Me)	8	–[c]
	4c (R = Et)	60	4.1
	4d (R = *n*-Pr)	64	6.2
	4e (R,R = –(CH$_2$)$_4$–)	62	2.8
	4f (R,R = –O(CH$_2$)$_2$O–)	0	–[c]

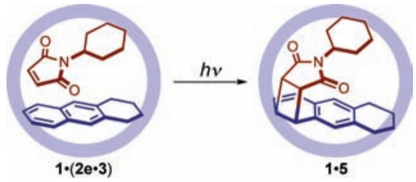
[a] Reaction conditions: **1**·(**2**·**3**) (5 mM), D$_2$O, 100 °C, 5−16 h. [b] NMR yields based on **1**·(**2**·**3**). [c] Not determined.

The tight packing of substrates within the cavity of cage **1** facilitates the increased reactivity. Alkyl substitution is essential, as revealed by the substituent effects summarized in Table 1. Although parent naphthalene **2a** and maleimide **3** formed a ternary complex **1**·(**2a**·**3**) within cage **1**, no Diels−Alder reaction occurred because of the reduced molecular volume and the resulting ill-defined substrate preorganization (see Figure S31a in the Supporting Information). The steric bulk afforded by methyl substitution in **2b** sufficed to induce reactivity, but the conversion was quite low (8%). Efficient packing and preorganization occurred when the alkyl chains were increased to ethyl, *n*-propyl, and fused cyclohexyl groups, and the adducts **4c**−**e** were formed in good yields (60−64%). The rate constants increased with increasing steric bulk [fused cyclohexyl (**2e**) < diethyl (**2c**) < di-*n*-propyl (**2d**)], suggesting that the packing and preorganization are more efficient in this order.

Substituted naphthalenes **2b**−**f** revealed that steric and not electronic factors control the reactivity and selectivity. First, the Diels−Alder reactions proceeded at the nonsubstituted naphthalene ring; in the confined space, the orientations of the substrates are restricted, and only the unsubstituted ring of **2b**−**e** can be in close proximity with the C=C double bond of dienophile **3**. Second, the electron-rich dialkoxy-substituted naphthalene **2f** provides a similar steric bulk as **2e** and formed the necessary ternary complex but did not undergo the Diels−Alder reaction. Presumably, the ether oxygen atoms reduced the hydrophobicity of **2f**, loosening its packing in the hydrophobic cavity.

The tight packing structure of the substrates within the cage also enables efficient [2 + 2] photoadditions (Scheme 1). When ternary complex **1**·(**2e**·**3**) was irradiated with a high-pressure mercury lamp for 1 h at room temperature, the single photoadduct **5** was obtained in 93% NMR yield with the syn configuration (Figure S22). Again, similar 5,6-regioselectivity was observed for the photoaddition of naphthalene **2e**.

Scheme 1. Photocycloaddition of Naphthalene **2e** with Maleimide **3** within Cage **1**



In summary, we successfully engineered the regio- and stereoselective Diels−Alder reaction of typically unreactive naphthalenes using a self-assembled molecular flask. The molecular flask brings the reactants into close proximity, fixes their relative orientations within the restrictive cage, and switches the reaction profile from a bimolecular to a pseudointramolecular reaction pathway.[8] The high entropy costs of bimolecular reactions are thus circumvented, and unusual reactions between otherwise unreactive molecules can occur.

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

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