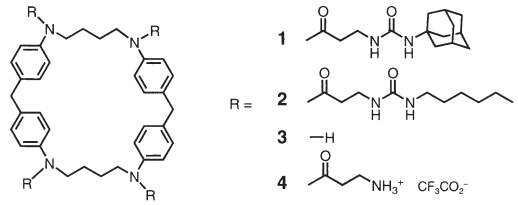
Molecular Recognition by Supramolecular Hosts Composed of an Adamantyl-appended Macrocycle with Cyclodextrins in Water

Osamu Hayashida* and Itaru Hamachi
Institute for Fundamental Research in Organic Chemistry, Kyushu University, Fukuoka 812-8581

(Received December 26, 2002; CL-021104)

A supramolecular system composed of a cyclophane bearing adamantyl moieties with cyclodextrins was developed. The binding affinities of cyclophane toward fluorescent guests such as TNS were effectively retained even when the host was assembled with α-cyclodextrin in neutral aqueous media. Its binding site was significantly apolar and well shielded from the bulk aqueous phase. The marked motional repression was also observed for the entrapped guest molecules.

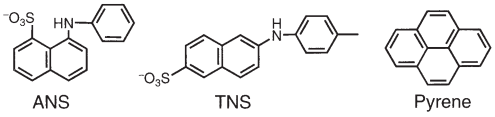
The development of supramolecular systems is a modern strategy for creating nanometer-sized cavities or capsules which are capable of performing sophisticated molecular recognition and catalytic function.[1,2] From such a view point, we have been employing a system composed of a cyclophane bearing adamantyl moieties with α- and β-cyclodextrins (CDs) as a supramolecular host in water. Under the formation of supramolecules, the cyclophane moiety was designed to provide a cavity for guest-binding, while CDs afford solubility in water by masking the hydrophobic adamantyl moieties of the cyclophane. We report here on molecular recognition behavior toward hydrophobic guests by the supramolecular hosts composed of adamantyl-appended cyclophane (**1**) with α-CD in neutral aqueous solution.



Cyclophane **1**[3] was prepared by the reaction of 1-adamantyl isocyanate with tetraammonium trifluoroacetate **4** which was synthesized by DCC condensation of tetraaza-[6.1.6.1]paracyclophane **3** with Boc-β-alanine, followed by removal of the protecting groups with trifluoroacetic acid. Host **1** shows hydrophobic characteristics originating from macrocyclic cyclophane and adamantyl moieties, so that host **1** alone has limited solubility in water. On the other hand, water-soluble α- and β-CDs provide apolar internal cavities with inner diameters[4] of 5.7 Å and 7.8 Å, respectively, which are capable of solubilizing hydrophobic guests with suitable molecular size and shape through inclusion complexes in water.[4] 1-Adamantanecarboxylate[5] and 1-adamantylammonium[6] are good guests for β-CD with binding constants (K) of 3.9×10^4 and $1.1 \times 10^5\ M^{-1}$, respectively, and moderate guests for α-CD with K of 141 and $269\ M^{-1}$, respectively. Upon addition of **1** to aqueous solutions containing a large excess amount of α-CD or β-CD, host **1** was successfully dissolved to give a supramolecular assembly (**1**·α-CD and **1**·β-CD, respectively), as shown in Scheme 1 for the former complexes. At least within the concentration range of $7\ \mu mol\ dm^{-3} - 0.04\ mmol\ dm^{-3}$ of **1** in the presence of CD ($10\ mmol\ dm^{-3}$), a good linear Beer's plot of absorbance at 240 nm was observed.[7] On the other hand, analogous derivative **2** lacking the adamantyl group gave precipitates in aqueous CD solution. Adamantyl residues of host **1** is responsible for the complexation with CDs and the resulting complexes are water-soluble. Upon complexation with β-CD, circular dichroism phenomena were induced in the absorption ranges of host **1** through its stereochemical interaction with chiral cavities of CD; $[\theta] = -2.3 \times 10^4\ deg\ cm^2 dmol^{-1}$ at 280 nm.[8]

Scheme 1. Schematic representation for the formation of supramolecular assembly composed of **1** and CDs, and its complex with guest.

The guest-binding behavior of the resulting supramolecular host (**1**·α-CD) toward various fluorescent guests such as 8-anilinonaphthalene-1-sulfonate (ANS), 6-*p*-toluidinonaphthalene-2-sulfonate (TNS), and pyrene was examined by fluorescence spectroscopy in neutral aqueous solution at 298 K.



Upon addition of **1** to aqueous α-CD solutions containing each of the guests, a fluorescence intensity originated from the guest molecules was subjected to increase (along with a concomitant blue shift of the fluorescence maximum for ANS and TNS), showing simple saturation behavior (Figure 1). The stoichiometry for the complexes was found to be 1:1 host:guest confirmed by Job plots. The K of **1**·α-CD toward ANS, TNS, and pyrene were evaluated on the basis of Benesi–Hildebrand

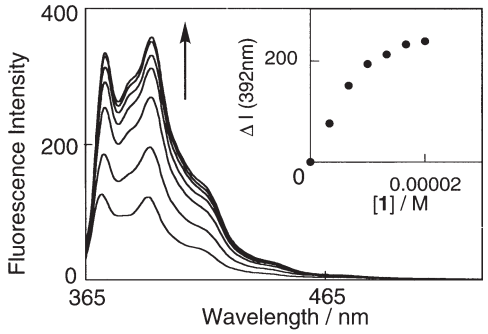


Figure 1. Fluorescence spectra of pyrene ($0.5\ \mu mol\ dm^{-3}$) upon addition of **1** in H_2O in the presence of α-CD ($10\ mmol\ dm^{-3}$). [**1**] (from bottom to top) = 0, 3.3, 6.7, 10, 13, 17, and 20 $\mu mol\ dm^{-3}$. Inset; fluorescence titration curve of pyrene with **1** in the presence of α-CD.

Table 1. Binding constants (K) for host-guest complexes in H_2O at 298 K

Host	K, M^{-1}		
	ANS	TNS	Pyrene
1·α-CD	4,100	11,000	110,000
α-CD[9–11]	26	25	148
3[a,12]	6,300	69,000	270,000

[a] In 50 mM KCl-HCl buffer (pH 2.0). Host **3** was not soluble in a neutral aqueous solution.

relationship, and are summarized in Table 1 together with the corresponding values reported for α-CD and simple cyclophane **3** as a cationic host. As is obvious from the data in Table 1, the K values for the supramolecular host with the guests are much greater than the corresponding values for α-CD and comparable orders to those of **3**. In contrast to that host **3** acts as a water-soluble host only in acidic aqueous media, the present **1**·α-CD can do even in neutral aqueous solution. The binding affinities of cyclophane toward such guest molecules are effectively retained even when the host is assembled with α-CD in neutral aqueous solution. On the other hand, there was little change in fluorescence spectra originating from the guests, upon addition of **1** to aqueous β-CD solutions containing these guests. The results indicate that the guest molecules were predominantly incorporated into β-CD, not into **1**.

Since the emission of fluorescent probes such as ANS and TNS is extremely sensitive to change in microenvironmental polarity experienced by the molecules, the microenvironmental characteristics were evaluated from the fluorescence maximum in a manner similar to that reported previously.[13] Supramolecular host **1**·α-CD provides relatively apolar microenvironments for the hydrophobic guest, ANS (Table 2). The microenvironmental polarity parameter,[14] E_T^N value for ANS in host **1** ($E_T^N = 0.45$; the value corresponding of 3-pentanol (0.45)) is much smaller than that for ANS upon complexation with α-CD and cationic cyclophane **3** ($E_T^N = 0.90$ and 0.87, respectively). Thus, the binding site provided supramolecularly by the macrocyclic cavity of **1** and the adamantly side-chains complexed with α-CD is considered to be significantly apolar and well shielded from the bulk aqueous phase. Furthermore, relatively large fluorescence polarization value (P) was obtained for ANS incorporated into **1**·α-CD compared with the values by host **3** (Table 2). This also indicates that a desolvated microenvironment is apparently provided by host **1**·α-CD so that the tight host-guest interaction, which brings about the marked motional repression of the entrapped guest, becomes effective. A possible computer-generated CPK model of the complex of **1**·α-CD with pyrene was shown in Figure 2, which was optimized using MM2 force fields. Similar microenvironmental properties of the internal cavity furnished by the present supramolecular host were also clarified for the complexation with TNS by the identical methods (Table 2).

Table 2. Microenvironmental polarity (E_T^N) and fluorescence polarization values (P) for entrapped guests in H_2O at 298 K

Guest	Host	E_T^N (λ_{ex}/nm; λ_{em}/nm)[a]	P
TNS	None	1.00 (326; 500)	—[b]
TNS	α-CD	0.92 (326; 476)	—[b]
TNS	**3**[c]	0.93 (326; 480)	0.11
TNS	**1**·α-CD	0.24 (326; 412)	0.33
ANS	None	1.00 (375; 515)	—[b]
ANS	α-CD	0.90 (375; 500)	—[b]
ANS	**3**[c]	0.87 (375; 495)	0.12
ANS	**1**·α-CD	0.45 (375; 465)	0.34

[a] Excitation and emission wavelengths, in this sequence.
[b] Not determined due to a weak fluorescence intensity.
[c] In 50 mM KCl–HCl buffer (pH 2.0).

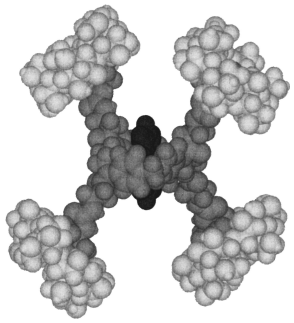


Figure 2. Possible computer-generated CPK model of the complex of **1**·α-CD with pyrene. Black, dark, and light dark represent pyrene, **1**, and α-CD, respectively.

In conclusion, the present study demonstrates the formation of supramolecular hosts formed with an adamantyl-appended cyclophane and CDs as well as the quantitative guest-binding affinity of **1**·α-CD toward hydrophobic guests. Branched cyclodextrins such as maltosyl-α-CD[15] were also found to be form supramolecular complexes with **1**. The resulting supramolecular hosts are expected to be used in saccharide-directed delivery or targeting systems of drugs as a guest to the specific saccharide-binding biological surfaces. Further studies are currently in progress along this line.

References and Notes

1 a) J. Rebek, Jr., *Chem. Commun.*, **2000**, 637. b) O. Hayashida, A. Shivanyuk, and J. Rebek, Jr., *Angew, Chem., Int. Ed. Engl.*, **41**, 3423 (2002).
2 M. Fujita, K. Umemoto, M. Yoshizawa, N. Fujita, T. Kuzukawa, and K. Biradha, *Chem. Commun.*, **2001**, 509.
3 **1**; 600 MHz ^{1}H NMR (DMSO-d_6, 298 K) δ 1.29 (NCH_2CH_2), 1.60, 1.82, and 1.98 (Ad-H), 1.93 ($NCOCH_2$), 3.03 ($CH_2NHCONH$), 3.50 (NCH_2CH_2), 3.95 ($ArCH_2Ar$), 5.6 (NHCONH), 7.00 (ArH(ortho)), 7.32 (ArH(meta)). HRMS (FAB) calcd for $C_{90}H_{121}N_{12}O_8$: 1497.9423. Found: 1497.9427.
4 J. Szejtli, *Chem. Rev.*, **98**, 1743 (1998).
5 a) R. I. Gelb, L. M. Schwartz, and D. A. Laufer, *Bioorg. Chem.*, **9**, 450 (1980). b) R. I. Gelb, L. M. Schwartz, and D. A. Laufer, *J. Chem. Soc., Perkin Trans. 2.*, **1984**, 15.
6 B. Zhang and R. Breslow, *J. Am. Chem. Soc.*, **115**, 9353 (1993).
7 At higher (>0.05 mmol dm^{-3}) concentrations of **1**, their optical density was deviated from Beer's law through formation of aggregates.
8 A similar induced circular dichroism band was observed for **1** in aqueous α-CD solution ($[\theta] = -1.2 \times 10^4$ deg $cm^2 dmol^{-1}$ at 240 nm), even though its intensity was weakened reflecting differences in their molecular arrangements of the complexes.
9 I. K. Chun and M. H. J. Lee, *J. Korean Pharm. Sci.*, **19**, 71 (1989).
10 F. Venema, H. F. M. Nelissen, P. Berthault, N. Birlirakis, A. E. Rowan, M. C. Feiters, and R. J. M. Nolte, *Chem. –Eur. J.*, **4**, 2237 (1988).
11 L. A. Blyshak, I. Warner, and G. Patonay, *Anal. Chem. Acta*, **232**, 239 (1990).
12 T. Soga, K. Odashima, and K. Koga, *Tetrahedron Lett.*, **21**, 4351 (1980).
13 O. Hayashida, K. Ono, and Y. Murakami, *Supramol. Chem.*, **11**, 1 (1995).
14 C. Reichardt, "Solvents and Solvent Effects in Organic Chemistry," VCH Verlagsesellschaft, Weinheim (1988), Chap. 7.
15 N. Ono, H. Arima, F. Hirayama, and K. Uekama, *Biol. Pharm. Bull.*, **24**, 395 (2001).