ORGANIC
LETTERS

2011
Vol. 13, No. 17
4570–4573

Strong Guest Binding by Cyclodextrin Hosts in Competing Nonpolar Solvents and the Unique Crystalline Structure

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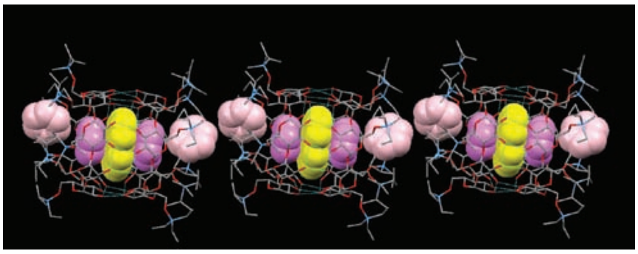
Received June 30, 2011

ABSTRACT



6-*O*-Modified β-cyclodextrins, such as heptakis(6-*O*-triisopropylsilyl)-β-cyclodextrin (TIPS-β-CD) and heptakis(6-*O*-*tert*-butyldimethylsilyl)-β-cyclodextrin (TBDMS-β-CD), formed 2:1 inclusion complexes with pyrene in benzene and cyclohexane with high association constants. The X-ray crystalline structure of the TIPS-β-CD−pyrene complex obtained from the benzene solution showed that one pyrene molecule was incorporated in the form of a sandwich-type complex with two benzene molecules within the cavity of the dimer formed by two TIPS-β-CD molecules.

Cyclodextrins (CDs) and their derivatives have played a crucial role in various fields including supramolecular chemistry and analytical science due to their unique properties to form inclusion complexes with a great variety of molecules.[1−3] However, in most cases, inclusion complex formation with CD hosts has been limited to aqueous media[4] and several kinds of polar organic media.[5,6] On the other hand, the effective guest inclusion into CD hosts in nonpolar media has not been achieved yet, possibly because the main driving force for the guest inclusion is hydrophobic interactions and/or van der Waals interactions between the guests and the CD cavity, and thus the enormous amounts of nonpolar solvents become a strong competitor for inclusion within the CD cavity.[7−10] The successful guest inclusion in nonpolar media can be expected to open new applications for CDs, for instance, the development of adsorbents and sensors for removal and detection of harmful organic compounds in oils, the creation of a stereoselective reaction field in nonpolar solvents, and the construction of supramolecular architectures in nonpolar media. In addition, there is a great potential to shed some light on improvements in CD−guest binding that has not been successfully carried out in water and polar media. Recently, we found that heptakis(6-*O*-*tert*-butyldimethylsilyl)-β-cyclodextrin (TBDMS-β-CD) formed inclusion complexes with polychlorinated aromatic compounds in nonpolar media such as benzene-d_6 and cyclohexane-d_{12}, possibly through dipole−dipole interactions

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10.1021/ol2017627

between the CD cavity and the guest molecule, as well as the spatial fit of the guest into the CD cavity.[11] More recently, by reference to our finding, Takata et al. succeeded in polyrotaxane formation by utilizing the complexation between permethylated α-CD and amine-terminated poly(tetrahydrofuran) in nonpolar media.[12] However, effective inclusion complex formation between CDs and guests in nonpolar media, which leads to stronger CD–guest binding than in aqueous and polar media, has remained a challenging subject. We report herein that the strong binding of pyrene, as a nonsubstituted aromatic guest, in benzene and cyclohexane was realized by using supramolecular dimers of 6-*O*-modified *β*-CDs as hosts. Crystallographic study of the 6-*O*-modified *β*-CD–pyrene complex obtained from the benzene solution showed a unique inclusion mode among 6-*O*-modified *β*-CD, pyrene, and the solvent. To the best of our knowledge, this is the first example of a crystalline structure for an inclusion complex formed between a cyclodextrin derivative and a guest in a nonpolar solvent.

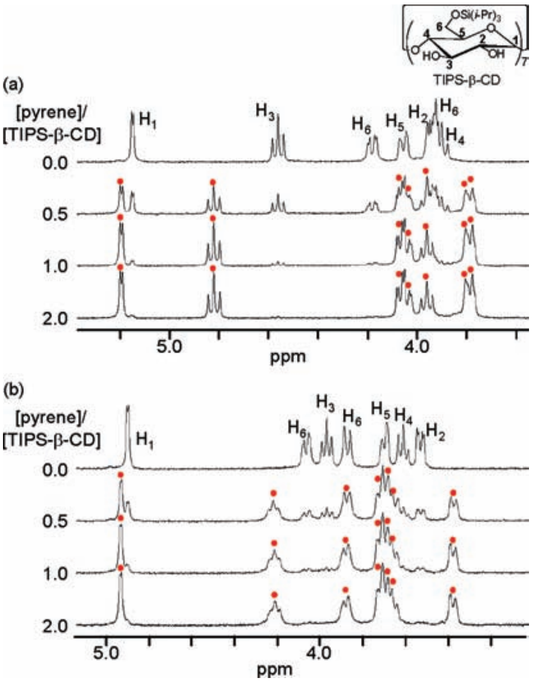

Figure 1. ^{1}H NMR spectral changes observed for TIPS-*β*-CD (1.0×10^{-3} mol L^{-1}) (a) in benzene-d_6 and (b) in cyclohexane-d_{12} upon addition of pyrene at 25 °C.

$$2\ \text{host} + \text{pyrene} \overset{K}{\rightleftarrows} (\text{host})_2 \cdot \text{pyrene} \qquad (1)$$

$$\text{host} + \text{pyrene} \overset{K_1}{\rightleftarrows} \text{host} \cdot \text{pyrene} \qquad (2)$$

$$\text{host} \cdot \text{pyrene} + \text{host} \overset{K_2}{\rightleftarrows} (\text{host})_2 \cdot \text{pyrene} \qquad (3)$$

Table 1. Association Constants between 6-*O*-Modified *β*-CDs (TIPS-*β*-CD and TBDMS-*β*-CD) and Pyrene in Nonpolar Solvents at 25 °C

	association constant		
	K (L^2 mol^{-2})^a	K_1 (L mol^{-1})^b	K_2 (L mol^{-1})^b
TIPS-*β*-CD			
in benzene	$(3.9 \pm 0.77) \times 10^7$	$(1.3 \pm 0.13) \times 10^3$	$(3.3 \pm 0.36) \times 10^4$
in cyclohexane	$(1.3 \pm 0.35) \times 10^8$	$(1.7 \pm 0.51) \times 10^3$	$(4.0 \pm 1.1) \times 10^4$
TBDMS-*β*-CD			
in benzene	$(6.1 \pm 1.6) \times 10^7$	$(2.8 \pm 0.49) \times 10^3$	$(1.8 \pm 0.37) \times 1\ 0^4$
in cyclohexane	$(1.3 \pm 0.42) \times 10^8$	$(3.1 \pm 0.81) \times 10^3$	$(2.7 \pm 0.38) \times 10^4$

[a] Determined by NMR titration in the corresponding deuteration solvent (benzene-d_6 or cyclohexane-d_{12}). [b] Determinated by fluorescence titration.

$$K = [(\text{host})_2 \cdot \text{pyrene}]/([\text{host}]^2[\text{pyrene}]) = K_1 \cdot K_2 \qquad (4)$$

We have chosen heptakis(6-*O*-triisopropylsilyl)-*β*-CD (TIPS-*β*-CD) and heptakis(6-*O*-*tert*-butyldimethylsilyl)-*β*-CD (TBDMS-*β*-CD) as CD hosts, based on our recent finding.[11] TIPS-*β*-CD was prepared by reference to the synthetic method for heptakis(2,3-di-*O*-methyl-6-*O*-triisopropylsilyl)-*β*-CD.[13] TBDMS-*β*-CD was prepared according to a previously reported method.[14] Figure 1 shows the changes of the ^{1}H NMR signals of TIPS-*β*-CD induced by the addition of pyrene in benzene-d_6 and cyclohexane-d_{12}. Upon the addition of pyrene, a new set of signals appeared. The intensity of these new signals increased with an increase in the pyrene/CD host ratio. In contrast, the intensity of the original proton signals of TIPS-*β*-CD decreased. When the pyrene/CD host ratio reached 2:1, the proton signals of TIPS-*β*-CD almost disappeared. These observations suggest the formation of a TIPS-*β*-CD–pyrene complex in both benzene-d_6 and cyclohexane-d_{12}. Job plots using a NMR method showed a maximum at a [TIPS-*β*-CD]/[pyrene] molar ratio of 2:1, clearly indicating that TIPS-*β*-CD formed a 2:1 complex with pyrene in these solvents (see Figures S4 and S5, Supporting Information). In the case of TBDMS-*β*-CD, similar ^{1}H NMR spectral changes upon the addition of pyrene were observed in both benzene-d_6 and cyclohexane-d_{12} (Figure S3, Supporting Information), and the Job plot also indicated a 2:1 stoichiometry of the TBDMS-*β*-CD–pyrene complex (see Figures S6 and S7, Supporting Information). These results showed that a difference in the substituents on the Si atom between TIPS-*β*-CD and TBDMS-*β*-CD has little effect on the complexation with pyrene in nonpolar solvents. The association constants (K) between two 6-*O*-modified *β*-CD molecules (two host molecules) and one pyrene molecule in benzene-d_6 and cyclohexane-d_{12} at 25 °C (eq 1), which were estimated from the ^{1}H NMR spectral changes of 6-*O*-modified *β*-CDs upon the addition of pyrene, are shown in Table 1. In both

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CD hosts, the association constant in cyclohexane-d_{12} was higher than that in benzene-d_6, implying that the inclusion mode of pyrene within the CD cavity may be different between these solvents. It is noteworthy that the association constants in these nonpolar solvents are much higher than the association constant between β-CD and pyrene in water (2/1 stoichiometry, $K = 8.53 \times 10^5$ L^2 mol^{-2}),[15] indicating that the pyrene inclusion by β-CD dimers is attained more effectively in the nonpolar solvents as compared with water.

The fluorescence spectral changes of pyrene against the TIPS-β-CD concentration in benzene and cyclohexane are shown in Figure 2. The fluorescence intensity of pyrene increased with an increase in the ratio of [TIPS-β-CD]/[pyrene], supporting the formation of inclusion complexes in benzene and cyclohexane. A larger increase in the fluorescence intensity of pyrene was observed in cyclohexane as compared with benzene, implying that there should be a difference in the inclusion mode of pyrene within the CD cavity between these solvents. The association constants K_1 and K_2 (eqs 2 and 3, respectively) were determined based on their fluorescence spectral changes upon the addition of 6-*O*-modified β-CD (Table 1).[16] A comparison of the association constants between benzene and cyclohexane solvents indicated that the difference in the 6-*O*-modified β-CD−pyrene association between these solvents could be mainly attributed to the difference in K_2, that is, the association between the 1:1 6-*O*-modified β-CD−pyrene complex and one 6-*O*-modified β-CD molecule to form the 2:1 6-*O*-modified β-CD−pyrene complex.

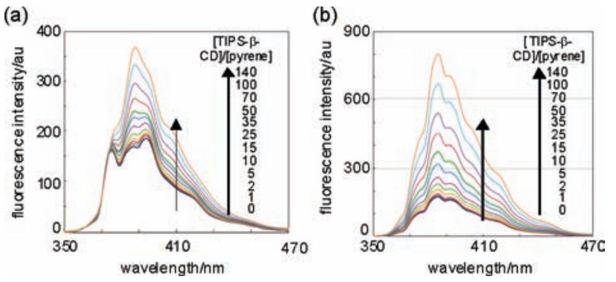

Figure 2. Fluorescence spectral changes of pyrene (1.0×10^{-6} mol L^{-1}) upon addition of increasing amounts of TIPS-β-CD (a) in benzene and (b) in cyclohexane at 25 °C; $\lambda_{ex} = 335$ nm.

Two-dimensional NMR studies are effective for obtaining useful information on inclusion complex structure in solution. In the NOESY spectra of the inclusion complexes between TIPS-β-CD and pyrene in benzene-d_6 and cyclohexane-d_{12} (see Figures S13 and S14, Supporting Information), remarkable correlations were clearly observed between the protons of pyrene and the H_3 and/or H_5 protons of TIPS-β-CD, confirming that pyrene was incorporated within the cavity of TIPS-β-CD in these solvents. In benzene-d_6, clear cross peaks between the H_3 protons of the host and all of the pyrene protons were observed, whereas cross peaks between the H_5 protons of the host and the pyrene protons were barely observed, implying that a pyrene molecule was included with its long axis almost perpendicular to the axis of TIPS-β-CD. On the other hand, in cyclohexane-d_{12}, cross peaks were observed between the H_5 protons as well as the H_3 protons of the host and all pyrene protons, suggesting that the long axis of the incorporated pyrene molecule tilts to the axis of TIPS-β-CD, and thus the pyrene molecule penetrates more deeply into the CD cavity as compared with the case of benzene-d_6. These results showed that there was a difference in the inclusion mode of pyrene between benzene-d_6 and cyclohexane-d_{12} solvents. Figure 3 shows the proposed structures of the inclusion complexes between TIPS-β-CD and pyrene in benzene-d_6 and cyclohexane-d_{12}, based on the NOESY spectra and CPK modeling studies.

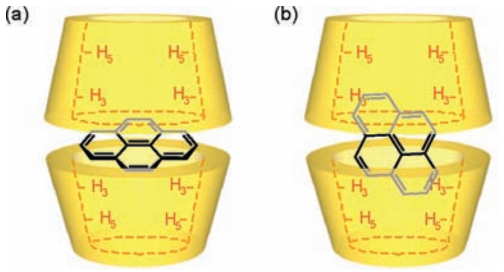

Figure 3. Proposed structures of the 2:1 inclusion complexes between TIPS-β-CD and pyrene (a) in benzene-d_6 and (b) in cyclohexane-d_{12} at 25 °C.

Crystals of the inclusion complex formed between TIPS-β-CD and pyrene were obtained from the benzene solution. The X-ray crystalline structure of the complex shows that one pyrene molecule is incorporated within the cavity of the host dimer formed by two TIPS-β-CD molecules through head-to-head hydrogen bonding interactions between the secondary hydroxyl groups (Figure 4). Interestingly, the pyrene molecule forms a sandwich-type complex with two benzene molecules through $\pi-\pi$ interactions and is located at the center of the dimer cavity. Two additional benzene molecules were also included near the C-6 position within the TIPS-β-CD cavity. The location of pyrene in the crystalline state is in reasonable agreement with the proposed one in the benzene solution as described above. Although crystals of the inclusion complex formed between TIPS-β-CD and pyrene in cyclohexane were not obtained, the interaction between the pyrene molecule and the nonpolar solvent appears to affect the inclusion mode of the pyrene molecule within the TIPS-β-CD dimer cavity.

In conclusion, we have demonstrated that 6-*O*-modified β-CDs effectively formed 2:1 inclusion complexes with pyrene in benzene and cyclohexane with considerably high

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[16] It was confirmed by NMR studies that, in the absence of pyrene, TIPS-β-CD and TBDMS-β-CD existed in the monomeric form at concentrations of 1.0×10^{-3} mol L^{-1} or less in benzene-d_6 and cyclohexane-d_{12}.

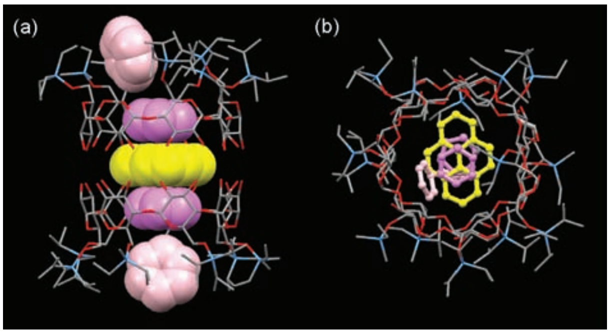

Figure 4. Crystal structure of TIPS-β-CD−pyrene inclusion complex. (a) Side view. TIPS-β-CD is shown with a cylinder representation, whereas pyrene and benzene are shown with space-filling representations. Hydrogen atoms in all compounds are omitted for clarity. (b) Top view. TIPS-β-CD is shown with a cylinder representation, whereas pyrene and benzene are shown with ball-and-stick representations. Color labels: gray, carbon in TIPS-β-CD; cyan, silicon; red, oxygen; yellow, pyrene molecule; violet, benzene molecules interacting with a pyrene molecule; pink, benzene molecules incorporated near the C-6 position of TIPS-β-CD.

association constants. The inclusion mode of pyrene within the dimer cavities of 6-*O*-modified β-CDs was switched by changing the type of solvent. Crystallographic study of the TIPS-β-CD−pyrene inclusion complex obtained from the benzene solution showed the formation of a unique ternary complex among TIPS-β-CD, pyrene, and the solvent. The crystalline structure suggested that the interaction between the solvent and pyrene affects the mode of pyrene inclusion within the CD dimer cavity. Further studies on inclusion complex formation between CD derivatives and various guests in nonpolar solvents are now in progress in our laboratory to open up a new field of cyclodextrin chemistry.

Acknowledgment. The authors appreciate the technical support for X-ray crystallographic analysis by Dr. M. Shiro (Rigaku Corporation Ltd., Japan). This work was partially supported by a Grant-in-Aid for Scientific Research (No. 22550122) from the Japan Society of the Promotion of Science, and Funding Program for Next Generation World-Leading Researchers (GR067).

Supporting Information Available. Experimental procedures, ^{1}H NMR spectra, fluorescence spectra, NOESY spectra, Job plots for complexes, crystal structures, and X-ray crystallographic data in CIF format. This material is available free of charge via the Internet at http://pubs.acs.org.