Terminal Trialkylsilyl Substituent Effect of Janus-type Molecular Tubes on the Inclusion of Unsaturated Fatty Acid Esters

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ABSTRACT: A new Janus-type cyclodextrin (CD) molecular tube bearing seven triisopropylsilyl (TIPS) groups at one end is synthesized from a heptakis(6-O-triisopropylsilyl)-β-cyclodextrin (TIPS-β-CD) dimer possessing multiple linkers through the selective removal of seven TIPS groups at the other end. This Janus-type CD tube exhibits a selective inclusion ability for a cis-fatty acid ester over the corresponding trans-fatty acid ester. In addition, the CD tube shows a twofold higher inclusion ability for unsaturated fatty acid esters than the corresponding CD tube bearing seven tert-butyldimethylsilyl (TBDMS) groups, indicating that the molecular size of the terminal substituents remarkably affects the inclusion ability of the CD tube.

INTRODUCTION

Organic molecular tubes composed of aromatic and/or aliphatic frameworks have attracted much interest in diverse fields, including supramolecular chemistry, organic synthesis, and biomedical science. In particular, short molecular tubes with a length of sub to several nanometers exhibit a unique internal cavity properties. Hence, they have been applied to molecular carriers, molecular recognition, and chemical sensing.

A molecular tube can be designed easily using conventional macrocyclic molecules as building blocks. Among such molecules, cyclodextrins (CDs) are attractive ones since they have subnanometer-sized cavity that can incorporate guest molecules with an appropriate size and shape. Recently, we developed new molecular tubes composed of two CD units connected by multiple linkers. These CD molecular tubes are easily synthesized by the reaction of 6-O-tert-butylidimethylsilylated β-CD (TBDMS-β-CD) and α,α′-dibromoxylene in the presence of sodium hydride, followed by desilylation of the TBDMS groups. Additionally, we synthesized a Janus-type CD molecular tube via selective elimination of seven TBDMS groups from the TBDMS-β-CD dimer. One end of this Janus-type CD tube is fully modified with TBDMS groups, while the other end is unmodified. This tube exhibits a higher inclusion ability toward cis-fatty acid esters than the corresponding trans- and saturated fatty acid esters. The rigid structure of the Janus-type CD tube constructed by two CD rings and seven aromatic linkers may realize the precise recognition of cis and trans structures of unsaturated fatty acids. The terminal TBDMS substituents of the Janus-type CD tube play an important role in enhancing the guest inclusion ability of the tubular host possibly by changing the internal environment of the tubular cavity. This interesting finding prompted us to examine the inclusion ability of the molecular tubes with different terminal substituents and to study the mechanism for enhanced guest inclusion.

There are several reports on the shape recognition of fatty acids by synthetic host molecules. For example, Glass et al. reported fluorescent sensors composed of four naphthol units, which allow selective sensing of linear long-chain fatty acids over the corresponding branched or shorter chain fatty acids. Yoshizawa et al. reported that a polyaromatic molecular tube composed of anthracene panels selectively includes methyl elaidate bearing a trans-double bond over the corresponding cis-isomer. The control of inclusion ability of these hosts toward the fatty acids has been attained by changing the host skeleton such as the ring size and shape. On the other hand, inclusion ability control by changing the terminal substituent of the tubular host without changing the skeleton has not been reported yet.

With these backgrounds, we report herein the synthesis of Janus-type β-CD tube bearing 6-O-triisopropylsilyl (TIPS) groups at one end and the inclusion complex formation with unsaturated fatty acid esters. A comparison of the inclusion ability of this Janus-type β-CD tube with the previous β-CD
RESULTS AND DISCUSSION

Synthesis. First, we synthesized TIPS-β-CD dimer 1, in which two TIPS-β-CD molecules are connected with seven m-xylene linkers through the C-2 hydroxyl groups via a reaction of TIPS-β-CD with five equivalents of m-xylene bromide in the presence of sodium hydride according to our previous report on the synthesis of TBDMS-β-CD dimer7 (Scheme 1). Similar to the case of TBDMS-β-CD dimer, dimerization gave the desired dimer 1 in 24% isolated yield. The structure of dimer 1 was confirmed by NMR (1H, 13C, NOESY) and the matrix-assisted laser desorption ionization-time of flight mass spectrometry (MALDI-TOF MS) analyses. Interestingly, in the nuclear Overhauser effect spectroscopy (NOESY) spectrum of TIPS-β-CD dimer 1 in cyclohexane-d12 (Figure S11a), the methyl protons of the isopropyl groups of the TIPS substituents and both the H3 and H2 protons of the CD units are clearly correlated. Since the H2 and H3 protons of CD are directed inside the cavity, this observation reveals that one or some of the TIPS groups are self-included in the CD cavity. Based on the optimized structure of 1 by a Macromodel calculation,11 we can confirm that one TIPS group at both ends is self-included in the CD cavity (Figure S13a). The TBDMS-β-CD dimer, which was synthesized as a control, exhibits similar correlations between both t-butyl and methyl protons of the TBDMS substituents and both H3 and H2 protons of the CD units (Figure S11b). The optimized structure of the TBDMS-β-CD dimer confirms that one of the seven TBDMS groups at each end is self-included in the CD cavity (Figure S13b), similar to 1.

Next, we examined the selective removal of the TIPS groups from one end of 1. In our previous report,10 reacting a TBDMS-β-CD dimer with tetramethylammonium fluoride (TMAF, 21 equiv) in 1,4-dioxane for 8 h at 100 °C gave a Janus-type TBDMS-β-CD tube. The mechanism of the selective elimination of TBDMS groups from one side of the two CD rings with TMAF is due to the steric hindrance created by seven TBDMS groups on the CD rings. The bulky TBDMS groups sterically inhibit the attack of the F− ion on the Si atom of TBDMS groups in the early stage of the reaction, but once one or two TBDMS groups are removed by a successful attack of the F− ion, the generated space decreases the steric hindrance and then the F− ion easily attacks the next Si atom on the same CD ring to give a Janus-type TBDMS-β-CD tube. Following this method, treatment of 1 with TMAF as a desilylation agent for 8 h at 100 °C yielded a considerable amount of unreacted 1 in MALDI-TOF MS spectra of the reaction products. Extending the reaction time to 3 days produced a complex mixture of the random desilylation products (Figure 1a). These results suggest that the TIPS-β-CD dimer is less reactive for desilylation with TMAF than the TBDMS-β-CD dimer because the TIPS group is bulkier than the TBDMS group.12 The desired Janus-type tube 2 was successfully synthesized when tetra(n-butyl)ammonium fluoride (TBAF), which has a more reactive fluoride anion than TMAF,13 was used (Figure 1b). The selective desilylation from one end can be explained by the same mechanism as the case of TBDMS-β-CD dimer. Although seven bulky TIPS groups suppress the attack of F− ion on the Si atom of TIPS groups in the early stage, the desilylation on the same CD ring proceeds smoothly once one or two TIPS groups are removed. After the removal of the ammonium salt from the reaction mixture using Dowex 50WX-8-400 (H+-form) and calcium carbonate, followed by the solvent evaporation, the residue was purified by silica gel column chromatography using chloroform/methanol (in a gradient 10:1 to 6:1) as an eluent and recrystallized by slow diffusion of methanol vapor into the chloroform solution. The integral ratio of peaks of isopropyl protons on the Si atoms (around 1.0 ppm) to peaks of H1 and H1′ (around 4.9 ppm) in the 1H NMR spectrum indicates the elimination of seven TIPS groups from 1 (Figure S3). In addition, the 1H NMR spectrum of 2 contains a set of CD and linker proton peaks, which are observed in 1, as well as another set of CD and linker proton peaks whose integral ratio with the former set is 1:1. These results confirm that 2 is composed of two types of CD rings in different chemical environments. That is, 2 contains TIPS-β-CD and unmodified β-CD. The elimination of seven TIPS groups was also confirmed by the matrix-assisted laser desorption ionization-high-resolution mass spectral analysis (MALDI-HRMS) spectrum, which has
a monoisotopic peak for the sodium adduct of a molecular ion at \( m/z \) 4098.9854 [M + Na]⁺, which corresponds to the theoretical molecular weight of the desired Janus-type tube 2 (C\(_{203}H_{322}O_{70}SiNa\)) (Figure S5). These results demonstrate that the selective elimination of the TIPS groups from one end of the TIPS-\(\beta\)-CD dimer occurs to give the Janus-type structure.

**Inclusion of Unsaturated Fatty Acid Esters.** We evaluated the inclusion ability of 2 toward cis- and trans-fatty acid esters (Figure 2) by the \(^1H\) NMR titration method using methanol-\(d_4\) as a solvent. Methyl oleate and methyl elaidate were chosen as cis- and trans-fatty acid esters, respectively. Oleic acid and elaidic acid are common fatty acids contained in various animal and vegetable fats and oil. Although selective recognition of these cis—trans isomers by synthetic receptors is important in the food industry,\(^{14}\) it remains a challenging subject. Figure 3 shows the changes in the \(^1H\) NMR signals of Figure 2. Unsaturated fatty acid esters used in this study.

**Figure 2.** Unsaturated fatty acid esters used in this study.

Table 1 summarizes the association constants between 2 and the guests along with those between the Janus-type \(\beta\)-CD tube bearing seven TBDMS groups (Janus-type TBDMS-\(\beta\)-CD tube) and the guests.\(^{9}\) The association constant with methyl oleate is 2.5 times higher than that with methyl elaidate. Thus, 2 exhibits a selective inclusion ability for the cis-fatty acid ester over the corresponding trans-fatty acid ester. Although this tendency is similar to the case of the Janus-type TBDMS-\(\beta\)-CD tube, 2 shows an increased cis/trans selectivity. Notably, 2 shows a 2-fold higher association with these guests compared to the Janus-type TBDMS-\(\beta\)-CD tube, suggesting that the molecular size of the terminal substituents affects the inclusion ability of CD tubes. Inouye et al. reported that fluorescent sensors possessing \(\alpha\)-CD units as a guest-binding moiety selectively detect oleic acid over elaidic acid in a buffer solution,\(^{15}\) but they did not quantitatively discuss the association constants and cis/trans selectivity for comparison with our results.

**Studies on the Structure of Janus-type CD Tubes.** In the NOESY spectrum of 2 in methanol-\(d_4\) (Figure S12a), the methyl protons of isopropyl groups of the TIPS substituents are clearly correlated with both the H₅ and H₆ protons of CD units. Similar to the case of TIPS-\(\beta\)-CD dimer 1, the optimized structure of 2 by a MacroModel calculation confirms that one of the TIPS groups is self-included in the CD cavity (Figure 4a). Using the Janus-type TBDMS-\(\beta\)-CD tube as a control, the results of the NOESY spectrum (Figure S12b) and the MacroModel calculation (Figure 4b) demonstrate that one of the TBDMS groups is self-included in the CD cavity. These structures suggest that the self-included trialkylsilyl group may be involved in the enhanced guest inclusion ability by constructing a more hydrophobic inner space. In fact, we previously observed that the Janus-type TBDMS-\(\beta\)-CD tube shows a higher inclusion ability toward unsaturated fatty acid esters than the corresponding \(\beta\)-CD tube without substituents at both ends.\(^{9}\) In addition, the bottom views of the structures of Janus-type \(\beta\)-CD tubes indicate that the TIPS groups more effectively block the opening at the end of the tube through dense packing (Figure 4c). Compared with the TBDMS groups, this provides a more hydrophobic inner space to the tubular host. For the Janus-type TBDMS-\(\beta\)-CD tube, some small gaps appear to be created, which may be because the TBDMS group is not large enough to fill the space (Figure 4d). This observation can explain the higher inclusion ability of 2 bearing TIPS substituents compared to the corresponding CD tube bearing TBDMS substituents. Moreover, it indicates that changing the molecular size of the terminal hydrophobic substituents may control the inclusion ability of the CD tube.

**CONCLUSIONS**

A new Janus-type CD tube bearing seven TIPS groups at one end is successfully synthesized from the TIPS-\(\beta\)-CD dimer through the selective removal of seven TIPS groups at one end with TBAF. This Janus-type CD tube exhibits a 2-fold higher

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**Table 1. Association Constants (K) between 2 or a Janus-type TBDMS-\(\beta\)-CD Tube and Unsaturated Fatty Acid Methyl Esters in Methanol-\(d_4\) at 25 °C**

| host               | guest         | association constants \((K/M^{+\text{a}})\) | selectivity \((\text{cis/trans})\) |
|--------------------|---------------|------------------------------------------|----------------------------------|
|                    | methyl oleate | (1.3 ± 0.15) \(\times\) 10^4             | 2.5                              |
| Janus-type TBDMS-\(\beta\)-CD tube | methyl oleate | (5.2 ± 0.43) \(\times\) 10^3             |                                  |
|                    | methyl elaidate | (6.7 ± 0.71) \(\times\) 10^{4\text{a}} | 2.2                              |
|                    | methyl oleate | (3.0 ± 0.46) \(\times\) 10^{4\text{a}} |                                  |

\(^{\text{a}}\)Ref 9.
inclusion ability for unsaturated fatty acid esters compared with the corresponding CD tube bearing seven TBDMS groups at one end. This enhanced inclusion ability can be explained by the more effective blocking of the opening at the end of the tube by the TIPS groups, leading to the formation of a more hydrophobic inner space. Changing the terminal trialkylsilyl groups to other substituents with different sizes and hydrophobicity without manipulating the CD skeleton should allow the inclusion ability and inclusion selectivity of the Janus-type tubular host to be tuned freely. The resulting CD molecular tube can function as a powerful molecular selector and molecular carrier. We also offered novel possibilities for the inclusion behavior of cyclodextrin, which had been difficult to achieve.

**EXPERIMENTAL SECTION**

**Materials and Methods.** Sodium hydride (60%) and tetrabutylammonium fluoride (ca. 1 mol/L in tetrahydrofuran) were purchased from Tokyo Chemical Industry (Japan). 1,4-Dioxane was purchased from Wako Pure Chemical Industries (Japan). These reagents were used without further purification. TIPS-β-CD,8 the TBDMS-β-CD dimer,9 and the Janus-type β-CD tube bearing TBDMS substituents10 were prepared according to our previously reported method. 1H and 13C NMR spectra were recorded on a JEOL NMR system (400 MHz).

The following abbreviations were used for chemical shift multiplicities: s = singlet, d = doublet, t = triplet, q = quartet, m = multiplet. NMR signal assignments were based on additional two-dimensional (2D)-NMR spectroscopy (e.g., COSY and HSQC). Infrared (IR) spectra were obtained with a Spectrum 100FT-IR spectrometer (Perkin Elmer). MALDI-TOF MS spectra were measured by Bruker Autoflex III. MALDI-HRMS spectra were measured by JEOL Spiral TOF/TOF JMS-3000. Melting points were measured with BUCHI Melting point B-545. Elemental analysis was performed with Perkin Elmer 240C. High-performance liquid chromatography (HPLC) was performed using a Shimadzu Prominence HPLC system equipped with a Soft 400 ELSD detector.

**Experimental Procedure for NMR Titration and Job Plots.** A solution of the host molecule (5.0 × 10–3 M, 0.5 mL) was titrated in an NMR tube with increasing amounts of guest stock solution (0.2 M). The titration curves (changes in the chemical shift of the host protons (Δδ) against the guest/host concentration ratio) were analyzed by a nonlinear least-squares curve fitting method to give the association constants between the hosts and the guests.

Job plots were carried out by monitoring the changes in the chemical shift of the host protons (Δδ) in a series of solutions with varying host/guest ratios while the total concentrations of the host and guest were kept constant (5.0 × 10–3 M). The relative concentration of the host–guest complex estimated from the Δδ value was plotted against ([host]/([host] + [guest])).

**ASSOCIATED CONTENT**

Supporting Information

The Supporting Information is available free of charge at https://pubs.acs.org/doi/10.1021/acsomega.0c05672.

Experimental details, spectral data, titration curves for complex formation, and Job plots for complexes (PDF)

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**Author Contributions**

The manuscript was written through contributions of all authors. All authors have given approval to the final version of the manuscript. These authors contributed equally.

**Notes**

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