

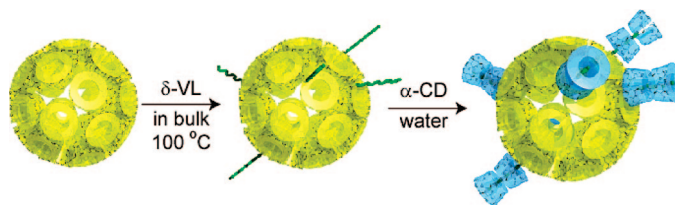
Nanospheres with Polymerization Ability Coated by Polyrotaxane

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β -Cyclodextrin (β -CD)-based nanosphere **1** initiated the oligomerization of δ -valerolactone (δ -VL) on the surface of **1** to give oligo(δ -VL)-tethered β -CD nanosphere **2** in bulk. Atomic force microscopy indicated that the molecular size of **2** is twice that of **1**. The addition of α -CD to **2** leads to the formation of poly-pseudo-rotaxane on the surface of **2** to give a nanosphere with poly-pseudo-rotaxane (α -CD \supset **2**). 2D-NOESY NMR experiments showed correlation peaks between the inner protons of α -CD and the oligo(δ -VL) chains in an aqueous solution, indicating that the oligo(δ -VL) chains are included in the α -CD cavity. α -CD \supset **2** has a core of β -CDs with poly-pseudo-rotaxanes on the surface. It should be noted that **2** did not show polymerization ability for δ -VL, but after the formation of poly-pseudo-rotaxanes, oligo(δ -VL) of α -CD \supset **2** repropagated upon the addition of δ -VL. α -CD \supset **2** is significantly larger than nanospheres **1** and **2**. Additionally, postpolymerization increases the size of α -CD \supset **2**. These behaviors are reminiscent of the function of a spherical virus, which forms an ordered spherical structure and releases RNA chains from the capsid surface.

Introduction

In biological systems, various spherical proteins function as a carrier or storage site for metal ions or genetic materials. Some of these biomolecules achieve catalytic activities with high efficiency and high specificity for substrates. Spherical viruses, such as the rice dwarf virus, form spherical structures and release RNA chains from their capsid surface.¹ Artificial spherical molecules with capsule or vesicle structures have received much attention as potential mimics of these biomolecules,^{2–5} as well

as promising materials for drug- and gene-delivery vehicles in biomedicine.^{6–12} Numerous studies on nanostructures with catalytic activity have focused on vesicles and capsule molecules, such as self-assembled amphiphilic block copolymers,^{13–15}

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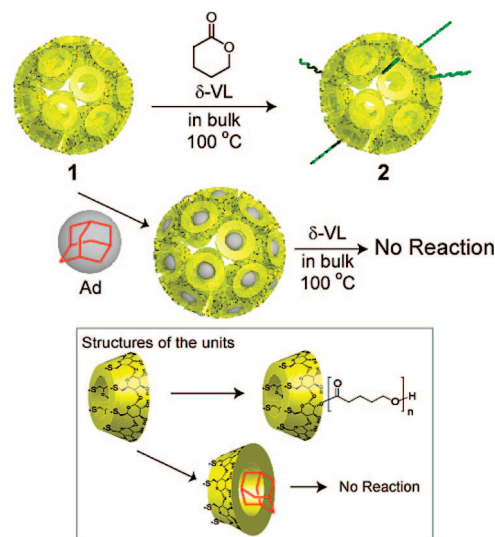
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phospholipid liposomes,^{16,17} dendrimers,¹⁸ ball molecules self-assembled from two resorcinarenes,¹⁹ and multicomponent transition metal-mediated self-assemblies.²⁰ However, to exhibit their catalytic activities, these vesicles and capsule molecules require highly reactive reagents such as enzymes or transition metal complexes.

Thus, our research has focused on constructing spherical supramolecules with polymerization ability that are similar to a spherical virus. Cyclodextrins (CDs) are typical host molecules as they form inclusion complexes, which accelerate hydrolysis of the substrates and serve as enzyme models.^{21–29} CDs have been found to initiate polymerization of lactones. CDs also produce polyesters with a single CD molecule at the end of each polyester only by mixing CDs and lactones in bulk without a cocatalyst. The secondary hydroxyl groups of CDs have a high nucleophilicity and activate monomers using molecular recognitions under the mild conditions.³⁰ Accordingly, CD is the best for the construction of the spherical supramolecule with polymerization ability. Herein we report the oligomerization of lactone on β -CD-based nanospheres and demonstrate that the addition of α -CD to nanospheres leads to the formation of spherical supramolecules with poly-pseudo-rotaxane. The for-

SCHEME 1



mation of poly-pseudo-rotaxane is essential to re-initiate polymerization on the surface of a nanosphere.

Results and Discussion

Oligomerization of Lactones on the Surface of a Nanosphere. β -CD nanosphere **1** was synthesized using a Au colloid template.³¹ β -CDs thiolated at the narrow rim assembled on the surface of the Au nanocolloid via reduction of HAuCl_4 in *N,N*-dimethylformamide (DMF). After using iodine as an oxidant to remove the Au colloid core, the β -CD units were linked via disulfide bonds so as to form a monolayer of β -CDs. To remove the sphere with a molecular weight less than 12 000, **1** without a Au-core was purified by dialysis. The weight ratio of $[\beta\text{-CD}]/[\text{Au-core}]$ in **1** with a Au-core obtained from thermogravimetric (TG) measurements confirmed that purified **1** was composed of 20 β -CDs. **1** was completely burned by 300 °C, indicating that iodine removed the Au-core. As determined by pulse field gradient spin-echo (PFG-SE) NMR, the hydrodynamic diameter of **1** with a Au-core was 2.0 nm, whereas that of **1** was 1.8 nm. Removing the Au-core decreased the nanosphere radius. The structure of **1** was observed as spherical images using a transmission electron microscope. Diffraction derived from Au was not observed, indicating that **1** without a Au-core has a spherical structure (see figures S4 and S5 in Supporting Information).

δ -VL was polymerized with **1** in bulk. δ -VL was converted to oligo(δ -VL) in 70% yield 48 h after the addition of δ -VL to **1** in bulk at 100 °C (Scheme 1).³² Previously, the substitutional position of the oligo(δ -VL) chain was clarified to be the hydroxyl group of the C_2 -position of β -CD. When the nanosphere **1** was used as an initiator, oligo(δ -VL) was attached at the C_2 -position of the wider rim of β -CD. The decreased integration value of the secondary hydroxyl group based on that of C_1H of β -CD indicates that **1** with oligo(δ -VL) (**2**) had on average five oligo(δ -VL) chains. The number-average molecular weight of each oligo(δ -VL) chain was 1400 (number of β -CDs units, 20; degree of polymerization, 14; the total unit of δ -VL,

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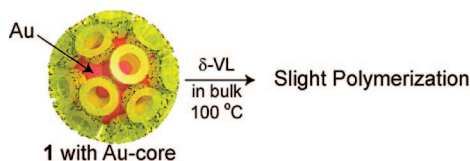
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SCHEME 2



70), which was calculated by (the number of δ -VL unit)/(the number of the substituent). These results confirmed the polymerization ability of **1** for δ -VL in bulk.

To investigate the active site of **1**, the inhibition of polymerization of δ -VL was studied using adamantane (Ad) as a competitive guest for the β -CD cavity.³³ **1**⊃Ad (**1** including Ad in the β -CD cavities) was prepared by mixing **1** and Ad in water. When a mixture of **1**⊃Ad and δ -VL was heated at 100 °C for 48 h (Scheme 1), **1**⊃Ad did not show polymerization activity for δ -VL. According to our previous study,³⁰ the β -CD cavities on the surface of **1** are the active sites, and the oligomers propagate from the β -CD cavities. Hence, we speculate that δ -VL cannot access the β -CD cavities on the surface of **1** because the cavities are occupied by Ad.

When **1** with a Au-core was used as an initiator, oligo(δ -VL) was produced in a considerably low yield (2% with 0.10 unit for one β -CD unit) under the same conditions (Scheme 2), indicating that the presence of the Au-core inhibits initiation and propagation. Our previous study indicated that β -CD promotes the initial reaction in the β -CD cavity, but the growing chain must be included in the CD cavity to promote a propagation reaction.^{30c} Hence, the growing polymer is unable to thread physically through the β -CD cavity of **1** with a Au-core because the narrow rim of β -CD is capped by a Au nanoparticle. The deficit of the inclusion ability for the growing polymer is responsible for the inactivated nanosphere **1** with Au-core. These results suggest that a spherical structure with an inner hollow of **1** is essential to initiate δ -VL.

Structure of Oligoester-Modified Nanosphere. The 2D-NOESY NMR spectrum of **2** showed correlation peaks between the protons of oligo(δ -VL) and the inner protons of the β -CD cavity (C_3H , C_5H , and C_6H) (Figure 1), whereas the outside protons of β -CD (C_1H) did not correlate with the protons of the oligo(δ -VL), indicating that the oligo(δ -VL) chains are included in the β -CD cavity on the surface of **2** at 20 μ mol/L. To determine the molecular sizes of β -CD sphere **1**, the diffusion coefficient at 20 μ mol/L was measured by calculating the hydrodynamic radius using PFG-NMR. The hydrodynamic diameter of **2** was 2.4 nm, indicating that the intermolecular aggregates do not form at a concentration of 20 μ mol/L. The oligo(δ -VL) chains were elongated outside the nanosphere, and then the oligomer chains were presumed to be included in the β -CD cavity. This result suggests that β -CD and oligo(δ -VL) form pseudo-rotaxanes on the surface of **2** (Figure 2). The parent β -CD cavity with an oligomer chain functions as the active site for the reaction to include the next monomer, so that the oligomer chain is likely included in adjacent β -CD cavities on the nanosphere, but not self-inclusions. The inner hollow of **1** should play a role in including the growing polymer chain in the oligomerization. Therefore, the filled hollow should exhibit low polymerization activity.

Formation of Poly-pseudo-rotaxanes on the Surface of a Nanosphere. We hypothesized that β -CD of **1** could initiate

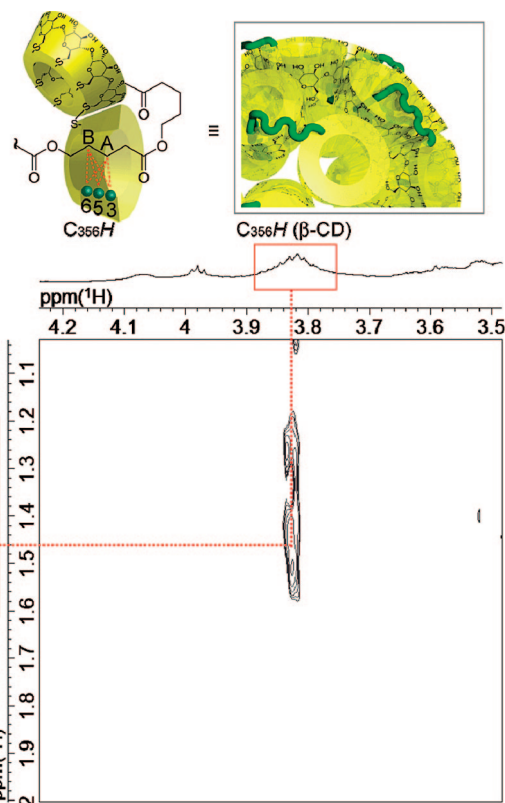


FIGURE 1. 2D-NOESY NMR spectrum of oligo(δ -VL)- β -CD sphere **2** in D_2O . Concentration: 20 μ mol/L. Mixing time: 200 ms.

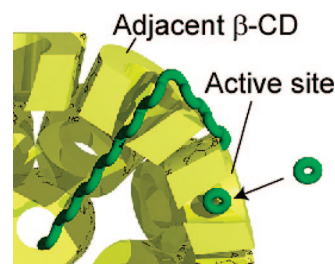


FIGURE 2. Schematic illustration of polymerization initiated by **1**. Figure shows the profile of a surface.

polymerization of new lactones. However, adding additional equivalents δ -VL to **2** did not alter the molecular weight of oligo(δ -VL) on **2**. We assumed that the covering the five oligo(δ -VL)s on the surface of **2** prevented new monomers from approaching parent β -CD cavities and the other units of β -CD cavities. Hence, the addition of α -CD to **2** in an aqueous solution ($[\alpha\text{-CD}]/[\delta\text{-VL unit}] = 1/1$) alleviated (or eliminated) the steric hindrance around β -CD cavities by forming poly-pseudo-rotaxane. The 2D-NOESY NMR spectrum showed that the inner protons of the α -CD cavity (C_3H) are correlated to the protons of poly(δ -VL) (Figure 3). Other correlations were not observed in the spectrum, indicating that poly-pseudo-rotaxanes form on the surface of nanosphere **2** ($\alpha\text{-CD}\supset\mathbf{2}$) (Scheme 3). The oligo(δ -VL) chains, which were included in β -CDs on the surface of **2**, are probably released from the β -CD cavities by the inclusion of α -CD. It should be noted that the spherical supramolecule $\alpha\text{-CD}\supset\mathbf{2}$ possesses a β -CD spherical molecule as its core, which can be functionalized with the poly-pseudo-rotaxane consisting of α -CD on the surface.

Re-initiation of the Polymerization by a Nanosphere. As mentioned in the previous section, a mixture of **2** and δ -VL

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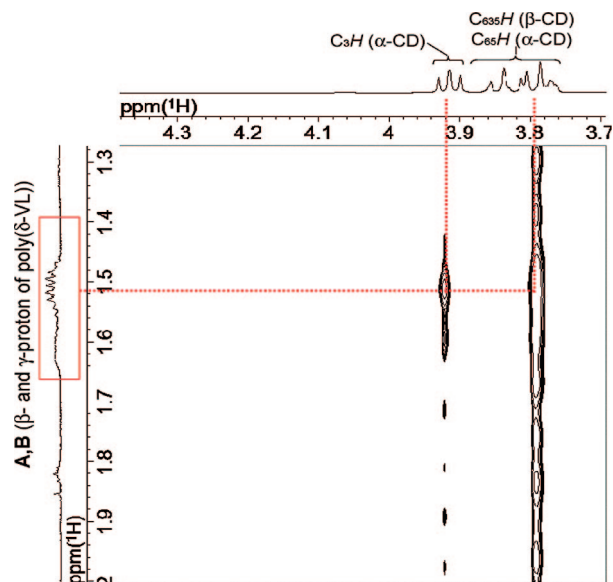
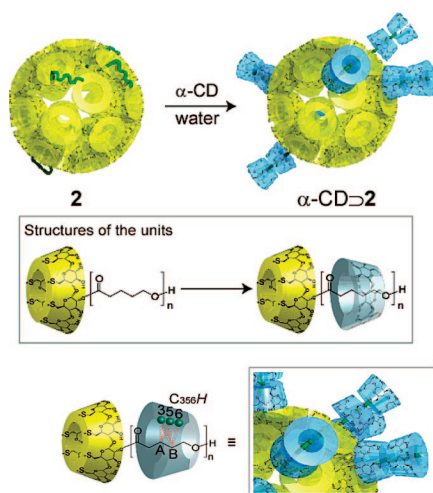


FIGURE 3. 2D-NOESY NMR spectrum of α -CD \supset poly(δ -VL)- β -CD sphere α -CD \supset 2 in D_2O . Concentration: 20 μ mol/L. Mixing time: 200 ms.

SCHEME 3



did not initiate postpolymerization in bulk at 100 °C (Scheme 4a). Hence, it is assumed that the surface of **2** is covered by the oligo(δ -VL) chains, which prevent initiation of further polymerization. On the other hand, a mixture of α -CD \supset 2 and δ -VL initiated the polymerization of δ -VL to give longer poly(δ -VL) chains of nanospheres in 36% yield and a molecular weight of 2100 (degree of polymerization, 21; the total unit of δ -VL, 106) (Scheme 4b), which was determined by the integration values of 1H NMR (see Figure S6 in Supporting Information). These results suggest that the polymer of **2** is propagated by the formation of poly-pseudo-rotaxanes, which are essential in the initiation of further polymerization of δ -VL.

AFM Measurements of the Nanospheres. The molecular sizes of the nanospheres were estimated by dynamic light scattering (DLS) measurements. However, DLS could not precisely measure the nanospheres in the dilute condition as the nanospheres were too small.³⁴ Although the radii of α -CD \supset 2

(34) When a measurable concentration of 400 μ mol/L was used in the DLS measurements, the formation of large aggregates interfered with the measurement accuracy.

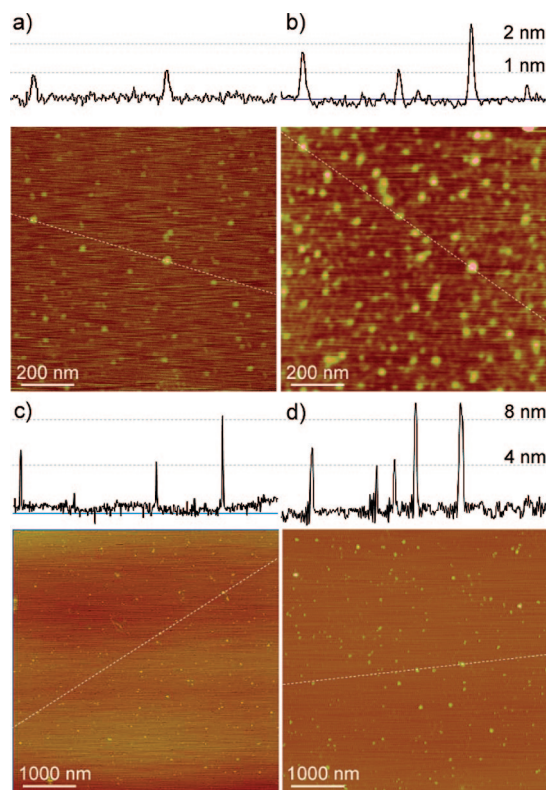
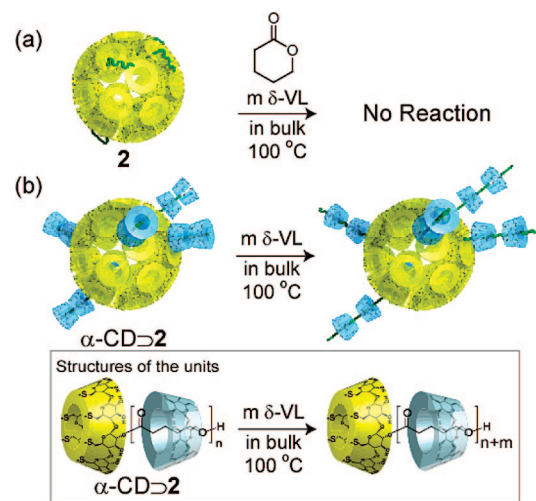


FIGURE 4. AFM images and their profiles of (a) β -CD nanosphere **1**, (b) poly(δ -VL)- β -CD nanosphere **2**, (c) α -CD \supset 2, and (d) the product by the postpolymerization initiated by α -CD \supset 2.

SCHEME 4



were estimated by the PFG-NMR technique, we do not discuss the obtained value here due to the low resolution of the data. Hence, the molecular sizes of the nanospheres were determined by atomic force microscopy (AFM). Highly dilute aqueous solutions of **1** (1.0 nmol/L) were cast and dried on mica substrates. The AFM image of **1** showed spherical particle objects with equal heights around 1.0 nm (Figure 4 a). The average height of **1** was 0.62 nm. Table 1 summarizes the measured average heights and the standard deviations that indicate the height distributions (Figure S9 in the Supporting Information shows the size distribution histogram). The average height of **2** was 1.25 nm, which is larger than that of **1** (Figure 4b). These results indicate that the diameter of **2** increases in

TABLE 1. Heights of β -CD Nanosphere **1**, Poly(δ -VL)- β -CD Nanosphere **2**, and α -CD \supset **2**^a

sample	average height/nm ^b	standard deviation/nm
1	0.62	0.17
2	1.25	0.44
α -CD \supset 2	5.53	2.06
α -CD \supset 2 ^c	6.12	2.20

^a Atomic force microscopy (AFM) measurements were carried out on a mica substrate. ^b Calculated by the heights of more than 100 spherical objects in plural AFM images. ^c Heated with δ -VL for further polymerization.

the presence of the oligomer chains on the nanosphere. Although the addition of α -CD to **1** without an oligomer chain did not produce such large objects, the average height of α -CD \supset **2** showed 5.53 nm, which is 4 times larger than that of **2**. The formation of poly-pseudo-rotaxane caused the oligomer chain on the surface of nanosphere **2**, which showed a significant increase in the height of α -CD \supset **2** (Figure 4c), to extend. These results support the formation of poly-pseudo-rotaxane consisting of α -CD and oligo(δ -VL) on the surface of **2** (Scheme 3). Figure 4d shows that the height of the nanosphere obtained from the postpolymerization of α -CD \supset **2** is on average 6.12 nm,³⁵ which is larger than that of α -CD \supset **2** (prepolymerization). Moreover, the increased height of α -CD \supset **2** indicates α -CD \supset **2** initiates postpolymerization.

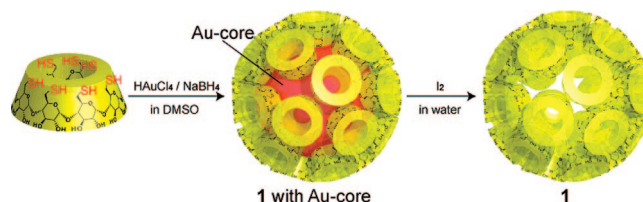
Conclusions

β -CD nanosphere **1** initiates the oligomerization of lactone without cocatalysts and reactive substrates so as to yield oligo(δ -VL)- β -CD nanosphere **2** with oligo(δ -VL) chains on the surface of **1**. **1** with a Au-core did not initiate polymerization. The spherical structure and the inner hollow of **1** are important for polymerization activity. The growing oligoester chains are included in the β -CD cavities of **2**. Adding α -CD triggers a complex formation between the α -CDs and oligo(δ -VL) chains to form poly-pseudo-rotaxane (α -CD \supset **2**). The formation of α -CD \supset **2** enables further polymerization activity for δ -VL to give poly(δ -VL) with a larger molecular weight on the surface of a nanosphere. These behaviors resemble spherical viruses, some of which have a multilayer spherical structure and release RNA chains from the capsid surface.

Thus, these behaviors should expand the concepts in supramolecular catalysis. The polymers studied herein show not only potential for artificial nanoreactors like an enzyme, but also supramolecular nanoarchitecture which consists of a rotaxane-tethered spherical structure. Hence, investigations to control the inclusion of substrates in the inner hollow of the nanosphere as well as to utilize rotaxane on the surface are currently in progress.

Experimental Section

Preparation of β -CD Nanosphere **1.**³¹ **Preparation of β -CD Nanosphere **1** with a Au-Core.**^{31a,b} HAuCl₄ (2.00 g, 4.86 mmol) was dissolved in 800 mL of dimethylsulfoxide (DMSO). Per-6-thiolated- β -CD^{30c} (0.56 g, 4.48 mmol) and NaBH₄ (3.02 g, 80.0 mmol) were dissolved in DMSO (800 mL). A HAuCl₄ solution was slowly added to the per-6-thiolated- β -CD solution and stirred. After 24 h, acetonitrile (1600 mL) was added to the solution to



precipitate **1** with a Au-core. Crude **1** with a Au-core was corrected by centrifugation and washed with DMSO/acetonitrile (v/v = 1/1) and ethanol. After drying in vacuo at 50 °C, **1** with a Au-core (1.52 g) was obtained (yield: 59%). ¹H NMR (D₂O, 30 °C, 500 MHz): δ 5.40–4.90 (br, 7.0H, C₁H), 4.35–3.71 (br, 28.0H, C₃₆₅H), 3.71–3.18 (br, 14.0H, C₂₄H).

Preparation of β -CD Nanosphere **1.** **1** with a Au-core (1.40 g, contains 2.44 mmol of Au), I₂ (1.0 g, 3.9 mmol), and KI (1.5 g, 9.0 mmol) were dissolved in 1000 mL of water. After stirring for 72 h, I₂ was removed by extracting with ethyl acetate, and the water phase was evaporated. The obtained powder was dissolved in 50 mL of water and dialyzed with seamless cellulose tubing in water for 72 h. The dialyzed solution was lyophilized to obtain 94.5 mg of **1** (yield: 13%). ¹H NMR (D₂O, 30 °C, 500 MHz): δ 5.37–4.97 (br, 7.0H, C₁H), 3.91–3.01 (br, 43.9H, C_{2,3,4,5,6}H). The TG measurement showed that **1** without a Au-core burned completely at 300 °C, indicating that the Au-core was completely removed.

Determination of the Number of β -CD Units in **1.** The weight ($M_{(\text{Au-core})}$) of **1** with a Au-core per single molecule was composed of a β -CD monolayer and a Au-core, which can be described by the following equations:

$$M_{(\text{Au-core})} = 4\pi r^3 \rho / 3 + nM / N_A$$

where n is the number of β -CD units, M is the molecular weight of β -CD unit (1240.4), r is the radius of the Au-core, ρ is the density of Au (19.3 g/cm³), and N_A is the Avogadro number (6.02×10^{23}).

The TG measurement indicated that 64% of **1** with a Au-core is β -CD. The relationship between the weight of the β -CD monolayer and the weight of the Au-core is described:

$$nM / N_A = 64/36 \times 4\pi r^3 \rho / 3$$

Assuming the radius (r) of the Au-core is equal to the hydrodynamic radius determined by PFG-NMR, $r = 2.0$ nm.³⁶ According to this approximation, the number of β -CDs is 20.

Polymerization of δ -VL Initiated by β -CD Nanosphere **1.** Lactone with a nanosphere was polymerized using the following method. Scheme 1 shows polymerization of δ -VL by **1**. **1** (26 mg, 19 μ mol of CD unit) was dried in vacuo at 80 °C, and then δ -VL (9.0 μ L, 9.7 mg, 97 μ mol) was added to **1**. The mixture was heated in bulk at 100 °C. After 48 h, the heterogeneous mixture was suspended in DMF (1 mL). The suspension was added to 10 mL of THF to precipitate the poly(δ -VL)-modified β -CD nanosphere **2**, as well as to remove unreacted δ -VL (yield: 33.1 mg, 70%). ¹H NMR (DMSO-*d*₆, 30 °C, 500 MHz): δ 6.22–5.31 (br, 274.7H, O_{2,3}H), 5.31–4.60 (br, 140.0H, C₁H), 4.00 (br, 111.2H, δ -polymer), 3.98–3.01 (br, overlapped with HOD, C_{2,3,4,5,6}H), 2.31 (br, overlapped with DMSO, α -polymer), 1.57 (br, 277.3H, β - and γ -polymer).

Synthesis of β -CD Nanosphere \supset Adamantane (1** \supset **Ad**).** **1** (12.0 mg, 10 μ mol of β -CD unit) and adamantane (6.8 mg, 50 μ mol) were mixed in an aqueous solution and stirred for 24 h. Then the solution was lyophilized in vacuo and heated at 50 °C to remove the excess Ad by sublimation. **1** \supset **Ad** was obtained as a white powder (yield: 12.5 mg, 93%). ¹H NMR (D₂O, 30 °C, 500 MHz):

(35) The increase in height is low because it is hypothesized that the propagated polymer chain is extremely flexible. During polymerization the monomer is sterically hindered for α -CD in the polymer chain.

(36) The size of **1** with a Au-core is larger than that of a nanosphere **1** without a Au-core. In the AFM measurements, nanosphere **1** should be pressed by the absence of the Au-core in the dry state.

δ 5.37–4.97 (br, 7.0H, C₁H), 3.91–3.01 (br, 48.4H, C_{2,3,4,5,6}H), 1.81 (br, 8.2H, methine of Ad), 1.25 (br, 24.0H, methylene of Ad).

Synthesis of α -CD \supset Poly(δ -VL)-Modified β -CD Nanosphere (α -CD \supset 2). 2 (3.4 mg, 1.0 μ mol of δ -VL unit) and α -CD (1.0 mg, 1.0 μ mol of α -CD) were mixed in an aqueous solution. The mixture was allowed to stand for 5 min. After subsequent lyophilization in vacuo, α -CD \supset 2 was obtained as a white powder (yield: 4.0 mg, 91%). ¹H NMR (D₂O, 30 °C, 500 MHz): δ 5.31–5.17 (br, 7.0H, C₁H of 2), 4.97 (d, 19.0H, C₁H of α -CD), 4.06 (br, 6.7H, α -polymer), 3.91 (t, 23.9H, C₃H of α -CD), 3.91–3.01 (br, 125.0H, C_{2,3,4,5,6}H of 2 and C_{2,4,5,6}H of α -CD), 2.76 (br, 5.7H, α -polymer), 1.31 (br, 10.5H, β - and γ -polymer).

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Supporting Information Available: Detailed description of the experimental method, NMR spectra of the nanospheres, and TEM images of the nanospheres. This material is available free of charge via the Internet at <http://pubs.acs.org>.

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