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Editor's Choice

Supramolecular Spherical β-Cyclodextrin$_{32}$-dendrimer: Inclusion Properties and Supramolecular Structure

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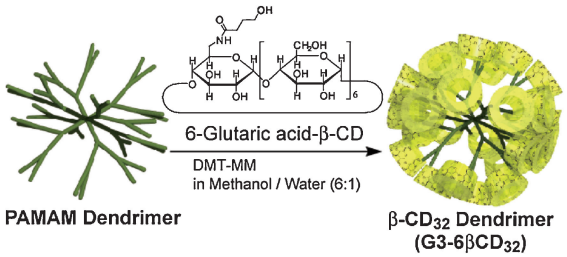
G3-6βCD$_{32}$, which has 32 β-cyclodextrins functionalized on the surface of a polyamidoamine dendrimer, was prepared as a multivalent host molecule. G3-6βCD$_{32}$ showed selective recognition behaviors for guest polymers. Using guest recognition sites on the surface, a supramolecular bilayer sphere was prepared in aqueous solutions. The molecular recognition properties and structure of G3-6βCD$_{32}$ are reminiscent of a virus structure.

In biological systems, certain viruses form spherical structures, which are precisely designed and have molecular recognition sites on the surface of a protein shell.[1] Coat proteins are selectively recognized on these molecular recognition sites.[2] To emulate natural cells and viruses, researchers have prepared artificial molecular viruses, such as liposomes and vesicles.[3–10] However, these molecules are larger than a virus, which makes it difficult to control the number of recognition sites. More recently, spherical molecules having host molecules on the surface were reported by using metal nanoparticles. Kim et al. prepared a spherical molecule noncovalently consisting of cucurbituril without a template.[11] In our studies, we have focused on preparing an accurate number of host molecules on a spherical molecule as well as determining the effect of the number of binding sites. Dendrimers with carbohydrates at the end of the terminals[12] have attracted much attention due to their water-solubility and definite nanostructure with multimolecular recognition sites. However, except for examples of dendrimers with a single or few cyclodextrins (CDs) on the surface,[13] there has yet to be a report on the preparation of dendrimers with a surface completely covered by CDs. This is probably because the bulkiness of CD, which is one nm in size, makes it extremely difficult to prepare dendrimers with a perfect surface. Herein, we report the preparation of dendrimers with CDs via a spacer on the surface to form almost perfect, dense coverage of CDs on the outside of the dendrimer.

β-CD$_{32}$ dendrimer (G3-6βCD$_{32}$) was prepared by reacting 6-glutaric acid-β-CD (6-Glu–β-CD) with polyamidoamine dendrimer (PAMAM generation 3 dendrimer) using 4-(4,6-dimethoxy-1,3,5-triazin-2-yl)-4-methylmorpholinium chloride (DMT-MM) in a mixed solvent of methanol and water (v/v = 6/1) as shown in Scheme 1. After 48 h, the precipitate, which was due to the decreased solubility of G3-6βCD$_{32}$ in organic media, was collected by centrifugation. The G3-6βCD$_{32}$ is hydrophilic in nature due to the high substitution of β-CD for the PAMAM dendrimer, while the PAMAM dendrimer is dissolved in organic media. The precipitate, which included the G3-6βCD$_{32}$, was purified by reverse phase HPLC. To determine the leaving amino group of dendrimer, fluorescamine was added to the solution of G3-6βCD$_{32}$ (Figure 1). Fluorescamine shows the emission due to the conformational change



Scheme 1.

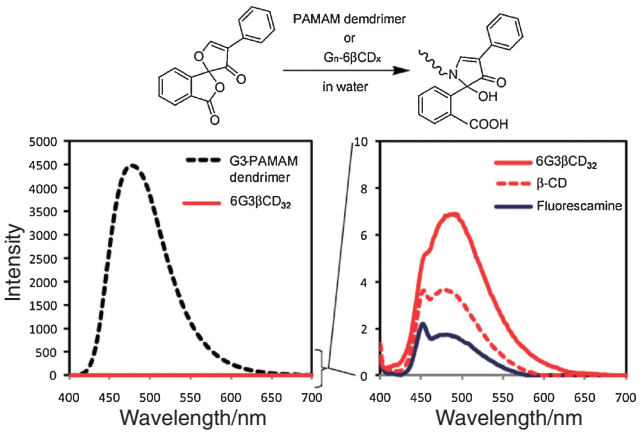


Figure 1. Fluorescence spectra of fluorescamine in the presence of β-CD (red dot line), G3 PAMAM dendrimer (black dot line), or G3-6βCD$_{32}$ (red line) and in the absence of any compounds (blue line) (ex, $\lambda = 390$ nm).

when fluorescamine reacts with the amino group. The mixture of PAMAM dendrimer and fluorescamine significantly showed the emission, whereas β-CD/fluorescamine and G3-6βCD$_{32}$/fluorescamine significantly showed low emission around 480 nm, respectively. ^{1}H NMR (Figure S3[19]) and elemental analysis (Table S1[19]) indicated that thirty-two NH_2 groups of the PAMAM dendrimer (Generation 3) were functionalized with 6-Glu-β-CDs, which is 99% substitution.

Moreover, the number of recognition sites and the association constants of G3-6βCD$_{32}$ for an adamantane derivative were determined by isothermal calorimetry (ITC) measurements. Assuming that β-CD and adamantanecarboxylic acid sodium salt form a 1:1 inclusion complex, the fitting analysis for the plots of the ITC results demonstrates that G3-6βCD$_{32}$ has 32.0 recognition sites and the association constant of a single unit is $K = 3.5 \times 10^4\,M^{-1}$. These results indicate that the surface of the dendrimer is almost completely functionalized by β-CDs.

Using the inclusion ability of G3-6βCD$_{32}$, we attempted to construct a bilayer supramolecular sphere with α-CD function-

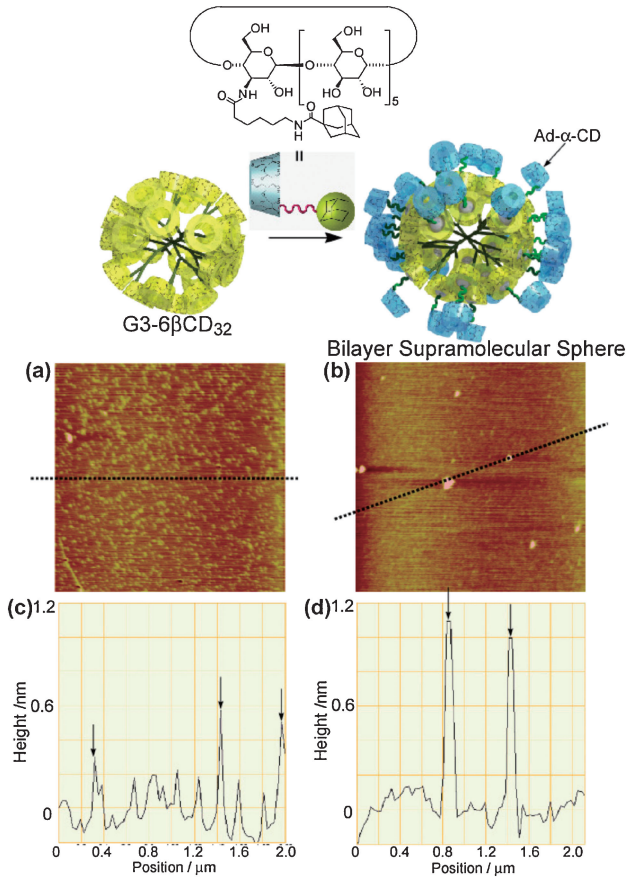


Figure 2. AFM images of G3-6βCD$_{32}$ (a) and G3-6βCD$_{32}$ with Ad–α-CD (b). The samples were added dropwise on mica substrates, followed by blow drying the substrate. Figures 2c and 2d showed the cross section of these images, respectively.

alized with an adamantyl group (Ad–α-CD). β-CD shows a high affinity for adamantyl derivatives, i.e., $K = 4.0 \times 10^4\,M^{-1}$ for adamantanecarboxylic acid sodium salt,[14,15] while α-CD shows a significantly lower affinity, i.e., $K = 140\,M^{-1}$ for adamantanecarboxylic acid sodium salt.[16,17] The ^{1}H NMR spectrum of a 32:1 mixture of Ad–α-CD and G3-6βCD$_{32}$ showed that the adamantyl protons shifted downfield upon the addition of G3-6βCD$_{32}$, whereas the peaks for Ad–α-CD without G3-6βCD$_{32}$ did not shift as the concentration increased. These results indicate that the adamantyl group of Ad–α-CD is included in the β-CD cavities of G3-6βCD$_{32}$ in aqueous solutions. The molecular size of a mixture of G3-6βCD$_{32}$ and Ad–α-CD was characterized by atomic force microscopy (AFM) measurements. Either a solution of G3-6βCD$_{32}$ or G3-6βCD$_{32}$ with Ad–α-CD was cast onto a mica substrate. Figures 2a and 2b show images of G3-6βCD$_{32}$ and G3-6βCD$_{32}$ with Ad–α-CD after blow drying the substrate, respectively. Although the average height and diameter of G3-6βCD$_{32}$ showed av. 0.60 and av. 32 nm,[18] which were derived from the height of 100 particles, the 1:1 mixture of G3-6βCD$_{32}$ and Ad–α-CD showed av. 0.90 nm (height) and av. 65 nm (diameter), which were about 50% larger than that for G3-6βCD$_{32}$. Ad–α-CD without G3-6βCD$_{32}$ showed av. 0.20 nm in height. When the sizes of the G3-6βCD$_{32}$ and G3-6βCD$_{32}$ with Ad–α-CD were characterized by dynamic light scattering (DLS) in aqueous solutions (1 mM), G3-6βCD$_{32}$ showed av. 3.0 nm, but G3-6βCD$_{32}$ with Ad–α-CD showed av. 6.5 nm. These results indicate the formation of bilayer supramolecular sphere, which was constructed by Ad–α-CD on the surface and G3-6βCD$_{32}$ as the core.

In conclusion, the multivalent interactions for guest molecules as well as the supramolecular bilayer structure remind us of biological viruses. Hence, research to prepare the β-CD$_{64}$ dendrimer using generation 4 dendrimer and to polymerize the lactone on the surface of G3-6βCD$_{32}$ is currently underway.

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18 The heights of β-CD$_{32}$ dendrimers were estimated to be small rather than the calculated size in the dry state because β-CD$_{32}$ dendrimers have unbridged shell and are hollow. The diameter of β-CD$_{32}$ dendrimer appeared larger than calculated because the scanning measurement method in AFM does not have accuracy in the x–y plane.

19 Supporting Information is available electronically on the CSJ-Journal Web site, http://www.csj.jp/journals/chem-lett/index.html.

