# NANO LETTERS

# Supramolecular Aggregates Formed by Intermolecular Inclusion Complexation of Organo-Selenium Bridged Bis(cyclodextrin)s with Calix[4]arene Derivative

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## ABSTRACT

A novel supramolecular assembly has been fabricated by the inclusion complexation between organo-selenium bridged bis(β-cyclodextrin)s 2 and calix[4]arene derivative 3 in water-acetonitrile (1:1) mixture solution and characterized by fluorescence, 2D NMR, TEM, SEM, and STM images, showing the nanometer structural wire-shaped aggregates.
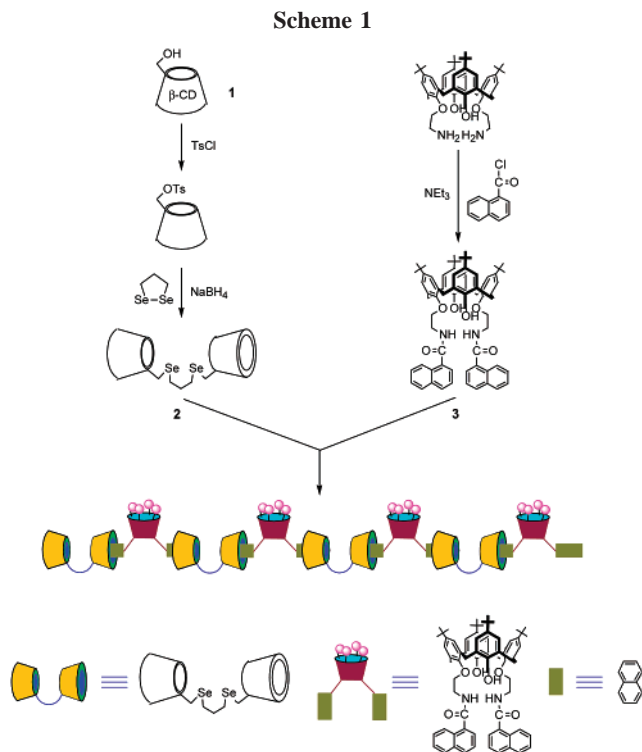
Natural and chemically modified cyclodextrins can be viewed as a molecular receptor selective binding a wide variety of organic, inorganic, as well as biologic, guest molecules, forming host−guest inclusion complexes or nanostructure supramolecular assemblies. Therefore, studies on the molecular recognition and molecular assembly or self-assembly of cyclodextrins and their derivatives are of current interest in chemical and biological systems.[1] Recently, Shigekawa et al.[2] reported the molecular abacus based on α-cyclodextrin necklace in the polyrotaxane, which is reversibly shuttled using a STM under ambient conditions. Harada et al.[3]

reported a cyclodextrin derivative which has a cinnamoyl group as a guest part on the 6-position of cyclodextrins forms an oligomeric supramolecular structure in aqueous solution and that the supramolecular structure could be stabilized by attaching bulky stoppers to give the cyclic trimer of [2]-rotaxane, daisy chain necklace. Kaifer et al.[4] reported that water-soluble gold nanoparticles (3.2 nm diameter) capped with thiolated γ-cyclodextrin hosts form large network aggregates (∼300 nm) in the presence of $C_{60}$ fullerene molecules. Reinhoudt and co-workers[5] have also shown that interconnective host−guest complexes of β-cyclodextrin-calix[4]arene couples are amphiphilic in nature and they form aggregates in aqueous solution such as vesicles or fibers. These studies on cyclodextrin-based molecular devices or molecular machines play important roles in the development

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## Scheme 1





**Figure 1.** Fluorescence spectral changes of calix[4]arene derivative **3** ($1.59 \times 10^{-6}$ M) upon addition of (a) bis($\beta$-cyclodextrin)s **2** ($0-2349 \times 10^{-6}$ M) and (b) $\beta$-cyclodextrin **1** ($0-8264 \times 10^{-6}$ M) in 0.8% CH$_3$CN aqueous solution.

of nanosupramolecular materials. However, the supramolecular assembly composed of the bridged bis(cyclodextrin)s are hardly reported so far. We recently reported a molecular assembly, bis(molecular tube)s of $\beta$-cyclodextrin derivatives containing selenium and platinum, which the nano bis-(molecular tube)s might be found important potential application in drug delivery system.[6] In the present communication, we wish to report a novel nanostructure supramolecular aggregate fabricated by the host−guest inclusion complexation between organo-selenium bridged bis($\beta$-cyclodextrin)s (**2**) and calix[4]arene derivative (**3**) in water-acetonitrile mixture solution (1:1). This aggregates formation was shown by the transmission electron microscopy (TEM), the scanning tunneling microscopy (STM), the scanning electron microscopy (SEM), and supported by 2D NMR spectroscopy and fluorescence spectroscopic measurement. It is of our particular interest to examine the molecular aggregate mechanism concerning the bridged bis(cyclodextrin)s, which will serve our further understanding of this recently developing on the host−guest inclusion complexation, but less investigated area of bridged bis($\beta$-cyclodextrin)s. A simple reason for choosing the (di)selenium tether in bis($\beta$-cyclodextrin)s is that selenium, possessing a larger radius and lower electronegativity than carbon, can provide an Se−Se bond that is longer and more flexible than a C−C bond. Therefore, the diseleno-bridged chain can act as the functional group in molecular assembly to control the reactions of guest molecules accommodated in the two $\beta$-cyclodextrin cavities.

The nanostructure supramolecular assembly was prepared according to the procedures shown in Scheme 1. As shown in Scheme 1, a sample of 5,11,17,23-tetra-*tert*-butyl-26,28-bis(2-aminoethoxy)-25,27-dihydroxycalix[4]arene[7] was added to a mixture of the 1-naphthoyl chloride and triethylamine
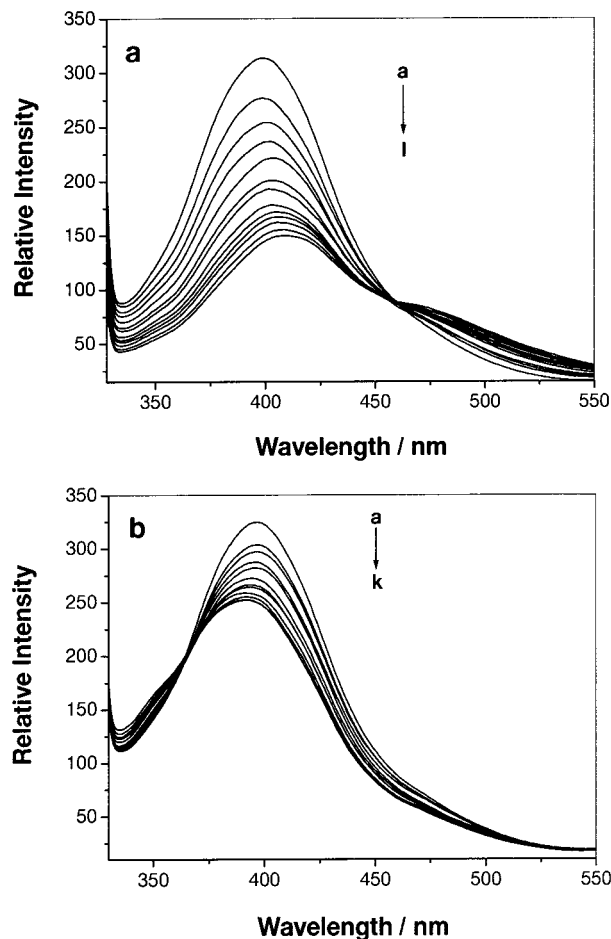
to get white pure 5,11,17,23-tetra-*tert*-butyl-25,27-bis[2-[$\alpha$-naphthoylamido]ethoxy]-26,28-dihydroxycalix[4]arene (**3**).[8] $\beta$-Cyclodextrin **1** was converted to mono[6-*O*-(*p*-toluenesulfonyl)]-$\beta$-cyclodextrin first. Subsequently, this intermediate reacted with 1,2-diselenacyclopentane in a mixture of *N,N*-dimethylformamide and ethanol in the presence of sodium borohydride to give 6,6′-trimethylenediseleno-bridged bis($\beta$-cyclodextrin) (**2**).[9] And then treatment of **3** with **2** in mixed solvent (water:acetonitrile = 1:1 v/v) gave a stable host-guest inclusion complex. It can be explained reasonably through experimental phenomena, i.e., calix[4]arene derivative with naphthyl **3** is only sparingly soluble in the mixed solvent, and that upon addition of 1.0 equiv bridged bis($\beta$-cyclodextrin) **2** the solution becomes clear. Such a significant increase in solubility has been recognized as a manifestation of the formation of host−guest inclusion complex.

The formation of host−guest inclusion complex between calixarene **3** and $\beta$-cyclodextrin dimer **2** was studied by fluorescence titration in mixed solvent (water:acetonitrile = 100:0 .8, v/v). Calixarene with naphthyl shows strong fluorescence originating from naphthalene group, and it has been demonstrated that its fluorescence spectrum is sensitive to the presence of hydrophobic environments.[10] Typical spectral changes are shown in Figure 1a. Upon bis($\beta$-cyclodextrin)
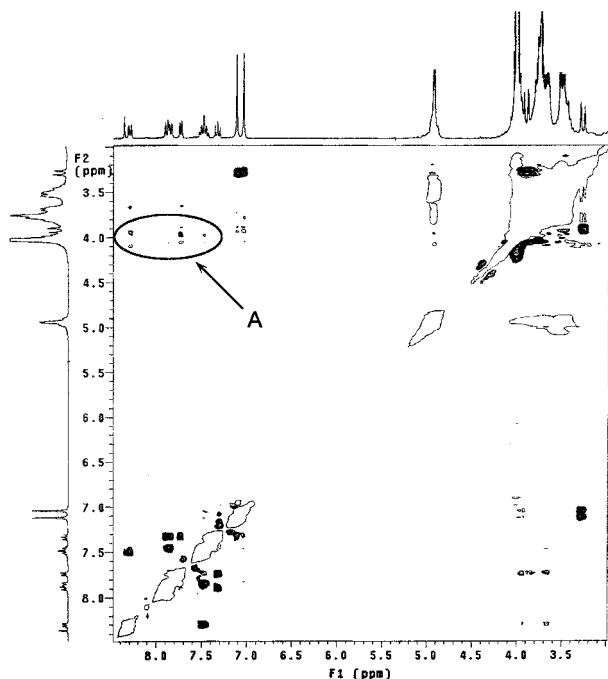
**Figure 2.** ¹H NOESY spectrum (300 MHz) of a mixture of **3** with **2** ([**3**] = [**2**] = 5.0 × 10⁻⁴ M) in 1:1 water-acetonitrile at 298 K with a mixing time of 800 ms.

**2** addition to water-acetonitrile solution of compound **3**, decrease in the fluorescence intensity was found, and an isosbestic point appears at 458 nm of long wavelengh, indicating the formation of a unique species.

In sharp contrast, the gradual addition of β-cyclodextrin **1** to a dilute water-acetonitrile solution of calix[4]arene derivative **3** (1.59 × 10⁻⁶ M) surprisingly gives an isosbestic point at 365 nm of short wavelengh under comparable conditions, as illustrated in Figure 1b. Such contrasting fluorescence behavior indicates that distinctly different complexes are obtained in the complexation of **3** with mono-cyclodextrin **1** and with bis(cyclodextrin) **2**. Apparently, simple inclusion complexes are formed between calixarene **3** and β-cyclodextrin **1**, whereas compound **3** including two naphthalene groups and bis(cyclodextrin) **2** possessing two cavities react to give more complicated inclusion complexes, such as linear aggregates.

To obtain detailed information about the solution structure of the calixarene **3** and β-cyclodextrin dimer **2** inclusion complex, we recorded the 300 MHz 2D-NOESY spectrum of a 0.5 mM solution of compound **3** in 1:1 (v/v) water–acetonitrile solution in the presence of 1 equivalent of compound **2**. As illustrated in Figure 2, the NOESY spectrum displays clear NOE cross-peaks between the H-5 and H-3 (weak) of cyclodextrin and the H-5, H-8, or H-6/H-7 of naphthalene ring in compound **3** (peaks A), which indicates distinctly that the naphthalene ring in **3** is lognitudinally included into the cavity from the secondary side of cyclo-dextrin. Hence, the result of the NOESY experiment not only supports the formation of host−guest inclusion complex between the calixarene **3** and β-cyclodextrin dimer **2**, but also infers reasonably the presumed aggregation modes as illustrated in Scheme 1. To verify the formation of calix[4]-

(a)
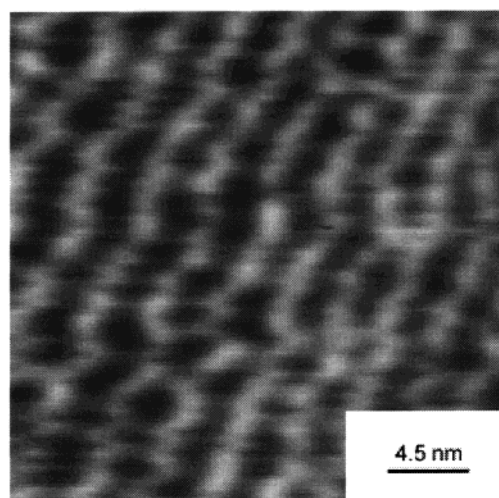


(b)
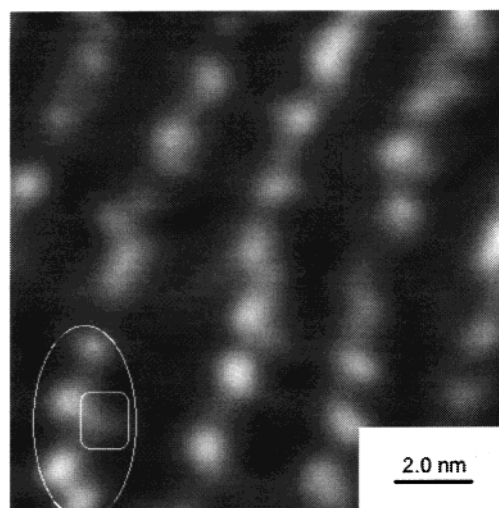


**Figure 3.** STM images of the supramolecular aggregates: (a) linear assemblies; (b) host−guest inclusion complexes composed of four β-cyclodextrins and a calix[4]arene units.

arene-bridged bis(β-cyclodextrin)s aggregation, STM was performed to characterize the structure.

The specimens for STM were prepared by dripping water-acetonitrile (1:1 v/v) solution in the concentration of 1.0 × 10⁻⁴ M of the equivalent mole β-cyclodextrin dimer **2** and calix[4]arene derivative **3** onto a freshly highly ordered pyrolytic graphite (HOPG) surfaces, followed by evaporating the liquid at least 2 h in a vacuum. Figure 3a shows a typical STM image of supramolecular aggregates on the graphite substrate (sample bias voltage +300 mV, tunneling current 2.10 nA, and a W tip). We may note that there exist lots of anomalous linear assemblies on the substrate. According to the size and shape, in the figure one white dot corresponds to a β-cyclodextrin unit or calix[4]arene unit, and the distances between two adjacent supramolecular aggregates are roughly 2.9 nm. To visualize the detailed structure, a sectional picture is shown in Figure 3b. Interestingly, it may

be noted from Figure 3b that four β-cyclodextrins and a calix-[4]arene units form a design like a flying sea-gull, in which the calix[4]arene unit is regarded as its head and two β-cyclodextrin dimers are regarded as a pair of sea-gull's wings. As schematically shown in Scheme 1, two naphthalene rings of **3** are accommodated in the cavities from the secondary side of two different bis(β-cyclodextrin) molecules, forming linear nanostructure supramolecular aggregate. An explanation for the formation of long, anomalous linear aggregations can be provided by molecular recognition of host−guest and has been supported by above 2D-NOESY spectrum. It is well documented that, among the several possible weak interactions contributing to the inclusion complexation of organic guests with cyclodextrins, the most crucial contributions are made by the van der Waals and hydrophobic interactions, both of which depend on how the size and/or shape of guest molecule fit into the host cavity. In this context, the naphthalene ring in the guest calix[4]arene derivative and the cavity of the host bis(β-cyclodextrin) give the strict size-fit relationship and relatively stronger hydrophobic interaction.[11] On the other hand, the unfavorable spacial orientation of two cyclodextrin moieties in a bis(β-cyclodextrin) molecule prevents two naphthyls in **3** inserting simultaneously two cavities in **2** from the secondary side by examination of the CPK models, making the operation of stoichiometric 1:1 inclusion complex difficult.

As can been seen in Figure 3b, the host−guest inclusion complexation between **2** and **3** gives a supramolecular aggregate. However, we cannot control every cyclodextrin moieties lie their longitudinal axis parallel to the graphite surface, so the distances between two adjacent β-cyclodextrin units as well as between β-cyclodextrin unit and calix[4]-arene ring present bigger diversity in STM image, for example, about 1.4∼2.0 nm for between two adjacent β-cyclodextrin units and rough 1.3∼1.8 nm for between β-cyclodextrin unit and calix[4]arene ring.

Transmission electron microscopy (TEM) has been also performed to further provide an insight into the size and shape of the aggregates in a drying effect. For visualization by TEM, a sample was prepared by one drop of the solution possessing the assembly tethered with **2** and **3** to be brought onto carbon-coated copper grid and then was shaded with palladium−iridium alloy to thicken and make the images more clear. Therefore, the TEM micrographs only have been used to measure the length of supramolecular assembly. From Figure 4 (inset), we may note that there exist some regular linear structures, i.e., nanowires, with lengths in the range of 400∼900 nm, which are joined together through about 80∼180 units of inclusion complex with a calixarene **3** molecule and a β-cyclodextrin dimer **2** molecule. As can been seen from Figure 4, a detailed TEM micrograph shows one of the nanowires with length of approximately 500 nm, indicating the nanometer structural wire-shaped aggregates formed by host−guest inclusion complexation.

Furthermore, surface morphologies of β-cyclodextrin dimer **2**, calix[4]arene derivative **3**, and the molecular aggregates based on compounds **2** and **3** are compared in Figure 5. SEM images in Figure 5a−c give macrostructrue
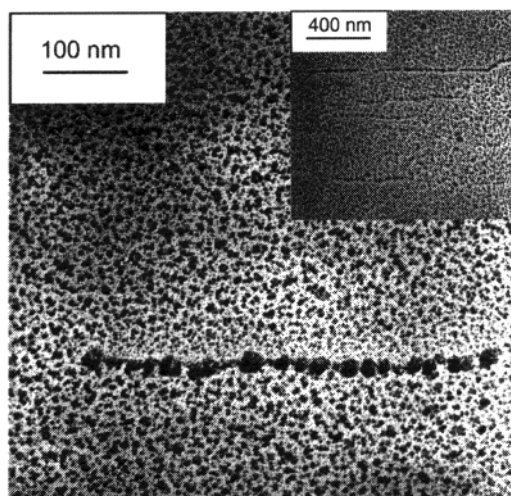


**Figure 4.** TEM images of the supramolecular aggregates.
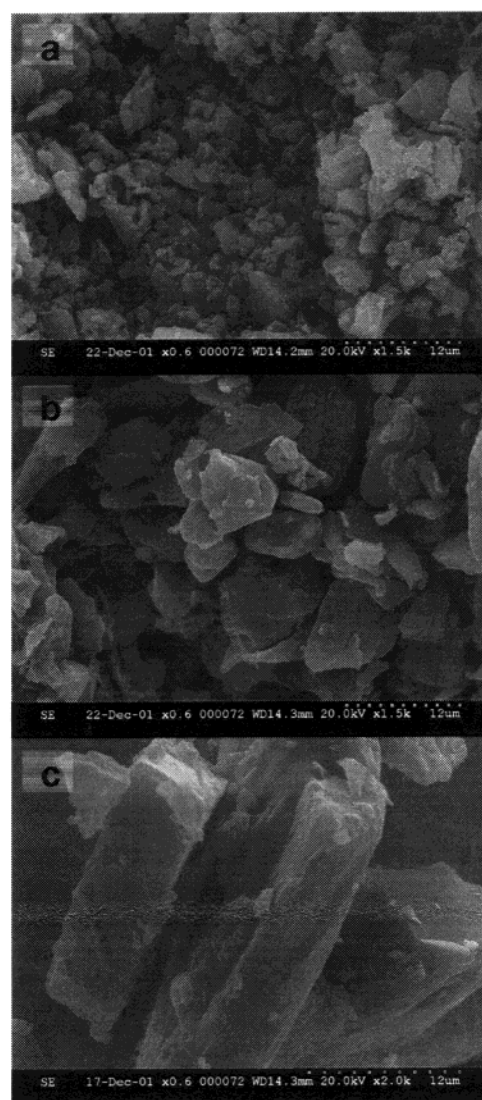


**Figure 5.** SEM images of (a) **3**, (b) **2**, and (c) the supramolecular aggregates.

information about the tethers **2**, **3**, and the molecular aggregates, respectively. As can be seen from Figure 5c, the

assembly macrostructure is 3D ordered square pillar structures. In sharp contrast, the SEM images of calixarene **3** (Figure 5a) and $\beta$-cyclodextrin dimer **2** (Figure 5b) present small and moderate irregular morphologies, respectively. Such difference in surface morphologies indicates that distinctly diverse species must exist in the linkers **2**, **3** and wire-shaped assembly.

In summary, we have demonstrated that a novel nano-structure supramolecular aggregate is formed by the host−guest inclusion complexation between bis($\beta$-cyclodextrin)s and calix[4]arene derivative in water-acetonitrile mixture solution. The result obtained suggests that bridged bis-(cyclodextrin) molecules provide a simple means for the linking of organic molecules containing two recognized groups into the wire-shaped nanometer structural aggregates, or nanotubes. Further studies are currently in progress concerning assembly of $\beta$-cyclodextrin dimers ligated metal center with calix[4]arene derivatives.

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