Supramolecular Chemistry

Water-Soluble Supramolecular Fullerene Assembly Mediated by Metallobridged β-Cyclodextrins**

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Fullerene (C_{60}), which has a spherical π-electron system, shows interesting magnetic,[1] superconductivity,[2] electrical,[3] and biochemical properties.[4] It is not surprising then that fullerenes and their derivatives have attracted a lot of attention in recent years and have been successfully applied to materials science and biological technology. However, the application of fullerenes and their derivatives has been limited, owing to their low solubility in water and other frequently used solvents. Several approaches have been explored for preparing water-soluble fullerenes,[5] such as carboxylic acid fullerene derivatives,[6] amino acid fullerene derivatives,[7] fullereneol,[8] peptide and oligonucleotide functionalized fullerene derivatives,[9] protein–fullerene conjugates,[10] pendant fullerene polymers,[11] main-chain fullerene polymers,[12] and dendrimeric fullerenes.[13] In addition, cyclodextrins and bridged bis-cyclodextrins as multifunctional molecular receptors can selectively bind a wide variety of organic,[14] inorganic, [15] and dye[16] guest molecules through hydrophobic interactions, forming host–guest inclusion complexes[17] or nanometer supramolecular assemblies.[18,19] Therefore, investigations on the molecular recognition and assembly or self-assembly of cyclodextrins and their derivatives are of current interest in chemical and biological systems. Besides, noncovalent supramolecular complexes based on cyclodextrins and fullerenes have been well documented,[20] and the obtained results indicate that water-soluble cyclodextrin–fullerene complexes show unique photophysical and biological properties. Recently, our studies indicated that the resultant complexes of bis-cyclodextrins and pharmacy molecules significantly enhance both water solubility and biological activity of fullerene derivatives.[21] Herein, we report a simple way to prepare a water-soluble fullerene assembly with a coordinated metal center through end-to-end intermolecular inclusion complexation of a dimeric cyclodextrin with a fullerene. Furthermore, the assembly behavior of this complex has been comprehensively

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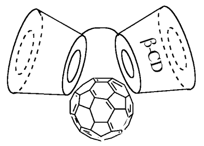
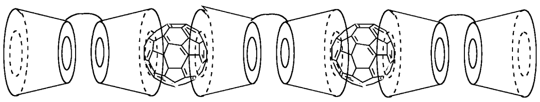
investigated by UV/Vis absorption, FTIR, ^{1}H NMR, and ^{13}C NMR spectroscopies, elemental analysis, thermogravimetric analysis (TGA), scanning tunneling microscopy (STM), transmission electron microscopy (TEM), and scanning electron microscopy (SEM). The biological activity of the assembly was assayed under visible light irradiation and another in dark as a control, which indicates that the assembly may serve as an effective photodriven DNA cleaver.

The supramolecular fullerene polymer, which has coordinated metal centers, was prepared according to the procedures shown in Scheme 1. The 6,6′-*O*-phenylenediseleno-bridged bis(β-CD) (**1**; CD = cyclodextrin) and its platinum(IV) complex (**2**) were synthesized according to the reported procedures.[22] The assembly **3** was synthesized with a yield of 4 % by treating **2** with fullerene (C_{60}) in a toluene/DMF (v/v = 4:6) solvent mixture. The solubility of **3** in water is approximately 7 mg mL^{-1} (calculated as C_{60} residue), which is larger than that of the 2:1 inclusion complex of natural β-CD and fullerene (4 mg mL^{-1}).[20c] One reasonable explanation for the increase of solubility is that the intrinsic solubility of bis-CD is larger than that of parent β-CD. The absorption at 343 nm and the peak broadening beyond 350 nm in the UV/Vis spectrum of **3** as well as the typical band at 527 cm^{-1} in the FTIR spectrum were assigned to C_{60}.

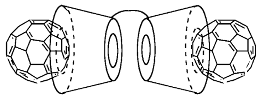
Theoretically, bis(β-CD) can form a 1:1 inclusion complex, a 1:1 intermolecular polymer, and a 1:2 inclusion complex with a fullerene guest, as illustrated in Figure 1. Energy-minimized calculations by use of MM2 force-field techniques and of a CPK model indicated that **2** cannot form stable 1:1 inclusion complex with C_{60} owing to steric hindrance. The resonance signal of H-3 protons of the CDs in **3** shift upfield (ca 0.04 ppm) relative to those of free **2** in ^{1}H NMR spectra (Figure 2), and no significant change in the chemical shift of the H-5 protons of the CD moieties was observed, thus indicating that fullerene was included only shallowly into the cavity from the secondary/wider side of the CDs to form end-to-end CD–C_{60} inclusion complexes (Figure 1 b or 1 c). Furthermore, the results of elemental analysis of **3** showed that the stoichiometry of metallobridged bis(β-CD) and C_{60} is 1:1. These results demonstrate that the bis(β-



a) 1:1 inclusion complex



b) 1:1 intermolecular polyfullerene



c) 1:2 inclusion complex

Figure 1. Three possible inclusion modes between metallobridged bis(β-CD) and fullerene.

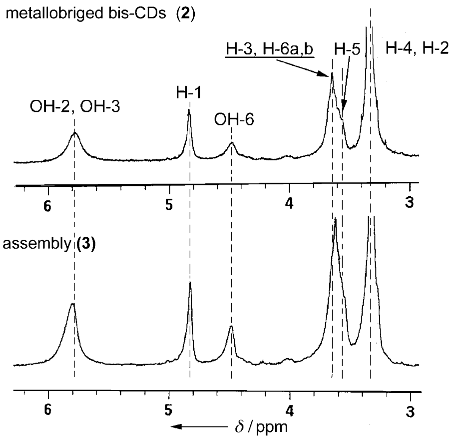
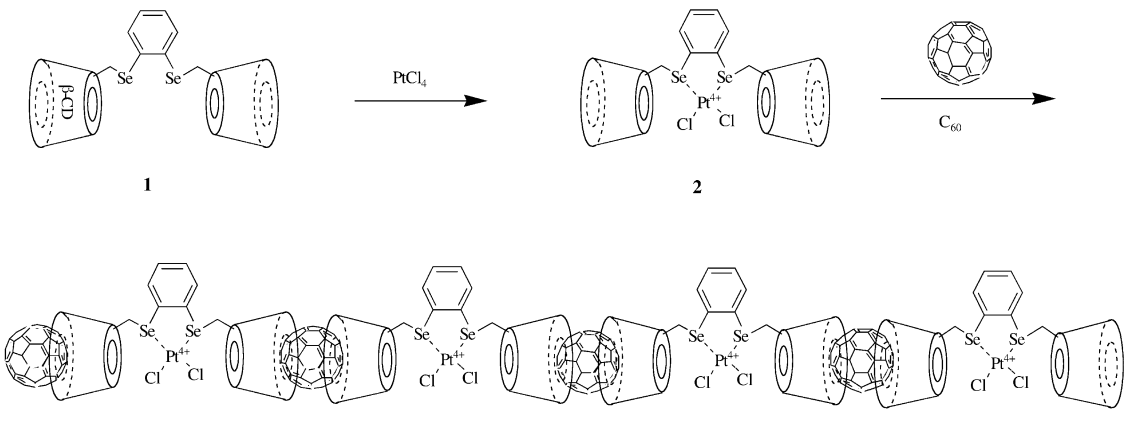


Figure 2. ^{1}H NMR spectra of **2** (top) and **3** (bottom) taken in [D$_6$]DMSO.



3

Scheme 1. Synthesis of **3**.

CD)–fullerene supramolecular assembly is formed by the 1:1 intermolecular inclusion mode, as shown in Figure 1b.

The most direct evidence for the formation of bis(β-CD)–fullerene assembly is given by STM. The samples for the STM experiment were prepared by dripping highly dilute aqueous solutions of the substrate onto freshly prepared highly ordered pyrolytic graphite (HOPG) surfaces, followed by evaporation of the aqueous solvents for at least 2 h in a vacuum. The STM image of **2** was recorded for comparison (Figure 3) and shows lots of analogical elliptical bright dots. The space between adjacent elliptical dots is about 1.6 nm. The length and width of an elliptical bright dot are about 2.1 nm and about 1.7 nm, respectively, thus indicating that one elliptical bright dot corresponds to one bis(β-CD) unit. Since the short and rigid bridge chain, which is coordinated to a metal ion, brings the cavities of the CDs close to each other, it is not possible to further distinguish the two CD units (Figure 3c). The height of the dimer is about 1.8 nm (Figure 3b), which is consistent with the actual external diameter for β-CD (1.54 nm). We conclude, from the previous reports by Kunitake and co-workers,[18i] Miyake et al.,[18j] and the from this study that the apolar outside wall of **2** interacts with the hydrophobic surface of the HOPG and self-assembles to form regular linear arrays. This intermolecular hydrogen-bonding interaction arises from the presence of the hydroxy groups of the secondary side of the CD (Figure 3d).

A typical STM image of **3** (Figure 4a)[23] shows a regular linear arrangement observed on HOPG. By combining the size and shape of the patterns in Figure 4a with those of **2** in Figure 3, one can affirm that each bright dot (height ca. 1.9 nm, width ca. 1.8 nm) corresponds to a unit of **2**. The average distance between two adjacent bis(β-CD) units is about 3.0 nm (Figure 4b), which is almost identical to the length of **2** (ca. 2.1 nm) and the diameter of C_{60} (ca. 1.0 nm) added together.[21c] We note that the height of the wave troughs in Figure 4b is about 1.2 nm, which further confirms that there is a C_{60} molecule between two units of **2** forming the supramolecular assembly, as illustrated in Figure 4c.

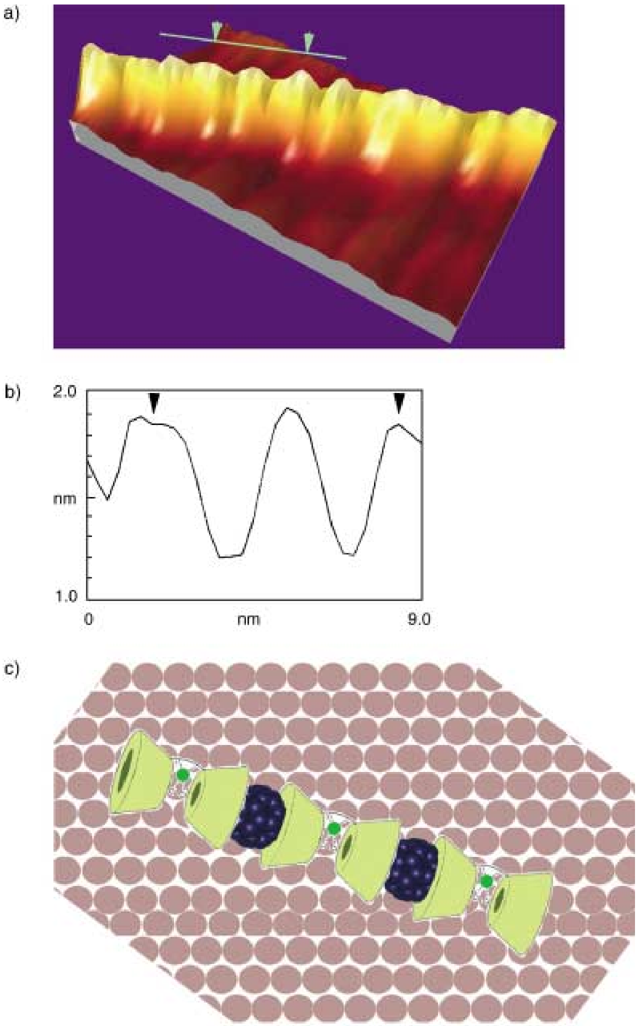


Figure 4. a) STM images of assembly **3** on HOPG a surface (tunneling current 1.0 nA).[23] b) Line profile of image shown in (a). c) Schematic structure of **3**.

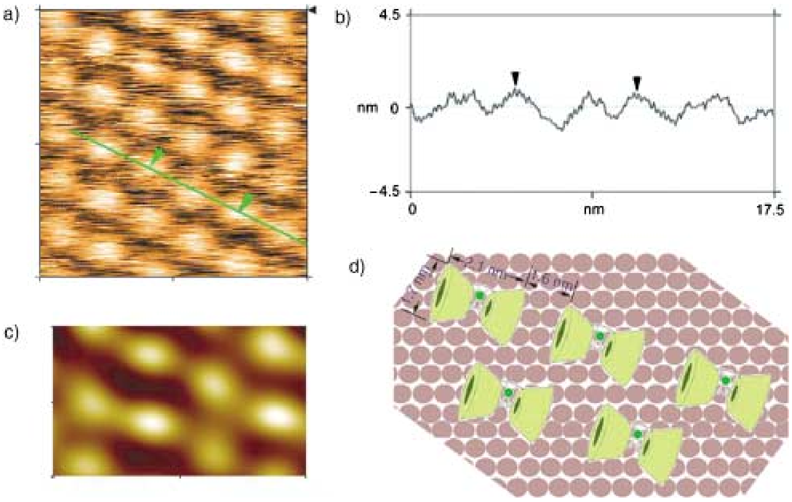


Figure 3. a) STM image of **2** on a HOPG surface (tunneling current 2.0 nA).[23] b) Line profile of the image shown in (a). c) Sectional image, and d) schematic structure of **2**.

TEM was also performed to provide further insight into the size and shape of the aggregates. For visualization by TEM, a sample was prepared by placing a drop of the solution of assembly **3** onto a carbon-coated copper grid, which was then was shaded with palladium–iridium alloy to thicken and make the images clearer. Thus, the TEM micrographs only were used to measure the length of the supramolecular assembly. From Figure 5, we may note that there exists some linear structures with lengths in the range of 150–200 nm, which are joined together through approximately 60–80 units of the inclusion complex of **2** with a fullerene molecule. In turn, we infer that the average molecular weight of **3** is 250 kg mol^{-1}. On the other hand, SEM images showed the macrostructure of **3** was cylindrical, which is different from the small and irregular morphologies found for **2** with fullerene.

We chose pIRES2-EGFP plasmid as a substrate to investigate the DNA-cutting ability of the assembly. In the dark, DNA was not cleaved in the presence of **1**, **2**,

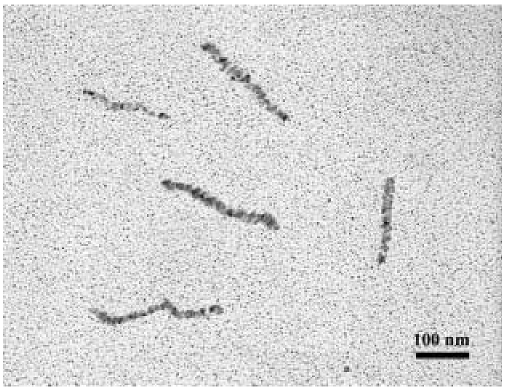


Figure 5. TEM images of **3**.

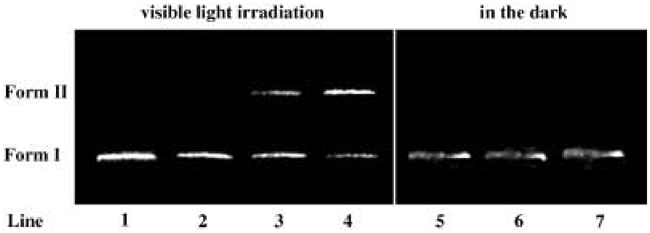


Figure 6. Agarose gel electrophoretic patterns of DNA and nicked DNA. The reaction samples contained 65 μmol dm^{-3} of pIRES2-EGFP plasmid. Line 1: no reagent in 50 mM Tris-HCl buffer (pH 7.4). Lines 2 and 5: 20 μmol dm^{-3} of **1**. Lines 3 and 6: 20 μmol dm^{-3} of **2**. Lines 4 and 7: 73 mg dm^{-3} of **3** (corresponding to 20 μmol dm^{-3} of **2** and 20 μmol dm^{-3} of fullerene). Lines 1–4: incubated under visible light irradiation at 20°C for 6 h. Lines 5–7: incubated in the dark for 6 h. Electrophoresis was performed by using 1 % agarose gel containing ethidium bromide (0.5 μg dm^{-3}).

or **3** (Figure 6, lines 5–7). Under visible-light irradiation, **2** showed some DNA-cleavage ability (line 3), which supports the argument that the "cationic" metallo bis(β-CD) unit is bound to the "anionic" DNA.[24] Compound **1** showed no DNA-cleavage ability (line 2). Under the same conditions, **3** showed DNA-cleavage activity (line 4). The closed supercoiled (Form I) DNA was converted into the nicked circular form of DNA (Form II) by incubating under visible-light irradiation, which is attributed to photoinduced electron transfer from the guanine moieties to the fullerenes.[4,24,25]

In conclusion, a novel supramolecular assembly has been synthesized by the intermolecular inclusion complexation of metallobridged bis(β-CD) and C_{60}. The supramolecular fullerene assembly mediated by the metallobridged bis(β-CD) shows both moderate water-solubility and effective DNA-cleavage ability under light irradiation, which has potential application in biological and medical chemistry.

Experimental Section

A mixture of **2** (0.1 mmol) and fullerene (C_{60}; 0.1 mmol) were stirred together for three weeks in a mixture of toluene and DMF (v/v = 4:6; 200 mL), during which the deep purple homogenous solution turned deep brown. After the solvent had been removed under vacuum, the crude solid residue was dissolved in water and purified by column chromatography (Sephadex G-25, distilled deionized water as eluent). Then membrane filtration over a polymer membrane with a molar mass cutoff of 3 kg mol^{-1} was used to obtain high molecular-weight aggregate **3** with a yield of 4 %. FTIR (KBr): $\tilde{\nu}$ 3339, 2928, 1723, 1660, 1593, 1430, 1030, 945, 527 cm^{-1}; ^{1}H NMR (300 MHz, [D$_6$]DMSO, TMS): δ = 3.5–3.8 (m, 12 H), 4.8–5.0 (m, 14 H), 5.7–6.0 (m, 28 H), 7.68–7.71 (m, 2 H), 7.94–7.96 ppm (m, 2 H); ^{13}C NMR (75 MHz, [D$_6$]DMSO): δ = 60.2, 67.6, 72.2, 72.6, 73.3, 81.7, 102.1, 109.5, 125.7, 128.8, 131.8, 133.7, 142–146 ppm (weak); elemental analysis (%) calcd for $C_{150}H_{142}O_{68}Se_2PtCl_4\cdot 6H_2O$: C 49.56, H 4.27; found: C 49.60, H 4.30.

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Keywords: cleavage reactions · cyclodextrins · DNA · fullerenes · supramolecular chemistry

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[23] STM experiments were performed by using a Nanosurf instrument (Switzerland) with a Pt–Ir tip, and were carried out with a sample bias voltage of +300 mV. All images were recorded in the constant-current mode. An aqueous solution of sample **2** and **3** were prepared at a diluted concentration of 5×10^{-6} M and dripped onto a freshly prepared highly ordered pyrolytic graphite surface at room temperature. The sample was then dried in a vacuum for 2 h. All measures were performed in air at room temperature.

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