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Supramolecular self-assembled aggregates formed by pentacosa-10,12-diynyl amidomethyl-β-cyclodextrin

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Abstract

Mono[6-deoxy-6-(pentacosa-10,12-diynyl amidomethyl)]- β-cyclodextrin was successfully synthesized by reacting mono-6-amino-6-deoxy-β-cyclodextrin with *N*-hydroxysuccinimide ester of 10,12-pentacosadiynoic acid in DMF. The modified β-cyclodextrin self-assembled and aggregated to form a worm-like supramolecular structure, and the novel supramolecular aggregates were studied using 2D nuclear magnetic resonance spectroscopy, X-ray powder diffraction, thermogravimetry, and electron microscopy. Interestingly, the synthesized pentacosa-10,12-diynyl amidomethyl-β-cyclodextrin formed columnar type self-aggregates and it was clearly differentiated from cage-like structure of native β-cyclodextrin.

Keywords: β-cyclodextrin; 10,12-pentacosadiynoic acid; Self-assembly; Supramolecular structure.

1. Introduction

Supramolecular self-assembly is the spontaneous association of molecules into patterns or suprastructures by noncovalent bonds. The supramolecular architectures are ubiquitous in biological systems such as proteins, nucleotides, and polysaccharides. They exhibit unique properties and functions that are not displayed by their individual components. Microtubules, flagella, and collagens are helical supramolecular polymers formed by proteins; their functionality is clearly differentiated from their individual polypeptides.[1] In this respect, researchers have mimicked structurally the important phenomena that occur in nature, and much attention has focused on building supramolecular structures by designing small molecular building blocks.[2,3] For example, host–guest inclusion complexes made from cyclodextrins and nonpolar chemicals.[4]

Cyclodextrins (CDs) are a series of cyclic oligosaccharides composed of six to eight glucose units connected through α-1,4 linkages. They are called α–, β–, and γCD, respectively; because of their complex-forming ability, they are widely used as enzyme mimics and drug carriers in the research fields of science and biotechnology.[5] The torus shape of CDs provides them the ability to incorporate hydrophobic compounds into the internal cavity; βCD is generally used as the enzyme mimic and drug carrier because of its easy availability and appropriate size. Furthermore, various βCD derivatives have been synthesized to widen and improve their catalytic and complex-forming abilities.[6] Recently, the intrinsic conformation and self-assembly properties of the modified βCD have gained extensive attention for mimicking supramolecular structures.[7-9] Because molecular cooperative interactions are highly complicated and poorly understood, more effort needs to be devoted to their mechanistic study.

Lipid molecules containing diacetylene moieties in their hydrophobic alkyl chains are used as another type of building block to form self-assembled suprastructure.[10] For instance, 10,12-pentacosadiynoic acid (PCDA) undergoes spontaneous molecular assembly in aqueous solution to yield supramolecules, polymerized via 1,4-addition of diacetylenes under UV irradiation. The resultant polydiacetylens (PDA) have alternating ene-yne backbone structures and exhibit distinctive electronic and optical properties because of the highly delocalized π-electron system of its polymer backbone. External stimuli (pH, heat, solvent, and biological substances) induce conformational changes in PDA, resulting in blue-to-red color transition of PDA. Therefore, PDAs have been used as fascinating sensor matrices for the detection of biologically interesting target molecules. PCDA functionalized with a specific carbohydrate, antibody, probe DNA, and enzyme has been developed for the preparation of a label-free PDA-based chemo/biosensor system.[11-14] However, hybrid materials made of the best known host, βCD, and the photonic sensor unit, PCDA, have not yet been reported.

Herein, we synthesize pentacosa-10,12-diynyl amidomethyl β-cyclodextrin (PCDA–βCD) using a combination of the functional carbohydrate, βCD, and the functional lipid, PCDA, and propose the modified βCD as the neoglycoconjugate building block for the self-assembled supramolecular structure. Because the long aliphatic tail can be threaded into the cavity of βCD,[15] PCDA–βCD is expected to form complicated molecular interactions within the self-assembled structure. The resulting supramolecular aggregates are studied using various analytical tools such as nuclear magnetic resonance (NMR) spectroscopy, X-ray powder diffraction (XRD), Thermogravimetry/differential thermal analysis (TG/DTA), Transmission electron

microscopy (TEM), and Scanning electron microscopy (SEM).

2. Results and Discussion

The carbohydrate-lipid hybrid molecule, PCDA-βCD, was synthesized from NHS-PCDA (*N*-hydroxysuccinimide ester of 10,12-pentacosadiynoic acid) and amino βCD (mono-6-amino-6-deoxy-β-cyclodextrin), as shown in Scheme 1. NHS-PCDA was prepared by the reaction between PCDA and NHS in the presence of chloroform (Scheme 1), and its structure was confirmed using FT-IR spectra. The C=O stretch of the carboxylic acid disappeared at 1693 cm^{-1} and new peaks were observed. The ketone C=O stretching vibrations of NHS were observed at 1819 and 1787 cm^{-1}, whereas the ester C=O and C–O stretching bands by linkage were observed at 1725 and 1071 cm^{-1}, respectively.

Amino βCD (mono-6-amino-6-deoxy-β-cyclodextrin) was synthesized from tosyl βCD (mono-6-*O*-*p*-toluenesulfonyl-β-cyclodextrin). Tosyl βCD is the most important intermediate that is required for modifying one of the 6-hydroxy groups of βCD into other functional groups on the primary side.[16] Accordingly, the mono-pentacosa-10,12-diynyl amidomethyl group was attached to βCD through mono-tosylation, azidation and amination, as described in Section 3.2.1. Although the selective functionalization of the primary hydroxyl groups within the cyclic oligosaccharides is difficult and low yielding, monosubstitution at the primary hydroxyl group is important because it has expanded the research scope of βCD.[17]

The desired product synthesized from NHS-PCDA and amino βCD was

analyzed using MALDI TOF mass spectrometry and NMR spectroscopy (Figure 1). The chemical structure of PCDA-βCD is shown in Figure 1A, and the mass difference of *m/z* 355, obtained by added mono-pentacosa-10,12-diynyl amidomethyl group, is shown in Figure 1B. Furthermore, the mono-functionalized βCD was obtained without any reactants and was confirmed by integrating the ^{1}H-NMR spectra (Figure 1C). The obtained PCDA-βCD shows self-assembly behavior due to its structural characteristics. The analysis of the binding mode among the PCDA-βCDs is useful to understand the remarkable complexity of the assembled supramolecular structure. In fact, the binding processes between artificial molecules, complexes, or aggregates within multicomponent mixtures have been investigated to understand the complexity of supramolecular systems.[18,19]

To gain insight into the molecular geometry of PCDA-βCD, nuclear Overhauser enhancement spectroscopy (NOESY) experiments in D_2O were carried out. Figure 2 shows the NOE cross-peaks between the H2-H6 protons of βCD and 3–6 and 11–19 protons of PCDA. It is highly probable that the 11–19 protons of PCDA group are located in another βCD cavity. With regard to the correlation of H2 and H4 protons outside the cavity, we speculate that 3–6 protons of the PCDA substituent are located between βCDs, but not inside the cavities. Most of the studies so far have described supramolecular polymers made from βCD substituted with aromatic rings such as 6-*O*-(4-formyl-phenyl), 6-deoxy-6-anilino, and 6-*O*-hydrocinnamoyl groups.[20-23] Because the size of substituents fits to the βCD cavity, consecutive and ordered three-dimensional suprastructures are obtained. However, the present substituent PCDA has a long alkyl chain with a diacetylene, and six carbons of the aliphatic chain can be

inserted in the βCD cavity.[24] Therefore, PCDA-βCD forms a novel self-assembled structure under aqueous condition, and the intermolecular association is expected to be more complicated.

To study the thermal behavior of the supramolecular structure, TG/DTA was performed with the PCDA, βCD, PCDA, and βCD physical mixture, and the synthesized PCDA-βCD. The TGA and DTA curves of each of these are shown in Figure 3. PCDA began to decompose at around 282 °C with a slow-down curve; however, the curve dropped more sharply when the temperature was increased to 433 °C. βCD began to decompose at 310 °C, with dehydration being observed at 73 °C. The TGA of the physical mixture of PCDA and βCD showed two curves characteristic of the individual components. However, the synthesized PCDA-βCD began to decompose at 317 °C, with a pattern different from that of PCDA or βCD. Additionally, DTA traces of each compound are shown in Figure 3B. The DTA curve for PCDA showed an endothermic peak at 69.1 °C and an exothermic peak at 322.9 °C relating to the melting point and crystallization of PCDA, respectively. Both peaks are also present in the DTA graph of the PCDA and βCD physical mixture; however, the DTA graph of PCDA-βCD shows no characteristic peaks of PCDA or βCD. These results suggest that the self-assembled PCDA-βCD structure forms through inclusion phenomena in the solid state.

The crystal structures of PCDA-βCD and βCD were compared using X-ray powder diffraction (XRD) (Figure 4A). βCD showed strong peaks at 10.6° and 12.4° with many small sharp peaks, indicating a cage-like structure (Figure 4B).[23] However, the XRD pattern of PCDA-βCD showed a smooth curve with three main peaks (2θ =

6.6°, 11.5°, and 17.7°). This pattern is assigned to a columnar structure;[25] the supramolecular structure of PCDA-βCD might be self-assembled and aggregated in a certain ordered structure by noncovalent bonds formed via hydrophobic interactions and hydrogen bonding.[26]

Transmission electron microscopy (TEM) was also carried out to gain an insight into the size and shape of the aggregates in the aqueous environment. In contrast to the micrometer planar aggregates formed by the original βCD (Figure 5A),[27] the worm-like supramolecular structure was formed by the self-assembly of PCDA-βCD (Figure 5B). The morphology of the novel nanostructure appeared to be similar to that of *Staphylococcus aureus*, and the length of the irregular supramolecules ranged from 40 to 400 nm with a width of ~20 nm. Considering that the outer diameter and height of βCD are 1.5 and 0.8 nm, respectively,[5] the supramolecules are joined longitudinally through 50–500 units and are intertwined. The PCDA-βCD formed intermolecular complexes to give supramolecular polymers.

Furthermore, the surface morphologies of βCD, PCDA, and PCDA-βCD were compared (Figure 6). Scanning electron microscopy (SEM) images of each (Figure 6A-C) provided macrostructure information in the solid state.[18] βCD and PCDA are characterized by their rod shape and plate piece shape, respectively. As shown in Figure 6C, the PCDA-βCD assembled macrostructure is an aggregated structure, distinct from the respective components. Such a difference in surface morphology clearly indicates the formation of a supramolecular structure.

In conclusion, we have synthesized mono[6-deoxy-6-(pentacosa-10,12-diynyl amidomethyl)]-β-cyclodextrin, which forms a novel self-assembled supramolecular

structure. The supramolecules were characterized using NMR, TG/DTA, XRD, TEM, and SEM. The structure showed worm-like nano-aggregates made of columnar-type units. Further studies are in progress to investigate the applicability of the present PCDA-βCD as an effective sensor system for detecting biological targets by using its dual function as a well-known receptor and a sensor matrix.

3. Experimental

3.1. Materials

βCD and 1-(*p*-toluenesulfonyl)imidazole were obtained from Tokyo Chemical Industry Co., Ltd. βCD was recrystallized from distilled water and dried *in vacuo* for 12 h. NHS was obtained from Fluka. PCDA, ammonium chloride, and chloroform were purchased from Sigma Aldrich. *N*,*N*-dimethylformamide (DMF) was obtained from Alfa Aesar, a Johnson Matthey Company. 1-(3-Dimethylaminopropyl)-3-ethyl carbodiimide hydrochloride (EDC) was purchased from Acros Organics, New Jersey, USA. Organic solvents such as hexane, ethyl acetate, acetone, and diethyl ether were of chromatographic purity, and the water used was triply distilled.

3.2. Synthesis of mono[6-deoxy-6-(pentacosa-10,12-diynyl amidomethyl)]-β-cyclodextrin (PCDA-βCD)

3.2.1. *N*-hydroxysuccinimide ester of 10,12-pentacosadiynoic acid (NHS-PCDA)

PCDA (1 g, 2.7 mmol) was dissolved in 10 mL of chloroform. To the organic solvent, NHS (337.5 mg, 2.9 mmol) and EDC (615 mg, 3.2 mmol) were added.[14] The

resulting solution was stirred at room temperature for 3 h. After removing the solvent *in vacuo*, the product was extracted with ethyl acetate and washed with water. The organic layer was dried with magnesium sulfate and filtered, and the solvent was removed *in vacuo*. The product was then recrystallized and a clean product was obtained in 70.3% yield. The product was confirmed using thin-layer chromatography (TLC, hexane:ethyl acetate 3:1) and FT-IR spectra.

3.2.2. Mono-6-amino-6-deoxy-β-cyclodextrin (amino βCD)

In a 250-mL three-necked round-bottomed flask, βCD (5.0 g, 4.4 mmol) was dissolved in 112.5 mL of water by heating to 60 ºC under vigorous stirring.[28] After cooling to room temperature, finely powdered 1-(*p*-toluenesulfonyl)imidazole (3.9 g, 17.7 mmol) was added to the suspension. After 6 h, a solution of sodium hydroxide (2.3 g, 56.3 mmol) in 6.3 mL of water was added over 20 min. After 10 min, unreacted 1-(*p*-toluenesulfonyl)imidazole was removed by filtration. To the filtrate was added ammonium chloride (6.1 g, 112.5 mmol) to quench the reaction. The resulting mixture was concentrated by blowing a stream of air across the mixture and the product began to precipitate out of the solution. The suspension was filtered, and the solid was washed with ice water and acetone. The vacuum-dried tosyl βCD was obtained in 28.2% yield. The mono-tosylated βCD was treated with an equivalent amount of sodium azide in 16 mL of water at 80 °C for 5 h.[29] After cooling, the solution was precipitated with acetone and then lyophilized. Lyophilized azido βCD and triphenylphosphine (PPh_3) (224 mg, 848 μmol) were dissolved in DMF (8 mL) and stirred for 2 h at room temperature. After adding 1.6 mL of water, the solution was stirred for 3 h at 90 °C, and the resulting

product was precipitated with acetone. Amino βCD was purified by cation-exchange chromatography (CM-Sephadex C25) using 0.5-M ammonium bicarbonate as a solvent and desalted with Bio-gel P2. The product was confirmed using ^{1}H-NMR spectra.

3.2.3. Synthesis of mono[6-deoxy-6-(pentacosa-10,12-diynyl amidomethyl)]-β-cyclodextrin (PCDA-βCD)

First, amino βCD (100 mg, 88.3 μmol) was dissolved in 3.1 mL of DMF, and then NHS-PCDA (56 mg, 118.7 μmol) was added. After stirring at 45 °C for 24 h, the product was washed and precipitated with ether. The dried product was afforded in 76.3% yield. The product was analyzed using MALDI TOF mass spectrometry and NMR spectroscopy.

3.3. Fourier-transform infrared (FT-IR) spectroscopy

FT-IR spectra were obtained using a KBr matrix with a Bruker IFS-66 spectrometer (AMX, Germany). The samples were recorded at wavenumbers ranging from 4000 to 500 cm^{-1}.

3.4. Matrix-assisted desorption/ionization time-of-flight mass spectrometry (MALDI-TOF MS)

The mass spectrum was obtained using a MALDI-TOF mass spectrometer (Voyager-DE^{TM} STR BioSpectrometry, PerSeptive Biosystems, Framingham, MA, USA) using the positive-ion mode. 2,5-Dihydroxybenzoic acid (DHB) was used as the matrix.

3.5. Nuclear magnetic resonance (NMR) spectroscopy

For the NMR spectroscopic analysis, a Bruker Avance 500 spectrometer was used to record the ^{1}H–NMR and NOESY spectra. The NOESY spectra were recorded with 256/2048 complex data points using a pulse train to achieve a spin-lock field with a mixing time of 800 ms for the complex. NMR analyses were performed in D_2O or d_6–DMSO at room temperature.

3.6. Thermogravimetry/differential thermal analysis (TG/DTA)

TGA and DTA were determined using a thermogravimetric analyzer (SEICO, Seiko Exstar 6000 (TG/DTA6100), Japan). The samples were put inside the platinum pans, which were hanging in the heating furnace. The weight percentage of the remaining material was recorded while the furnace was heated from 25 to 630 ºC. Nitrogen was used as the purge gas and a heating rate of 10 ºC/min was employed.

3.7. X-ray powder diffraction (XRD)

Powder X-ray diffraction patterns were recorded with D8 FOCUS (Bruker Corp., Germany) X-ray diffractometer by using a Ni-filtered CuKαλ radiation (λ = 1.5406 Å) in the $5° \leq 2\theta \geq 60°$ range. The measurement conditions were as follows: voltage of 40 kV, current of 100 mA, step size of 0.02°, scan speed of 5 °/min.

3.8. Transmission electron microscopy (TEM)

First, 100 μL of distilled water was added to 1.5 mg of PCDA–βCD. To agitate the particles in a sample, 30-s sonication and 1-min voltex were carried out. The

aqueous suspension (10 μL) containing the supramolecular aggregates formed by PCDA–βCD was adsorbed onto a carbon-coated copper grid (300-mesh) and air-dried for 1 min. The equivalent concentration of βCD was loaded onto a carbon-coated grid and air-dried. For clear negative staining, we used the supernatant of 2% uranyl acetate following centrifugation at 13,200 rpm for 2 min. Then, the aggregates were examined using transmission electron microscopy (JEOL, JEM 1010, Tokyo, Japan).

3.9. Scanning electron microscopy (SEM)

The samples were mounted onto stubs using double-sided adhesive tape and then made electrically conductive by coating with a thin layer of gold. The surface morphologies of the materials were examined using scanning electron microscopy (JEOL, JSM 6380, Tokyo, Japan).

Acknowledgements

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Figure legends

Scheme 1. Synthesis of pentacosa-10,12-diynyl amidomethyl β-cyclodextrin (PCDA–βCD).

Figure 1. Chemical structure (A), MALDI-TOF mass spectrum (B), and ^{1}H-NMR spectrum (d_6–DMSO) of PCDA–βCD (C). The mass shows *m/z* 1512.8 ([mono-pentacosa-10,12-diynyl amidomethyl βCD + Na]$^{+}$). Peaks designated with H or OH represent signals by βCD moiety, and only numerically designated peaks denote protons of the attached pentacosa-10,12-diynyl amidomethyl group.

Figure 2. Partial NOESY spectrum (500 MHz) of PCDA–βCD, in D_2O at 298 K with a mixing time of 800 ms. The signals in the F1 and F2 chemical shift are attributed to pentacosa-10,12-diynyl amidomethyl group and βCD moieties, respectively.

Figure 3. TGA (A) and DTA (B) graphs of 10,12-pentacosadiynoic acid (PCDA), βCD, PCDA+βCD physical mixture, and PCDA–βCD.

Figure 4. X-ray diffraction patterns (A) and proposed structures (B) of PCDA–βCD and β–CD.

Figure 5. TEM images of βCD (A) and supramolecular assembly by PCDA–βCD (B).

Figure 6 SEM images of βCD (A), PCDA (B), and PCDA−βCD (C).

ChemDraw/IsisDraw files

Scheme 1.

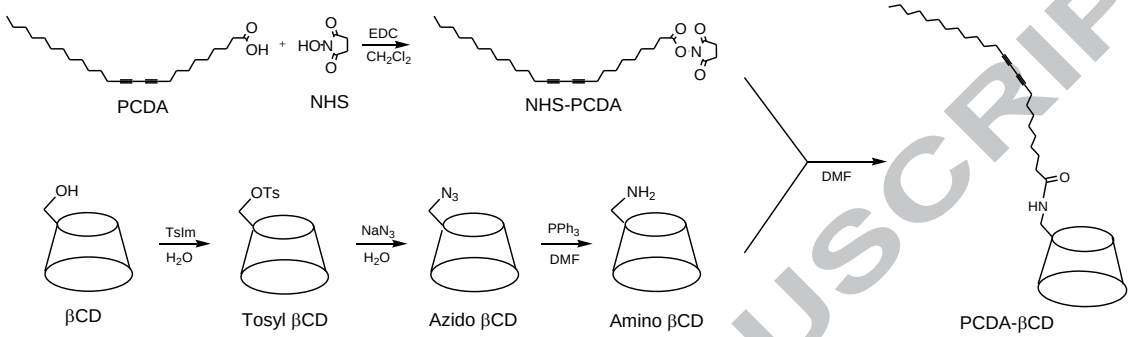
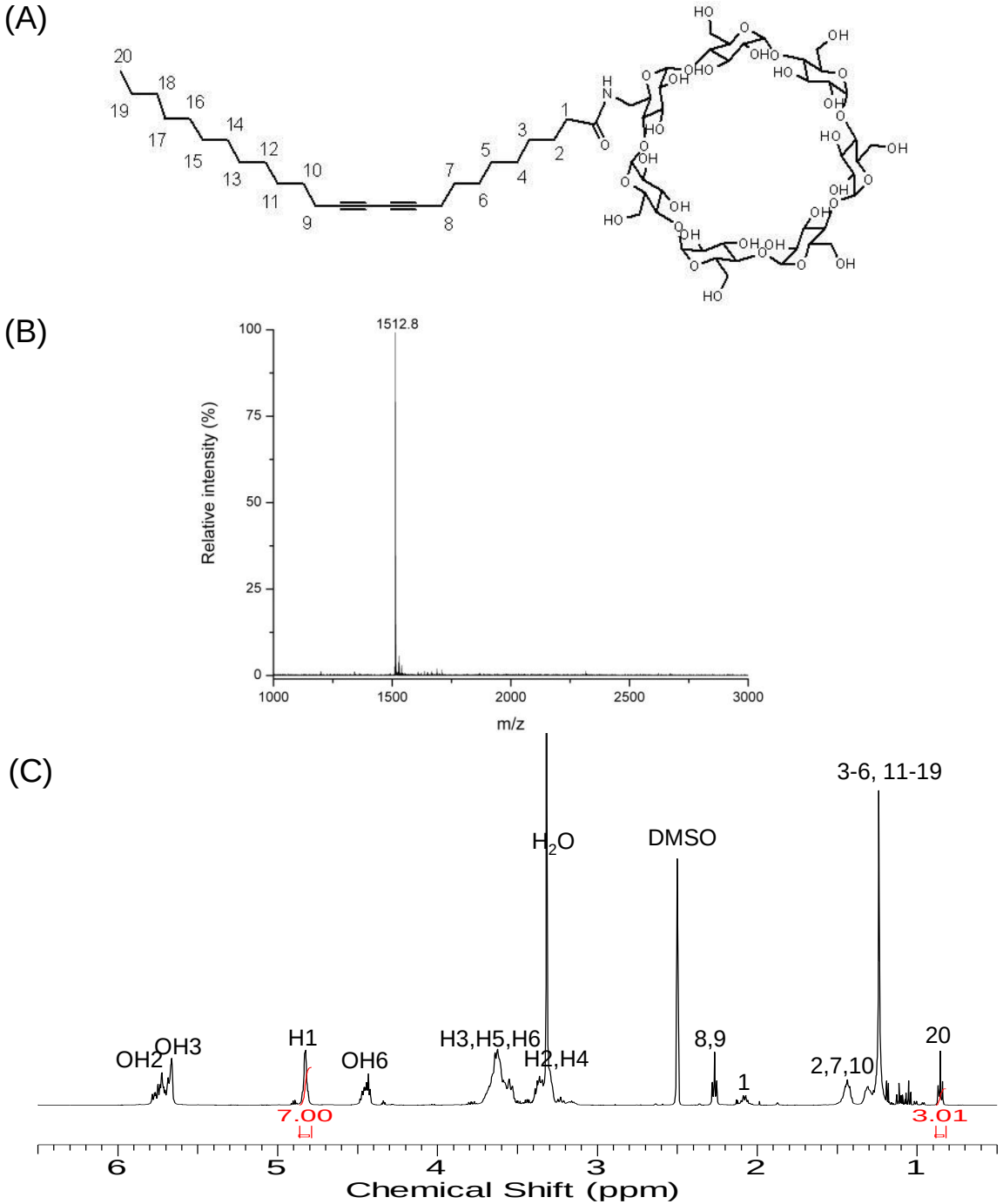


Figure 1


(A)
(B)
1512.8
Relative intensity (%)
m/z
(C)
H2O
DMSO
3-6, 11-19
OH2
OH3
H1
OH6
H3,H5,H6
H2,H4
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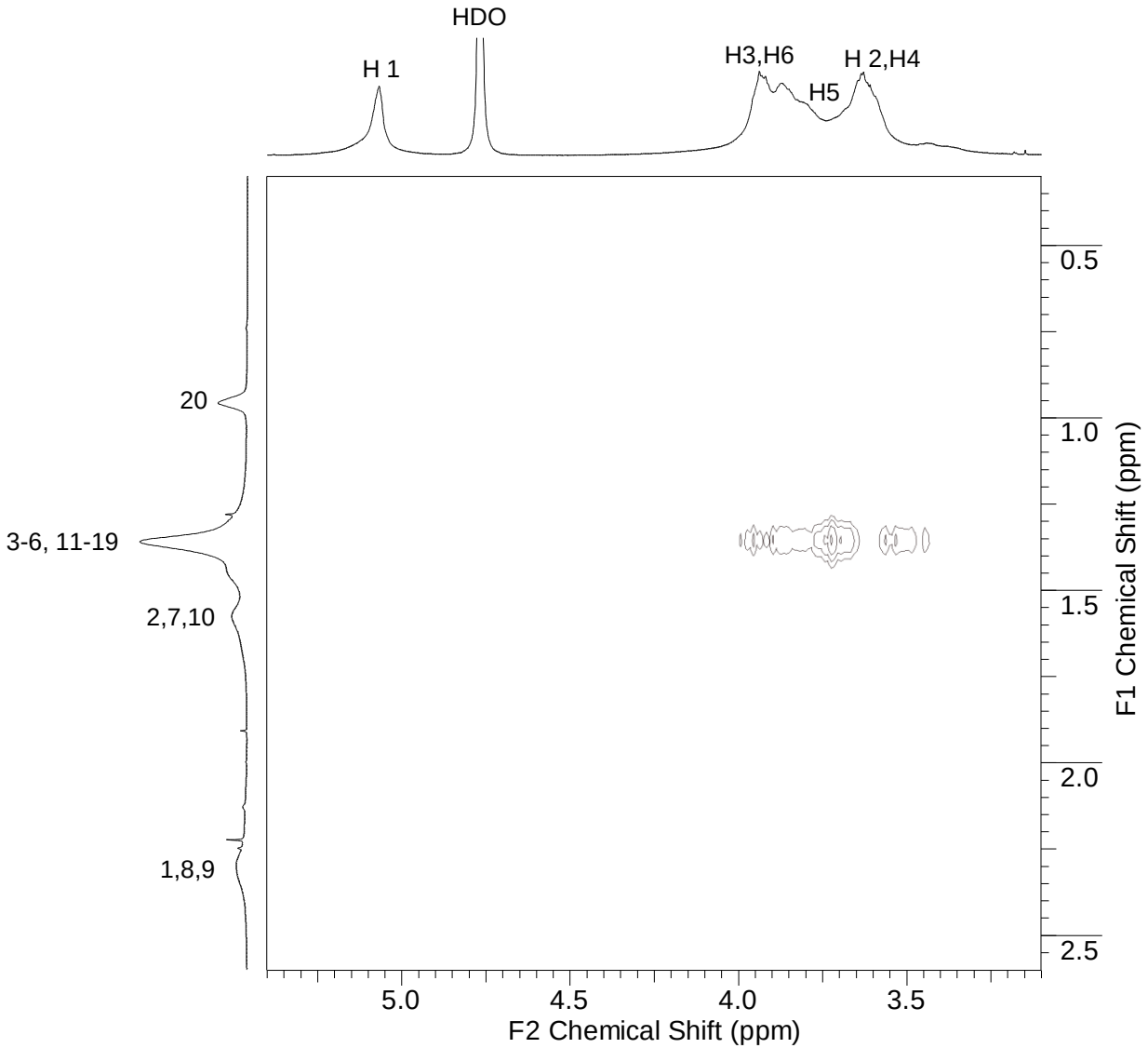
1
2,7,10
20
7.00
3.01
Chemical Shift (ppm)

Figure 2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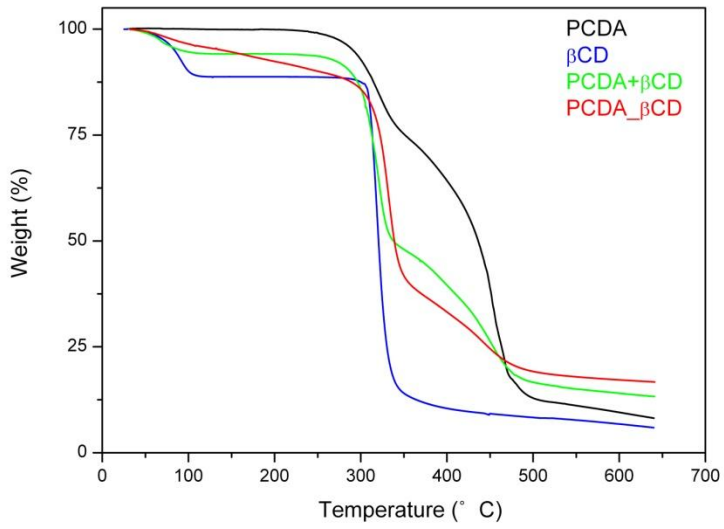
H3,H6
H5
H 2,H4
20
3-6, 11-19
2,7,10
1,8,9
0.5
1.0
1.5
2.0
2.5
F1 Chemical Shift (ppm)
5.0
4.5
4.0
3.5
F2 Chemical Shift (ppm)

Figure 3

(A)


PCDA
βCD
PCDA+βCD
PCDA_βCD
Weight (%)
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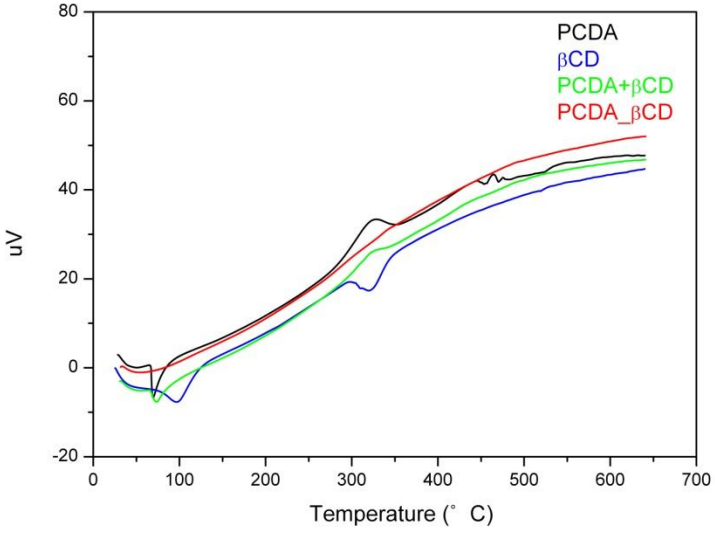
0
100
200
300
400
500
600
700

(B)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βCD
PCDA+βCD
PCDA_βCD
uV
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20
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-20
0
100
200
300
400
500
600
700

Figure 4

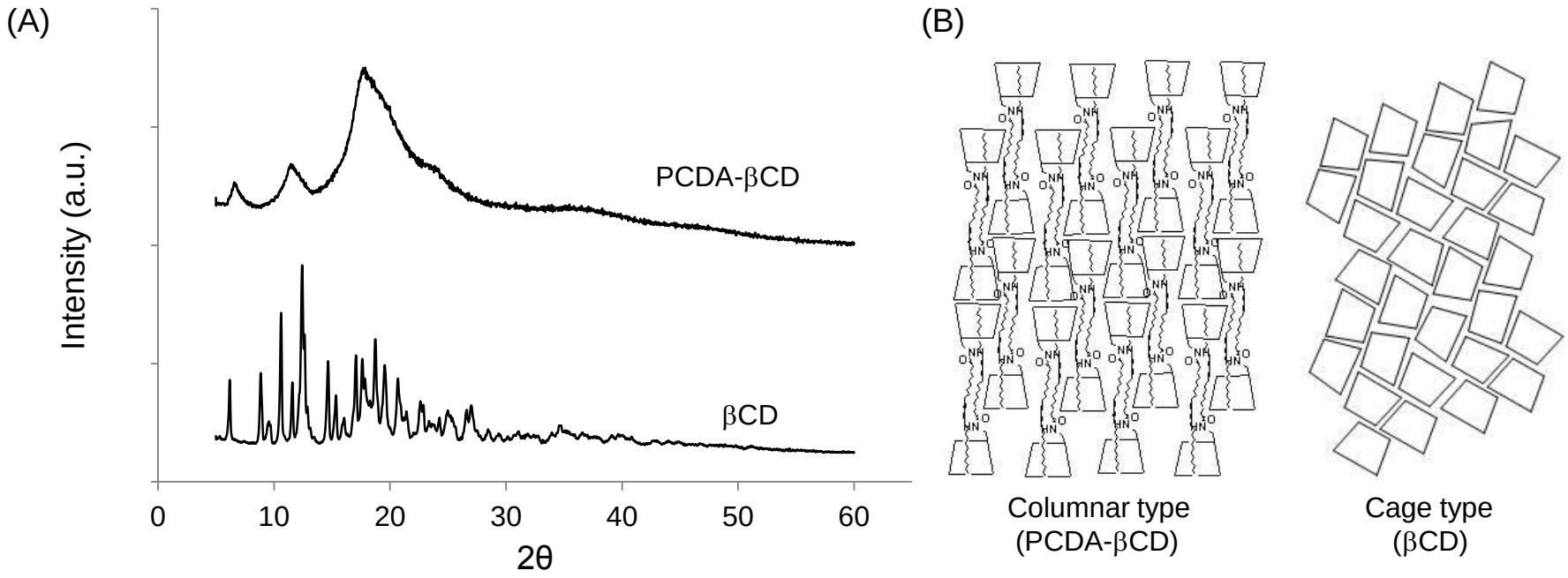

(A)
Intensity (a.u.)
PCDA-βCD
βCD
0
10
20
30
40
50
60
2θ
(B)
Columnar type
(PCDA-βCD)
Cage type
(βCD)

Figure 5

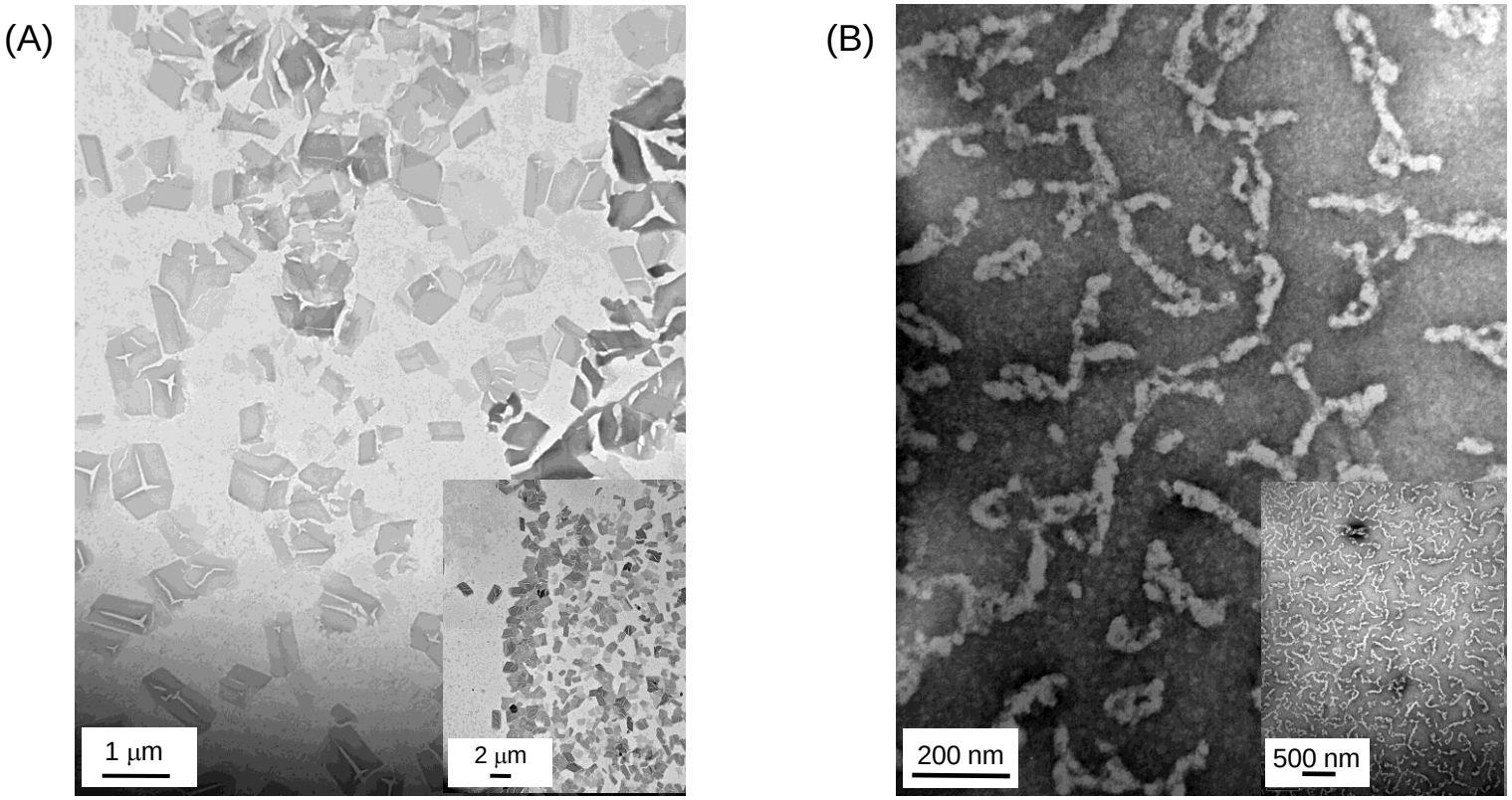
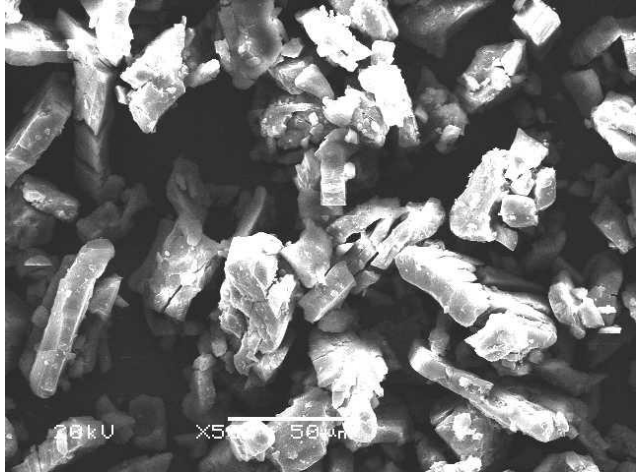
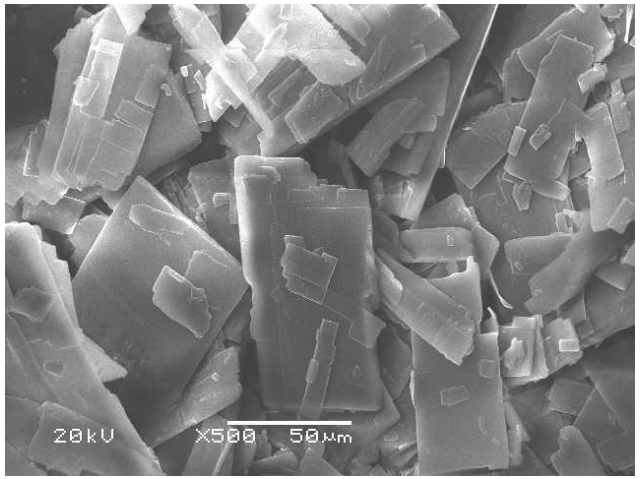


Figure 6

(A)



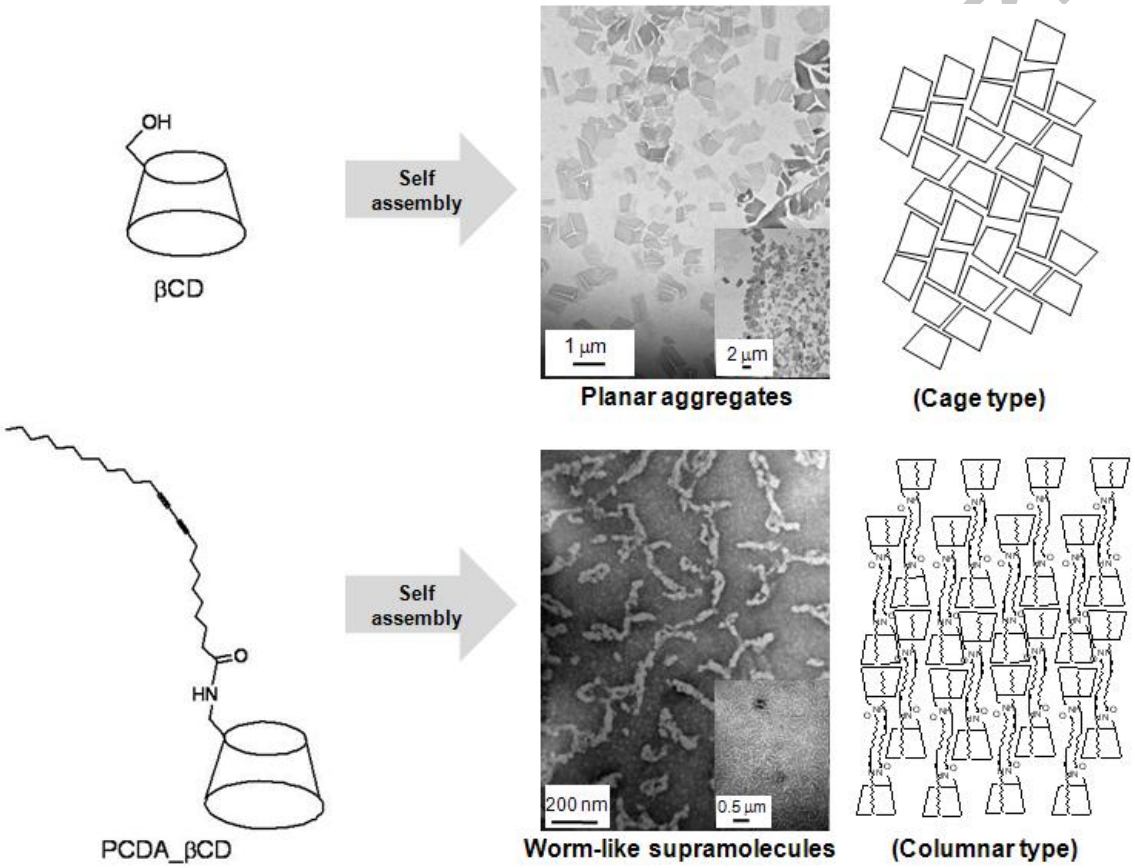
(B)



(C)

Supramolecular self-assembled aggregates formed by pentacosa-10,12-diynyl amidomethyl β-cyclodextrin

Eunae Cho, Hwanhee Kim, Jee Eun Yang, Bong-Hyun Jun, Seung R. Paik, and Seunho Jung*



Highlights.

- **A pentacosa-10,12-diynyl amidomethyl-β-cyclodextrin was newly synthesized.**
- **Self-assembled supramolecular aggregates were formed by the modified β-cyclodextrin.**
- **A novel supramolecular structure showed worm-like nano-aggregates of columnar-type.**