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Construction of Supramolecular Polymers with Alternating α-, β-Cyclodextrin Units Using Conformational Change Induced by Competitive Guests

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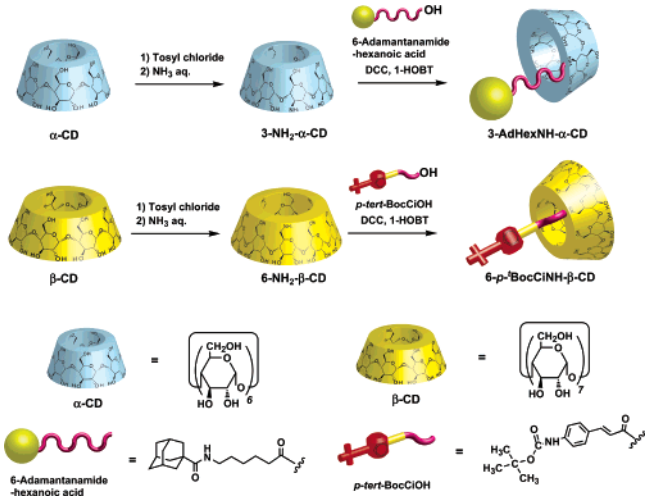
Supramolecular chemistry has been expanding to supramolecular polymer chemistry.[1] When a guest part is covalently attached to a cyclic host, it may form intramolecular complexes or intermolecular complexes to give supramolecular polymers.[2,3] In nature, proteins, polysaccharides, and nucleotides form sophisticated supramolecular systems. For example, hemoglobin is formed from two α-chains and two β-chains to give a tetramer. Allosteric interactions are one of the most important effects on the control of biological structures and functions. The binding of a small molecule to the binding site of a host molecule leads to conformational changes, which cause large effects on the binding of another molecule to give new functions. Now, we have succeeded in preparing supramolecular polymers having an alternating structure using conformational change induced by competitive guests, in which an α-cyclodextrin (α-CD) derivative and a β-CD derivative were bound to form a heterodimer that gave a supramolecular polymer.

Host−guest conjugates are prepared according to the route shown in Scheme 1.[4,5]

α-CD with the adamantane group (3-AdHexNH-α-CD) was chosen as one component because the adamantane group is strongly bound to a β-CD cavity, although α-CD does not bind the adamantane group in the cavity. β-CD with the *t*Boc-cinnamoyl group (6-*p*-*t*BocCiNH-β-CD) was chosen as another component, because the *t*BocCi group can be included in an α-CD cavity. However, interestingly, 6-*p*-*t*BocCiNH-β-CD formed only intramolecular complexes, and no intermolecular complexes are formed with other CDs. Figure 1 shows the ^{1}H NMR spectra of 3-AdHexNH-α-CD of various concentrations (a), those of 6-*p*-*t*BocCiNH-β-CD (b), and those of the 1:1 mixture (c). The ^{1}H NMR spectrum of 3-AdHexNH-α-CD is superimposable to those of adamantane-carboxylic acid and α-CD. The spectra did not change over the range of the concentrations tested. These results indicate that the adamantyl group is not included in the α-CD cavity. The ^{1}H NMR spectra of 6-*p*-*t*BocCiNH-β-CD did not change over the range of the concentrations tested, indicating that 6-*p*-*t*BocCiNH-β-CD did not form intermolecular complexes. However, the spectrum is very similar to that of the 1:1 mixture of β-CD and a model guest (*t*Boc-cinnamic acid), suggesting that they formed intramolecular complexes. The ROESY spectrum of 6-*p*-*t*BocCiNH-β-CD shows that there are correlation peaks between the aromatic protons and inner protons of β-CD, indicating that guest parts are included in its cavities.

Moreover, the circular dichroism (cd) spectrum of 6-*p*-*t*BocCiNH-β-CD in water shows simple minus Cotton effects in a phenyl absorption band (^{1}La band), indicating that the phenyl part is included in a CD cavity with a slantwise state.[6] However, when 3-AdHex-α-CD is mixed with 6-*p*-*t*BocCiNH-β-CD in water in a 1:1 ratio, they form intermolecular complexes proved by NMR spectroscopy. Figure 1c shows the ^{1}H NMR spectra of the 1:1 mixture of 3-AdHexNH-α-CD and 6-*p*-*t*BocCiNH-β-CD in a D_2O solution at various concentrations. The peaks of the adamantane group shifted 0.1 ppm, as the concentrations increased, indicating that the Ad group was included in a β-CD cavity. Moreover, the peaks of the cinnamoyl group shifted 0.2 ppm, as the concentrations increased, indicating that the cinnamoyl group was included in an α-CD cavity. Since the Ad group has specific interactions with β-CD (association constant: $K_a = 10^5$ M^{-1}), the Ad group kicked out the *t*Boc phenyl group of β-CD derivative from the CD cavity. Accordingly, the phenyl ring was exposed to water. Then the phenyl group was included in an α-CD cavity of 3-AdHexNH-α-CD, because the phenyl ring can be easily included in an α-CD cavity. As a result, 3-AdHexNH-α-CD and 6-*p*-*t*BocCiNH-β-CD formed supramolecular polymers with an alternating order, αβ−αβ−αβ.

Scheme 1. Synthesis of α-CD and β-CD Derivatives



The mechanism has been confirmed as follows: when 1-adamantane carboxylic acid (1-AdCA) was added to D_2O solutions of 6-*p*-*t*BocCiNH-β-CD (5.0 mM), the ^{1}H NMR spectrum of the cinnamoyl part of 6-*p*-*t*BocCiNH-β-CD was well-resolved and identical to that of the free *p*-*t*Boc-cinnamoyl part in the absence of CD, indicating that the cinnamoyl group was exposed to water. When an excess amount of α-CD was added into this solution, the ^{1}H NMR spectra of the cinnamoyl group showed peak shifts and broadening, indicating that the cinnamoyl group was included in α-CD. When an excess amount of α-CD was added to a D_2O solution of 6-*p*-*t*BocCiNH-β-CD in the absence of 1-AdCA, there were no changes in the ^{1}H NMR spectrum and the cd spectrum, indicating that the *p*-*t*Boc-cinnamoyl group was still in its own β-CD. When the *p*-*t*Boc-cinnamoyl group was added into the D_2O solution of 3-AdHexNH-α-CD, the ^{1}H NMR spectrum of the cinnamoyl group showed peak shifts and broadening, indicating that cinnamoyl group was included in an α-CD cavity. Accordingly, 3-AdHexNH-α-CD and 6-*p*-*t*BocCiNH-β-CD formed a heterodimer,

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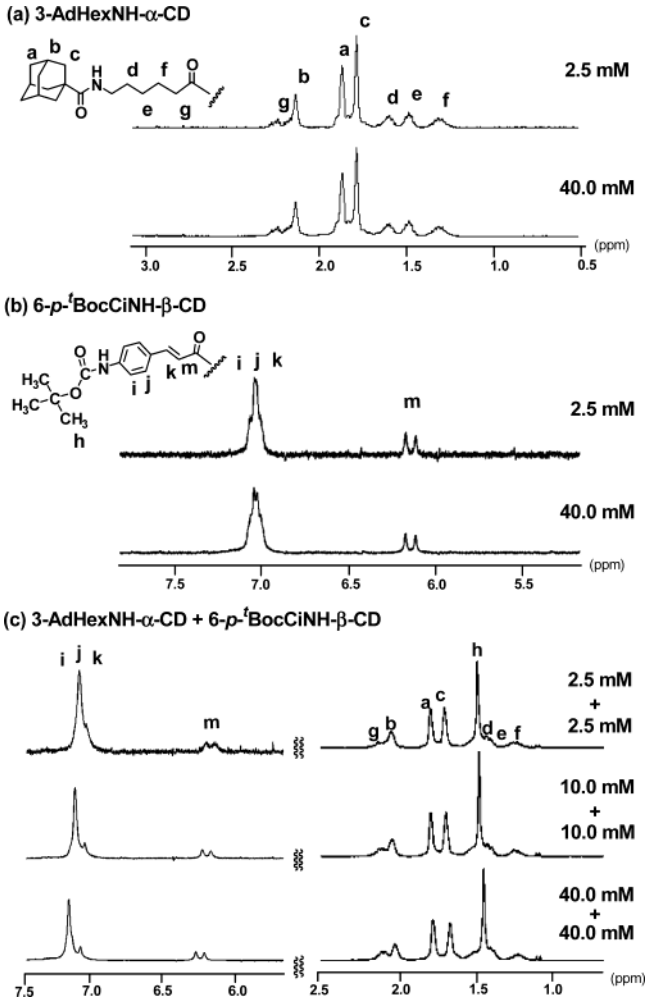

Figure 1. ^{1}H NMR spectra (270 MHz) of 3-AdHexNH-α-CD (a), 6-*p*-BocCiNH-*β*-CD (b), and 3-AdHexNH-α-CD + 6-*p*-BocCiNH-*β*-CD in a 1:1 ratio at various concentrations in D_2O.

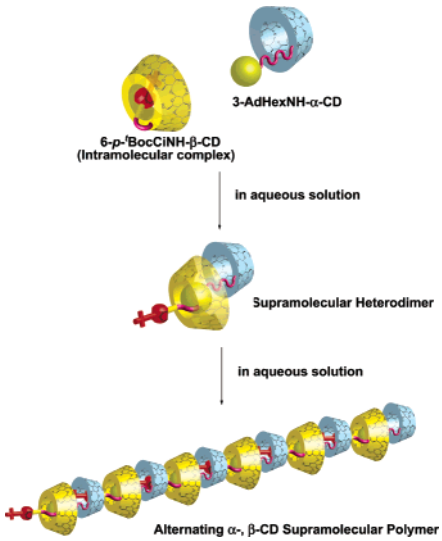

Figure 2. Proposed structures of supramolecular structures of the 3-AdHexNH-α-CD and 6-*p*-^{t}BocCiNH-*β*-CD.

which lines up end-to-end in longitudinal rows to form supramolecular polymers in alternating manner. The molecular weight of the complexes estimated by vapor pressure osmometry measurements increased with an increase in the concentrations and reached about 10 000 at 10 mM. The pulsed field gradient NMR measurements confirm the formation of supramolecular polymers. Figure 2 shows a schematic representation of a possible supramolecular structure formed by 3-AdHexNH-α-CD and 6-*p*-^{t}BocCiNH-*β*-CD in aqueous solutions.

These results remind us of the formation of supramolecular polymers in biological systems, such as microtubules. Microtubules are formed from heterodimers of α-tubulin and *β*-tubulin to give supramolecular polymers with alternating structures. These structures are very unique, and to the best of our knowledge, this is the first observation for the formation of cyclodextrin-based supramolecular polymers with alternating structures.[7]

The detailed mechanism of the formation of supramolecular polymers is now under investigation.

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Supporting Information Available: ^{1}H NMR, 2D NMR spectra, and cd spectra of 3-AdHexNH-α-CD with 6-*p*-^{t}BocCiNH-*β*-CD. This material is available free of charge via the Internet at http://pubs.acs.org.

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(4) Synthesis and characterization of 3-AdHexNH-α-CD. To a solution of 3-NH_2-α-CD (1.0 g, 1.0×10^{-3} mol) in 30 mL of DMF was added 1-adamantanamide hexanoic acid (586 mg, 2.0×10^{-3} mol). After the solution was cooled below 0 °C, *N*,*N*′-dicyclohexyl-carbodiimide (268 mg, 1.3×10^{-3} mol) and 1-hydroxybenzotriazole (175 mg, 1.3×10^{-3} mol) were added. The resulting mixture was stirred at room temperature for 5 days. After the removal of insoluble materials by filtration, we poured the filtrate into acetone (1 L) and then collected and washed the precipitate with acetone. The crude product was purified by preparative size exclusion chromatography. Yield, 46%. Positive ion MALDI-TOF mass *m*/*z* 1287.3 (M + Na^+). ^{1}H NMR (DMSO-d_6, 270 MHz): *δ* 9.47 (s, 1H, −NH−COO-), 8.07 (d, 1H, −NHCO−), 7.52−7.46 (q, 2H− and 3H− of phenyl), *δ* 7.31 (d, 1H, ═CH−CO), *δ* 6.41 (d, 1H, ═CH−CO), 5.90−5.18 (m, 11H, O(2)H and O(3)H of α-CD), 4.89−4.64 (m, 6H, C(1)H of α-CD), 4.52−4.49 (m, 7H, O(6)H of α-CD), 3.93−3.29 (m, C(2)H−C(5)H of α-CD overlaps with HOD, *δ* 7.52(t, 1H, −NH−), *δ* 3.00 (q, 2H, *ϵ*-H), 2.16 (t, 2H, α-H), 1.93 (s, 3H, adamantane), 1.72 (s, 6H, adamantane), 1.64 (s, 6H, adamantane), 1.47 (s, 12H, *δ*-H), 1.47 (s, 2H, *β*-H), 1.36 (s, 2H, *β*-H), 1.20 (s, 2H, *γ*-H). IR (KBr, cm^{-1}): 1660 (vs, $^{\nu}$C═O). Anal. calcd for $C_{53}H_{87}N_2O_{32}\cdot 6H_2O$: C, 46.39; H, 7.27; N, 2.04. Found: C, 46.62; H, 7.08; N, 2.10.

(5) Synthesis of 6-*p*-^{t}BocCiNH-α-CD is essentially the same way with 3-AdHexNH-α-CD. Yield, 49%. Positive ion MALDI-TOF mass *m*/*z* 1240.25 (M + Na^+). ^{1}H NMR (DMSO-d_6, 400 MHz): *δ* 9.47 (s, 1H, −NH−COO−), 8.07 (d, 1H, −NHCO−), 7.52−7.46 (q, 2H− and 3H− of phenyl), *δ* 7.31 (d, 1H, ═CH−CO), *δ* 6.41 (d, 1H, ═CH−CO), 5.90−5.18 (m, 11H, O(2)H, and O(3)H of α-CD), 4.89−4.64 (m, 6H, C(1)H of α-CD), 4.52−4.49 (m, 7H, O(6)H of α-CD), 3.93−3.29 (m, C(2)H−C(5)H of α-CD overlaps with HOD. IR (KBr, cm^{-1}): 1660 (vs, $^{\nu}$C═O). Anal. calcd for $C_{56}H_{86}N_2O_{37}\cdot 7H_2O$: C, 44.68; H, 6.70; N, 1.86. Found: C, 44.36; H, 6.67; N, 2.12.

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