Journal of Inclusion Phenomena and Macrocyclic Chemistry **50**: 57–62, 2004.

Original Article

Formation of Supramolecular Polymers Constructed by Cyclodextrins with Cinnamamide

MASAHIKO MIYAUCHI, YOSHINORI KAWAGUCHI and AKIRA HARADA*
Department of Macromolecular Science, Graduate School of Science, Osaka University, Toyonaka, Osaka, 560-0043, Japan

(Received: 19 September 2003; in final form: 7 October 2003)

Key words: cyclodextrin, host–guest interaction, inclusion complex, supramolecular polymer, vapor pressure osmometry, 2D NMR

Abstract

α-Cyclodextrin having cinnamamide at 6- or 3-positions (6-CiNH-α-CD, 3-CiNH-α-CD) and β-cyclodextrin with cinnamamide on 6-position (6-CiNH-β-CD) have been prepared. Supramolecular structures were formed in the solid state or aqueous solutions and characterized by measurements of NMR and vapor pressure osmometry (VPO). The results indicate that 6-CiNH-β-CD formed insoluble supramolecular polymers in the solid state, while 6-CiNH-α-CD and 3-CiNH-α-CD formed supramolecular complexes in aqueous solutions. 6-CiNH-α-CD was found to form a dimer in an aqueous solution. 3-CiNH-α-CD formed intermolecular complexes to give supramolecular polymers. The differences of the position of guest part on cyclodextrins caused to give a variety of supramolecular structures in aqueous solutions.

Introduction

Recently, much attention has been focused on design and synthesis of interlocked molecules, such as rotaxanes and catenanes, because of their unique structures and properties [1]. Host–guest interactions are used for efficient preparation of such interlocked molecules. When a guest group is covalently attached to a cyclic host, the molecule may form an intramolecular complex [2] or intermolecular complexes [3] to give supramolecular polymers (Chart 1). Cyclodextrins (CDs) are known to have the ability and selectivity to form inclusion complexes with guest molecules. Therefore, we chose cyclodextrin as a cyclic host and a phenyl group as a guest moiety, because a phenyl group is suitable for fitting in a cyclodextrin cavity. However, benzoyl CD did not form supramolecular polymers [4]. This result suggests that some spacer groups are required for efficient formation of intermolecular complexes.

In previous works, we found that α-cyclodextrin derivative which has a cinnamoyl group as a guest moiety on the 6-position of cyclodextrin formed intermolecular complexes to give rise to oligomeric supramolecular structure in aqueous solutions [5]. Now, to control the supramolecular structure constructed by modified CDs, we prepared α-CD derivatives which have a cinnamamide group as a guest part on the 6-position or 3-position of cyclodextrin respectively. β-cyclodextrin modified cinnamamide on 6-position (6-CiNH-β-CD) are also synthesized. These supramolecular structures and sizes formed via intermolecular complexes were studied by various spectroscopic methods and VPO measurements in aqueous solution and in the solid state.

* Author for correspondence. E-mail: harada@chem.sci.osakau.ac.jp

Experimental section

Materials

α-CD was obtained from Wako Pure Chemical Industries. *trans*-Cinnamoyl chloride and *trans*-cinnamic acid were obtained from Nacalai Tesque Inc. DIAION HP-20® were obtained Mitsubishi Chemical corporation DMSO-d_6 and D_2O used as solvents in the NMR measurements were obtained from Aldrich.

Measurements

^{1}H-NMR spectra were recorded at 270 MHz on a JEOL JNM EX-270 NMR spectrometer. Chemical shifts were referenced to the solvent values (δ 2.50 ppm for DMSO-d_6 and δ 4.70 ppm for HOD) or the internal standard (δ 2.06 ppm for CH_3CN in D_2O). ^{13}C NMR spectra were recorded at 67.8 MHz on a JEOL JNM EX-270 NMR spectrometer. Chemical shifts were referenced to the solvent values (δ 39.50 ppm for DMSO-d_6). 2D ROESY

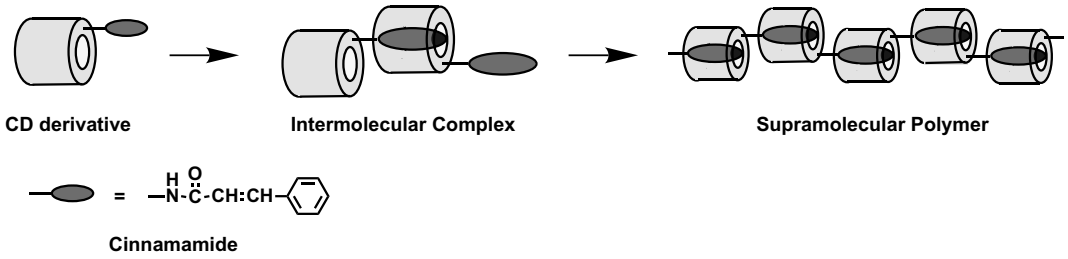


Chart 1. Schematic representation of supramolecular polymer constructed by CD derivatives.

NMR experiments and Pulsed gradient spin echo NMR were recorded at 600 MHz in D_2O on a VARIAN JNM UNITY-600 NMR spectrometer at 30 °C. Diffusion coefficients were measured using the BPPSTE pulse sequence. The experimentally observed diffusion coefficients were calculated from plots of ln *I versus* g^2 (the *I* and *g* are the integrated intensity of a part region of the correspond spectrum and pulsed gradients' strength respectively) and then determined from the slope of the line of this curve. FT-IR spectra were measured at JASCO FT/IR-410 spectrometer. Absorption spectra were recorded on a SIMADZU UV-2500PC spectrometer at room temperature. Positive-ion matrix assisted laser desorption ionization time of flight (MALDI-TOF) mass spectrometry experiments were performed using a Shimadzu/KRATOS mass spectrometer. Vapor pressure osmometry (VPO) measurements were used KNAUER no. A0280 vapor osmometer at 40 °C.

Synthesis

N-Methyl cinnamamide (CiNHMe)
trans-Cinnamoyl chloride (5.50 g, 3.3×10^{-2} mol) was dissolved in CH_3NH_2 dissolved 2.0 M THF solution (45 mL, 9.0×10^{-2} mol). The reaction was carried out with stirring at rt for 6 h. The precipitates were filtered off, and then the filtrate was evaporated. The resulting residue was dried under vacuum to give 5.18 g of the crude product. The crude product was recrystallized from water. Yield, 4.92 g (89.6%). ^{1}H-NMR (DMSO-d_6, 270 MHz): δ 8.05–7.95 (s, 1H, —NH—), δ 7.51–7.47 (m, 1H, 2H of phenyl), 7.37 (d, 1H, Ph=CH—), 7.45–7.37 (m, 3H, 3H- and 4H- of phenyl), 6.56 (d, 1H, =CH—CO), 2.50 (s, 1H, CH_3—).

Mono-6-deoxy-6-amino-β-CD (6-NH_2-β-CD), Mono-6-deoxy-6-amino-α-CD (6-NH_2-α-CD) and Mono-3-deoxy-3-amino-α-CD (3-NH_2-α-CD)
These were prepared according to a way reported previously [6].

Mono-6-deoxy-6-cinnamamide-β-CD (6-CiNH-β-CD)
To a solution of 6-NH_2-β-CD (501.1 mg, 4.41×10^{-4} mol) in 50 mL DMF was added *trans*-cinnamic acid (327.3 mg, 2.21×10^{-3} mol). After the solution was cooled below 0 °C, *N*,*N*′-dicyclohexylcarbodiimide (96.8 mg, 7.22×10^{-4} mol) and 1-hydroxybenzotriazole (150.0 mg, 7.22×10^{-3} mol) were added. The resulting mixture was stirred at rt for 5 days. After insoluble materials were removed by filtration, the filtrate was poured into acetone (1 L), and the precipitate was collected and washed with acetone, then the crude product was purified by column chromatography on DIAION HP-20 column (eluted with water/methanol = 100/0 to 50/50). The 60/40 (water/methanol) eluent was concentrated, and recrystallized from hot water to give 6-CiNH-β-CD. Yield, 262.0 mg (46%). Mp: 220 °C (dec); positive ion MALDI-TOF mass *m*/*z* 1287 ($M + Na^+$); ^{1}H-NMR (DMSO-d_6, 270 MHz): δ 7.88 (s, 1H, —NH—), 7.55 (d, 1H, Ph=CH—), 7.35–7.43 (m, 4H, PH=CH—, 3H- and 4H- of phenyl), δ 6.69 (d, 1H, =CH—CO), 5.79–5.65 (m, 14H, O(2)H and O(3)H of β-CD), 4.91–4.83 (m, 7H, C(1)H of β-CD), 4.52–4.20 (m, 8H, O(6)H and C(6′)H of β-CD), 3.93–3.29 (m, overlaps with HOD); ^{13}C-NMR (DMSO-d_6, 67.8 MHz) 164.91 (C=O), 138.53 (Ph—CH=), 134.8, 129.15, 128.04, 127.31 (C of phenyl), 121.97 (Ph—*C*H=*C*H—),101.71 (C(1) of β-CD), 81.17 (C(4) of β-CD), 72.4, 72.04, 71.89, 69.51 (C(2), C(3), C(4) and C(5) of β-CD), 59.84, 59.57 (C(6), C(6′) of β-CD). IR (KBr, cm^{-1}): 1660 (vs, $^{\nu}$C=O). Anal. Calcd for $C_{51}H_{77}NO_{35}{\cdot}7H_2O$: C, 44.06; H, 6.60; N, 1.01. Found: C, 44.35; H, 6.63; N, 1.10.

Mono-6-deoxy-6-cinnamamide-α-CD (6-CiNH-α-CD)
6-CiNH-α-CD was synthesized on the same way essentially with 6-CiNH-β-CD. After the purification of DIAION column, followed by the chromatography on Sephadex G-25 column (ϕ 2 × 95 cm eluent: H_2O). Yield, 18%. Positive ion MALDI-TOF mass *m*/*z* 1125.0 ($M + Na^+$); ^{1}H-NMR (DMSO-d_6, 270 MHz): δ 7.94 (s, 1H, —NH—), 7.53 (d, 2H, 3H- of Ph-), 7.40–7.35 (m, 4H, Ph=CH—, 3H- and 4H- of phenyl), 6.69 (d, 1H, =CH—CO), 5.79–5.65 (m, 14H, O(2)H and O(3)H of β-CD), 4.91–4.83 (m, 7H, C(1)H of α-CD), 4.52–4.20 (m, 8H, O(6)H and C(6′)H of α-CD), 3.93–3.29 (m, overlaps with HOD); IR (KBr, cm^{-1}): 1660 (vs, $^{\nu}$C=O). Anal. Calcd for $C_{45}H_{68}NO_{30}{\cdot}1.9H_2O$: C, 47.53; H, 6.36; N, 1.23. Found: C, 47.52; H, 6.56; N, 1.34.

Mono-3-deoxy-3-cinnamamide-α-CD (3-CiNH-α-CD)
3-CiNH-α-CD was synthesized on the same way essentially with 6-CiNH-β-CD. Yield, 27%. Positive ion MALDI-TOF mass *m*/*z* 1125.0 ($M + Na^+$); ^{1}H-NMR

(DMSO-d_6, 270 MHz): δ 8.16 (s, 1H, —NH—), 7.62 (d, 2H, 3H- of Ph-), 7.43–7.37 (m, 4H, Ph=C*H*—, 3H- and 4H- of phenyl), 6.54 (d, 1H, =CH—CO), 5.97-5.17 (m, 14H, O(2)H and O(3)H of β-CD), 4.91–4.78 (m, 7H, C(1)H of α-CD), 4.66–4.44 (m, 8H, O(6)H and C(6′)H of α-CD), 4.21–3.33 (m, overlaps with HOD); IR (KBr, cm^{-1}): 1660 (vs, $^{\nu}$C=O). Anal. Calcd for $C_{45}H_{68}NO_{30}\cdot 1.9H_2O$: C, 47.53; H, 6.36; N, 1.23. Found: C, 47.52; H, 6.56; N, 1.34.

Results and discussion

α-, β-CD derivatives have been prepared by the reactions of 6- or 3-NH_2- α, β-CD and cinnamic acid with dicyclohexylcarbodiimide (DCC) and 1-hydroxybenzotriazole (1-HOBT) (Scheme 1).

Supramolecular structure of 6-CiNH-β-CD in solid state

In the previous works, we found that β-CD having a cinnamate group at 6-position was insoluble in water [7], although most of other 6-substituted β-CDs are soluble. 6-CiNH-β-CD is sparingly soluble in water. To investigate the supramolecular structure of 6-CiNH-β-CD, the ^{13}C-NMR measurements were carried out in the solid state. Figure 1 shows that the ^{13}C resonances of C-1 and C-4 of β-CD shows multiplet lines because of the asymmetric glucopyranosyl conformations of β-CD in the crystal when it does not include a guest in the cavity. However, the resonances of C(1) and C(4) of 6-CiNH-β-CD are obtained as simple singlets, indicating that the β-CD ring includes cinnamoyl moiety and takes a symmetrical conformation.

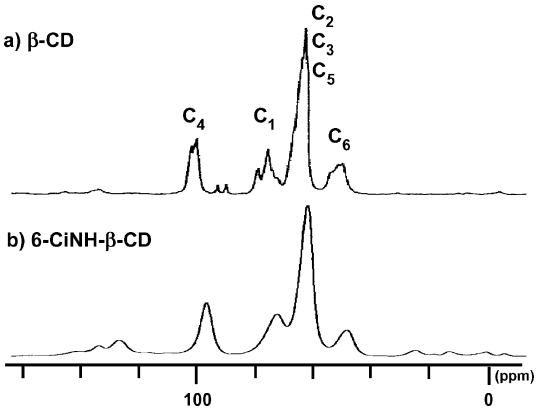
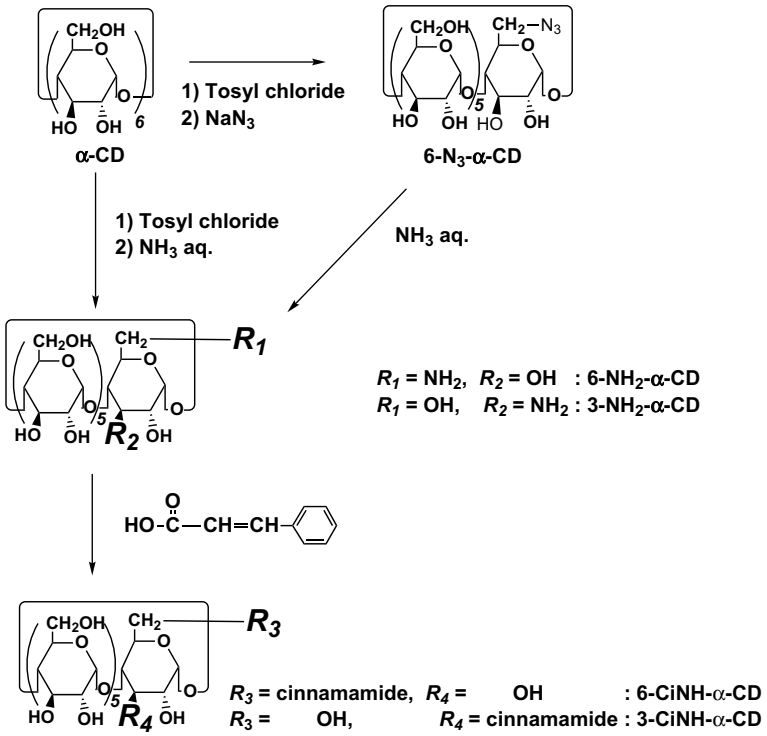


Figure 1. ^{13}C CP/MAS NMR spectra of β-CD (a) and 6-CiNH-β-CD (b).

The crystal structures of CD complexes are mainly classified into three types: cage, channel and layer type. The powder X-ray diffraction patterns of the complex between ethyl cinnamate and β-CD was reported to form guest/host = 2/2 stoichiometry in the layer of CD dimer by single crystal X-ray diffraction analysis [8]. The powder X-ray diffraction pattern of 6-CiNH-β-CD is very similar to those of the complexes between ethyl cinnamate and β-CD, indicating that 6-CiNH-β-CD forms layer structure of CD dimer rather than a cage or channel type. The β-CD cavities include cinnamamide



Scheme 1. Synthesis of 6-CiNH-α-CD and 3-CiNH-α-CD.

moieties of 6-CiNH-β-CD and their orientation shows layer structures in the solid state. On the addition of 1-adamantane carboxylic acid ($K_c = 300{,}000$ for β-CD) [9] to the heterogeneous D_2O suspension of 6-CiNH-β-CD, the solution became gradually clear. The ^{1}H-NMR spectra of the solution showed that the signal/noise ratio and its resolution of the spectrum of the filtrate D_2O solution shows better than that of the solution of supernatant of heterogeneous 6-CiNH-β-CD solution. These results indicate that added guest molecules were included in a CD cavity and a cinnamoyl group was exposed to water. From these experimental results, a proposed structure of 6-CiNH-β-CD is described in Figure 2.

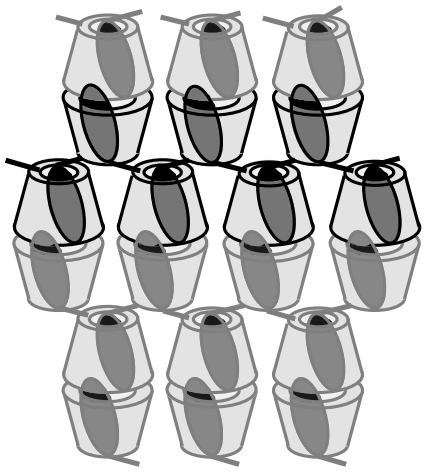


Figure 2. Schematic representation of 6-CiNH-β-CD in solid state.

Supramolecular structures of 6-CiNH-α-CD and 3-CiNH-α-CD in aqueous solutions

6-CiNH-α-CD and 3-CiNH-α-CD are soluble in water. We investigated the supramolecular structures of both modified CDs in aqueous solutions. When the guest moieties of CD are included in another CD cavities to form intermolecular complexes in D_2O, the ^{1}H-NMR spectra show peak shifts with increase of the concentrations. Figure 3 shows the ^{1}H-NMR spectra of 6-CiNH-α-CD and 3-CiNH-α-CD at various concentrations in D_2O. These spectra of both modified CDs change with their concentrations, although those in DMSO-d_6 are independent of its concentration. These results indicate that both modified CDs form the intermolecular complexes in D_2O solution.

Figure 4 shows the ROESY NMR spectra of 6-CiNH-α-CD and 3-CiNH-α-CD in D_2O solutions, respectively. The NOEs between phenyl signals of

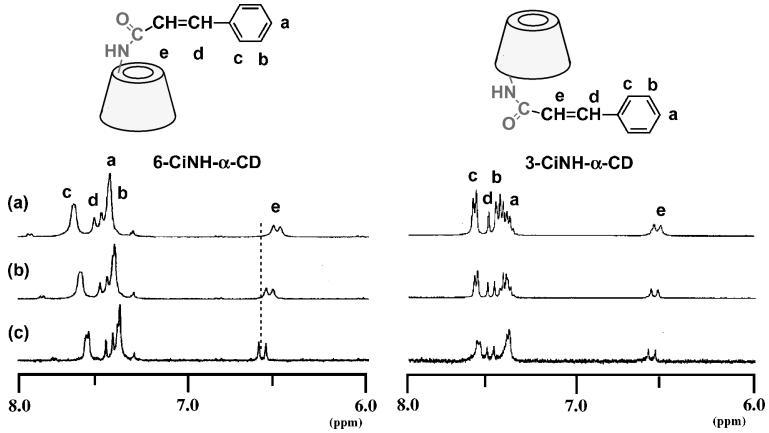


Figure 3. 400 MHz ^{1}H-NMR spectra of 6-CiNH-α-CD and 3-CiNH-α-CD in D_2O solution at 30 °C. Each concentrations are 1 mM (a), 20 mM (b) and 40 mM (c).

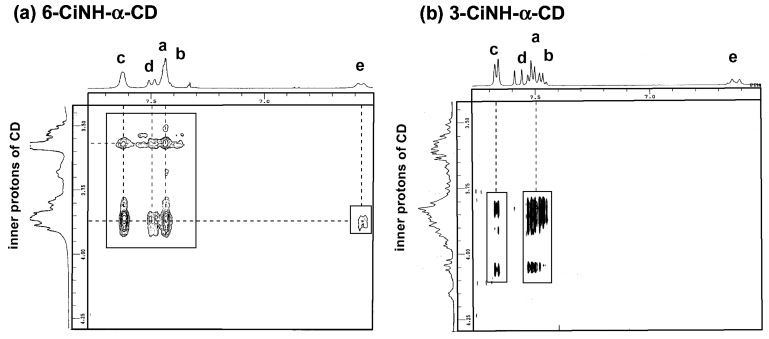


Figure 4. 2D ROESY NMR spectra of 6-CiNH-α-CD (a) and 3-CiNH-α-CD (b) in D_2O solution at 30 °C.

cinnamamide and inner protons of CD ring are observed. These data show the formation of inclusion complex in D_2O. Moreover, in 6-CiNH-α-CD, the NOEs between double bond and CD ring are also obsorbed. These results indicate the cinnamoyl moieties of 6-CiNH-α-CD are deeply into CD cavity than that of 3-CiNH-α-CD comparatively. The inclusion modes of both complexes seem to be different in D_2O solution.

6-CiNH-α-CD and 3-CiNH-α-CD form intermolecular complexes in aqueous solution. When 3 M excess of *p*-iodoaniline is added as a competitive guest to the D_2O solution of both modified CDs, the chemical shifts of the cinnamamide moiety went back to the direction. These results indicate that guest molecules added were competitively included in the CD cavity and a cinnamamide group is exposed to water.

Size estimations of intermolecular inclusion complexes in aqueous solution

Pulsed gradient spin echo NMR (PGSE NMR) technique is often used to probe the sizes of inclusion complex [10]. The comparison of the diffusion coefficients obtained by PGSE NMR is allowed to assume the relative complex sizes formed in the solvent. Previously, Auram and Cohen [11] reported the diffusion coefficient of α-CD to be $3.0 \pm 0.01 \times 10^{-6}$ cm^2 s^{-1}. In the case of modified CDs which enabled to form intermolecular complexes, the diffusion coefficient should be gradually decreased with increase in the concentration because of increasing the intermolecular complex sizes. When the concentration of 3-CiNH-α-CD was increased from 1.0 to 40 mM, the diffusion coefficients were decreased to $2.12 \pm 0.01 \times 10^{-6}$ cm^2 s^{-1}, although in 6-CiNH-α-CD it was $2.67 \pm 0.01 \times 10^{-6}$ cm^2 s^{-1}. These data indicate that the sizes of intermolecular complexes constructed by 3-CiNH-α-CD are apparently much larger than that of 6-CiNH-α-CD in D_2O solution.

VPO measurements are also useful to estimate the size of intermolecular complex in aqueous solution. Figure 5 shows the results of VPO measurements of α-CD and their derivatives at 40 °C in H_2O. Although α-CD showed no concentration dependency of the molecular weight, 3-CiNH-α-CD and 6-CiNH-α-CD showed concentration dependence. The molecular weight of 3-CiNH-α-CD increased with increase in the concentrations and reached saturation at about 16,000 (ca 12 mer). In contrast, the molecular weight of 6-CiNH-α-CD gave at about 2000. These results indicate that 6-CiNH-α-CD formed a dimer in aqueous solution via intermolecular inclusion complex, while 3-CiNH-α-CD formed supramolecular polymer under the conditions of high concentration.

Molecular models show that *N*-methyl cinnamamide might enter the α-CD cavity from the both primary and secondary hydroxyl group sides. However, in the case of modified CDs, the cinnamamide moiety might enter from the primary-hydroxyl group side of α-CD to form

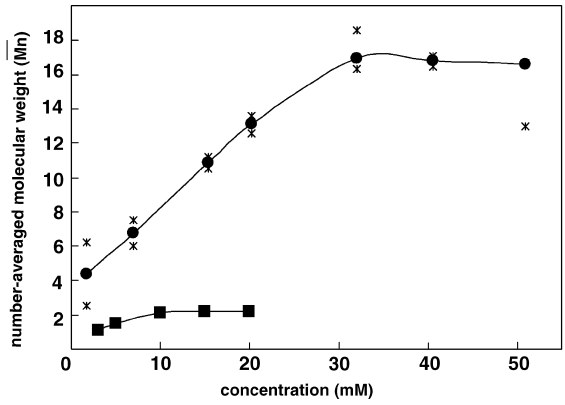


Figure 5. Effects of the concentrations on the molecular weight of 6-CiNH-α-CD (■) and 3-CiNH-α-CD (●) observed by VPO in water at 40 °C.

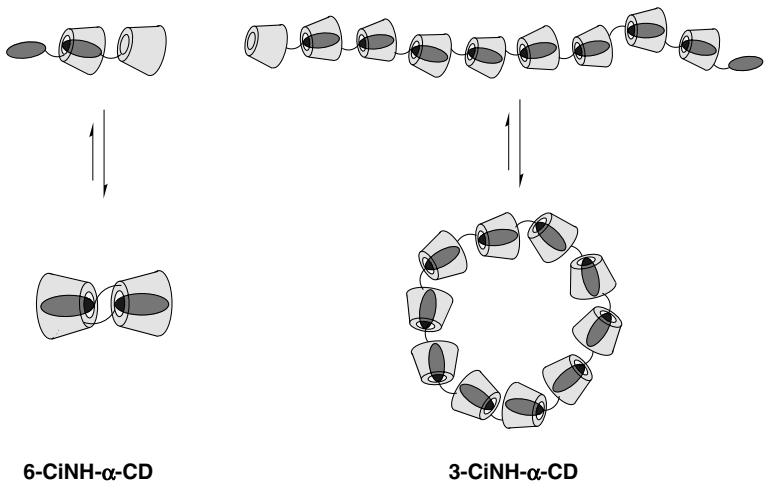


Figure 6. Schematic representation of intermolecular inclusion complexes constructed by 6-CiNH-α-CD (a) and of supramolecular polymers constructed by 3-CiNH-α-CD (b) in aqueous solution.

intermolecular complexes. Accordingly, in 6-CiNH-α-CD, the guest moieties enter into the other CD cavities mutually to form dimerized complexes. On the other hand, 3-CiNH-α-CD is thought to form supramolecular polymers with head-to-tail fashion. Moreover, owing to observe the saturation in VPO measurements, 3-CiNH-α-CD might form cyclic supramolecular polymers rather than linear structure. Figure 6 is showed the proposed supramolecular structures constructed by each modified CDs in the concentrated aqueous solutions.

Conclusions

In conclusion, 6-CiNH-β-CD forms supramolecular complexes in solid state. 6-CiNH-α-CD formed dimer, while 3-CiNH-α-CD gave supramolecular oligomers in aqueous solution. It was also suggested that the supramolecular structure of the latter possessed head-to-tail fashion. This is the first observation that the position of cinnamamide moiety modified on α-CD considerably affects the supramolecular structure *via* intermolecular complex in aqueous solution. Studies on detailed structures and dynamic aspects are now in progress. We believe that construction of these kinds of supramolecular polymers leads to extending widely the field of ecological chemistry for nature.

References

1. (a) J.-P. Sauvage and C. Dietrich-Buchecker: *Molecular Catenanes, Rotaxanes and Knots*, Wiley-VCH, Weinheim (1999); (b) A. Harada: *Adv. Polym. Sci.* **133**, 141 (1997); (c) A. Harada: *Acc. Chem. Res.* **34**, 456 (2001); (d) D.B. Amabilino and J.F. Stoddard: *Chem. Rev.* **95**, 2725 (1995); (e) V. Balzani, A. Credi, F.M. Raymo, and J.F. Stoddart, *Angew. Chem. Int. Ed.* **39**, 3348 (2000).
2. (a) K. Hamasaki, H. Ikeda, A. Nakamura, A. Ueno, F. Toda, I. Suzuki, and T. Osa: *J. Am. Chem. Soc.* **115**, 5035 (1993); (b) A. Ueno, S. Minato, I. Suzuki, M. Fukushima, M. Ohkubo, T. Osa, F. Hamada, and K. Murai: *Chem. Lett.* 605 (1990); (c) R. Corradini, A. Dossena, R. Marchelli, A. Panagia, G. Sartor, M. Saviano, A. Lombardi, and V. Pavone: *Chem. Eur. J.* **2**, 373 (1996); (d) R. Corradini, A. Dossena, G. Galaverna, R. Marchelli, A. Panagia, and G. Sartor: *J. Org. Chem.* **62**, 6283 (1997); (e) Y. Wang, T. Ikeda, H. Ikeda, A. Ueno, and F. Toda: *Bull. Chem. Soc. Jpn.* **67**, 1598 (1994).
3. (a) A. Zanotti-Gerosa, E. Sorali, L. Giannini, A. Chiesi-Villa, and C. Rizzoli: *Chem. Commun.* 119 (1996); (b) N. Yamaguchi, D.S. Nagvekar, and H.W. Gibson: *Angew. Chem., Int. Ed.* **37**, 2361 (1998); (c) J. Bulger, N.M. Sommerdik, A.J.W.G. Visser, A. van Hoek, R.J. M.Nolte, J.F.J. Engbersen, and D.N. Houldt: *J. Am. Chem. Soc.* **121**, 28 (1999).
4. L.H-. Tong, Z.-J. Hou, Y. Inoue, and A. Tai: *J. Am. Chem. Soc. Perkin Trans.* 2 1253 (1992).
5. T. Hoshino, M. Miyauchi, Y. Kawaguchi, H. Yamaguchi, and A. Harada: *J. Am. Chem. Soc* **112**, 9876 (2000).
6. (a) S.E. Brown, J.H. Coates, D.R. Coghlan, C.J. Easton, S.J. van Eyk, W. Janowski, A. Lepore, A.F. Lincolun, Y. Luo, B.L. May, D.S. Schiesser, P. Wang, and M.L. Williams: *Aust. J. Chem.* **46**, 953 (1993); (b) K. Takahashi, K. Hattori, and F. Toda: *Tetrahedron Lett.* **25**, 3331 (1984); (c) H. Ikeda, Y. Nagano, Y. Du, T. Ikeda, and F. Toda: *Tetrahedron Lett.* **31**, 5045 (1990).
7. A. Harada, Y. Kawaguchi, and T. Hoshino: *J. Incl. Phenom.* **41**, 115 (2001).
8. M.B. Hursthouse, C.Z. Smith, M. Thornton-Pett, and J.H.P. Utley: *J. Chem. Soc., Chem. Commun.* 881 (1982).
9. J.L. Atwood, J.E.D. Davies, D.D. MacNicol, and F. Vögtle: *Comprehensive Supramolecular Chemistry*, vol. 3, Pergamon, Oxford (1996).
10. (a) P. Stilbs. *Prog. NMR. Spectrosc.* **19**, 1–45 (1987); (b) E.O. Stejskal and J.E. Tanner. *J. Chem. Phys.* **42**, 288 (1965); (c) K.S. Cameron and L. Fielding. *J. Org. Chem.* **66**, 6891 (2001).
11. L. Avram and Y. Cohen. *J. Org. Chem.* **67**, 2639 (2002).