# A Helical Supramolecular Polymer Formed by Host–Guest Interactions

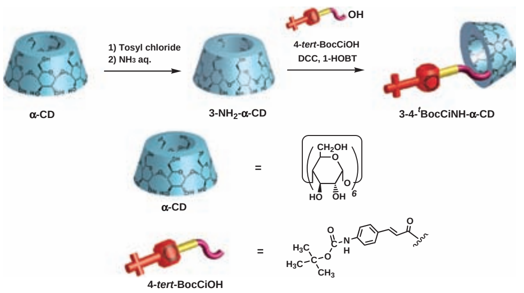
Masahiko Miyauchi and Akira Harada*
*Department of Macromolecular Science, Graduate School of Science, Osaka University,*
*1-1 Machikaneyama, Toyonaka, Osaka 560-0043*

(Received October 1, 2004; CL-041160)

3-[4-(*tert*-Boc-amino)cinnamoylamino]-α-cyclodextrin (3-4-$^t$BocCiNH-α-CD) has been found to form a supramolecular polymer in an aqueous solution. The supramolecular polymer was found to take a helical structure. This is the first example of the formation of a helical supramolecular polymer formed by host–guest interactions.

Supramolecular polymers are ubiquitous in nature, especially in biological systems. Microtubules, microfilaments, and flagella are helical supramolecular polymers formed by proteins. If such supramolecular polymers are formed by synthetic molecules, they might have unique properties and functions.[1] In order to design such supramolecular polymers, we have to incorporate a host part and a guest part in a single molecule.[2] Previously, we found and reported that 6-cinnamoyl-α-cyclodextrin (6-CiO-α-CD) formed supramolecular oligomers in aqueous solutions. When the supramolecular oligomers were stabilized by attaching a bulky substituent (a trinitrophenyl group), "a cyclic daisy chain" was obtained, in which a guest part was found to be included into a CD cavity of the other molecule from its primary hydroxy side.[3] In order to obtain linear supramolecular polymers, the formation of cyclic oligomers should be avoided. In order to avoid the formation of cyclic supramolecular structures, a guest part should be attached on a secondary hydroxyl side. 3-cinnamoylamino-α-CD (3-CiNH-α-CD) was found to form longer supramolecular polymers.[4] We also reported that 6-4-$^t$BocCiNH-β-CD formed intramolecular complexes in aqueous solution.[5] With an addition of α-CD having the adamantane group as a competitive guest to 6-4-$^t$BocCiNH-β-CD aqueous solution supramolecular polymers with alternating α-, β-CD units could be formed using conformational change. However, we could not observe that these supramolecular polymers are helical. Now, we found that 3-4-$^t$BocCiNH-α-CD formed helical supramolecular polymers in aqueous solutions. We report herein for the first time the formation of helical supramolecular polymers from a host–guest system.

3-4-$^t$BocCiNH-α-CD was synthesized according to Scheme 1. To a solution of 3-NH$_2$-α-CD ($6.08 \times 10^{-4}$ mol) in 50-mL DMF was added 4-*tert*-BocCiOH ($2.08 \times 10^{-3}$ mol). After the solution was cooled below 0 °C, *N*,*N'*-dicyclohexylcarbodiimide ($8.29 \times 10^{-4}$ mol) and 1-hydroxybenzotriazole ($8.29 \times 10^{-4}$ 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 the precipitate was collected and washed with acetone. The crude product was purified by preparative reversed phase chromatography. After the concentration of the solution containing 40% of methanol under vacuum, the residue was separated with preparative size exclusion chromatography. Yield, 46%. The product was characterized by $^1$H NMR and 2D NMR spectroscopy (COSY, TOCSY, and NOESY measurements).[6]



**Scheme 1.** Synthesis of 3-4-$^t$BocCiNH-α-CD.

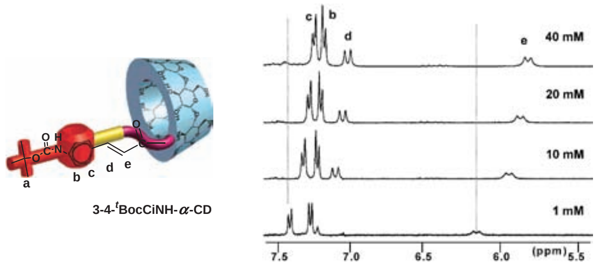


**Figure 1.** $^1$H NMR spectra (400 MHz) of 3-4-$^t$BocCiNH-α-CD at various concentrations in D$_2$O.

Figure 1 shows the $^1$H NMR spectra of 3-4-$^t$BocCiNH-α-CD at various concentrations. The peaks of cinnamoyl groups shifted to higher fields as its concentration increased, indicating that the cinnamoyl group is included in the CD cavity to form intermolecular complexes. The 2D NOESY spectra showed that the *t*-Boc group is deeply included in the CD cavity. The molecular weights of the complexes estimated by VPO (vapor pressure osmometry) increased with an increase in the concentrations, and reached 20000 at 10 mM, indicating that 3-4-$^t$BocCiNH-α-CD formed supramolecular polymers in aqueous solutions.

Figure 2 shows the circular dichroism spectra of 3-4-$^t$BocCiNH-α-CD in water at 0.1 to 1.5 mM, because the upper limit of the concentration detected the circular dichroism spectra was 1.5 mM. The bands showed ICD (induced circular dichroism) bands with a negative band around 323 nm at 0.25 mM. However, the bands were gradually separated and shifted to a negative band at 327 nm and a positive band at 288 nm with increasing the concentration. In contrast, the circular dichroism spectrum of 3-4-$^t$BocCiNH-α-CD (0.25 mM) in the presence of excess amount of α-CD showed only a negative band around 311 nm. These spectra are quite different from those of the complex between 4-*tert*-BocCiOH and α-CD in an aqueous solution. In this case, the spectra showed only a positive band around 313 nm. According to the theoretical treatment by Kodaka

Copyright © 2005 The Chemical Society of Japan

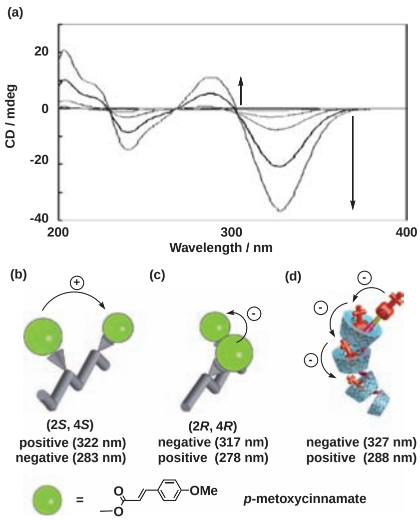


**Figure 2.** Circular dichroism spectra of 3-4-$^t$BocCiNH-$\alpha$-CD in water (0.1, 0.25, 0.5, 1.0, and 1.5 mM) (a), structure of (2*S*,4*S*)-2,4-*anti*-hexanediol bis-*p*-methoxycinnamates (b), structure of (2*R*,4*R*)-2,4-*anti*-pentanediol bis-*p*-methoxycinnamates (c) and schematic structure of 3-*p*-$^t$BocCiNH-$\alpha$-CD (d).

et al.,[7] the observed positive Cotton effect is ascribable to the fact that 4-*tert*-BocCiOH is included in the $\alpha$-CD cavity in parallel with the CD axis. The observed negative Cotton effect of 3-4-$^t$BocCiNH-$\alpha$-CD at less than 0.25 mM is also ascribable to the fact that the 4-$^t$BocCi part exists parallel to the $\alpha$-CD axis in monomeric structure. Moreover, the Cotton effect shifted by an addition of $\alpha$-CD is assigned to slantwise inclusion of the 4-$^t$BocCi part, indicating the formation of a 3-4-$^t$BocCiNH-$\alpha$-CD–$\alpha$-CD heterodimer by $\alpha$-CD. Nakanishi et al., previously reported that (2*S*,4*S*)-2,4-*anti*-hexanediol bis-*p*-methoxycinnamates gave rise to the splitting positive and negative Cotton bands around 322 and 285 nm in the $^1L_a$ transition, respectively.[8] (2*R*,4*R*)-2,4-*anti*-pentanediol bis-*p*-methoxycinnamate also showed a splitting Cotton band with the opposite signs at 278 and 317 nm. These observations showed the existence of the pair-wise exciton-coupling interactions (cinnamate/cinnamate interactions) in the compound and the rotational configuration affect on the sign of ICD spectrum. On the basis of this report, the splitting Cotton bands in the $^1L_a$ transition absorption of 3-4-$^t$BocCiNH-$\alpha$-CD are ascribable to the existence of cinnamoyl (guest)/cinnamoyl (guest) interactions between the adjacent units at the concentration of more than 0.5 mM. Furthermore, the guest part of 3-4-$^t$BocCiNH-$\alpha$-CD can be oriented as a left handed *anti*-configuration. These results indicate the formation of helical supramolecular polymers by 3-4-$^t$BocCiNH-$\alpha$-CD.

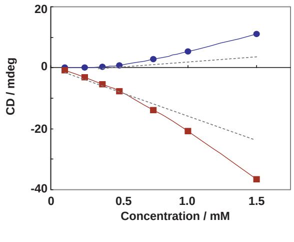


**Figure 3.** Intensities of positive (●) and negative (■) Cotton bands of 3-4-$^t$BocCiNH-$\alpha$-CD in water.

**Figure 4.** A proposed supramolecular structure of 3-4-$^t$BocCiNH-$\alpha$-CD.

Figure 3 shows the intensities of the peaks of the circular dichroism spectra as a function of the concentrations. The peak intensities of the positive and negative bands respectively increased and decreased as the concentrations increased, but the change was not linear as observed in the case of 3-CiNH-$\alpha$-CD, indicating the existence of some cooperativity.

Figure 4 shows a schematic representation of a possible supramolecular structure formed by 3-4-$^t$BocCiNH-$\alpha$-CD in aqueous solutions. This is the first observation of a synthetic host–guest system forming a helical supramolecular structure in an aqueous solution.

The studies on detailed supramolecular structures and their dynamic aspects are now in progress.

This work was partially supported by a Grant-in-Aid No. S14103015 for Scientific Research from the Ministry of Education, Culture, Sports, Science and Technology, Japan.

## References and Notes

1 a) J.-M. Lehn, "Supramolecular Chemistry," VCH, Weinheim, Germany (1995). b) P. S. Corbin and S. C. Zimmerman, "Supramolecular Polymers," ed. by A. Ciferri, Marcel Dekker, New York (2000). c) R. P. Sijbesma, F. H. Beijer, L. Brunsveld, B. J. B. Folmer, J. H. K. K. Hirschberg, R. F. M. Lange, J. K. L. Lowe, and E. W. Meijer, *Science*, **278**, 1601 (1997). d) J. H. K. K. Hirschberg, L. Brunsveld, A. Ramzi, J. A. J. M. Vekemans, R. P. Sijbesma, and E. W. Meijer, *Nature*, **407**, 167 (2000). e) R. K. Castellano, D. M. Rudkevich, and J. Rebek, Jr., *Proc. Natl. Acad. Sci. U.S.A.*, **94**, 7132 (1997).

2 a) A. Harada, Y. Kawaguchi, and T. Hoshino, *J. Inclusion Phenom.*, **41**, 115 (2001). b) A. Harada, *Acc. Chem. Res.*, **34**, 456 (2001). c) A. Harada, M. Miyauchi, and T. Hoshino, *J. Polym. Sci., Part A: Polym. Chem.*, **41**, 3519 (2003). Another reports in cyclodextrin system: for example d) T. Kaneda, T. Yamada, T. Fujimoto, and Y. Sakata, *Chem. Lett.*, **2001**, 1264. e) H. Onagi, C. J. Easton, and S. F. Lincoln, *Org. Lett.*, **3**, 1041 (2001). f) Y. Liu, Z. Fan, H. Y. Zhang, and C. H. Diao, *Org. Lett.*, **5**, 251 (2003).

3 T. Hoshino, M. Miyauchi, Y. Kawaguchi, H. Yamaguchi, and A. Harada, *J. Am. Chem. Soc.*, **122**, 9876 (2000).

4 M. Miyauchi, Y. Kawaguchi, and A. Harada, *J. Inclusion Phenom.*, **50**, 57 (2004).

5 M. Miyauchi and A. Harada, *J. Am. Chem. Soc.*, **126**, 11418 (2004).

6 Positive ion MALDI-TOF Mass $m/z$ 1240.25 ($M + Na^+$). $^1H$ NMR (DMSO-$d_6$, 400 MHz): $\delta$ 9.47 (s, 1H), 8.07 (d, 1H, $J = 8.79$), 7.52–7.46 (q, 4H, $J = 8.55$), 7.31 (d, 1H, $J = 15.63$), 6.41 (d, 1H, $J = 15.59$), 5.90–5.17 (m, 11H), 4.86–4.64 (m, 6H), 4.52–4.49 (m, 6H), 3.93–3.29 (m, overlaps with HOD), 1.45 (s, 9H). IR (KBr, cm$^{-1}$): 1702 (vs, $^{\nu}$C=O, urethane), 1658 (vs, $^{\nu}$C=O, amide). Anal. calcd for $C_{50}H_{76}N_2O_{32}\cdot 7H_2O$: C, 44.71; H, 6.75; N, 2.09. Found: C, 44.97; H, 6.63; N, 2.18%.

7 M. Kodaka and T. Fukaya, *Bull. Chem. Soc. Jpn.*, **62**, 1154 (1989).

8 "Circular Dichroism, Principles and Applications," 2nd ed., ed. by N. Berova, K. Nakanishi, and R. W. Woody, Wiley-VCH, New York, Chichester, Weinheim, Brisbane, Singapore, Tronto (2000).

Published on the web (Advance View) December 18, 2004; DOI 10.1246/cl.2005.104