Heterodimerization of Dye-Modified Cyclodextrins with Native Cyclodextrins

Tetsuo Kuwabara,* Taiyo Aoyagi,† Makoto Takamura,† Akiko Matsushita,† Asao Nakamura,‡ and Akihiko Ueno†

Department of Applied Chemistry and Biotechnology, Faculty of Engineering, Yamanashi University, 4-3-11 Takeda, Kofu 400-8511, Japan, Department of Bioengineering, Faculty of Bioscience and Biotechnology, Tokyo Institute of Technology, 4259 Nagatsuta-cho, Midori-ku, Yokohama 226-8501, Japan, and Inoue Photochirogenesis Project, ERATO, JST, 4-6-3 Kamishinden, Toyonaka 560-0085, Japan

kuwabara@ab11.yamanashi.ac.jp

Received July 10, 2001

The heterodimerization behavior of dye-modified β-cyclodextrins (**1**−**6**) with native cyclodextrins (CDs) was investigated by means of absorption and induced circular dichroism spectroscopy in an aqueous solution. Three types of azo dye-modified β-CDs (**1**−**3**) show different association behaviors, depending on the positional difference and the electronic character of substituent connected to the CD unit in the dye moiety. *p*-Methyl red-modified β-CD (**1**), which has a 4-(dimethylamino)-azobenzene moiety connected to the CD unit at the 4′ position by an amido linkage, forms an intramolecular self-complex, inserting the dye moiety in its β-CD cavity. It also associates with the native α-CD by inserting the moiety of **1** into the α-CD cavity. The association constants for such heterodimerization are 198 M^{-1} at pH 1.00 and 305 M^{-1} at pH 6.59, which are larger than the association constant of **1** for β-CD (43 M^{-1} at pH 1.00). Methyl red-modified **2**, which has the same dye moiety as that for **1** although its substituent position is different from that of **1**, does not associate even with α-CD due to the stable self-intramolecular complex, in which the dye moiety is deeply included in its own cavity of β-CD. Alizarin yellow-modified CD (**3**), which has an azo dye moiety different from that of **1** and **2**, caused a slight spectral variation upon addition of α-CD, suggesting that the interaction between **3** and α-CD is weak. On the other hand, phenolphthalein-modified β-CD (**4**), which forms an intermolecular association complex in its higher concentrations, binds with β-CD with an association constant of 787 M^{-1} at pH 10.80, where **4** exists as the dianion monomer in the absence of β-CD. *p*-Nitorophenol-modified β-CDs (**5** and **6**), each having *p*-nitorophenol moieties with a different connecting part with an amido and amidophenyl group, respectively, associated with α-CD with association constants of 66 and 16 M^{-1} for **5** and **6**, respectively. The phenyl unit in the connecting part of **6** may prevent the smooth binding with α-CD. All these results suggest that the dye-modified CDs, in which the dye part is not tightly included in its CD cavity, associate with the native CD to form heterodimer composed of two different CD units by inserting the dye moiety into the native CD unit. The resulting heterodimers have a cavity that can bind another appending moiety of host molecules. On this basis, more ordered molecular arrays or the supramolecular hereropolymers can be constructed.

Introduction

Noncovalent interactions play an important role in biological systems for forming organized molecular arrays from relatively simple subunits. The resulting supramolecular entities show excellent functions with high selectivity and efficiency by means of the cooperative or synergistic effects of component molecules. To get insight into the mechanism of the formation of such molecular assemblies at the molecular level, several model systems have been studied.

One recent topic is an association or a dimerization of host molecules based on the noncovalent interactions.[1] Rebek et al. have reported homodimerization of self-complementary subunits[2] and of calixarene derivatives[3] in organic solution. These systems involve the intermolecular hydrogen bond between the identical subunits or calixarenes, encapsulating small guest molecules into the formed cavity. Shinkai et al. have reported, on the other hand, the association of two different kinds of calixarenes.[4] The calixarene having carboxyl groups associates with the calixarene having the pyridine rings even in the absence of the guest molecule.

Other examples for dimerization of host molecules are reported by Hamai. He found that the addition of β-cyclodextrin (β-CD) causes the eximer fluorescence of

* To whom correspondence should be addressed. Tel: +81-552-20-8548. Fax: +81-552-20-8772.
† Tokyo Institute of Technology.
‡ Inoue Photochirogenesis Project.

(1) Conn, M. M.; Rebek, J., Jr. *Chem. Rev.* **1997**, *97*, 1647.

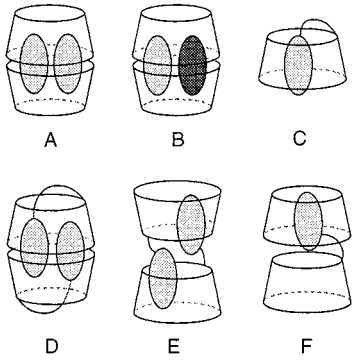
(2) (a) Heinz, T.; Rudkevich D. M; Rebek, J., Jr. *Nature* **1998**, *394*, 764. (b) Branda, N.; Grotzfeld, R. M.; Valdés, C.; Rebek, J., Jr. *J. Am. Chem. Soc.* **1995**, *117*, 85.

(3) (a) Castellano, R. K.; Rudkevich D. M.; Rebek, J., Jr. *J. Am. Chem. Soc.* **1996**, *118*, 10002. (b) Castellano, R. K.; Kim, B. H.; Rebek, J., Jr. *J. Am. Chem. Soc.* **1997**, *1198*, 112671. (a) Atwood, J. L.; Orr, G. W.; F. Hamada; Bott, S. G.; Robinson, K. D. *Supramol. Chem.* **1992**, *1*, 15.

(4) Koh, K.; Araki, K.; Shinkai, S. *Tetrahedron Lett.* **1994** *35*, 8255.

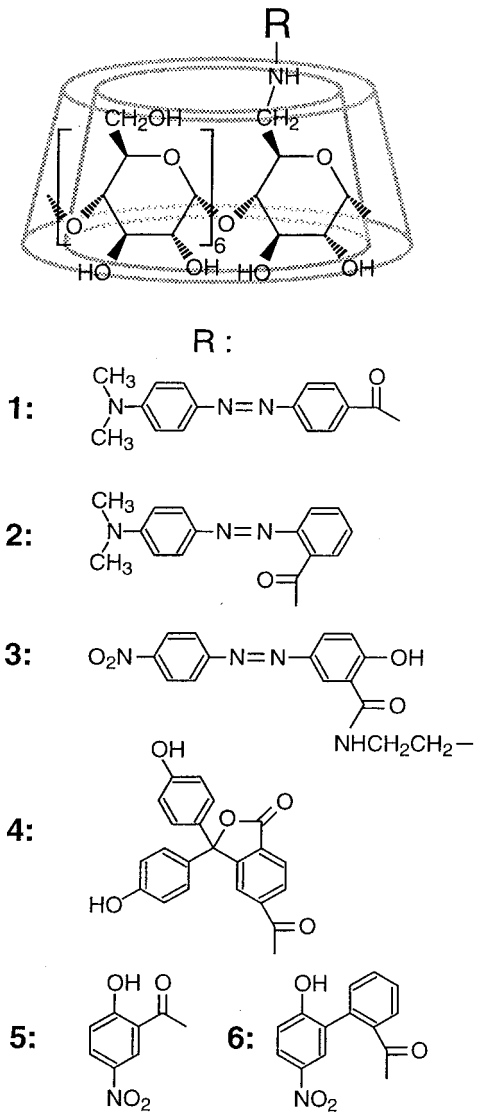
10.1021/jo010696u CCC: $22.00
Published on Web 01/11/2002

naphthalene in an aqueous solution and proposed 2:2 complexes (A) of these components.[5] The formation of 2:2 complexes occurred by self-association of the 1:1 complexes of β-CD and naphthalene. Self-association of the 1:1 complexes of β-CD have been reported also for the system of some monosubstituted naphthalene[6] or anthracene derivatives.[7] The addition of γ-CD also causes the eximer fluorescence of pyrene[8] or 2-methylnaphthalene[9] with larger self-association constants as compared to those for β-CD system.[10] On the other hand, the encapsulation of two kinds of guests into the CD association dimer (B) was reported for the systems of 2-methoxynaphthalein/*o*-phthalonitrile/β-CD[11] and 4-(dimethylamino)benzonitrile/some aromatic compounds/glucosyl-β-CD.[12] In these complexes, two CD molecules are coupled by intermolecular hydrogen bonds between secondary hydroxyl groups to form a CD dimer, which accommodates the two guest molecules. The study using molecular mechanics and molecular dynamics calculations also suggests that the dimer, with the secondary hydroxyl groups of CD units being coupled with each other, is more stable than the other dimerization structure.[13]



Modified CDs often dimerize even in the absence of the guest molecules. Usually, the chromophore-modified CDs accommodate the chromophore moiety into its own CD cavity forming the intramolecular self-inclusion complex (C).[14] In the case of a pyrene-modified γ-CD, however, the intramolecular inclusion complex converts into the association dimer (D), in which the secondary hydroxyl groups of CD units are faced with each other, in the absence of the guest, and shows pyrene eximer.[15] An azobenzene-modified β-CD also exhibits the self-associastion phenomenon with a geometry similar to that for the case of pyrene-modified γ-CD.[16] In contrast to these, Kaneda et al. have reported another type of the homodimer (E) and the homotetramer of the modified CD, whose geometry is different from the previous case.[17] Harada et al. have also prepared the cyclic homotrimer, in which each cinnamoyl-modified CD is threaded by the cinnamoyl moiety of another molecule.[18] These assembling species consist of the identical modified CD and can be led to the supramolecular homopolymers.

On the other hand, we have reported the association of *p*-methyl red-modified β-CD (**1**) with a native CD with accompanying color change.[19] This association species (F) inserts the appending moiety of modified CD into the cavity of native CD and is different from the previous dimer cases. [20] In this paper, we describe the assembling of various types of dye-modified CDs into heterodimers by cooperation of two different CDs and that assembling ability may depend on the structure of the dye unit and the kind of the CD. Such heterodimerization can be applicable to prepare the supramolecular heteropolymer.



Experimental Section

Materials. α- and β-CD were kind gifts from Nihon Shokuhin Kako Co. Ltd and were used after two recrystallizations from water. Six types of dye-modified CDs have been prepared by literature methods. The modified β-CDs bearing a *p*-methyl red (**1**) and a methyl red (**2**) unit are structural isomers having a 4-(dimethylamino)azobenzene moiety with a carbonyl sub-

(5) Hamai, S. *Bull. Chem. Soc. Jpn.* **1982**, *55*, 2721.
(6) Hamai, S. *Bull. Chem. Soc. Jpn.* **1996**, *69*, 2469.
(7) Tamaki, T.; Kokubu, T. *J. Inclusion Phenom.* **1984**, *2*, 815.
(8) Hamai, S. *J. Phys. Chem.* **1989**, *93*, 6527.
(9) Hamai, S. *Bull. Chem. Soc. Jpn.* **1996**, *69*, 543.
(10) Hamai, S.; Hatamiya, A. *Bull. Chem. Soc. Jpn.* **1996**, *69*, 2469.
(11) Hamai, S. *Bull. Chem. Soc. Jpn.* **1982**, *55*, 2721.
(12) Nakamura, A.; Sato, S.; Hamasaki, K.; Ueno, A.; Toda, F. *J. Phys. Chem.* **1995**, *99*, 10952.
(13) Bonnet, P.; Jaime, C.; Morin-Allory, L. *J. Org. Chem.* **2001**, *66*, 689.
(14) (a) Ikeda, H.; Nakamura, M.; Ise, N.; Oguma, N.; Nakamura, A.; Ikeda, T.; Toda, F.; Ueno, A. *J. Am. Chem. Soc.* **1996**, *118*, 10980. (b) Wang, Y.; Ikeda, T.; Ikeda, H.; Ueno, A.; Toda, F. *Bull. Chem. Soc. Jpn.* **1994**, *67*, 1598. (c) Hamasaki, K.; Ikeda, H.; Nakamura, A.; Ueno, A.; Toda, F.; Suzuki, I.; Osa, T. *J. Am. Chem. Soc.* **1993**, *115*, 5039.
(15) Ueno, A.; Suzuki, I.; Osa, T. *J. Am. Chem. Soc.* **1989**, *111*, 6391.
(16) Ueno, A.; Fukushima, M.; Osa, T. *J. Chem. Soc., Perkin Trans. 2* **1990**, 1067.

stituent at the 4′ and 2′ positions, respectively.[21] Alizarin yellow-modified β-CD (**3**) also has the azo dye moiety with a carbonyl substituent at the 3′ position and has an ethylene unit between the dye moiety and the CD.[22] Phenolphthalein-modified β-CD (**4**)[23] and two types of *p*-nitrophenol-modified CDs (**5**, **6**)[24] were also used in this study. Compound **6** has a phenyl spacer between the *p*-nitrophenol unit and CD. All these compounds were identified by elemental analysis and ^{1}H NMR.

Measurements. Absorption and induced circular dichroism spectra were recorded on a Shimadzu UV-3100 and a JASCO J-600, respectively. All of the measurements were performed at 25 °C in an aqueous solution except for the case of **1** and **2**, which were performed in a 10% ethylene glycol aqueous solution because of the poor solubility of **1** and **2**. The acidic solutions of **1** and **2** were prepared by using hydrochloric acid to achieve pH 1.00, while the phosphate buffer was used for preparing the neutral solution of **1** (pH 6.59) and **6** (pH 6.50). On the other hand, formate buffer was used for preparing the solutions involving **3** (pH 2.99) or **5** (pH 4.50). The alkaline solutions of **3** and **4** were made by sodium hydroxide to set the solutions at pH 12.00 and 10.80, respectively. The pH of the solutions was measured on a TOA pH meter HM-60S, which had been calibrated at 25 °C with pH standard solutions of pH 4.01 ± 0.01, 6.86 ± 0.01, and 9.22 ± 0.01.

Determination of Association Constants. The association constants of the dye-modified CDs with α- or β-CD were determined by the following equation, which holds under the conditions of large excess of α- or β-CD and 1:1 host−guest stoichiometry

$$\Delta I = \frac{K \cdot CD \cdot \Delta I_{max}}{1 + K \cdot CD}$$

where K is the association constant of the dye-modified CD for α- or β-CD. CD represents the initial concentration of α- or β-CD. ΔI is the α- or β-CD-induced absorption variation of the modified CD, measured at 510, 560, 400, and 390 nm for **1**, **4**, **5**, and **6**, respectively. In the case of **1**, in the neutral medium at pH 6.59, ΔI expresses the α-CD-induced dichroism variation of **1** at 420 nm.

Results and Disscusion

Heteroassociation of Azo Dye-Modified CDs with Native CD. Previously, we described the spectroscopic behaviors of **1** and **2** in an aqueous solution.[21] The addition of α-CD to the acidic solution of **1** caused a color change from red to colorless decreasing the strong band around 510 nm and increasing absorption intensity around 320 nm (Figure 1). This indicates the structural change of the *p*-methyl red moiety from the azonium form into the ammonium one, each being protonated on the azo group and the dimethylamino group, respectively. Since there exists no intermolecular interaction of **1**, which is proved by no observation in the concentration dependency in the absorption spectrum of **1**, α-CD-induced spectral variation is interpreted in terms of the inclusion of the *p*-methyl red moiety of **1** into the cavity of α-CD (F), as shown in Scheme 1. The azo group of **1** is located in the hydrophobic environment inside the α-CD cavity, while the dimethylamino group projecting from the α-CD cavity is exposed to bulk water, being protonated. Such association of **1** with α-CD was confirmed by induced circular dichroism spectra.[25] The small negative dichroism band of **1** around 500 nm disappeared upon addition of α-CD, and the positive ones appeared around 420 nm. This result suggests that the *p*-methyl red moiety, which weakly interacts with its β-CD cavity in the absence of α-CD, is included in the α-CD cavity with an orientation parallel to the α-CD axis. **1** associates with α-CD not only in the acidic medium but also in the neutral one. Upon addition of α-CD at pH 6.59, a slight hyperchromic effect was observed. This indicates the conformational change of **1**, which is confirmed by induced circular dichroism of **1** (Figure 2). Upon addition of α-CD, the negative dichroism band of **1** around 410 nm, associated with $\pi-\pi^*$ transition, changed to the positive one and the intensity of the positive band around 480 nm, associated with $n-\pi^*$ transition, decreased. This implies that the association of **1** with α-CD occurred even in the neutral medium.

The curve-fitting analysis of the α-CD-induced spectral variations of **1** performed by using a Benesi−Hildebrand-type equation gave the association constant. The association constants of **1** for α-CD are estimated to be 198 and 305 M^{-1} at pH 1.00 and pH 6.59, respectively, which are much smaller than those of methyl orange (925 M^{-1} at pH 1.00 and 6300 M^{-1} at pH 11.0).[26] The difference between **1** and methyl orange resides in the type of the substituent linked to the azobenzene unit, as shown by

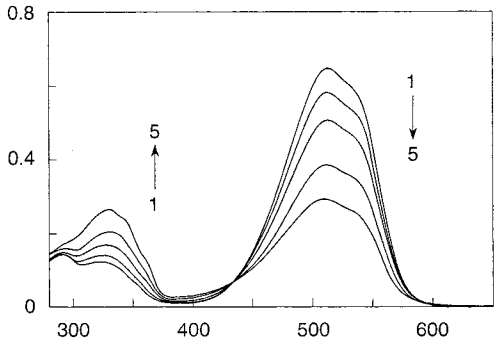
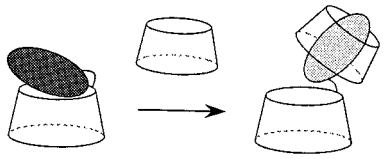


Figure 1. Absorption spectra of **1** (1.5×10^{-5} M) at pH 1.00, alone and in the presence of α-CD in a 10% ethylene glycol aqueous solution. Concentration of α-CD: (1) 0, (2) 7.5×10^{-4}, (3) 2.3×10^{-3}, (4) 6.0×10^{-3}, (5) 1.2×10^{-2} M.

Scheme 1. Schematic Representation of the Formation of the Supramolecular Heterodimer Consisting of Modified CD and the Native CD



(17) (a) Fujimoto, T.; Uejima, Y.; Imaki, H.; Kawabayashi, N.; Hwa Jung, J.; Sakata, S.; Kaneda, T. *Chem. Lett.* **2000**, 564. (b) Fujimoto, T.; Sakata, S.; Kaneda, T. *Chem. Lett.* **2000**, 764.

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

(19) Kuwabara, T.; Nakamura, A.; Ikeda, T.; Ikeda, H.; Ueno, A.; Toda, F. *Supramol. Chem.* **1996**, *7*, 235.

(20) The association of CD of this type, see; (a) Ueno, A.; Tomita, Y.; Osa, T. *J. Chem. Soc., Chem. Commun.* **1983**, 1515. (b) Takahashi, K.; Imotani, K.; Kitsuta, M. *Polymer J.* **2001**, *33*, 242.

(21) Kuwabara, T.; Nakamura, A.; Ueno, A.; Toda, F. *J. Phys. Chem.* **1994**, *98*, 6297.

(22) Aoyagi, T.; Nakamura, A.; Ikeda, H.; Ikeda, T.; Mihara, H.; Ueno, A. *Anal. Chem.*, **1997**, *69*, 659.

(23) Kuwabara T.; Takamura, M.; Matsushita, A.; Nakamura, A.; Ueno, A.; Toda, F. *J. Org. Chem.* **1998**, *63*, 8729.

(24) Matsushita, A.; Kuwabara, T.; Nakamura, A.; Ikeda, H.; Ueno, A. *J. Chem. Soc., Perkin Trans. 2* **1997**, 1705.

(25) (a) Harata, K.; Uedaira, H. *Bull. Chem. Soc. Jpn.* **1975**, *48*, 375. (b) Shimizu, H.; Kaito, A.; Hatano, M. *Bull. Chem. Soc. Jpn.* **1979**, *52*, 2678.

(26) Buvári, Á.; Barcza, L. *J. Inclusion Phenom.* **1989**, *7*, 313.

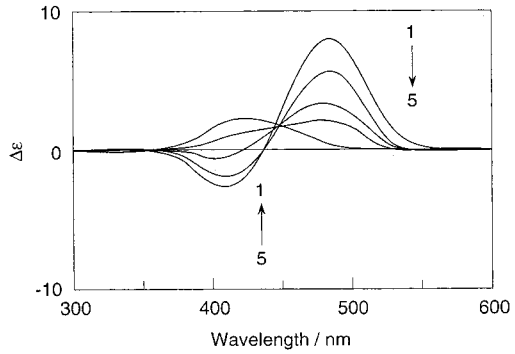


Figure 2. Induced circular dichroism spectra of **1** (1.5×10^{-5} M) at pH 6.59, alone and in the presence of α-CD in a 10% ethylene glycol aqueous solution. Concentration of α-CD: (1) 0, (2) 1.5×10^{-3}, (3) 3.0×10^{-3}, (4) 6.0×10^{-3}, (5) 1.2×10^{-2} M.

the replacement of the amido-*β*-CD unit in **1** by the simple sulfonyl group in methyl orange. So the smaller binding ability of **1** for α-CD must be due to a steric hindrance between these components. Two large bulky CD units might be difficult to draw near. In this assembling system, however, the *p*-methyl red-modified moiety serves as a connector between two CD units with a geometry different from that reported previously.[14,15]

Similar trends in the absorption spectrum were observed when *β*-CD was added to the solution of **1** at pH 1.00. However, the degree in the spectral variation was smaller than that for α-CD. The association constant of **1** for *β*-CD is estimated to be 43 M^{-1}, while it could not be obtained in the neutral condition because of the small spectral change. These results indicate that the azo dye of **1** fits better to the α-CD cavity than to the *β*-CD cavity, being consistent with the fact that the association constant of methyl orange for α-CD is larger than that for *β*-CD.[26]

In contrast to **1**, **2** has no binding ability with CDs. The addition of α-CD or *β*-CD to the solution of **2** caused no change in the spectrum under both acidic and neutral conditions. This suggests that **2** prefers to form the intramolecular self-inclusion complex form (C), which is the form that the methyl red moiety is included in its own CD cavity with an orientation parallel to the CD axis, rather than to form the intermolecular complex form even in the presence of a large excess of native CDs. The difference in assembling ability between **1** and **2** is attributed to the positional difference of the substitution in the dye unit. The azo dye-modified CD with *p*-substituent is favorable to form the intermolecular complex.

Compound, **3**, which has an azo dye unit different from these azo dyes of **1** and **2**, exhibits a slight spectral change upon addition of α-CD. Figures 3 and 4 show the absorption and its second derivative curve of **3** together with the induced circular dichroism spectra alone and in the presence of α-CD at different pHs. At pH 2.99 (Figure 3), **3** exists as the phenol form.[18] Upon addition of α-CD to the solution of **3**, the slight red shift in absorption peak of **3** from 367 to 370 nm was observed, while the dichroism intensity of **3** decreased around 450 nm and increased around 370 nm. The analysis of the secondary derivative of absorption spectrum of **3** gave the electronic transition at 370 and 480 nm, each ascribing to $\pi-\pi^*$ and $n-\pi^*$ transition, respectively. These

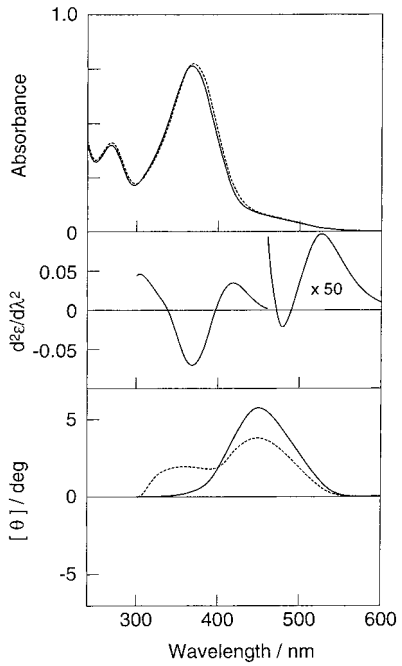


Figure 3. Absorption, its second derivative and induced circular dichroism spectra of **3** (5.0×10^{-5} M) at pH 2.99, alone (—) and in the presence of α-CD (5.0×10^{-3} M) (— — —).

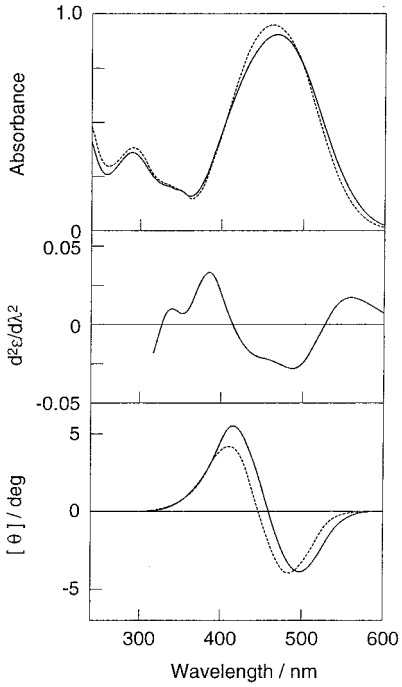


Figure 4. Absorption, its second derivative and induced circular dichroism spectra of **3** (5.0×10^{-5} M) at pH 12.00, alone (—) and in the presence of α-CD (5.0×10^{-3} M) (— — —).

spectral variations indicate the association of **3** with α-CD. The intramolecular complex, in which the alizarin yellow moiety is included in its own *β*-CD cavity with an orientation perpendicular to the *β*-CD axis, converts into the intermolecular one, in which the moiety is included in the cavity of α-CD with an orientation parallel to the α-CD axis, as shown in Scheme 1. However, the association constant could not be obtained because of the small change in both spectra. In the absence of α-CD at pH 12.00 (Figure 4), the absorption peak was observed at

468 nm and the positive and negative dichroism bands were observed around 425 and 490 nm, corresponding to the electronic transition moment of the shorter and longer direction in the dye moiety, respectively. This indicates that the dye moiety of **3** exists as the phenolate anion form, interacting with its β-CD cavity with an orientation perpendicular to the CD axis. The addition of α-CD caused the blue shift in the absorption peak and decrease in the positive dichroism intensity in the dichroism band around 425 nm. This suggests that the intramolecular interaction between dye moiety and β-CD unit become weaker because the inclusion of the dye moiety into the α-CD cavity may occur. These spectral variations are too small to estimate the association constants of **3**. These results suggest that, under both acidic and alkaline conditions, **3** associates with α-CD weakly.

The β-CD-induced spectral changes were similar to those in the case of α-CD with much smaller degree than those of α-CD. This fact indicates that there occurs the similar association of **3** with β-CD. It seems, however, that the association constants for β-CD were much smaller than those for α-CD.

The modified CD **3** has less intermolecular association ability with the native CD. In this case, the electonic character of the dye unit is one of the reasons for the poor intermolecular association ability of **3**. Since the electron-attractive nitro group should make the hydroxyl proton in the azophenol unit acidic, the strong ionic interaction between the negative hydroxyl group and the protonated secondary amine connector in the molecule may cause the stable intramolecular interaction of the dye moiety and its CD unit. This may lead to the decrease in the intermolecular association ability.

All these results suggest that the azo dye modified CDs reveal different association behaviors for native CDs, reflecting the positional and structural difference of the substitution in the dye moiety. The modified CD with a para-substituent prefers the intermolecular complex rather than the intramolecular one in the presence of the native CD (F). The smaller association ability of the dye-modified CD, as compared with the case of the association between the simple free dye and CD, might arise from the steric hindrance of large CD unit. On the other hand, the modified CD with an ortho substituent adopts the stable intramolecular complex form (C). The electronic character of the substitution in the dye moiety may also influence the intramolecular or intermolecular interaction.

Heteroassociation of 4 with β-CD. Phenolphthalein is known to change color from purple to colorless when it binds to β-CD.[27] The purple dianion form of phenolphthalein, in which two phenol rings are incorporated into a planar resonance form, changes the conformation to a lactonoid form even in the alkaline solution when included in the cavity of β-CD. As reported previously,[23] phenolphthalein-modified β-CD, **4**, includes the dye moiety not only in its β-CD cavity but also in the cavity of another molecule of **4**, as shown by the fact that pH titration curve of **4** was shifted toward the alkaline side when the concentration of **4** is higher. When the solution is above pH 10.80, however, such intermolecular association of **4** disappeared because of no difference in the molecular extinction of **4** above this pH. This suggests that **4** exists as a monomer at this pH. At this pH, we have investigated the association behavior of **4** with CD.

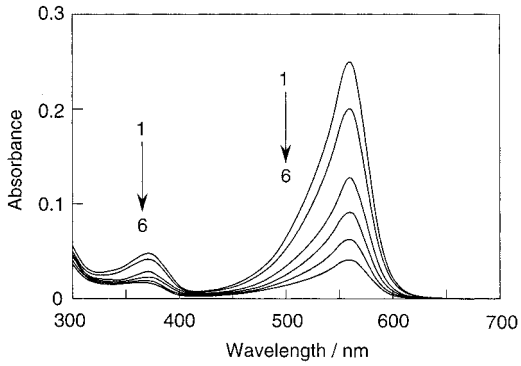


Figure 5. Absorption spectra of **4** (5.0×10^{-6} M) alone and in the presence of β-CD at pH 10.80. Concentration of β-CD: (1) 0, (2) 3.0×10^{-4}, (3) 1.5×10^{-3}, (4) 3.0×10^{-3}, (5) 6.1×10^{-3}, (6) 1.2×10^{-2} M.

Figure 5 shows the absorption spectra of **4**, alone and in the presence of β-CD. At pH 10.80 in the absence of β-CD, the absorption band around 560 nm was observed. This indicates that the phenolphthalein unit in **4** exists as the dianion form, in which the phenolphthalein moiety dissociates two protons. Upon addition of β-CD, the band around 560 nm decreased and disappeared in the excess of β-CD, resulting in colorless solution. This fact implies that the association of the phenolphthalein unit in **4** with β-CD occurs, in which the conformation of the phenolphthalein unit is restricted in the added β-CD cavity. The curve-fitting analysis of the β-CD-induced spectral variations of **4** at 560 nm performed by using Benesi−Hildebrand-type equation gave an association constant of 787 M^{-1}. This value is much smaller than that for complexation of β-CD and phenolphthalein (23000 M^{-1} at pH 10.50),[28] whose tendency is well coincident with the results obtained in the system for **1** and α−CD. The smaller binding ability of **4** for β-CD suggests that there exists a steric hindrance for the two bulky CD units to come close to each other.

Heteroassociation of 5 and 6 with α-CD. The association abilities of **5** and **6**, both having a *p*-nitrophenol moiety with a different connecting spacer between dye and CD units, were investigated under neutral conditions. The pH titration experiments indicate that **5** and **6** exhibit their pK_a values at 4.82 and 6.40, respectively, which can be related to the equilibrium between the phenol and phenolate anion form in the dye moiety. The difference between the two pK_a values may be due to the spacer between the dye moiety and the CD unit.

Figure 6 shows the absorption spectra of **5** at pH 4.50 induced by α-CD. There occurs a progressive red shift in the absorption peak around 390 nm and increases in the absorption intensity with increasing concentration of α-CD. This indicates that the modified *p*-nitrophenol moiety converts into the phenolate anion form from the phenol one by inclusion of the *p*-nitrophenol moiety in the cavity of α-CD. This result is coincident with the fact that *p*-nitrophenol changes color from colorless to yellow when it binds to α-CD.[29] The association constant is estimated to be 66 M^{-1} at pH 4.6. Similar trend was

(27) (a) Buvári-Barcza, Á.; Kajtár, M.; Szente L.; Barcza, L. *J. Chem. Soc., Perkin Trans. 2* **1996**, 489. (b) Buvári, Á.; Barcza, L.; Kajtár, M. *J. Chem. Soc., Perkin Trans. 2* **1988**, 1687.

(28) Barcza, L.; Buvári-Barcza, Á. *Carbohydr. Res.* **1989**, *192*, 103.

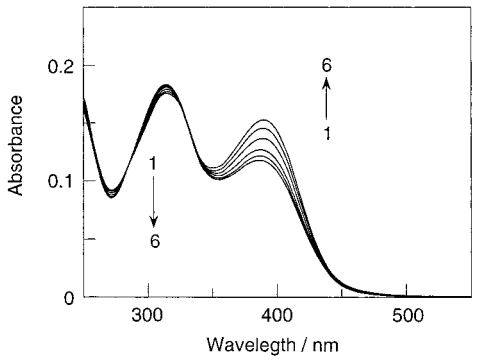


Figure 6. Absorption spectra of **5** (3.0×10^{-5} M) alone and in the presence of β-CD in formate buffer at pH 4.50. Concentration of α-CD: (1) 0, (2) 5.0×10^{-4}, (3) 1.0×10^{-3}, (4) 2.5×10^{-3}, (5) 3.8×10^{-3}, (6) 5.0×10^{-3} M.

observed when α-CD was added to the solution of **6** at pH 6.50 and the association constant is estimated to be 16 M^{-1}. These association constants are much smaller than the system of *p*-nitrophenol and α-CD.[30] The large CD unit of **5** or **6** may prevent the association of these molecules. Furthermore, the phenyl spacer in **6** also increases the difficulty to form heteroassociation species with α-CD. These results suggest that the spacer unit between dye and CD unit also play an important role for the association.

Geometry of Heterodimer Complexes. When the dye is included in the cavity of CD, there are two directional ways in the insertion, which reflect the geometry of the complex. Furthermore, because of the electronic reason and the steric consideration,[31] the dye is likely to insert from the more open side of the CD cavity. So the heterodimer complex of the dye-modified CD with the native CD may adopt the geometry of structure F, rather than the another geometry that the dye moiety is inserted through the primary hydroxyl side of the native CD.

The geometry of the complex between methyl orange and α-CD was confirmed by X-ray crystallography in the solid state. [32] While in this complex the azo group of methyl orange was located in the cavity of α-CD, the dimethylamino group and the sulfonate group project from the narrow and wide side of the α-CD cavity, respectively. Therefore, in the heterodimer of **1**, the dye moiety of **1** may thread the native CD cavity through the secondary hydroxyl group side of the native CD and the dimethylamino group may project from the primary side of the native CD.

While **4** seems to make the heterodimer complex with the similar geometry to that of **1**. As mentioned above, **4** trends to form the intermolecular complex in the higher concentration of **4**. This is due to the weak intramolecular interaction between β-CD and phenolphthalein units in **4**. In other word, the phenolphthalein unit is difficult to be included in the β-CD cavity of **4** from through the primary hydroxyl group side, but is easy to be included through the secondary side. So the phenolphthalein unit of **4** may be exposed in the bulk solution and trends to interact with another CD cavity of **4** in the higher concentration. When native β-CD presents, **4** forms the heterodimer complex with β-CD, whose geometry should be the F structure, which is similar to that for the case of **1**.

Conclusion

The supramolecular assembling of the dye-modified CDs and the native CD occurs by inclusion of the dye moiety into the native CD, accompanying color change in an aqueous solution. The position of substituent connected to CD unit in the dye moiety as well as the electronic character of the dye moiety is important for strong assembling. Furthermore the spacer between the dye moiety and the CD unit and the kind of CD also affect the formation of the assembling complex. The association constants for these systems are estimated to be in the order of 10^2 M^{-1}, which are much smaller than those of free dyes and native CDs because of the steric hindrance for bulky CD units to come close. The resulting supramolecular species is attractive because it has a geometry different from that reported before and an unoccupied cavity, which provides space to fix another guest molecule. Although a self-incorporated polymeric complex is difficult to form in this condition due to the lower concentration of the modified CD, the supramolecular homopolymer can be formed in the higher concentration of the modified CD. Furthermore, based on this, the supramolecular heteropolymer, which has different CDs linked by the noncovalent interactions, may be constructed when another host molecule is used.

JO010696U

(29) Cramer, F.; Saenger, W.; Spatz, H.-Ch. *J. Am. Chem. Soc.* **1967**, *89*, 14.
(30) Connors, K. A.; Lipari, J. M. *J. Pharm. Sci.* **1976**, *65*, 379.
(31) Connors, K. A. *Chem. Rev.* **1997**, *97*, 1325
(32) Harada, K. *Bull. Chem. Soc. Jpn.* **1976**, *49*, 1493.