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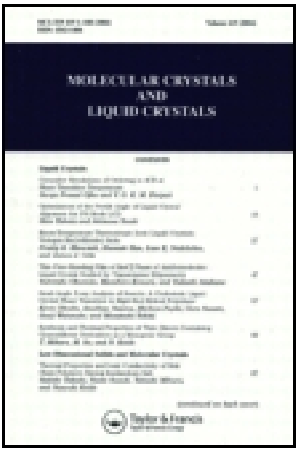

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We investigated a series of carbocyanine dye dimers formed in a cyclodextrin (CD) nanocavity by analyzing their steady-state absorption spectra in aqueous solution. As increasing CD concentrations, a blue-shifted additional peak was enhanced in several dye/CD combinations. This blue-shifted peak indicates that a 'sandwich-type' dimer is formed in CD. In order to obtain dimer-formation constants, we fitted dimer/monomer absorbance ratio to a theoretical equilibrium equation and the dimer structure was estimated on the basis of observed energy splittings in the absorption spectra. These values are significantly influenced by steric factors (poly-methine chain length, bulkiness of the end-group, CD cavity-size, etc.).

Keywords Carbocyanine; cyclodextrin; inclusion complex formation; sandwich-type dimer

1. Introduction

Understanding and development of molecular recognition involving cyclodextrins (CDs) is one of the major topics for supramolecular host/guest chemistry [1]. CDs are a series of cyclic oligomers consisting of six, seven, or eight D-glucopyranose units. CDs are shaped like a truncated cone with a relatively hydrophobic cavity. Due to their unique structure, CDs can include a variety of organic, inorganic, and biological molecules as a guest. For example, those of long alkyl chains, aromatic groups, fullerenes, and prostaglandin derivatives, the latter of which are typical physiological activity substances, and linear macromolecules are investigated based on their host/guest interaction [2–4]. CDs are also widely used in the field of food industry, cosmetics, pharmacy, and architectural material in order to improve solubility, stability, and the bioavailability of drugs [5,6]. Many studies on CD complexes using spectroscopic method also have been reported. The aim of these

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studies is to understand and control the photophysical and photochemical behavior of guest molecules such as fluorescence enhancement and excimer formation [7, 8]. Additionally, CD complexation has been widely used as a scaffold for supramolecular assembly. For example, a composite of tetraphenyl porphyrin linked with β-CD has been utilized as a self-assembled energy transfer complex and highly ordered J-aggregate [9–11].

Cyanine dye (Cy) have long been used in photography, and recently received much attention as a material for DNA labeling, laser medium and non-linear optics [12, 13]. Cys are a small group within a much larger class of compounds known as polymethine dyes that are characterized by the presence of a conjugated olefin terminated at each end by a heterocyclic group. Kasatani et al. have reported that the Cy dimer formation is significantly enhanced in the presence of CDs [14, 15]. Subsequently, it was shown that the sandwich-type Cy dimers stabilized inside the CD cavity by means of molecular mechanics (MM) calculations [16] and by circular dichroic measurements [17–19]. Improvements of the dye photostability due to CD complexations were also demonstrated [20]. In the present study, formation constants of several Cy_2/CD inclusion complexes were investigated.

2. Experiment

2.1 Materials

Figure 1 shows the molecular structure of carbocyanine dyes used in the present study. 1,1′,3,3,3′,3′-Hexamethylindodicarbocyanine iodide (HIDCI), 3,3′-Diethyloxadicarbocyanine iodide (DODCI) and 3,3′-Diethyloxatricarbocyanine iodide (DOTCI)

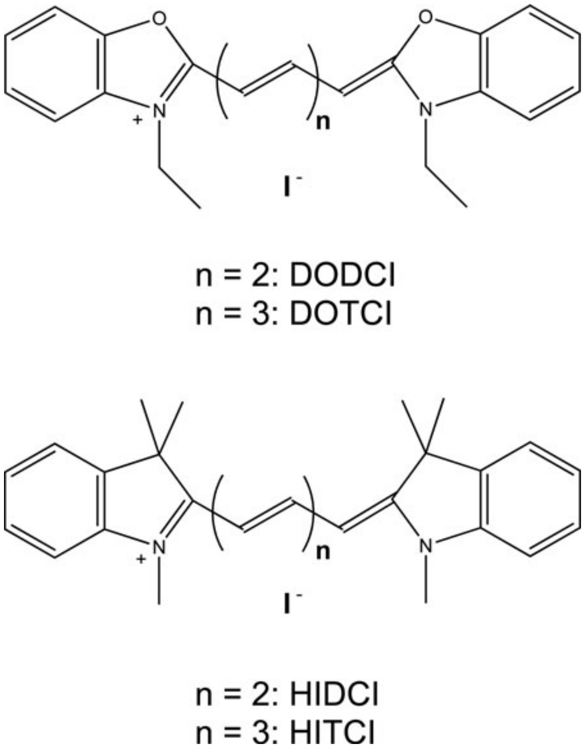

Figure 1. Chemical structure of carbocyanine-dyes.

were obtained from Acros Organics. 1,1′,3,3,3′,3′-Hexamethylindotricarbocyanine iodide (HITCI) was obtained from Exciton. β-Cyclodextrin (β-CD) and γ-cyclodextrin (γ-CD) were obtained from Kanto Kagaku. All chemicals were used as received. A Milli-Q system (Millipore, Bedford, MA) was used for purification of water.

2.2 Spectroscopic Measurements

Steady-state absorption spectra at room temperature were measured on a Hitachi spectrophotometer U-3010. The spectroscopic measurements of aqueous solutions containing different concentrations of CDs were carried out, keeping the Cy's concentration at $\approx 10^{-5}$ M. CD concentrations were varied from 0 to 3.0×10^{-2} M.

3. Results

3.1 Cy_2/CD Formation Constants

Figure 2 shows the CD-concentration dependence of absorption spectra of DODCI/γ-CD in aqueous solution. As increasing CD concentrations, the intensity of absorption at 576 nm associated with the monomeric Cy was decreased consecutively, while the intensity of absorption at 532 nm was increased. This new peak at 532 nm was previously assigned to the Cy dimer by Kasatani et al. [14, 15]. Similar spectral changes due to the dimer formation were also observed for DODCI/β-CD, but enhancement was less than that observed for γ-CD. For other host/guest combinations, CDs also promoted dimerization except for HIDCI/CDs systems. In the HIDCI/CDs systems, the shape of absorption spectra was hardly changed by the addition of CDs.

In order to compare the ability of dimer formation quantitatively, we plotted dimer/monomer band ratios vs. CD concentrations, and fitted to a theoretical equilibrium equation. As for the stoichiometry of the inclusion complex, we followed the literature which reported a Cy_2-CD type dimer formation in aqueous solution [14, 15]. The inclusion

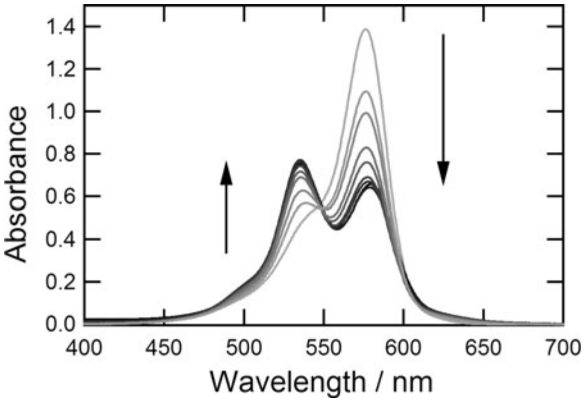

Figure 2. Absorption spectra of DODCI/γ-CD in water. CD concentration was changed from 0 to 3.0×10^{-2} M, keeping the concentration of DODCI at 1.3×10^{-5} M.

reactions are as follows

$$Cy + CD \overset{K_1}{\rightleftarrows} Cy\text{-}CD, \tag{1}$$

$$Cy - CD + Cy \overset{K_2}{\rightleftarrows} Cy_2\text{-}CD, \tag{2}$$

$$2Cy + CD \overset{K_1K_2}{\rightleftarrows} Cy_2\text{-}CD, \tag{3}$$

where K_1K_2 is the equilibrium constant for the formation of 2:1 inclusion complex. The initial concentration of Cy and CD are represented by

$$[Cy]_0 = [Cy] + [Cy - CD] + 2[Cy_2 - CD], \tag{4}$$

$$[CD]_0 = [CD] + [Cy - CD] + [Cy_2 - CD] \approx [CD], \tag{5}$$

$[Cy\text{-}CD]$ and $[Cy_2\text{-}CD]$ can be assumed to be very small compared to $[CD]$, since $[CD]_0$ is sufficiently larger than $[Cy]_0$. In this system, the absorbance of inclusion complexes is given as

$$A_m = (\varepsilon_{Cy}^{monomer}[Cy] + \varepsilon_{Cy}^{monomer}K_1[Cy][CD] + \varepsilon_{Cy_2-CD}^{monomer}K_1K_2[Cy]^2[CD])L, \tag{6}$$

$$A_d = (\varepsilon_{Cy}^{dimer}[Cy] + \varepsilon_{Cy}^{dimer}K_1[Cy][CD] + \varepsilon_{Cy_2-CD}^{dimer}K_1K_2[Cy]^2[CD])L, \tag{7}$$

where A_m and A_d are the absorbance at the monomer and dimer bands, respectively. ε represents a molar extinction cofficient and L a light path length. The ε_{Cy}^{dimer} value was obtained from the absorbance of CD-free Cy solution, where only the monomeric specie should exist in the system at the dimer peak position. The molar extinction coefficients were assumed to be equal for $[Cy]$ and $[Cy\text{-}CD]$ species, namely, $\varepsilon_{Cy-CD}^{monomer} = \varepsilon_{Cy}^{monomer}$ or $\varepsilon_{Cy-CD}^{dimer} = \varepsilon_{Cy}^{dimer}$. Taking K_1, K_2, $\varepsilon_{Cy_2-CD}^{monomer}$, $\varepsilon_{Cy_2-CD}^{dimer}$ as adjustable parameters, we performed a least-square fitting for A_d/A_m vs. $[CD]$ curves. Figure 3 shows the best-fit curves for A_d/A_m, and the best-fit parameters K_1, K_2, K_1K_2 are given in Table 1. K_1K_2 for DODCI/β-CD system was determined to be 1.7×10^7 mol^{-2} dm^6. For comparison, the equilibrium

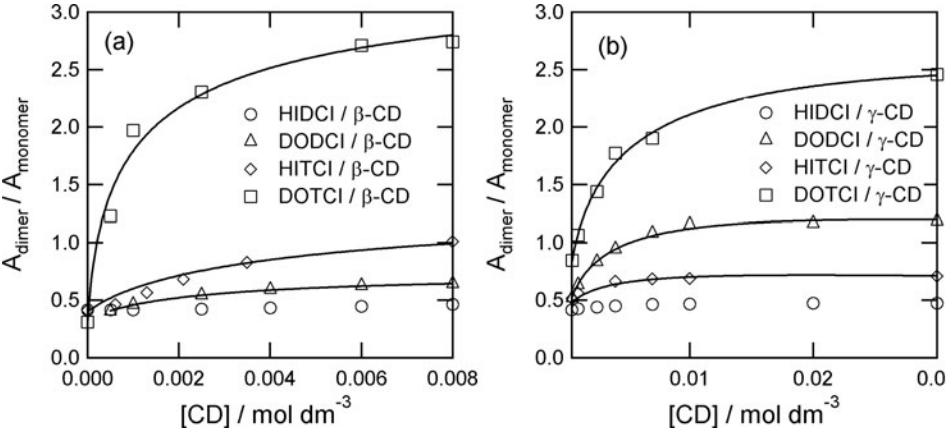

Figure 3. The best-fit simulation for the ratio of absorbance between the dimer band and the monomer band as a function of CD concentration. (a) Cy/β-CD systems, (b) Cy/γ-CD systems. In HIDCI/both CDs systems, curve fittings were not carried out due to the inertness of CD addition.

Table 1. Best fit values of equilibrium constants calculated from simulation for each system

	β-CD			γ-CD		
	K_1	K_2	K_1K_2	K_1	K_2	K_1K_2
HIDCI	—	—	—	—	—	—
DODCI	41	4.1×10^5	1.7×10^7	37	9.5×10^5	3.5×10^7
HITCI	30	9.0×10^5	2.7×10^7	50	3.6×10^5	1.8×10^7
DOTCI	18	5.4×10^6	9.7×10^7	16	5.5×10^6	8.8×10^7

constant for the same system have been reported to be 3.2×10^7 and 1.3×10^7 mol^{-2} dm^6 at 20 and 30°C, respectively, by using singular value decomposition analysis [18]. The equilibrium constant obtained in present study reasonably agreed with the literature values, since our measurements were carried out at 25°C.

3.2 Calculations of Dipole-dipole Interaction Energy for Dimers

According to the molecular exciton model, dimer formation leads to an energy splitting of the excited states [21]. Figure 4 shows a schematic energy diagram for monomer and dimer states. When the two chromophores are stacked with parallel transition dipoles, optical transition is only allowed between the ground state and the higher split level. From the peak splitting in the absorption spectra, the dipole-dipole interaction energy (β) between Cy monomers was obtained as $2\beta = 2390 \sim 3524$ cm^{-1}. In order to discuss the structure of dimers, the observed splitting was analyzed by a point dipole-dipole interaction model. The dipole-dipole interaction energy (2β) between two chromophores is given by the relation [21]

$$2\beta = \frac{1}{2\pi\varepsilon_0\varepsilon}\frac{e^2|M|^2}{R^3}\cos\theta_{12}, \tag{8}$$

where e is the elementary charge, M a transition dipole moment, R a distance between the centers of chromophores, θ_{12} an angle between the transition dipoles of two chromophores, ε_0 and ε are the dielectric constants of vacuum and inside cyclodextrin nanocavities, respectively. The value of $\varepsilon = 5.0$ was employed from literature [4, 22], and $\theta_{12} = 0$ was assumed because only the blue-shifted peak, which is attributable to the parallel dimer, was

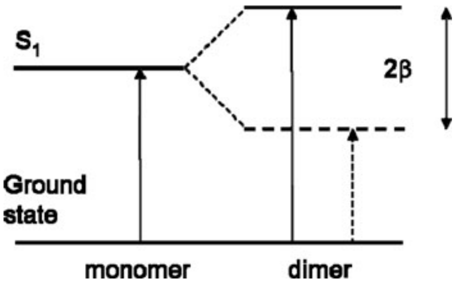

Figure 4. Energy diagram of monomer and dimer states.

Table 2. Interplanar distance estimated on the basis of the observed energy splitting*

	$2\beta/\mathrm{cm}^{-1}$	f	M/m	R/A
DODCI/β-CD	2800	0.76 ± 0.12	$(2.0 \pm 0.15) \times 10^{-10}$	4.1 ± 0.2
DODCI/γ-CD	2626			4.2 ± 0.2
HITCI/β-CD	2588	1.1 ± 0.06	$(2.7 \pm 0.08) \times 10^{-10}$	5.1 ± 0.1
HITCI/γ-CD	2390			5.2 ± 0.1
DOTCI/β-CD	3370	0.41 ± 0.03	$(1.6 \pm 0.05) \times 10^{-10}$	3.3 ± 0.1
DOTCI/γ-CD	3128			3.4 ± 0.1

*The interplanar distance of the dimer R can be estimated from two adjustable parameters θ_{12} and ε. The angle between the transition dipoles of two chromophores is assumed as $\theta_{12} = 0$ (attribute to the parallel dimer). The dielectric constants of inside cyclodextrin nanocavities is assumed as $\varepsilon = 5$ (available in literature [19]).

observed. The transition moment is expressed as

$$M = \sqrt{\frac{3hf}{8\pi^2 m_e c\tilde{\nu}}}, \tag{9}$$

where h is the Planck's constant, f an oscillator strength, m_e the electron mass, c the light speed, and $\tilde{\nu}$ a wavenumber for a S_0-S_1 transition. The oscillator strength is given by

$$f = 4.32 \times 10^{-9} \times \frac{1}{n} \times \int \varepsilon(\tilde{\nu})d\nu, \tag{10}$$

where n is refractive index of solvent, $\varepsilon(\tilde{\nu})$ is a molar extinction coefficient of Cys. The values of R thus obtained are summarized in Table 2. Significant differences in R were found among each Cys. To elucidate one of the most potent configurations of Cys dimmer, we carried out geometrical optimization on the basis of Hartree Fock (HF)/STO-3G level. The calculation was performed using Gaussian 03 program package [23]. The obtained configuration was indicated in Fig. 5. The result was in good agreement with the MM calculation about Cy/CD [16]. The C_{2h} symmetry expects to be the most compact structure and the least steic repulsion on the formation of an inclusion with a CD.

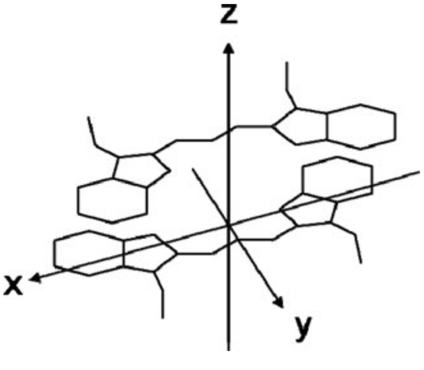

Figure 5. The most potent alignment of Cys dimer.

4. Discussion

The very low dimer formation constant of HIDCI by the CD addition may be explained by its molecular structure; the inclusion complex of HIDCI dimer with CD is considered to be unstable, because HIDCI has bulky end groups with a short poly-methine chain length, and the steric hindrance between HIDCI and CD interrupts the dimer formation. As increasing poly-methine chain, for the case of HITCI, the ability to form dimer was improved; K_1K_2 value was 2.7×10^7 mol^{-2} dm^6 for β-CD, and 1.8×10^7 mol^{-2} dm^6 for γ-CD as shown in Table 1. The elongated poly-methine chain has an enough size to retain the CD molecule, resulting in easier dimer formation. For DODCI system, both CDs enhanced dimerization because of the relatively small size of oxygen atom compared to $C(CH_3)_2$ group; K_1K_2 values were 1.7×10^7 for β-CD and 3.5×10^7 mol^{-2} dm^6 for γ-CD, respectively. Due to the steric hindrance between β-CD (smaller cavity size) and the end groups, γ-CD accelerated dimerization in comparison with β-CD. The longer chain of DOTCI diminishes the steric hindrance between CD and the end group, therefore dimer formation was easily occurred by the addition of both CDs and then their formation constants K_1K_2 were estimated very close values as 9.7×10^7 for β-CD and 8.8×10^7 mol^{-2} dm^6 for γ-CD, respectively. According these results, Cy_2/CD inclusion complex formation was strongly influenced by steric factors such as poly-methine chain length of the dye, bulkiness of the end group and CD cavity size. In addition, the systems which moderately enhanced dimerization such as DODCI/β-CD or HITCI/γ-CD, K_1 tended to be relatively large, hence contribution from a 1:1 complex is considerably large. The steric hindrance governs not only the formation constants but also the interplanar distances between Cys. For the Cy which has bulky end groups (HITCI), the distance R was increased to avoid repulsion between Cys.

5. Conclusions

The complex formation reactions between cyanine dyes and β, γ-CDs were investigated by steady-state UV-vis absorption spectra. Cyanine dye could form “sandwich-type” dimer in CD nanocavities. Dimer formation constants were calculated from the concentration change of absorption spectra in the presence of CD. Interplanar distances of the dimer were estimated on the basis of the observed energy splitting in the absorption spectra. These values are significantly influenced by steric factors (poly-methine chain length of the dyes, bulkiness of the end group, CD cavity size, etc.).

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