Excimer Formation and Induced-Fit Type of Complexation of β-Cyclodextrin Capped by Two Naphthyl Moieties

Fumio Moriwaki, Hiromi Kaneko, Akihiko Ueno,* Tetsuo Osa,*
Fumio Hamada,† and Koichi Murai†
Pharmaceutical Institute, Tohoku University, Aobayama, Sendai 980
†Department of Fuel Chemistry, Mining College, Akita University, Gakuen-cho, Tegata, Akita 010
(Received February 16, 1987)

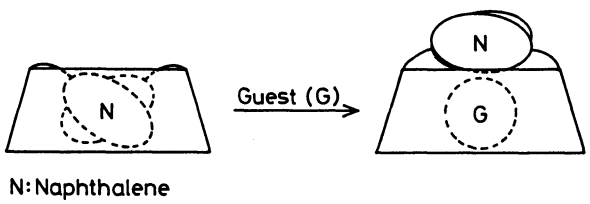
Host-guest complexation of β-Cyclodextrin bearing two naphthyl moieties (**1**) has been studied by circular dichroism and fluorescence spectroscopic methods. The circular dichroism spectrum exhibits a positive band around 225 nm while the fluorescence spectrum exhibits a predominant monomer peak with a shoulder of excimer emission. These data suggest that **1** can take two forms, one of two naphthyl moieties being included in the cavity of the predominant form (A) while both naphthyl moieties being located outside of the cavity in another form (B). With increasing concentration of guests, the dichroism intensity diminishes but the excimer intensity increases. This result indicates that **1** moves the included naphthyl moiety outward from the interior of the cavity during guest binding and then the two naphthyl moieties act as hydrophobic caps. The binding of **1** was stronger for cyclohexanol and 1-adamantanecarboxylic acid but weaker for cyclododecanol than that of the corresponding γ-cyclodextrin derivative in correspondence with size-fitting between the guests and hosts.

Cycloamyloses (Cyclodextrins, CDs) are water-soluble receptors and have been extensively studied as enzyme models, catalysts, miracle additives in pharmacy and food processing, and others.[1] The number of glucopyranose unit is designated by a Greek letter: α for six, β for seven, γ for eight, and so on. The smaller α- and β-CDs have been widely used because of their appropriate cavity sizes for forming 1:1 inclusion complexes with usual organic molecules.[1] However, recently, γ-CD has excited much attention because of the inclusion of two guest molecules in its large cavity.[2-5] As an extension of the works on the two guest accommodation by γ-CD, inclusion phenomena of some γ-CD derivatives have been studied,[6-8] and the γ-CD derivative bearing two naphthyl moieties (**2**) was found to act as a flexible host in which the two naphthyl moieties move outward from the interior of the cavity during guest binding to act as hydrophobic caps (Scheme 1).

In this report, we describe the binding behavior of β-CD bearing two naphthyl moieties **1** in which simultaneous accommodation of the two naphthyl moieties seems impossible because of its smaller cavity size. The guest-dependent excimer formation as well as the solvent-induced conformational changes of **1** will also be shown.

Results

Compound **2** was prepared by the procedure reported previously.[7b] Compound **1** was synthesized in the same manner as that of **2** via azobenzene-capped β-CD (**3**). Figure 1 shows the absorption and circular dichroism spectra of **1** in aqueous 10% ethylene glycol (EG) solutions at various concentrations of 1-adamantanecarboxylic acid (1-ACA). The solvent composition used is due to the poor solubility of **1** in pure



Scheme 1.

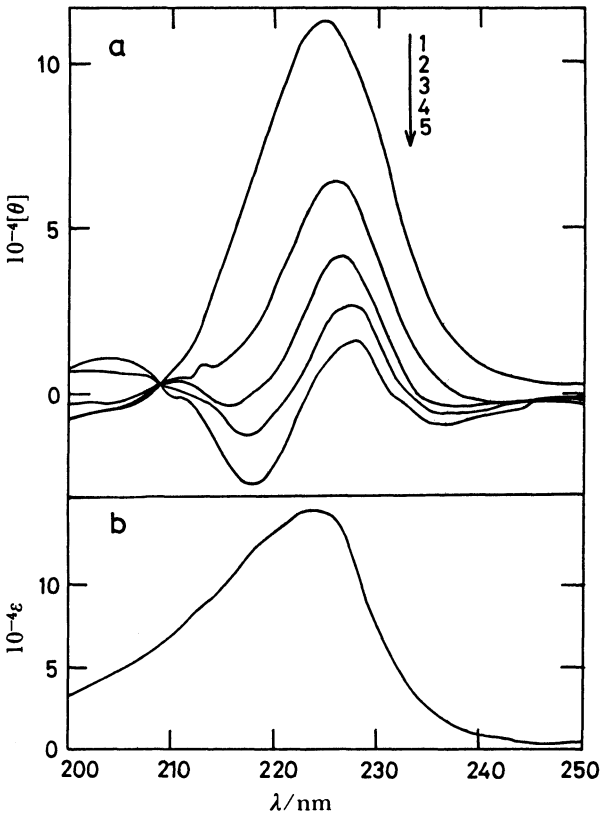
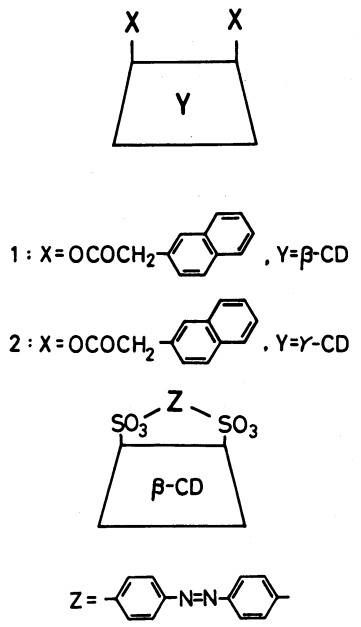


Fig. 1. Circular dichroism (a) and absorption (b) spectra of **1** in aqueous 10% EG solutions (6.5×10^{-6} mol dm^{-3}) at various 1-ACA concentrations (a, 1, 0.0; 2, 3.3×10^{-5}; 3, 6.7×10^{-5}; 4, 1.3×10^{-4}; 5, 3.0×10^{-4} mol dm^{-3}; b, 0.0 mol dm^{-3}).



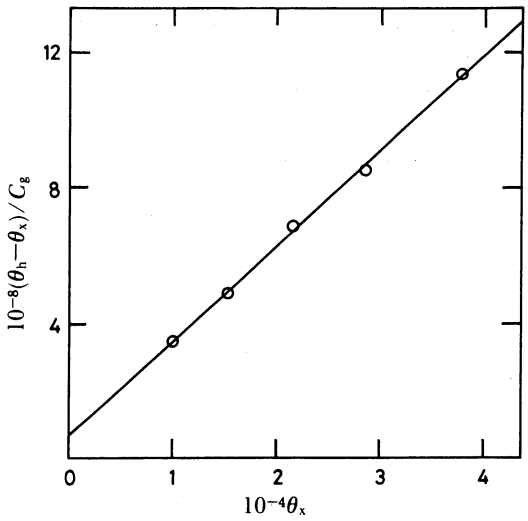


Fig. 2. The plot of $(\theta_h-\theta_x)/C_g$ as a function of θ_x in the system of **1** and 1-ACA.

water. Here, circular dichroism measurements were performed only in the naphthalene ^1B_b transition region. No reliable data in the ^1L_a transition region was obtained due to the limited solubility of **1** and the small circular dichroism ellipticity of the band. The circular dichroism spectrum in the absence of 1-ACA reveals a positive peak around 225 nm with the molar ellipticity of 110000 associated with the naphthalene ^1B_b transition. The intensity of the positive peak diminished with increasing 1-ACA concentration. When (−)-borneol and cyclohexanol were used as guest molecules, similar phenomena were observed. The guest-induced variations in the molar ellipticity were analyzed to obtain binding constants (K) of **1**, by using Eq. 1 which can be used in the presence of large excess

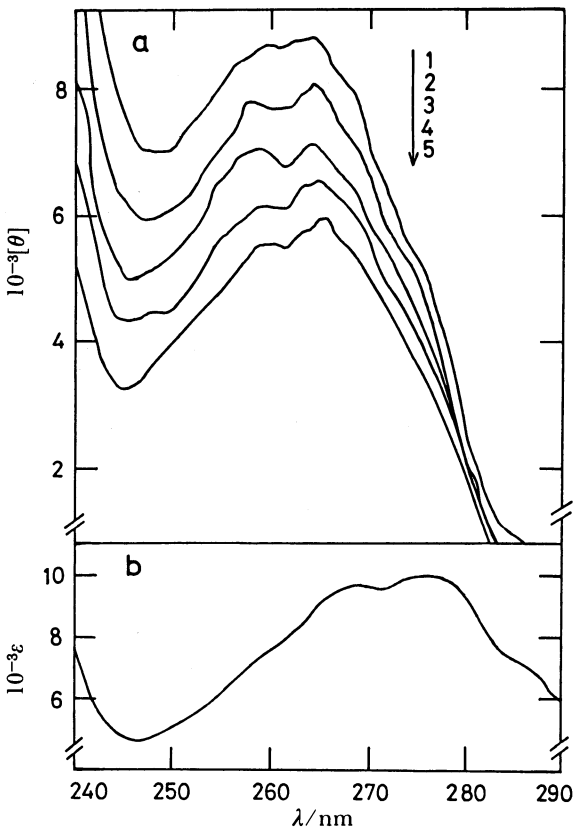


Fig. 3. Circular dichroism (a) and absorption (b) spectra of **1** in aqueous 10% DMSO solutions (6.5×10^{-5} mol dm^{-3}) at various cyclododecanol concentrations (a, 1, 0.0; 2, 3.3×10^{-5}; 3, 6.7×10^{-5}; 4, 1.3×10^{-4}; 5, 2.0×10^{-4} mol dm^{-3}; b, 0.0 mol dm^{-3}).

of guest.[9]

$$\frac{\theta_h-\theta_x}{C_g}=k\theta_x-k\theta_c \qquad (1)$$

Figure 2 shows the plot of $(\theta_h-\theta_x)/C_g$ against θ_x in the case of 1-ACA. Here, θ is molar ellipticity (the molar ellipticity at 225 nm in this study), θ_x for sample, θ_h for host alone, θ_c for complex, and C_g is total guest concentration. Cyclododecanol was also used as a guest molecule. In the case of cyclododecanol, aqueous 10% dimethyl sulfoxide (DMSO) was used as a solvent instead of aqueous 10% EG, because of the poor solubility of cyclododecanol in aqueous 10% EG. Circular dichroism measurements of the aqueous 10% DMSO solutions of **1** were performed in the naphthalene ^1L_a transition region since the measurements in the shorter wavelengths could not be achieved due to the absorption of DMSO. It is noted that the solubility of **1** in aqueous 10% DMSO was large enough to perform the circular dichroism measurements in the naphthalene ^1L_a transition region. The guest-induced variation of the molar ellipticity at 265 nm (Fig. 3) was analyzed by using the curve-fitting method because, in this case, the guest is not in large excess and Eq. 1 cannot be applicable.[7b] The binding constants of **2** for

Table 1. Binding Constants of **1** and **2** at 25 °C[a)]

Guest	Solvent	K/mol^{-1} dm^{3}[b)]	
		1	**2**
1-ACA	10% EG	28000	1000
(−)-Borneol	10% EG	1900	1800
Cyclododecanol	10% DMSO	4600	26000[c)]
Cyclohexanol	10% EG	90	32

a) Values were obtained by the plot of $(\theta_h-\theta_x)/C_g$ vs. θ_x except for the value for cyclododecanol which was obtained by the curve-fitting method. b) Errors are within ±9%. c) Reported in Ref. 7b.

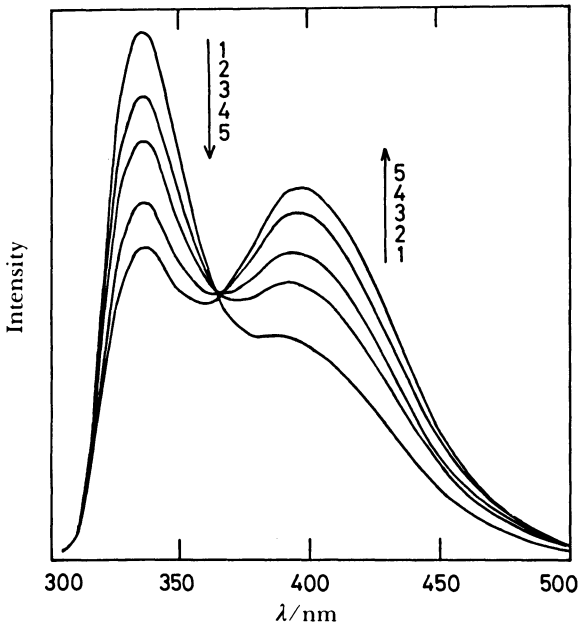


Fig. 4. Fluorescence spectra of **1** in aqueous 10% EG solutions (6.5×10^{-6} mol dm^{-3}) at various 1-ACA concentrations (1, 0.0; 2, 3.3×10^{-5}; 3, 6.7×10^{-5}; 4, 1.3×10^{-4}; 5, 2.3×10^{-4} mol dm^{-3}). Excitation wavelength is 290 nm.

1-ACA, cyclohexanol, and (−)-borneol were also obtained to be compared with those of **1** by the analysis (Eq. 1) of the circular dichroism variations at 215 nm of **2** (6.5×10^{-6} mol dm^{-3}) in aqueous 10% EG solutions. The binding constant of **2** for cyclododecanol in aqueous 10% DMSO solution was reported previously.[7b)] The obtained binding constants are listed in Table 1.

Figure 4 shows the fluorescence spectra of **1** in aqueous 10% EG solutions at various 1-ACA concentrations. The spectrum in the absence of 1-ACA exhibits a predominant monomer fluorescence around 336 nm and a shoulder of excimer emission around 394 nm. With increasing 1-ACA concentration, the intensity of the monomer fluorescence decreases while that of the excimer emission increases. When (−)-borneol and cyclohexanol were used in place of 1-ACA as guests, similar phenomena were observed.

It was found that EG content in the solutions of **1** markedly influences the circular dichroism and fluorescence patterns. The circular dichroism intensity of the positive peak around 225 nm decreased with increasing EG content. The EG-dependency of the fluorescence pattern was more complicated, that is, the intensity of the monomer fluorescence increases monotonously while the intensity of the excimer emission reaches a maximum around 50% of EG and then decreases with increasing EG content (Fig. 5).

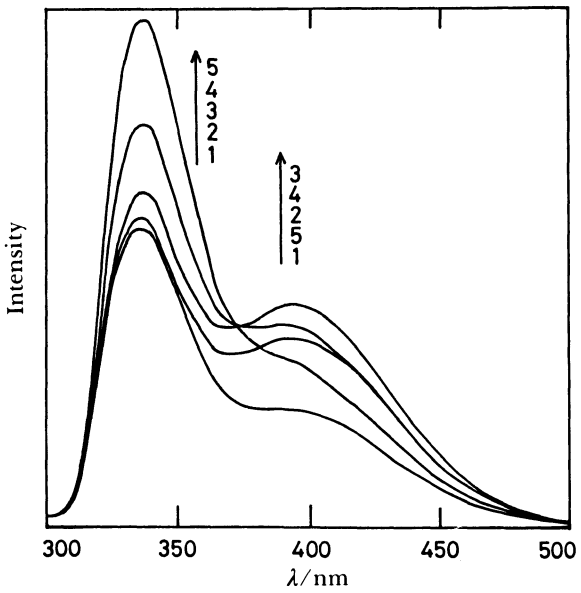
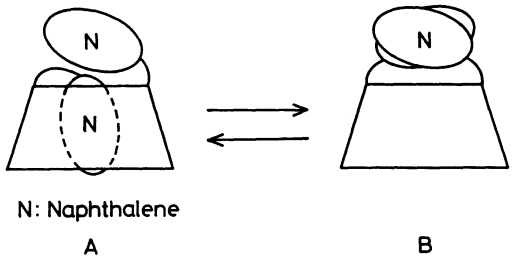


Fig. 5. Fluorescence spectra of **1** (5.4×10^{-6} mol dm^{-3}) at various EG content (1, 10; 2, 30; 3, 50; 4, 80; 5, 100%).

Discussion

The synthesis of **1** was performed via β-CD capped by azobenzene-4,4′-disulfonate moiety (**3**). Therefore, the positions of the two naphthyl moieties are those of primary hydroxyls sulfonated by azobenzene-4,4′-disulfonyl dichloride. When glucose units of CD ring are denoted by A, B, C, D, etc., in the order, primary hydroxyl groups of A and D glucose units of β-CD were reported to be selectively sulfonated by stilbene-4,4′-disulfonyl dichloride.[10)] Similar selectivity may be expected with azobenzene-4,4′-disulfonyl dichloride. The determination of the modified positions of **3** was performed by the reversed-phase high-performance liquid chromatography (HPLC). The diazido-β-CD, which was prepared by the reaction of **3** with sodium azide, was assigned to the AD-isomer by comparing its retention time with those of the AB-, AC-, AD-diazido-β-CD.[11)] Consequently, the modified positions of **1** and **3** are A and D of primary hydroxyls of β-CD.

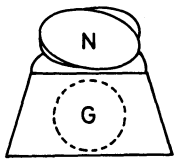
The circular dichroism and fluorescence spectra of **1** may be used for determing the location of the two naphthyl moieties. By using the spectroscopic data, we first discuss the structural features of **1** in the absence of any guest. Considering the fact that **1** cannot include the two naphthyl moieties simultaneously



Scheme 2.

because of its small cavity size, the positive peak observed in the region of ^1B_b transition, which is longitudinally polarized, may arise from the form A (Scheme 2), in which one of the two naphthyl moieties is included axially.[12] Since face-to-face interaction between the two naphthyl moieties is not allowed for such a geometry, it is obvious that excimer formation should not occur in the A form. However, excimer emission was observed as shoulder of the main peak of monomer fluorescence; therefore **1** can be either in A or B form as shown in Scheme 2. In the B form, the two naphthyl moieties are both out of the CD cavity, interacting with each other.

The guest-induced decreases in the molar ellipticity suggest that **1** moves one of its pendant naphthyl moieties outward from the interior of the cavity during guest binding. The guest-induced decreases in the monomer fluorescence and increases in the excimer emission suggest that the two naphthyl moieties are close in the complexes. The two naphthyl moieties are likely to contact with the included guest molecule as flexible caps, as illustrated below. It is noted that the



excimer formation in the complex may be compared with the reported base-base interactions in the complexes of β-CD derivatives, which have two nucleobases.[13] The binding constants of **1** and **2** are listed in Table 1. It is noted that the guest-induced circular dichroism variations of **2** as well as those of **1** could be analyzed based on a simple 1 : 1 stoichiometry.[7b] The binding constants of **1** for 1-ACA and cyclohexanol are larger than those of **2**. These results suggest that **1** is a better host for these guests than **2**, in accordance with the fact that the cavity size of **2** is too large to include these guests tightly. The binding constants of **1** and **2** for (−)-borneol are similar in spite of the difference of their cavity sizes. The binding constant of **1** for cyclododecanol is smaller than that of **2**. This result may arise from the fact that **2** has an appropriate cavity to include cyclododecanol while **1** has the cavity too small to include the guest completely. The examination of the Corey-Pauling-Koltun models supports this argument. Consequently, γ-CD derivative **2** seems to exhibit the better binding ability than β-CD derivative **1**, for large guests such as cyclododecanol. This is in contrast with the fact that β-CD derivative **1** is better host than **2** for small guests.

Figure 6 shows the plots of excimer-monomer ratio and circular dichroism intensity at 225 nm against EG content. The solvent-induced decrease in the circular dichroism intensity suggests that EG tends to convert the intramolecular complex form of A into the relaxed form of B (Scheme 2). It is frequently seen that fluorescence of aromatic compounds is solvent-dependent, usually with greater intensity in apolar solvents than in polar solvents. In this case, the monomer fluorescence seems basically to be stronger in EG-rich solutions than in EG-poor solutions. However, the complicated result that there is a maximum ratio of excimer emission around 50% of EG requires an additional explanation. One possible explanation is that the face-to-face interaction needed for excimer formation is attained only in one of three forms of **1** (B in Scheme 3). It is noted that 50% EG is the solvent in

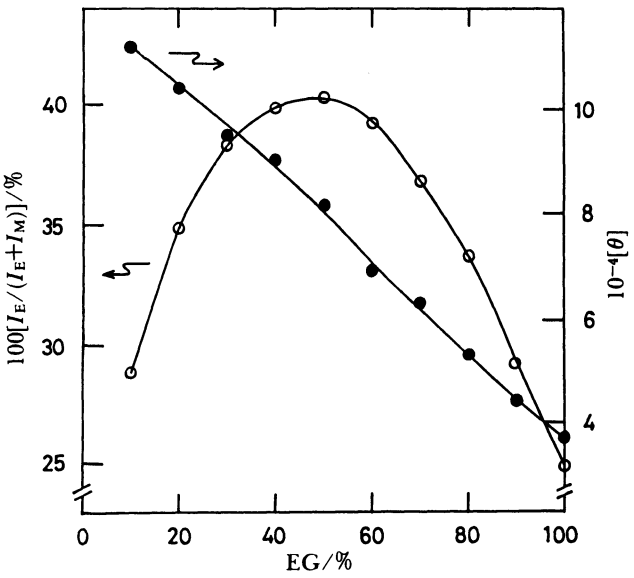
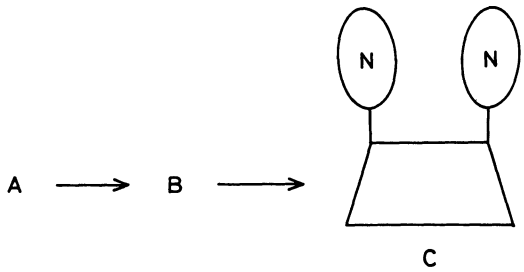


Fig. 6. Plots of excimer-monomer fluorescence ratio (I_M and I_E are intensities at 336 and 394 nm, respectively) and the molar ellipticity at 225 nm of **1** (5.4×10^{-6} mol dm^{-3}) as a function of EG content.



Scheme 3.

which hydrophobic interaction is still important; so two naphthyl moieties tend to interact with each other by the hydrophobic driving force. In the solutions with higher EG contents, the driving force becomes weaker and the two naphthyl moieties are likely to be located apart at the opposite sides of β-CD rim (C in Scheme 3). In the form of A, which mainly exists in the solutions with lower EG contents, excimer formation is stereochemically impossible. Consequently, A converts to C via B with increasing EG content.

Experimental

Materials. The following commercially available reagents (guaranteed grade) were used without further purification, β-CD, 1-ACA, (−)-borneol, cyclododecanol, cyclohexanol, and EG. DMSO was Dotite-spectrosol grade. Azobenzene-4,4′-disulfonyl dichloride and bis(2-naphthylacetyl)-γ-CD (**2**) were prepared by the same methods previously reported.[7b] Isomers of diazido-β-CD were prepared as the standard samples by the method of Fujita et al.[11]

Measurements. HPLC was performed analytically on a JASCO 800 series with a TSKgel ODS 120A column (4.6 ×250 mm, 5 μm, Toyo Soda, Japan). A linear gradient elution of 10% aqueous CH_3CN–25% aqueous CH_3CN was applied, and the diazido-β-CD was detected by monitoring the UV absorption at 210 nm. The circular dichroism, UV and fluorescence spectra were measured at 25 °C using a JASCO J-400X spectrodichrometer, a Shimadzu UV-250 spectrophotometer and a Shimadzu RF-500 spectrofluorophotometer, respectively. The circular dichroism intensities were expressed as molar ellipticity (in degree cm^2 $dmol^{-1}$) on the basis of the total concentration of **1** or **2**.

***trans*-Azobenzene-4,4′-disulfonyl-β-CD (3).** To a stirred solution of dry β-CD (4.0 g, 3.5 mmol) in dry pyridine (100 ml), azobenzene-4,4′-disulfonyl dichloride (1.3 g, 4.1 mmol) was added, and then heated at 60 °C for 1 h. After cooling the reaction mixture, pyridine was removed by evaporation under reduced pressure. Water addition to the residue followed by evaporation was repeated several times until no pyridine odor was detected. The resultant oily residue was dissolved in a small amount of water and subjected to Sephadex G-15 column chromatography. Recrystallization from methanol afforded the product (0.54 g, 10%): R_f=0.33 (5:1 CH_3CN-H_2O); Found: C, 43.47; H, 5.54; N, 1.97; S, 4.47%. Calcd for $C_{54}H_{76}N_2O_{39}S_2 \cdot 3H_2O$: C, 43.37; H, 5.53; N, 1.87; S, 4.29%.

Bis(2-naphthylacetyl)-β-CD (1). A mixture of **3** (0.54 g, 0.36 mmol), sodium 2-naphthyl acetate (0.31 g, 1.5 mmol) and DMSO (10 ml) was stirred at 80 °C for 6 h. After cooling, the reaction mixture was poured into 500 ml acetone. The precipitates were collected by filtration and subjected to column chromatography on silica gel (8:1 CH_3CN-H_2O). Recrystallization from water gave the desired product (0.15 g, 26%): R_f=0.50 (5:1 CH_3CN-H_2O). ^1H NMR (DMSO-d_6, 25 °C) δ=3.2—4.0 (42H, m, CD protons other than C_1H and OH), 4.2—4.6 (9H, m, O_6H and CH_2Ar), 4.7—4.9 (7H, m, C_1H), 5.6—5.9 (14H, m, O_2H and O_3H), 7.4—7.9 (14H, m, ArH); UV (9:1 H_2O-EG) (ε) 224 nm (150000); IR (KBr) 1720 cm^{-1} (CO). Found: C, 48.81; H, 6.01%. Calcd for $C_{66}H_{86}O_{37} \cdot 8H_2O$: C, 49.07; H, 6.36%.

This work was supported by Grant-in-Aid (Nos. 61470152 and 61550585) from the Ministry of Education, Science and Culture.

References

1) M. L. Bender and M. Komiyama, "Cyclodextrin Chemistry," Springer-Verlag (1978).

2) A. Ueno, K. Takahashi, and T. Osa, *J. Chem. Soc., Chem. Commun.*, **1980**, 921; N. Kobayashi, R. Saito, Y. Hino, A. Ueno, and T. Osa, *ibid.*, **1982**, 706; N. Kobayashi, R. Saito, Y. Hino, A. Ueno, and T. Osa, *J. Chem. Soc., Perkin Trans. 2*, **1983**, 1031; A. Harada and S. Nozakura, *Polym. Bull.*, **8**, 141 (1982); T. Yorozu, M. Hoshino, and M. Imamura, *J. Phys. Chem.*, **86**, 4426 (1982); K. Kano, I. Takenoshita, and T. Ogawa, *Chem. Lett.*, **1982**, 321; J. Emert, D. Kodali, and R. Catena, *J. Chem. Soc., Chem. Commun.*, **1981**, 758; N. J. Turro, T. Okubo, and G. C. Weed, *Photochem. Photobiol.*, **35**, 325 (1982); N. Kobayashi, Y. Hino, A. Ueno, and T. Osa, *Bull. Chem. Soc. Jpn.*, **56**, 1849 (1983); R. A. Yellin and D. F. Eaton, *J. Phys. Chem.*, **87**, 5051 (1983); M. Itoh and Y. Fujiwara, *Bull. Chem. Soc. Jpn.*, **57**, 2261 (1984).

3) N. Kobayashi, A. Ueno, and T. Osa, *J. Chem. Soc., Chem. Commun.*, **1981**, 340; N. Kobayashi, R. Saito, A. Ueno, and T. Osa, *Makromol. Chem.*, **184**, 837 (1983).

4) A. Ueno, K. Takahashi, Y. Hino, and T. Osa, *J. Chem. Soc., Chem. Commun.*, **1981**, 194; K. Kano, I. Takenoshita, and T. Ogawa, *J. Phys. Chem.*, **86**, 1833 (1982); K. Takamura, S. Inoue, and F. Kusu, *Chem. Lett*, **1983**, 233; H. Hirai, N. Toshima, and S. Uenoyama, *Bull. Chem. Soc. Jpn.*, **58**, 1156 (1985).

5) T. Tamaki, *Chem. Lett.*, **1984**, 53.

6) A. Ueno, Y. Tomita, and T. Osa, *J. Chem. Soc., Chem. Commun.*, **1983**, 976; A. Ueno, Y. Tomita, and T. Osa, *Tetrahedron Lett.*, **1983**, 5245; A. Ueno, Y. Tomita, and T. Osa, *Chem. Lett.*, **1983**, 1635; A. Ueno, F. Moriwaki, Y. Tomita, and T. Osa, *ibid.*, **1985**, 493.

7) a) A. Ueno, F. Moriwaki, T. Osa, F. Hamada, and K. Murai, *Tetrahedron Lett.*, **26**, 3339 (1985); b) A. Ueno, F. Moriwaki, T. Osa, F. Hamada, and K. Murai, *Bull. Chem. Soc. Jpn.*, **59**, 465 (1986).

8) F. Moriwaki, A. Ueno, T. Osa, F. Hamada, and K. Murai, *Chem. Lett.*, **1986**, 1865.

9) M. P. Pack, R. R. Hendrixson, R. A. Palmer, and R. G. Ghirardelli, *J. Am. Chem. Soc.*, **98**, 7830 (1976).

10) I. Tabushi, K. Yamamura, and T. Nabeshima, *J. Am. Chem. Soc.*, **106**, 5267 (1984).

11) K. Fujita, H. Yamamura, and T. Imoto, *J. Org. Chem.*, **50**, 4393 (1985).

12) K. Harata and H. Uedaira, *Bull. Chem. Soc. Jpn.*, **48**, 375 (1975).

13) K. Nagai, K. Hayakawa, S. Ukai, and K. Kanematsu, *J. Org. Chem.*, **51**, 3931 (1986).