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EXCIMER FORMATION IN INCLUSION COMPLEXES OF MODIFIED CYCLODEXTRINS

Akihiko Ueno,* Fumio Moriwaki and Tetsuo Osa*

Pharmaceutical Institute, Tohoku University, Aobayama, Sendai 980, Japan

Fumio Hamada and Koichi Murai

Department of Fuel Chemistry, Mining College, Akita University,
Gakuen-cho, Tegata, Akita 010, Japan

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Abstract - A β-cyclodextrin derivative, which possesses a polyether chain with a naphthyl moiety at its end, shows excimer emission in its concentrated solutions. The excimer was suggested to be formed between the two naphthyl moieties included in the long cylindrical cavity of the cyclodextrin dimer.

Cyclodextrins (CDs) are cyclic oligomers of D-glucose and named as α, β and γ for hexamer, heptamer and octamer, respectively. They form inclusion complexes with various types of organic molecules in aqueous solution and may be regarded as artificial receptors. The smaller α- and β-CDs have been widely used because of their appropriate cavity sizes for forming 1:1 complexes with many organic molecules.[1] However, γ-CD, which has a larger cavity size, had not been used frequently before its unique ability of including two guest molecules was found.[2] This inclusion property of γ-CD implies that it can be used as a molecular flask in which two guest molecules can meet and react, and actually formation of charge transfer complexes[3] and excimers[2,4-9] has been shown to be promoted by γ-CD. Including the use of derivatives of γ-CD, various γ-CD systems, in which two aromatic rings form excimers in the CD cavity, are shown in Figure 1, where A and B are complexes of native γ-CD while C and D are complexes of modified γ-CDs. Naphthalene as an aromatic nucleus has been shown to form excimers in such systems as A,[2] B,[4] C[5] and D.[6]

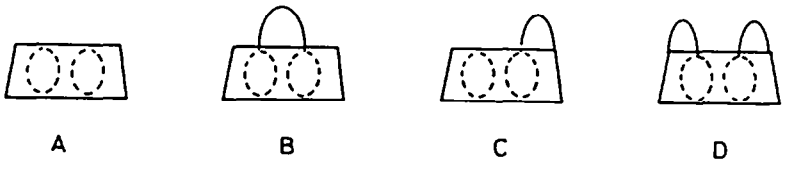
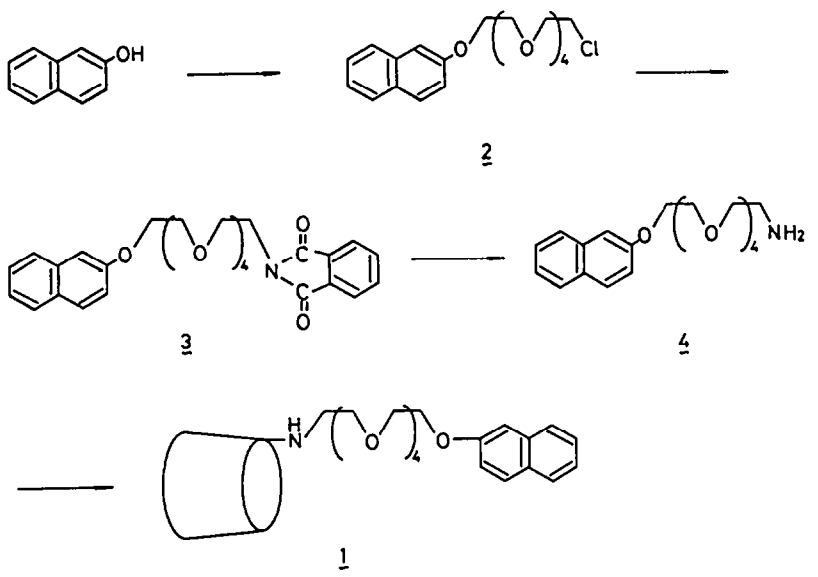


Figure 1 - Various γ-CD systems in which two aromatic rings form excimers.



Scheme 1

Anthracene, which is slightly larger than naphthalene, has been shown to form excimers in a system of D[7]. In the case of pyrene, which is much larger than naphthalene, some inconsistent data supporting A or a dimer of 1:1 host-guest complex have been reported.[8,9] Although β-CD cavity is too small to accommodate two molecules of such arenes, excimer formation of naphthalene and anthracene has been shown to be facilitated by β-CD.[10,11] The excimer formation was suggested to occur in 2:2 host-guest complexes. The observation tempted us to examine association behavior of β-CD derivatives as a clue to construct new types of receptors with a long cylindrical cavity. The present study deals with association of a β-CD derivative bearing a long chain with a naphthyl moiety at its end (**1**).

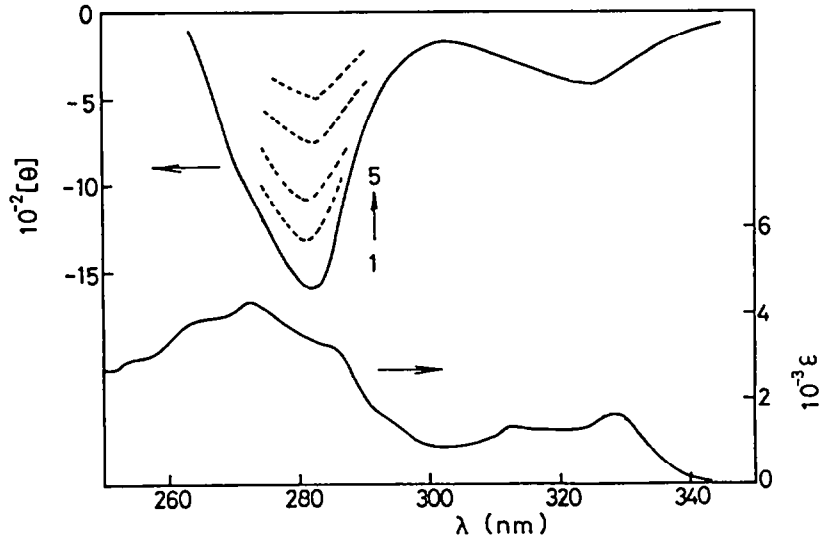


Figure 2 - Circular dichroism (top, cyclohexanol: 1, 0; 2, 0.0192; 3, 0.0383; 4, 0.0762; 5, 0.133 M) and absorption (bottom) spectra of 1 in water (0.157 mM).

RESULTS AND DISCUSSION

The β-CD derivative **1** was prepared as shown in Scheme 1. Since 6-O-deoxy-6-iodo-β-CD, which was prepared from 6-O-tosyl-β-CD,[12] was used for the final step, the polyether chain was attached to 6-C site of β-CD. It means that the narrower mouth of β-CD was modified by the polyether chain. Figure 2 shows circular dichroism and absorption spectra of **1** in water. The circular dichroism spectrum of **1** exhibits troughs at 283 nm and 325 nm in the absorption regions of naphthalene ^1L_a and ^1L_b transitions, respectively. The absolute intensities of the bands diminished upon addition of cyclohexanol. The analysis of the circular dichroism variations[6b] at 283 nm gave 8.4 M^{-1} as the binding constant. Cyclohexanol should be included by extruding the preinvolved naphthyl moiety from the cavity (Figure 3).

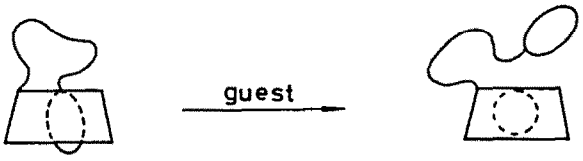


Figure 3 - Induced-fit type of complexation of **1**.

Since the host undergoes a conformational change so as to be suited for guest accommodation, an induced-fit type of complexation[13] is achieved here.

Figure 4 shows fluorescence spectra of **1** in water at its various concentrations. The spectra of **1** in the concentration range below 0.1 mM exhibit only naphthalene-like emission (normal fluorescence) around 352 nm. When the concentration of **1** became high, a new broad emission was observed at longer wavelength region, which has the same excitation spectrum as the 352-nm emission. The analysis of the fluorescence patterns revealed that the broad emission has a peak around 422 nm. The plot of the intensity at 422 nm (I_{ex}) against the sum of intensities at 422 nm and 352 nm ($I_{ex} + I_f$) is shown in Fig. 4 (B). It reveals that the 422-nm emission becomes remarkable with increasing concentration of **1**. Turro et al. observed exciplex emission of 1-α-naphthyl-3-(dimethylamino)propane in aqueous β-CD solution.[14] Such emission would be expected for tertiary amine-naphthalene systems, but is readily ruled out for **1**, which has a secondary amine. Therefore, the 422-nm emission is likely to be due to excimer produced by association of **1**. It is noted that the 352-nm emission of **1** in dilute solution (1.56×10^{-6} M) simply decreased with increasing concentration of amine-containing derivative **3** up to 1.05×10^{-2} M by the quenching effect of the amino group of **3** in the complex **4**. Since **1** has pH sensitive amine and hydroxyl groups, we examined pH effect on the fluorescence pattern of **1** by using 4 mM solutions. Figure 5 shows a plot of the intensity ratio of 422-nm emission against pH of the solutions. The profile reveals a transition around pH 12, the emission at 422 nm being remarkable below pH 11 while negligible above pH 12.5. Since the PKa of the secondary hydroxyl groups of β-CD is 12.1,[15] the transition phenomenon of the excimer emission observed around pH 12 seems to be related to the formation of anionic forms of the secondary hydroxyl groups of **1**. Although dimers and micelles of **1** are candidates which form the excimer, the possibility of the micelles, which are produced by aggregation of molecules of **1** and have naphthyl moieties in the core, β-CD units

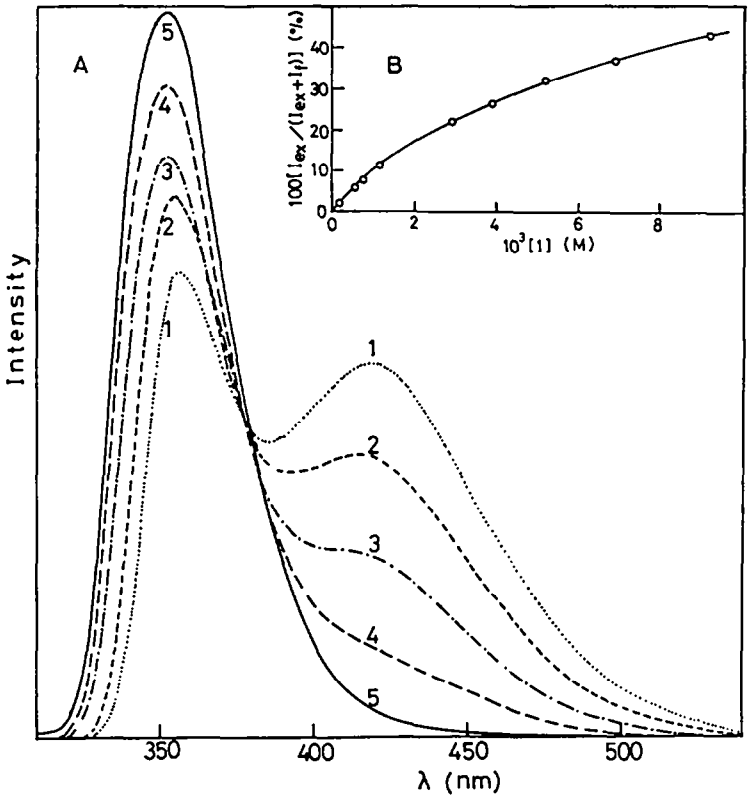


Figure 4 - Fluorescence spectra of 1 at its various concentrations (A: 1, 9.14; 2, 5.15; 3, 2.90; 4, 0.971; 5, 0.145 mM) and a plot of the ratio of 422-nm emission intensity as a function of concentration of 1 (B). The sensitivity of the instrument was changed so as to be suitable for measuring each spectrum. I_{ex} and I_f are emission intensities at 422 nm and 352 nm, respectively. The excitation wavelength was 290 nm.

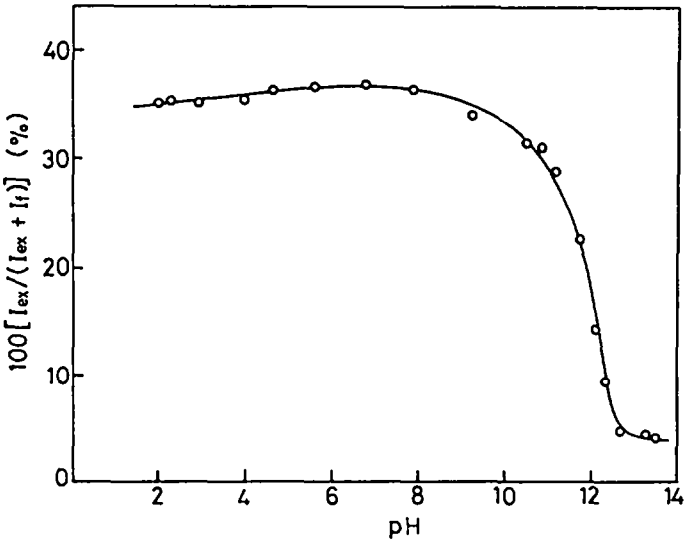
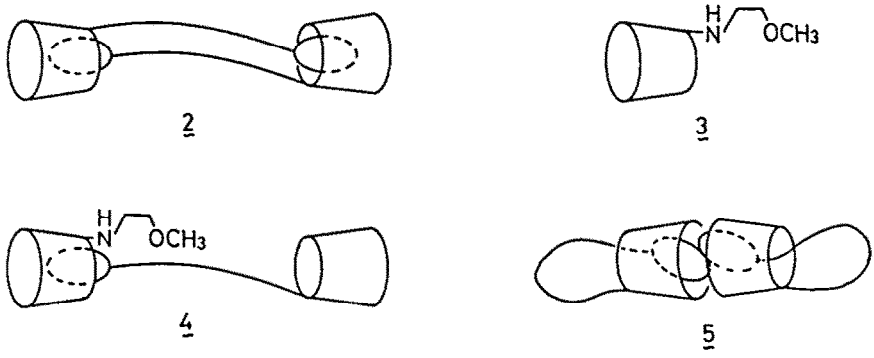


Figure 5 - A plot of the ratio of 422-nm emission intensity of 1 (4 mM) as a function of pH.

in water-micelle interface and polyether chains between both regions, is unlikely since no sign of critical micelle concentration was observed in the concentration-dependency of the excimer emission (Fig. 4 (B)). This was also confirmed by the observation of the negative circular dichroism band around 283 nm on the concentrated solution (8 mM) of **1**, which has a similar molar ellipticity to that of the diluted solution. Such circular dichroism behavior would not be observed in micelles because of the remote location of the naphthyl



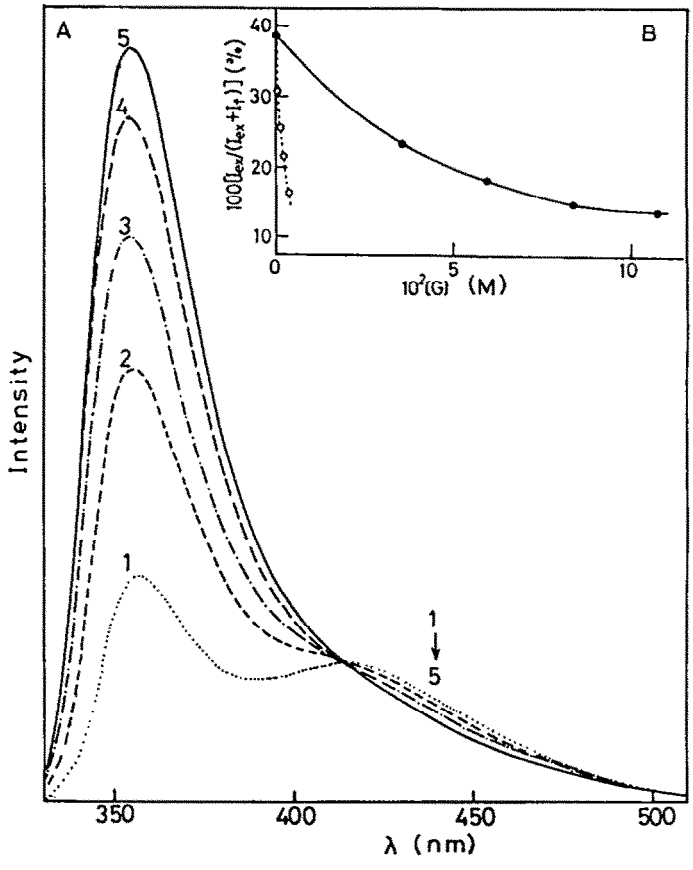


Figure 6 - Guest-induced variation of the fluorescence pattern of **1** (6 mM). A, guest: cyclohexanol (1, 0; 2, 0.036; 3, 0.060; 4, 0.084; 5, 0.108 mM). B, Guest: cyclohexanol (——), sodium adamantanecarboxylate (----).

moieties from the chiral β-CD units. Figure 6 reveals the effects of guest addition on the fluorescence pattern of **1**. Sodium adamantanecarboxylate decreased the ratio of the excimer intensity much more efficiently than cyclohexanol (Figure 6 (B)). This behavior corresponds to the fact that adamantanecarboxylate is a better guest than cyclohexanol in complexation with β-CD or its derivatives. Such parallel relationship between excimer and host-guest complex formation is surely in conflict with the micelle mechanism. All these data support the dimer form **5**, in which secondary hydroxyl sites of the CD units face each other, as the excimeric species. The dimer accommodates two naphthyl moieties in its long cylindrical cavity and may be dissociated to 1:1 host-guest complexes of **1** by guest addition depending on the affinity of the guest molecules for the cavity of **1**. The abrupt decrease in the excimer intensity ratio observed above pH 12 may be explained in terms of electronic repulsion between alkoxide anions of the secondary hydroxyls of the two β-CD units of the dimer.

CDs are known to accelerate the hydrolysis of ester substrates in alkaline solution by attack of an alkoxide anion of its secondary hydroxyls to the carbonyl of the bound ester.[15] We measured the rate of hydrolysis of p-nitrophenyl acetate at 25 °C in the solutions of pH 10.6 to check how the dimer formation influences the hydrolysis. It is noted that diethanolamine was used as a reference compound to ensure the absence of any effect of the amino moiety of **1** on the rate of ester hydrolysis. Figure 7 shows the plot of the rate of hydrolysis (k_{obsd}) as a function of concentration of β-CD or **1**. The data shows that the hydrolysis rate is slightly enhanced by **1** below 4 mM, but depressed at its higher concentrations. Such abnormal behavior was not observed in the case of β-CD, the Lineweaver-Burk analysis of the data affording 0.038 s^{-1} for k_{cat} (rate constant of intracomplex reaction) and 7.2 mM for K_m (dissociation constant). Since the enhanced rates observed with **1** at its lower concentration are smaller than the corresponding values observed with β-CD, the free **1** is a

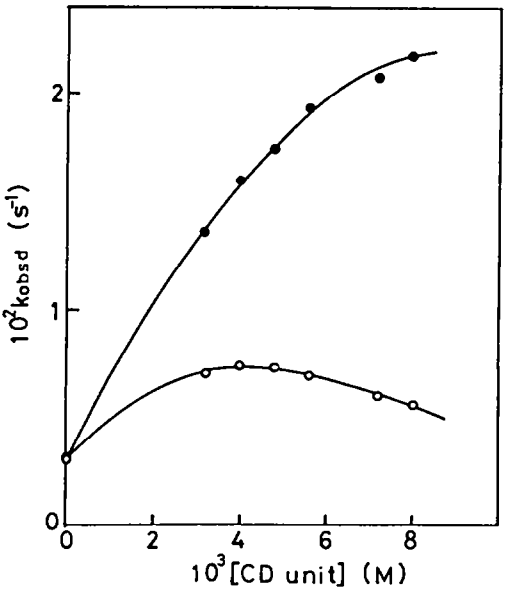


Figure 7 - Plots of the rate of hydrolysis of p-nitrophenyl acetate as a function of the concentration of **1** (○) or β-CD (●) (25°, pH 10.6 (0.02 M carbonate buffer)).

poorer catalyst than β-CD. The depressed rates observed at higher concentrations of **1** suggest that the dimer form **5** is almost inactive as a catalyst probably due to the occupation of its cavity by the covalently-linked naphthyl moieties.

No indication has been given so far about the exact location of the included two arene rings in the reported 2:2 complexes of β-CD.[10,11] Our study illustrates that **1** forms a dimer, in which the wider mouths (secondary hydroxyl site) of the β-CD units face each other, using the two covalently-linked naphthyl moieties as connectors. This geometrical feature of the complex suggests that a large cavity, in which two species can meet or one bulky species can be accommodated, is formed near the joint part of the dimeric β-CD units.

EXPERIMENTAL

Materials. β-CD (Tokyo Kasei) was recrystallized from water and dried in vacuo. 2-Naphthol, potassium phthalimide, cyclohexanol and adamantanecarboxylic acid were purchased from Tokyo Kasei Co., Ltd. Pentaethylene glycol dichloride was prepared according to the reported method;[16] b.p. 135°/0.3 mmHg (lit. b.p. 90-95°/0.08 mmHg). 6-Deoxy-6-iodo-β-CD was prepared by reaction of 6-O-tosyl-β-CD[12] with potassium iodide in DMF at 80°. The crude product was recrystallized from the mixed solvent of n-butanol, ethanol and water (5:4:3 by volume).

Measurements. Circular dichroism spectra were measured at 25° on a JASCO J-400X spectrodichrometer. Cells with 10 mm and 0.2 mm pathlengths were used. Fluorescence spectra were measured at 25° on a Shimadzu RF-500 spectrofluorometer. The excitation wavelength was 290 nm. The hydrolysis of p-nitrophenyl acetate was performed with a Shimadzu UV-360 spectrophotometer. Reaction temperature was kept at 25 ± 0.1° by using a Haake water circulation instrument. A run was initiated by injecting a soln of substrate in acetonitrile (3 μl) into the catalyst soln (0.9 ml, pH 10.6 (0.02 M carbonate buffer)). The absorbance at 400 nm of p-nitrophenol was monitored as a function of time.

14-(2-Naphthoxy)-3,6,9,12-(tetraoxa)tetradeca-1-chloride (**2**). A mixture of 31 g (0.113 mol) of pentaethylene glycol dichloride, 0.81 g (0.075 mol) of 2-naphthol and 75 ml of n-BuOH was stirred at 130°. To this soln was added 4.3 g (0.108 mol) of NaOH in 20 ml of water over a period of 2.5 h and the soln was allowed to react for another 1 h. After evaporation of the solvent, the residue was diluted with water and then extracted with $CHCl_3$. The organic layer was washed with water, dried over Na_2SO_4 and concentrated under reduced pressure to give colorless oil, which was distilled to afford 14.18 g (32.7 %) of pure **2**. b.p. 240-242°; IR (film) ν 2870, 1650, 1590, 1120 cm^{-1}; ^{1}H-NMR (CCl_4) δ 3.50-4.44 (m, 20H), 7.20-7.72 (m, 7H, Ar). (Found: C, 61.92; H, 7.21. Calc for $C_{20}H_{27}O_5Cl$: C, 62.20; H, 7.11%.)

14-(2-Naphthoxy)-3,6,9,12-(tetraoxa)tetradeca-1-amine-phthalimide (**3**). To a soln of 52.7 g (0.138 mol) of **2** in 380 ml of DMF was added 29.7 g (0.161 mol) of potassium phthalimide and the mixture was stirred at 90° for 6 h. After cooling to room temp, the soln was poured into 400 ml of water and then extracted with $CHCl_3$. The organic layer was washed with 120 ml of 0.1 N NaOH, dried over Na_2SO_4 and concentrated under reduced pressure. Purification by chromatography on silica gel with n-hexane-EtOAc (3:2) gave 42.5 g (87%) of **3** as a pale yellow oil. IR (CCl_4) ν 1715 cm^{-1} (C=O); ^{1}H-NMR ($CDCl_3$) δ 3.64-4.44 (m, 20H), 7.24-8.24 (br, 11H, Ar). (Found: C, 68.01; H, 6.51; N, 2.73. Calc for $C_{28}H_{31}NO_7$: C, 68.13; H, 6.33; N, 2.80%.)

14-(2-Naphthoxy)-3,6,9,12-(tetraoxa)tetradeca-1-amine (**4**). A mixture of 14.4 g (0.023 mol) of **3**, 148 ml of MeOH and 3.8 ml of 80% hydrazine hydrate was refluxed for 1 h. After cooling to room temp, the soln was diluted with 74 ml of water and concentrated under reduced pressure. To the residual suspension was added 74 ml of conc HCl. The mixture was treated with 50 ml of 2N NaOH and extracted with $CHCl_3$. The organic layer was dried over Na_2SO_4 and concentrated under reduced pressure. Purification by chromatography on silica gel with $CHCl_3$-MeOH-NH_4OH (10:1:1) gave 6.59 g of **4**. ^{1}H-NMR (CCl_4) δ 2.84 (t, 2H), 3.20-4.30 (m, 18H), 7.32-8.08 (m, 7H, Ar). (Found: C, 63.07; H, 7.99; N, 3.52. Calc for $C_{20}H_{29}NO_5.H_2O$: C, 62.97; H, 8.19; N, 3.67%.)

6-Deoxy-6-[14-(2-naphthoxy)-3,6,9,12-(tetraoxa)tetradeca-1-amino]-β-CD (**1**). To a soln of 3.0 g (2.22 mmol) of **4** in 100 ml of DMF was added 9.9 g (0.0272 mmol) of 6-deoxy-6-iodo-β-CD and the mixture was stirred at 80° for 24 h under nitrogen. After cooling to room temp, the reaction mixture was poured into 1000 ml of acetone and the precipitates were collected and dried. Purification by Sephadex G-15 chromatography afforded 0.807 g (23%) of **1** as pentahydrate. Rf 0.1 (n-BuOH-EtOH-H_2O 5:4:3); UV (H_2O) 263 nm (ε 4380); ^{1}H-NMR (DMSO-d_6) δ 3.0-3.90 (m, 62H), 4.20 (6H, O_6H), 4.80 (7H, C_1H), 5.2-6.0 (14H, O_2H, O_3H), 7.0-7.88 (m, 7H, Ar). (Found: C, 47.48; H, 6.60; N, 0.78. Calc for $C_{62}H_{97}NO_3.5H_2O$: C, 47.41; H, 6.88; N, 0.89%.)

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