CHEMISTRY LETTERS, pp. 2005-2008, 1992.

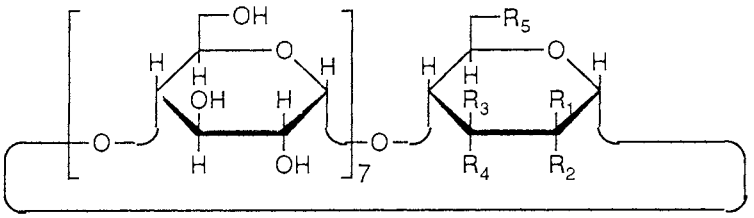
Extremely Promoted Guest Binding Ability of γ-Cyclodextrin Bearing a Pyrene Derivative on the Secondary Hydroxyl Side

Iwao SUZUKI, Yoshinobu SAKURAI, Masahiro OHKUBO, Akihiko UENO,† and Tetsuo OSA*
Pharmaceutical Institute, Tohoku University, Aobayama, Sendai 980
†Department of Bioscience and Bioengineering, Faculty of Biotechnology, Tokyo Institute of Technology, 4259 Nagatsuta, Midori-ku, Yokohama 227

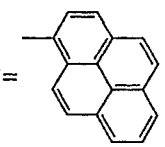
Guest binding ability of N-(1-pyrenecarbonyl)-3^{A}-amino-3^{A}-deoxy-(2^{A}S,3^{A}S)-γ-cyclodextrin (**1**) was evaluated by its fluorescence intensity variation induced by guest, and compared with that of primary hydroxyl side modified analogue (**2**). The results showed that **1** was an extremely better host than **2** in binding guest, promising that the secondary hydroxyl side modified CDs can become useful molecular recognition sensory systems.

The ability of cyclodextrins (CDs) to accommodate a wide variety of guest compounds ranging from nonpolar to polar ones has permitted them to be used as potential molecular vessels and containers.[1] To modify this ability for particular usages, a number of studies[2] have been performed on the chemically modified CDs for constructing artificial enzymes,[3] molecular recognition sensors,[4] and so on. The guest accommodation of the modified CDs has been shown to be promoted by effective capping to CDs with hydrophobic residues, but a number of studies has been done with primary hydroxyl side modified CDs and detail examinations on the guest binding ability of secondary hydroxyl side modified CDs are very scarce.[5] We wish to report here the marked binding ability of a γ-CD derivative (**1**), bearing a pyrene moiety through an amide bond at the secondary hydroxyl side, compared to that of the primary hydroxyl side modified analogue (**2**).

The host compounds **1** and **2** were prepared from 3^{A}-amino-3^{A}-deoxy-(2^{A}S,3^{A}S)-γ-CD and 6^{A}-amino-6^{A}-deoxy-γ-CD, respectively, and 1-pyrenecarboxylic acid by DCC coupling reactions. Both **1** and **2** were purified with preparative HPLC equipped with an ODS column (YMC S-343-15, 20 x 250 mm), using water-MeOH as an eluent.[6]



1: R_1=OH, R_2=H, R_3=H, R_4=NHCOPy, R_5=OH
2: R_1=H, R_2=OH, R_3=OH, R_4=H, R_5=NHCOPy
3: R_1=OH, R_2=H, R_3=H, R_4=NHCOCH$_3$, R_5=OH
4: R_1=H, R_2=OCOPy, R_3=OH, R_4=H, R_5=OH

Py= 

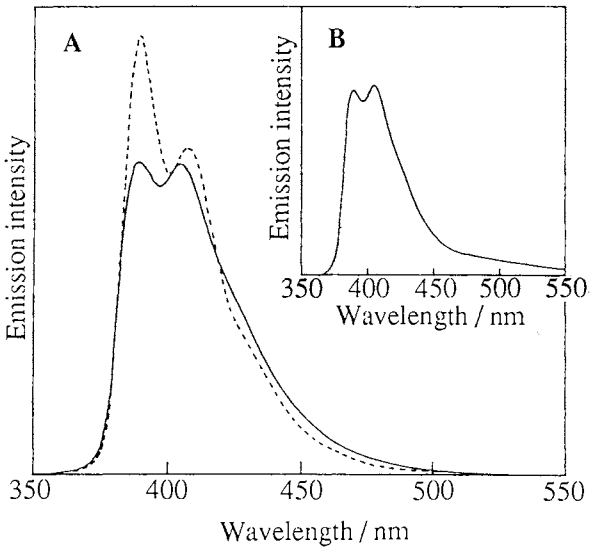


Fig. 1. Fluorescence spectra of **1** in an aqueous solution (**A**; 3.08 x 10^{-7} M, a solid line for **1**, alone, and a dashed line for **1** in the presence of *l*-borneol (1.67 x 10^{-4} M): **B**; 3.08 x 10^{-5} M) excited at 345 nm.

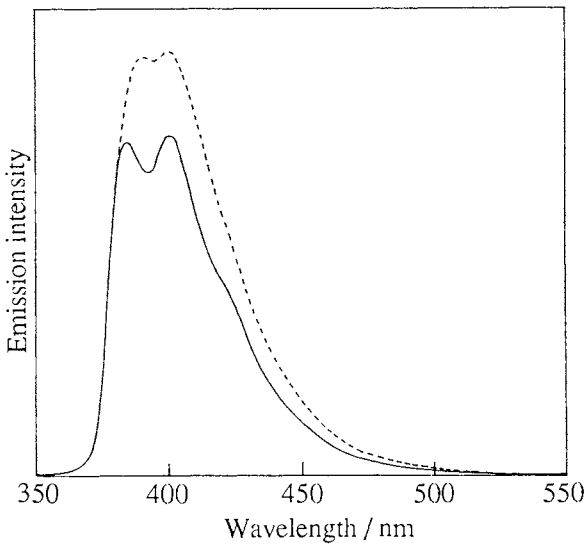


Fig. 2. Fluorescence spectra of **2** in an aqueous solution (3.03 x 10^{-5} M, a solid line for **2**, alone, and a dashed line for **2** in the presence of *l*-borneol (1.67 x 10^{-4} M)) excited at 345 nm.

Figures 1 and 2 show the fluorescence spectra of **1** and **2** in an aqueous solution, respectively. Both **1** and **2** exhibited pyrene normal emissions around 400 nm with the peak maxima at 388 and 405 nm for **1** and 385 and 402 nm for **2**. In addition, relatively concentrated solution (3.08 x 10^{-5} M^{-1} (M=mol dm^{-3}), Fig. 1B) of **1** exhibited broad structureless fluorescence around 500 nm. Since this band disappeared in dilute solution (3.08 x 10^{-7} M^{-1}, Fig. 1A), it could be attributed to an excimer emission resulting from the formation of an association dimer of **1**. The addition of a guest compound into the dilute solutions of **1** and **2** increased the normal emission intensity and the guest concentration dependency of the normal fluorescence intensity of **1** and **2** allowed to determine the binding constants (K) for various guests with an assumption for 1:1 host-guest

$$\mathbf{1}\text{ or }\mathbf{2} + \text{Guest} \underset{}{\overset{K}{\rightleftharpoons}} (\mathbf{1}\text{: Guest}) \text{ or } (\mathbf{2}\text{: Guest}) \qquad (1)$$

complexation (Eq. 1). Figure 3 shows an example of the plots for determining the K value and the results for several guests are summarized in Table 1. At a first glance, one finds larger K values of **1** compared to those of **2** at least with a factor of 3. This indicates that the pyrene moiety was more effective on guest binding when it was introduced at the hydrophilic secondary hydroxyl side than when it was introduced at a primary hydroxyl side. Since the pyrene moiety actually acted as a spacer[7] or a capping residue,[8] we are now progressing a study to clarify which factor mainly operates on guest binding of 1 and 2. In Table 1, Fc/F_0 value represents the ratio of the fluorescence intensity (388 and 402 nm for **1** and **2**, respectively) of 1:1 host-guest complex (Fc) to that of host alone (F_0), where the Fc value could be obtained from the curve fitting analysis together with the K value. This Fc/F_0 value suggests the form of the 1:1 host-guest complex. A large Fc/F_0 value may reflect a large conformational change in **1** and **2** induced by guest accommodation.

Both **1** and **2** have larger K values for bicyclic compounds (borneol and fenchone) than those for and

acyclic compounds, except for the case of **1**-cyclooctanol combination. This indicates that the molecular shape of each guest is important to be snugly accommodated in **1** and **2**. Table 1 includes the K values for three pairs of optical isomers (borneol, fenchone, and menthol). Although **1** and **2** could not recognize the chirality of borneol, **1** had substantially different K values between *d*- and *l*-isomers of fenchone and menthol. In addition, the chirality of fenchone was recognized by **2**. The ring shape of **1** was oval or triangular based on the examinations of ^{1}H-NMR of 3^A-acetoamidyl-3^A-deoxy-(2^{A}S,3^{A}S)-γ-CD (**3**)[9] and the CPK molecular model, and this structural feature is supposed to result in the chiral discriminating ability of **1** for the isomers of fenchone and menthol. This ring conformational change from native γ-CD to **1** also reflects a small tendency to form the association dimer of **1** compared to **4**[10] which has a symmetrically cyclic ring conformation.[11] Although the different binding constants were found for the enantiomeric pairs, almost similar Fc/F_0 values were obtained for each of them. These similar Fc/F_0 values strongly indicate that the 1:1 host-guest complexes between **1** and each enantiomer of fenchone or menthol

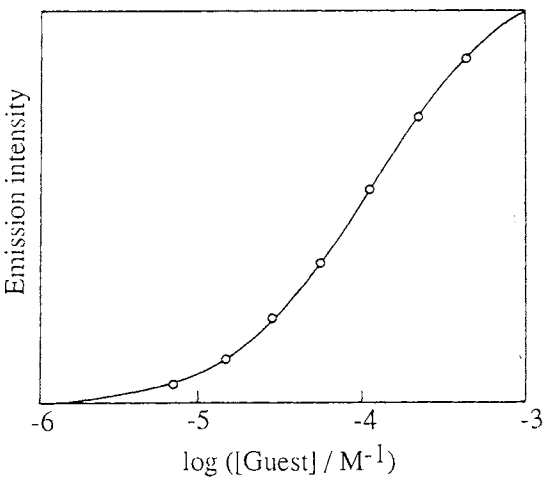


Fig. 3. Plots of the fluorescence intensity of **1** as a function of *d*-menthol concentration. A solid line is a calculated curve for K=9000 M^{-1}.

Table 1. 1:1 Host-Guest Binding Constants of **1** and **2** for Various Guests in an Aqueous Solution at 25 °C

	1		**2**	
Guest	K[a] / M^{-1}	Fc/F_0	K[a] / M^{-1}	Fc/F_0
Cyclohexanol	2500	2.06	85	1.31
Cyclooctanol	190000	2.54	290	2.40
d-Borneol	278000	2.54	1750	2.87
l-Borneol	255000	2.50	1800	2.85
d-Fenchone	120000	2.44	1600	2.47
l-Fenchone	27000	2.52	850	2.51
d-Menthol	9000	1.77	430	1.45
l-Menthol	21000	1.77	540	1.55
Nerol	b)	b)	240	1.95
Geraniol	14000	2.19	280	1.80
Deoxycholic acid	106000	1.98	18000	2.39
Chenodeoxycholic acid	92000	1.63	29000	2.84
Ursodeoxycholic acid	b)	b)	26000	2.85
Lithocholic acid	4000000	2.19	b)	b)

a) Errors were within ±15%.

b) The values could not be obtained owing to the presence of other stoichiometries in host-guest complexation.

have a similar conformation with respect to the pyrene moiety. This trend was also found for **2**, although it exhibited less chiral discriminating ability. Hydrogen bonding between the hydroxyl of γ-CD framework and the functional group (alcohol or ketone) of the guest may also be related to the different K values for the enantiomeric pairs.

In summary, secondary hydroxyl side modified γ-CD with oval shape was a better host in accommodating guest and discriminating the chirality of guests than the primary hydroxyl side modified γ-CD. Our results promise the use of secondary hydroxyl side modified CDs not only as an NMR shift reagent[12] but also as molecular recognition sensory systems.[4,13]

We are grateful to Nihon Shokuhin Kako Ltd. for generous gift of γ-CD. This work was supported by a Grant-in Aid for Scientific Research from Ministry of Education, Science and Culture, Japan.

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6) **1**: Anal. Found: C, 46.01; H, 6.21; N, 0.89%. Calcd for $C_{65}H_{89}O_{40}N\cdot 9H_2O$: C, 46.29; H, 6.40; N, 0.83%. MASS (FAB): M/z 1524 ([M+H]$^+$]. ^{1}H-NMR (DMSO-d_6): δ (ppm) 3.0-3.9 (m), 4.03-4.64 (8H, m), 4.83-4.93 (8H, m), 5.20-6.20 (15H, m), 8.10-8.67 (10H, m). **2**: Anal. Found: C, 47.24; H, 6.11; N, 0.84%. Calcd for $C_{65}H_{89}O_{40}N\cdot 7H_2O$: C, 47.29; H, 6.29; N, 0.85%. MASS (FAB): M/z 1524 ([M+H]$^+$]. ^{1}H-NMR (DMSO-d_6): δ (ppm) 3.0-4.2 (m), 4.3-4.7 (7H, m), 4.7-5.2 (8H, m), 5.4-6.0 (16H, m), 8.0-8.7 (10H, m).
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9) We attempted to measure ^{1}H-NMR spectrum of **1** in D_2O, but we could not measure it due to the poor solubility of **1** to D_2O. Thus **3** was synthesized as a model compound and its ^{1}H-NMR spectrum of the anomeric region indicated that **1** had an altrose residue whose configuration was $^1C_4$, showing a doublet resonance at δ=4.89 ppm whose *J* value (6.8 Hz) was larger than others (*J*=3.1-4.4 Hz).[11]
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11) Although the position attaching the pyrene moiety at a glucose or altrose residue was different, the pyrene moieties of **1** and **4** are oriented toward the interior of the cavity. This orientation is prerequisite for **4** to form the association dimer.[10]
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(Received July 8, 1992)