ORGANIC LETTERS

2006
Vol. 8, No. 22
4997−5000

Fluorescent Detection for Cyclic and Acyclic Alcohol Guests by Naphthalene-Appended Amino-β-cyclodextrins

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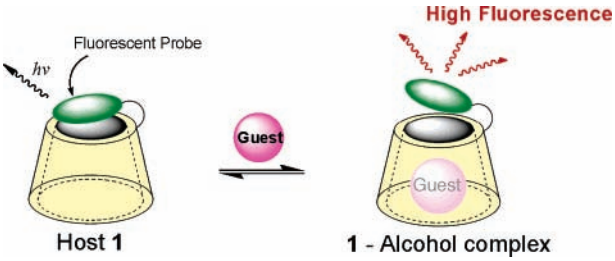
Received June 29, 2006

ABSTRACT



Spectroscopic and thermodynamic investigations on complexation of naphthalene-appended amino-β-cyclodextrins 1 and 2 with cyclic alcohols (cyclohexanol and cycloheptanol) and acyclic alcohols (1-pentanol, 2-pentanol, 1-hexanol, and 1-heptanol) have been carried out. Host 1 exhibits a drastic fluorescent enhanced-signal change in the presence of alcohol guests in aqueous solution.

The development of fluorescent sensors for detection of cation,[1] anion,[2] and neutral molecules[3] has received considerable attention in recent years. Many kinds of fluorescent-sensing molecules have been synthesized and found to possess high sensitivity and selectivity. In particular, selective recognition and optical sensing for organic neutral molecules with artificial fluorescent cyclodextrins are also of current interest.[4,5] Cyclodextrins (CDx) are capable of forming inclusion complexes with a large variety of organic molecules in their hydrophobic interior. Both the CDx cavity as a binding site and the appended fluorophore as a signaling unit with the spacer group are indispensable for the substrate-specific photoresponsive function. Ueno and co-workers have indicated that pyrene-,[6] naphthalene-,[7] dansyl-,[8] or *N*,*N*-dimethylaminobenzoyl-modified[9] CDx derivatives act as fluorescent sensors for detecting a variety of organic

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10.1021/ol0616079 CCC: $33.50
Published on Web 10/05/2006

molecules including biologically important substances. However, few reports on the large-enhanced signal change and thermodynamic study upon binding of modified cyclodextrins with organic molecules have appeared to date.

In our previous paper,[10a] we have established the fact that water-soluble fluorescent amino-β-cyclodextrin derivatives **1** and **2** with the naphthalene moiety linked via an amide bond to the CDx ring exhibit excellent temperature-[10b] and pH-sensing ability in aqueous solution (Figure 1).

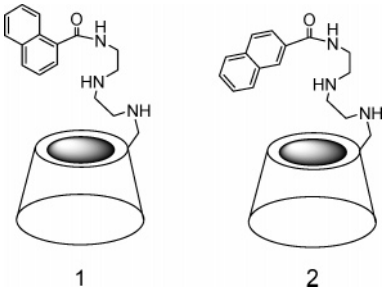


Figure 1. Amino-β-cyclodextrins **1** and **2** bearing the naphthalene fluorophore.

In particular, host **1** may be a fluorescent anion sensor toward hydrophobic anions such as ClO_4^-. As a further extension of our work, we wish to report herein the fluorescent sensing by host **1** for cyclic and acyclic alcohol guests (see Figure 2). The thermodynamic quantities in the host **1**−alcohol guest system are also reported.

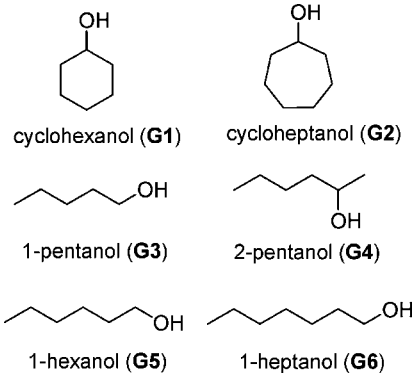


Figure 2. Structures of the cyclic and acyclic alcohol guests.

Figure 3 shows the fluorescent spectral change of **1** upon addition of cycloheptanol (**G2**) at neutral pH and $T = 298$ K. Upon addition of **G2**, a gradual increase of fluorescence intensity (I_f) and a slight red shift in λ_{max} were observed. In contrast to this remarkable increase of I_f, the fluorescence intensity of **2** decreases slightly upon addition of **G2**.

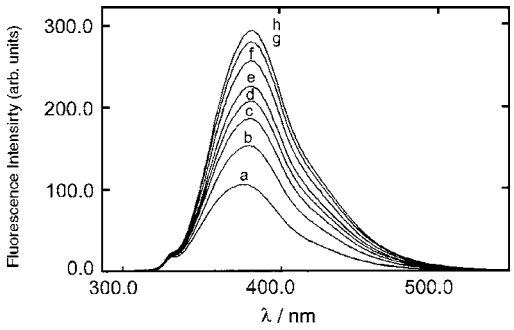
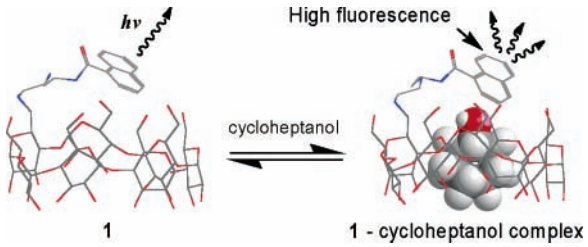


Figure 3. Fluorescence spectra of **1** in aqueous solution containing various concentrations of cycloheptanol (**G2**). [**1**] = 1.25×10^{-5} mol dm^{-3}, pH 7.0 and 25 °C. $\lambda_{ex} = 295$ nm. [**G2**] = (a) 0, (b) 1.25×10^{-3}, (c) 2.50×10^{-3}, (d) 3.75×10^{-3}, (e) 5.00×10^{-3}, (f) 7.50×10^{-3}, (g) 1.00×10^{-2}, (h) 1.25×10^{-2} mol dm^{-3}.

Therefore, host **2** is unsuitable as a fluorescent host, compared with host **1**. The unexpected enhancement of fluorescence of **1** upon binding with various alcohol guests would be rationalized by the relatively increased rigidty and/or the subtle change in microenvironmental hydrophobicity around the naphthalene fluorophore arising from the cooperative host−guest complexation. The binding mode of cyclohexanol (**G1**) with **1** is illustrated as Scheme 1.

Scheme 1. Mode of Binding Interaction between the Host **1** and Cycloheptanol Guest



The analysis of binding curves (ΔI_f vs [**G2**]) using the least-squares method shows the 1:1 host−guest interaction as shown in Figure 4. The binding constants (K_f) obtained for the complexation of **1** with various alcohol guests are summarized in Table 1.

The higher binding constant for the **1**−**G2** system as compared with the **1**−**G1** system indicates a more tight inclusion. It is noteworthy that the increase in the extending chain length of acyclic alcohols such as 1-pentanol (**G3**), 2-pentanol (**G4**), 1-hexanol (**G5**), and 1-heptanol (**G6**) leads

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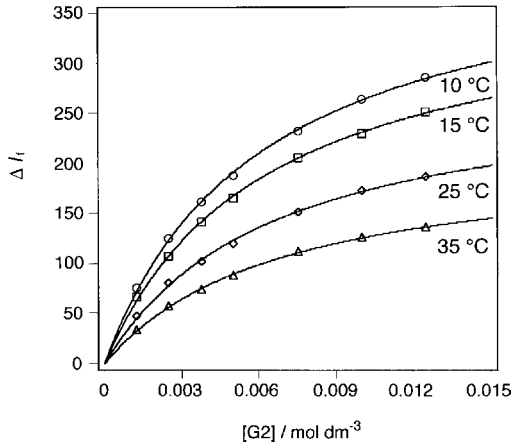

Figure 4. Binding curves for the interaction of **1** with cycloheptanol (**G2**) at various temperatures. λ_{obs}(em) = 380 nm.

to higher stability. These results indicate that the size, shape, and hydrophobicity of the alcohol molecule affect primarily the stability of the **1**−alcohol complex. In all cases, however, the values of binding constants are lower than those found for the β-CDx−alcohol system.[11] The appended naphthalene moiety of **1** may interfere with the guest inclusion into the CDx cavity due to the steric hindrance.

In order to obtain more detailed information on complexation in the host **1**−alcohol system, the thermodynamic parameters such as $\Delta H°_{incl}$ and $\Delta S°_{incl}$ were determined from the van't Hoff plot (log K_f vs $1/T$). The values of $\Delta H°_{incl}$, $\Delta S°_{incl}$, and the Gibbs energy term ($\Delta G°_{incl}$) are listed in Table 1. Generally, the inclusion reaction by native CDx is enthalpically favored ($\Delta H°_{incl} < 0$), and standard entropy ($\Delta S°_{incl}$) is either negative or positive.[12] It is interesting that both $\Delta H°_{incl}$ and $\Delta S°_{incl}$ for the inclusion reaction of **1** with acyclic alcohol guests (**G3**−**G6**) are positive. The favorable entropic contribution to the $\Delta G°_{incl}$ term is larger than the enthalpic contribution ($\Delta H°_{incl}$), suggesting that the inclusion process of the **1**−acyclic alcohol system is mainly controlled by hydrophobic interactions ($\Delta H°_{incl} > 0$, $\Delta S°_{incl} > 0$, and $\Delta G°_{incl} < 0$). To our knowledge, the entropy-driven inclusion process by the modified cyclodextrin has not been found yet. On the other hand, complexation of **1** with cyclic alcohols such as cyclohexanol (**G1**), cycloheptanol (**G2**), and adamantanol is enthalpically more favorable and entropically less favorable. Such a tendency in $\Delta H°_{incl}$ may be attributed to the increase in the contribution of van der Waals interaction for complexation with the more size- and shape-compatible guests.

The $\Delta H°$ vs $T\Delta S°$ plot for inclusion reactions of **1** with various alcohol guests shows a good linear relationship. A straight line (r = 0.94) with a slope (α) of 0.62 and an intercept ($T\Delta S°$) of 2.51 was obtained as shown in Figure 5.

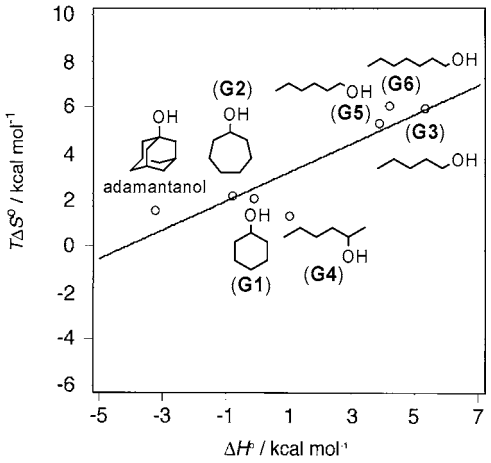

Figure 5. Plot of $\Delta H°$ vs $T\Delta S°$ for the interactions of **1** with various alcohol guests (**G1**−**G6** and adamantanol).

Inoue et al. have suggested that the slope α and the intercept $T\Delta S$ could be used as a quantitative measure of the conformational change and the desolvation upon binding of the guests, respectively.[13] The slope of 0.62 for the present system is significantly smaller than that found for binding by native β-CDx (α 0.80).[14] This indicates that the binding of **1** with alcohol guests may occur with the slight conformational change. On the other hand, the desolvation effect of **1** is very similar to that observed for β-CDx system ($T\Delta S°$ 2.6). Inoue have also suggested that the modified CDx linked by flexible hydrophilic side-arms give more extensive desolvation upon binding of the guests.[15]

Although a limited number of thermodynamic data were available in our case, the more negative $T\Delta S°$ value obtained for **1** may be rationalized in terms of the decreased number

Table 1. Binding Constants and Thermodynamic Parameters for the Inclusion Reactions of **1** with Various Alcohols[a]

guest	K_f/mol dm^{-3}	$\Delta G°$/kcal mol^{-1}	$\Delta H°$/kcal mol^{-1}	$\Delta S°$/cal mol^{-1} K^{-1}
cyclohexanol (G1)	39.2	−2.18 ± 0.50	−0.09 ± 0.25	7.03 ± 0.83
cycloheptanol (G2)	154.3	−2.99 ± 0.14	−0.80 ± 0.07	7.37 ± 0.24
1-pentanol (G3)	2.9	−0.64 ± 1.02	5.33 ± 0.51	20.0 ± 1.75
2-pentanol (G4)	1.6	−0.30 ± 0.38	1.04 ± 0.38	4.49 ± 1.28
1-hexanol (G5)	10.3	−1.42 ± 1.20	3.88 ± 0.60	17.8 ± 2.03
1-heptanol (G6)	25.4	−1.90 ± 0.76	4.18 ± 0.38	20.4 ± 1.30

[a] Experiments were carried out at 25 °C and pH 7.0 using 2 mmol dm^{-3} HEPES-NaOH in water.

of trapped water molecules that can be released upon complexation. If the naphthalene moiety is partially included into the CDx cavity of **1**, the guest inclusion may take place with a release of a small amount of water bound in CDx cavity.

Figure 6 shows the induced circular dichromism (ICD)

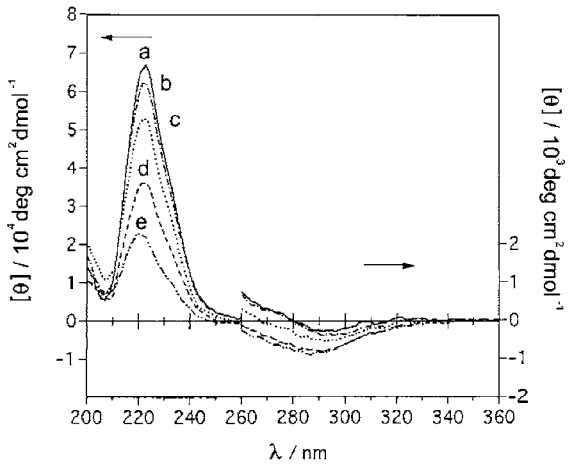

Figure 6. Circular dichromism spectra of **1** containing various concentrations of cyclohexanol (**G1**). [**1**] = 1.25×10^{-5} mol dm^{-3}, pH 7.0 and 25 °C. [**G1**] = (a) 0, (b) 1.25×10^{-4}, (c) 1.25×10^{-3}, (d) 6.25×10^{-3}, (e) 1.25×10^{-2} mol dm^{-3}.

spectrum of **1** at various concentrations of cyclohexanol (**G1**). The ICD spectral change provides precise structural information such as the orientation of chromophore in the CDx cavity.[16] If the directional polarization of $\pi-\pi^*$ transition of the chromophore is almost parallel to the C_7 symmetry axis of CDx cavity, the relative strong positive ICD sign should be observed. The ICD sign of **1** in the absence of **G1** shows a larger positive value and its intensity decreases gradually upon addition of **G1**. These results indicate that the long-axis polarized $\pi-\pi^*$ transition of the naphthalene chromophore of **1** is inclined against the CDx axis upon binding with **G1** (Scheme 1). A similar guest-induced ICD spectral change pattern was observed in other amino-β-cyclodextrins.[17] On the other hand, ICD changes of **2** at various concentrations of **G1** are smaller than those of the **1**−**G1** system as shown in Figure S2 (Supporting Information). Since the naphthalene moiety of **2** is included deeply and tightly into the CDx cavity, the exclusion of the fluorophore from interior of the CDx toward the external environment may not occur sufficiently on complexation with **G1**. In other words, host **2** forms hardly a quantitative complex with **G1** due to the steric hindrance of included naphthalene moiety.

In this paper, we have shown the fluorescent guest-responsive ability of naphthalene-appended amino-β-cyclodextrin isomers **1** and **2** in aqueous solution. Quite excellent responses of the fluorescence of **1** on complexation with various alcohol molecules were observed. All of the inclusion processes of **1** with the alcohol guests are principally entropy-driven except for adamantanol. By contrast, the guest-induced fluorescent change of **2** is silent. It is likely that self-inclusion and intermolecular aggregation of naphthalene unit of **2** interferes with binding of the guest molecules. The data from the induced circular dichromism studies suggested that a slight conformational change takes place in the binding of **1** with the alcohol guests. The application of **1** to fluorescent detection for other organic molecules is now in progress.

Acknowledgment. We thank Prof. M. Higashi (Ibaraki University) for the measurement of ICD spectra of **1** and **2**.

Supporting Information Available: UV spectra of hosts **1** and **2** and ICD spectral data of **2** containing various concentrations of cyclohexanol **(G1)**. This material is available free of charge via the Internet at http://pubs.acs.org.

OL0616079

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