Molecular Recognition of Organic Ammonium Ions by Diaza-Crown Ether-Modified β-Cyclodextrin in Aqueous Media

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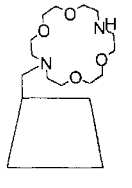
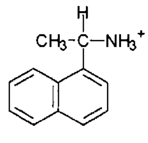
β-Cyclodextrin (β-CD) functionalized with diaza-18-crown-6 at primary face shows 7-10 fold greater binding constants for aromatic ammonium ions in aqueous media than the unmodified β-CD by the cooperative binding of the aromatic group to β-CD and ammonium group to crown ether moiety.

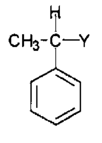
Cyclodextrins (CDs)[1] and crown ether type macrocycles[2,3] are prototypical receptor moieties in molecular recognition and supramolecular chemistry. CDs form inclusion complexes with a variety of organic molecules in aqueous solution. One of drawbacks in utilizing CDs in various applications is low binding constant with most guest molecules. Much efforts have been exercised to modify CDs to provide non-covalent and/or induced-fit interactions to improve the guest binding characteristics of CDs.[1,4] In contrast to CDs, crown ethers and their derivatives bind with metal ions by coordination and ammonium ions via hydrogen bonding in organic media.[2,3] However, characteristics of CDs and crown ethers were rarely combined to obtain a receptor with multiple recognition sites. Willner and Goren first reported the synthesis of diaza-18-crown-6-modified β-CD (β-CD-DACE: **1**) and showed enhanced binding of alkali metal salts of *p*-nitrophenolates to the bifunctional host in DMF.[5] Nocera and coworkers reported enhanced excitation energy transfer from β-CD-encased aromatics to lanthanide ions encapsulated in crown ether moiety of **1** in CH_3CN solution.[6,7] In this communication, we show that the modification of β-CD with crown ether greatly improves the molecular recognition ability of β-CD for organic ammonium ions **2,3,5-7** in aqueous media by the cooperative effect of β-CD cavity and crown ether ring.



1, β-CD-DACE

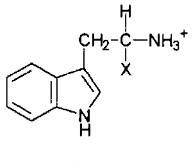


2, 1-(1-naphthyl)ethyl-ammonium



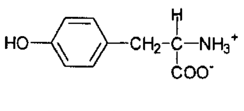
3, 1-phenylethylammonium ($Y = NH_3^+$)

4, 1-phenylethanol (Y =OH)



5, tryptophan ($X = COO^-$)

6, tryptophan methyl ester ($X = COOCH_3$)



7, tyrosine

β-CD functionalized with diaza-18-crown-6 at primary face (β-CD-DACE) **1** was prepared by employing a reported method,[6] but the work-up procedure was slightly modifed.[8] The complexation of the guest molecules with β-CD or β-CD-DACE in D_2O at pD = 7.5 ± 0.5 was followed by NMR spectra using a Bruker DPX-250 spectrometer at 20 °C. Sodium salt of 3-(trimethylsilyl)propionic-2,2,3,3-d_4 acid (TSP) was used as an external reference.

Inclusion complexation between the guests and hosts leads to changes in the chemical shift (Δδ) of guest and host protons, and the sensitivity of Δδ depends on the position of protons in the guest and host molecules. In general, inclusion of aromatic guests into the cavity of β-CD causes up-field shifts of H3 and H5 protons of β-CD, due to ring current of the guests.[9] However, in case of β-CD-DACE, the NMR spectrum of CD moiety becomes complicated due to breakdown of the symmetry and thus chemical shifts of CD hydrogens could not be used to monitor the complexation. Instead, down-field shift of the signal from N-$(\underline{CH_2})_2$- groups of the diaza-crown ether moiety was observed upon guest binding. Also the signals from α-protons, attached to the carbon atom where ammonium group is bonded, of guest molecules moved up-field by the addition of β-CD-DACE. Aromatic protons of tyrosine and H1 proton of indole ring of tryptophan **5** and its methyl ester **6** showed up-field and down-field shifts, respectively, upon binding with β-CD-DACE as well as β-CD. Figure 1 shows partial NMR spectra of **2** in the presence and in the absence of β-CD or β-CD-DACE. The dependence of Δδ of the α-proton of **2** on the initial concentration ratio between the host and the guest, $[H]_0/[G]_0$, is presented in Figure 2.

Assuming 1:1 complexation between the host and the guest, Δδ of a host or guest molecule is related to γ, $\gamma = [G]_0/[H]_0$, and the binding constant (*K*) of the guest with the host by equation (1) or (2).[10]

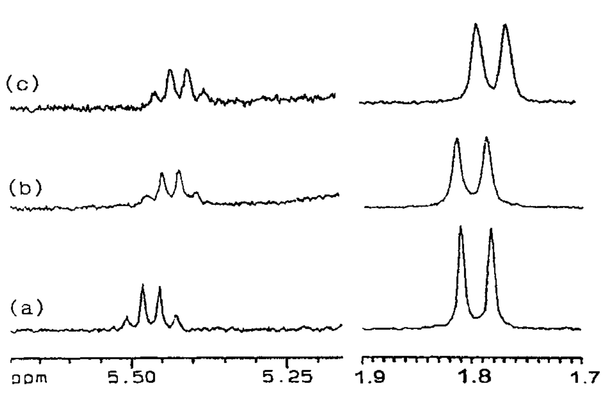


Figure 1. Partial NMR spectra of α-(1-naphthyl)ethyl-amine·HCl **2** (0.90 mM) in the absence (a) or in the presence of 3.3 mM β-CD (b) or 1.5 mM β-CD-DACE (c). The signals near 5.4 and 1.8 ppm are from α- and methyl protons of the guest, respectively.

$$\Delta\delta_{\mathrm{host}} = 0.5\ \Delta\delta_{\mathrm{c,\ host}}\ [(1 + \gamma + 1/K[\mathrm{H}]_{\mathrm{o}}) - \{(\gamma - 1 + 1/K[\mathrm{H}]_{\mathrm{o}})^2 + 4/K[\mathrm{H}]_{\mathrm{o}}\}^{1/2}] \tag{1}$$

$$\Delta\delta_{\mathrm{guest}} = 0.5\ \Delta\delta_{\mathrm{c,\ guest}}\ [(1 + 1/\gamma + 1/K[\mathrm{G}]_{\mathrm{o}}) - \{(1/\gamma - 1 + 1/K[\mathrm{G}]_{\mathrm{o}})^2 + 4/K[\mathrm{G}]_{\mathrm{o}}\}^{1/2}] \tag{2}$$

where $\Delta\delta_{\mathrm{c,\ host}}$ and $\Delta\delta_{\mathrm{c,guest}}$ are the chemical shift changes expected when all of the host and the guest molecules, respectively, form the complex.

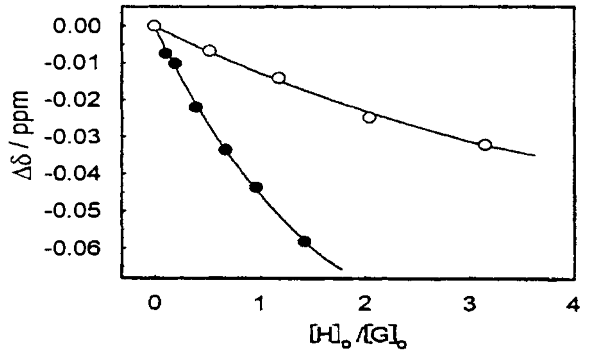


Figure 2. Dependence of the change in chemical shift for the α-proton of **2** on the concentration ratio of β-CD (○) or β-CD-DACE (●) to **2**. The concentration of **2** was kept constant to 0.90 mM.

A host solution was titrated with a guest to follow $\Delta\delta_{\mathrm{host}}$, and a guest solution was titrated with a host to monitor $\Delta\delta_{\mathrm{guest}}$. The choice for this was guided by the sensitivity of Δδ on the complexation and isolation of the NMR signals from the other peaks (see Table 1). The *K* and $\Delta\delta_{\mathrm{c}}$ values were obtained from the non-linear-least-square fitting of the dependence of Δδ on γ to equation (1) or (2). The results are summarized in Table 1. In fact, we studied both enantiomers of the guests **2-7**, but could not observe any noticeable difference in the *K* and $\Delta\delta_{\mathrm{c}}$ values between them, in the uncertainty limit of the fitting, ±10 %.

Table 1 shows that the binding constants of organic ammonium ions with β-CD-DACE are 7–10 times greater than the corresponding values with unmodified β-CD, whereas for the guest **4** which does not have an ammonium group, the binding constant with β-CD-DACE is about half of that with β-CD. This is a clear indication that β-CD-DACE behaves as a receptor with two recognition sites in aqueous media, which cooperatively binds aromatic rings by β-CD cavity and ammonium groups by crown ether moiety.

Table 1. 1:1 Association Constants for Organic Ammonium Compounds with β-CD and β-CD-DACE in Water at 25 °C[a]

Guest		β-CD		β-CD-DACE	
		K/M^{-1}	$\Delta\delta_{\mathrm{C}}$/ppm	*K*/M^{-1}	$\Delta\delta_{\mathrm{C}}$/ppm
2	NEA•HCl	105(75)[b]	-0.24(-0.10)[b]	870	-0.13
3	PEA•HCl	_[c]	_[c]	480	-0.13
4	PEOH	110	-0.13	53[d]	+0.17[d]
5	Try	30	-0.14	270[e]	-0.041[e]
6	Try-Me	50	-0.16	510	-0.081
7	Tyr	40[f]	-0.09[f]	280[f]	-0.092[f]

[a] Unless otherwise specified, signals from H3 of β-CD for complexation with β-CD and α-proton of the guests for β-CD-DACE were used for fitting. [b] From signal of α-proton of the guest. [c] Binding constant is too small (<10 M^{-1}) to give reliable data. [d] From signal of methyl proton of the guest. [e] From signal of H1 proton of indole ring. [f] From signal of aromatic protons.

The observation that the binding constant of **4** with β-CD-DACE is about half of that with β-CD can be attributed to inhibition of the insertion of **4** from the primary face to β-CD cavity of β-CD-DACE, due to steric hindrance. If this is the case, the microscopic binding constants of the guest to unmodified β-CD from the primary and the secondary faces would be similar to each other, despite of the difference in the entrance size of the faces. In connection with this, it might be worthwhile to mention that the association constant of ammonium ion with 18-crown-6 was reported to be 10–17 M^{-1} in water,[11] and ammonium ions bind to aza crown ethers with almost equal affinity as the all oxygen analogs.[12]

In conclusion, this work demonstrates that the binding constants of aromatic ammonium ions to β-CD in aqueous media are improved about 10-fold upon derivatization of β-CD with diaza-18-crown-6. Also, it is suggested that insertion of indole, 1-naphthyl, and phenyl groups into the cavity of β-CD from the primary and the secondary face is almost equally favored. Studies are underway for modification of the secondary face of β-CD with crown ether and further functionalization of β-CD-crown ether to provide three-point interactions for improvement of molecular and chiral recognition characteristics of the host molecules.

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References and Notes

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8 The crude product from the reaction between 6-*O*-tosyl-β-CD and 1,4,10,13-tetraoxa-7,16-diazacyclooctadecane (Aldrich) was acidified to pH 3.5 and purified by repeated ion exchange chromatography on a Sephadex CM C-25 column using linear gradient of NaCl (0–1 M). The desired product was recovered by selective solubilization in DMF and further purified by silica-gel chromatography using EtOAc/*i*-PrOH/H_2O(7:7:8) as an eluent after neutralization to pH 10. The product was characterized by ^{1}H nmr[6] and FAB MS. FAB MS, Found: *m/z* 1379.5565. Calcd. for $C_{54}H_{95}O_{38}N_2$: M+1, 1379.5563.

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