Notes

Encapsulation of 6-Hydroxyquinoline in Heptakis(2,6-di-*O*-methyl)-*β*-cyclodextrin

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Cyclodextrins have attracted long-standing interests in the field of artificial catalysts.[1-3] Their cone-shaped cages consist of α-D-glucose subunits and possess nonpolar cavities with polar rims containing primary hydroxyl and secondary methoxy groups. Cyclodextrins are soluble in water and their hydrophobic interiors are capable of sequestering a variety of polar and nonpolar compounds, controlling the chemistry of reactive molecules. Three different types of water are generally assumed to exist in aqueous cyclodextrin solutions: water inside the cavity, water near the rim, and bulk water.[2] A number of studies have reported the effects of micelles and cyclodextrins on proton transfer to shed light on the influence of lipophilic environment.[4-9]

Proton transfers of hydroxyquinolines having two prototropic groups of enol and imine in a molecule have been extensively explored.[10-16] The excited-state proton transfer of 7-hydroxyquinoline (7HQ) in the molecular cage of *β*-cyclodextrin or heptakis(2,6-di-*O*-methyl)-*β*-cyclodextrin (CD) has also been studied.[4,5] The anionic intermediate during the excited-state proton transfer of 7HQ forms slower but decays faster in *β*-cyclodextrin cages than in water.[5] However, the fluorescence spectral overlaps of normal molecule, enol-deprotonated anion, and imine-protonated and enol-deprotonated tautomer at S_1, as well as the low solubility in water and the low association constant of *β*-cyclodextrin with 7HQ, make the excited-state proton transfer kinetics of 7HQ very complex to require a sophisticated analysis. This has led us to investigate the encapsulation of 6-hydroxyquinoline (6HQ) in the molecular cage of CD in this work. CD is a derivative of *β*-cyclodextrin with a greatly improved solubility in water, encapsulating a predominant fraction of 6HQ to form host-guest complexes.

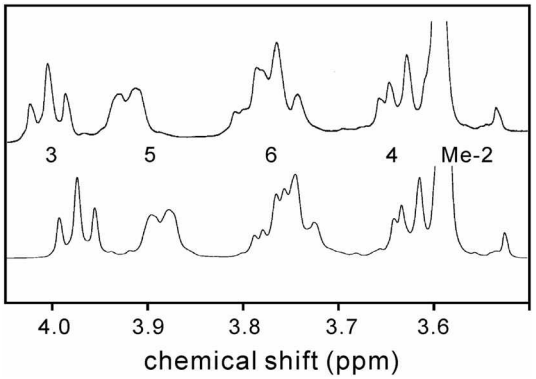

Figure 1. ^{1}H NMR spectra of CD (10 mM) in ^2H_2O without (top) and with 2-mM 6HQ (bottom).

Table 1. Changes in the ^{1}H Chemical Shifts of 10-mM CD in ^2H_2O with the Presence of 2-mM 6HQ

$\Delta\delta^a$ (ppm)			
Me-2-H	3-H	4-H	5-H
−0.02	−0.13	−0.01	−0.03

[a]Defined as $\delta - \delta_0$, where δ and δ_0 are the experimentally measured chemical shifts of CD with and without 6HQ, respectively.

The observed ^{1}H chemical shifts of CD in water decrease

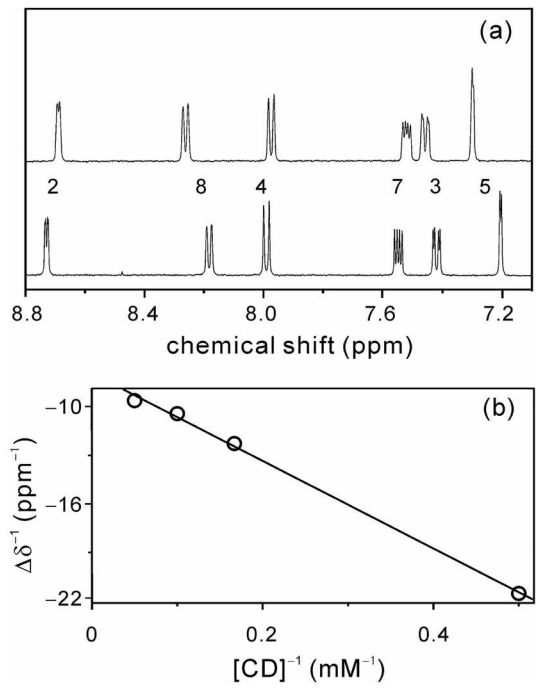

Figure 2. (a) ^{1}H NMR spectra of 6HQ (2 mM) in ^2H_2O without (top) and with 10-mM CD (bottom). (b) Benesi-Hildebrandt plot of the chemical shift at 5-H, giving 295 M^{-1} for the K of 6HQ with CD.

Table 2. Changes in the ^{1}H Chemical Shifts of 2-mM 6HQ in ^2H_2O with the Presence of 10-mM CD

$\Delta\delta^a$ (ppm)					
2-H	3-H	4-H	5-H	7-H	8-H
0.04	−0.04	0.02	−0.10	0.03	−0.08

[a]Defined as $\delta - \delta_0$, where δ and δ_0 are the experimentally measured chemical shifts of 6HQ with and without CD, respectively.

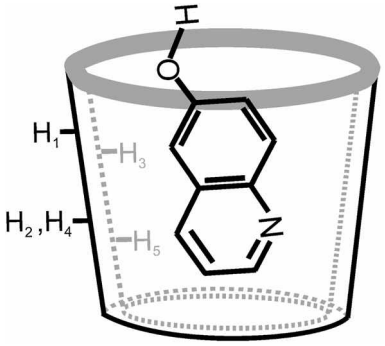

Figure 3. Schematic for the inclusion complex of 6HQ with CD.

with the presence of 6HQ (Figure 1 and Table 1). This indicates that 6HQ enters the molecular cage of CD expelling water molecules therein to form an inclusion complex with CD. The largest change was observed at 3-H, indicating that the inclusion of 6HQ induces the largest polarity change at 3-H.

The ^{1}H chemical shifts of 6HQ show large changes at the positions of 5-H and 8-H with the presence of CD (Figure 2a and Table 2). This with the largest chemical-shift change at the 3-H of CD suggests that both the 5-H and the 8-H positions of 6HQ are located near the 3-H position of CD in the inclusion complex. Then, the enolic group of 6HQ is considered to exist at the large opening of the CD cage. The small change of the 4-H chemical shift of 6HQ with inclusion, together with the imino group of 6HQ hindered sterically less than the 4-H in the cage and the enolic group of 6HQ interacting attractively with alcoholic groups at the rim, suggests that 6HQ in the molecular cavity is tilted against the cage axis of CD as shown in Figure 3.

The 1 : 1 association constant (K) of 6HQ with CD has been deduced to be 295 M^{-1} by plotting the Benesi-Hildebrandt relation of eq. 1 with the chemical shift of 5-H (Figure 2b).[17]

$$1/\Delta\delta = 1/(K\,\Delta\delta_{max}[CD]) + 1/\Delta\delta_{max} \quad (1)$$

$\Delta\delta_{max}$ in eq. 1 is $\delta_M - \delta_C$ while δ_M and δ_C are the extractable chemical shifts of free 6HQ and CD-complexed 6HQ, respectively, at 5-H.

The K of 6HQ with CD has also been estimated by monitoring the absorption spectral changes of 6HQ with [CD] (Figure 4). Figure 4a shows that the lowest $^1(\pi,\pi^*)$ absorption band of normal molecule shifts to the red gradually with the concentration increase of CD in water.

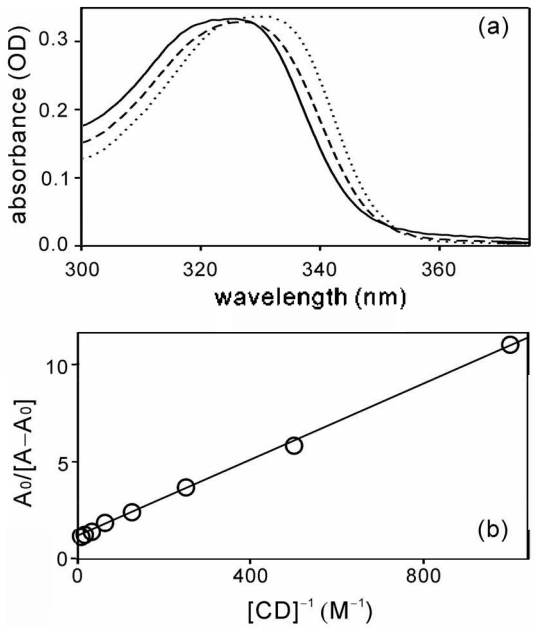

Figure 4. Absorption spectra of 0.1-mM 6HQ in water at CD concentrations of 0 (solid), 8 (dashed), and 128 mM (dotted) (a) and a plot of $A_0/(A-A_0)$ versus $[CD]^{-1}$ (b). A and A_0 are absorbances measured at 343 nm with and without CD, respectively, and the best linear fit (line) of **b** yields 125 M^{-1} for the K of 6HQ with CD.

This spectral change suggests that 6HQ incorporates into the hydrophobic interior of CD in water and that the dipole moment of normal molecule at S_1 is greater than that of normal molecule because of increase in enol acidity and imine basicity with excitation (vide infra). The K of 6HQ with CD has been extracted with absorbance changes at 343 nm. By plotting the relation of eq. 2 (Figure 4b), we have obtained 125 M^{-1} for K.

$$\frac{A_0}{A-A_0} = \frac{\varepsilon_M}{\varepsilon_M-\varepsilon_C}\left(\frac{1}{K[CD]}+1\right) \quad (2)$$

A_0 in eq. 2 denotes absorbance without CD while ε_M and ε_C are the molar extinction coefficients of free 6HQ and CD-complexed 6HQ, respectively, at the monitored wavelength of 343 nm. The good linearity of the plot also confirms that the molecules of 6HQ and CD form 1 : 1 inclusion complexes. However, we consider that the K value of 295 M^{-1} obtained with NMR spectra is more accurate than that of 125 M^{-1} with absorption spectra in principle. Thus, we suggest that at least 97% of 6HQ molecules in the samples having 6HQ of 0.1 mM and CD of 128 mM are encapsulated in CD molecular cages.

In summary, 6HQ enters the molecular cage of CD in water with the K of 295 M^{-1} to form a 1 : 1 6HQ-CD complex having its imino group inside the cage and its enolic group at the wider rim of the CD cage. Thus, 6HQ in the molecular cavity is tilted against the cage axis of CD. The K value indicates that at least 97% of 6HQ molecules in the samples having 6HQ of 0.1 mM and CD of 128 mM are encapsulated in CD molecular cages.

Experimental Section

Materials and Methods. 6HQ purchased from Sigma-Aldrich was further purified via column chromatography and vacuum sublimation, while CD and ^2H_2O (isotopic purity ≥ 99.9%) purchased from Sigma-Aldrich were used without further purification. Aqueous solutions of 6^1HQ and 6^2HQ were prepared by dissolving 6HQ in triply distilled water and in ^2H_2O, respectively. The p^1H and p^2H of 6HQ aqueous solutions were adjusted to be 7.0 by adding aqueous ^{1}HCl or NaO^{1}H and aqueous ^{2}HCl or NaO^{2}H, respectively. The p^2H was corrected from the pH meter reading.[18] Equilibrium constants[19] indicate that 99% of 6HQ exists as normal molecule at pH 7.0. NMR and absorption spectra were recorded by using an NMR spectrometer (Bruker, Avance 500) and a UV/vis spectrometer (Scinco, S-3100), respectively, at room temperature.

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