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Hydrogen Bonding in Inclusion Complexes of Heptakis(2,3,6-tri-*O*-methyl)-*β*-cyclodextrin with Chlorophenols in Organic Solvents

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Heptakis(2,3,6-tri-*O*-methyl)-*β*-cyclodextrin (TM*β*CD) has been found to form inclusion complexes with *p*- and *m*-chlorophenol in organic solvents such as cyclohexane. In the inclusion complex, the guest *p*- or *m*-chlorophenol incorporated into the TM*β*CD cavity is hydrogen bonded to the host TM*β*CD. The equilibrium constants for the formation of the inclusion complexes of *p*- and *m*-chlorophenol with TM*β*CD in saturated hydrocarbons are an order of magnitude greater than those in water. The finding that the $-\Delta S$ values for the formation of the inclusion complex in saturated hydrocarbons are significantly greater than those in water suggests a rigid inclusion-complex structure which is reinforced by the hydrogen bond between the guest and TM*β*CD in saturated hydrocarbons.

Cyclodextrins (CDs) are cyclic oligosaccharides comprising six, seven, and eight glucose residues, which are named as *α*-, *β*-, and *γ*-CD, respectively. Since these CDs have a cavity in the molecular center, they can accommodate various guest molecules in their cavity in aqueous solutions, forming inclusion complexes. As the driving forces for association with guest molecules, several intermolecular interactions have been proposed:$^{1)}$ (1) hydrophobic interaction, (2) van der Waals interaction, (3) hydrogen bonding interaction, (4) relief of high-energy water from the CD cavity upon inclusion of a guest, and (5) relief of the conformation strain in a "vacant" CD (CD–water complex) upon inclusion of a guest. Among these interactions, the hydrogen-bonding interaction for crystalline inclusion complexes has been investigated by means of X-ray and neutron diffraction spectroscopies.$^{2-15)}$ In optical resolution or molecular recognition, inclusion complexes of CD with guests, which are hydrogen bonded to the host CD, have been pointed out.$^{16-18)}$ Furthermore, inclusion complexes with CD, in which there is host-guest hydrogen bonding, are proposed as intermediates in chemical reactions catalyzed by CDs.$^{19,20)}$ In spite of such significance in cyclodextrin chemistry, however, there have been few studies concerning the hydrogen-bonding interaction for inclusion complexes in liquid phases on the basis of spectroscopies.$^{21)}$ We thus aimed to examine the hydrogen bonding interaction in inclusion complexes of heptakis(2,3,6-tri-*O*-methyl)-*β*-cyclodextrin (TM*β*CD) with *o*-, *m*-, and *p*-chlorophenol in organic solvents, such as cyclohexane, by means of absorption, induced circular dichroism (icd), and NMR spectroscopies. The results show the hydrogen bonding from the guest *m*- or *p*-chlorophenol entering the TM*β*CD cavity to the host TM*β*CD in the organic solvents.

Experimental

Heptakis(2,3,6-tri-*O*-methyl)-*β*-cyclodextrin (TM*β*CD) purchased from Wako Pure Chemical Industries, Ltd. and *o*-, *m*-, and *p*-chlorophenol obtained from Tokyo Kasei Kogyo Co., Ltd. were used without further purification. *β*-Cyclodextrin (*β*CD) was purchased from Nacalai Tesque, Inc. and recrystallized from water three times. Cyclohexane and methylcyclohexane were Dotite Spectrosol reagents obtained from Dojin Laboratories. For determining the equilibrium constants, the concentrations of TM*β*CD in organic solvents and those in water were in the ranges of 1.0×10^{-4} to 5.0×10^{-4} and 1.5×10^{-3} to 1.0×10^{-2} mol dm^{-3}, respectively, and the concentrations of *β*CD in aqueous solutions ranged from 1.5×10^{-3} to 1.0×10^{-2} mol dm^{-3}.

Absorption spectra were run on a Shimadzu UV-260 spectrophotometer. Induced circular dichroism (icd) and ^{1}H NMR spectra were recorded on a JASCO J-600 spectropolarimeter and a Bruker AC-250P spectrometer operated at 250 MHz, respectively. Measurements of the absorption spectra were made at 25 °C, except for variable-temperature experiments. Other spectroscopic measurements were carried out at room temperature.

Results and Discussion

Inclusion Complex of *p*-Chlorophenol with TM*β*CD in Cyclohexane. Figure 1 (top) shows absorption spectra of *p*-chlorophenol (5.08×10^{-4} mol dm^{-3}) in cyclohexane in the absence and presence of TM*β*CD. With increasing the TM*β*CD concentration, the intensity of an absorption peak at 289.5 nm is reduced, accompanied by isosbestic points at 289 and 290 nm, while the other absorption peak at 281 nm is intensified. At the same time, the absorption edge is shifted to longer wavelengths. These spectral changes indicate complex formation between TM*β*CD and *p*-chlorophenol. Because the hydrophobic interaction that usually takes place in inclusional complexation in water is not expected in cyclohexane, there is the possibility that *p*-chlorophenol associates with TM*β*CD from the outside of the TM*β*CD cavity. We thus examined an icd spectrum of *p*-chlorophenol in cyclohexane containing 5×10^{-4} mol dm^{-3} TM*β*CD, which is also shown in Fig. 1 (bottom). As evidenced by the positive icd spectrum, *p*-chlorophenol is accommodated into the TM*β*CD cavity, forming an inclusion complex. Taking into account the cavity size and the *p*-chlorophenol dimensions, it is most

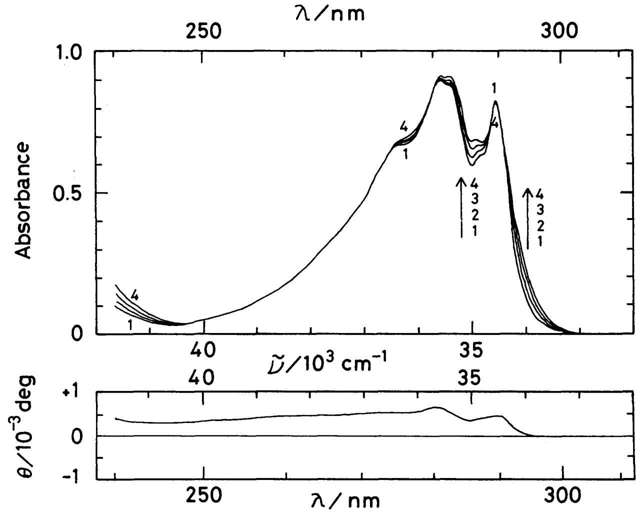

Fig. 1. Top: absorption spectra of *p*-chlorophenol (5.08×10^{-4} mol dm^{-3}) in cyclohexane containing varying concentrations of TMβCD. Concentration of TMβCD: (1) 0, (2) 1.5×10^{-4}, (3) 3.0×10^{-4}, and (4) 5.0×10^{-4} mol dm^{-3}. Bottom: an icd spectrum of *p*-chlorophenol (5.08×10^{-4} mol dm^{-3}) in cyclohexane containing 5×10^{-4} mol dm^{-3} TMβCD.

likely that the inclusion complex has a 1 : 1 stoichiometry.

$$\mathrm{TM\beta CD} + p\mathrm{CP} \overset{K}{\rightleftharpoons} \mathrm{TM\beta CD}\cdot p\mathrm{CP}. \tag{1}$$

Here, *p*CP and TMβCD·*p*CP represent *p*-chlorophenol and a 1 : 1 inclusion complex of TMβCD with *p*-chlorophenol, respectively, and *K* is an equilibrium constant for the formation of TMβCD·*p*CP.

Upon the addition of TMβCD to a benzene solution of *p*-chlorophenol, an absorption spectral change was observed (>280 nm), although unlike cyclohexane there were no isosbestic points and the intensities of absorption bands at 282 and 290 nm were enhanced. Consequently, the TMβCD–*p*-chlorophenol complex is also present in benzene. ^{1}H NMR spectra of TMβCD were investigated in benzene-d_6. Addition of 0.1 mol dm^{-3} *p*-chlorophenol results in higher-field shifts of ^{1}H NMR signals of TMβCD. The differences in chemical shift between TMβCD solutions with and without *p*-chlorophenol, $\Delta\delta$, are −0.029, −0.046, −0.044, and −0.075 ppm for H-2, H-3, H-4, and H-5 protons, respectively. The greater $\Delta\delta$ values for H-3 and H-5 than those for H-2 and H-4 seem to indicate the accommodation of *p*-chlorophenol within the TMβCD cavity.

Figure 2 demonstrates absorption spectral change of *p*-chlorophenol (5.08×10^{-4} mol dm^{-3}) in cyclohexane by the addition of diethyl ether. As the diethyl ether concentration is raised, the intensity of the absorption peak at 289.5 nm is decreased, accompanied by isosbestic points at 248, 275, 280, 281, 289, and 290 nm, indicating hydrogen bonding between a phenolic hydroxyl group (proton donor) of *p*-chlorophenol and an oxygen atom (proton acceptor) of diethyl ether. The spectral change shown in Fig. 2 quite resembles that in Fig. 1, which exhibits the formation of the TMβCD–*p*-chlorophenol inclusion complex. Therefore, the spectral change in Fig. 1 is attributed to hydrogen bonding between TMβCD and *p*-chlorophenol. When TMβCD was added to a cyclohexane solution of *p*-chloroanisole, which cannot be hydrogen bonded to TMβCD because of the absence of a hydroxyl group, no absorption spectral changes were observed. This finding provides additional evidence that *p*-chlorophenol bound to the TMβCD cavity has a hydrogen bond to the host TMβCD. Since TMβCD has methoxyl groups on the wider and narrower rims, it can serve as a proton acceptor for a hydrogen atom of a hydroxyl group of *p*-chlorophenol that is incorporated into the TMβCD cavity. Inspection of a molecular model suggests that the phenolic hydroxyl group in *p*-chlorophenol entering the cavity is most likely to be hydrogen bonded to an oxygen atom of the methoxyl group on the wider rim. In the crystal of a 1 : 1 TMβCD–*p*-iodophenol inclusion complex tetrahydrate, an iodine atom of *p*-iodophenol is located at the center of the TMβCD ring, and a hydroxyl group protrudes from the O(2) and O(3) sides of the TMβCD cavity.[7] As a consequence, the spatial restriction allows the hydroxyl group to form a hydrogen bond with two water molecules outside of the cavity, rather than the host TMβCD. Because an iodine atom in *p*-iodophenol is much bulkier than a chlorine atom in *p*-chlorophenol, a hydroxyl group of *p*-iodophenol seems to extrude from the cavity to a greater extent compared to that of *p*-chlorophenol. Consequently, *p*-iodophenol may not be hydrogen bonded to the host TMβCD. On the other hand, in a crystalline inclusion complex of permethylated βCD with *m*-iodophenol, there is a host-guest hydrogen bond, in which an O(2) atom of the host works as a proton acceptor.[12] These results imply that the geometrical requirement is important in the occurrence of such a

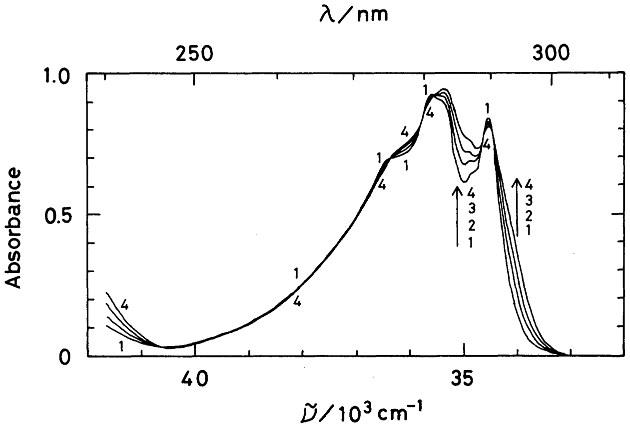

Fig. 2. Absorption spectra of *p*-chlorophenol (5.08×10^{-4} mol dm^{-3}) in cyclohexane containing varying concentrations of diethyl ether. Concentration of diethyl ether: (1) 0, (2) 9.55×10^{-3}, (3) 1.91×10^{-2}, and (4) 3.82×10^{-2} mol dm^{-3}.

host–guest hydrogen bond.

Evaluation of Equilibrium Constants for the Formation of the Inclusion Complex. The TMβCD concentrations employed for the determination of K were comparable with the p-chlorophenol concentration. We thus used the following approach for determining K.

[1]: An approximate equilibrium constant for the formation of TMβCD·pCP, K', was estimated according to the usual double reciprocal plot in which the initial concentration of TMβCD was utilized as [TMβCD]:

$$1/\Delta A = 1/a + 1/aK'[\mathrm{TM}\beta\mathrm{CD}]. \qquad (2)$$

Here, ΔA is the difference in absorbance between p-chlorophenol solutions with and without TMβCD, and a is a constant.

[2]: Using this K' value, the concentration of uncomplexed TMβCD was evaluated to be

$$[\mathrm{TM}\beta\mathrm{CD}] = [\mathrm{TM}\beta\mathrm{CD}]_0/(1 + K'[p\mathrm{CP}]_0), \qquad (3)$$

where suffix 0 stands for the initial concentration.

[3]: Then, the concentration of uncomplexed p-chlorophenol was calculated using [TMβCD] to be

$$[p\mathrm{CP}] = [p\mathrm{CP}]_0/(1 + K'[\mathrm{TM}\beta\mathrm{CD}]). \qquad (4)$$

[4]: Next, [TMβCD] was re-estimated from the following equation:

$$[\mathrm{TM}\beta\mathrm{CD}] = [\mathrm{TM}\beta\mathrm{CD}]_0/(1 + K'[p\mathrm{CP}]). \qquad (5)$$

[5]: A new K' value was evaluated from a plot based on Eq. 2 in which [TMβCD], thus obtained, was used.

[6]: Processes [3]—[5] were iteratively performed until a variation in the magnitude of a slope of a new plot for Eq. 2 converged within 20% relative to the slope of the previous plot for Eq. 2. We took the finally obtained K' value as K. In the system of TMβCD–p-chlorophenol in cyclohexane, the first K' value and the last K' value (K) were evaluated to be 580±70 and 990±90 mol^{-1} dm^3, respectively. Figure 3 gives double-reciprocal plots for processes [1] and [5] in this system. Figure 3 also shows a plot whose variation in slope converged within 5% relative to a previously drawn line. It was found that in methylcyclohexane an inclusion complex is similarly formed between TMβCD and p-chlorophenol. According to the method described above, K for methylcyclohexane was determined to be 1400±100 mol^{-1} dm^3, which is slightly greater than K for cyclohexane. Table 1 summarizes K for these systems. In aqueous solutions, p-chlorophenol was found to form inclusion complexes

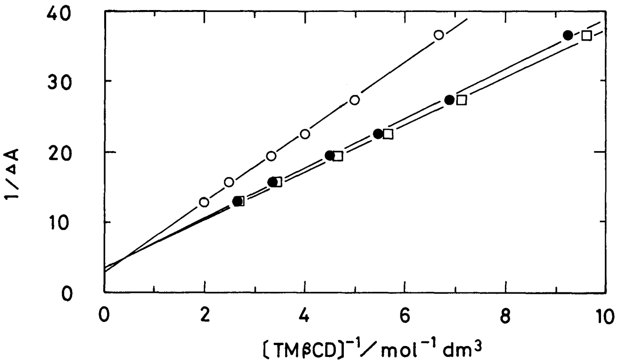

Fig. 3. Plots of $1/\Delta A$ vs. 1/[TMβCD]. The concentration of p-chlorophenol in cyclohexane is 5.08×10^{-4} mol dm^{-3}. (○): Plot employing the initial concentrations of TMβCD as [TMβCD]; (●): Plot employing calculated concentrations of TMβCD as [TMβCD]. The variation in the magnitude of the slope of this plot is converged within 20% relative to a line drawn immediately before; (□): Plot employing calculated concentrations of TMβCD as [TMβCD]. The variation in the magnitude of the slope of this plot is converged within 5% relative to of a line drawn immediately before.

Table 1. Equilibrium Constants for the Formation of the Inclusion Complex, K, Those for Hydrogen Bonding with Diethyl Ether, and ΔH and ΔS for These Complexation

Guest	Host	Solvent	K/mol^{-1} dm^3	ΔH/kJ mol^{-1}	ΔS/J K^{-1} mol^{-1}
pCP	TMβCD	CH[a]	990±90	−51±4	−110±10
	TMβCD	MCH[b]	1400±100	−68±11	−170±100
	TMβCD	H_2O	100±6	−18±1	−21±2
	βCD	H_2O	250±10	−16±2	−7±5
	DEE[c]	CH	25±1[d]	−17±1	−30±1
mCP[e]	TMβCD	CH	2500±200	−53±6	−110±20
	TMβCD	MCH	2600±200	−71±4	−170±10
	TMβCD	H_2O	120±4	−17±1	−19±2
	βCD	H_2O	200±10	−19±2	−18±5
	DEE[c]	CH	22±1[d]	−32±1	−81±4
oCP[f]	TMβCD	H_2O	86±4	−23±3	−43±11
	βCD	H_2O	200±30	−19±4	−20±10
	DEE[c]	CH	ca. 0.7[d]	ca. −11	ca. −39

a) Cyclohexane. b) Methylcyclohexane. c) Diethyl ether used as a proton acceptor in a hydrogen bonded complex. d) Equilibrium constant for hydrogen bonding. e) m-Chlorophenol. f) o-Chlorophenol.

with TMβCD and βCD. Thus, the K values for TMβCD and βCD in aqueous solutions were estimated, and are shown in Table 1 which also includes an equilibrium constant for the hydrogen bonding between *p*-chlorophenol and diethyl ether in cyclohexane. In the evaluation of K for aqueous solutions, we employed only the usual double reciprocal plot based on Eq. 2, since the concentration of TMβCD or βCD was much higher than that of *p*-chlorophenol. Examination of Table 1 reveals that K of TMβCD in the organic solvents are considerably greater than that in water, and that the equilibrium constant for hydrogen bonding between *p*-chlorophenol and diethyl ether is the smallest of these equilibrium constants. These findings suggest that the host-guest hydrogen bonding stabilizes the inclusion complex in organic solvents to a great extent. The K value for βCD in water is about twice as great as that for TMβCD in water.

Inclusion Complexes of *m*-Chlorophenol. Although in aqueous solution *o*-chlorophenol was found to form an inclusion complex with TMβCD, the complex formation in cyclohexane was not confirmed in the TMβCD concentration range examined. On the other hand, the complexation of *m*-chlorophenol with TMβCD was observed in cyclohexane, as shown in Fig. 4 (top). Figure 4 (bottom) shows an icd spectrum of *m*-chlorophenol in cyclohexane containing TMβCD. The icd curve for *m*-chlorophenol as well as *p*-chlorophenol has a positive sign. This finding shows that *m*-chlorophenol is also incorporated into the TMβCD cavity, forming an inclusion complex, whose stoichiometry is likely to be 1 : 1, based on the dimensional point of view of a *m*-chlorophenol molecule and the TMβCD cavity. Figure 5 illustrates absorption spectra of *m*-chlorophenol solutions containing varying concentrations of diethyl ether, indicating the hydrogen bonding between *m*-chlorophenol (proton donor) and diethyl ether (proton acceptor) in cyclohexane. Due to the good similarity between Figs. 4 and 5, it is concluded that a hydrogen bond is formed between an ether group in TMβCD and a hydroxyl group in *m*-chlorophenol bounded to the TMβCD cavity. Using the same procedure as that employed for *p*-chlorophenol, the K values of *m*-chlorophenol were determined, and are tabulated in Table 1, together with the equilibrium constant for the hydrogen bonding between *m*-chlorophenol and diethyl ether. The K values of *m*-chlorophenol as well as *p*-chlorophenol in organic solvents are one and two orders of magnitude greater than that in water and the equilibrium constant for the hydrogen bonding with diethyl ether, respectively. Table 1 also lists the K of *o*-chlorophenol in water and the equilibrium constant for the hydrogen bonding between *o*-chlorophenol and diethyl ether.

Thermodynamic Parameters for the Complexation. Arrhenius plots for K of *p*-chlorophenol in cyclohexane and water are depicted in Fig. 6. From the temperature

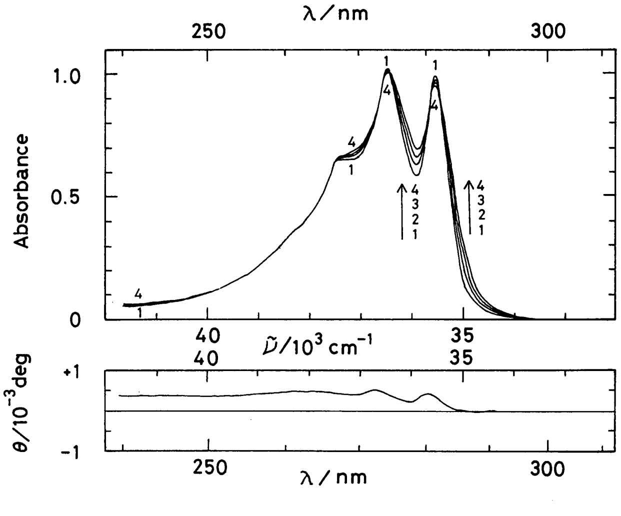

Fig. 4. Top: absorption spectra of *m*-chlorophenol (5.12×10^{-4} mol dm^{-3}) in cyclohexane containing varying concentrations of TMβCD. Concentration of TMβCD: (1) 0, (2) 1.5×10^{-4}, (3) 3.0×10^{-4}, and (4) 5.0×10^{-4} mol dm^{-3}. Bottom: an icd spectrum of *m*-chlorophenol (5.12×10^{-4} mol dm^{-3}) in cyclohexane containing 5.0×10^{-4} mol dm^{-3} TMβCD.

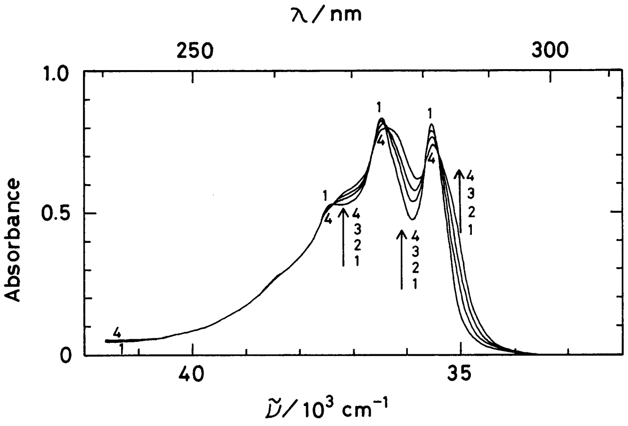

Fig. 5. Absorption spectra of *m*-chlorophenol (4.10×10^{-4} mol dm^{-3}) in cyclohexane containing varying concentrations of diethyl ether. Concentration of diethyl ether: (1) 0, (2) 9.55×10^{-3}, (3) 1.91×10^{-2}, and (4) 3.82×10^{-2} mol dm^{-3}.

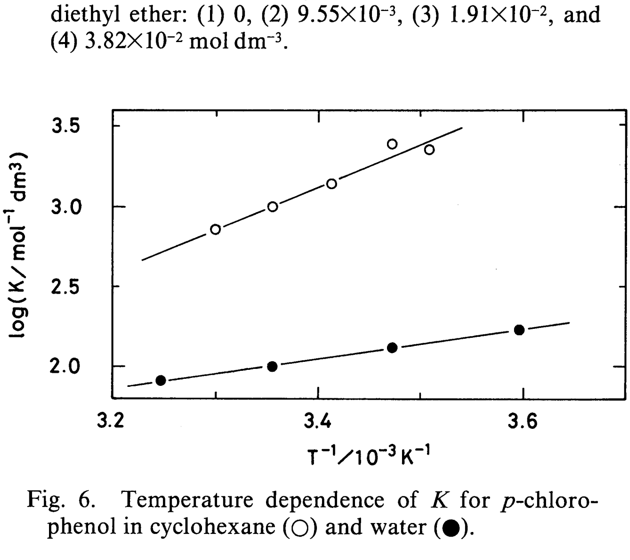

Fig. 6. Temperature dependence of K for *p*-chlorophenol in cyclohexane (○) and water (●).

dependence of K, both enthalpy changes (ΔH) and entropy changes (ΔS) could be determined for *p*-, *m*-, and *o*-chlorophenol (Table 1). Table 1 also summarizes the thermodynamic parameters of the equilibrium constants for hydrogen bonding with diethyl ether. Both $-\Delta H$ and $-\Delta S$ for K of *p*- and *m*-chlorophenol in the saturated hydrocarbons are several times greater than those in water as well as those for the hydrogen bonding with diethyl ether. In aqueous solutions the hydrogen bond of *p*- or *m*-chlorophenol is formed regardless of whether or not the chlorophenol is located inside the cavity: outside the cavity, the chlorophenol makes a hydrogen bond with a solvent water molecule. In this case, the host-guest hydrogen bonding makes little or no contribution to ΔH and ΔS for the formation of the inclusion complex. On the other hand, in the organic solvents, hydrogen bonding of the chlorophenol occurs when chlorophenol exists inside the TMβCD cavity; it does not occur when chlorophenol exists outside the cavity (in the bulk solvents). Consequently, the thermodynamic parameters for the formation of the inclusion complex in the organic solvents involves those for the hydrogen bonding between TMβCD and the guest. The negatively large ΔS for the organic solvents is partly due to the rigid structure of the inclusion complex in the organic solvents which is built up by the hydrogen bond between TMβCD and the guest entering the TMβCD cavity.

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