Effect of β-Cyclodextrin Charge Type on the Molecular Recognition Thermodynamics of Reactions with (Ferrocenylmethyl)dimethylaminium Derivatives

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Received: July 30, 2007; In Final Form: October 31, 2007

Complex stability constants (K_S), standard molar enthalpic changes ($\Delta H°$), and entropic changes ($T\Delta S°$) for the inclusion complexations of native β-cyclodextrin (**1**) and two oppositely charged β-cyclodextrins, i.e., mono(6-amino-6-deoxy)- β-cyclodextrin (**2**) and mono[6-*O*-6-(4-carboxylphenyl)]- β-cyclodextrin (**3**), with two (ferrocenylmethyl)dimethylaminium derivatives, i.e., $FC_4^+Br^-$ and $FC_8^+Br^-$, were determined at 25 °C in aqueous phosphate buffer solution (pH 7.20) by means of isothermal titration microcalorimetry (ITC). Cyclic voltammetry studies showed that the ferrocene groups of the guests were included in the β-cyclodextrin cavity to form host−guest complexes. As compared with neutral β-cyclodextrin, the positively charged host **2** showed decreased binding toward (ferrocenylmethyl)dimethylaminium guests. This was attributed to electrostatic repulsion, while the negatively charged host **3** displayed increased binding due to electrostatic attractions. Thermodynamically, the ionization of host CDs affects both enthalpic and entropic changes of host−guest complexations presumably by changing the hydrophobicity and the desolvation effect of hosts upon inclusion complexation. Moreover, the solvent effect was also discussed from the viewpoint of thermodynamics.

Introduction

Cyclodextins (CDs), a class of cyclic oligosaccharides mainly with six to eight D-glucose units linked by α-1,4-glucose bonds, have been extensively applied in diverse fields such as pharmaceutical chemistry, food technology, analytical chemistry, chemical synthesis, and catalysis.[1] This is due to their capability to include a variety of organic/inorganic/biological molecules into their inherently hydrophobic cavities.[2] However, the limitations in the binding abilities and molecular selectivities of native CDs hinder the range of their further applications. In order to improve the binding abilities and selectivities of CDs toward guest molecules and to explore the possible binding mechanisms between the hosts and the guests, numerous modified CDs with functional substituents as additional binding sites have been synthesized.[3] It is well-known that the van der Waals and hydrophobic interactions, both of which are related to the size/shape matching between guest molecule and CD cavity, are those among the several possible weak noncovalent interactions which provide the most crucial contributions toward the complexation of organic guests with CDs.[4] Moreover, other intermolecular interactions such as hydrogen bonding and electrostatic interactions contribute to the inclusion complexation behaviors of CDs, to varying extents.[5] Recently, the electrostatic interactions between the hosts and the guests have attracted increased interest of chemists during the design of functionally modified CDs. Lincoln,[6] Kano,[7] and Inoue[8] reported the complexation and/or chiral recognition thermodynamics of aminated β-CDs possessing a positive charge with neutral and charged guests. This revealed the counterbalance between electrostatic and conventional intracavity interactions including van der Waals, hydrogen bonding, and hydrophobic interactions. Meanwhile, Kano and co-workers reported the inclusion complexes between anionic N-acetylated α-amino acids ($AcTrp^-$, $AcPhe^-$, $AcLeu^-$, and $AcVal^-$) and protonated heptakis(6-amino-6-deoxy)-β-CD (per-NH_3^+-β-CD) by a cooperative effect of inclusion and Coulombic interactions.[9] In addition, they also determined the thermodynamic parameters for the complexation of multiply charged CD cations and anions with oppositely charged guest molecules.[10] More recently, we reported that the cationic aminated β-CDs could significantly alter the molecular binding ability and selectivity of the parent β-CD toward the anionic steroids through cooperative electrostatic interactions, van der Waals, and hydrophobic interactions between hosts and guests.[11]

On the other hand, ferrocene is widely regarded as a rigid body having large harmonic potentials between all carbon−iron pairs.[12] Early in 1975, Siegel and Breslow reported the first ferrocene/β-CD inclusion complex.[13] From then on, host−guest complexes formed by CDs and ferrocenes in solution and in the solid state have been widely reported.[14] Harada and Takahashi reported that the binding stoichiometry of CDs with ferrocenes was 1:1 for α-CD and β-CD but 2:1 for γ-CD.[15] Kaifer and co-workers reported the complexation thermodynamics of CDs with positively charged derivatives of (ferrocenylmethyl)dimethylamine bearing the ferrocene backbone and varying length of alkyl chains.[16] However, these pioneering works were mainly focused on the complexations of native CDs with ferrocenes and comparative studies of the inclusion complexations of neutral and differently charged CDs with ferrocenes are still rare. To make some contributions to this category, we wish to report a comparative study on the inclusion complexation behaviors of native β-CD and two oppositely charged β-CD derivatives with two positively charged ferrocene derivatives (Charts 1 and 2) using isothermal titration microcalorimetry (ITC) and cyclic voltammetry. On the basis of these

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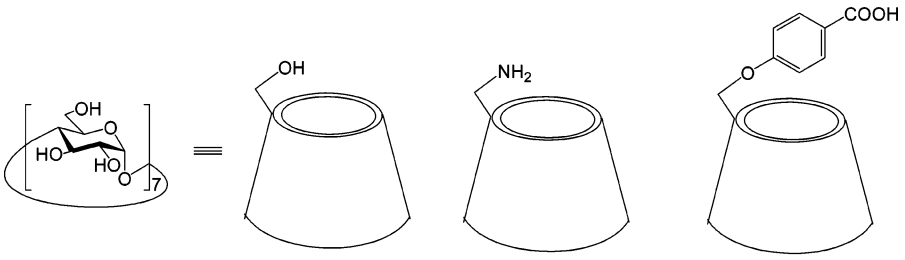
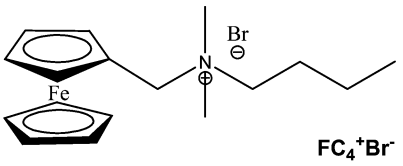
10.1021/jp0760206 CCC: $40.75
Published on Web 01/15/2008

CHART 1

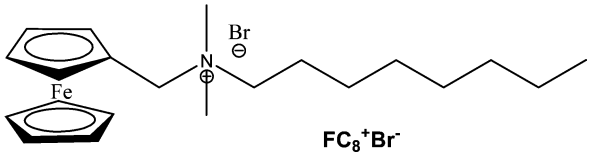


1 **2** **3**

CHART 2



$FC_4^+Br^-$



$FC_8^+Br^-$

studies, we can establish the existence of correlations between the thermodynamic parameters and the binding modes. The latter will serve to increase our understanding of the factors governing the molecular binding abilities and selectivities of ferrocenes toward differently charged CDs. This applies especially to the influences of ionization and electrostatic interactions on the selective binding.

Experimental Section

Materials. β-CD was purchase from Wako and recrystallized twice from water and dried *in vacuo* at 100 °C for 24 h prior to use. Mono(6-amino-6-deoxy)-β-CD (**2**),[17] mono[6-*O*-6-(4-carboxyl-phenyl)]-β-CD (**3**),[18] $FC_4^+Br^-$,[18] and $FC_8^+Br^-$[19] were prepared according to reported procedures and fully characterized by ^{1}H NMR, ESI-MS, and elemental analysis.

Mesurements. The cyclic voltammetry (CV) measurements were performed on a BAS Epsilon electrochemical analyzer. As the supporting electrolyte, sodium chloride was dissolved in distilled, deionized water to make 0.05 M solution for the cyclic voltammetry measurements. Disodium hydrogen phosphate and sodium dihydrogen phosphate were dissolved in distilled, deionized water to make a 0.1 M phosphate buffer solution of pH 7.20 for microcalorimetric titrations. It should be noted that, at pH 7.2, the amino group of **2** (Chart 1) is protonated and exists in cationic form,[8a] and the carboxylic group of **3** (Chart 1) is deprotonated and exists in the anionic form.[20] On the other hand, both of (ferrocenylmethyl)dimethylamine guests are in the cationic form at pH 7.2. All of the microcalorimetric titrations experiments were performed on a Microcal VP-ITC titration microcalorimeter, which permits the simultaneous calculation of the enthalpy and the equilibrium constant from a single titration curve. The instrument was calibrated chemically by performing the complexation reaction of β-CD with cyclohexanol, which gave thermodynamic parameters in good agreement with the literature data.[21] During each injection, 10 μL of guest buffer solution was released into the sample cell containing a buffer solution of host CD while stirring at 300 rpm at 25 °C under atmospheric pressure. The sample cell volume was 1.4227 mL in all experiments. Each titration experiment was composed of 29 successive injections. All solutions were degassed and thermostated using a Thermo-Vac accessory before the titration experiments were performed. (Ferrocenylmethyl)dimethylaminium solutions were applied in the concentration range of 4.02−4.03 mM, and the concentrations of host CDs were 0.201−0.208 mM.

Results and Discussions

Microcalorimetric Titration. During isothermal titration microcalorimetry, each addition of (ferrocenylmethyl)dimethylaminium solution into the sample cell gave rise to a heat of reaction, caused by the formation of inclusion complexes between (ferrocenylmethyl)dimethylaminium guests and CDs. The heats of reaction decreased after each injection because of decreases in host CD concentrations available to form inclusion complexes. A typical titration curve is shown in Figure 1. A control experiment was performed to determine the heat of dilution by injecting a guest buffer solution into a pure buffer solution containing no host CDs. The dilution enthalpy was subtracted from the apparent enthalpy obtained in each titration run, and the net reaction enthalpy was analyzed by using the "one set of binding sites" model.

The ORIGIN software (Microcal), used for the calculation of binding constant (K_S) and standard molar reaction enthalpy ($\Delta H°$) from each titration curve, gave the relevant standard derivation on the basis of the scatter of data points in a single titration experiment. The "one set of binding sites" model means that all binding sites are assumed to have the same K_S and $\Delta H°$ no matter how many interaction sites are available. So we have the following equations,[22]

$$K = \frac{\Theta}{(1-\Theta)[X]} \tag{1}$$

$$X_t = [X] + n\Theta M_t \tag{2}$$

where K = binding constant, Θ = fraction of sites occupied by ligand X, [X] is free concentration of ligand, X_t is bulk concentration of ligand, n = number of sites, and M_t is bulk concentration of macromolecule in V_0.

Combining eqs 1 and 2 above gives

$$\Theta^2 - \Theta\left[1 + \frac{X_t}{nM_t} + \frac{1}{nKM_t}\right] + \frac{X_t}{nM_t} = 0 \tag{3}$$

The total heat content Q of the solution contained in V_0 at fractional saturation Θ is

$$Q = n\Theta M_t \Delta H° V_0 \tag{4}$$

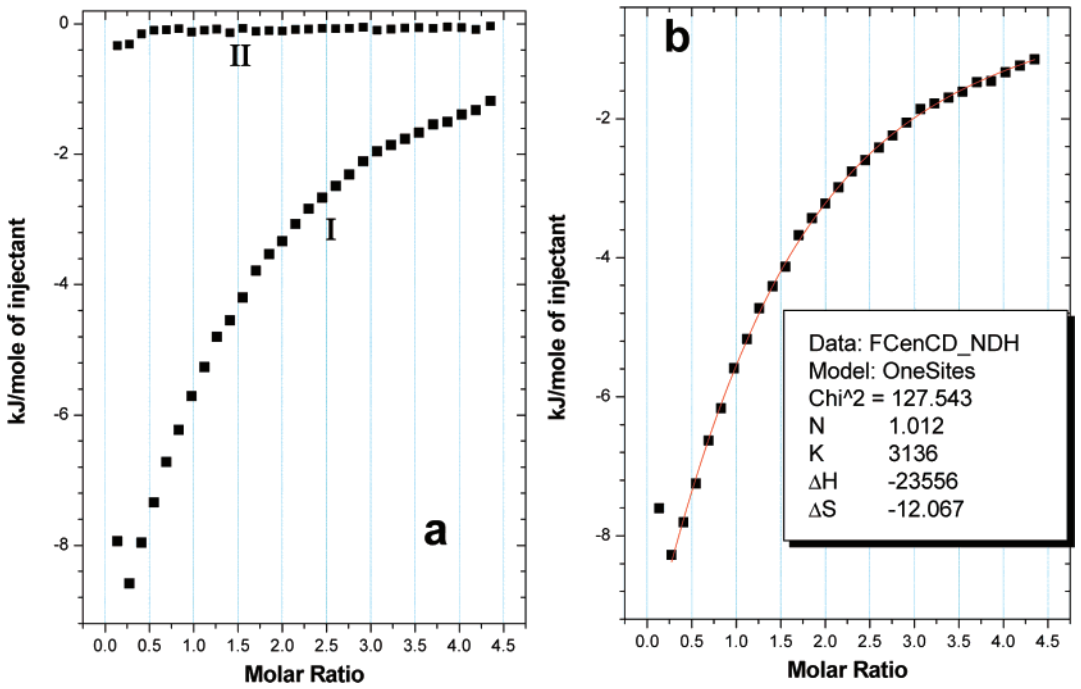


Figure 1. (a) Heat effects of complexation (I) and of dilution (II) of **2** with $FC_4^+Br^-$ for each injection during titration microcalorimetric experiment. (b) "Net" heat effect obtained by subtracting the heat of dilution from the heat of reaction, which was analyzed by computer simulation using the "one set of binding sites" model.

TABLE 1: Complex Stability Constant (K_S), Standard Enthalpic ($\Delta H°$), and Entropic Changes ($T\Delta S°$) for Inclusion Complexations of (Ferrocenylmethyl)dimethylaminium Guests with Hosts 1−3 in Phosphate Buffer Solutions at pH 7.20 and 298.15 K

guest	host	K_S (M^{-1})	$\Delta H°$ (kJ·mol^{-1})	$T\Delta S°$ (kJ·mol^{-1})	$\Delta G°$ (kJ·mol^{-1})
$FC_4^+Br^-$	**1**	4137 ± 63	−24.69 ± 0.28	−4.05 ± 0.32	−20.64 ± 0.04
	2	3130 ± 22	−23.57 ± 0.03	−3.62 ± 0.03	−19.95 ± 0.02
	3	7679 ± 14	−17.14 ± 0.07	5.04 ± 0.07	−22.18 ± 0.01
$FC_8^+Br^-$	**1**	5122 ± 67	−20.56 ± 0.16	0.61 ± 0.19	−21.17 ± 0.03
	2	3680 ± 52	−19.65 ± 0.18	0.70 ± 0.23	−20.35 ± 0.04
	3	9328 ± 178	−14.19 ± 0.13	8.47 ± 0.16	−22.66 ± 0.05

Solving the quadratic eq 3 for Θ and then substituting this into eq 4 gives

$$\Theta = \frac{NX_t\Delta HV_0}{2}\left[1 + \frac{M_t}{NX_t} + \frac{1}{NK_sX_t} - \sqrt{\left(1 + \frac{M_t}{NX_t} + \frac{1}{NK_sX_t}\right)^2 + \frac{4M_t}{NX_t}}\right] \quad (5)$$

The value Q above can be calculated (for any designed values of n, K, and $\Delta H°$) at the end of the ith injection and designated $Q(i)$. However, the change in heat content (ΔQ) from the completion of the $i-1$ injection to completion of the i injection is more interesting for comparison with experiment. Therefore, the calculation after the ith injection from the $i-1$ injection for ΔQ is given below. After completion of an injection, it is obvious that a correction must be made for displaced volume since some of the liquid in V_0 after the $i-1$ injection will no longer be in V_0 after the ith injection, even though it will contribute to the heat effect before it passes out of the working volume V_0. The liquid in the displaced volume contributes about 50% as much heat effect as an equivalent volume remaining in V_0. The correct expression then for heat released, ΔQ, from the ith injection is

$$\Delta Q(i) = Q(i) + \frac{dV_i}{V_0}\left[\frac{Q(i) + Q(i-1)}{2}\right] - Q(i-1) \quad (6)$$

The process of fitting experimental data then involves the following: (1) initial guesses (which most often can be made accurately by Origin) of n, K, and $\Delta H°$; (2) calculation of $\Delta Q(i)$ for each injection and comparison of these values with the measured heat for the corresponding experimental injection; (3) improvement in the initial values of n, K, and $\Delta H°$ by standard Marquardt methods; (4) iteration of the above procedure until no further significant improvement in fit occurs with continued iteration.[22] Along with obtaining K_S and $\Delta H°$ in this fitting program, the N value in eq 5 can also be obtained, which was given as a parameter when fitting the binding isotherm (panel b in Figure 1). To check the accuracy of the observed thermodynamic quantities and afford self-consistent parameters, at least two independent titration experiments were carried out. The average values obtained for the complex stability constant (K_S), standard free energy ($\Delta G°$), enthalpic ($\Delta H°$), and entropic changes ($T\Delta S°$) for inclusion complexations of various guest molecules with hosts are summarized in Table 1.

Binding Stoichiometry. It has been reported[16] that β-CD forms stoichiometric 1:1 inclusion complexes with ferrocenes. Our titration data also give the 1:1 binding stoichiometry between host and guest in accordance with the "N" values obtained in the curve fitting. Moreover, the Corey−Pauling−Koltun (CPK) molecular model studies demonstrate that the β-CD cavities in hosts **1**−**3** can only accommodate one ferrocene group, which subsequently rationalize the 1:1 binding stoichiometry between host and guest.

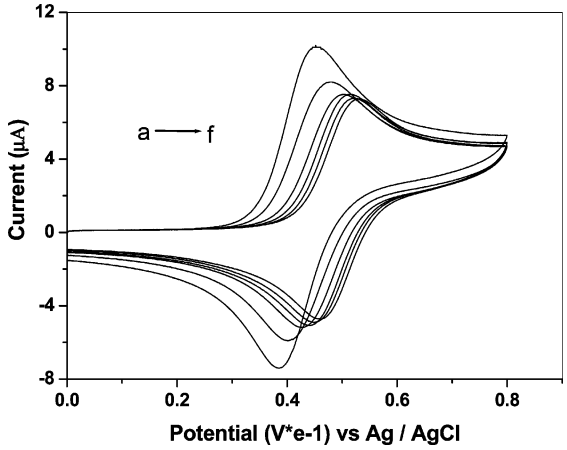


Figure 2. Cyclic voltammogram of $FC_4^+Br^-$ (1.0 mM) obtained on a GC electrode immersed in phosphate aqueous buffer solution (pH 7.20, 50 mM NaCl as supporting electrolyte) with the addition of **2** ([**2**] = 0, 1.0, 3.0, 5.0, 7.0, 10.0 mM from a to f). Scan rate = 50 mV/s.

Cyclic Voltammetry. Kaifer reported that the CD/ferrocene inclusion complex has a lower diffusion coefficient than free ferrocene, which leads to the decreased peak currents observed in the cyclic voltammograms.[16] Similar phenomena are also observed in the inclusion complexations of ferrocenes with hosts **1**−**3**. Figure 2 shows a typical cyclic voltammogram of $FC_4^+Br^-$ (1.0 mM) with the gradual addition of host **2** (0 to 10 mM). In Figure 2 each sequential addition of **2** was accompanied by two effects: (a) the peak current decreased with each addition of **2** and (b) the peak current was shifted to more positive potentials with each addition of **2**. The first effect is due to the fact that the inclusion complex has a considerably lower diffusion coefficient than uncomplexed substrate, while the second effect, the positive shift of the peak potential, is due to the thermodynamically favorable equilibrium constant, and the shift is expected to continue with further additions of **2** until the equilibrium becomes saturated with respect to **2**. The actual electrode process taking place when there is significant quantities of both substrate and host is the weighted average of the two different electrode processes, that of free substrate and that of complexed substrate. This phenomenon does indicate that the ferrocene group is included in the β-CD cavity of **2** to form the host−guest complex. Other inclusion complexes of selected (ferrocenylmethyl)dimethylaminium guests with hosts **1**−**3** display similar cyclic voltammetry behavior as that of **2**/FC_4^+-Br^- system. Although it is possible to evaluate the equilibrium constant from electrochemical data, our qualitative CV data is not suitable for that purpose.

Binding Ability. It is well-known that aminated β-CDs, which possess positive charge at pH 7.2,[8a,23] improve the original binding abilities of native CDs toward negatively charged guest molecules due to the additional electrostatic interactions.[8] However, when the guest molecules are positively charged in the present system, the electrostatic effect are reversed. As can be seen in Table 1, the binding constants for the cationic hosts were observed to be 3130 and 3680 M^{-1} for the inclusion complexations with $FC_4^+Br^-$ and $FC_8^+Br^-$, respectively, which are only 0.76 and 0.72 times as great as the corresponding values observed for the native β-CD due to electrostatic repulsion. In contrast, owing to the favorable electrostatic attraction, the negatively charged host **3** displays higher binding abilities (1.86 times for $FC_4^+Br^-$ and 1.82 times for $FC_8^+Br^-$) toward (ferrocenylmethyl)dimethylaminium guest than native β-CD. Besides the contributions of electrostatic attraction or repulsion, the ionization of CDs also change both the hydrophobicity and

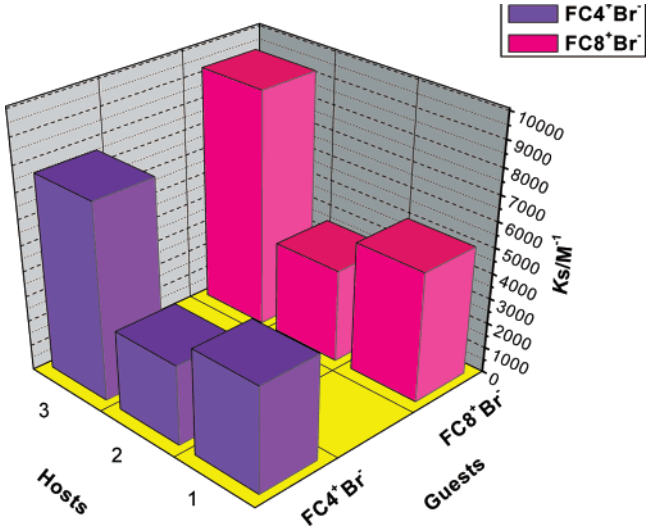


Figure 3. Complex stability constants (K_S) of inclusion complexation of hosts **1**−**3** with (ferrocenylmethyl)dimethylaminium guests in aqueous phosphate buffer solutions at 298.15 K.

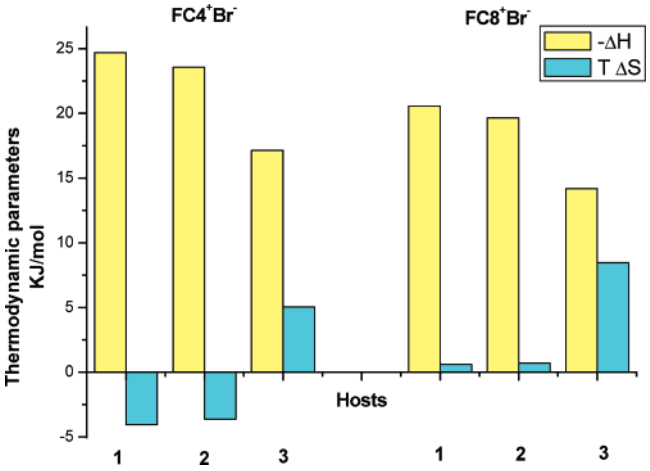


Figure 4. Standard enthalpic ($\Delta H°$) and entropic changes ($T\Delta S°$) for the inclusion complexations of hosts **1**−**3** in phosphate aqueous buffer solutions at 298.15 K.

the desolvation effect of hosts upon inclusion complexation with guest molecules. These factors inevitably affect the enthalpic and entropic changes of host−guest complexation, which will be discussed in detail below.

Complexation Thermodynamics. From the viewpoint of thermodynamics, all of the inclusion complexations between (ferrocenylmethyl)dimethylaminium guests and hosts **1**−**3** are driven by favorable enthalpic changes ($\Delta H° < 0$), accompanied by either favorable ($T\Delta S° > 0$) or unfavorable ($T\Delta S° < 0$) entropic changes. It is well documented that, among several weak noncovalent interactions between host and guest, the hydrophobic, hydrogen bond, $\pi-\pi$, C−H···π, and van der Waals interactions are the main contributions to the enthalpic changes, while conformational changes and desolvation contribute to the entropic changes. Therefore, we can deduce that the van der Waals and hydrophobic interactions play crucial roles in the enthalpy contributions to the inclusion complexations of hosts **1**−**3** with (ferrocenylmethyl)dimethylaminium guests. The relatively complicated entropic changes can be analyzed with less certainty from the standpoints of both hosts and guests. Generally, the host−guest association process, which leads to the loss of conformational freedom, is inherently accompanied by a decrease in entropy. On the other hand, before association, both the host CD and the guest molecule are highly solvated,

TABLE 2: Complex Stability Constant ($\pm\kappa_S$), Standard Enthalpic ($\Delta H°$), and Entropic Changes ($T\Delta S°$) of 3/$FC_8^+Br^-$ System in the Presence of Alcohols (4 vol %) at 298.15 K

alcohol	K_S (M^{-1})	$\Delta H°$ (kJ·mol^{-1})	$T\Delta S°$ (kJ·mol^{-1})	$\Delta G°$ (kJ·mol^{-1})
none	9328 ± 178	−14.19 ± 0.13	8.47 ± 0.16	−22.66 ± 0.05
methanol	7982 ± 186	−14.66 ± 0.16	7.61 ± 0.22	−22.27 ± 0.06
ethanol	6061 ± 288	−15.09 ± 0.25	6.49 ± 0.37	−21.58 ± 0.12
2-propanol	2068 ± 15	−20.14 ± 0.06	−1.22 ± 0.07	−18.92 ± 0.02

and the solvent molecules around the host and the guest are highly ordered. During the association, the solvation shells of both the host and the guest undergo reorganization accompanied by the loss of some solvent molecules. This process creates disorder in the system and thus leads to a favorable entropic gain, which compensates for the entropic change, to various degrees, arising from the loss of conformational freedom upon association. As the combined result of these factors, the inclusion complexes of (ferrocenylmethyl)dimethylaminium guests with hosts **1**−**3** give either positive or negative entropic changes. For the sake of the direct visualization of all series of data, the complex stability constants (K_S), standard enthalpic ($\Delta H°$), and entropic changes ($T\Delta S°$) are illustrated by the bar graphs shown in Figure 3 and Figure 4.

As can also be seen from the data in Table 1, all of the inclusion complexations of (ferrocenylmethyl)dimethylaminium guests with charged hosts **2** and **3** display less favorable enthalpic changes (−14.19 to −23.57 kJ/mol for **2** and **3** vs −20.56 to −24.69 kJ/mol for β-CD) but more favorable entropic changes (−3.62 to 8.47 kJ/mol for **2** and **3** vs −4.05 to 0.61 kJ/mol for β-CD) than observed for the neutral host β-CD. A possible reason for this may be that the ionizations of substituents in **2** or **3** decrease the hydrophobicity of host **2** or **3**, which consequently weakens the hydrophobic interactions between the host and the guest and thus results in less exothermic enthalpic changes. On the other hand, as compared with native β-CD, the charged hosts **2** and **3** are more heavily solvated in aqueous solution and have to lose more water molecules durig complexation, which leads to a more extensive desolvation effect which contributes to the favorable entropic gain. A further comparison on the thermodynamic parameters for the inclusion complexations of oppositely charged hosts **2** and **3** shows that the enthalpic changes for the inclusion complexations of negatively charged **3** are less negative, while the entropic changes are much more positive, than those for positively charged **2**. This means that the stronger binding abilities of negatively charged **3** toward (ferrocenylmethyl)dimethylaminium guests can be attributed more to favorable entropic gains than to the exothermic enthalpic changes. A plausible explanation is that the electrostatic attraction between the negatively charged **3** and the positively (ferrocenylmethyl)dimethylaminium guest enables a closer proximity of host and guest. This proximity decreases the distance while increasing the surface contact between the host and the guest, which favors the destruction of the solvation shells around the host and the guest to some extent. The favorable entropic gains arising from the enhanced desolvation effect gives rise to the strongest binding abilities for negatively charged **3** among the host CDs examined.

Solvent Effect. Warner et al. have demonstrated that the addition of small amounts of organic solvents, such as alcohols, could alter the binding abilities of CDs toward model substrates in aqueous solution.[24] In this context, we also quantitatively examined the influence of alcohols on the binding abilities of host CDs toward (ferrocenylmethyl)dimethylaminium guests. In the microcalorimetric titration experiments, a small amount (4%, by volume) of methanol, ethanol, and 2-propanol, respectively, were added to the phosphate buffer solution and the binding constants between the hosts and guests in the presence and absence of alcohols were assessed. The results for a representative system (**3**/$FC_8^+Br^-$) are listed in Table 2. The data in Table 2 indicate that the binding constants of the **3**/FC_8^+-Br^- system decrease from 9328 M^{-1} to 7982 M^{-1}, 6061 M^{-1}, and 2068 M^{-1} when small amounts of methanol, ethanol, and 2-propanol, respectively, were added. Thermodynamically, these decreases of the binding abilities are not due to the favorable enthalpic gain ($\Delta H°_{\text{with alcohol}} - \Delta H°_{\text{without alcohol}} = -0.47$ to -5.95 kJ/mol) but rather to the less favorable entropic loss ($T\Delta S°_{\text{with alcohol}} - T\Delta S°_{\text{without alcohol}} = -0.86$ to -9.69 kJ/mol). As demonstrated in the previous section, the enthalpic changes of the **3**/$FC_8^+Br^-$ system mainly arises from the van der Waals and hydrophobic interactions. According to our previous report,[25] the addition of alcohols could bring about the extrusion of water from the CD cavity and thus render the CD cavity more hydrophobic. The strengthened hydrophobic interactions between the CD cavity and the guest molecule consequently lead to a more negative enthalpic change. However, this favorable enthalpic gain is overwhelmed by the dominating entropic loss brought about by the weakened desolvation effect when some water molecules are replaced by alcohols, which consequently results in the significantly weakened host−guest binding.

Conclusion

In summary, the molecular selectivity of native β-CD for charged guests can be efficiently attenuated by introducing differently charged substituents. Because of the different electrostatic interactions (attraction or repulsion) between the host and the guest, the oppositely charged hosts give rise to either increased or decreased binding abilities toward (ferrocenylmethyl)dimethylaminium guests as compared to neutral β-cyclodextrin. The addition of organic solvents disrupt the stability of complex, which is a consequence of changes in the desolvation process, although the cavity becomes more hydrophobic.

Acknowledgment. We are grateful to the 973 program (2006CB932900), NNSFC (90306009, 20421202, and 20673061), the special Fund for the Doctoral Program from the Ministry of Education of China (20050055004), and the Tianjin Natural Science Foundation (06YFJMJC04400) for financial support.

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