Complexation of Polyvalent Cyclodextrin Ions with Oppositely Charged Guests: Entropically Favorable Complexation Due to Dehydration

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Abstract: Thermodynamic parameters for complexation of polyvalent cyclodextrin (CD) cation and anion with oppositely charged guests have been determined in D_2O containing 0.02 M NaCl by means of ^{1}H-NMR spectroscopy. Protonated heptakis(6-amino-6-deoxy)-β-CD (per-NH_3^+-β-CD) forms stable inclusion complexes with monovalent guest anions. The enthalpy (ΔH) and entropy changes (ΔS) for complexation of per-NH_3^+-β-CD with *p*-methylbenzoate anion (*p*-CH_3-Ph-CO_2^-) are 3.8 ± 0.7 kJ mol^{-1} and 88.6 ± 2.2 J mol^{-1} K^{-1}, respectively. The ΔH and ΔS values for the native β-CD-*p*-CH_3-Ph-CO_2^- system are -8.6 ± 0.1 kJ mol^{-1} and 15.3 ± 0.7 J mol^{-1} K^{-1}, respectively. The thermodynamic parameters clearly indicate that dehydration from both the host and guest ions accounts for the entropic gain in inclusion process of *p*-CH_3-Ph-CO_2^- into the per-NH_3^+-β-CD cavity. The fact that the neutral guests such as 2,6-dihydroxynaphthalene and *p*-methylbenzyl alcohol hardly form the complexes with per-NH_3^+-β-CD exhibits that van der Waals and/or hydrophobic interactions do not cause the complexation of the polyvalent CD cation with the monovalent anion. The acetate anion is not included into the per-NH_3^+-β-CD cavity, while the butanoate and hexanoate anions form the inclusion complexes. The complexation of the alkanoate anions is entropically dominated. Judging from these results, it may be concluded that Coulomb interactions cooperated with inclusion are required for realizing the large entropic gain due to extended dehydration. Entropically favorable complexation was also observed for the anionic CD-cationic guest system. The present study might present a general mechanism for ion pairing in water.

Keywords: cyclodextrins · dehydration · entropy-driven complexation · ion association · thermodynamics

Introduction

Cyclodextrins (CD) behave as hosts which include apolar guests into their hydrophobic cavities.[1] In some cases, CDs show enzyme-like function and, therefore, inclusion complexes of CDs are regarded as supramolecules.[2] Several forces have been proposed as the driving forces for forming inclusion complexes. Van der Waals interactions are the most common forces for inclusion complexes where guest molecules well fit with the CD cavities.[3] Hydrophobic interaction is currently assumed for apolar guests whose molecular sizes are somewhat smaller than the size of the CD cavity.[4] It is characteristic of the hydrophobic interaction to show positive entropy change.[5] Dipolar interactions are considered in complexation of polar guests with CDs.[6] Although hydrogen bonding is plausible as an attractive force,[7] no evidence for this interaction in water has been presented in CD chemistry.

Native CD has the lined primary and secondary OH groups at narrower and wider rims of its cavity, respectively. Therefore, a wide variety of chemical reactions can be applied to modify CD.[8] Several CD derivatives having positive or negative charges have been prepared. Applying these charged CDs, Coulomb interactions can be utilized to increase stability of complexes and to realize molecular recognition including chiral recognition.[1f, 9] Since α-amino acids, aliphatic and aromatic carboxylic acids, or amines can bear charge(s) under particular conditions, inclusion behavior and molecular recognition involving Coulomb interactions have been studied with these guests using charged CDs.[8] Aminated CDs in their protonated forms have widely been used as the cationic CDs.[10] Especially 6^A-amino-6^A-deoxy-β-CD (mono-NH_2-β-CD) and heptakis(6-amino-6-deoxy)-β-CD (per-NH_2-β-CD) in protonated forms are common cationic CDs whose reported pK_a values are 8.5 and 6.9–8.5, respectively.[11, 12] At pH <6, mono-NH_2-β-CD and per-NH_2-β-CD exist as the monovalent and polyvalent cations, respectively (mono-NH_3^+-β-CD and per-NH_3^+-β-CD). It has been reported that the binding constants (K) for the mono-NH_3^+-β-CD com-

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plexes of aromatic carboxylic acids in the undissociated forms are considerably larger than those of the complexes of the corresponding carboxylate anions,[11] suggesting that Coulomb interaction between a monovalent CD cation and a monovalent guest anion is not effective for stabilizing an inclusion complex. Destruction of hydrophobic environment of the CD cavity by introducing an NH_3^+ group makes difficult to include a hydrophobic guest into the mono-NH_3^+-β-CD cavity.[13] Stability of inclusion complexes of monovalent guest anions, however, drastically increases when a polyvalent host cation, per-NH_3^+-β-CD, is used in place of the monovalent one.[14, 15] Per-NH_3^+-β-CD forms an extremely stable association complex with a polyvalent CD anion, the heptaanion of heptakis(6-carboxymethylthio-6-deoxy)-β-CD (per-COO^--β-CD).[12] These phenomena can apparently be understood by the following equation,

$$W_{el} = (Ne^2\nu\lambda)/d\varepsilon \quad (1)$$

where W_{el} is the electric work to be gained per mol for ion association, N is the Avogadro's number, e is the electronic charge, d is the distance between oppositely charged ions, ε is the dielectric constant, and ν and λ are numbers of positive and negative charges, respectively.[16] W_{el} is essentially correspondent to enthalpy change (ΔH) for ion association in homogeneous solution where only Coulomb interaction acts as binding force. Interactions of ionic CD with oppositely charged guest ion, however, cannot wholly be explained by such a simple model. Thermodynamic quantities are expected to provide significant information to clarify the mechanism for complexation. Usefulness of the thermodynamic study in CD chemistry has been pointed out previously.[17] Thermodynamic study is very useful to understand the ion association cooperated by inclusion as suggested by previous studies.[17]

Abstract in Japanese:

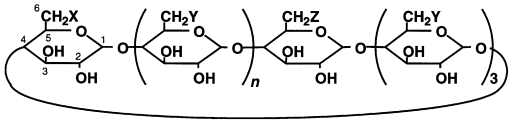
シクロデキストリン(CD)多価カチオンあるいはアニオンと反対電荷を有するゲストイオンとの錯形成に対する熱力学的パラメータを，0.02 M の NaCl を含む重水中において，^{1}H NMR 法により求めた．プロトン化されたヘプタキス（6-アミノ-6-デオキシ）-β-CD（per-NH_3^+-β-CD）は一価のゲストアニオンと安定な包接錯体を形成する．per-NH_3^+-β-CD と p-メチル安息香酸アニオン(p-CH_3-Ph-CO_2^-)との錯形成に対するエンタルピー(ΔH)およびエントロピー変化(ΔS)は，それぞれ 3.8±0.7 kJ mol^{-1} および 88.6±2.2 J mol^{-1}K^{-1} であった．β-CD-p-CH_3-Ph-CO_2^-系のΔH と ΔS の値はそれぞれ-8.6±0.1 kJ mol^{-1} および 15.3±0.7 J mol^{-1}K^{-1} であった．得られた熱力学的パラメータから，p-CH_3-Ph-CO_2^-の per-NH_3^+-β-CD 空洞への包接現象におけるエントロピー獲得は，包接にともなうホストとゲスト両分子からの脱水和に起因することがわかる．2，6-ジヒドロキシナフタレンや p-メチルベンジルアルコールのような中性のゲスト分子は per-NH_3^+-β-CD とほとんど錯体を形成しないという事実は，van der Waals 相互作用あるいはまた疎水性相互作用が多価 CD カチオンと一価アニオンとの錯形成には主たる結合力として働かないことを示している．酢酸アニオンは per-NH_3^+-β-CD の空洞には包接されないが，ブタン酸アニオンやヘキサン酸アニオンは包接錯体を形成する．これらの脂肪酸アニオンの包接もエントロピー支配である．このような結果から，包接と協同する Coulomb 相互作用が，大きな脱水和による大きなエントロピー獲得をもたらすと結論することができる．エントロピー的に有利な錯形成はアニオン性 CD-カチオン性ゲストの系においても観察された．本研究から水中におけるイオン対形成の一般的な機構を提出することができるだろう．

Recently, we reported entropically favorable complexation of the guest anions of p-methylbenzoic acid (p-Me-Ph-CO_2H) and N-acetyl-α-amino acids with per-NH_3^+-β-CD.[14, 15] In the present work, we studied such an entropically favorable process in more detail and would like to report that stabilization of the complexes of polyvalent host cation (or anion) and monovalent guest anion (or cation) is ascribed to extended dehydration from both host and guest during complexation, which causes positive entropy change.

Results

The structures of the host and guest compounds used in this study are shown in Table 1 and Figure 1.

Table 1. Structures and abbreviations of cyclodextrins.



Abbreviation	n	X	Y	Z
α-CD	1	OH	OH	OH
per-NH_2-α-CD	1	NH_2	NH_2	NH_2
β-CD	2	OH	OH	OH
mono-NH_2-β-CD	2	NH_2	OH	OH
di-NH_2-β-CD	2	NH_2	OH	NH_2
per-NH_2-β-CD	2	NH_2	NH_2	NH_2
per-CO_2H-β-CD	2	SCH_2CO_2H	SCH_2CO_2H	SCH_2CO_2H

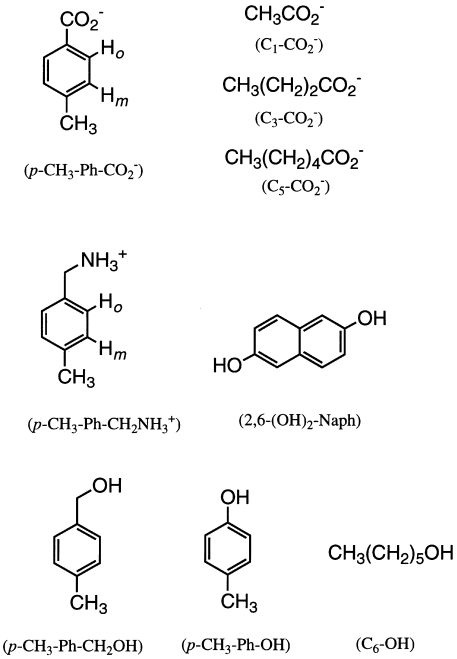


Figure 1. Structures of the guest molecules used herein.

Structures of inclusion complexes of anionic guests: Rotating frame nuclear Overhauser and exchange spectroscopy (ROESY) as well as ordinary ^{1}H-NMR spectroscopy provided the information about the structures of the CD complexes of anionic guests such as p-CH_3-Ph-CO_2^- and alkanoates (C_n-

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CO_2^-). The equimolar host–guest solutions in D_2O (pD 6.0 or 9.0) were the samples of the ROESY measurements. The examples of the ROESY spectra are shown in Figure 2. The relative intensities of the cross peaks and the deduced orientations of the guest anions in the CD cavities are shown in Table 2.

Addition of *p*-CH_3-Ph-CO_2^- into the α-CD solution causes the upfield shift of the protons at the 3-positions (H^3) and the slight downfield shifts of the protons at the 5- and 6-positions of α-CD (H^5 and H^6); this suggests formation of a relatively shallow inclusion complex of this host–guest pair (see Supporting Information). The ROESY spectrum (Supporting Information) clearly indicates that the *p*-CH_3-Ph-CO_2^- anion penetrates into the α-CD cavity from the secondary OH group side of the host and that the CH_3 group of the guest is located inside the cavity and, inevitably, the CO_2^- group protrudes from the cavity to place it in the aqueous bulk phase. Such an orientation (normal orientation) may be favorable because only small dehydration needs upon complexation. The benzoate and *p*-nitrophenolate anions penetrate into the α-CD cavity from the secondary OH group side to take such a normal orientation.[6a, 6b, 18] On the contrary, the complex having a reversed orientation of the guest is formed in the case of β-CD. In the ROESY spectrum (Figure 2a), the strong cross peaks were observed between H_o-H^5 and H_m-H^3 and no cross peak for *p*-CH_3. The ROESY spectrum indicates that the CO_2^- group is located at the vicinity of the primary OH groups of β-CD and the *p*-CH_3 group of the guest is placed at the secondary OH group side. Such a novel orientation (reversed orientation) has never been reported except for the complex of the (*S*)-1,1′-binaphthyl-2,2′-diyl phosphate anion and heptakis(2,3,6-tri-*O*-methyl)-β-CD (TMe-β-CD).[19] Although Gelb et al.[6c] reported the reversed orientation for the benzoic acid-α-CD system, other studies suggest the normal orientation of this complex.[6b, 18b] Since relatively few studies have been carried out with the orientations of the aromatic ions or aromatic polar compounds in the β-CD cavity as compared with the α-CD complexes, it cannot be said that reversed orientation is really novel. As mentioned below, the reversed orientation would be explained reasonably in the present study.

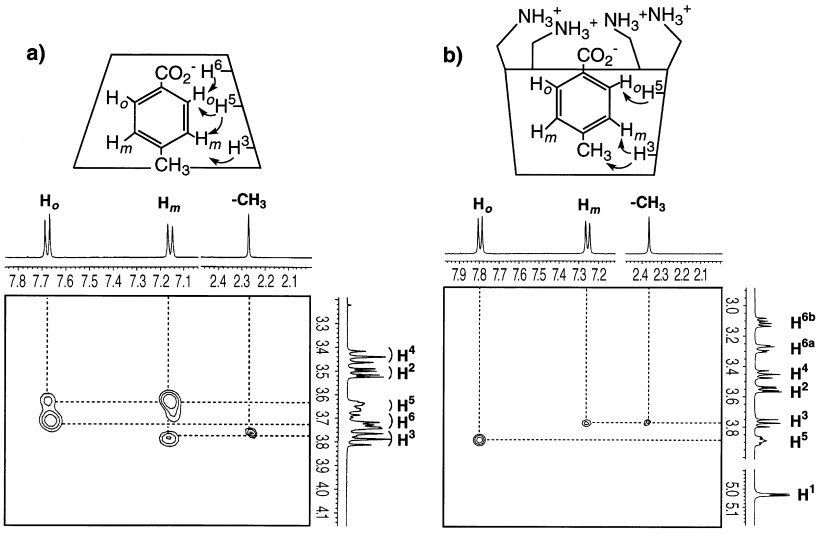

Figure 2. ROESY spectra of the equimolar solutions of a) the *p*-CH_3-Ph-CO_2^--β-CD (1×10^{-2} M) and b) the *p*-CH_3-Ph-CO_2^--per-NH_3^+-β-CD systems (5×10^{-3} M) in D_2O at pD 9.0 for a) and at pD 6.0 for b) and at 25 °C.

Table 2. Cross peaks observed in the ROESY spectra of the anionic guest–host systems in D_2O at pD 6.0.[a]

Host	Guest	Guest proton[b]	Host protons				Orientation of complex
			H^2	H^3	H^5	H^6	
α-CD	*p*-CH_3-Ph-CO_2^-	H_o	–	–	–	–	
		H_m	–	+++	–	–	
		p-CH_3	–	–	+++	–	
per-NH_3^+-α-CD	*p*-CH_3-Ph-CO_2^-	H_o	–	–	+++	–	
		H_m	+	+++	–	–	
		p-CH_3	-	–	–	–	
β-CD	*p*-CH_3-Ph-CO_2^-	H_o	–	–	+++	+	
		H_m	–	+++	+	–	
		p-CH_3	–	+++	–	–	
per-NH_3^+-β-CD	*p*-CH_3-Ph-CO_2^-	H_o	–	–	+++	–	
		H_m	–	+	–	–	
		p-CH_3	–	+	–	–	
per-NH_3^+-β-CD	C_3-CO_2^-	H_a	–	+	+++	–	
		H_b	–	+	+	–	
		CH_3	–	+++	+	–	
per-NH_3^+-β-CD	C_5-CO_2^-	H_a	–	–	+++	–	
		H_b	–	+	+++	–	
		$H_{c,d}$	–	+++	+	–	
		CH_3	–	+++	–	–	
per-NH_3^+-β-CD	C_5-CO_2^-	H_a	–	–	+++	–	
		H_b	–	–	+++	–	
		$H_{c,d}$	–	+++	+++	–	
		CH_3	–	+++	–	–	

[a] The marks indicate the intensity of the cross peaks: +++: strong, +: medium; –: no interaction. [b] The protons in the alkyl chains of alkanoic acids are marked from the CO_2H groups.

Since the aminated CDs used herein exist as their cationic forms under the present conditions, Coulomb interactions are expected between the CD cations and the carboxylate anions. Indeed, the ROESY spectra indicate that the CO_2^- group of the aliphatic and aromatic carboxylates is located at the vicinity of the NH_3^+ group(s) of the cationic hosts. A remarkable upfield shift of the H^3 protons and the fairly large downfield shift of the H^5 protons of per-NH_3^+-α-CD upon addition of p-CH_3-Ph-CO_2^- indicate somewhat shallow inclusion of the guest anion into the cationic host cavity. Meanwhile, both the signals due to the H^3 and H^5 protons of aminated β-CDs markedly shift to higher magnetic fields upon addition of p-CH_3-Ph-CO_2^- (see Supporting Information); this suggests that the guest anion is included deeply into the cavities of the aminated β-CDs.

Binding constants and thermodynamic parameters for complexation of neutral and cationic CDs: The K values for complexation of p-CH_3-Ph-CO_2^- and C_n-CO_2^- with neutral and cationic CDs were determined from the ^{1}H-NMR titrations in D_2O at pD 6.0 containing 0.02 M NaCl. 2,6-$(OH)_2$-Naph and p-CH_3-Ph-CH_2OH were used as the reference guests. Judging from the pK_a values of the conjugate acids of mono- (pK_a 8.49)[20] and di-NH_2-β-CDs (pK_a 8.3),[21] it is evident that these aminated CDs exist in the cationic forms as the case of per-NH_3^+-β-CD. The K values determined are listed in Table 3. The guest anions are hardly bound to neutral, native CDs. The cationic CDs, especially polyvalent per-NH_3^+-β-CD, scarcely interact with neutral guests, while they form the stable complexes with the guest anions having the appropriate sizes.

Table 3. Complexation of anionic and neutral guests with native and cationic CDs in D_2O at pD 6.0 and 25 °C.[a]

Entry	Guest	Host	K [M^{-1}]
1	p-CH_3-Ph-CO_2^-	α-CD	41 ± 2
2	p-CH_3-Ph-CO_2^-	per-NH_3^+-α-CD	2040 ± 100
3	p-CH_3-Ph-CO_2^-	β-CD	200 ± 20[b]
4	p-CH_3-Ph-CO_2^-	mono-NH_3^+-β-CD	520 ± 20[b]
5	p-CH_3-Ph-CO_2^-	di-NH_3^+-β-CD	750 ± 40
6	p-CH_3-Ph-CO_2^-	per-NH_3^+-β-CD	9180 ± 480[b]
7	C_1-CO_2^-	per-NH_3^+-β-CD	nd[c]
8	C_3-CO_2^-	per-NH_3^+-β-CD	370 ± 20
9	C_5-CO_2^-	per-NH_3^+-α-CD	5750 ± 380
10	C_5-CO_2^-	per-NH_3^+-β-CD	2230 ± 20
11	2,6-$(OH)_2$-Naph	β-CD	730 ± 30
12	2,6-$(OH)_2$-Naph	mono-NH_3^+-β-CD	360 ± 30[d]
13	2,6-$(OH)_2$-Naph	di-NH_3^+-β-CD	120 ± 20[d]
14	2,6-$(OH)_2$-Naph	per-NH_3^+-β-CD	51 ± 2
15	p-CH_3-Ph-CH_2OH	β-CD	73 ± 8
16	p-CH_3-Ph-CH_2OH	mono-NH_3^+-β-CD	16 ± 2
17	p-CH_3-Ph-CH_2OH	di-NH_3^+-β-CD	nd[c]
18	p-CH_3-Ph-CH_2OH	per-NH_3^+-β-CD	nd[c]

[a] The K values were determined in the presence of 0.02 M NaCl. [b] Ref. [14]. [c] The K value were too small to be determined. [d] The K values were determined in the absence of NaCl.

In order to obtain the thermodynamic quantities, the K values were determined as a function of temperature. The slopes of the van't Hoff plots ($R\ln K$ vs. T^{-1} and ΔG vs. T) provided the enthalpy (ΔH) and entropy changes (ΔS) for complexation. The results are summarized in Table 4. In all cases, the van't Hoff plots were apparently linear within the applied temperature range (Supporting Information). Therefore, changes in the heat capacity ΔC_p were neglected in this study. The effects of ΔC_p in the host–guest complexation have been discussed previously.[22] Except for the case of α-CD, the complexation of p-CH_3-Ph-CO_2^- and C_n-CO_2^- is entropically favorable. The entropic gain increases with increasing the number of charges of the host (entries 3-6). α-CD is only the host whose complexation with p-CH_3-Ph-CO_2^- shows negative ΔS. Complexation involving negative ΔH and ΔS is typically explained by the van der Waals interactions between host and gust. The inclusion of the neutral guest 2,6-$(OH)_2$-Naph (entry 14) is also enthalpically favorable, though small entropic gain is realized in this system.

Table 4. Complexation of anionic guests with native and cationic CDs in D_2O at pD 6.0 and 25 °C.

Entry	Guest	Host	ΔH [kJ mol^{-1}]	ΔS [J mol^{-1} K^{-1}]
1	p-CH_3-Ph-CO_2^-	α-CD	− 22.0 ± 1.9	− 42.1 ± 5.5
2	p-CH_3-Ph-CO_2^-	per-NH_3^+-α-CD	− 9.6 ± 0.8	31.2 ± 2.6
3	p-CH_3-Ph-CO_2^-	β-CD	− 8.6 ± 0.1	15.3 ± 0.7[a]
4	p-CH_3-Ph-CO_2^-	mono-NH_3^+-β-CD	− 10.4 ± 1.8	18.1 ± 0.6[a]
5	p-CH_3-Ph-CO_2^-	di-NH_3^+-β-CD	− 8.1 ± 0.6	27.8 ± 2.2
6	p-CH_3-Ph-CO_2^-	per-NH_3^+-β-CD	3.8 ± 0.7	88.6 ± 2.2[a]
9	C_5-CO_2^-	per-NH_3^+-α-CD	− 6.0 ± 0.3	51.8 ± 1.1
10	C_5-CO_2^-	per-NH_3^+-β-CD	8.4 ± 1.1	91.9 ± 3.8
14	2,6-$(OH)_2$-Naph	per-NH_3^+-β-CD	− 7.2 ± 1.2	9.2 ± 4.1
20	p-CH_3-Ph-$CH_2NH_3^+$	per-CO_2^--β-CD	− 14.3 ± 0.9	25.1 ± 2.9
22	2,6-$(OH)_2$-Naph	per-CO_2^--β-CD	− 22.7 ± 0.6	− 12.7 ± 2.2
25	p-CH_3-Ph-OH	per-CO_2^--β-CD	− 18.1 ± 0.2	− 8.2 ± 0.8

[a] Ref. [14].

Binding constants and thermodynamic parameters for complexation of anionic CD: Complexation of a cationic guest with an anionic CD has also been studied. Protonated p-methylbenzylamine (p-CH_3-Ph-$CH_2NH_3^+$) and per-CO_2^--β-CD were used as the guest and the host, respectively. Neutral guests such as 2,6-$(OH)_2$-Naph, p-methylbenzyl alcohol (CH_3-Ph-CH_2OH), p-methylphenol (p-CH_3-Ph-OH), and C_6-OH were used as the reference guests. Since the pK_a values of per-CO_2H-β-CD are $< 2.8-5.6$,[12] this host molecule exists in the polyvalent anion form under the experimental conditions (pD 6). The K values obtained from the ^{1}H-NMR titrations are listed in Table 5.

β-CD forms the unstable complex of p-CH_3-Ph-$CH_2NH_3^+$. Meanwhile, a very stable complex is formed in the case of per-CO_2^--β-CD. In contrast with the case of the cationic CDs, per-CO_2^--β-CD forms fairly stable inclusion complexes with the neutral guests.

The thermodynamic parameters for the p-CH_3-Ph-CH_2-NH_3^+-per-CO_2^--β-CD system are shown in Table 4, which indicates that the stability of the p-CH_3-Ph-$CH_2NH_3^+$-per-CO_2^--β-CD complex is ascribed to the relatively large and negative ΔH value and the positive ΔS value. The complexation of neutral guest such as 2,6-$(OH)_2$-Naph or p-CH_3-Ph-OH is enthalpically favorable but entropically unfavorable process.

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Table 5. Complexation of cationic and neutral guests with native and anionic CDs in D_2O at pD 7.0 and 25 °C.

Entry	Guest	Host	K [M^{-1}]
19	p-CH_3-Ph-$CH_2NH_3^+$	β-CD	33 ± 12
20	p-CH_3-Ph-$CH_2NH_3^+$	per-CO_2^--β-CD	6840 ± 510
21	2,6-$(HO)_2$-Naph	β-CD	730 ± 30
22	2,6-$(HO)_2$-Naph	per-CO_2^--β-CD	2100 ± 170
23	p-CH_3-Ph-CH_2OH	β-CD	73 ± 8
24	p-CH_3-Ph-CH_2OH	per-CO_2^--β-CD	590 ± 50
25	p-CH_3-Ph-OH	per-CO_2^--β-CD	550 ± 60
26	C_6-OH	per-CO_2^--β-CD	890 ± 40

Discussion

Native CD-p-CH_3-Ph-CO_2^- systems: p-CH_3-Ph-CO_2^- is a good NMR probe because of its very simple NMR pattern. This guest anion is too large to be included completely into the α-CD cavity resulting in the small K value ($41\,M^{-1}$) and the formation of the shallow inclusion complex. The complexation of p-CH_3-Ph-CO_2^- with α-CD is an enthalpically favorable ($\Delta H = -22.0$ kJ mol^{-1}) but entropically unfavorable process ($\Delta S = -42.1$ J mol^{-1} K^{-1}). The CO_2^- group of p-CH_3-Ph-CO_2^- is located outside of the α-CD cavity (vide supra). The main binding forces for such a normal inclusion complex are the van der Waals interactions. Complexation through van der Waals interactions is characterized by negative enthalpy and entropy changes.

On the contrary, the formation of the β-CD complex is accompanied by the positive entropy change ($\Delta S = 15.3$ J mol^{-1} K^{-1}) and the negative enthalpy change ($\Delta H = -8.6$ kJ mol^{-1} K^{-1}). Similar entropically-favorable complexation has also been reported for the benzoate anion-β-CD system where the thermodynamic parameters were measured by the potentiometric method,[23b] though the inconsistent result has been obtained from the calorimetric measurement.[23h] There are many examples of host–guest complexation whose ΔS values are positive.[3a, 23] Hydrophobic interaction is one of the plausible binding forces for such an entropically favorable process. As indicated by the 2D-ROESY spectrum, however, the CO_2^- group of the p-CH_3-Ph-CO_2^- molecule is placed inside the β-CD cavity. Therefore, it is very hard to consider the hydrophobic interaction as the main binding force for the complexation of p-CH_3-Ph-CO_2^- with β-CD. It has been known that CDs include inorganic and organic anions into their hydrophobic cavities,[6a, 6b, 6c, 6e, 24] though the mechanism for inclusion has not been clarified. Penetration of a hydrophilic group of a guest into a hydrophobic environment requires dehydration from the guest. Such a process is enthalpically unfavorable but entropically favorable. The p-CH_3-Ph-CO_2^--β-CD system seems to be an obvious example of the complexation where entropic gain due to dehydration participates in stabilization of complex and in orientation of guest in CD cavity.

The K values for the complexation of benzoic acid in the undissociated form with native α- and β-CDs and with hexakis(2,3,6-tri-O-methyl)-α-CD have been determined.[3c, 25] In these cases, the complexation is dominated by the enthalpy terms, suggesting that the van der Waals interactions promote the inclusion of this undissociated carboxylic acid. These previous results are contrastive to the complexation of p-CH_3-Ph-CO_2^- with β-CD. Judging from the ΔH (-8.6 kJ mol^{-1}) and $T\Delta S$ values (4.6 kJ mol^{-1}), it can be concluded that both the van der Waals interactions and the dehydration participate in the complex formation of p-CH_3-Ph-CO_2^- with β-CD.

Cationic CD-p-CH_3-Ph-CO_2^- systems: The thermodynamic quantities for complexation of p-CH_3-Ph-CO_2^- with per-NH_3^+-α-CD are quite different from those for the α-CD complex. The large and positive entropy change (31.2 J mol^{-1} K^{-1}) for the per-NH_3^+-α-CD system (entry 2) is not ascribed undoubtedly to hydrophobic interaction. The ROESY spectrum of this system exhibits that the guest anion, p-CH_3-Ph-CO_2^-, penetrates headlong into the host cation from the secondary OH group side, where the polar CO_2^- group of the guest acts as a head. Such an orientation is reverse to that of the α-CD complex, so to indicate the effects of Coulomb interaction between the host cation and the guest anion on the orientation of the guest anion in the per-NH_3^+-α-CD cavity. The complexation of p-CH_3-Ph-CO_2^- with per-NH_3^+-α-CD, therefore, requires the dehydration from the guest as well as from the host. Since the dehydration is an endothermic process, the ΔH value for this system should be larger than that for the α-CD system. Indeed, ΔH for the per-NH_3^+-α-CD system is larger than that for the α-CD system, but it is still negative. The negative ΔH value for the p-CH_3-Ph-CO_2^--per-NH_3^+-α-CD system may be ascribed to the effective van der Waals contacts of the guest with the host.

The p-CH_3-Ph-CO_2^- complex of mono-NH_3^+-β-CD ($K = 520\,M^{-1}$) is more stable than that of β-CD ($K = 200\,M^{-1}$). The stability of the p-CH_3-Ph-CO_2^- complex depends on the number of the positive charges of the host ($K = 520$, 750, and $9180\,M^{-1}$ for mono-, di-, and per-NH_3^+-CDs, respectively). The stabilization is brought by the entropic gain accompanied by the enthalpic loss. Both the enthalpy and entropy changes increases in the order mono-NH_3^+-β-CD < di-NH_3^+-β-CD < per-NH_3^+-β-CD (Table 4). Since hydrophobic interaction is not enhanced by the NH_3^+ group(s) attached to CD, the significant increase in ΔS for the poly-aminated CD complex should be ascribed to the more extended dehydration from the NH_3^+ groups upon complexation. The complexation of p-CH_3-Ph-CO_2^- with per-NH_3^+-β-CD is the entropy-dominating process ($\Delta H = 3.8$ kJ mol^{-1}, $\Delta S = 88.6$ J mol^{-1} K^{-1}). Bianchi and García-España reviewed the thermodynamics for ion-association host–guest systems where the hosts and the guests are mainly the macrocyclic polycations and the inorganic anions, respectively.[16] They introduce the examples of entropy-dominating complexation. Complexation via ion pairing is accompanied by desolvation resulting in slightly unfavorable ΔH and largely favorable ΔS. Recently, Bazzicalupi et al. reported a new example of the entropy-dominated complexation of the phosphate and pyrophosphate anions with the polyammonium cations where hydrogen bonding of -$NH^+ \cdots {}^-$O- participates in the stability of the ion-pair complexes.[26] There is no necessity to consider the hydrogen-bond interaction for the present system, though such an interaction cannot be excluded completely. The entropy-

dominated process showing positive ΔH and ΔS has also been reported for inclusion of alkanols and alkanoates into the β-CD cavity, where the hydrophobic interaction is mostly assumed as the main binding force.[3a, 23] Only few examples have been known as the entropy-driven complexation of α- and γ-CDs.[4c, 27]

Rekharsky and Inoue reviewed the thermodynamics of the CD complex formation.[17] They summarized numerous data of the thermodynamic quantities for complexation of CDs and treated these data on the basis of the enthalpy and entropy compensation relationship. They demonstrated that a slope (α) and an intercept ($T\Delta S_0$) in a linear relationship between ΔH^0 and $T\Delta S^0$ are the quantitative measures for the conformational change of CD and for the extent of dehydration, respectively, upon complexation. Such a conclusion has been presented previously by Inoue and his co-workers.[28] In the case of the native CDs, the linear relationship between ΔH^0 and $T\Delta S^0$ for complexation of various guests including carboxylic acids, carboxylates, alkanols, naphtharenesulfonates, and other neutral compounds provides α of 0.9 and $T\Delta S_0$ of 13 kJ mol^{-1}.[28a] For chemically modified CDs such as TMe-α-CD, TMe-β-CD, and CDs having amine ligands and their metal complexes, α and $T\Delta S_0$ are 1.1 and 21 kJ mol^{-1}, respectively, when 2-naphthalenesulfonate, benzoic acid, and its monosubstituted derivatives, *p*- and *m*-nitrophenols, and *p*-nitroaniline are used as the guests.[28b] We are short of data to discuss the $\Delta H - \Delta S$ compensation relationship in the present system. Only the data of entries 4, 5, and 6 can be applied for discussing the $\Delta H - \Delta S$ compensation relationship. A linear relationship is temporarily held between ΔH and ΔS in the complexation of *p*-CH_3-Ph-CO_2^- with the aminated CDs; $T\Delta S = 1.49\Delta H + 20.7$ (in kJ mol^{-1}, $R^2 = 0.999$). Although we need to collect more data to derive conclusion, the present results, at least, do not deny our assumption that the complexation of *p*-CH_3-Ph-CO_2^- with the cationic CD is accompanied by a large conformational change of the host (the large α) and by extended dehydration (the large $T\Delta S_0$). The energetically minimized conformation of per-NH_3^+-β-CD in water was derived from the MM/MD calculations (Figure 3). The electrostatic repulsion between the NH_3^+ groups causes a bucket-type structure of this CD (Figure 3a). Upon complexation with *p*-CH_3-Ph-CO_2^-, the structure of per-NH_3^+-β-CD gets back to a normal upturned-bucket form as shown in Figure 3b. Coulombic binding between the guest anion and the host cation requires conformational changes of the aminated CDs. This may be the reason for the large α value.

Both the ΔH and ΔS values increase linearly with increasing the number of positive charges of the host (n): $\Delta H = 2.4n - 12.8$ (in kJ mol^{-1}, $R^2 = 1.00$) and $\Delta S = 11.9n + 5.2$ (in J mol^{-1} K^{-1}, $R^2 = 0.999$). A linear relationship is also hold between ln$K$ and n: $\ln K = 0.49n + 5.7$ ($R^2 = 0.999$). Since the electric work W_{el} exhibited by Equation (1) is essentially correspondent to ΔH,[16] ΔH is consequentially proportional to n [n corresponds to $\tilde{\nu}$ in Equation (1)]. The linear relationship between ΔH and n means the proportional relationship between ΔS and n, because there is the $\Delta H - \Delta S$ compensation relationship in this system. Such a simple model suggests that the difference in the ΔG ($\Delta\Delta G$) values between

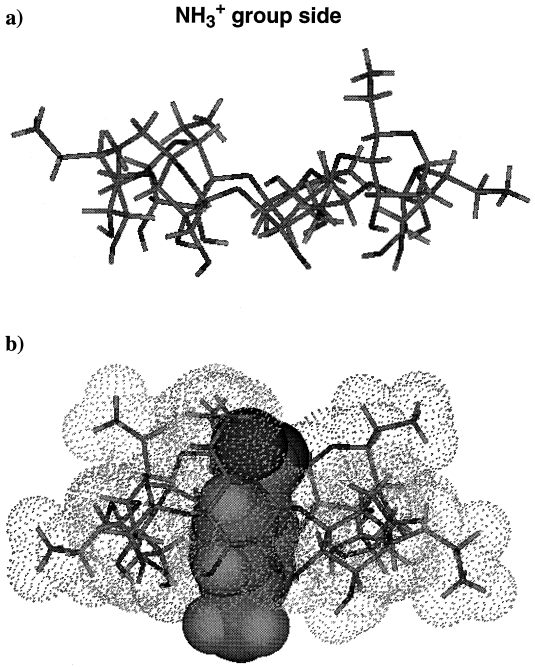

Figure 3. Optimized structures of per-NH_3^+-β-CD in water in the absence and the presence of *p*-CH_3-Ph-CO_2^- which were derived from the MM-MD calculations.

the aminated CDs is mainly ascribed to the difference in the extents of dehydration upon complexation. Recently, it was found that a linear relationship does not hold between ΔH as well as ΔS and n when hydrogen bond interaction -$NH^+ \cdots {}^-O$- participates in the formation of ion-pair complexes.[26] It is reasonable to assume, therefore, that hydrogen-bond interaction does not play an important role in the present system.

Cationic CD-C_n-CO_2^- systems: The acetate anion (C_1-CO_2^-) is too hydrophilic as well as too small to be included into the per-NH_3^+-β-CD cavity. The butanoate anion (C_3-CO_2^-) weakly complexes with per-NH_3^+-β-CD ($K = 370\,\mathrm{M}^{-1}$). The hexanoate anion (C_5-CO_2^-) forms the stable inclusion complexes of per-NH_3^+-α-CD and per-NH_3^+-β-CD, the per-NH_3^+-α-CD complex ($K = 5750\,\mathrm{M}^{-1}$) being more stable than the per-NH_3^+-β-CD complex ($K = 2230\,\mathrm{M}^{-1}$). On the basis of the difference in the ΔH values, it seems that the lower stability of the peraminated β-CD complex is ascribed to the weaker van der Waals interactions. The per-NH_3^+-β-CD cavity is too large to acquire the enthalpic gain due to effective van der Waals contacts between the host and the guest. It is expected that contribution of the van der Waals interactions is very small in the C_5-CO_2^- and per-NH_3^+-β-CD system. As indicated in Table 4, the enthalpic loss ($\Delta H = 8.4$ kJ mol^{-1}) and the entropic gain ($\Delta S = 91.9$ J mol^{-1} K^{-1}) for the C_5-CO_2^--per-NH_3^+-β-CD pair are the most remarkable in the present study. The extremely large $\Delta\Delta S$ value (40.1 J mol^{-1} K^{-1}) between the C_5-CO_2^--per-NH_3^+-α-CD and -per-NH_3^+-β-CD systems may not be explained only by the difference in extent of dehydration. Probably, both dehydration and hydrophobic interaction contribute to the large entropic gain in the C_5-CO_2^--per-NH_3^+-β-CD system. A large entropic gain in the C_6OH-β-CD and a fairly large entropic loss in the C_6-OH-α-

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CD system have been reported.[3a] We cannot exclude the hydrophobic effect in the complexation of the alkanoate anions with aminated CD, because these guest and host are amphiphilic. Since lots of factors contribute to thermodynamic parameters, effort toward separating these factors should be done in future.

Cationic CD-neutral guest systems: The stability of the complex of a neutral guest, 2,6-$(OH)_2$-Naph, decreases as introducing the positive charges to the host CD (entries 11–14). No complexation practically occurs in the case of *p*-CH_3-Ph-CH_2OH (entries 16–18). These results can be explained by destruction of hydrophobic environment by the NH_3^+ group(s) as pointed out by Easton et al.[13] A very small K value ($51\,M^{-1}$) for the 2,6-$(OH)_2$-Naph-per-NH_3^+-β-CD system as well as the fact that no complexation occurs in the *p*-CH_3-Ph-CH_2OH system suggests that both van der Waals and hydrophobic interactions hardly promote complexation of hydrophobic, neutral guest with polyvalent per-NH_3^+-β-CD. However, we cannot conclude that the contribution of these intermolecular interactions to the thermodynamic parameters is negligible in the complexation of the carboxylate anions with the polyvalent cationic CD, because the ion association accompanied by the dehydration may change the conformation of the host and may provide an environment to cause hydrophobic interaction. The cooperative work of Coulomb interactions and inclusion seems to be important to promote extended dehydration resulting in large entropic gain.

Anionic CD-cationic guest systems: In the case of per-NH_3^+-β-CD, the complexation with the monovalent guest anions is enthalpically unfavorable. Meanwhile, the fairly large and negative ΔH value ($-14.3\,kJ\,mol^{-1}$) was measured for the *p*-CH_3-Ph-$CH_2NH_3^+$-per-CO_2^--β-CD system (entry 20). Such a result can be interpreted in terms of the effective van der Waals interactions between *p*-CH_3-Ph-$CH_2NH_3^+$ and per-CO_2^--β-CD as described below. An important point is that the complexation of the polyvalent CD anion with the monovalent guest cation is the entropically favorable process ($\Delta S = 25.1\,J\,mol^{-1}\,K^{-1}$) similar to the case of the oppositely charged system. Dehydration is also assumed as the main process to gain favorable entropy change in the anionic host-cationic guest system.

Per-CO_2^--β-CD shows the unexpected behavior in complexation with neutral guests such as 2,6-$(OH)_2$-Naph and *p*-CH_3-Ph-CH_2OH. In the case of polyvalent CD cation, the hydrophilic NH_3^+ groups destroy the hydrophobic environment of the CD cavity leading to weak ability of this host to include a hydrophobic guest. However, the complex of 2,6-$(OH)_2$-Naph and per-CO_2^--β-CD ($K = 2100\,M^{-1}$) is much more stable than the β-CD complex ($K = 730\,M^{-1}$). Similar results were obtained in the case of *p*-CH_3-Ph-CH_2OH (entries 23 and 24). *p*-CH_3-Ph-OH and C_6-OH also form stable complexes with per-CO_2^--β-CD (entries 25 and 26). The complexation of 2,6-$(OH)_2$-Naph or *p*-CH_3-Ph-OH with per-CO_2^--β-CD is enthalpically favorable but entropically unfavorable; this suggests that the van der Waals interactions are the main binding forces for these systems. The depth of the hydrophobic cavity of per-CO_2^--β-CD is larger than that of β-CD itself because of the attached $SCH_2CO_2^-$ groups. The elongation of the hydrophobic cavity by the attached $SCH_2CO_2^-$ groups seems to be the reason for high ability of per-CO_2^--β-CD to include neutral, hydrophobic guests through the van der Waals interactions. Similar polyvalent CD anions whose hydrophobic cavities are elongated by substituents have been known.[29]

The structure of the *p*-CH_3-Ph-$CH_2NH_3^+$-per-CO_2^--β-CD complex was confirmed by the ROESY spectrum (Supporting Information). The cross peaks were observed between the H^5 protons of the host and the H_o, H_m, and *p*-CH_3 protons of the guest and between the H^3 protons and the H_m protons, suggesting that the *p*-CH_3-Ph-$CH_2NH_3^+$ molecule are bound to the $SCH_2CO_2^-$ group side of the host. The $SCH_2CO_2^-$ groups of the host sling up the guest through Coulomb interactions. The entropic gain due to dehydration from the host and the guest and the enthalpic gain due to the van der Waals interactions enhanced by the $SCH_2CO_2^-$ groups stabilize this inclusion complex.

Conclusion

The most important conclusion of the present study is that the inclusion of a charged guest into the cavity of an oppositely charged polyvalent-CD ion is promoted by the entropic gain acquired mainly by the dehydration from both host and guest upon complexation. Judging from the fact that no complexation occurs in the C_1-CO_2^--per-NH_3^+-β-CD pair while C_5-CO_2^- forms the stable inclusion complex with the polyvalent CD cation, the cooperative work of Coulomb interactions and inclusion might be important to cause extended dehydration from host and guest.

The same inclusion mechanism might be applied for the ionic guest–nonionic host pairs. For example, the entropically favorable inclusion occurs in the case of the *p*-CH_3-Ph-CO_2^- and β-CD system. Since the entropic gain is acquired by the dehydration, the ionic group (CO_2^-) of the guest penetrates into the hydrophobic β-CD cavity to take the reversed orientation of the complex. Inclusion of organic anions into the native β-CD cavity mostly shows positive entropy changes.[3d, 23i, 28a] The entropically favorable inclusion of the guest anions into the native β-CD cavity can be explained by the dehydration upon complexation. By the way, the anion inclusion into the α-CD cavity tends to show negative enthalpy and entropy changes.[16] This might be ascribed to the effective van der Waals contacts of guest anions with the α-CD cavity having a smaller cavity size. The difference in the mechanisms for inclusion of the anionic guest between α- and β-CDs is reflected on the orientations of the guest anion in the CD cavities. The hydrophilic CO_2^- group of the guest is faced to the aqueous bulk phase at the secondary OH group side of α-CD. Such a normal orientation has also been measured for the benzoate and *p*-nitrophenolate anions in the α-CD cavity by means of NMR spectroscopy.[6b, 18a]

The molecular recognition using Coulomb interactions is a new trend in host–guest chemistry.[16, 30] Thermodynamic studies might essentially be important to understand these new systems.

Experimental Section

Native α- and β-CDs (Nacalai) were purchased and recrystallized from water after an antioxidant containing in these compounds was removed by extraction with THF using a Soxhlet extractor. Hexakis(6-amino-6-deoxy)-α-CD (per-NH_2-α-CD)[31], per-NH_2-β-CD[31], mono-NH_2-β-CD[32], 6^A,6^D-diamino-6^A,6^D-dideoxy-β-CD (di-NH_2-β-CD),[33] and per-CO_2H-β-CD[34] were prepared according to the procedures described in the literatures. Sodium salts of the carboxylic acids (Nacalai) were prepared by neutralization with NaOH of the corresponding carboxylic acids. *p*-Methylbenzylamine (*p*-CH_3-Ph-CH_2NH_2, Wako), *p*-methylphenol (*p*-CH_3-Ph-OH, Tokyo Kasei), 2,6-dihydroxynaphtharene (2,6-$(OH)_2$-Naph, Aldrich), *p*-methylbenzyl alcohol (*p*-Me-Ph-CH_2OH, Wako), and 1-hexanol (C_6-OH, Nacalai) were purchased. The guest compounds were purified by the usual ways in cases of necessity.

^{1}H-NMR spectra were recorded on a JEOL JNM A-400 spectrometer (400 MHz) in D_2O (CEA, 99.8%) in the presence of 0.02 M NaCl. Sodium [D_4]3-(trimethylsilyl)propionate (TSP, Aldrich) was used as an external standard. The binding constants were determined from the ^{1}H-NMR titration curves ([guest] = 1×10^{-3} M) which were analyzed by a non-linear least-squares method on the basis of the assumption of the 1:1 complex formation.[35] The examples of the NMR titrations are shown in Figure 4.

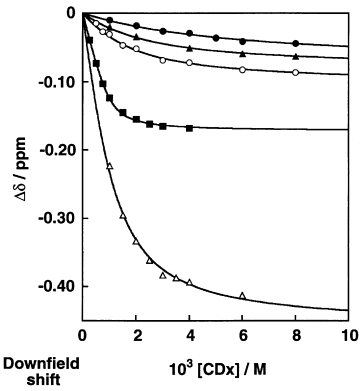

Figure 4. Changes in the proton chemical shifts of *p*-CH_3-Ph-CO_2^- (H_o) upon addition of β-CD (●), mono-NH_3^+-β-CD (▲), di-NH_3^+-β-CD (○), per-NH_3^+-β-CD (■), and per-NH_3^+-α-CD (△) in D_2O at pD 6.0 and 25 °C. The solid lines represent the best fit of the data to the 1:1 equilibria.

The K values were determined at several temperatures (15–60 °C). The thermodynamic parameters (ΔH and ΔS) were evaluated from the slopes of the van't Hoff plots ($R\ln K$ vs. T^{-1} and ΔG vs. T). The ROESY spectra were measured by a field-gradient method using a 250 ms mixing time for the degassed solutions of the mixtures of hosts and guests.

The molecular mechanics/molecular dynamics (MM/MD) calculations involving the effects of water were carried out.[36] Before the MM/MD calculations, the information of the charges of the host and the guest was obtained from the MOPAC (version 6 developed by J.J.P. Stewart, US Airforce Academy, USA) calculations. The MM/MD calculations were performed by an AMBER program system (version 4, presented by P. Kollman, University of California at San Francisco, USA) on a COMTEC 4D RPC XS24Z R4000 workstation. For calculations, 216 water molecules were placed in the 7.5 nm cube. The calculations were carried out at 250 K for the initial temperature and at 298 K for the reference temperature and for 12 ps at the time step of 0.001 ps. After verification of convergence of the data, the structure having the minimum energy was employed.

Acknowledgements

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[1] a) R. J. Bergeron, *J. Chem. Educ.* **1977**, *54*, 204; b) M. L. Bender, M. Komiyama, *Cyclodextrin Chemistry*, Springer, Berlin, **1978**; c) J. Szejtli, *Cyclodextrin Technology*, Kluwer, Dordecht, **1988**; d) S. Li, W. C. Purdy, *Chem. Rev.* **1992**, *92*, 1457; e) K. Kano in *Bioorganic Chemistry Frontiers*, *Vol. 3* (Eds.: H. Dugas, F. P. Schmidtchen), Springer, Berlin, **1993**, pp. 1; f) K. Kano, *J. Phys. Org. Chem.* **1997**, *10*, 286.

[2] a) D. W. Griffiths, M. L. Bender, *Adv. Catal.* **1973**, *23*, 209; b) R. Breslow in *Structure and Reactivity in Aqueous Solution*, *ACS Symposium Series 568* (Eds.: C. J. Cramer, D. G. Truhlar), American Chemical Society, Washington, DC, **1994**, pp. 291.

[3] a) Y. Matsui, K. Mochida, *Bull. Chem. Soc. Jpn.* **1979**, *52*, 2808; b) E. S. Hall, H. J. Ache, *J. Phys. Chem.* **1979**, *83*, 1805; c) K. Harata, K. Tsuda, K. Uekama, M. Otagiri, F. Hirayama, *J. Inclusion Phenom.* **1988**, *6*, 135; d) M. R. Eftink, M. L. Andy, K. Bystrom, H. D. Permutter, D. S. Kristol, *J. Am. Chem. Soc.* **1989**, *111*, 6765; e) M. Ohashi, K. Kasatani, H. Shinohara, H. Sato, *J. Am. Chem. Soc.* **1990**, *112*, 5824.

[4] a) Y. Matsui, K. Mochida, *Bull. Chem. Soc. Jpn.* **1978**, *51*, 673; b) I. Tabushi, Y. Kiyosuke, T. Sugimoto, K. Yamamura, *J. Am. Chem. Soc.* **1978**, *100*, 916; c) W. C. Cromwell, K. Byström, M. R. Eftink, *J. Phys. Chem.* **1985**, *89*, 326.

[5] In this paper, the term *hydrophobic interaction* is used according to the traditional definition. Namely, an attractive force acquired by an entropic gain due to the change of the water structure is called *hydrophobic interaction*.

[6] a) R. J. Bergeron, M. A. Channing, G. J. Gibeily, D. M. Pillor, *J. Am. Chem. Soc.* **1977**, *99*, 5146; b) R. J. Bergeron, M. A. Channing, K. A. McGovern, *J. Am. Chem. Soc.* **1978**, *100*, 2878; c) R. I. Gelb, L. M. Schwartz, B. Cardelino, H. S. Fuhrman, R. F. Johnson, D. A. Laufer, *J. Am. Chem. Soc.* **1981**, *103*, 1750; d) R. I. Gelb, L. M. Schwartz, M. Radeos, D. A. Laufer, *J. Phys. Chem.* **1983**, *87*, 3349; e) K. Kano, K. Mori, B. Uno, M. Goto, T. Kubota, *J. Am. Chem. Soc.* **1990**, *112*, 8645.

[7] M. Komiyama, *J. Am. Chem. Soc.* **1989**, *111*, 3046.

[8] C. J. Easton, S. F. Lincoln, *Modified Cyclodextrins*, Imperial College Press, London, **1999**.

[9] F. P. Schmidtchen in *Supramolecular Chemistry of Anions* (Eds.: A. Bianchi, K. Bowman-James, E. García-España), Wiley-VCH, New York, **1997**, pp. 79.

[10] For examples: a) W. Tagaki, K. Yano, K. Yamanaka, H. Yamamoto, T. Miyasaka, *Tetrahedron Lett.* **1990**, *31*, 3897; b) R. C. Petter, J. S. Salek, C. T. Sikorski, G. Kumaravel, F.-T. Lin, *J. Am. Chem. Soc.* **1990**, *112*, 3860; c) A. K. Yatsimirsky, A. V. Eliseev, *J. Chem. Soc. Perkin Trans. 2* **1991**, 1759; d) W. Tagaki, H. Yamamoto, *Tetrahedron Lett.* **1991**, *32*, 1207; e) H. Parrot-Lopez, C.-C. Ling, P. Zhang, A. Baszkin, G. Albrecht, C. de Rango, A. W. Coleman, *J. Am. Chem. Soc.* **1992**, *114*, 5479; f) P. Mu, T. Okada, N. Iwami, Y. Matsui, *Bull. Chem. Soc. Jpn.* **1993**, *66*, 1924; g) A. V. Eliseev, H. J. Schneider, *Angew. Chem.* **1993**, *105*, 1423; *Angew. Chem. Int. Ed. Engl.* **1993**, *32*, 1331; h) Y. Matsui, E. Tanemura, T. Nonomura, *Bull. Chem. Soc. Jpn.* **1993**, *66*, 2827; i) A. Nardi, A. Eliseev, P. Bocek, S. Fanali, *J. Chromatogr.* **1993**, *638*, 247; j) R. Corradini, A. Dossena, G. Impellizzeri, G. Maccarrone, R. Marchelli, E. Rizzarelli, G. Sarfor, G. Vecchio, *J. Am. Chem. Soc.* **1994**, *116*, 10267; k) A. V. Eliseev, H.-J. Schneider, *J. Am. Chem. Soc.* **1994**, *116*, 6081; l) N. Ito, N. Yoshida, K. Ichikawa, *J. Chem. Soc. Perkin Trans. 2* **1995**, 965; m) S. Tamagaki, K. Fukuda, H. Maeda, N. Mimura, W. Tagaki, *J. Chem. Soc. Perkin Trans. 2* **1995**, 389; n) C. J. Easton, S. F. Lincoln, D. M. Schliebs, *J. Chem. Soc. Chem. Commun.* **1995**, 1167; o) K. Hamasaki, A. Ueno, *Chem. Lett.* **1995**, 859; p) R. P. Bonomo, B. Di Blasio, G. Maccarrone, V. Pavone, C. Pedone, E. Rizzarelli, M. Saviano, G. Vecchio, *Inorg. Chem.* **1996**, *35*, 4497; q) V. Cucinotta, F. D'Alessandro, G. Impellizzeri, G. Maccarrone, E. Rizzarelli, G. Vecchio, *J. Chem. Soc. Perkin Trans. 2* **1996**, 1785; r) L. A. Godínez, L. A. J. Lin, M. Muñoz, A. W. Coleman, A. E. Kaifer, *J. Chem. Soc. Faraday Trans.* **1996**, *92*, 645; s) F. Lelièvre, P. Gareil, A. Jardy, *Anal. Chem.* **1997**, *69*, 385–392; t) F. Lelièvre, P. Gareil, Y. Bahaddi, H. Galons, *Anal. Chem.* **1997**, *69*, 393; u) D. Vizitiu, G. R. Thatcher, *J. Org. Chem.* **1999**, *64*, 6235.

[11] S. E. Brown, J. H. Coates, P. A. Duckworth, S. F. Lincoln, C. J. Easton, *J. Chem. Soc. Faraday Trans.* **1993**, *89*, 1035.

[12] B. Hamelin, L. Jullien, F. Guillo, J.-M. Lehn, A. Jardy, L. De Robertis, H. Driguez, *J. Phys. Chem.* **1995**, *99*, 17877.

  0947-6539/00/0615-2712 $ 17.50+.50/0

[13] C. J. Easton, S. F. Lincoln, J. Papageorgiou, D. M. Schliebs, *J. Chem. Res.* (*S*), **1995**, 381.
[14] K. Kano, T. Kitae, H. Takashima, Y. Shimofuri, *Chem. Lett.* **1997**, 899.
[15] T. Kitae, T. Nakayama, K. Kano, *J. Chem. Soc. Perkin Trans. 2*, **1998**, 207.
[16] A. Bianchi, E. García-España in *Supramolecular Chemistry of Anions* (Eds.: A. Bianchi, K. Bowman-James, E. García-España), Wiley-VCH, New York, **1997**, pp. 217.
[17] M. V. Rekharsky, Y. Inoue, *Chem. Rev.* **1998**, *98*, 1875s.
[18] a) R. I. Gelb, L. M. Schwartz, R. F. Johnson, D. A. Laufer, *J. Am. Chem. Soc.* **1979**, *101*, 1869; b) M. Komiyama, H. Hirai, *Bull. Chem. Soc. Jpn.* **1981**, *54*, 828; c) V. Rüdiger, A. Eliseev, S. Simova, H.-J. Schneider, M. J. Blandamer, P. M. Cullis, A. J. Meyer, *J. Chem. Soc. Perkin Trans. 2* **1996**, 2119.
[19] K. Kano, Y. Kato, M. Kodera, *J. Chem. Soc. Perkin Trans. 2* **1996**, 1211.
[20] Y. Matsui, M. Fujie, K. Hanaoka, *Bull. Chem. Soc. Jpn.* **1989**, *62*, 1451.
[21] The apparent pK_a vcalue of di-NH_3^+-β-CD was determined from the pH titration to be 8.3. We could not distinguish between pK_{a1} and pK_{a2}.
[22] For examples see: a) D. A. Stauffer, R. E. Barrans, Jr., D. A. Dougherty, *J. Org. Chem.* **1990**, *55*, 2762; b) D. B. Smithrud, T. B. Wyman, F. Diederich, *J. Am. Chem. Soc.* **1991**, *113*, 5420.
[23] a) M. Maeda, S. Takagi, *Netsu Sokutei* **1983**, *10*, 43 [*Chem. Abstr.* **1983**, *99*, 129161b]; b) M. Maeda, S. Takagi, *Netsu Sokutei* **1983**, *10*, 103 [*Chem. Abstr.* **1983**, *99*, 201392x]; c) S. Takagi, M. Maeda, *J. Inclusion Phenom.* **1984**, *2*, 775; d) R. I. Gelb, L. M. Schwartz, *J. Inclusion Phenom. Mol. Recognit. Chem.* **1989**, *7*, 465; e) M. Fujisawa, T. Kimura, S. Takagi, *Netsu Sokutei* **1991**, *18*, 71 [*Chem. Abstr.* **1991**, *115*, 117798w]; f) M. V. Rekharsky, F. P. Schwarz, Y. B. Tewari, R. N. Goldberg, *J. Phys. Chem.* **1994**, *98*, 10282; g) P. D. Ross, M. V. Rekharsky, *Biophys. J.* **1996**, *71*, 2144; h) M. V. Rekharsky, M. P. Mayhew, R. N. Goldberg, P. D. Ross, Y. Yamashoji, Y. Inoue, *J. Phys. Chem. B* **1997**, *101*, 87; i) V. Rüdiger, A. Eliseev, S. Simova, H.-J. Schneider, M. J. Blandamer, P. M. Cullis, A. J. Meyer, *J. Chem. Soc. Perkin Trans. 2* **1996**, 2119.
[24] a) R. L. Van Etten, J. F. Sebastian, G. A. Clowes, M. L. Bender, *J. Am. Chem. Soc.* **1967**, *89*, 3242; b) M. R. Eftink, M. L. Andy, K. Bystrom, H. D. Perlmutter, D. S. Kristol, *J. Am. Chem. Soc.* **1989**, *111*, 4900; c) K. Kano, N. Tanaka, H. Minamizono, Y. Kawakita, *Chem. Lett.* **1996**, 925.
[25] a) E. A. Lewis, L. D. Hansen, *J. Chem. Soc. Perkin Trans. 2* **1973**, 2081; b) A. Harata, *Bioorg. Chem.* **1981**, *10*, 265.
[26] C. Bazzicalupi, A. Bencini, A. Bianchi, M. Cecchi, B. Escuder, V. Fusi, E. García-España, C. Giorgi, S. V. Luis, G. Maccagni, V. Marcelino, P. Paoletti, B. Valtancoli, *J. Am. Chem. Soc.* **1999**, *121*, 6807.
[27] a) R. I. Gelb, L. M. Schwartz, M. Radeods, R. B. Edmonds, D. A. Laufer, *J. Am. Chem. Soc.* **1982**, *104*, 6283; b) E. E. Tucker, S. D. Christian, *J. Am. Chem. Soc.* **1984**, *106*, 1942; c) A. Aversa, W. Etter, R. I. Gelb, L. M. Schwartz, *J. Inclusion Phenom. Mol. Recognit. Chem.* **1990**, *9*, 277; d) R. I. Gelb, S. Raso, J. S. Alper, *Supramol. Chem.* **1995**, *4*, 279.
[28] a) Y. Inoue, T. Hakushi, Y. Liu, L.-H. Tong, B.-J. Shen, D.-S. Jin, *J. Am. Chem. Soc.* **1993**, *115*, 475; b) Y. Inoue, Y. Liu, L.-H. Tong, B.-J. Shen, D.-S. Jin, *J. Am. Chem. Soc.* **1993**, *115*, 10637.
[29] a) M. N. Berberan-Santos, J. Canceill, J.-C. Brochon, L. Jullien, J.-M. Lehn, J. Pouget, P. Tauc, B. Valeur, *J. Am. Chem. Soc.* **1992**, *114*, 6427; b) L. Jullien, J. Canceill, B. Valeur, E. Bardez, J.-M. Lehn, *Angew. Chem.* **1994**, *106*, 2582; *Angew. Chem. Int. Ed. Engl.* **1994**, *33*, 2438; c) M. Nowakowska, N. Loukine, D. M. Gravett, N. A. D. Burke, J. E. Guillet, *J. Am. Chem. Soc.* **1997**, *119*, 4364.
[30] For examples see: M. A. Hossain, H.-J. Schneider, *Chem. Eur. J.* **1999**, *5*, 1284 and references cited therein.
[31] a) A. Gadelle, J. Defaye, *Angew. Chem.* **1991**, *101*, 94; *Angew. Chem. Int. Ed. Engl.* **1991**, *30*, 78; b) K. Tsujihara, H. Kurita, M. Kawazu, *Bull. Chem. Soc. Jpn.* **1977**, *50*, 1567; c) J. Boger, R. J. Corcoran, J.-M. Lehn, *Helv. Chem. Acta* **1978**, *61*, 2190.
[32] K. Takahashi, K. Hattori, F. Toda, *Tetrahedron Lett.* **1984**, *25*, 3331.
[33] a) I. Tabushi, Y. Kuroda, K. Yokota, L. C. Yuan, *J. Am. Chem. Soc.* **1981**, *103*, 711; b) I. Tabushi, K. Yamamura, T. Nabeshima, *J. Am. Chem. Soc.* **1984**, *106*, 5267; c) I. Tabushi, Y. Kuroda, *J. Am. Chem. Soc.* **1984**, *106*, 4580.
[34] F. Guillo, B. Hamelin, L. Jullien, J. Canceill, J.-M. Lehn, L. DeRobertis, H. Driguez, *Bull. Soc. Chim. Fr.* **1995**, *132*, 857.
[35] H.-J. Schneider, R. Kramer, S. Simova, U. Schneider, *J. Am. Chem. Soc.* **1988**, *110*, 6442.
[36] K. Kano, K. Minami, K. Horiguchi, T. Ishimura, M. Kodera, *J. Chromatogr. A* **1995**, *694*, 307.

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