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Complexation and Chiral Recognition Thermodynamics of 6-Amino-6-deoxy-β-cyclodextrin with Anionic, Cationic, and Neutral Chiral Guests: Counterbalance between van der Waals and Coulombic Interactions

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Abstract: The stability constant (K), standard free energy ($\Delta G°$), enthalpy ($\Delta H°$), and entropy changes ($T\Delta S°$) for the complexation of 6-amino-6-deoxy-β-cyclodextrin with more than 50 negatively or positively charged as well as neutral guests, including 22 enantiomer pairs, have been determined in aqueous phosphate buffer (pH 6.9) at 298.15 K by titration microcalorimetry. The thermodynamic parameters obtained in this study and the relevant data for native β-cyclodextrin indicate that the complexation and chiral discrimination behavior of the cationic host with charged guests are governed by the critical counterbalance between the electrostatic interactions of the charged groups in host and guest and the conventional intracavity interactions of the hydrophobic moiety of guest, such as hydrophobic, van der Waals, solvation/desolvation, and hydrogen-bonding interactions.

Introduction

β-Cyclodextrin (β-CD) is a truncated cone-shaped macrocyclic molecule with a hollow, tapered cavity with an inside volume of ~260 Å^3 (Chart 1).[1] In aqueous solution, the cavity is usually occupied by 8−9 water molecules, which are excluded from the cavity upon complexation with a guest of proper shape and size. As a result of the α-1,4-linkage of each glucopyranose unit, all of the hydrophilic 2-, 3-, and 6-hydroxyl groups are located exterior of the hydrophobic cavity (Chart 1). As amply exemplified in the literature,[2,3] the most probable binding mode of native and modified cyclodextrins (CDs) with various guests involves the insertion of the less hydrophilic part of the guest molecule into the CD cavity, while the more hydrophilic, often charged, group stays just outside the primary or secondary rim of the cavity. In many cases, the hydrophobic and van der Waals interactions are the principal intermolecular weak forces responsible for the formation of stable supramolecular complexes, although it is difficult to rigorously separate the contributions of these two forces in general[4] and particularly in the complexation of CDs.[5] Furthermore, the intracavity interactions between CD and guest could be better described by a "nonclassical" hydrophobic model, where the enthalpy ($\Delta H°$) and entropy changes ($\Delta S°$) can be either positive or negative,[4,6,7] rather than by a "classical" one, where both $\Delta H°$ and $\Delta S°$ are positive.[8,9] Indeed, the degree of hydrophobicity is not uniform over the whole CD cavity but varies from point to point, and the cavity surrounded by several C−O dipoles should be considered moderately polar rather than totally nonpolar.[10a,b] In view of the intermolecular forces involved, there are several significant differences between the classical hydrophobic process, i.e., the transfer of organic molecule from water to nonpolar organic media, and the inclusion complexation by CD which involves the insertion of a less-polar part of the guest into the CD cavity. First, the size and shape of the CD cavity are defined by the covalently bonded glucose units. Hence, the cavity allows more pronounced van der Waals interactions than nonpolar organic media, in which solvent molecules freely move around, and thus, a more exothermic heat effect is observed as demonstrated in our recent study for several guests.[11] Second, the dipole−dipole, dipole−induced dipole, and ion−dipole interactions between host and guest play significant roles upon complexation of CD with lipophilic inorganic ions (e.g., PF_6^-, ClO_4^-, or SCN^-)[5] and with readily polarizing neutral and charged aromatics (e.g., substituted phenols),[3] with all of these interactions likely to contribute significantly to the observed large negative enthalpies of complexation. Third, specific host−guest interactions, such as hydrogen bonding, are possible for CD complexes.[3,11−13] All of the above-mentioned intermolecular interactions, occurring

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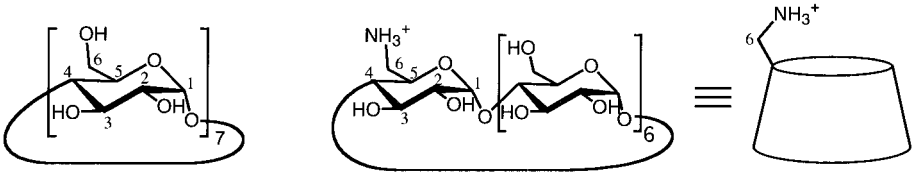
Chart 1



β-Cyclodextrin (β-CD) 6-Amino-6-deoxy-β-cyclodextrin (am-β-CD)

inside the cavity, are "short-range" forces, which are effective only when the host and guest are located in a nearly contact distance. Thus, these interactions may be called "intracavity attractive forces" and a host−guest complexation driven by such attractive forces may be defined as "conventional" guest inclusion.

One of the intriguing issues observed in the guest inclusion by native CDs is that only the specific part of a guest that penetrates into the cavity contributes to the overall complexation thermodynamics. Indeed, the introduction of a methyl group to the less-polar, penetrating part of a guest consistently enhances the binding constant by a factor of 2−4,[3] while the methylation of such a charged group as an ammonio that stays outside the cavity upon complexation does not affect at all the complexation thermodynamics.[13] Furthermore, the chemical nature, structure, and even sign of the charged group do not play any significant thermodynamic roles upon complexation with native CDs as far as the same hydrophobic part of the guest is included in the cavity.[11] This is obviously nonclassical thermodynamic behavior from the viewpoint of the ordinary solute−solvent interaction or the conventional water-to-nonpolar media transfer. To force the charged group of a guest to contribute appreciably to the overall complexation thermodynamics, we may need to introduce an oppositely charged group into CD, which is expected to enhance the binding ability through the attractive "long-range" Coulombic interaction.

In fact, it has been reported that cationic mono- and diammonio-CDs exhibit higher/lower affinities toward negatively/positively charged guests than the corresponding native CDs.[3,14−17] Unfortunately, most of these reports provide us with only the binding constants for charged guests of relatively small structural variations, and few thermodynamic parameters are available at present. The lack of accumulated thermodynamic data for the complexation of charged CD with oppositely charged guests of systematic structural variations obviously hinders the comprehensive understanding of the unique complexation thermodynamic behavior of oppositely charged host−guest pairs.

As far as the chiral discrimination by aminated CD is concerned, the cooperative Coulombic and other inclusion-related weak interactions as well as the critical balance between them are essential for effective chiral recognition of anionic guests as demonstrated by Kano et al. in their recent study.[14] We have also reached similar general conclusions concerning the chiral discrimination by native cyclodextrins. Thus, almost any structural alterations in the guest molecule that result in stronger binding with β-CD lead to a loss of chiral recognition, since practically in all cases the additional weak interactions involved in the complexation process result in noncomplimentarity between the chiral guest and CD cavity.[11] Furthermore, we have shown[11] that the thermodynamic origin of poor chiral discrimination ability of natural CDs is the existence of nearly perfect enthalpy−entropy compensation, which cancels the originally small differences in $\Delta H°$ and $T\Delta S°$ for both enantiomers. Again, the limited amount of experimental data for aminated CDs is the main reason general correlations between guest structure and chiral discrimination have not been elaborated.

In the present study, we performed the microcalorimetric titrations of the complexation reactions of a series of chiral/achiral charged/neutral guests with 6-amino-6-deoxy-β-cyclodextrin (am-β-CD; Chart 1) to elucidate the fundamental complexation thermodynamic and chiral recognition behavior as well as the role and relative contributions of the "short-range" intracavity attractive forces and the "long-range" electrostatic (Coulombic) interactions. It should be emphasized that the use of a large number of guests with wide yet serial structural variations and the global and detailed analyses of the thermodynamic data obtained are essential, since our original intention is to elucidate the general rules governing the thermodynamic and chiral discrimination behavior of am-β-CD and neutral β-CD. For the sake of comparison and generality, not only negatively charged but also neutral and positively charged guests were employed.

Experimental Section

Materials. Most of the guest compounds used in this study, their Chemical Abstracts registry number, empirical formula, formula weight, and supplier are given in our previous publications.[11,18] Commercially available samples of the highest purities were used in the microcalorimetric experiments without any further purification. The vendors employed a variety of methods (i.e., HPLC, LC, GC, titration, or elemental analysis) to determine and guarantee the purities of the guests as >98−99%. The β-CD, am-β-CD, and some of the guest compounds contained water of hydration or crystallization, for which appropriate corrections were made on the basis of the values determined by the vendors or by us using the Karl-Fisher technique. Two different samples of am-β-CD were used in this study. One was purchased from Cyclolab and another was supplied by H. Yamamura (Nagoya Institute of Technology).[19] Complexation reactions of (*S*)- and (*R*)-10-camphorsulfonic acid, (*S*)-hexahydromandelic acid, and 4-tolylic acid were

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repeated with both samples of am-β-CD to give satisfactory, consistent, and reproducible thermodynamic parameters within experimental error.

Microcalorimetric Titrations. An isothermal calorimeter (ITC), purchased from Microcal Inc., was used in all microcalorimetric experiments. Titration microcalorimetry allows us to determine simultaneously the enthalpy and equilibrium constant from a single titration curve. The ITC instrument was periodically calibrated electrically using an internal electric heater. The instrument was also calibrated chemically by using the neutralization enthalpy of the reaction of HCl with NaOH and the ionization enthalpy of T buffer. These standard reactions gave excellent agreement (±1−2%) with the literature data.[20a,b] The thermodynamic parameters for the complexation reaction of cyclohexanol with β-CD were also in good agreement with our previous results.[11,13,18]

Detailed description of microcalorimetric experimental procedure and justification of the applicability of the simple 1:1 model for the complexation reactions under study were presented in our previous papers.[11,13,18] The uncertainties in the observed thermodynamic quantities for 1:1 complexation, shown in Table 1, are two standard deviations of the mean value unless otherwise stated.

Microcalorimetric experiments were performed at pH 6.9, except for the Gly-Phe case, where pH 6.1 was used to satisfy the common requirement $|K_a(\text{guest}) - \text{pH}| > 2$.[11,18] p$K_a$ of am-β-CD was experimentally determined by us as 8.5, and thus, the difference between pK_a(host) and buffer solution with pH 6.9 was slightly smaller than 2. Therefore, we performed microcalorimetric experiments at two different pHs of 6.9 and 6.5 in order to check the effect of pH changes on the thermodynamic parameters for the complexation of (*R*)- and (*S*)-3-bromo-2-methyl-1-propanol, (*R*)- and (*S*)-hexahydromandelic acid, (*R*)- and (*S*)-mandelic acid, (*R*)- and (*S*)-mandelic acid methyl ester, 4-phenylbutylamine, and (*R*)- and (*S*)-phenyllactic acid. For all of these guests, exactly the same thermodynamic parameters were obtained upon complexation with am-β-CD at pH 6.9 and at pH 6.5.

We have previously shown that the nonideality corrections are not necessary under the experimental conditions employed.[11,18]

Results and Discussion

The stability constant (K), standard free energy ($\Delta G°$), enthalpy ($\Delta H°$), and entropy changes ($T\Delta S°$) determined for the complexation reactions of am-β-CD with more than 50 chiral/achiral charged/neutral guests are listed in Table 1, along with the relevant data reported for native β-CD.[11] The enthalpy changes obtained are consistently negative ($-25.5 < \Delta H° < -3.5$ kJ mol^{-1}) in all complexation reactions of am-β-CD and β-CD with the employed guests, while the entropy changes vary from large negative values to relatively large positive values ($-19.2 < T\Delta S° < 10.7$ kJ mol^{-1}). As have been demonstrated amply in our previous studies,[3,11,12] large negative enthalpy changes are accounted for in general in terms of the pronounced van der Waals interactions arising from the precise matching in size and shape between the host and guest involved. Large negative entropy changes usually arise from the significantly reduced translational and conformational freedoms of host and guest upon complexation.[3,11,12] On the other hand, large positive entropy changes are attributable to the relatively high flexibility of guest after complexation, the extensive desolvation from the hydrophilic moieties of host and guest, or the release/restructuring of the water molecules inside and around the cavity.[3,11,12]

It may be reasonable to classify the obtained thermodynamic data into a few categories in terms of the sign and magnitude of the major thermodynamic parameter(s) ($\Delta H°$, $\Delta S°$) contributing to the overall complex stability, since different types of interaction, recognition mechanism, and complex structure involved are the origin of the distinctly different thermodynamic behavior actually observed. In other words, the thermodynamic consequences of the additional electrostatic and relevant interactions induced by the oppositely charged groups in host and guest should be completely different, depending whether the major driving force for complexation is the strong intracavity van der Waals interaction, accompanying $\Delta H° < 0$ and $T\Delta S° < 0$, or the solvent reorganization, giving $T\Delta S° > 0$ and $\Delta H° < 0$ with $|T\Delta S°| > |\Delta H°|$. Accordingly, the experimental results are separately presented and discussed in several subsections classified by the sign and magnitude of the $\Delta H° < 0$ and $T\Delta S°$ values.

Exclusively Enthalpy-Driven Complexation ($\Delta H° < 0$; $T\Delta S° < 0$). In the first part of Table 1 are grouped the thermodynamic parameters obtained with category A guests, which give favorable enthalpy changes ($\Delta H° < 0$) with accompanying unfavorable entropy changes ($T\Delta S° < 0$). As stated above, these enthalpic and entropic features are usually attributed to the predominant contribution of the van der Waals interactions arising from the precise host−guest complimentarity in size and shape and to the accompanying significant decreases in translational and structural freedoms upon complexation.

It should be noted, however, that the large enthalpic gain, certainly originating from the van der Waals interactions, is not always attributable to the global size/shape complimentarity but rather to the specific van der Waals interactions of particular guest moieties, although the physical origin and detailed mechanism of such specific interactions are not necessarily clear and may differ in each case. For instance, the size and shape of the unsymmetrical indole ring of *N*-acetyl-D/L-tryptophan does not appear to be complementary with the symmetrical CD cavity, yet its complexation with β-CD and am-β-CD is entirely enthalpy driven, affording the largest enthalpic gains among the guests examined. The highest enthalpy for *N*-acetyl-D/L-tryptophan may be reasonable, if the indole ring can make stronger van der Waals contacts with CD than the benzene ring of, for example, *N*-acetyl-D/L-phenylalanine. This hypothesis is supported by our previous observations that the complexation enthalpies obtained with Cbz-D/L-tryptophan and even Cbz-D/L-histidine upon stacking complexation with γ-CD are almost 3 times larger than that of Cbz-D/L-phenylalanine.[12] It is also supported by the large negative complexation enthalpies of small imidazole ring toward α- and β-CD.[21a] Although these aza-aromatic rings, i.e., indole and imidazole, are more hydrophilic than the nonheteroaromatics and hence are considered to be solvated to some extent in water, desolvation experienced by them upon complexation is not extensive and the relatively small entropy gain from desolvation does not exceed the loss in positional/translational entropy upon complexation, as judged from the large negative overall reaction entropy observed. As expected, the introduction of a positive charge on the host enhances host/guest desolvation at least in part in the case of *N*-acetyl-D/L-tryptophan, and the reaction entropy becomes less negative. However, even upon complexation with am-β-CD, the overall reaction entropy remains highly negative.

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Table 1. Complex Stability Constant (K), Standard Free Energy (ΔG°), Enthalpy (ΔH°), and Entropy Changes ($T\Delta S^\circ$) (in kJ mol^{-1}) for 1:1 Inclusion Complexation of Chiral and Achiral Guests with 6-Amino-6-deoxy-β-cyclodextrin (am-β-CD) and β-Cyclodextrin (β-CD) at T = 298.15 K

guest (charge)	host	[guest]/mM	[host]/mM	pH	N[a]	K/M^{-1}	ΔG°	ΔH°	$T\Delta S^\circ$	ref
A. Exclusively Enthalpy-Driven Complexation with Negatively Charged Guests ($\Delta H^\circ < 0$; $T\Delta S^\circ < 0$)										
N-acetyl-D-tryptophan (−1)	am-β-CD	140	1.46	6.9[b]	2	15.5 ± 0.6	−6.8 ± 0.1	−20.8 ± 0.7	−14.0 ± 0.7	*f*
	β-CD	192	2.19	6.9[b]	2	12.7 ± 0.5	−6.3 ± 0.1	−25.5 ± 0.6	−19.2 ± 0.6	*g*
N-acetyl-D-tryptophan (−1)	am-β-CD	135	1.49	6.9[b]	2	26.2 ± 0.8	−8.10 ± 0.08	−17.8 ± 0.4	−9.7 ± 0.4	*f*
	β-CD	169	2.63	6.9[b]	2	17.1 ± 0.5	−7.04 ± 0.08	−23.8 ± 0.4	−16.8 ± 0.4	*g*
N-acetyl-D-tyrosine (−1)	am-β-CD	102	1.38	6.9[b]	2	114 ± 3	−11.74 ± 0.07	−12.4 ± 0.3	−0.7 ± 0.3	*f*
	β-CD	100−102	1.35−1.43	6.9[b]	3	124 ± 2	−11.94 ± 0.04	−17.2 ± 0.3	−5.3 ± 0.3	*f*
N-acetyl-L-tyrosine (−1)	am-β-CD	107	1.02	6.9[b]	2	134 ± 2	−12.14 ± 0.04	−15.1 ± 0.2	−3.0 ±0.2	*f*
	β-CD	97−103	1.55−1.59	6.9[b]	3	130 ± 2	−12.07 ± 0.04	−17.1 ± 0.3	−5.0 ± 0.3	*g*
(*R*)-camphanic acid (−1)	am-β-CD	104	1.38	6.9[b]	2	173 ± 3	−12.77 ± 0.04	−16.50 ± 0.15	−3.7 ± 0.2	*f*
	β-CD	90−131	1.07−185	6.9[b]	4	178 ± 2	−12.85 ± 0.03	−17.8 ± 0.2	−5.0 ± 0.2	*g*
(*S*)-camphanic acid (−1)	am-β-CD	114	1.38	6.9[b]	2	205 ± 2	−13.20 ± 0.03	−16.40 ± 0.15	−3.2 ± 0.2	*f*
	β-CD	80−125	1.07−2.01	6.9[b]	4	207 ± 3	−13.22 ± 0.04	−17.7 ± 0.2	−4.5 ± 0.2	*g*
(*R*)-10-camphorsulfonic acid (−1)	am-β-CD	53−56	0.76−0.81	6.9[b]	4	781 ± 8	−16.51 ± 0.03	−23.8 ± 0.3	−7.3 ± 0.3	*f*
	β-CD	103	1.12−1.82	6.9[b]	2	564 ± 10	−15.70 ± 0.05	−20.7 ± 0.2	−5.0 ± 0.2	*g*
(*S*)-10-camphorsulfonic acid (−1)	am-β-CD	54−57	0.76−0.85	6.9[b]	4	840 ± 9	−16.69 ± 0.03	−24.6 ± 0.3	−7.9 ± 0.3	*f*
	β-CD	76	1.93	6.9[b]	3	489 ± 10	−15.35 ± 0.05	−19.5 ± 0.2	−4.2 ± 0.2	*g*
3-(2-hydroxyphenyl)-propionicacid (−1)	am-β-CD	161	1.87	6.9b	2	138 ± 2	−12.21 ± 0.04	−14.03 ± 0.15	−1.8 ± 0.2	*f*
	β-CD	100	2	6.9	2	81 ± 2	−10.89 ± 0.06	−15.2 ± 0.2	−4.3 ± 0.2	*g*
3-(4-hydroxyphenyl)-propionicacid (−1)	am-β-CD	109	1.24	6.9[b]	2	436 ± 5	−15.07 ± 0.03	−12.55 ± 0.15	2.5 ± 0.2	*f*
	β-CD	100	1	6.9	2	297 ± 4	−14.11± 0.*03*	−14.23 ± 0.08	−0.12 ± 0.09	*g*
(*R*)-α-methoxy-α-trifluoromethylphenyl-acetic acid (−1)	am-β-CD	103	1.29	6.9[b]	2	560 ± 10	−15.69 ± 0.05	−19.1 ± 0.2	−3.4 ± 0.2	*f*
	β-CD	106−114	1.93−2.08	6.9[b]	4	175 ± 2	−12.80 ± 0.03	−17.48 ± 0.15	−4.7 ± 0.2	*g*
(*S*)-α-methoxy-α-trifluoromethylphenyl-acetic acid (−1)	am-β-CD	86	1.00	6.9[b]	2	375 ± 6	−14.69 ± 0.05	−16.2 ± 0.2	−1.5 ± 0.2	*f*
	β-CD	102−106	152−2.08	6.9[b]	5	141 ± 2	−12.27 ± 0.04	−16.35 ± 0.15	−4.1 ± 0.2	*g*
sodium hexaflouro-phosphate (−1)	am-β-CD	86	1.00−1.07	6.9[b]	2	145 ± 2	−12.34 ± 0.04	−20.9 ± 0.2	−8.6 ± 0.2	*f*
	β-CD	86	1.55	6.9[b]	2	102 ± 2	−11.47 ± 0.05	−23.1 ± 0.2	−11.6 ± 0.2	*f*
sodium perchlorate (−1)	am-β-CD	490	2.41	6.9[b]	1	27.3 ± 0.5	−8.20 ± 0.05	−17.8 ± 0.2	−9.6 ± 0.2	*f*
	β-CD	490	2.18	6.9[b]	1	15.2 ± 0.5	−6.75 ± 0.09	−19.2 ± 0.2	−12.5 ± 0.2	*f*
sodium thiocyanate (−1)	am-β-CD	614	2.41	6.9	1	10 ± 1	−5.7 ± 0.3	−16.5 ± 1.5	−11 ± 2	*f*
	β-CD	614	3.18	6.9	1	5 ± 1	−4.0 ± 0.6	−18 ± 3	−14 ± 3	*f*
2-tolylacetic acid (−1)	am-β-CD	204	1.68	6.9[b]	1	e				*f*
	β-CD	152	2	6.9[b]	2	*e*				*g*
3-tolylacetic acid (−1)	am-β-CD	182	1.69	6.9[b]	2	54 ± 1	−9.89 ± 0.05	−7.83 ± 0.07	2.06 ± 0.08	*f*
	β-CD	150	2	6.9[b]	4	11.9 ± 1.4	−6.1 ± 0.3	−11.5 ± 1.1	−5.4 ±1.2	*g*
4-tolylacetic acid (−1)	am-β-CD	229	1.68	6.9[b]	2	181 ± 4	−12.89 ± 0.06	−11.05 ± 0.15	1.8 ± 0.2	*f*
	β-CD	73−146	2	6.9[b]	6	40.4 ± 1.7	−9.17 ± 0.11	−12.1 ± 0.4	−2.9 ±0.4	*g*
B. Complexation with Negatively Charged Guests Primarily Driven by Enthalpy with Entropic Assistance ($\Delta H^\circ < 0$; $T\Delta S^\circ > 0$; $\lvert\Delta H^\circ\rvert > \lvert T\Delta S^\circ\rvert$)										
N-acetyl-D-phenylalanine(−1)	am-β-CD	136	1.49	6.9[b]	2	58 ± 2	−10.07 ± 0.09	−6.62 ± 0.15	3.5 ± 0.2	*f*
	β-CD	182	2.19	6.9[b]	2	60.7 ± 1.3	−10.18 ± 0.05	−8.14 ± 0.07	2.04 ± 0.08	*g*
N-acetyl-L-phenylalanine (−1)	am-β-CD	129	1.49	6.9[b]	2	78 ± 1	−10.80 ± 0.04	−7.14 ± 0.07	3.66 ± 0.08	*f*
	β-CD	171	2.19−3.08	6.9[b]	2	67.5 ± 1.4	−10.44 ± 0.05	−8.17 ± 0.08	2.27 ± 0.09	*g*
N-*t*-Boc-D-alanine (−1)	am-β-CD	57	1.08	6.9[b]	2	695 ± 25	−16.22 ± 0.09	−11.0 ± 0.3	5.2 ± 0.3	*f*
	β-CD	62	1.19	6.9[b]	2	392 ± 4	−14.80 ± 0.03	−9.7 ± 0.1	5.1 ± 0.1	*g*
N-*t*-Boc-L-alanine (−1)	am-β-CD	62	1.04	6.9[b]	2	593 ± 15	−15.83 ± 0.07	−10.7 ± 0.2	5.1 ± 0.2	*f*
	β-CD	57	0.95	6.9[b]	2	367 ± 4	−14.64 ± 0.03	−9.8 ± 0.1	4.8 ± 0.1	*g*
N-Cbz-D-alanine (−1)	am-β-CD	56	0.99	6.9[b]	2	183 ± 4	−12.91 ± 0.05	−10.5 ± 0.2	2.4 ± 0.2	*f*
	β-CD	45−74	0.78−1.00	6.9[b]	2	149 ± 4	−12.40 ± 0.07	−8.9 ± 0.2	3.5 ± 0.2	*g*
N-Cbz-L-alanine (−1)	am-β-CD	52−66	0.93−0.99	6.9[b]	2	172 ± 4	−12.76 ± 0.06	−10.6 ± 0.2	2.2 ± 0.2	*f*
	β-CD	57	0.84	6.9[b]	2	147 ± 4	−12.37 ± 0.07	−10.0 ± 0.2	2.4 ± 0.2	*g*
N-Cbz-D-aspartic acid (−2)	am-β-CD	115	1.17	6.9	2	163 ± 2	−12.63 ± 0.03	−12.18 ± 0.15	0.45 ± 0.15	*h*
	β-CD	154	2.23	6.9	2	70.7 ± 1.5	−10.56 ± 0.05	−9.50 ± 0.15	1.1 ± 0.2	*h*
N-Cbz-L-aspartic acid (−2)	am-β-CD	123	1.17	6.9	2	161 ± 2	−12.60 ± 0.03	−12.04 ± 0.15	0.54 ± 0.15	*h*
	β-CD	152	2.23	6.9	1	74.3 ± 1.5	−10.68 ± 0.05	−9.59 ± 0.15	1.1 ± 0.2	*h*
(*R*)-2-phenylbutyric acid (−1)	am-β-CD	59−133	0.58−1.55	6.9[b]	4	226 ± 3	−13.44 ± 0.04	−8.20 ± 0.15	5.2 ± 0.2	*f*
	β-CD	204	1.82−1.92	6.9[b]	2	94 ± 2	−11.26 ± 0.06	−9.79 ± 0.15	*1.5* ± 0.*2*	*g*
(*S*)-2-phenylbutyric acid (−1)	am-β-CD	131	1.76	6.9[b]	2	200 ± 3	−13.13 ± 0.04	- 8.36 ± 0.15	4.8 ± 0.2	*f*
	β-CD	184−203	1.82−1.92	6.9[b]	3	95 ± 2	−11.29 ± 0.05	−9.91 ± 0.15	1.4 ± 0.2	*g*
(*R*)-phenylbutyric acid (−1)	am-β-CD	45	0.52	6.9[b]	2	428 ± 15	−15.02 ± 0.09	−8.4 ± 0.2	6.6 ± 0.2	*f*
	β-CD	113	1.80	6.9[b]	2	402 ± 4	−14.86 ± 0.03	−8.62 ± 0.09	6.24 ± 0.09	*g*
(*S*)-3-phenylbutyric acid (−1)	am-β-CD	45	0.54	6.9[b]	2	439 ± 14	−15.08 ± 0.09	−8.6 ± 0.2	6.5 ± 0.2	*f*
	β-CD	110	1.79	6.9[b]	2	430 ± 4	−15.03 ± 0.02	−8.68 ± 0.09	6.35 ± 0.09	*g*
(*R*)-phenyllactic acid (−1)	am-β-CD	89−101	1.28−1.61	6.5[c]−6.9b	3	254 ± 3	−13.73 ± 0.04	−12.7 ± 0.3	1.0 ± 0.3	*f*
	β-CD	195	2.45	6.9[b]	2	88 ± 1	−11.10 ± 0.03	−9.34 ± 0.08	1.8 ± 0.1	*g*
(*S*)-phenyllactic acid (−1)	am-β-CD	92−105	1.28−1.69	6.5[c]−6.9[b]	2	189 ± 2	−12.99 ± 0.03	−10.5 ± 0.3	2.5 ± 0.3	*f*
	β-CD	225	2.59	6.9[b]	2	83 ± 1	−10.95 ± 0.03	−8.65 ± 0.08	2.3 ± 0.1	*g*
3-phenylpropionic acid (−1)	am-β-CD	118	1.24	6.9	*2*	278 ± 3	−13.95 ± 0.03	−7.70 ± 0.10	6.25 ± 0.10	*f*
	β-CD	86−18*6*	1.54−2.20	6.9[b]	4	162 ± *4*	−12.61 ± 0.06	−6.9 ± 0.1	5.7 ± 0.1	*g*
4-tolylic acid (−1)	am-β-CD	109−168	0.85−1.35	*6.9*	*4*	291 ± 4	−14.06 ± 0.04	−10.21 ± 0.15	3.9 ± 0.2	*f*
	β-CD	109−168	1.35−1.61	6.9	3	95 ± 3	−11.29 ± 0.08	−8.79 ± 0.15	2.5 ± 0.2	*f*

Table 1. (Continued)

guest (charge)	host	[guest]/mM	[host]/mM	pH	N^a	K/M^{-1}	$\Delta G°$	$\Delta H°$	$T\Delta S°$	ref
C. Complexation with Negatively Charged Guests Predominantly Driven by Entropy and Moderately by Enthalpy ($\Delta H° < 0$; $T\Delta S° > 0$; $\|T\Delta S°\| > \|\Delta H°\|$) and Special Cases of Complex Formation										
O,*O*′-dibenzoyl-D-tartaric acid (−2)	am-β-CD	133	1.46	6.9[b]	2	63 ± 2	−10.27 ± 0.08	−5.09 ± 0.15	5.2 ± 0.2	*f*
	β-CD	189−202	2.18−3.77	6.9[b]	4	32 ± 2	−8.6 ± 0.2	−7.0 ± 0.8	1.6 ± 0.8	*g*
O,*O*′-dibenzoyl-L-tartaric acid (−2)	am-β-CD	141	1.46	6.9[b]	2	44 ± 2	−9.38 ± 0.15	−3.66 ± 0.15	5.7 ± 0.2	*f*
	β-CD	199−212	2.17−3.80	6.9[b]	5	20 ± 2	−7.4 ± 0.2	−4.9 ± 0.6	2.5 ± 0.6	*g*
O,*O*′-di-*p*-toluoyl-D-tartaric acid (−2)	am-β-CD	116	1.14	6.9[b]	2	237 ± 6	−13.56 ± 0.07	−6.67 ± 0.10	6.9 ± 0.1	*f*
	β-CD	80−174	0.86−1.86	6.9[b]	3	105 ± 6	−11.54 ± 0.10	−5.78 ± 0.15	5.8 ± 0.2	*g*
O,*O*′-di-*p*-toluoyl-L-tartaric acid (−2)	am-β-CD	121	1.32	6.9[b]	2	240 ± 9	−13.57 ± 0.08	−5.28 ± 0.15	8.3 ± 0.2	*f*
	β-CD	87	0.82−1.37	6.9[b]	3	94 ± 8	−11.3 ± 0.2	−4.59 ± 0.15	6.7 ± 0.3	*g*
Gly-D-Phe (zwitterion)	am-β-CD	113	1.64	6.1[c]	2	39 ± 2	−9.08 ± 0.15	−7.4 ± 0.3	1.7 ± 0.3	*f*
	β-CD	100	1.93	6.1[c]	2	47 ± 1	−9.54 ± 0.07	−7.93 ± 0.15	1.6 ± 0.2	*g*
Gly-L-Phe (zwitterion)	am-β-CD	110	1.85	6.1[c]	2	42 ± 2	−9.26 ± 0.15	−8.4 ± 0.2	0.9 ± 0.2	*f*
	β-CD	96	2.54	6.1[c]	2	54 ± 1	−9.89 ± 0.06	−8.59 ± 0.15	1.3 ± 0.2	*g*
(*R*)-hexahydromandelic acid (−1)	am-β-CD	96−109	1.28−1.61	6.5[c]−6.9[b]	2	2290± 50	−19.18 ± 0.07	−10.3 ± 0.2	8.9 ± 0.2	*f*
	β-CD	94−149	2.06−2.09	6.9[b]	4	648 ± 12	−16.05 ± 0.05	−5.61 ± 0.07	10.44 ± 0.08	*g*
(*S*)-hexahydromandelic acid (−1)	am-β-CD	101−105	1.28−1.43	6.5[c]−6.9[b]	4	1490 ± 30	−18.11 ± 0.07	−7.4 ± 0.2	10.7 ± 0.2	*f*
	β-CD	98−169	1.89−1.96	6.9[b]	4	603 ± 10	−15.87 ± 0.05	−5.36 ± 0.05	10.51 ± 0.07	*g*
(*R*)-mandelic acid (−1)	am-β-CD	144	1.60	6.9[b]	2	55 ± 2	−9.93 ± 0.09	−6.75 ± 0.07	3.2 ± 0.1	*f*
	β-CD	232	1.66	6.9[b]	2	11 ± 2	−5.9 ± 0.5	−4.9 ± 0.3	1.0 ± 0.6	*g*
(*S*)-mandelic acid (−1)	am-β-CD	148−158	1.28−1.57	6.5[c]−6.9[b]	2	44 ± 2	−9.4 ± 0.1	−4.9± 0.1	4.5 ± 0.2	*f*
	β-CD	224	2.73	6.9[b]	2	9 ± 2	−5.4 ± 0.6	−4.6 ± 0.3	0.8 ± 0.7	*g*
(*R*)-α-methoxyphenylacetic acid (−1)	am-β-CD	192	1.74	6.9[b]	2	33 ± 3	−8.7 ± 0.3	−3.8 ± 0.3	4.9 ± 0.4	*f*
	β-CD	231	6.74	6.9[b]	2	11 ± 2	−5.9 ± 0.5	−4.4 ± 0.3	1.5 ± 0.6	*g*
(*S*)-α-methoxyphenylacetic acid (−1)	am-β-CD	226	1.74−6.40	6.9[b]	3	12 ± 3	−6.2 ± 0.5	−3.5 ± 0.6	2.7 ± 0.7	*f*
	β-CD	242	6.89	6.9[b]	2	10 ± 1	−5.7 ± 0.3	−5.1 ± 0.3	0.6 ± 0.4	*g*
D. Complexation with Neutral and Positively Charged Guests										
N-*t*-Boc-D-alanine methyl ester (0)	am-β-CD	78	1.29	6.9[b]	2	395 ± 4	−14.82 ± 0.03	−13.73 ± 0.15	1.1 ± 0.2	*f*
	β-CD	74	1.74	6.9[b]	2	659 ± 6	−16.09 ± 0.02	−13.82 ± 0.15	2.3 ± 0.2	*g*
N-*t*-Boc-L−alanine methyl	am-β-CD	78	1.38	6.9[b]	2	351 ± 4	−14.53 ± 0.03	−12.94 ± 0.15	1.6 ± 0.2	*f*
	β-CD	72	1.72	6.9[b]	2	578 ± 4	−15.77 ± 0.02	−12.80 ± 0.15	3.0 ± 0.2	*g*
(*R*)-3-bromo-2-methyl-1-propanol (0)	am-β-CD	53	1.35	6.5[c]−6.9b	2	116 ± 6	−11.78 ± 0.15	−8.5 ± 0.2	3.3 ± 0.3	*f*
	β-CD	51	1.29−1.47	6.9[b]	2	142 ± 4	−12.29 ± 0.07	−9.3 ± 0.2	3.0 ± 0.2	*g*
(*S*)-3-bromo-2-methyl-1-propanol (0)	am-β-CD	49−53	1.28−1.41	6.5[c]−6.9b	2	113 ± 5	−11.72 ± 0.10	−9.41 ± 0.15	2.3 ± 0.2	*f*
	β-CD	51	1.29	6.9[b]	2	140 ± 4	−12.25 ± 0.07	−10.1 ± 0.2	2.2 ± 0.2	*g*
cyclohexanol (0)	am-β-CD	115	1.09	6.9	2	496 ± 6	−15.39 ± 0.03	−5.79 ± 0.10	9.60 ± 0.10	*f*
	β-CD	136	1.59	6.9[b]	2	701 ± 6	−16.24 ± 0.02	−6.3 ± 0.1	9.9 ± 0.1	*g*
(*R*)-1-cyclohexylethyl-amine (+1)	am-β-CD	155	1.69	6.9[b]	2	188 ± 4	−12.98 ± 0.05	−6.86 ± 0.08	6.1 ± 0.1	*f*
	β-CD	147−184	1.43−1.97	6.9[b]	3	329 ± 3	−14.37 ± 0.03	−7.85 ± 0.08	6.5 ± 0.1	*g*
(*S*)-1-cyclohexylethyl-amine (+1)	am-β-CD	147	1.55	6.9[b]	2	194 ± 4	−13.06 ± 0.05	−6.87 ± 0.08	6.2 ± 0.1	*f*
	β-CD	167−180	1.97−2.15	6.9[b]	4	328 ± 3	−14.36 ± 0.03	−7.87 ± 0.08	6.5 ± 0.1	*g*
(*R*)-mandelic acid methyl ester (0)	am-β-CD	90−117	1.35−1.57	6.5[c]−6.9b	3	42 ± 5	−9.3 ± 0.3	−6.9 ± 0.5	2.8 ± 0.6	*f*
	β-CD	79	2.08−2.69	6.9[b]	2	67 ± 2	−10.42 ± 0.08	−7.8 ± 0.1	*2.6 ± 0.1*	*g*
(*S*)-mandelic acid methyl ester (0)	am-β-CD	100−104	1.35−1.41	6.5[c]−6.9b	2	42 ± 3	−9.3 ± 0.2	−6.9 ± 0.2	2.4 ± 0.3	*f*
	β-CD	82	2.69	6.9[b]	2	72 ± 2	−10.60 ± 0.07	−8.2 ± 0.1	2.4 ± 0.1	*g*
1-methyl-3-phenylpropyl-amine (+1)	am-β-CD	163	1.43	6.9[b]	1	92 ± 4	−11.2 ± 0.1	−7.58 ± 0.15	3.6 ± 0.2	*f*
	β-CD	117	1.95	6.9[b]	2	188 ± 3	−12.98 ± 0.04	−8.64 ± 0.08	4.34 ± 0.09	*g*
4-phenylbutylamine (+1)	am-β-CD	99−119	1.28−1.59	6.5[c]−6.9b	2	201 ± 5	−13.15 ± 0.07	−9.7 ± 0.3	3.5 ± 0.3	*f*
	β-CD	87	1.88	6.9[b]	2	405 ± 6	−14.88 ± 0.04	−10.4 ± 0.1	4.5 ± 0.1	*g*

[a] Number of microcalorimetric titration experiments performed. [b] Phosphate buffer [NaH_2PO_4 (0.025 M) + $NaHPO_4$ (0.025 M)]. [c] Phosphate buffer [NaH_2PO_4 (0.025 M) + $NaHPO_4$ (0.025 M) + HCl]. [d] Acetate buffer [$NaC_2H_3O_2$ (0.05 M) + $C_2H_4O_2$]. [e] K and $\Delta H°$ for this reaction were too small to determine with titration microcalorimeter. [f] This work. [g] Reference 11. [h] Reference 27a.

The enthalpic and entropic changes observed for the other four anionic organic guests, i.e., 3- and 4-tolylacetic acids and (*R*)- and (*S*)-camphanic acids, are also well compatible with the critically balanced van der Waals versus electrostatic interaction model discussed above in the oppositely charged host−guest complexation. For instance, 3- and 4-tolylacetic acids exhibit significantly smaller enthalpic gains upon complexation with am-β-CD than with native β-CD ($\Delta\Delta H°_{am} = \Delta H°_{am-\beta-CD} - \Delta H°_{\beta-CD} = 1-4$ kJ mol^{-1}), which are however "over"compensated by greater entropic gains ($T\Delta\Delta S°_{am} = T\Delta S°_{am-\beta-CD} - T\Delta S°_{\beta-CD} = 3-7$ kJ mol^{-1}) to give 4−5 times larger K's. It should be noted that, as was the case with β-CD,[21b] 2-tolylacetic acid does not form stable complex with am-β-CD. It is likely that the steric hindrance of the *o*-methyl is so severe that even the strong electrostatic interaction cannot overcome it.

Interestingly, large univalent inorganic anions, such as hexafluorophosphate (PF_6^-), perchlorate (ClO_4^-), and thiocyanate (SCN^-), display thermodynamic features similar to those observed for the anionic organic guests discussed above. The thermodynamic parameters obtained for these inorganic anions, shown in Table 1 (category A), are in good agreement with the literature data,[22−25] although more precise comparison is difficult due to the low affinities of ClO_4^- and SCN^- toward β-CD and large experimental uncertainties. The moderate to large negative reaction enthalpies observed not only for cationic am-β-CD but also for neutral β-CD clearly indicate the large potential ability of these inorganic ions to make strong van der Waals contacts with CDs. Although the physical origin of these strong interactions is not necessarily clear, it is reasonable to assume that the large polarizability of these anions plays a crucial role upon inclusion into the CD cavity, causing substantial dipole−induced

dipole interactions or dispersion forces. Furthermore, increasing anionic diameter ($SCN^- < ClO_4^- < PF_6^-$) enhances closer van der Waals contacts with CD, which also greatly contribute to the favorable enthalpic change and complex stability. Indeed, the enthalpic gain ($-\Delta H°$) and complex stability (K) rapidly increase by changing the anion from SCN^- to ClO_4^- and then to PF_6^- (Table 1). Judging from the fairly negative entropy changes, these inorganic anions are not heavily hydrated in bulk aqueous solution or not extensively desolvated upon complexation as is the case with the aza-aromatic moieties discussed above.

Global examinations of the data in Table 1 reveal that the introduction of an amino group into native β-CD causes a very similar influence to the complexation thermodynamic behavior of both organic and inorganic anions. Indeed, all of the category A guests, with exceptions of 10-camphorsulfonic acid and α-methoxy-α-trifluoromethylphenylacetic acid,[26] exhibit less exothermic reaction enthalpy and less negative reaction entropy upon complexation with am-β-CD than with β-CD. The less negative $\Delta H°$ for am-β-CD is likely to arise from the disturbance of the originally well-optimized van der Waals host−guest interactions in the β-CD cavity, which is caused by attractive electrostatic interaction. However, the effective electrostatic interaction between host and guest usually leads to a more exothermic reaction enthalpy of up to 2−3 kJ mol^{-1}, as clearly demonstrated for the complexation of Cbz-Asp and Cbz-Glu with mono- and diaminated β-CDs.[27a] Hence, it is reasonable to assume that the "net" experimentally observed enthalpic losses most likely consist of two contributions: enthalpic losses from the reduced van der Waals contacts upon complexation with am-β-CD rather than β-CD and enthalpy gains from effective electrostatic interactions upon complexation with am-β-CD versus β-CD. If so, then the van der Waals interaction energy losses may be about 3−5 kJ mol^{-1} for PF_6^-, ClO_4^-, and SCN^- and to 6−9 kJ mol^{-1} for *N*-acetyl-D/L-tryptophan. The less negative $\Delta S°$ observed for am-β-CD than for native β-CD is likely to arise from more pronounced desolvation of the charged groups in both host and guest upon ion-pairing interactions. First, overlapping of relatively large hydration shells around the charged groups in am-β-CD and guest leads to the release of a significant amount of water molecules to the bulk solution, gaining entropy. Second, water molecules remaining in the shell can possess greater freedom as a result of inevitable water-mediated intermolecular vibrations between the charged groups in host and guest, resulting in a combined hydration shell where the water molecules possess more chances to participate in hydrogen bond network of increased freedom.[27b]

We have hitherto discussed the thermodynamic behavior of such guests that form complexes with CDs predominantly through the van der Waals, electrostatic, and solvation−desolvation interactions. It is interesting to examine the thermodynamic consequences of transferring a guest from the β-CD to the am-β-CD cavity, where some specific intracavity interactions such as hydrogen bonding are involved upon complexation. For that purpose, 3-(2-hydroxyphenyl)propionic acid, 3-(4-hydroxyphenyl)propionic acid, and *N*-acetyltyrosine were subjected to the microcalorimetric study. These guests, possessing a phenolic hydroxyl group, form an intracavity host−guest hydrogen bond upon complexation with CDs, as proved experimentally.[12,13]

The guests possessing phenolic OH exhibit typical thermodynamic features common to all of the above-mentioned guests. Thus, the transfer of a guest from the β-CD to the am-β-CD cavity led to a less favorable reaction enthalpy and a less unfavorable reaction entropy. The most likely explanation for such results may be noncooperativity or conflict between the hydrogen-bonding interaction of the OH group and the electrostatic interaction of the carboxylate group with am-β-CD. There are strict requirements in distance and angle for optimal hydrogen-bonding interaction. Hence, it is likely that the additional electrostatic interaction near the rim of am-β-CD impairs the optimal geometry for the intracavity hydrogen-bonding interaction by altering the original position of the guest included in the native CD cavity, which inevitably results in the loss of enthalpic gain as observed.

The thermodynamic consequences of the hydroxyl group introduced in the guest are significantly different for 3-(2-hydroxyphenyl)- or 3-(4-hydroxyphenyl)propionic acid and for *N*-acetyltyrosine. A comparison of the thermodynamic parameters for 3-(hydroxyphenyl)propionates with those for the reference guest, 3-phenylpropionate (see the last part of category B in Table 1), clearly indicates that the hydroxyl group is exclusively responsible for the enthalpic loss caused by changing the host from β-CD to am-β-CD, as 3-phenylpropionic acid exhibits more exothermic enthalpy upon complexation with am-β-CD than with β-CD. In contrast, *N*-acetyltyrosine and the reference guest, *N*-acetylphenylalanine, exhibit quite a similar thermodynamic behavior upon transfer from the β-CD to the am-β-CD cavity, thus giving less favorable reaction enthalpy and less unfavorable reaction entropy. The structural reason for this difference in thermodynamic behavior is not immediately clear, but one of the plausible explanations would involve the hydrogen-bonding interaction of the amide proton in *N*-acetylamino acids, which is disturbed upon complexation with the am-β-CD cavity, as discussed above.

The ability of the fluorine atom in a guest to form hydrogen bonding [27c−e] or van der Waals interactions with the CD walls upon inclusion is supported by the highly exothermic reaction enthalpies obtained for α-methoxy-α-trifluoromethylphenyl-

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(26) The thermodynamic consequence of introducing an amino group into β-CD is very sensitive to the substitution pattern in structurally related guests. For instance, camphanic acid and 10-camphorsulfonic acid share a camphor-like skeleton but differ in a few aspects: (1) the presence of oxygen in the bicyclic skeleton and (2) the position and type of the dissociable group (although the type of charged group in guest has been demonstrated not to affect the complexation thermodynamics).[11,13] Despite the apparent structural resemblances in size and shape, the two camphor derivatives exhibit entirely opposite thermodynamic behavior. Thus, the transfer of 10-camphorsulfonic acid from the β-CD to the am-β-CD cavity leads to an enthalpic gain of 3−5 kJ mol^{-1} and an entropic loss ($T\Delta S°$) of 2−4 kJ mol^{-1}, while the same transfer of camphanic acid results in enthalpic loss of 1 kJ mol^{-1} and entropic gain of 1−2 kJ mol^{-1}. The unusual complexation behavior of α-methoxy-α-trifluoromethylphenylacetic acid is discussed below in connection with the guests capable of intracavity hydrogen bonding.
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acetic acid upon complexation with both am-β-CD and β-CD; $-\Delta H^\circ = 16-19$ kJ mol^{-1}. These large exothermic reaction enthalpies are particular impressive if compared with those for the lower homologue α-methoxyphenylacetic acid lacking a trifluoromethyl group; $-\Delta H^\circ = 4-5$ kJ mol^{-1} (see the last part of section C of Table 1). The differences in ΔH° amount to 11−15 kJ mol^{-1}, which are much larger than the typical enthalpic gain for a methyl group (3−4 kJ mol^{-1}).[3] It is concluded therefore that the trifluoromethyl group is the main hydrophobic guest group responsible for the large exothermic complexation enthalpy of α-methoxy-α-trifluoromethylphenylacetic acid toward both CDs. The above discussion does not contradict with the unfavorable enthalpy of transfer from the β-CD to the am-β-CD cavity for guests possessing single phenolic hydroxyl since three fluorine atoms of α-methoxy-α-trifluoromethylphenylacetic acid, pointing to the CD cavity walls at varying angles, certainly have a much larger chance to make at least one F···H bond compared with the ability of a single phenolic hydroxyl.

Now we discuss the effect of host amination upon chiral discrimination. The loss of complexation enthalpy, caused by amination of β-CD, is defined for each guest by the differential reaction enthalpy: $\Delta\Delta H^\circ_{am} = \Delta H^\circ$(am-β-CD) − ΔH°(β-CD). Thus, the enthalpic loss for *N*-acetyl-D-tyrosine is calculated as $\Delta\Delta H^\circ_{amD} = 4.8$ kJ mol^{-1}, which is almost 3 kJ mol^{-1} larger than that for L-isomer, $\Delta\Delta H^\circ_{amL} = 2.0$ kJ mol^{-1}. However, this significant difference of the enthalpic losses for D- and L-isomers is almost completely compensated by the comparable entropic gains ($T\Delta\Delta S^\circ_{amD} = 4.6$ kJ mol^{-1}; $T\Delta\Delta S^\circ_{amL} = 2.0$ kJ mol^{-1}), ultimately giving a very modest enhancement in enantiomer selectivity from $K_L/K_D = 1.05$ for β-CD to 1.18 for am-β-CD. Two other amino acid derivatives, i.e., *N*-acetyl-D/L-tryptophan (category A) and *N*-acetyl-D/L-phenylalanine (category B), behave similarly. Indeed, both CDs prefer the L-amino acids, while am-β-CD shows better performance than β-CD; by employing am-β-CD, the K_L/K_D ratio is enhanced from 1.37 to 1.69 for *N*-acetyltryptophan and from 1.11 to 1.34 for *N*-acetyl-D/L-phenylalanine. In the case of α-methoxy-α-trifluoromethylphenylacetic acid, the *R*-enantiomer is favored by both CDs and am-β-CD shows a higher enantiomer selectivity (K_R/K_S) of 1.49 than β-CD ($K_R/K_S = 1.24$). It should be emphasized that the β-CD cavity exhibits consistent enantiomer selectivity toward a series of structurally related guests[11] and that the amino substitution does not alter but rather enhances the original enantiomer selectivity obtained with native β-CD.

The enantiomer selectivity (K_S/K_R) obtained for camphanic acid increased only slightly from 1.16 to 1.19 by changing the host from β-CD to am-β-CD. This result may suggest that the additional electrostatic interaction does not significantly alter the guest conformation in the cavity, probably due to the rigid guest structure to which the anionic group is attached. However, 10-camphorsulfonic acid, possessing an apparently similarly rigid skeleton, behaves quite differently. The enantiomer preference was switched from *R* to *S* by the host amination inverting K_S/K_R from 0.87 to 1.08. Thus, 10-camphorsulfonic acid is an exception to other category A guests not only from the point of view of complexation thermodynamics (see discussion above) but also due to inverted chiral preference by am-β-CD versus β-CD.

Complexation Primarily Driven by Enthalpy with Entropic Assistance ($\Delta H^\circ < 0$; $T\Delta S^\circ > 0$; $|\Delta H^\circ| > |T\Delta S^\circ|$). Thermodynamic parameters for such host−guest combinations that give favorable enthalpy and entropy changes with a predominant role of enthalpy are listed in the second part (category B) of Table 1. For category B guests, the thermodynamic consequence of transferring guest from a native to an aminated CD cavity is quite different from that observed for category A guests. Indeed, the host amination led to a decrease in the enthalpic gain upon complexation with most category A guests (except 10-camphorsulfonic acid and α-methoxy-α-trifluoromethylphenylacetic acid), while most category B guests (except *N*-acetylphenylalanine and 2- and 3-phenylbutyric acids) afforded higher enthalpic gains upon complexation with am-β-CD than with β-CD. As already discussed above, the smaller enthalpic gain obtained for a category A guest with am-β-CD is attributable to the deviation from the best-fitted, but fairly restricted, guest conformation within the native β-CD cavity, as the originally optimized van der Waals contacts are more or less disturbed by the additional electrostatic interaction upon complexation with am-β-CD. Contrary to the *negative* entropy changes obtained with category A guests, all category B guests give *positive* entropy changes, which indicate that they experience less-significant conformational restriction upon complexation. Possible positional flexibility inside the cavity allows these guests to minimize the enthalpic loss arising from the positional deviation and even to add some enthalpic gains, both of which are induced by the strong electrostatic interaction. Furthermore, it is interesting to note that the additional electrostatic interaction with am-β-CD does not significantly restrict the guest conformation, accompanying only slight changes in $T\Delta S^\circ$, mostly smaller than ±1 kJ mol^{-1}.

However, there are some exceptional cases. Both enantiomers of *N*-acetylphenylalanine afford smaller enthalpic, and larger entropic, gains upon complexation with am-β-CD than with native β-CD. As suggested above, one of the possible reasons for this exceptional thermodynamic behavior is the possible hydrogen-bonding interaction of *N*-acetylamide moiety, which would be disturbed by the electrostatic interaction with am-β-CD.

The other exceptions include enantiomeric 2- and 3-phenylbutyric acids, which differ only in the methyl position. Nevertheless, this apparently small variation in structure results in the profound difference in complexation thermodynamics. Despite virtually the same hydrophobicity (i.e., the distribution ratio between water and nonpolar organic solvent), the affinity of 3-phenylbutyric acid toward β-CD ($K = 402-430$ M^{-1}) is more than 4 times larger than that of 2-phenylbutyric acid ($K = 94-95$ M^{-1}). This is a good example of the critical role of steric factor in CD complexation, highlighting the intrinsic difference between inclusion complexation by CD and classical hydrophobic process (e.g., transfer from water to nonpolar organic media). From the relatively large positive entropy changes observed, it is inferred that 3-phenylbutyric acid is not severely restricted in conformation upon complexation with β-CD, but rather enjoys strong van der Waals interaction and, at the same time, participates in the solvation/desolvation processes or rearrangement of the water molecules inside the CD cavity, eventually giving almost the same affinity toward β-CD as straight-chain 4-phenylbutyric acid.[18,21b] It is deduced

that the interactions of 3-phenylbutyric acid with the β-CD cavity are so nicely optimized that the additional electrostatic interaction cannot improve in such a way that increases the affinity toward am-β-CD, thus exhibiting similar affinities toward both CDs despite the steric bulk of the methyl group.

The position of the phenyl group introduced to the butyric acid guest dramatically alters the thermodynamic consequence of complexation of 2- and 3-phenylbutyric acids with β-CD and am-β-CD. The entropic gains for the complexation of 2-phenylbutyric acid with β-CD are substantially smaller (by 5 kJ mol^{-1}) than that for 3-phenylbutyric acid, which are compensated only in part by slightly enhanced enthalpic gains (by 1 kJ mol^{-1}), ultimately affording the much reduced affinities. These smaller entropic gains may be ascribed to more restricted conformation of 2-phenylbutyric acid or less extensive desolvation upon complexation with β-CD, the latter of which appears more likely since the positional/conformational restriction upon complexation is accompanied in general not only by a large entropic loss but also by a simultaneous and almost comparable enthalpic gain. The contribution of desolvation is further supported by the large entropic gains obtained upon complexation of the same guest with am-β-CD, where 2-phenylbutyric acid suffers from the pronounced desolvation as a result of additional ion-pairing interaction.

A comparison of the complexation thermodynamic behavior of isomeric 3-phenylpropionic, 3-tolylacetic, and 4-tolylacetic acids and their lower homologue 4-tolylic acid is interesting. The thermodynamic parameters obtained for these guests upon complexation with β-CD and am-β-CD are extremely sensitive to the varying guest structure, i.e., the presence and position of an added methyl/methylene group. Indeed, external electrostatic interaction is cooperative with conventional intracavity interactions with 3-phenylpropionic acid and 4-tolylic acid, giving more favorable reaction enthalpy and entropy for am-β-CD than for β-CD. On the contrary, 3- and 4-tolylacetic acids suffer an enthalpic loss but gain large amounts of entropy upon transfer from the β-CD to the am-β-CD cavity, which are attributable to weaker van der Waals interactions and more pronounced host/guest desolvation, respectively.

If the penetrating group of a guest is not three-dimensionally large enough to fully occupy the CD cavity upon complexation, it seems reasonable to assume that some water molecules manage to coexist with the included guest moiety inside the same cavity.[27a,f,g] To examine this possibility, let us compare the complexation thermodynamic behavior of am-β-CD versus β-CD toward such guests as camphanic acid and camphorsulfonic acid that possess the right size and shape fitted to the β-CD cavity (thus leaving no water molecule in the cavity upon complexation) with the other extreme case of less-hydrophobic, less-perfectly size/shape-fitted guests, such as hexaflourophosphate, perchlorate, and thiocyanate, which most likely allow some water molecules to coexist in the cavity upon complexation. The complexation thermodynamic parameters obtained for these inorganic guests, and almost all other category A guests as well, show a common changing pattern of enthalpy and entropy upon transfer from the β-CD to the am-β-CD cavity (see Table 1), i.e., less favorable enthalpy and less unfavorable entropy changes. The size and shape of 4-tolylic acid (category B) would also allow the presence of some water molecules in the cavity upon complexation. Nevertheless, this guest exhibits common thermodynamic behavior shared by the other category B guests. On the other hand, camphorsulfonic acid is exceptional as a category A guest from the thermodynamic point of view. It is thus concluded that the size, shape, and substitution pattern play more significant roles in enthalpy and entropy changes upon transfer from the β-CD to the am-β-CD cavity than the presence or absence of the water molecule(s) inside the cavity.

Now, the chiral recognition abilities of am-β-CD and β-CD are comparatively discussed for category B and other guests. As was the case with chiral category A guests (e.g., *N*-acetyltryptophan, *N*-acetyltyrosine, camphanic acid, and α-methoxy-α-trifluoromethylphenylacetic acid), both β-CD and am-β-CD prefer the identical enantiomers of *N*-acetylphenylalanine, *N*-*t*-Boc-alanine, and phenyllactic acid, as well as two category C guests (*O*,*O*′-dibenzoyltartaric acid and hexahydromandelic acid) and a category D guest (*N*-*t*-Boc-alanine methyl ester). Only one chiral guest (10-camphorsulfonic acid), among the 22 enantiomer pairs examined, exhibits the opposite enantiomer preference upon complexation with β-CD and am-β-CD. At present, we have no convincing explanations for such a consistent enantiomer preference shared by β-CD and am-β-CD, despite the different types of intracavity or external interactions involved upon complexation. However, it is not unreasonable to suppose that the van der Waals interactions inside the CD cavity play the major role in the chiral recognition process and differentiate the relevant antipodes through the difference in the 3-D shape of the guest molecule and that the additional electrostatic or any other extracavity interactions may play auxiliary roles as far as the chiral recognition is concerned, enhancing or reducing the original affinity and enantiomer selectivity of native β-CD. Thus, β-CD is considered to preserve the original enantiomer preference, or "chiral template", for most enantiomeric guests even after peripheral modifications. The present finding is important in designing new CD derivatives with higher chiral recognition abilities, since this means that we can freely introduce "functional" or "nonfunctional" moiety(ies) to native CDs for specific or nonspecific extracavity interactions with the included guest. Obviously, this is just a working hypothesis to be verified by further thermodynamic studies using a wide variety of modified CDs and chiral guests.

Generally, am-β-CD exhibits better performance as compared with native β-CD as far as magnitude of chiral discrimination is concerned. However, in some specific cases, the host amination affects little or even reduces the enantiomer selectivity. The complexation thermodynamics of am-β-CD with Cbz-aspartic acid, 3-phenylbutyric acid, *O*,*O*′-dibenzoyltartaric acid, *O*,*O*′-di-*p*-toluoyltartaric acid, and Gly-Phe indicate that the additional electrostatic interaction can lead to reduced chiral discrimination, probably as a result of noncooperativity with the conventional intracavity interactions. In this context, it is interesting to point out that three out of the five chiral guests possess two negatively charged groups (carboxylates). The dianionic, compared with the conventional monoanionic, guests possess greater freedom to fine-tune their position and conformation in the cavity upon complexation with cationic am-β-CD, which should be responsible at least in part for the reduced thermodynamic differences between antipodal complexes.

Complexation Predominantly Driven by Entropy and Moderately by Enthalpy ($\Delta H^\circ < 0$; $T\Delta S^\circ > 0$; $|T\Delta S^\circ| > |\Delta H^\circ|$) and Some Special Cases. Category C guests (Table 1)

are differentiated from category B guests by the highly positive entropy changes and equal or less favorable enthalpy changes ($|\Delta H^\circ| \leq |T\Delta S^\circ|$) upon complexation with β-CD or am-β-CD, at least in the case of one enantiomer. Strictly speaking, mandelic acid is classified into category B but is included in this section in order to comparatively discuss its thermodynamic behavior with that of the structurally related guests such as α-methoxyphenylacetic acid (mandelic acid methyl ether) and hexahydromandelic acid. Zwitterionic Gly-Phe is also an exemption, but we added this guest just below the tartaric acid derivatives in order to compare the thermodynamic consequence of the electrostatic interactions of negative/negative or positive/negative dual charges in a guest with the positively charged ammonio group of am-β-CD.

It is somewhat puzzling why both of the enthalpy-driven (category A) and entropy-driven (category C) guests, with very limited exceptions, give more positive, or less negative, entropy changes upon transfer from the β-CD to the am-β-CD cavity. As discussed above, the favorable entropy changes for category A guests are derived from the disturbed optimal van der Waals contacts and the increased conformational freedom, both caused by the newly introduced external electrostatic interaction.

However, the consistently enhanced entropic gains for category C guests upon transfer from the β-CD to the am-β-CD cavity are not readily understood or attributable to the same reason, since the entropy changes are originally positive for complexation of category C guests with β-CD, and category B guests, which also form entropy-favored complexes with both β-CD and am-β-CD, do not show such a pronounced entropic enhancement. One of the possible explanations is the more extensive host/guest desolvation associated with the ion-pairing interactions. This sounds reasonable, since most of the category C guests possess two charged or neutral hydrophilic groups (i.e., carboxylate, ammonio, hydroxyl, or all three) and even the complexation with neutral β-CD give positive entropy changes with substantial enthalpic stabilization, probably through the host/guest desolvation. For guests with hydrophilic moieties, further desolvation caused by the ion-pairing interaction is not unreasonable. Such ion-pairing interactions could be cooperative with the conventional intracavity interactions, affording more negative enthalpy changes through strong electrostatic interactions or less negative enthalpy changes through significant disturbance of originally existing van der Waals contacts (Table 1, section C).

Possessing two charged/neutral hydrophilic groups, the chiral recognition behavior of category C guests is particularly interesting. In a previous study,[11] we pointed out that any additional weak interactions introduced by host/guest/solvent modification to the existing host−guest system very frequently result in reduced enantiomer selectivity, probably through the noncomplimentary relationship between the chiral guest and CD cavity. This is exactly the case with the complexation of *O*,*O*′-dibenzoyltartaric acid, *O*,*O*′-di-*p*-toluoyltartaric acid, and Gly-Phe. Indeed, the enantiomer pair of dibenzoyltartaric acid gives appreciable K_D/K_L ratios of 1.60 and 1.43 for β-CD and am-β-CD, respectively, while the extra methyls in di-*p*-toluoyltartaric acid completely destroy the enantiomer selectivity to give the K_D/K_L ratios of 1.0−1.1, although the introduced methyls enhance the binding ability by a factor of 2.3−2.6.

If a chiral monoanionic guest has a hydrophobic moiety of appropriate size and shape to penetrate into the CD cavity, extra electrostatic interaction induced can cause conformational/positional changes in guest, which are significantly different in magnitude for each of the antipodal guest, leading to the enhanced enantiomer selectivity. The complexation thermodynamic behavior of structurally related mandelic, hexahydromandelic, and α-methoxyphenylacetic acids with β-CD and am-β-CD is reasonably accounted for in terms of this mechanism. The smallest guest, i.e., mandelic acid, exhibits much higher affinity to am-β-CD than to β-CD but gives practically the same enantiomer selectivity for both CDs ($K_R/K_S \sim 1.2$). The more negative enthalpy change and positive entropy change for am-β-CD are jointly responsible for such a large enhancement in affinity. The aminated host exhibited 2.5−3.5 times higher affinity to hexahydromandelic acid than for native β-CD, with a moderate increase in enantiomer selectivity (K_R/K_S) from 1.07 to 1.54. Interestingly, this affinity enhancement observed for am-β-CD is achieved predominantly through the increased enthalpic gain, which is critically enantiomer-dependent. Thus, the enthalpic gains obtained for *R*- and *S*-enantiomers are 4.7 and 2.0 kJ mol^{-1}, respectively, while the corresponding entropic losses are 1.5 and −0.2 kJ mol^{-1}. The relatively large enhancement in K_R/K_S may be attributed to the different ability of antipodal guests for the conformational adjustment upon applying external elecrostatic forces. If so, it is likely that a slightly bulkier group introduced around the chiral center hinders more or less the conformational adjustment inside the chiral CD cavity. The additional bulk should not be too large, since a large hydrophobic group could freeze any conformational alterations inside the cavity, leading to the exclusively enthalpy-driven complexation as discussed above.

One of the best candidate guests satisfying such conditions is α-methoxyphenylacetic acid. Indeed, the methylation of the hydroxyl group of mandelic acid resulted in large differences in both complexation thermodynamics and chiral discrimination. α-Methoxyphenylacetic acid exhibits lower affinity toward am-β-CD than mandelic acid, probably due to the steric hindrance caused by the additional methyl group. However, the most remarkable consequence is the significantly enhanced enantiomer selectivity observed for am-β-CD, as K_R/K_S increases from 1.25 for mandelic acid to 2.75 for α-methoxyphenylacetic acid.

It should be emphasized that am-β-CD, rather than native β-CD, shows higher chiral recognition ability toward most chiral guests with some exceptions mentioned above. One of the major reasons is the less-symmetrical arrangement of glucopyranose units in am-β-CD. Thus, the introduction of an amino group in one of the glucose units of CD makes this glucose unique in view of the molecular symmetry as well as the hydrogen-bonding ability, eventually endowing a higher chiral recognition ability. For the optimal realization of this potential ability of the less-symmetrical chiral cavity of am-β-CD, one should avoid guests capable of multiple ion-paring interactions, which often compensate the thermodynamic differences for antipodes as discussed above. Nevertheless, the general rule that a less symmetrical CD cavity exhibits better performance in chiral discrimination is further supported by our recent study of the complexation behavior of disubstituted CDs.[27a] Thus, enantiomeric Cbz-glutamic acid is better discriminated by *A*,*B*-, *A*,*C*- and *A*,*D*-bis(6-trimethylammonio-6-deoxy)-β-CDs than by na-

tive β-CD, and the K_D/K_L ratio increases from 1.14 to 1.18 and then to 1.40 with increasing degree of "less-symmetrical" substitution, or in the order *A,D*- < *A,C*- < *A,B*-isomers.[27a]

In our previous study,[11] we established a direct correlation between the mode of penetration and the chiral recognition by β-CD of aromatic amino acid derivatives and some other classes of chiral organic compounds. As demonstrated above, the complexation by am-β-CD is governed by the same rule, favoring the L-isomers of *N*-acetylphenylalanine, *N*-acetyltryptophan, and *N*-acetyltyrosine. This rule is further verified by the same mode of penetration and the same D-preference upon complexation of *N*-*t*-Boc-alanine and *N*-Cbz-alanine, although we could not claim the D-preference for *N*-Cbz-alanine in our previous study,[11] due to the poor chiral discrimination by β-CD. However, the amination of β-CD enabled us to discriminate the *N*-Cbz-alanine enantiomers, giving appreciable D-preference. The most impressive example of the same enantiomer preference of am-β-CD, which is determined by the same mode of penetration, is the *R*-preference observed for mandelic acid, hexahydromandelic acid, α-methoxyphenylacetic acid, phenyllactic acid, and 2-phenylbutyric acid. The penetration mode for all of these guests are unambiguously determined by the position of the phenyl or cyclohexyl group as the most hydrophobic group around the chiral center and consequently the consistent *R*-preference was observed.

Thermodynamic Cooperativity upon Transfer between the CD Cavities and Ordering Entropy.[12,28] Transferring a guest from one host to another can cause enthalpic and entropic changes, which are either compensating or cooperative with each other. Although most of the guests examined in the present study give compensatory enthalpic and entropic changes upon transfer from β-CD to am-β-CD, some cause cooperative favorable changes. In the latter cases, the additional electrostatic interaction operative upon complexation with am-β-CD significantly enhances the complex stability through the simultaneous contributions of more exothermic reaction enthalpy (enthalpic gain), arising from the strong electrostatic interactions and newly formed van der Waals contacts, and more positive or less negative reaction entropy (entropic gain) from the host/guest desolvation or rearrangement of the water molecules inside the cavity.

We now define a new term, "ordering entropy". Usually, even a simple modification in host or guest causes considerable changes in complexation thermodynamics, but in some special cases, the original enthalpic change is not appreciably affected by the alterations in host/guest structure and therefore interactions involved, which however leads to an extrasignificant gain in entropy or "ordering entropy". Furthermore, to make a clear case for "ordering entropy", it is also important that the entropy increase (more positive or less negative) should be significant as compared to the enthalpy change. Careful examination of the thermodynamic data presented in Table 1 reveals several cases with ordering entropy, where the conventional intracavity attractive forces and the additional electrostatic force jointly strengthen complexation. There is only one such case in category A, i.e., the exclusively enthalpy-driven complexation of α-methoxy-α-trifluoromethylphenylacetic acid, and it should be noted that only one enantiomer (*S*-configuration) of this guest reveals a clear case of "ordering entropy". However, the cooperative enthalpy and entropy gains upon transfer from β-CD to am-β-CD are obtained more frequently for category B guests (*N*-*t*-Boc-alanine, phenyllactic acid, 3-phenylpropionic acid, 4-tolylic acid) and for category C guests (mandelic acid, hexahydromandelic acid, *O*,*O*′-di-*p*-toluoyltartaric acid). Nevertheless, only *S*-isomers of phenyllactic and hexahydromandelic acids present clear cases of "ordering entropy" in a manner similar to α-methoxy-α-trifluoromethylphenylacetic acid as stated above. As pointed out in previous papers,[1−6] complexation reactions of various guests toward native and modified CDs reveal many similarities to biochemical and biological systems and thus the above observation would infer that "ordering entropy", when observed only for one enantiomer, could play a significant role in chiral discrimination in biology. In this section, we will extract and discuss the structural features that are responsible for the existence of the thermodynamic cooperativity observed for the above-mentioned guests.

In the first case of α-methoxy-α-trifluoromethylphenylacetic acid, the cooperativity is valid due to the ability of trifluoromethyl group to form hydrogen bonds in the different directions depending on the specific complex structure as discussed above.

In the second case, the cooperative enhancement is feasible when the hydrophobic moiety of the guest has a spherical symmetry and high rotational freedom within the cavity. For instance, the *t*-Boc group meets such requirements, carrying a spherical *tert*-butyl capable of freely rotating inside the cavity without changing the global van der Waals contacts with the CD walls. In contrast, the phenyl ring of phenyllactic acid or 3-phenylpropionic acid is not so spherical/symmetrical as *tert*-butyl that its positional alteration inside the cavity can be accompanied by significant changes in van der Waals contacts as demonstrated by us previously.[27a] The more flexible, less bulky tethers of phenyllactic acid and 3-phenylpropionic acid provide these guests with more freedom to adjust their conformation inside the cavity to optimize the van der Waals contacts upon transferring from the β-CD to the am-β-CD cavity, as clearly demonstrated in the present study.

Third, when the guest is small enough to almost freely move around inside the cavity or its hydrophobic moiety is flexible enough to allow multiple conformations to exist inside the cavity, such a guest can fine-tune the host/guest solvation or rearrangement of the water molecules inside the cavity, yet maintain comparable van der Waals contacts. Indeed, mandelic acid and 4-tolylic acid are the smallest among the guests presented in Table 1 and thus it is reasonable to expect that they enjoy the highest degree of molecular freedom upon complexation with CDs. In addition, as demonstrated in our previous study,[11] a *p*-methyl added to the phenyl group (as in 4-tolylic acid) not only enthalpically enhances the affinity through the increased van der Waals contacts but also entropically improves the binding ability through the rearrangement of water molecules inside the cavity. We may call this effect of para methylation the "dualistic" thermodynamic enhancement. Comparison of the complexation behavior of di-*p*-toluoyltartaric acid and dibenzoyltartaric acid nicely illustrates this effect. Indeed, the affinity of di-*p*-toluoyltartaric acid toward β-CD is 3−4 times larger than that for the lower homologue lacking *p*-methyls, despite the smaller exothermic enthalpy for the

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former rather than the latter guest. However, upon transfer from the β-CD to the am-β-CD cavity, the "dualistic" enhancement by *p*-methyls operates, affording a much increased affinity predominantly through the cooperative enthalpy and entropy changes. On the other hand, the affinity enhancement of homologous dibenzoyltartaric acid is entirely entropic in origin with accompanying loss of enthalpy arising from the disturbed van der Waals contacts originally existed in the β-CD cavity.

The cyclohexane ring of hexahydromandelic acid is a nice example of a conformationally adaptable hydrophobic moiety, which is flexible enough to allow various conformers to exist within the cavity. As a consequence of variable conformation and high hydrophobicity, hexahydromandelic acid exhibits relatively large affinity toward β-CD predominantly through the favorable entropic gains ($T\Delta S°$ >9−10 kJ mol^{-1}) as well as moderate enthalpic gains ($-\Delta H°$ >5 kJ mol^{-1}). The conformational flexibility enables the cyclohexyl to sustain the original intracavity interactions even upon guest transfer from β-CD to am-β-CD; i.e., despite the additional electrostatic interaction involved, am-β-CD affords 2−5 kJ mol^{-1} higher enthalpic gains than native β-CD upon complexation with hexahydromandelic acid. However, as mentioned above, only (*S*)-hexahydromandelic acid reveals a clear case of "ordering entropy". The most likely reason is the very different adjustment in reaction enthalpy for *R*-isomer versus *S*-isomer upon their transfer from the β-CD to the am-β-CD cavity. Indeed, the enthalpy enhancement for the *R*-isomer is as large as 4.7 kJ mol^{-1} but for the *S*-isomer it is only 2.0 kJ mol^{-1}. As discussed above, the more exothermic enthalpy may arise from additional van der Waals contacts or from effective electrostatic interactions. It is hard to believe that the electrostatic interactions made by the *R*-isomer versus the *S*-isomer are sufficient to cause the difference in reaction enthalpy equal almost to 3 kJ mol^{-1}; thus, probably additional van der Waals contacts made by *R*-isomer are predominantly responsible for this difference. If so, than it would be very natural that more pronounced additional van der Waals contacts (more enhancement in enthalpy) should lead to more conformational restriction of the guest inside the cavity, and consequently, after a certain extent of the restriction, even the high flexibility of the hexane ring is not enough to afford or to maintain large favorable entropy changes upon complexation. Thus, the very large gain in enthalpy for the *R*-isomer is naturally accompanied by a loss in entropy leading to the commonly observed enthalpy−entropy compensation. The same explanation may be applied for two other cases of phenyllactic and α-methoxy-α-trifluoromethylphenylacetic acids where the *S*-isomer reveals a case of "ordering entropy" however the *R*-isomer is a subject of enthalpy−entropy compensation. Indeed, in accordance with the above discussion, the *R*-isomer of both the guests exhibits larger enthalpy gains compared with the *S*-isomer upon transfer from the β-CD to the am-β-CD cavity and thus probably becomes more conformationally restricted.

As frequently observed in most supramolecular host−guest systems including CD-guest complexes, a favorable/unfavorable change in complexation entropy, caused for example by some host modification, often accompanies a subsequent enthalpic change in the opposite direction and vice versa, thus minimizing the stability change arising from the enthalpic/entropic gain/loss. This is the basis for the enthalpy−entropy compensation effect, which is widespread in supramolecular chemistry. In this context, the simultaneous enhancement in enthalpic and entropic gains, observed above upon guest transfer from β-CD to am-β-CD, is rather exceptional and may be related to the ordering entropy. It should be emphasized that since we are dealing with the supramolecular systems, in which multiple components are associated by weak noncovalent interactions, it is unrealistic to expect that the same supramolecular structure/architecture is maintained after the introduction of an additional attractive interaction.[12] For instance, even in a relatively simple system like cyclodextrin complexes, introduction of an additional external force could significantly alter the structure of the resulting complex, which can be extensive enough to switch the direction of penetration into the CD cavity, as revealed in our previous study.[27a] Nevertheless, such a supramolecular system that accompanies favorable changes in both enthalpy and entropy upon guest transfer from one host to another should be regarded as a process associated with ordering entropy (see the definition of ordering entropy given above).

Complexation Thermodynamics and Chiral Discrimination of Neutral and Positively Charged Guests. There are two options to investigate the influence of a charged group introduced to cyclodextrin upon overall complexation thermodynamics, first through examination of the effects of additional ion-pairing interaction with oppositely charged guests, as described above, and second through assessment of the solvation changes in/around the CD cavity caused by the charged group attached. In fact, it has been deduced that in certain conformers of am-β-CD the hydration shell around the charged ammonio group is located at least partially in the interior of cavity.[11] If this is the case, the hydration structural changes in am-β-CD should affect the overall thermodynamics upon complexation with not only charged guests but also neutral ones as well. To experimentally check this possibility, cyclohexanol, (*R*)/(*S*)-3-bromo-2-methyl-1-propanol, *N*-*t*-Boc-D/L-alanine methyl ester, and (*R*)/(*S*)-mandelic acid methyl ester were chosen as neutral reference guests, the complexation behavior of which is then compared with that of the relevant charged guest employed above.

All of these neutral guests consistently show appreciably lower affinities toward am-β-CD than β-CD, giving the relative binding constants, $K_{am-\beta-CD}/K_{\beta-CD}$, of 0.71, 0.82, 0.60, and 0.60 (averaged for enantiomeric guests) for cyclohexanol, 3-bromo-2-methyl-1-propanol, Boc-alanine methyl ester, and mandelic acid methyl ester, respectively. Probably, the reduced hydrophobicity of am-β-CD is responsible for the smaller *K*'s for the neutral guests. The reaction enthalpies for Boc-D- and L-alanine methyl esters were not appreciably affected by the amination of CD, while the other neutral guests afforded less exothermic enthalpies by 0.5−1.3 kJ mol^{-1} upon complexation with am-β-CD, which could be accounted for in terms of weaker van der Waals interactions. Similarly, practically the same or appreciably decreased entropic gains were obtained for the neutral guest upon complexation with am-β-CD. The observed thermodynamic behavior is quite sensible if the presence of an amino group contributes significantly to the overall hydration of the CD cavity. First, the hydration shell around the charged group in the host diminishes the hydrophobicity of the cavity and disturbs some of the van der Waals contacts which originally exist in the neutral β-CD cavity, as indicated by the less exothermic enthalpies observed for some neutral guests upon complexation with am-β-CD. Second, the CD cavity, carrying

a charged group at the rim, will not promptly be desolvated as neutral β-CD, as evidenced by the less favorable entropic gains obtained upon complexation with am-β-CD than with β-CD.

All of the three neutral enantiomer pairs, i.e., (*R*)/(*S*)-3-bromo-2-methyl-1-propanol, *N*-*t*-Boc-D/L-alanine methyl ester, and (*R*)/(*S*)-mandelic acid methyl ester, gave virtually the same transfer enthalpy ($\Delta\Delta H°_{am} = \Delta H°$(am-$\beta$-CD) $- \Delta H°$(β-CD)) for both enantiomers of each guest; the obtained differential transfer enthalpies ($\Delta\Delta H°_{L(R)} - \Delta\Delta H°_{D(S)}$) are as small as 0.2 ± 0.3, 0.2 ± 0.2, and 0.4 ± 0.5 kJ mol^{-1}, respectively. Similarly, the differential transfer entropies ($\Delta T\Delta S°_{L(R)} - \Delta T\Delta S°_{D(S)}$) for the enantiomeric pairs are practically zero; i.e., 0.0 ± 0.3, 0.2 ± 0.3, and 0.2 ± 0.6 kJ mol^{-1}, respectively. It is obvious that there is no thermodynamic, enthalpic, or entropic driving force to alter the original chiral discrimination ability, and the same chiral discrimination abilities were obtained for am-β-CD and β-CD upon complexation with all of the neutral enantiomeric guest pairs.

A global look at these apparently negative results immediately leads to a general conclusion that the alteration of chiral recognition ability is achieved only through such a host modification that provides additional host−guest interaction(s), e.g., ion pairing and hydrogen bonding, which are strong enough to change significantly the location, position, or conformation of the guest included in the cavity of modified CD.

A detailed comparison of the thermodynamic parameters for the enantiomeric pairs of *N*-*t*-Boc-alanine and its methyl ester provides us with further insights into the effect of guest charge on the complexation thermodynamics of am-β-CD and β-CD. It should be emphasized that the two enantiomeric guest pairs share a common Boc-Ala structure and in particular the same hydrophobic *t*-Boc group that penetrates into the CD cavity. Upon complexation with β-CD, *N*-*t*-Boc-D- and L-alanines give significantly smaller *K*'s (392 and 367 M^{-1}) than those for *N*-*t*-Boc-D- and L-alanine methyl esters (659 and 578 M^{-1}, respectively). In sharp contrast, upon complexation with am-β-CD, *N*-*t*-Boc-D- and L-alanine exhibit larger *K*'s (695 and 593 M^{-1}) compared with those for the corresponding methyl esters (395 and 351 M^{-1}, respectively). As a result of the opposite trends, the affinities of neutral *N*-*t*-Boc-D/L-alanine methyl ester toward neutral β-CD (659 and 578 M^{-1}) become very similar to those of negatively charged *N*-*t*-Boc-D/L-alanine toward positively charged am-β-CD (695 and 593 M^{-1}). Correspondingly, the affinities of neutral *N*-*t*-Boc-D/L-alanine methyl ester toward positively charged am-β-CD (395 and 351 M^{-1}) are very similar to those of negatively charged *N*-*t*-Boc-D/L-alanine toward neutral β-CD (392 and 367 M^{-1}). In summary, a charged group introduced to either host or guest has almost the same effects on the global hydrophobicity and therefore on the overall complexation thermodynamics. It is also interesting to note that decreased hydrophobicity is well compensated by increased electrostatic contributions and that the impact of introducing a charge in guest or host is "symmetrical" in view of the overall complexation thermodynamics.

We now comparatively discuss the effects of a positive charge on the guest upon the complexation thermodynamics of am-β-CD and β-CD. It should be emphasized that the relative binding constants, $K_{am-\beta-CD}/K_{\beta-CD}$, for cationic 1-cyclohexylethylamine, 1-methyl-3-phenylpropylamine, and 4-phenylbutylamine are 0.58, 0.49, and 0.50, respectively, which are appreciably smaller than the corresponding values obtained with above-mentioned neutral guests. This is quite reasonable as the positively charged host has to associate with positively charged guests, and therefore, the reduction of affinity arises not only from the reduced hydrophobicity of the CD cavity but also from the electrostatic repulsion. It is also sensible that the "negative" effect of the repulsive interaction is less extensive than the above-mentioned "positive" effect of the attractive interaction for the oppositely charged host−guest pairs, since the repulsive interaction between the charged groups on host and guest tends to maximize the distance between the charges, thus minimizing the repulsion. In contrast, the attractive interaction between oppositely charged host and guest should minimize the distance between the charges. As the potential energy of electrostatic interaction is inversely proportional to the distance between the charges, the "positive" effect on the complexation thermodynamics should be much more exaggerated than the "negative" effect. Indeed, as demonstrated in this study, the electrostatic attraction between the host and guest is strong enough to overcome the reduced hydrophobicity of the am-β-CD cavity, enhancing the binding ability by a factor of 3−5, while the repulsive interaction causes a modest reduction of affinity by ~20−30% from the corresponding values observed for the relevant neutral guests.

All of these cationic guests, i.e., (*R*)- and (*S*)-1-cyclohexylethylamine, 1-methyl-3-phenylpropylamine, and 4-phenylbutylamine, afford less exothermic enthalpies by 0.7−1.0 kJ mol^{-1} upon complexation with am-β-CD than with β-CD. It is likely that these enthalpic losses upon host amination are mostly ascribed to the reduced van der Waals contacts resulting from the conformational changes to minimize the repulsive electrostatic interactions. Similarly, the entropy changes are less favorable for am-β-CD by 0.3−1.0 kJ mol^{-1}, for which the less extensive desolvation from host or guest is responsible, since the electrostatic repulsion, which keeps the two cationic groups away from each other, does not allow full penetration of guest into the cavity.

As was the case with enantiomeric bromo-2-methyl-1-propanol and mandelic acid methyl ester, (*R*)- and (*S*)-1-cyclohexylethylamine were not differentiated by neutral β-CD or cationic am-β-CD. This is in line with the above discussion, since these host−guest pairs involve no strong additional interactions or thermodynamic (enthalpic or entropic) driving force that can alter the intrinsic chiral discrimination ability of the CD cavity.

Transfer of a neutral or cationic guest from the neutral β-CD to the positively charged am-β-CD cavity is an interesting process, which accompanies synchronous unfavorable changes in both enthalpy and entropy, as this apparently conflicts with the enthalpy−entropy compensation frequently observed in a variety of supramolecular systems.

Enthalpy−Entropy Compensation upon Transfer from the β-CD to the am-β-CD Cavity. In our previous study,[11] the differential enthalpy changes ($\Delta\Delta H°$) were plotted against the differential entropy changes ($T\Delta\Delta S°$) for the hypothetical exchange equilibrium between the *R*- and *S*-enantiomers of several chiral guests (eq 1).

$$[\beta\text{-CD}\cdot R] + S = [\beta\text{-CD}\cdot S] + R \qquad (1)$$

The compensation plot gave an excellent straight line with a slope equal to unity and a very small intercept ($T\Delta\Delta S_0 = 0.4$ kJ mol^{-1}). This is quite impressive since the conventional $\Delta H°-T\Delta S°$ plot for the same sets of chiral guests led to a linear, but much more scattered, relationship as was the case with the global fit of all available thermodynamic parameters for β-CD complexation collected in our recent review.[3] Indeed, these contrasting results are not unreasonable, as the differential thermodynamic parameters for enantiomer pairs reflect only the minimal change in the system, i.e., the difference in chirality, without involving any other significant changes in host, guest, and solvent. In this treatment dealing with the exchange equilibrium [β-CD·*R*] + *S* = [β-CD·*S*] + *R*, we can simplify the system and offset the effects of all other structural variations except the chirality of the guest, thus reducing the contribution of the nominal part (ΔG_{nom}, ΔH_{nom}, and ΔS_{nom}) almost to zero.[29]

It should be emphasized that the general concept and methodology developed by Grunwald et al.[29] provides us with a reliable tool for the analysis of thermodynamic parameters and particularly the prediction of existence or nonexistence of meaningful enthalpy−entropy compensation in a particular set of limited thermodynamic data. The idea is based on the separation of overall complexation thermodynamic parameters into two terms: *nominal* and *environmental*. The nominal part (ΔG_{nom}, ΔH_{nom}, and ΔS_{nom}) is associated with the complexation of solvated host with solvated guest to form solvated host−guest complex, while the environmental part (ΔG_{env}, ΔH_{env}, and ΔS_{env}) is associated with water molecules involved in solvation/desolvation processes upon complexation. It was shown that ΔG_{env} is equal to zero in dilute solution, and thus, only ΔH_{env} and ΔS_{env} terms are subject to distinct enthalpy−entropy compensation.[29]

In this study, we have attempted to examine and compare the statistic quality of the enthalpy−entropy compensation plot for the hypothetical exchange equilibrium between the *R*- and *S*-enantiomers of a chiral guest (eq 1) with a similar plot for a hypothetical exchange equilibrium between β-CD and am-β-CD for the chiral and achiral guests (G) listed in Table 1 (eq 2).

$$[\beta\text{-CD}\cdot\text{G}] + \text{am-}\beta\text{-CD} = [\text{am-}\beta\text{-CD}\cdot\text{G}] + \beta\text{-CD} \quad (2)$$

It should be noted that in our previous[11] and present studies we employed the same sets of chiral guests, microcalorimetric equipment and methods, and physicochemical experimental conditions. Thus, the two enthalpy−entropy compensation plots for the enantiomeric guest exchange and host exchange reactions (eqs 1 and 2) were based on the thermodynamic parameters of exactly the same quality and precision. Hence, the mathematical properties of the plots directly reflect the physical properties of the exchange reactions under consideration. Furthermore, it should be emphasized that in both cases the $\Delta\Delta H°$ and $T\Delta\Delta S°$ values have the same absolute magnitude ranging from −5 to +8 kJ mol^{-1} and from −4 to +8 kJ mol^{-1}, respectively.

Differential thermodynamic parameters calculated for the hypothetical host exchange equilibrium between β-CD and am-β-CD for the chiral and achiral guests are used to build the compensation plot in Figure 1a. For comparison purposes, the relevant plot for the hypothetical exchange equilibrium between *R*- and *S*-enantiomers of the identical chiral guests in the β-CD cavity[11] is shown in Figure 1b; interestingly, despite the same accuracy level and encompassing range of the original data, the two compensation plots show strikingly different scattering levels. The compensatory enthalpy−entropy relationship is a direct experimental confirmation that ΔG_{env} is equal to zero in dilute solution and thus only ΔH_{env} and ΔS_{env} are subject to the enthalpy−entropy compensation. Indeed, it is obvious that a larger contribution from the nominal part (ΔG_{nom}, ΔH_{nom}, and ΔS_{nom}), associated with the particular complex structure, is expected for the host exchange from β-CD to am-β-CD than for the enantiomeric guest exchange in the same β-CD cavity.

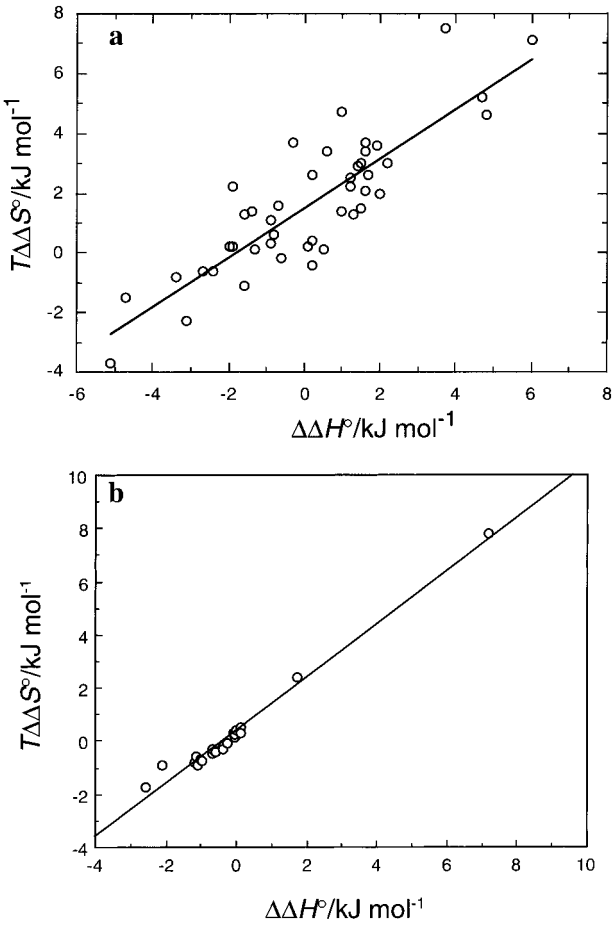

Figure 1. (a) Compensation plot for the differential entropy change ($T\Delta\Delta S°_{am}$) against the differential enthalpy ($\Delta\Delta H°_{am}$) upon transfer of negatively charged guests from β-cyclodextrin to 6-amino-6-deoxy-Δ-cyclodextrin in aqueous solution (pH 6.9) at 298.15 K. (b) Compensation plot for the differential entropy change ($T\Delta\Delta S°_{D/L}$ or $T\Delta\Delta S°_{R/S}$) against the differential enthalpy ($\Delta\Delta H°_{D/L}$ or $\Delta\Delta H°_{R/S}$) upon complexation of 20 D/L- or *R*/*S*-enantiomeric pairs with β-cyclodextrin, which give statistically meaningful chiral discrimination.

As we stated in Introduction, the thermodynamic origin of the poor chiral discrimination ability of native CDs is the existence of nearly perfect enthalpy−entropy compensation, which cancels the originally small differences in $\Delta H°$ and $T\Delta S°$ for both enantiomers (Figure 1b). Relatively large deviations of the data points in Figure 1a from the regression line ($\Delta H° = T\Delta S°$) originate from the significant alteration of the chiral discrimination ability of β-CD by introducing an amino group. Finally, it should be emphasized that the slope (α) and intercept ($T\Delta S_0$) of the $\Delta H°-T\Delta S°$ plot contain useful information and

(29) (a) Grunwald, E.; Steel, C. *J. Am. Chem. Soc.* **1995**, *117*, 5687. (b) Grunwald, E. *Thermodynamics of Molecular Species*; Wiley-Interscience: New York, 1996.

can be taken as quantitative measures of the conformation changes and the extent of desolvation, respectively, in diverse chemical and biological supramolecular systems, including cyclodextrins.[30−35] However, one should be cautious in applying the compensation plot and subsequent analysis when the quality of the fit to a regression line is poor as a result of additional strong host−guest interactions induced by host modification.

Conclusions

The newly obtained thermodynamic quantities of high accuracy have clearly demonstrated that charged am-β-CD serves in general as a potentially better chiral discriminator than native β-CD. However, this potential ability is not always exhibited explicitly but rather depends on the structure and properties of the guest employed. The comparative thermodynamic studies on inclusion complexation of various neutral, anionic, and cationic chiral guests with cationic am-β-CD and neutral β-CD lead to several new insights into the contribution of electrostatic interaction to the complexation and chiral discrimination behavior of charged β-CD.

1. Direct correlation between the mode of penetration and chiral recognition proposed previously for β-CD[11] holds even for am-β-CD and could be a fairly general rule applicable to a variety of cyclodextrin complexations. Furthermore, the modified CD preserves the original enantiomer preference of native CD upon complexation with almost all chiral guest pairs employed, which may be called "chiral template" or "chiral memory."

2. Negatively charged guests exhibit larger affinities in general toward am-β-CD than β-CD. Flexible (e.g., hexahydromandelic acid) or less-bulky (e.g., mandelic acid) guests often exhibit increased affinities by a factor of 3−5, while bulky or rigid guests (e.g., camphanic acid) show only slightly higher (less than 2 times) or even the same affinity toward am-β-CD.

3. The enhanced chiral discrimination of anionic guests by am-β-CD rather than β-CD is attributed to the substantially different ability of enantiomers to adjust location, position, and conformation inside the chiral cavity in the process of maximizing the electrostatic attraction (e.g., α-methoxyphenylacetic acid). No significant enhancement of chiral discrimination was observed for neutral and cationic guests upon complexation with am-β-CD as compared with β-CD.

4. The excellent enthalpy−entropy correlation, using high-quality thermodynamic data, can be taken as evidence for the similarity of conformational changes upon complexation of am-β-CD and β-CD.

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Supporting Information Available: Table 2. Differential enthalpies ($\Delta\Delta H°$) and entropies ($T\Delta\Delta S°$) for the complexation of negatively charged guests with native and 6-amino-6-deoxy-β-cyclodextrins in aqueous buffer (pH 6.9) at 298.15 K. This material is available free of charge via the Internet at http://pubs.acs.org. See any current masthead page for ordering information and Web access instructions.

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