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Solvent and Guest Isotope Effects on Complexation Thermodynamics of α-, β-, and 6-Amino-6-deoxy-β-cyclodextrins

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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 native α- and β-cyclodextrins (CDs) and 6-amino-6-deoxy-β-CD with more than 30 neutral, positively, and negatively charged guests, including seven fully or partially deuterated guests, have been determined in phosphate buffer solutions (pH/pD 6.9) of hydrogen oxide (H_2O) or deuterium oxide (D_2O) at 298.15 K by titration microcalorimetry. Upon complexation with these native and modified CDs, both nondeuterated and deuterated guests examined consistently exhibited higher affinities (by 5−20%) in D_2O than in H_2O. The quantitative affinity enhancement in D_2O versus H_2O directly correlates with the size and strength of the hydration shell around the charged/hydrophilic group of the guest. For that reason, negatively/positively charged guests, possessing a relatively large and strong hydration shell, afford smaller K_{H2O}/K_{D2O} ratios than those for neutral guests with a smaller and weaker hydration shell. Deuterated guests showed lower affinities (by 5−15%) than the relevant nondeuterated guests in both H_2O and D_2O, which is most likely ascribed to the lower ability of the C−D bond to produce induced dipoles and thus the reduced intracavity van der Waals interactions. The excellent enthalpy−entropy correlation obtained can be taken as evidence for the very limited conformational changes upon transfer of CD complexes from H_2O to D_2O.

Introduction

Complexation behavior of cyclodextrins (CDs) is often evaluated in deuterated solvents, in particular, in NMR spectral titrations, and the complex stability constants are not supposed to be affected significantly by the deuterated solvents. However, a direct comparison of complex stability constants in D_2O and H_2O has not been performed until recently, and the results reported appear inconsistent with each other.[1−6] As stated in our recent review,[7a] the accuracy of the thermodynamic data reported so far is often too poor to precisely discuss the solvent isotope effects on complexation thermodynamics of CDs in H_2O versus D_2O. There are some reported examples suitable for comparing the relevant data from NMR study in D_2O[2] and from calorimetric study in H_2O.[5] In the two studies, the $\Delta G°$ values for complexation of octanedioate in H_2O[2] and D_2O[5] clearly disagree with each other, while those for nonanedioate and decanedioate with α-CD can be compared. However, the difference between the $\Delta H°$ values obtained in H_2O[2] and D_2O[5] is inconsistent in the alkanedioate series, varying from 2 to 8 kJ mol^{-1}. The literature data of solvent isotope effect on $\Delta H°$ and $\Delta S°$ are very limited in general, and our previous study was restricted to the comparison of complex stability ($\Delta G°$) in H_2O and D_2O.[6] Furthermore, a very recent study by Schmidtchen is devoted to careful consideration of complexation thermodynamics of only one chiral pair of camphor toward α-CD in D_2O and H_2O.[7b]

In the present study to examine more precisely the solvent isotope effects on the $\Delta G°$ as well as $\Delta H°$ and $\Delta S°$ values for the complexation by CDs in D_2O and H_2O, we have employed the microcalorimetry as the well-established, most-reliable method of reasonable precision.[8] The accuracy and reproducibility of the microcalorimetric method have been proved and verified to be satisfactory in determining the minute differences in the complexation thermodynamics of CDs with a variety of enantiomer pairs.[8]

The use of a wide variety of guests (more than 30 charged and neutral guests, including 7 totally or partially deuterated ones) is essential in this sort of study, since our main goal is to elucidate the global trend of thermodynamic behavior in D_2O versus H_2O. For general validity of the conclusions derived, we employed not only native α- and β-CDs but also positively

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charged 6-amino-6-deoxy-β-CD (am-β-CD) as hosts in this microcalorimetric study.

Experimental Section

Materials. Chemical Abstracts registry number, empirical formula, formula weight, and supplier of most of the guest compounds used in this study are given in our previous publications.[8,9] Commercially available samples of the highest purities were used in the microcalorimetric experiments without any further purifications. 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 α-, β-CD, and 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 Fischer technique.

Microcalorimetric Titrations. An isothermal calorimeter (ITC), purchased from Microcal Inc., MA, 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 in water and the ionization enthalpy of TRIS buffer. These standard reactions gave excellent agreement (±1−2%) with the literature data.[10,11] The thermodynamic parameters for the complexation reaction of cyclohexanol with β-CD were also in good agreement with our previous results.[8,9,12,13]

The ORIGIN software (Microcal), used for the calculation of the equilibrium constant and standard molar enthalpy of reaction from the titration curve, gave the relevant standard deviation based on the scatter of the data points in a single titration curve. As usual,[8,9] the accuracy and reproducibility of the thermodynamic quantities calculated for 1:1 complexations were checked by performing multiple independent titration runs ($N = 2-6$). The uncertainties in the thermodynamic quantities reported for 1:1 complexation in Table 1 are two standard deviations of the mean value unless stated otherwise.

Applicability of the 1:1 host−guest complex model was carefully checked for each complexation reaction. In addition to the calculation based on 1:1 stoichiometry, we also performed calculations assuming 1:n and n:1 binding models ($n \neq 1$), whenever such higher-order complexes were suspected to exist. However, such calculations did not lead to any appreciable improvement of the overall fit, rendering these more complicated models irrelevant in the present cases, and the assumption of the 1:1 model with a single binding site appears to be the only reasonable choice for all of the host−guest combinations examined.

In each microcalorimetric experiments, a constant volume (5 μL/injection; 20 injections total) of guest solution in 0.05 M standard phosphate buffer was injected into the reaction cell (1.36 mL) charged with a CD solution in the same buffer; the initial concentrations of guest and CD in each run are indicated in Table 1.

The heat of dilution of the guest solution upon addition to the buffer solution in the absence of CD was determined in each run using the same number of injections of the guest solution at the same concentration employed in the titration experiments. The dilution enthalpies determined in these control experiments were subtracted from the enthalpies obtained in the titration experiments. The enthalpies of dilution obtained in all runs were in the same order of magnitude as the enthalpies of dilution of simple electrolytes such as NaCl at the same concentration. Thus, it was concluded that there is no significant self-association of any guest under the experimental conditions used.

We have previously shown that the nonideality corrections are not necessary under the experimental conditions employed.[8,9]

Results and Discussion

Complexation Thermodynamics in D_2O versus H_2O. According to the "solvophobic theory" originally proposed in Sinanoglu's pioneering papers,[14] the free-energy change of complex formation is regarded as a linear function of the surface tension of solvent (γ). To visualize this idea applied to the inclusion complexation of hydrophobic organic guests in CDs, one could imagine a sort of "cavity" or "solvent cage", which exists around the hydrophobic part of a guest in bulk water but disappears upon insertion of the hydrophobic part of the guest into a CD cavity. Indeed, a linear correlation of $\Delta G°$ against γ was observed experimentally for several cyclodextrin complexation reactions, for example, indole + β-CD (1:1 complex)[15] and adamantanecarboxylate + β-CD (1:1 complex).[16] However, the solvophobic effect cannot properly rationalize the higher complex stabilities in D_2O than in H_2O (Table 1), simply because the surface tension of D_2O is slightly smaller than that of H_2O. The difference in surface tension between D_2O (0.07193 N m^{-1}) and H_2O (0.07196 N m^{-1}) is less than 0.05% and is much smaller than the free-energy differences of 0.2−0.5% observed in D_2O versus H_2O (Table 1). It is thus obvious that we need some rationalizations further than the surface tension and conventional solvophobic theory to understand the nature of alterations in the thermodynamic parameters for CD complexation in H_2O versus D_2O.

Careful examinations of the thermodynamic parameters in Table 1 may provide us with an additional support for the above discussion. Indeed, if the difference in surface tension plays an important role, then a larger "cavity" around the hydrophobic part of a guest in the bulk solvent should lead to a greater difference in thermodynamic parameters upon complexation in D_2O rather than H_2O. However, regardless of the size of hydrophobic moiety penetrating into β-CD cavity, all the cycloalkanol guests (C_5–C_7) afford almost the same K_{H2O}/K_{D2O} ratios. Similarly, both the less bulky guests such as benzoic and toluic acids and the more bulky guests such as camphanic and camphorsulfonic acids give virtually the same K_{H2O}/K_{D2O} ratios upon complexation with both β-CD and am-β-CD. In addition, α-CD affords almost the same K_{H2O}/K_{D2O} ratios upon complexation with the alkanol series from butanol to hexanol. Other examples in line with these may be found in Table 1.

In this context, it is interesting to compare the thermodynamic parameters for the transfer from H_2O to D_2O of ammonium ion (NH_4^+) with those for the lower homologues of semihydrophobic tetraalkylammonium ions, that is, Me_4N^+ and Et_4N^+. The enthalpies of transfer ($\Delta H°_{tr}$) from H_2O to D_2O reported for the above three cations are 1.3, 1.8, and 0.9 kJ mol^{-1}, respectively.[17] Taking into account the accompanying uncertainties (±1 kJ mol^{-1}), these three values are indistinguishable from each other, indicating that the short alkyl chains of R_4N^+ do not appreciably affect the $\Delta H°_{tr}$ value. More bulky,

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Table 1. Complex Stability Constant (K), Standard Free Energy ($\Delta G°$), Enthalpy ($\Delta H°$), and Entropy Changes ($T\Delta S°$) for 1:1 Inclusion Complexation of Various Guest Compounds with α-Cyclodextrin (α-CD), β-Cyclodextrin (β-CD), and 6-Amino-6-deoxy-β-cyclodextrin (am-β-CD) in H_2O and D_2O at $T = 298.15$ K

host	[host]/mM	guest (charge)	[guest]/ mM	sol- vent	pH or pD	N[a]	K/M^{-1}	K_{H2O}/K_{D2O}[b]	K^H/K^{Dc}	$\Delta G°$/ kJ mol^{-1}	$\Delta H°$/ kJ mol^{-1}	$T\Delta S°$/ kJ mol^{-1}
α-CD	1.98	1-butanol (0)	310	H_2O	*d*	2	79.5 ± 1.5			−10.85 ± 0.06	−10.9 ± 0.2	−0.1 ± 0.2
	1.85		210	D_2O	*d*	2	83.8 ± 0.8	0.949		−10.98 ± 0.03	−10.70 ± 0.10	0.28 ± 0.10
	1.72−2.56	1-butanol-d_{10} (0)	225	H_2O	*d*	2	73.0 ± 1.0		1.09	−10.64 ± 0.04	−10.82 ± 0.10	−0.18 ± 0.10
	1.45		231	D_2O	*d*	2	79.0 ± 1.0	0.924	1.06	−10.83 ± 0.03	−10.22 ± 0.10	0.61 ± 0.10
	1.88	1-pentanol (0)	122	H_2O	*d*	2	287 ± 4			−14.03 ± 0.03	−14.7 ± 0.1	−0.7 ± 0.1
	0.95−1.12		106	D_2O	*d*	2	302 ± 2	0.950		−14.16 ± 0.02	−14.4 ± 0.1	−0.2 ± 0.1
	0.99	1-hexanol (0)	37−44	H_2O	*d*	2	840 ± 30			−16.69 ± 0.09	−17.5 ± 0.2	−0.8 ± 0.2
	1.12		45	D_2O	*d*	2	895 ± 30	0.939		−16.85 ± 0.08	−17.4 ± 0.2	−0.6 ± 0.2
	1.00	hexanoic acid (−1)	155	H_2O	6.9	2	300 ± 4			−14.14 ± 0.04	−14.3 ± 0.2	−0.2 ± 0.2
	1.31		103	D_2O	6.9	2	339 ± 3	0.885		−14.44 ± 0.03	−13.17 ± 0.10	1.27 ± 0.10
	1.25−1.26	hexanoic acid-d_{11} (−1)	119−122	H_2O	6.9	4	289 ± 3		1.04	−14.05 ± 0.03	−13.54 ± 0.15	0.51 ± 0.15
	1.35−1.42		112−114	D_2O	6.9	3	306 ± 3	0.944	1.11	−14.18 ± 0.03	−13.14 ± 0.15	1.04 ± 0.15
	1.00	hexylamine (+1)	84−190	H_2O	6.9	6	389 ± 4			−14.78 ± 0.03	−17.5 ± 0.2	−2.7 ± 0.2
	1.06		107	D_2O	6.9	2	421 ± 4	0.924		−14.98 ± 0.03	−16.8 ± 0.2	−1.8 ± 0.2
	0.80	octanoic acid (−1)	43	H_2O	6.9	2	2450 ± 130			−19.34 ± 0.15	−20.5 ± 0.3	−1.2 ± 0.3
	0.84		37	D_2O	6.9	2	2610 ± 70	0.939		−19.50 ± 0.07	−20.0 ± 0.2	−0.5 ± 0.2
	0.92	octanoic acid-d_{15} (−1)	38	H_2O	6.9	2	2140 ± 60		1.14	−19.01 ± 0.07	−20.3 ± 0.3	−1.3 ± 0.3
	0.76−0.84		34	D_2O	6.9	2	2440 ± 70	0.877	1.07	−19.34 ± 0.08	−19.5 ± 0.3	−0.2 ± 0.3
β-CD	2.00	cyclopentanol (0)	209	H_2O	6.9	2	175 ± 5			−12.76 ± 0.08	−4.6 ± 0.1	8.2 ± 0.2
	1.00		123	D_2O	6.9	2	186 ± 4	0.941		−12.95 ± 0.06	−3.89 ± 0.06	9.06 ± 0.08
	1.59	cyclohexanol (0)	136	H_2O	6.9	2	701 ± 6			−16.24 ± 0.02	−6.3 ± 0.1	9.9 ± 0.1
	1.14−1.15		92−113	D_2O	6.9	3	746 ± 12	0.940		−16.40 ± 0.04	−5.98 ± 0.10	10.42 ± 0.10
	1.69	cyclohexanol-d_{12} (0)	124	H_2O	6.9	2	624 ± 6			−15.95 ± 0.02	−6.18 ± 0.10	9.77 ± 0.10
	1.60		120	D_2O	6.9	2	690 ± 6	0.904		−16.20 ± 0.02	−5.58 ± 0.10	10.62 ± 0.10
	1.00	cycloheptanol (0)	44	H_2O	6.9	2	2200 ± 70			−19.08 ± 0.09	−12.4 ± 0.1	6.7 ± 0.2
	1.04		41	D_2O	6.9	2	2320 ± 40	0.949		−19.20 ± 0.05	−11.75 ± 0.10	7.45 ± 0.10
	1.07−185	(*R*)-camphanic acid (−1)	90−131	H_2O	6.9	4	178 ± 2			−12.85 ± 0.03	−17.8 ± 0.2	−5.0 ± 0.2
	1.09		115	D_2O	6.9	2	204 ± 2	0.873		−13.18 ± 0.03	−18.5 ± 0.2	−5.3 ± 0.2
	1.12−1.82	(*R*)-camphor sulfonic acid (−1)	103	H_2O	6.9	2	564 ± 10			−15.70 ± 0.05	−20.7 ± 0.2	−5.0 ± 0.2
	1.09		96	D_2O	6.9	2	633 ± 6	0.891		−15.99 ± 0.03	−21.6 ± 0.2	−5.6 ± 0.2
	1.88	4-phenylbutylamine (+1)	87	H_2O	6.9	2	405 ± 6			−14.88 ± 0.04	−10.4 ± 0.1	4.5 ± 0.1
	1.31		89	D_2O	6.9	2	474 ± 9	0.854		−15.27 ± 0.06	−11.31 ± 0.10	3.96 ± 0.10
	1.95	1-methyl-3-phenylpropylamine (+1)	117	H_2O	6.9	2	188 ± 3			−12.98 ± 0.04	−8.64 ± 0.08	4.34 ± 0.09
	1.15		119	D_2O	6.9	2	215 ± 4	0.874		−13.31 ± 0.05	−9.51 ± 0.09	3.80 ± 0.10
	1.35−1.56	4-toluic acid (−1)	109−168	H_2O	6.9	3	95 ± 2			−11.29 ± 0.05	−8.7 ± 0.2	2.6 ± 0.2
	1.31−1.90		87−106	D_2O	6.9	3	109 ± 3	0.872		−11.63 ± 0.07	−9.2 ± 0.2	2.4 ± 0.2
	1.54−2.20	3-phenylpropionic acid (−1)	86−186	H_2O	6.9	4	162 ± 4			−12.6 ± 0.06	−6.9 ± 0.1	5.7 ± 0.1
	1.90		79	D_2O	6.9	2	183 ± 4	0.885		−12.91 ± 0.06	−7.48 ± 0.09	5.43 ± 0.10
	2.00	3-(2-hydroxyphenyl)propionic acid (−1)	100	H_2O	6.9	2	81 ± 2			−10.89 ± 0.06	−15.2 ± 0.2	−4.3 ± 0.2
	1.12		158	D_2O	6.9	2	102 ± 2	0.794		−11.47 ± 0.05	−16.0 ± 0.2	−4.5 ± 0.2
	1.00	3-(4-hydroxyphenyl)propionic acid (−1)	100	H_2O	6.9	2	297 ± 4			−14.11 ± 0.03	−14.23 ± 0.08	−0.12 ± 0.09
	1.12		95	D_2O	6.9	2	363 ± 4	0.818		−14.61 ± 0.03	−15.06 ± 0.08	−0.45 ± 0.09
	2.00	2-phenylethylamine (+1)	200	H_2O	6.9	2	24 ± 2			−7.9 ± 0.2	−6.4 ± 0.4	1.5 ± 0.4
	2.10		217	D_2O	6.9	2	28.5 ± 1.5	0.842		−8.30 ± 0.15	−6.7 ± 0.2	1.6 ± 0.3
	1.5	tyramine (+1)	150	H_2O	6.9	2	70 ± 2			−10.53 ± 0.07	−13.8 ± 0.2	−3.3 ± 0.2
	1.54		143	D_2O	6.9	2	82.1 ± 1.0	0.853		10.93 ± 0.04	−14.90 ± 0.10	−3.97 ± 0.10
	2.19−3.08	*N*-acetyl-L-phenylalanine (−1)	171	H_2O	6.9	2	67.5 ± 1.4			−10.44 ± 0.05	−8.17 ± 0.08	2.27 ± 0.09
	1.05		199	D_2O	6.9	2	80 ± 2	0.844		−10.86 ± 0.06	−8.80 ± 0.09	2.06 ± 0.10
	1.72	*N*-acetyl-L-phenylalanine-d_5 (−1)	170	H_2O	6.9	2	63.3 ± 1.5		1.07	−10.28 ± 0.06	−8.48 ± 0.10	1.80 ± 0.15
	1.77		223	D_2O	6.9	2	75 ± 2	0.844	1.07	−10.70 ± 0.07	−8.82 ± 0.10	1.88 ± 0.15
	1.70	*N*-acetyl-L-phenylalanine-d_8 (−1)	159	H_2O	6.9	2	62.7 ± 1.5		1.08	−10.26 ± 0.06	−8.40 ± 0.10	1.86 ± 0.15
	1.58		165	D_2O	6.9	2	73.6 ± 1.5	0.852	1.09	−10.66 ± 0.05	−8.83 ± 0.10	1.83 ± 0.15
	1.55−1.59	*N*-acetyl-L-tyrosine (−1)	97−103	H_2O	6.9	3	130 ± 2			−12.07 ± 0.04	−17.1 ± 0.3	−5.0 ± 0.3
	1.11		188	D_2O	6.9	2	156 ± 2	0.833		−12.52 ± 0.04	−19.0 ± 0.2	−6.5 ± 0.2
	2.06−2.09	(*R*)-hexahydromandelic acid (−1)	94−149	H_2O	6.9	4	648 ± 12			−16.05 ± 0.05	−5.61 ± 0.07	10.44 ± 0.08
	1.01−1.14		79−96	D_2O	6.9	3	721 ± 10	0.899		−16.31 ± 0.04	−5.56 ± 0.06	10.75 ± 0.07
	1.43−1.97	(*R*)1-cyclohexylethylamine (+1)	147−184	H_2O	6.9	3	329 ± 3			−14.37 ± 0.03	−7.85 ± 0.08	6.52 ± 0.09
	1.14−1.31		112−123	D_2O	6.9	3	341 ± 3	0.964		−14.46 ± 0.03	−7.52 ± 0.08	6.94 ± 0.09
am-β-CD	1.60	(*R*)-mandelic acid (−1)	144	H_2O	6.9	2	55 ± 2			−9.93 ± 0.09	−6.75 ± 0.07	3.2 ± 0.1
	1.10−1.70		194−216	D_2O	6.9	3	61.2 ± 1.0	0.899		−10.20 ± 0.04	−7.70 ± 0.10	2.50 ± 0.10
	2.15	4-toluic acid (−1)	168	H_2O	6.9	1	285 ± 8			−14.01 ± 0.07	−10.30 ± 0.15	3.7 ± 0.2
	1.10−1.97		82−87	D_2O	6.9	2	337 ± 6	0.846		−14.43 ± 0.05	−10.22 ± 0.10	4.21 ± 0.10
	1.34	benzoic acid (−1)	212	H_2O	6.9	3	69 ± 2			−10.50 ± 0.08	−7.66 ± 0.15	2.8 ± 0.2
	1.31		171	D_2O	6.9	2	78 ± 3	0.885		−10.80 ± 0.10	−7.65 ± 0.15	3.2 ± 0.2
	1.49	benzoic acid-d_5 (−1)	144	H_2O	6.9	2	64 ± 2		1.08	−10.31 ± 0.08	−7.92 ± 0.15	2.4 ± 0.2
	1.48		143	D_2O	6.9	4	74 ± 2	0.865	1.05	−10.67 ± 0.07	−7.62 ± 0.15	3.1 ± 0.2

[a] Number of independent microcalorimetric runs. [b] Solvent isotope effect on binding constant. [c] Isotope effect of guest deuteration on binding constant. [d] Pure H_2O or D_2O; not buffered.

hydrophobic organic cations, such as Ph_4As^+, n-Bu_4N^+, and n-Pr_4N^+, for which electrostatic interaction of the charged central atom (N^+) with surrounding water molecules is greatly reduced by the organic groups, also give very small $|\Delta H°_{tr}|$ values of <1 kJ mol^{-1}. These data indicate that the contribution of the hydrophobic part of lipophilic ions does not significantly contribute to the overall transfer thermodynamics from H_2O to D_2O, and also that the difference in "hydrophobic" hydration

(or "cavity" formation in the bulk solvent) of organic residues in D_2O versus H_2O is not likely to be the major origin of the alterations of the complexation thermodynamics in these two solvents.

Another independent approach to the elucidation of the difference in complexation thermodynamics in D_2O versus H_2O would be comparative theoretical calculations of binding energies in these two solvents. However, it is likely that the quantitative quantum-mechanical calculations on such large supramolecular systems as CD complexes particularly in aqueous solutions are too complicated to obtain enough reliable data to judge such minute differences. Recent calculations employed in the assessment of the interaction energies of complex supramolecular system (enzyme + inhibitor, antigen + antibody, etc.)[18,19] usually regard water as rigid molecule and thus it is impossible to properly evaluate the solvent isotope effect upon complex formation. In addition, the "best" accuracy (or noise level) of these calculations[19] are ca. 1−2 kJ mol^{-1} which is comparable or even larger than the differences in the experimental thermodynamic parameters presented in Table 1.

It is not clear whether the isotope effect, assessed by the theoretical calculations on such simple model systems as Ar_2−HX versus Ar_2−DX in gas phase,[20] is valid for cyclodextrin complexation. However, it is interesting to point out that the differences in binding energy because of the isotope effect, evaluated using several approximations, do not exceed 3−5%.[20] This indicates in turn that it is unrealistic in general to expect a large difference in binding energy in D_2O versus H_2O.

The comparative solubility data for various guests in D_2O and H_2O available in the literature[21] cannot be used for straightforward predictions of magnitude or direction of affinity change upon guest complexation with CD in D_2O versus H_2O. To make such predictions, we have to determine the solubilities of not only free host and guest but also host−guest complex in D_2O and H_2O. It would be possible also that the solubility changes in D_2O versus H_2O show the same trends for all relevant species involved in CD complexation reaction to give only negligible changes in free energy of complexation in both solvents. In fact, we have demonstrated previously[6] that, despite the appreciably lower solubilities of both 6-O-benzenecarboxylate-β-CD (free host) and its complex with various guests in D_2O versus H_2O, the equilibrium constants are the same in both solvents within the experimental error (± 0.15 kJ mol^{-1} in $\Delta G°$).

It is more sensible to consider that the different degree and shell structure of solvation to CD cavity by D_2O versus H_2O are the major sources of the alterations in complexation thermodynamic parameters. In our recent study,[22] we have demonstrated indeed that the heavily solvated cavity of am-β-CD provides a smaller driving force for the inclusion of the hydrophobic moiety of guest than the less-solvated cavity of native β-CD. Consequently, not only positively charged but also neutral guests are bound more weakly by am-β-CD than by β-CD. However, it is not feasible or realistic to find a specific bulk physical property of these two solvents as a measure for discussing quantitatively or even qualitatively the differences in CD cavity solvation by D_2O versus H_2O. Indeed, the large heat capacity (C_p^{H2O} = 75.3 J K^{-1} mol^{-1} and C_p^{D2O} = 84.5 J K^{-1} mol^{-1}), high dielectric constant (which is almost identical to that of ice; ϵ = 88 and 100 for liquid H_2O and ice Ih at 0 °C, respectively), abnormal coefficient of isothermal compressibility, thermal expansion coefficient, and radial molecular correlation function are regarded as the experimental evidence for a highly ordered structure of D_2O and H_2O, where crystal lattices of solid ice are still remaining to a significant extent. If so, the higher temperature that gives the maximum density (11.23 °C for D_2O versus 3.98 °C for H_2O) and the larger heats of vaporization (45.5 kJ mol^{-1} for D_2O versus 44.0 kJ mol^{-1} for H_2O) and melting (6.3 kJ mol^{-1} for D_2O versus 6.0 kJ mol^{-1} for H_2O), along with some of the above-mentioned physical properties such as the larger C_p for D_2O versus H_2O, provide us with a clue that D_2O is a more structured solvent than H_2O at any temperature. The stronger self-association of D_2O than H_2O in the bulk solution can lead to a reduction of hydration ability and hence to less-extensive solvation in the CD cavity. On the other hand, despite virtually the same dipole moment (1.84 and 1.834 D for D_2O and H_2O, respectively), D_2O and H_2O possess significantly different polarizabilities. With larger polarizability (1.536×10^{-30} m^3 for D_2O versus 1.456×10^{-30} m^3 for H_2O), D_2O molecules can interact stronger with dipoles surrounding the CD cavity, thus enhancing the hydration around the cavity.

As can be seen from the above discussion, all of the experimental data and theoretical considerations reveal that the more consistent substantial enhancement of CD complex stability in D_2O than in H_2O cannot be attributed to the differences in hydration of the hydrophobic part of the guest or of the CD cavity in D_2O and H_2O. However, there is one more molecular mechanism, which significantly contributes to the complex stability, that is, the hydration shell around the charged/hydrophilic group of a guest. It is generally recognized and reconfirmed in our recent study[8] that, upon complexation of CD with a series of guests possessing an identical hydrophobic moiety and varying hydrophilic groups, the complex stability decreases with increasing size and strength of the hydration shell around the guest's hydrophilic group. Thus, the affinity toward CDs decreases in the order: alkane > alkanol > alkanoate ≈ alkylammonium.

Possessing an electrostatic charge and large dipole moment, a charged guest experiences much stronger interactions with D_2O and H_2O than a hydrophobic or neutral hydrophilic guest. One can expect therefore that the differences in physical properties between D_2O and H_2O are more clearly revealed in the hydration shell formed around a charged guest rather than hydrophobic/neutral host/guest. In this context, it is reasonable to compare alkali and alkaline earth metal cations; thus, the divalent ions, that is, Ca^{2+}−Ba^{2+}, interact more strongly with D_2O and H_2O than the relevant monovalent ions of similar sizes, that is, Na^+−Cs^+, as judged from the values of absolute hydration energies.[17] Hence, the differences in thermodynamic parameters obtained in D_2O versus H_2O should be more pronounced for divalent cations than for monovalent ones. Indeed, the enthalpies of transfer ($\Delta H°_{tr}$) from H_2O to D_2O for divalent cations (5.4−6.1 kJ mol^{-1} for Ca^{2+}−Ba^{2+}) are significantly and consistently larger than those for monovalent cations (2.6−3.0 kJ mol^{-1} for Na^+−Cs^+).[17] Such a large enthalpy difference of up to 5−6 kJ mol^{-1} would appear to work as a strong thermodynamic driving force to shift chemical

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equilibrium enormously. However, it is often the case that the enthalpy difference is not fully but only partially reflected in the free-energy change, as a consequence of the enthalpy−entropy compensation. Nevertheless, in our previous study,[23,24] we observed dramatically improved extraction of aqueous trivalent lanthanoid cations with crown ether from D_2O rather than H_2O into the organic phase, while virtually no enhancement was observed for mono- and divalent cations. This result is in good agreement with the trend in ΔH°_{tr} and indicates that the less favorable hydration enthalpy in D_2O than in H_2O is more or less reflected in a less favorable free energy, affording the enhanced extraction of trivalent cations from D_2O.

The unfavorable enthalpy of transfer from H_2O to D_2O may be taken as evidence for weaker hydration shell in D_2O than in H_2O, which is easily deformed. Furthermore, because of the enthalpy−entropy compensation, the enthalpic loss of transfer is canceled out at least in part by the entropic gain of transfer to minimize the free-energy change. The entropic gain upon transfer from H_2O to D_2O means increased flexibility (adjustability) of hydration shell in D_2O than in H_2O. The most important conclusion, relevant to the present study, is that the larger the difference in interaction of molecule or ion with H_2O and with D_2O, the more pronounced the alteration of flexibility (adjustability) of hydration shell in D_2O versus H_2O. For instance, hydration shell of di- and trivalent, rather than monovalent, cations should suffer more significant alterations in D_2O than in H_2O upon complexation with crown ether, since the enthalpies of transfer between the two solvents are larger for multivalent cations.

The host−guest combinations and therefore the major driving forces for complexation are distinctly different in the above and present cases, both of which however certainly share a similarity at least in the behavior of hydration shell upon complexation of charged species/moiety. Thus, both processes, that is, the solvent extraction of hydrated cation with crown ether and the inclusion of charged/ hydrophilic guest into the hydrophobic CD cavity, inevitably cause significant dehydration with accompanying rearrangement of the hydration shell. The weaker, less-structured hydration shell of D_2O facilitates the transfer of hydrated species to the hydrophobic environment of CD cavity or organic solvent to give the more consistent increase of complex stability in D_2O than in H_2O. Furthermore, the flexible hydration shell of D_2O, being more tolerant to the structural changes upon dehydrating complexation, may also contribute to the optimization of the intracavity interactions. The above discussion is supported by the fact that both the negatively and positively charged guests (carboxylate and ammonium ions) afford consistently greater D_2O-enhanced affinities toward β-CD and am-β-CD than the neutral ones (Table 1). This is quite logical, since the stronger hydration to charged, rather than neutral, guests exaggerates the differences in physical/thermodynamic properties in D_2O and H_2O, leading to a more pronounced affinity enhancement.

It is somewhat puzzling that α-CD does not exhibit a particularly high degree of the affinity enhancement in D_2O, as compared with that observed for β-CD or am-β-CD. Thus, the K_{H2O}/K_{D2O} ratios observed for complexation of neutral and charged guests with α-CD are almost comparable: 0.92−0.95 and 0.88−0.94, respectively. In contrast, the neutral and charged guests, except hexahydromandelic acid and 1-cyclohexylethylamine (for a rationalization, see below), give significantly different K_{H2O}/K_{D2O} of 0.82−0.89 and 0.90−0.94, respectively, upon complexation with β-CD. One possible explanation is that the smaller cavity of α-CD causes less extensive dehydration upon guest inclusion and therefore gives comparable solvent isotope effect for neutral and charged guests. Another more likely explanation is related to the role of flexibility of penetrating moiety in altering the complexation thermodynamics in D_2O versus H_2O. This idea may be supported by the observation that not only the complexation of charged *n*-alkyl guests with α-CD but also that of flexible cyclohexane derivatives (1-cyclohexylethylamine and hexahydromandelic acid) with β-CD give high K_{H2O}/K_{D2O} ratios of 0.90−0.96, which are comparable to those obtained with the neutral guests (0.90−0.94). In contrast, all of the charged guests with rigid hydrophobic (aromatic or aliphatic) moiety afford K_{H2O}/K_{D2O} of 0.82−0.89. This may be an intriguing example of the Le Chatelier-Braun's principle. Thus, when the host−guest system possesses extra degrees of freedom, for example, arising from the flexible penetrating moiety in guest, the whole system moves to such direction that minimizes the internal/external impact, such as the change in hydration shell in D_2O versus H_2O.

Also, not only the free energy but also the enthalpy and entropy of complexation in D_2O versus H_2O exhibit very consistent behavior associated with the flexibility of penetrating group. Indeed, the affinity enhancement in D_2O versus H_2O is exclusively entropy-driven in all examined cases where the penetrating group is flexible, as exemplified by the complexation of α-CD with straight-chain aliphatic alkanols, alkylamines, and alkanoates and of β-CD with cycloalkanols, 1-cyclohexylethylamine, and hexahydromandelic acid. Furthermore, the above-mentioned guests exhibit significant losses of reaction enthalpy in D_2O versus H_2O. This is usually attributable to the less pronounced van der Waals interactions in D_2O. Probably, the disturbance of the van der Waals interactions, originally existing in H_2O, is the only option for the Le Chatelier-Braun's principle to reduce the impact of the change in hydration shell around the charged group.

On the other hand, all charged guests with rigid aromatic (phenyl) or aliphatic (camphor) moieties exhibit more favorable enthalpy changes upon complexation in D_2O than in H_2O. This observation is related to the existence of more flexible and adjustable hydration shell in D_2O versus H_2O. Indeed, since the rigid penetrating groups have only limited ability to fine-tune their conformation acceptable to the CD cavity, the deeper guest penetration is achieved in D_2O as a result of the weaker hydration shell, affording additional van der Waals contacts and therefore more favorable enthalpy. The only exceptions are found in the complexation of benzoic and toluic acids with am-β-CD, for which the larger conformational freedom of the smallest and less-bulky aromatic penetrating group (benzene ring) and the greater contribution of hydration/dehydration process upon inclusion of a negatively charged guest by positively charged am-β-CD would be jointly responsible.

It is also useful to compare the present results with those obtained in our previous study on the complexation of unsubstituted cycloalkanes (C_5–C_8) and cycloalkanols (C_5–C_8) with

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β-CD and 6-*O*-benzoyl-β-CD, in which only the $\Delta G°$ values were determined in D_2O and H_2O by circular dichroism spectrometry with an experimental error of ± 0.15 kJ mol^{-1}.[6] In the study using cycloalkanes and cycloalkanols as guests and the neutral β-CD derivative as host, we found that two cycloalkanes (cyclopentane and cyclooctane) exhibit higher affinity toward the host in D_2O than in H_2O, whereas two other cycloalkanes (cyclohexane and cycloheptane) reveal the opposite trend. In contrast, all C_5–C_8 cycloalkanols showed higher affinities in D_2O than in H_2O. However, the observed enhancement was very small and seemed statistically insignificant in view of the experimental error of ± 0.15 kJ mol^{-1} in $\Delta G°$, and therefore we concluded: "K_S values ... are essentially identical in both solvents".[6] In this connection, the average enhancement of $\Delta G°$ in D_2O versus H_2O obtained in this study for (cyclo)alkanol guests (i.e., cyclopentanol, cyclohexanol, cyclohexanol-d_{12}, and cycloheptanol with β-CD and butanol, butanol-d_{10}, pentanol, and hexanol with α-CD) is equal to 0.17 ± 0.05 kJ mol^{-1}, which could not be detected by the method employed in our previous study.[6] Furthermore, the affinity differences anticipated for (cyclo)alkane guests could be much smaller than those observed for alkanols and certainly for charged guests, since no strong hydration shells are expected to be formed around the hydrocarbon guests. Although it would be interesting to assess such a small solvent isotope effect, the microcalorimetric method is not suitable for that purpose not because of the insufficient accuracy and reproducibility but because of the very low solubilities of (cyclo)alkanes in D_2O and H_2O.

Effect of Intracavity Hydrogen Bonding. As briefly mentioned above, the extensive hydrogen bond network of liquid water gives rise to many anomalies in physical properties, such as unusually high heat capacity, high static dielectric constant, unusual isothermal compressibility and thermal expansion coefficients, radial molecular correlation function, and so on. In heavy water (D_2O), such anomalies in physical properties are even more pronounced (see above discussion).

There are only a limited number of studies on the thermodynamics of hydrogen bond formation in H_2O solutions by using simple model compounds and no such studies performed with D_2O solution. Particular attention has been paid to the hydrogen bond of amides owing to its occurrence in proteins. The first and yet the most "pure" assessment of hydrogen bond formation thermodynamics of amide was performed by Schellman[25] and Kresheck and Scheraga.[26] They determined the enthalpy of hydrogen bond formation of amide as ca. -6 kJ mol^{-1}, which is comparable to the values (-6 to -8 kJ mol^{-1}) obtained for the phenolic hydrogen bond formation upon complexation with CDs.[8,12,13] Several other chemical processes, such as dimerizations of *N*-methylacetamide,[27] lactams,[28,29] and carboxylic acids,[30] as well as dissolution of diketopiperazine,[31] and other cyclic dipeptides carrying amino acid side chains,[32] were also employed in the thermodynamic study of hydrogen bond formation. Although these investigations are informative, the systems employed usually possess additional complicating factors contributing to the thermodynamics, such as the hydrophobic effect arising from the organic side chains and the effect of crystal lattice in the solid state.

In our previous studies,[8,12,13] we determined the thermodynamic parameters for complexation of β-CD with two guest series of alkanoates and arylalkylamines with and without phenolic hydroxyl group: Arylalkanoate series: (a) 3-phenylpropionic acid versus 3-(4-hydroxyphenyl)propionic acid and (b) 3-phenylpropionic acid versus 3-(2-hydroxyphenyl)propionic acid; Arylalkylamine series: (c) 2-phenylethylamine versus tyramine and (d) *N*-acetyl-L-phenylalanine versus *N*-acetyl-L-tyrosine. The structural difference in each pair is the presence of one extra oxygen atom, which may be one of the simplest structural alterations available. Sharing almost the same skeleton except for the phenolic hydroxyl, such guest pairs should provide us with an excellent measure of the thermodynamic properties associated with the formation of a single hydrogen bond. In H_2O solution, the difference in reaction enthalpy between the guest pair was $6-8$ kJ mol^{-1}.[8,12,13] In addition, positive heat capacity changes ($\Delta\Delta C_p°$) of ca. 80 J mol^{-1} K^{-1} were observed for the first three pairs,[12] which agree with the theoretical considerations.[33] The hydrogen bond formation between the phenolic hydroxyl of the guest with the oxygen atoms of the inside wall of CD was confirmed spectroscopically,[12] and similar spectroscopic behavior was reported for the hydroxyl group of tyrosine, forming a hydrogen bond in the hydrophobic protein environment.[34]

In the present study, we performed the microcalorimetric determination of thermodynamic parameters for complexation of the above four guest pairs a−d with β-CD in D_2O solution. The solvent isotope effects (K_{H2O}/K_{D2O}) observed for the nonphenolic guests ($K_{H2O}/K_{D2O} = 0.89$ for 3-phenylpropionic acid; 0.84 for 2-phenylethylamine; 0.84 for *N*-acetyl-L-phenylalanine) are at least comparable to or appreciably larger than those obtained for the relevant phenolic guest ($K_{H2O}/K_{D2O} = 0.79$ for 3-(2-hydroxyphenyl)propionic acid; 0.82 for 3-(4-hydroxyphenyl)propionic acid; 0.85 for tyramine; 0.83 for tyrosine). The average K_{H2O}/K_{D2O} ratio is 0.86 ± 0.03 for nonphenolic guests and 0.82 ± 0.03 for phenolic guests. Even if the average ratios obtained are very close to each other, the relevant variations in reaction enthalpy and entropy can be much larger and statistically significant as a consequence of the enthalpy−entropy compensation effect.

It is well known that the heat production of about 100−120 J mol^{-1} upon addition of H_2O into D_2O or of D_2O into H_2O is a very exaggerated estimation of the isotope effect on the enthalpy of hydrogen bond formation. Actually, this heat production involves the heat effect of exchange reaction: $H_2O + D_2O = 2HOD$. A more accurate evaluation of the isotope effect was achieved by Kimura et al.[35] in precise microcalorimetric experiments, which revealed that the difference of intermolecular interaction (excess enthalpy of mixing) between OH and OD in methanol and ethanol is as small as 2 J mol^{-1}. In view of the uncertainties of 100−200 J mol^{-1} associated with the determined enthalpies of cyclodextrin complexation presented in Table 1, we cannot immediately count on the elucidation of the "net" difference between the O···H···O and

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Table 2. Differential Complexation Enthalpies ($\Delta\Delta H°$) and Entropies ($T\Delta\Delta S°$) for Various Guests Pairs with and without Phenolic Hydroxyl Group in H_2O and in D_2O and the Differences in $\Delta\Delta H°$ and $T\Delta\Delta S°$ because of the Solvent Change upon Complexation with β-cyclodextrin in H_2O and D_2O at $T = 298.15$ K

guest without OH	guest with OH	solvent	$\Delta\Delta H°$/kJ mol^{-1}[a]	$T\Delta\Delta S°$/kJ mol^{-1}[b]	$\Delta(\Delta\Delta H°)_{OH-OD}$[c]	$\Delta(T\Delta\Delta S°)_{OH-OD}$[d]
3-phenylpropionic acid	3-(2-hydroxyphenyl)propionic acid	H_2O	-8.3 ± 0.2	-10.0 ± 0.2	0.2 ± 0.2	0.1 ± 0.2
		D_2O	-8.5 ± 0.2	-9.9 ± 0.2		
3-phenylpropionic acid	3-(4-hydroxyphenyl)propionic acid	H_2O	-7.38 ± 0.15	-5.82 ± 0.15	0.2 ± 0.2	0.1 ± 0.2
		D_2O	-7.58 ± 0.15	-5.88 ± 0.15		
2-phenylethylamine	tyramine	H_2O	-7.4 ± 0.4	-4.8 ± 0.4	1.1 ± 0.6	0.7 ± 0.6
		D_2O	-8.5 ± 0.4	-5.5 ± 0.4		
N-acetyl-L-phenylalanine	*N*-acetyl-L-tyrosine	H_2O	-8.9 ± 0.3	-7.3 ± 0.3	1.3 ± 0.4	1.3 ± 0.4
		D_2O	-10.2 ± 0.2	-8.6 ± 0.2		

[a] $\Delta\Delta H° = \Delta H°$(phenolic guest) $- \Delta H°$(nonphenolic guest). [b] $\Delta\Delta S° = \Delta S°$(phenolic guest) $- \Delta S°$(nonphenolic guest). [c] $\Delta(\Delta\Delta H°)_{OH-OD} = \Delta\Delta H°_{OH} - \Delta\Delta H°_{OD}$; the subscripts OH and OD refer to the data obtained in H_2O and D_2O, respectively. [d] $\Delta(T\Delta\Delta S°)_{OH-OD} = T\Delta\Delta S°_{OH} - T\Delta\Delta S°_{OD}$; the subscripts OH and OD refer to the data obtained in H_2O and D_2O, respectively.

O···D···O bond on the basis of the overall heat production of CD complexation. Nevertheless, we could rely on the thermodynamic isotope effect observed in the enthalpy of CD complexation, if there is the "snowball effect" or accumulation of the small isotope effect arising from multiple hydrogen bonding interactions. Thus, since the phenolic hydroxyl group is hydrated quite differently in D_2O and H_2O as discussed above and is almost totally dehydrated upon inclusion into CD cavity, it is likely that the overall complexation thermodynamics is affected not only by the difference between the O···H···O versus O···D···O bonding interaction inside the cavity but also by the difference in the total hydration properties of phenolic hydroxyl in D_2O versus H_2O.

To examine this possibility, we calculated the enthalpic and entropic gains ($\Delta\Delta H°$ and $T\Delta\Delta S°$) attributable to the presence of the phenolic hydroxyl, by using the $\Delta H°$ and $T\Delta S°$ values obtained for the complexation of β-CD with the above-mentioned four guest pairs in H_2O and D_2O. The results are shown in Table 2. As discussed above, these differential values allow us to make a fair estimation of the thermodynamic parameters associated with a single phenolic hydrogen bond formation inside the CD cavity in H_2O and D_2O. Further subtractions of $\Delta\Delta H°_{OD}$ from $\Delta\Delta H°_{OH}$ and of $T\Delta\Delta S°_{OD}$ from $T\Delta\Delta S°_{OH}$ afford the $\Delta(\Delta\Delta H°)_{OH-OD}$ and $\Delta(T\Delta\Delta S°)_{OH-OD}$ values as thermodynamic measures of the differences associated with the phenolic O···H···O versus O···D···O bonding interaction inside the CD cavity. As a result of the error propagation upon subtraction, the uncertainties associated with the differential parameters ($\Delta\Delta$ and $\Delta\Delta\Delta$ values) inevitably become greater than those of the original $\Delta H°$ and $T\Delta S°$ values. Hence, the $\Delta(\Delta\Delta H°)_{OH-OD}$ and $\Delta(T\Delta\Delta S°)_{OH-OD}$ values for the first two guest pairs, that is, 3-phenylpropionic acid versus 3-(2-hydroxyphenyl)propionic acid and 3-phenylpropionic acid versus 3-(4-hydroxyphenyl)propionic acid, are indistinguishable from zero. However, in the last two guest pairs, that is, 2-phenylethylamine versus tyramine and *N*-acetyl-L-phenylalanine versus *N*-acetyl-L-tyrosine, the $\Delta(\Delta\Delta H°)_{OH-OD}$ and $\Delta(T\Delta\Delta S°)_{OH-OD}$ values obtained are definitely different from zero (Table 2). The magnitudes of $\Delta(\Delta\Delta H°)_{OH-OD}$ and $\Delta(T\Delta\Delta S°)_{OH-OD}$ appear to be correlated with the chemical nature/structure of guest, as the carboxylate guests and the amine/amino acid guests give clearly different $\Delta\Delta\Delta$ values.

The most striking result is not the small $\Delta\Delta\Delta$ values (which would be anticipated) but the fact that we could indeed find the real differences of up to 1.3 kJ mol^{-1} **in $\Delta(\Delta\Delta H°)_{OH-OD}$ and $\Delta(T\Delta\Delta S°)_{OH-OD}$,** particularly for amine/amino acid guests, beyond the accumulated uncertainties. The most important implication of the present result is that the overall thermodynamics of more sophisticated supramolecular/biological systems, which experience extensive solvation/ desolvation of water around numerous charged/hydrophilic residues upon complexation/decomplexation, can suffer catastrophic changes in D_2O. Indeed, significant effect of D_2O versus H_2O was reported on the association/dissociation equilibria,[36] conformational[37] and denaturation[38] stability, and kinetics[39] for a variety of protein systems.[40]

Effect of Guest Deuteration. Not only solvent deuteration but also guest deuteration significantly affected the complexation thermodynamics of CDs in H_2O and D_2O. The deuterated guests examined with specific CD include 1-butanol-d_{10}, hexanoic acid-d_{11}, and octanoic acid-d_{15} with α-CD, cyclohexanol-d_{12}, *N*-acetyl-L-phenylalanine-d_5 and -d_8 with β-CD, and benzoic acid-d_5 with am-β-CD. As shown in Table 1, all of the deuterated guests examined consistently gave appreciably lower affinities toward α-, β-, or am-β-CDs than the relevant nondeuterated guests in both H_2O and D_2O.

Interestingly, the average solvent isotope effect obtained for the deuterated guests ($K^D_{H2O}/K^D_{D2O} = 0.89 \pm 0.03$) is identical to that for the nondeuterated guests examined above ($K^H_{H2O}/K^H_{D2O} = 0.90 \pm 0.03$). The neutral and charged guests do not exhibit any appreciable difference in K_{H2O}/K_{D2O} value upon guest deuteration, that is, $(K^H_{H2O}/K^H_{D2O})/(K^D_{H2O}/K^D_{D2O}) = 1.03 \pm 0.04$ for neutral guests and 1.00 ± 0.04 for negatively charged guests. This result seems reasonable since guest deuteration does not alter the property of hydration shell around the charged/hydrophilic moiety of guest.

The above results and discussion lead us to a conclusion that the consistently lower affinity of deuterated guests toward CDs in both H_2O and D_2O originates from the physicochemical properties of the hydrophobic moiety of deuterated guest. Indeed, the C−D bond is shorter than the C−H bond, which means that the induced dipole is smaller for C−D than for C−H under the identical conditions. Since induced dipole plays an essential part of the van der Waals interactions upon guest

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inclusion by CD, it is reasonable to expect a reduced affinity to CD for the deuterated guest as a consequence of the lower induced dipole of the C−D bond. This theoretical anticipation nicely coincides with the experimental data presented in Table 1.

A further experimental verification of such a theory is to examine the effect of the number of C−D bonds in guest molecule on the complex stability. The comparison should be done with a series of guests which share the same molecular structure but possess different numbers of deuterium. In this context, the guest series of *N*-acetyl-L-phenylalanine-d_0, -d_5, and -d_8 is a perfect set for examining the effect of gradual deuteration of guest upon complexation thermodynamics. Indeed, the affinity toward β-CD gradually decreased in the order of increasing number of deuterium: *N*-acetyl-L-phenylalanine-d_0 > -d_5 > -d_8 (Table 1). The same tendency was observed in both H_2O and D_2O; thus, the observed K values gradually decrease from 67.5 to 63.3 and then to 62.7 M^{-1} in H_2O, and from 80 to 75 and then to 73.6 M^{-1} in D_2O for the d_0, d_5, and d_8 guests, respectively, although the relatively large uncertainties of 1.4−2 M^{-1} do not allow us more strict comparison.

Another possible examination of the effect of the number of C−D bonds on the overall complexation thermodynamics is to compare the relative affinity reduction caused by the full deuteration of alkyl group of pseudo-homologous guest series, that is, butanol, hexanoate, and octanoate. The % reduction of affinity induced by guest deuteration (average of the data in D_2O and H_2O) are 7 ± 2%, 7 ± 3%, and 10 ± 3%. for butanol, hexanoate, and octanoate, respectively. The % reduction values appear to display an increasing tendency with increasing number of the effective deuterium in guest from 9 to 11 in butanol/hexanoate to 15 in octanoate, although again we cannot rigorously claim this trend owing to the large uncertainties involved.

Isotope Effect and Enthalpy−Entropy Compensation. Enthalpy−entropy compensation has long been a hot topic in the chemical literature. In principle, no explicit relationship between the enthalpy change and the entropy change can be derived from the fundamental thermodynamics. Nevertheless, the compensatory enthalpy−entropy relationship has often been observed in both activation and thermodynamic quantities determined for a very wide variety of reactions and equilibria, as pointed out by Leffler half a century ago.[41] Further exemplification and more thorough and critical analyses have been carried out by Leffler and Grunwald,[42] Grunwald and Steel,[43] Exner,[44] Chen,[45] Danil de Namor et al.,[46] and Linert et al.[47] It is clear from the original and review articles that widely observed compensatory enthalpy−entropy relationship is a powerful tool to understand and even to predict thermodynamic behavior on the basis of the experimental data already available. Nevertheless, the concept of compensatory enthalpy−entropy relationship has reached a sort of confusion,[48] which urges us not only to present our new experimental thermodynamic data for the solvent isotope effect upon supramolecular interaction but also to elucidate the origin and meanings of the observed enthalpy−entropy relationship in view of Grunwald's theory.

In chemical reactions and equilibria, the rate constant (k) and the equilibrium constant (K) are critically varied by changing substituent, solvent, and other internal and external factors. However, the change in k or K ($\Delta\Delta G^{\ddagger}$ or $\Delta\Delta G^{\circ}$) caused by such alterations is generally much smaller than that expected from the induced enthalpic change alone ($\Delta\Delta H^{\ddagger}$ or $\Delta\Delta H^{\circ}$), since the relevant entropy term ($\Delta\Delta S^{\ddagger}$ or $\Delta\Delta S^{\circ}$) often compensates to cancel out a substantial part of the enthalpic change. Qualitatively, this is the source of the $\Delta H-\Delta S$ compensation effect.

The linear $\Delta H-\Delta S$ relationship observed experimentally leads to eq 1, where the proportional coefficient β has the dimension of temperature.[41−43] From eq 1 and the differential form of the Gibbs−Helmholtz eq 2, we obtain eq 3.

$$\Delta\Delta H^{\circ} = \beta\Delta\Delta S^{\circ} \quad (1)$$

$$\Delta\Delta G^{\circ} = \Delta\Delta H^{\circ} - T\Delta\Delta S^{\circ} \quad (2)$$

$$\Delta\Delta G^{\circ} = (1 - T/\beta)\Delta\Delta H^{\circ} \quad (3)$$

Equation 3 clearly indicates that, at the critical point, or so-called isokinetic or isoequilibrium temperature (β), the rate or equilibrium constant is entirely independent of the enthalpic change caused by any alterations in substituent, solvent, and so on. It is interesting that such phenomena have been abundantly observed for a wide variety of reactions.[41−45]

However, much debate has been devoted to the basis of this extrathermodynamic relationship,[47,49−56] since the enthalpy and entropy changes are not independent of one another in their determination, especially when using the van't Hoff or Arrhenius equations.[47] Therefore, even a minute error in either term may propagate to the other, leading to an apparent enthalpy−entropy compensation effect.[57] Hence, the accuracy in experiment and data treatment as well as the quality of correlation coefficient associate with the enthalpy−entropy plot could be criteria for the significance of such a correlation. While using a greater number of data sets is preferable for more global analysis of such a correlation, integration of all the data available from various sources with different levels of accuracy and precision inevitably leads to more or less scattered plots with smaller correlation coefficients. However, this does not immediately rule out the correlation itself, since such correlations often show high levels of significance. Recently, some experimental and theoretical support for the validity of the enthalpy−entropy compensation has also been reported.[58]

More recently, somewhat different quantitative correlation analyses of compensatory enthalpy−entropy relationships were performed, by using the thermodynamic quantities reported for a wide variety of molecular recognition systems in chemistry

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and biology.[59−64] In these analyses, the $T\Delta S°$ value was linearly correlated with the $\Delta H°$ value to give eq 4. When integrated, this gives us eq 5 and subsequent combination with eq 2 affords eq 6.

$$T\Delta\Delta S° = \alpha\Delta\Delta H° \quad (4)$$

$$T\Delta S° = \alpha\Delta H° + T\Delta S°_0 \quad (5)$$

$$\Delta\Delta G° = (1 - \alpha)\Delta\Delta H° \quad (6)$$

Thus, the slope (α) of the $T\Delta S°$-versus-$\Delta H°$ plot (eq 5) indicates to what extent the enthalpic gain ($\Delta\Delta H°$), which is induced by any alterations in host, guest, or solvent, is canceled by the accompanying entropic loss ($\Delta\Delta S°$). In other words, only a fraction ($1 - \alpha$) of the enthalpic gain can contribute to the enhancement of complex stability. On the other hand, the intercept ($T\Delta S°_0$) represents the inherent complex stability ($\Delta G°$) obtained at $\Delta H° = 0$, which means that the complex is stabilized even in the absence of enthalpic gain, as far as the $T\Delta S°_0$ term is positive.[62,63] From comparative analyses of the thermodynamic data for cation binding by three types of ionophores (glymes, crown ethers, and cryptands) with different topologies or dimensionalities, the slope (α) and the intercept ($T\Delta S°_0$) of the regression line were related to the degree of conformational change and to the extent of desolvation upon complexation, respectively.[62,63] Using α and $T\Delta S°_0$ as quantitative measures for changes in conformation and desolvation of both host and guest, diverse chemical and biological supramolecular systems can be analyzed consistently, despite the quite different weak interactions involved in each supramolecular system.[59−65]

It was somewhat puzzling for us why in various cases using the experimental data of high precision the statistical quality of observed compensation plot are significantly different from one case to another. A reasonable question may immediately arise: What is the criterion of statistical quality (significance) of enthalpy−entropy compensation plot? This was answered by the Grunwald theory at least for complexation reactions in solution. The general concept and methodology developed by Grunwald et al.[43,66] provide us with reliable tools for analyzing thermodynamic parameters and particularly for diagnosing the existence or nonexistence of meaningful compensatory enthalpy−entropy relationship 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.[43,66]

In our previous study,[8] the differential entropy changes ($T\Delta\Delta S°$) were plotted against the differential enthalpy changes ($\Delta\Delta H°$) for the hypothetical exchange equilibrium between the (*R*)- and (*S*)-enantiomers of several chiral guests (eq 7).

$$[\beta\text{-CD}\cdot R] + S = [\beta\text{-CD}\cdot S] + R \quad (7)$$

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 $\Delta H° \angle T\Delta S°$ 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 entire thermodynamic parameters available for β-CD complexation collected in our recent review.[7] In reality, these contrasting plots are not unreasonable, as the differential thermodynamic parameters for enantiomer pairs reflect only the minimal change in the system, that is, the difference in chirality. In this treatment dealing with the exchange equilibrium $[\beta\text{-CD}\cdot R] + S = [\beta\text{-CD}\cdot S] + R$, we can simplify the system and offset the effects of all other structural variations except for the guest chirality, thus reducing the contribution of the nominal part (ΔG_{nom}, ΔH_{nom}, and ΔS_{nom}) almost to zero.[43,66]

Additional experimental support for Grunwald's theory[43,66] was obtained in our recent study,[22] where the statistic quality of the enthalpy−entropy compensation plot for the hypothetical exchange equilibrium between the enantiomeric guest pairs (eq 7) was compared with that for a hypothetical exchange equilibrium between β-CD and am-β-CD for chiral and achiral guests (G) (eq 8).

$$[\beta\text{-CD}\cdot\text{G}] + \text{am-}\beta\text{-CD} = [\text{am-}\beta\text{-CD}\cdot\text{G}] + \beta\text{-CD} \quad (8)$$

In the two studies mentioned above,[8,22] we employed the same sets of chiral guests, microcalorimetric equipment and procedures, and physicochemical experimental conditions. Thus, the two enthalpy−entropy compensation plots for the enantiomeric guest exchange and host exchange reactions (eqs 7 and 8) were based on the thermodynamic parameters of exactly the same quality and precision. Hence, the statistical qualities of the plots directly reflect the physical properties of the exchange reactions under consideration. Furthermore, the $\Delta\Delta H°$ and $T\Delta\Delta S°$ values obtained in the two cases fall in almost the same range varying from −5 to +8 kJ mol^{-1} and from −4 to +8 kJ mol^{-1}, respectively. Intriguingly, despite the same accuracy level and similar magnitude of the original data, the two compensation plots show strikingly different scattering levels, accompanying much larger scattering in the latter case (eq 8). If the ΔG_{env} value is equal to zero in dilute solution and therefore only the ΔH_{env} and ΔS_{env} values are subject to the enthalpy−entropy compensation, then 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 to occur upon host exchange from β-CD to am-β-CD (eq 8) rather than the enantiomeric guest exchange in the same β-CD cavity (eq 7).

As emphasized above, the observed changes in CD complexation thermodynamics in D_2O versus H_2O originate predominantly from the different physicochemical properties of the hydration shell around the charged/hydrophilic group of guests

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Table 3. Differential Complexation Enthalpies ($\Delta\Delta H^\circ$) and Entropies ($T\Delta\Delta S^\circ$) for Transfer of Various Cyclodextrin Complexes from H_2O to D_2O at $T = 298.15$ K

host	guest	$\Delta\Delta H^\circ_{H2O-D2O}$[a]/kJ mol^{-1}	$T\Delta\Delta S^\circ_{H2O-D2O}$[b]/kJ mol^{-1}
α-CD	1-butanol (0)	−0.2	−0.4
	1-butanol-d_{10} (0)	−0.6	−0.8
	1-pentanol (0)	−0.3	−0.5
	1-hexanol (0)	−0.1	−0.2
	hexanoic acid (−1)	−1.1	−1.5
	hexanoic acid-d_{11} (−1)	−0.4	−0.5
	hexylamine (+1)	−0.7	−0.9
	octanoic acid (−1)	−0.5	−0.7
	octanoic acid-d_{15} (−1)	−0.8	−1.1
β-CD	cyclopentanol (0)	−0.7	−0.9
	cyclohexanol (0)	−0.3	−0.5
	cyclohexanol-d_{12} (0)	−0.6	−0.9
	cycloheptanol (0)	−0.7	−0.8
	(R)-camphanic acid (1−)	0.7	0.3
	(R)-camphorsulfonic acid (−1)	0.9	0.6
	4-phenylbutylamine (+1)	0.9	0.5
	1-methyl-3-phenylpropylamine (+1)	0.9	0.5
	4-toluic acid (−1)	0.5	0.2
	3-phenylpropionic acid (−1)	0.6	0.3
	3-(4-hydroxyphenyl)propionic acid (−1)	0.8	0.3
	3-(2-hydroxyphenyl)propionic acid (−1)	0.8	0.2
	2-phenylethylamine (+1)	0.3	0.1
	tyramine (+1)	1.1	0.7
	N-acetyl-L-phenylalanine (−1)	0.6	0.2
	N-acetyl-L-phenylalanine-d_5 (−1)	0.4	−0.1
	N-acetyl-L-phenylalanine-d_8 (−1)	0.4	0.0
	N-acetyl-L-tyrosine (−1)	1.9	1.5
	(R)-hexahydromandelic acid (−1)	−0.1	−0.3
	(R)1-cyclohexylethylamine (+1)	−0.3	−0.4
am-β-CD	(*R*)-mandelic acid (−1)	1.0	0.7
	4-toluic acid (−1)	−0.1	−0.5
	benzoic acid (−1)	0.0	−0.4
	benzoic acid-d_5 (−1)	−0.3	−0.7

[a] $\Delta\Delta H^\circ_{H2O-D2O} = \Delta H^\circ_{H2O} - \Delta H^\circ_{D2O}$. [b] $\Delta(T\Delta S^\circ)_{H2O-D2O} = T\Delta S^\circ_{H2O} - T\Delta S^\circ_{D2O}$.

in both solvents. It is likely therefore that the solvation/desolvation process is the major source of the varying thermodynamic parameters in D_2O versus H_2O, which are related to ΔH_{env} and ΔS_{env}. Consequently, we expect a high-quality enthalpy−entropy compensation plot for the transfer of CD complex from H_2O to D_2O (eq 3), as was the case with the enantiomer exchange equilibrium (eq 7) rather than the host exchange equilibrium (eq 8).

$$[\beta\text{-CD}\cdot\text{G}]_{H2O} + n\text{D}_2\text{O} = [\beta\text{-CD}\cdot\text{G}]_{D2O} + n\text{H}_2\text{O} \quad (9)$$

Differential thermodynamic parameters for the transfer of CD complex from H_2O to D_2O (eq 9) were calculated from the data in Table 1 to give the $\Delta\Delta H^\circ_{H2O-D2O}$ ($=\Delta H^\circ_{H2O} - \Delta H^\circ_{D2O}$) and $T\Delta\Delta^\circ S_{H2O-D2O}$ ($=T\Delta S^\circ_{H2O} - T\Delta S^\circ_{D2O}$) values presented in Table 3. As anticipated above, the compensation plot of $T\Delta\Delta S^\circ_{H2O-D2O}$ against $\Delta\Delta H^\circ_{H2O-D2O}$, illustrated in Figure 1, shows an excellent fit to the regression line of nearly unit slope (0.90) and a very small intercept (0.29 kJ mol^{-1}) with a correlation coefficient of 0.986. This result confirms our conclusion that the smaller the conformational/structural changes in complex (inducing minimal ΔG_{nom}, ΔH_{nom}, and ΔS_{nom}), the better the quality of enthalpy−entropy compensation plot.

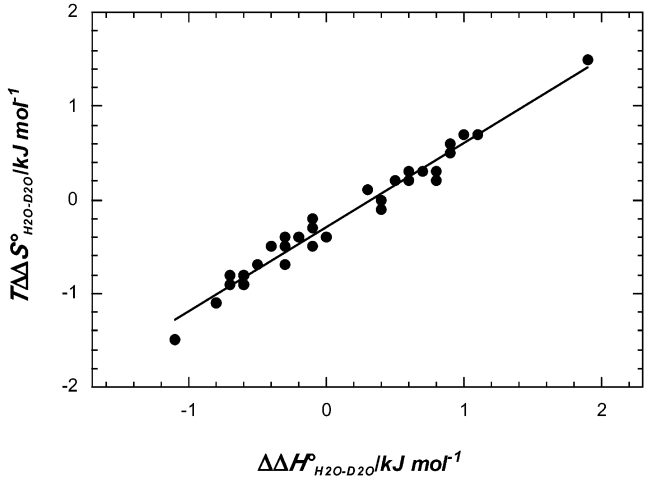

Figure 1. Compensation plot of the differential entropy change ($T\Delta\Delta S^\circ_{H2O-D2O} = T\Delta S^\circ_{H2O} - T\Delta S^\circ_{D2O}$) against the differential enthalpy ($\Delta\Delta H^\circ_{H2O-D2O} = \Delta H^\circ_{H2O} - \Delta H^\circ_{D2O}$) for the transfer of complexes of various guests with α-cyclodextrin, β-cyclodextrin, and 6-amino-6-deoxy-β-cyclodextrin from H_2O to D_2O at 298.15 K.

Conclusions

The newly obtained thermodynamic quantities of high accuracy and precision have clearly demonstrated that the deuterium isotopic effects of solvent and guest cause significant changes in complexation thermodynamic behavior of α-, β-, and am-β-CD. The comparative thermodynamic studies on inclusion complexation of neutral/anionic/cationic nondeuterated/deuterated guests with neutral α- and β-CD and cationic am-β-CD in H_2O and D_2O reveal that the thermodynamic outcome of the solvent isotope effect is reasonably interpreted in terms of the chemical nature and structure of guest rather than the size and properties of CD cavity and that the effect of guest deuteration is related to the change in van der Waals interaction inside the CD cavity arising from the shorter bond length and lower induced dipole of C−D than C−H. Careful

analyses and discussion of the obtained thermodynamic data lead us to several new insights into the solvent and guest isotope effects on the complexation thermodynamics of not only CDs but also other synthetic and natural supramolecular systems where water is the solvent and hydrophobic and van der Waals interactions are the major driving forces for complexation.

1. Guest affinity toward CDs is consistently enhanced by the use of D_2O as the solvent. The quantitative affinity enhancement in D_2O versus H_2O directly correlates with the size and strength of the hydration shell around the charged/ hydrophilic group of the guest. For that reason, negatively/positively charged guests, possessing a relatively large and strong hydration shell, afford smaller K_{H2O}/K_{D2O} ratios than those for neutral guests with a smaller and weaker hydration shell.

2. The enhanced affinity observed in D_2O for guests with rigid and bulky hydrophobic moieties is enthalpic in origin and attributable to the more favorable intracavity interactions in D_2O. In contrast, the increased affinity for flexible, less-bulky hydrophobic guests is entropic in origin and ascribable to the conformational adjustability of the flexible guest group upon inclusion in the CD cavity.

3. Partial or total deuteration of the guest leads to the reduced affinity toward CDs in both H_2O and D_2O, which is probably ascribed to the lower ability of the C−D bond to produce induced dipoles and thus the reduced intracavity van der Waals interactions.

4. The excellent enthalpy−entropy correlation obtained can be taken as evidence for the very limited (or negligible) conformational changes upon transfer of CD complexes from H_2O to D_2O.

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