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Heat Capacity Contributions to the Formation of Inclusion Complexes

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An analysis scheme for the formation of the inclusion complexes in water is presented. It is exemplified for the case where the host is α -cyclodextrin and the guest is a linear alcohol (1-propanol to 1-octanol) or the isomers of 1-pentanol. Eight transfer isobaric heat capacities, $\Delta_t C_p$, involving different initial and final states are evaluated at infinite dilution of the guest using both data determined in this work and from the literature. Apart from the usual definition for the inclusion heat capacity change, three inclusion transfers are used. The sign of each $\Delta_t C_p$ indicates if the transfer is an order-formation or an order-destruction process. From the $\Delta_t C_p$ data, the main contributions to the heat capacity of cyclodextrin complexation, namely, those due to dehydration of the hydrophobic section of the guest molecule, H-bond formation, formation of hydrophobic interactions, and release of water molecules from the cyclodextrin cavity, are estimated. The relative weight of each of these contributions to the $\Delta_t C_p$ values is discussed, providing a better characterization of the molecular recognition process involved in the inclusion phenomena.

Introduction

Supramolecular chemistry deals with a wide range of naturally occurring and artificially made molecular assemblies.^{1,2} Understanding the factors that control the formation and properties of assemblies such as enzyme–substrate, enzyme–inhibitor, ligand–protein, antigen–antibody, and protein–protein complexes is of primary scientific interest and also a requirement for the development of technologies in areas ranging from molecular machines to structure-based drug design.^{3–12} The formation of molecular assemblies involves a binding or complexation event between two or more molecules. Complexation occurs when the shapes and arrangements of binding sites in host and guest molecules fit each other. This host–guest complementarity was recognized a long time ago as the lock and key principle that explained the remarkable specificity of enzyme catalysis. Host–guest complexes are held together in unique structural arrangements by forces other than those of full covalent bonds. These forces are weak, and often, none are dominant, but rather, a concerted interplay between several noncovalent forces is necessary to archive recognition between the host and guest molecules. Comprehension of the molecular recognition process requires knowledge of the thermodynamic properties of the system that, interpreted in microscopic terms, provides an insight into the contributions that determine the formation and stability of the molecular assembly. The acquisition and analysis of thermodynamic information are the two main goals of this work, the systems under examination being a series of inclusion complexes.

To study the general characteristics and behavior of inclusion complexes, cyclodextrins (CD) are often used as host molecules.¹³ The most abundant are α -, β -, and γ -cyclodextrin with six, seven, and eight α -1,4-linked D-glucopyranose units, respectively. These naturally occurring oligosaccharides are

truncated cone-shaped molecules with a cavity of 7.9 Å depth and with wide and narrow diameters of 4.7 and 5.3 Å for α -CD, of 6.0 and 6.5 Å for β -CD, and of 7.5 and 8.3 Å for γ -CD, respectively. These cone ends are delineated by primary and secondary hydroxyl groups whose hydrophilic character makes CDs soluble in water. The cavity is lined by hydrogen atoms and glucosidic oxygen bridges whose electron pairs are directed toward the interior of the cavity, producing a high electron density. In aqueous solution, the CD cavities are occupied by water molecules that can be readily substituted by other molecules. For this reason, CDs were among the first host structures whose ability to bind organic guests was recognized. They have been and continue to be studied extensively by various experimental techniques, both spectroscopic and thermodynamic,^{13–17} as well as a variety of theoretical tools.¹⁸ The most frequently studied CD inclusion complexes in water are those where the guest molecules are of amphiphilic character, that is, molecules with a dual nature consisting of a nonpolar or hydrophobic part and another polar, and often charged, section. Many studies indicate that the mode of binding involves the insertion of the nonpolar part of the guest molecule into the cavity, while its polar section (or charged group) is exposed to the bulk solvent just outside of the wider opening of the cavity.^{16–18} From the thermodynamic point of view, the formation of host–guest complexes can be conveniently studied using heat capacity measurements that are particularly sensitive to the formation or destruction of organization or structure in the system.^{19–21} Using a series of experimentally determined heat capacities for several transfer processes, we present here a detailed analysis for the formation of the inclusion complexes in water constituted by α -CD and a linear alcohol (1-propanol to 1-octanol) or the isomers of 1-pentanol. This analysis allowed the evaluation of the main contributions to the heat capacity of cyclodextrin complexation, but it can also be applied to other systems.

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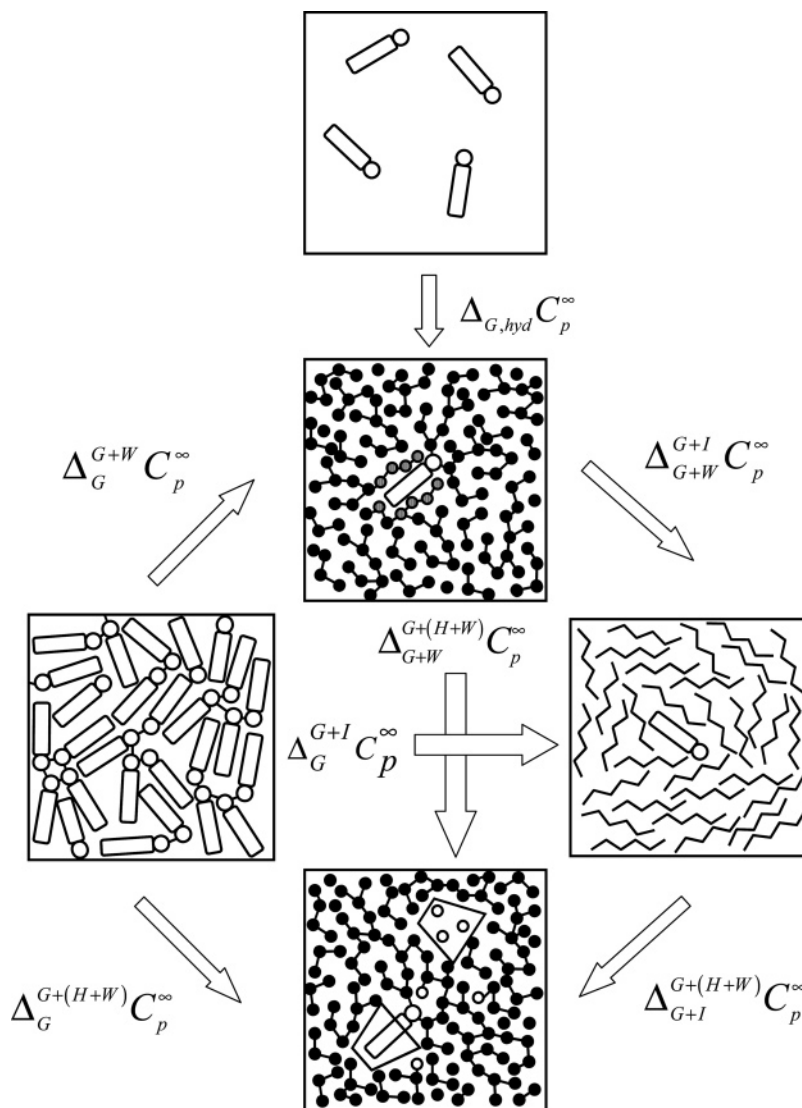


Figure 1. Schematic representation of the initial and final states of the transfer processes defined by eqs 1 and 3–8 for the case of a 1-alcohol as the guest molecule and a cyclodextrin as the host molecule. The code is as follows: 1-alcohol molecule (rectangle representing the hydrocarbon chain and a circle representing the hydroxyl group), bulk water molecules (dark circles), water molecules structured around the hydrophobic section of the 1-alcohol (dashed circles), water molecules inside of the cyclodextrin cavity (open circles), cyclodextrin molecule (truncated cone), inert solvent (zigzag lines), and H-bonds (lines joining circles). In the lower panel, the open circles shown in the bulk water represent the water molecules inside of the cyclodextrin cavity that were displaced upon 1-alcohol penetration; although represented as open circles, these water molecules form part of the bulk water.

Heat Capacity Changes

The formation of host (H)–guest (G) complexes in water (W) can be studied using the following experimentally determined heat capacity changes. In order to avoid the contribution due to guest–guest interactions, these heat capacity changes are defined at infinite dilution. For the case of a 1-alcohol as the guest molecule and a cyclodextrin as the host molecule, Figure 1 shows schematically the initial and final states considered.

The heat capacity change for guest hydration, that is, for the transfer of 1 mol of G from the pure ideal gas to the infinitely dilute aqueous solution is

$$\Delta_{G,\text{hyd}} C_p^\infty = C_{p,G}^{\infty,W} - C_{p,G}^{\text{id}} \quad (1)$$

where $C_{p,G}^{\infty,W}$ is the limiting partial molar heat capacity of G in water and $C_{p,G}^{\text{id}}$ is the molar heat capacity of G in the ideal gas state. The heat capacity change for host hydration can also be

defined using an expression analogous to eq 1. For most H compounds, the ideal heat capacity is not known, although it can be estimated using a group contribution method.²²

The heat capacity changes for the host and guest dissolution processes, that is, for the transfer of 1 mol of H or G from its pure state at the experimental temperature to the infinitely dilute aqueous solution is

$$\Delta_H^{H+W} C_p^\infty = C_{p,H}^{\infty,W} - C_{p,H}^o \quad (2)$$

$$\Delta_G^{G+W} C_p^\infty = C_{p,G}^{\infty,W} - C_{p,G}^o \quad (3)$$

where $C_{p,H}^{\infty,W}$ and $C_{p,G}^{\infty,W}$ are the limiting partial molar heat capacities of H and G in water, and $C_{p,H}^o$ and $C_{p,G}^o$ are molar heat capacities for pure H and G, respectively. For most host–guest systems, at the experimental temperature, H is a solid, and G is either a liquid or a solid.

The heat capacity changes for the transfer of 1 mol of G from its pure state at the experimental temperature and from infinite

dilution in water both to infinite dilution in an inert (I) solvent, an *n*-alkane for example, are

$$\Delta_G^{G+I} C_p^\infty = C_{p,G}^{\infty,I} - C_{p,G}^o \quad (4)$$

$$\Delta_{G+W}^{G+I} C_p^\infty = C_{p,G}^{\infty,I} - C_{p,G}^{\infty,W} \quad (5)$$

where $C_{p,G}^{\infty,I}$ is the limiting partial molar heat capacity of G in the inert media. As such, eq 4 represents the contribution to the heat capacity of the pure G due to self-association²³ and eq 5 the heat capacity change upon total dehydration of the guest molecule.

The heat capacity changes for the transfer of 1 mol of G from its pure state at the experimental temperature, from infinite dilution in water, and from infinite dilution in an inert solvent, all to infinite dilution in a (H + W) mixture of known concentration are

$$\Delta_G^{G+(H+W)} C_p^\infty(H) = C_{p,G}^{\infty,H+W}(H) - C_{p,G}^o \quad (6)$$

$$\Delta_{G+W}^{G+(H+W)} C_p^\infty(H) = C_{p,G}^{\infty,H+W}(H) - C_{p,G}^{\infty,W} \quad (7)$$

$$\Delta_{G+I}^{G+(H+W)} C_p^\infty(H) = C_{p,G}^{\infty,H+W}(H) - C_{p,G}^{\infty,I} \quad (8)$$

where $C_{p,G}^{\infty,H+W}(H)$ is the limiting partial molar heat capacity of G in the (H + W) mixture that depends on H concentration. Equations 6–8 represent the inclusion process at infinite dilution of the guest G and a given concentration of the host H, starting from different initial states.

The heat capacity change for the inclusion process at infinite dilution of the guest using, as initial states, pure G and H, that is, the usual definition for the formation of an inclusion complex, is

$$\Delta_{\text{incl}} C_p^\infty(H) = \Delta_G^{G+(H+W)} C_p^\infty(H) - \Delta_G^{G+W} C_p^\infty - \Delta_H^{H+W} C_p^\infty \quad (9)$$

The right-hand sides of eqs 1–9 can be obtained by measuring the heat capacities of the pure components, of dilute binary mixtures (H + W, G + W, and G + I), and of the ternary mixtures G + (H + W) at the temperature of interest. For the binary mixtures, the measurements must be performed in dilute solutions as a function of G or H concentrations to allow the required extrapolation to infinite dilution. For the ternary mixtures G + (H + W), the heat capacity must be determined also for dilute solutions of G in several binaries (H + W) of known concentration and extrapolated to infinite dilution of G at each H concentration. The consistency of the gathered data for the ternary and binary systems can be verified using the fact that the $\lim(H \rightarrow 0) C_{p,G}^{\infty,H+W}(H)$ must be equal, within the experimental uncertainty, to $C_{p,G}^{\infty,W}$.

Experimental Section

The systems studied in this work are dilute mixtures of α -cyclodextrin (α -CD) in water, six isomeric pentanols in *n*-heptane, and six linear alcohols (from 1-propanol to 1-octanol) and seven isomeric pentanols in several (α -CD + water) solutions.

Materials. High-purity α -CD was a generous gift from Cerestar (Cargill Co, U.S.A.), and it was used without further purification. Its water content was determined by the Karl Fischer method (701 KF Titrino, Metrohm, Switzerland), giving 10.62 wt % of water, which corresponds to an average of 6.42 water molecules per CD, that is, $\alpha\text{-CD} \cdot (6.42)\text{H}_2\text{O}$. The alcohols were all obtained from Sigma-Aldrich with a stated purity of

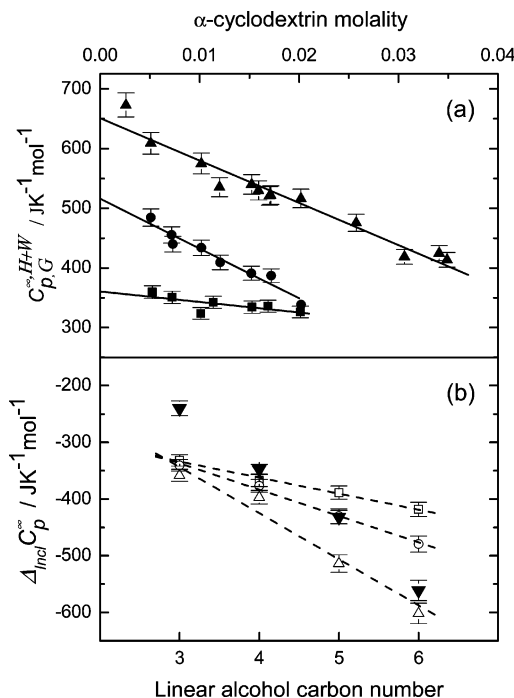


Figure 2. (a) Limiting partial molar heat capacity, $C_{p,G}^{\infty,H+W}(H)$, at 298.15 K of the guests 1-propanol (■), 1-pentanol (●) and 1-heptanol (▲) in (α -CD + water) mixtures of indicated α -CD molality. (b) $\Delta_{\text{incl}} C_p^\infty$ at 298.15 K from eq 9 for 1-propanol to 1-hexanol at α -CD molalities of 0.005 (□), 0.01 (○), and 0.02 (Δ) together with the results from ref 31 (▼) obtained from binding enthalpies measured with an isothermal titration calorimeter at 288.15, 298.15, and 308.15 K. In this case, the final α -CD molalities were not reported, but from the information given in ref 31, they are estimated to be between 0.0015 and 0.01.

99% or better, with the exception of 1-hexanol, 1-heptanol, 2-pentanol, 3-pentanol, and 3-methyl-2-butanol, for which the purity was 98%. Optically active alcohols (2-pentanol, 2-methyl-2-butanol, and 3-methyl-2-butanol) were racemic mixtures of the respective stereoisomers. The alcohols and *n*-heptane (J.T. Baker, with a purity of 99.3%) were used without further purification but were stored over 0.4 nm Merck molecular sieves to remove water. Water was distilled and deionized using Barnstead Nanopure Infinity equipment, its resistivity being 18 $\text{M}\Omega \text{ cm}^{-1}$.

Instrumentation and Procedures. The solutions (10 cm^3) were prepared by mass (Mettler AT250). When involved, the α -CD water content was taken into account. Depending on the type of mixture, different number of samples of varying concentration were prepared, namely, (a) for α -CD + water, 31 dilute samples (α -CD molality, m , from 0.01 to 0.13), (b) for each isomeric pentanol + *n*-heptane, at least six samples (alcohol mole fractions ranging from 5×10^{-4} to 0.12), and (c) for the six linear alcohols and the seven isomeric pentanols, for each α -CD + water solution (minimum of five solutions, from $m = 0.005$ to 0.02), at least five samples were prepared for each alcohol (alcohol mole fractions ranging from 2×10^{-5} to 7×10^{-4}). The uncertainties resulting from weighting were $\pm 2 \times 10^{-5}$ for the alcohol mole fractions and 0.2% for CD molalities.

Volumetric heat capacities were measured at 298.15 K using a Picker flow microcalorimeter (Sodev Inc., Sherbrooke, P.Q., Canada) and were transformed to a molar basis through densities obtained with a vibrating-tube densimeter (Sodev Inc.). The instrumentation and procedures have been described in detail in the literature.²⁴ In the flow calorimeter, the volumetric heat

TABLE 1: Pure Component and Ideal Gas Molar Heat Capacities, Limiting Partial Molar Heat Capacities in Water and in an Inert Solvent, and Transfer Heat Capacities (in J K⁻¹ mol⁻¹) from Eqs 1, 3, 4, and 5 for Linear Alcohols (C3–C8) and all Isomeric Pentanols at 298.15 K

guest	$C_{p,G}^o$	$C_{p,G}^{id}$	$C_{p,G}^{\infty,W}$	$C_{p,G}^{\infty,I}$	$\Delta_{G,hyd}C_p^\infty$	$\Delta_G^{G+W}C_p^\infty$	$\Delta_G^{G+I}C_p^\infty$	$\Delta_{G+W}^{G+I}C_p^\infty$
1-propanol	143.9 ^a	85.4 ^a	354.9 ^b	129 ^d	269.5	211.0	-14.9	-226
1-butanol	177.1 ^a	107.9 ^a	445.4 ^b	158 ^e	337.5	268.3	-19.1	-287
1-pentanol	208.1 ^a	132.8 ^a	534.1 ^b	188 ^f	401.3	326.0	-20.1	-346
1-hexanol	240.5 ^a	155.7 ^a	612 ^c	215 ^e	456.3	371.5	-25.5	-397
1-heptanol	272.8 ^a	178.6 ^a	704 ^c	245 ^e	525.4	431.2	-27.8	-459
1-octanol	304.6 ^a	201.4 ^a	800 ^c	276 ^d	598.6	495.4	-28.6	-524
2-methyl-1-butanol	215.0 ^b	133.3 ^a	518.1 ^b	185 ^g	384.8	303.1	-30.0	-333
3-methyl-1-butanol	209.3 ^b	134.3 ^a	517.4 ^b	210 ^g	383.1	308.0	0.7	-307
2-pentanol	235.3 ^b	137.5 ^a	548.8 ^b	167 ^g	411.3	313.5	-68.3	-382
2-methyl-2-butanol	251.1 ^b	132.1 ^a	548.1 ^b	189 ^f	416.0	297.0	-62.1	-359
3-methyl-2-butanol	249.5 ^b	133.9 ^a	527.7 ^b	200 ^g	393.8	278.2	-49.5	-328
3-pentanol	254.6 ^b	136.5 ^a	544.8 ^b	158 ^g	408.3	290.2	-96.6	-387
2,2-dimethyl-1-propanol		131.8 ^a	508.8 ^b	195 ^g	377.0			-314

^a Ref 26. ^b Ref 30. ^c Ref 29. ^d Interpolated from the data in Ref 23. ^e Ref 23. ^f Ref 51. ^g This work, using *n*-heptane as an inert solvent.

capacity of the liquid flowing through the working cell was measured against that of the reference cell. For the alcohol + *n*-heptane mixtures, the heat capacity of each solution was determined using pure *n*-heptane as the reference (1.525528 J K⁻¹ cm⁻³).²⁵ For the α -CD + water and alcohol + (α -CD + water) mixtures, the heat capacity of each solution was determined using pure water as the reference (4.16828 J K⁻¹ cm⁻³).²⁶ The densimeter was calibrated with water (0.99705 g cm⁻³ from ref 26) and dry nitrogen as the references. The calorimeter and densimeter were connected in series, and their temperature was controlled to ± 0.003 K using a CT-L thermostat (Sodev Inc.).

The apparent molar heat capacities, $C_{\phi,1}$ of the solute (component 1) for the binary mixtures were calculated using

$$C_{\phi,1}^b = \frac{C_{p,m}^b - x_2 C_{p,m,2}^b}{x_1} \quad (10)$$

where x_i is the mole fraction of component i and $C_{p,m}^b$ and $C_{p,m,2}^b$ are the molar heat capacities of the binary solution and the pure solvent, respectively. For the ternary mixtures, $C_{\phi,1}$ is given by

$$C_{\phi,1}^t = \frac{C_{p,m}^t - x_2^* C_{p,m,2}^*}{x_1} \quad (11)$$

with x_2^* is the mole fraction of the binary (α -CD + water) mixture, that is, $x_2^* + x_1 = 1$, and $C_{p,m}^t$ and $C_{p,m,2}^*$ are the molar heat capacities of the ternary and binary solutions, respectively.

The $C_{\phi,1}^b$ and $C_{p,m}^t$ data have been deposited as Supporting Information. Taking into account various possible sources of error, the estimated standard uncertainty of the molar heat capacities as well as their infinite dilution values is less than 2%, whereas that for the transfer heat capacities is between 2% and 3%.

Results

For the dilute binary mixtures (α -CD + water) and (isomeric pentanol + *n*-heptane), $C_{\phi,1}^b$ exhibited a linear dependence with CD molality and alcohol mole fraction, respectively. Extrapolation of $C_{\phi,1}^b$ to infinite dilution produced $C_{p,H}^{\infty,W}$ in eq 2 for α -CD and $C_{p,G}^{\infty,I}$ in eqs 4 and 5 for each of the isomeric pentanols (taking only the most diluted concentrations). For α -CD, the obtained value for $C_{p,H}^{\infty,W}$ was 1482 ± 6 J K⁻¹ mol⁻¹. In ref 27, a value of 1431 ± 11 J K⁻¹ mol⁻¹ was reported. However, this value is a misprint, the correct one being 1481

± 11 J K⁻¹ mol⁻¹.²⁸ Using the value of $C_{p,H}^o = 1153 \pm 10$ J K⁻¹ mol⁻¹ in ref 27, $\Delta_H^{H+W}C_p^\infty$ in eq 2 takes the value of 329 J K⁻¹ mol⁻¹. Table 1 reports, for the 13 alcohols guests, pure component ($C_{p,G}^o$) and ideal gas ($C_{p,G}^{id}$) molar heat capacities, the limiting partial molar heat capacities in water ($C_{p,G}^{\infty,W}$) and in the inert solvent *n*-heptane ($C_{p,G}^{\infty,I}$), and the transfer heat capacities $\Delta_{G,hyd}C_p^\infty$, $\Delta_G^{G+W}C_p^\infty$, $\Delta_G^{G+I}C_p^\infty$, and $\Delta_{G+W}^{G+I}C_p^\infty$ from eqs 1 and 3–5 at 298.15 K. $C_{p,G}^{\infty,W}$ data for the three longer linear alcohols are from ref 29, while for the other 10 alcohols, they were previously reported in ref 30. For these 10 alcohols, in ref 30, a detailed comparison with other data in the literature was presented. The data for $C_{p,G}^{\infty,I}$ are from the literature for the linear alcohols, whereas those for the isomeric pentanols were measured in this work. The values for the transfer heat capacities $\Delta_{G,hyd}C_p^\infty$ and $\Delta_G^{G+W}C_p^\infty$ in Table 1 differ slightly (maximum deviation of 0.8%) from those previously reported³⁰ due to the employment of different pure component and ideal gas heat capacities.

For the dilute alcohol + (α -CD + water) ternary mixtures, $C_{p,m}^t$ also varied linearly with the alcohol mole fraction, that is, $C_{p,m}^t = C_{p,m,2}^* + Ax_1$. Then, for each binary (H + water) mixture of fixed concentration, $C_{\phi,1}^t = A + C_{p,m,2}^* = C_{p,G}^{\infty,H+W}(H)$ in eqs 6–9. For 1-propanol, 1-pentanol, and 1-heptanol, Figure 2a illustrates the behavior of $C_{p,G}^{\infty,H+W}(H)$ as a function of α -CD molality. Clearly, $C_{p,G}^{\infty,H+W}(H)$ varies linearly with m . For each of the 13 alcohol guests, $C_{p,G}^{\infty,H+W}(H)$ was fitted to a straight line, allowing the comparison between alcohols at the same α -CD molality. $C_{p,G}^{\infty,H+W}(H)$ and the transfer heat capacities $\Delta_G^{G+(H+W)}C_p^\infty(H)$, $\Delta_{G+W}^{G+(H+W)}C_p^\infty(H)$, $\Delta_{G+I}^{G+(H+W)}C_p^\infty(H)$, and $\Delta_{incl}C_p^\infty(H)$ from eqs 6–9 at three small α -CD molalities and 298.15 K are given in Table 2. Extrapolating the heat capacities $C_{p,G}^{\infty,H+W}(H)$ to infinite dilution of α -CD gave values which differ only slightly from the $C_{p,G}^{\infty,W}$ values in Table 1; as a percentage of $C_{p,G}^{\infty,W}$, the maximum deviation is 7.5% for 1-heptanol among the linear alcohols and 4.6% for 3-pentanol among the isomeric pentanols. This proves that the data reported here for the ternary solutions are consistent with the data for the binary mixtures in refs 29 and 30 for 1-alcohols and in this work for pentanols. For the 1-alcohols, Figure 2b displays $\Delta_{incl}C_p^\infty(H)$ values at three α -CD molalities as a function of alcohol carbon number. As the alcohol chain length increases, the dependence of $\Delta_{incl}C_p^\infty(H)$ with α -CD concentration becomes more important. Figure 2b also shows the $\Delta_{incl}C_p^\infty(H)$ values obtained³¹ from $d\Delta H_{incl}/dT$ using isothermal titration calorimetry (ITC) where the α -CD concentration changes

TABLE 2: Limiting Partial Molar Heat Capacities of the Guests in the Binary Mixtures (α -Cyclodextrin + Water) and Transfer Heat Capacities (in $\text{J K}^{-1} \text{mol}^{-1}$) from Eqs 6–9 for Linear Alcohols (C3–C8) and for all Isomeric Pentanols at 298.15 K

guest	$C_{p,G}^{\infty,H+W}$			$\Delta_G^{G+(H+W)}C_p^\infty$			$\Delta_{G+W}^{G+(H+W)}C_p^\infty$			$\Delta_{G+I}^{G+(H+W)}C_p^\infty$			$\Delta_{incl}C_p^{\infty a}$		
	α -Cyclodextrin Molality														
	0.005	0.0075	0.01	0.005	0.0075	0.01	0.005	0.0075	0.01	0.005	0.0075	0.01	0.005	0.0075	0.01
1-propanol	352	347	343	208	203	199	−3	−8	−12	223	219	214	−332	−336	−341
1-butanol	407	402	397	230	225	220	−38	−43	−48	249	244	239	−367	−372	−377
1-pentanol	474	453	433	265	245	224	−60	−81	−102	286	265	245	−389	−410	−431
1-hexanol	522	491	461	278	247	217	−90	−121	−151	307	276	246	−418	−449	−479
1-heptanol	615	598	580	342	325	307	−89	−106	−124	370	353	335	−417	−435	−453
1-octanol	727	686	645	421	380	339	−74	−114	−155	451	410	369	−402	−443	−484
2-methyl-1-butanol	535	531	528	320	316	313	17	13	10	349	346	342	−313	−316	−319
3-methyl-1-butanol	485	464	442	276	254	232	−32	−54	−76	275	254	232	−361	−386	−405
2-pentanol	538	525	511	303	289	276	−11	−24	−38	371	358	344	−340	−353	−367
2-methyl-2-butanol	528	522	517	277	271	266	−20	−26	−31	339	333	327	−349	−355	−360
3-methyl-2-butanol	498	489	480	249	240	231	−30	−39	−47	298	289	280	−359	−368	−376
3-pentanol	555	548	541	301	293	286	10	3	−4	397	390	383	−319	−326	−333
2,2-dimethyl-1-propanol	488	472	456				−21	−36	−52	293	277	261	−350	−365	−381

^a Using $\Delta_H^{H+W}C_p^\infty = 329 \text{ J K}^{-1} \text{mol}^{-1}$ from $C_{p,H}^{\infty,W} = 1482 \text{ J K}^{-1} \text{mol}^{-1}$ (this work) and $C_{p,H}^0 = 1153 \text{ J K}^{-1} \text{mol}^{-1}$ (in ref 27).

TABLE 3: Contributions per Methylene Group ($\text{J K}^{-1} \text{mol}^{-1}$) to the Heat Capacities

heat capacity	contribution per CH_2
$C_{p,G}^0$	32.1 ± 0.1^a
$C_{p,G}^{\infty,W}$	23.3 ± 0.2^a
$C_{p,G}^{\infty,I}$	88.0 ± 1.2^a
$C_{p,G}^{\infty,L}$	29.2 ± 0.3^a
$\Delta_{G,\text{hyd}}C_p^\infty$	64.7 ± 1.3^a
$\Delta_G^{G+W}C_p^\infty$	55.9 ± 1.2^a
$\Delta_{G+I}^{G+I}C_p^\infty$	$−2.8 \pm 0.3^a$
$\Delta_{G+I}^{G+I}C_p^\infty$	$−58.8 \pm 0.9^a$
$\Delta_{G+W}^{G+W}C_p^\infty$	57.7 ± 2.5^b
$C_{p,G}^{\infty,H+W}$	24.5 ± 2.9^b
$\Delta_G^{G+(H+W)}C_p^\infty$	$−28.3 \pm 1.7^b$
$\Delta_{G+W}^{G+(H+W)}C_p^\infty$	28.9 ± 2.1^b
$\Delta_{G+I}^{G+I}C_p^\infty$	$−28.0 \pm 1.7^b$
$\Delta_{\text{incl}}C_p^\infty$	$−61.9 \pm 1.3$
hydrophobic chain dehydration ^c	
H-bond formation ^c	2.8 ± 0.3
formation of hydrophobic interactions ^c	6.0 ± 1.8
expulsion of water molecules from the CD ^{c,d}	24.5 ± 2.9

^a Evaluated using data from 1-propanol to 1-octanol. ^b Evaluated at α -cyclodextrin molality of 0.005 and using data from 1-propanol to 1-hexanol (see text). ^c The molecular interactions involved and the assumptions made to obtain these contributions are detailed in the text. ^d Transfer of water molecules from a hydrophobic environment to bulk water.

continuously during the experiment. The two sets of values are not directly comparable since, in ref 31, the final α -CD concentrations are not reported and only a range can be estimated (final molality, 0.0015–0.01).

Using the data for 1-propanol to 1-hexanol, Table 3 displays the contributions per methylene group (CH_2) to all of the heat capacities. No distinction has been made between the methylene groups and the methyl group of the linear alcohols. For the heat capacities that depend on the host concentration, the contributions per CH_2 group were evaluated at the lowest α -CD molality used here (0.005). Two of the values in Table 3 can be compared against previous reports. First, for the transfer of an alkyl group from water to a nonaqueous hydrophobic environment ($\Delta_{G+I}^{G+I}C_p^\infty$) the value in Table 3 is in very good agreement with those obtained earlier (from $−50$ to $−60 \text{ J K}^{-1} \text{mol}^{-1}$).^{29,32–35} Second, for $\Delta_{\text{incl}}C_p^\infty(\text{H})$, the value in Table 3 is much smaller

than those formerly evaluated using ITC, $−102 \text{ J K}^{-1} \text{mol}^{-1}$ in ref 31 using data for 1-alcohols (shown in Figure 2b) and $−90 \text{ J K}^{-1} \text{mol}^{-1}$ in ref 36 using data for α - ω -diols. Since these literature values were obtained using inclusion heat capacities at different α -CD concentrations, they do not truly reflect the contribution per CH_2 to $\Delta_{\text{incl}}C_p^\infty(\text{H})$.

Discussion

Transfer Heat Capacities as Order-Formation or Order-Destruction Processes. The heat capacity occupies a privileged place among the thermodynamic quantities. Due its relation with entropy changes ΔS , that is, $\Delta C_p = T(\partial\Delta S/\partial T)_p$, heat capacity changes ΔC_p are particularly sensitive to the presence of order or organization in the system. More precisely, ΔC_p values are a measure of the temperature variation of such order. At a given temperature, the transfer heat capacity, $\Delta_t C_p$, reflects the formation or destruction of order occurring in that transfer.^{19–21} For an order-destroying transfer, the enthalpy of transfer $\Delta_t H$ must be positive and, since order falls with increasing temperature at constant pressure, $\Delta_t C_p = (\partial\Delta_t H/\partial T)_p$ must be negative. On the other hand, for an order-formation transfer, $\Delta_t C_p$ must be positive. These simple considerations allow an analysis of all of the $\Delta_t C_p$ values reported here.

The heat capacities of hydration, dissolution, and for the guest transfers from the pure state and from infinite dilution in water both to infinite dilution in an inert solvent are shown in Figure 3 for the 13 alcohols. The $\Delta_{G,\text{hyd}}C_p^\infty$ and $\Delta_G^{G+W}C_p^\infty$ values are positive and hence correspond to an order-formation transfers. They increase linearly with the 1-alcohol size, while for the isomeric pentanols, it is observed that their values deviate to some extent from that for the linear 1-pentanol. On the other hand, the $\Delta_{G+I}^{G+I}C_p^\infty$ and $\Delta_{G+W}^{G+I}C_p^\infty$ values are negative, indicating an order-destroying transfers. Again, they vary linearly with alcohol size for the 1-alcohols, and for the isomeric pentanols, deviations from the 1-pentanol values are observed. Clearly, the observed differences between the linear 1-pentanol and the isomeric pentanols are due to the different chemical structures or geometries of these alcohols. However, no simple correlation between such geometries and the heat capacities has been found.

Figure 4 shows the experimentally obtained limiting partial molar heat capacity of the 1-alcohol guests in the α -CD + water mixture at three α -CD molalities, $C_{p,G}^{\infty,H+W}(\text{H})$, together with the limiting partial molar heat capacities of the same guests in

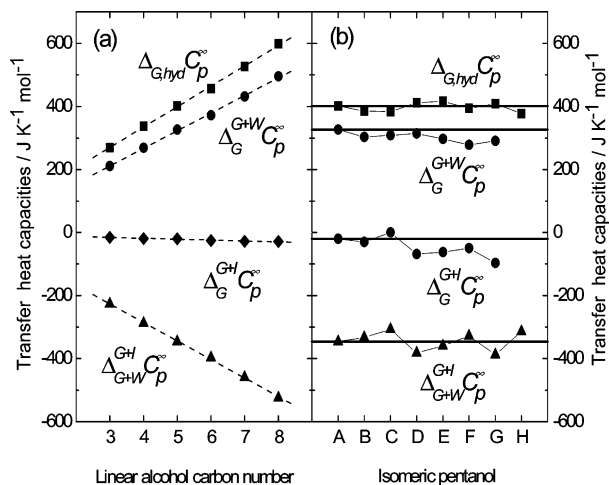


Figure 3. Heat capacity change for alcohol hydration, $\Delta_{G,hyd}C_p^\infty$ (■), for alcohol dissolution, $\Delta_{G^G+W}C_p^\infty$ (●), for the transfer of one mole of alcohol from its pure state to infinite dilution in an inert solvent, $\Delta_{G^G+I}C_p^\infty$ (◆), and for the transfer of one mole of alcohol from infinite dilution in water to infinite dilution in an inert solvent, $\Delta_{G^G+H+W}C_p^\infty$ (▲) at 298.15 K for (a) linear alcohols; the dashed straight lines are the best fit to the data, their slopes providing the corresponding contributions per CH_2 group reported in Table 3; and (b) isomeric pentanols: (A) 1-pentanol, (B) 2-methyl-1-butanol, (C) 3-methyl-1-butanol, (D) 2-pentanol, (E) 2-methyl-2-butanol, (F) 3-methyl-2-butanol, (G) 3-pentanol, and (H) 2,2-dimethyl-1-propanol. To aid in visualization, the horizontal lines show the corresponding values for 1-pentanol.

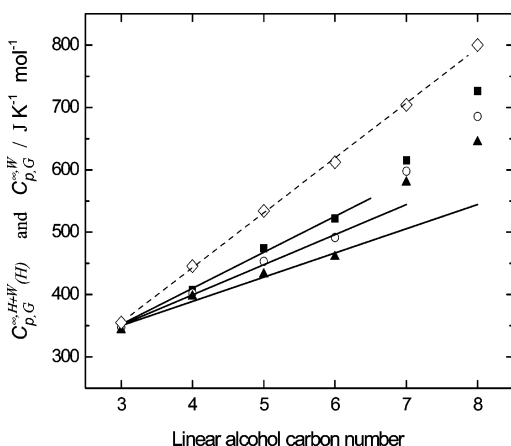


Figure 4. Limiting partial molar heat capacity, $C_{p,G}^{\infty,H+W}(H)$, at 298.15 K of 1-alcohols at three α -CD molalities, 0.005 (■), 0.0075 (○), and 0.01 m (▲). The straight lines are the best fit to the data from 1-propanol to 1-hexanol; the slope of the line corresponding to a α -CD molality of 0.005 is reported in Table 3. The values of $C_{p,G}^{\infty,H+W}(H)$ for 1-heptanol and 1-octanol deviate from this linear behavior. Also indicated is the limiting partial molar heat capacity of the 1-alcohols in water at 298.15 K, $C_{p,G}^{\infty,W}(H)$ (◊) from Table 1.

water, $C_{p,G}^{\infty,W}$. The fact that these two heat capacities are different is a clear indication of the interaction between the host and the guest molecules. Since many techniques indicate that 1-alcohol guests do penetrate the α -CD cavity, these differences are the heat capacity signature for the formation of the inclusion complex. In other words, if the guest and host molecules were to ignore each other in the aqueous media, these two heat capacities would be equal. Figure 4 shows this is not the case, but rather, that the formation of the inclusion complex decreases the heat capacity of the system. For 1-propanol, the difference between $C_{p,G}^{\infty,W}$ and $C_{p,G}^{\infty,H+W}(H)$ is quite small, implying that for this 1-alcohol, the inclusion complex must be rather faint, in agreement with the reported equilibrium constant.^{17,31} Two other

results in Figure 4 must be highlighted, namely, (i) while for the short chain guests 1-propanol and 1-butanol, $C_{p,G}^{\infty,H+W}(H)$ are practically α -CD concentration independent, but for longer chain 1-alcohols, they become α -CD concentration dependent, and (ii) the linear variation of $C_{p,G}^{\infty,H+W}(H)$ with the 1-alcohol chain length observed from 1-propanol to 1-hexanol is broken in going to 1-heptanol and 1-octanol. For these two 1-alcohols, the $C_{p,G}^{\infty,H+W}(H)$ values are closer to $C_{p,G}^{\infty,W}$ than what the linear variation for the shorter members of the series would predict.

The transfer heat capacities of the 1-alcohol and pentanol isomer guests from the different initial states to the α -CD + water mixture (eqs 6–8) at an α -CD molality of 0.005 are shown in Figures 5 and 6, respectively, together with $\Delta_{incl}C_p^\infty$ (eq 9). Each of the four quantities in Figures 5 and 6 are obtained by subtracting a constant from $C_{p,G}^{\infty,H+W}(H)$. In Figure 5, a linear increase or decrease with carbon number from 1-propanol to 1-hexanol followed by a deviation from this linearity for the longer two 1-alcohols is seen. This is a clear indication that for 1-heptanol and 1-octanol, only six carbon atoms of their aliphatic chains are able to penetrate the α -CD cavity, in agreement with previous estimates.^{31,36–40} The results in Figure 5 show that a formation of order occurs as a result of the $\Delta_{G^G+H+W}C_p^\infty$ and $\Delta_{G^G+I}C_p^\infty$ inclusion transfers. In contrast, a destruction of order characterizes the $\Delta_{G^G+H+W}C_p^\infty$ inclusion transfer and $\Delta_{incl}C_p^\infty$, the usual definition for the heat capacity change due to the formation of an inclusion complex. In the later case, eq 9 indicates that $\Delta_{incl}C_p^\infty$ is the result of a balance between three transfer processes, the net result being that there is a net destruction of order during the inclusion process. It appears that the formation of an inclusion complex can be described as a order-formation or an order-destruction process depending on the initial states considered. For the isomeric pentanols, the observed general trend in Figure 6 is that their transfer and inclusion heat capacities are bigger than those for 1-pentanol. These deviations from the linear 1-pentanol behavior are a reflection of the position of the hydroxyl group in the isomers and their different molecular shapes which, in turn, determine their flexibility and the section of their structures that is included in the α -CD cavity.

Evaluation of the Heat Capacity Contributions to Cyclodextrin Complexation. Using the heat capacity data in Tables 1–3, a dissection and evaluation of the main contributions to ΔC_p is possible. Seven principal single or grouped processes can be identified in Figure 1, involving molecular interactions that are either formed or destroyed depending on the transfer being considered. They are (1) hydration/dehydration of the hydrophobic chain of the G molecule that includes the formation/closure of a cavity in the water network to accommodate/liberate the G solute, the structuring/unstructuring of water molecules around the hydrophobic chemical groups of G, and the formation/rupture of contacts between these hydrophobic chemical groups and water; (2) the formation/rupture of H-bonds among the hydroxyl groups in G and water molecules; (3) the rupture of hydroxyl–hydroxyl H-bonds in pure G; (4) the rupture of chain–chain and chain–hydroxyl contacts in pure G; (5) the formation/rupture of contacts between the chain and the hydroxyl group of G and the hydrocarbon chain of the inert solvent; (6) the formation of contacts between the hydrophobic chain of G and the interior of the H cyclodextrin molecule; and (7) the release of water molecules from the H cyclodextrin cavity. On the basis of the comparison between the molar heat capacity of bulk water and for water inside of the cyclodextrin cavity,²⁷ other analyses have considered that process (7) is not

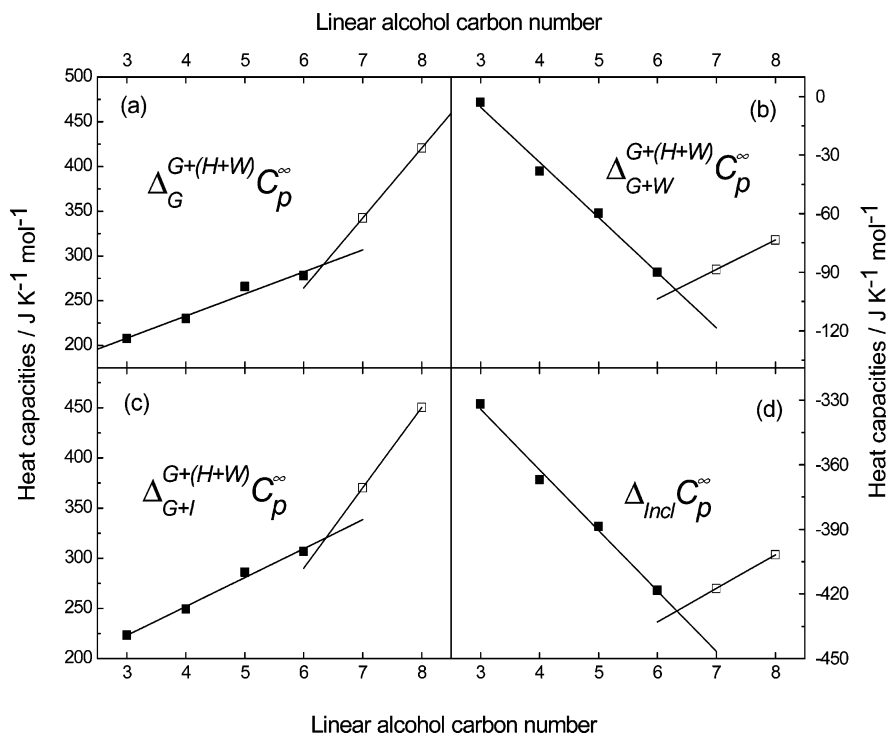


Figure 5. Heat capacity changes for the transfer of 1 mol of 1-alcohol at 298.15 K (a) from its pure state $\Delta_{\text{G}}^{\text{G}+(H+W)}C_p^\infty$, (b) from infinite dilution in water $\Delta_{\text{G+W}}^{\text{G}+(H+W)}C_p^\infty$, and (c) from infinite dilution in an inert solvent $\Delta_{\text{G+I}}^{\text{G}+(H+W)}C_p^\infty$ all to an α -CD + water solution with an α -CD molality of 0.005. These quantities represent the inclusion process starting from different initial states. The results employing the usual definition for the formation of an inclusion complex, $\Delta_{\text{incl}}C_p^\infty$, are shown in (d) at 298.15 K. In all cases, 1-heptanol and 1-octanol are seen to deviate from the linear trend signaled by the shorter 1-alcohols.

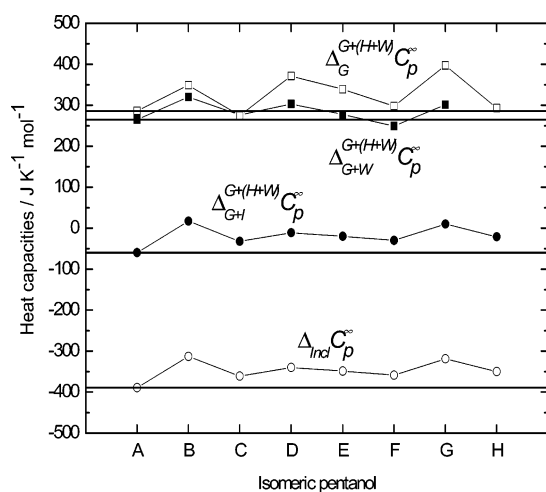


Figure 6. Heat capacity changes for the transfer of 1 mol of an isomeric pentanol at 298.15 K (a) from its pure state $\Delta_{\text{G}}^{\text{G}+(H+W)}C_p^\infty$, (b) from infinite dilution in water $\Delta_{\text{G+W}}^{\text{G}+(H+W)}C_p^\infty$, and (c) from infinite dilution in an inert solvent $\Delta_{\text{G+I}}^{\text{G}+(H+W)}C_p^\infty$ all to an α -CD + water solution with an α -CD molality of 0.005. These quantities represent the inclusion process starting from different initial states. The results employing the usual definition for the formation of an inclusion complex, $\Delta_{\text{incl}}C_p^\infty$, are shown in (d) at 298.15 K. The isomeric pentanols are (A) 1-pentanol, (B) 2-methyl-1-butanol, (C) 3-methyl-1-butanol, (D) 2-pentanol, (E) 2-methyl-2-butanol, (F) 3-methyl-2-butanol, (G) 3-pentanol, and (H) 2,2-dimethyl-1-propanol; to aid in visualization, the horizontal lines show the corresponding values for 1-pentanol.

expected to contribute to $\Delta_{\text{I}}C_p$.⁴⁰ In contrast, other approaches judged that this contribution must be considered.³⁶

The evaluation of the above-listed contributions can be simplified by making three assumptions, namely, (i) the hydroxyl–water and the hydroxyl–hydroxyl H-bonds are thermodynamically (enthalpy and entropy) identical, (ii) the

chain–chain and chain–hydroxyl interactions are the same irrespective of the chain being that of the G molecules or that of an inert (*n*-alkane) solvent, and (iii) the hydrophobic interior of the H cyclodextrin cavity behaves as an inert media. With these assumptions, the contributions to $\Delta_{\text{I}}C_p$ arising from processes (2) and (3) are equal, and on the other hand, those emerging from processes (4), (5), and (6) are the same. Using eqs 1 and 3–8 together with the corresponding contributions per methylene group in Table 3, the four main contributions to $\Delta_{\text{I}}C_p$ can be evaluated. The contributions from processes (7) and (2) = (3) are simply given by eqs 6 and 4, respectively. The contributions from processes (1) and (4) = (5) = (6) are given by (eq 1 + eq 4) and (eq 3 – eq 1 – eq 4), respectively. The values for these four contributions to the heat capacities are reported in Table 3. Note that with the exception of the contribution due to the expulsion of water molecules from the CD cavity, these contributions are independent of cyclodextrin concentration. Together with a contribution emerging from conformational changes or strain release of the cyclodextrin molecule upon complexation,^{17,41} the four contributions in Table 3 have been considered as those responsible for the formation of inclusion complexes.^{17,31} Although several attempts to evaluate some of these contributions have been reported,^{35,42} this is the first time that they have been estimated simultaneously from a given set of data.

The four contributions to cyclodextrin complexation in Table 3 allow a more detailed understanding of the transfer heat capacities. The order-formation transfers $\Delta_{\text{G,hyd}}C_p^\infty$ and $\Delta_{\text{G}}^{\text{G}+(H+W)}C_p^\infty$ are dominated by the hydration of the 1-alcohol hydrophobic chain, the contributions emerging from the formation of H-bonds (in $\Delta_{\text{G,hyd}}C_p^\infty$) and from the rupture of chain–chain contacts (in $\Delta_{\text{G}}^{\text{G}+(H+W)}C_p^\infty$) being marginal. The order created in these transfers is mainly due to induced water structuring

around the solute. According to the results in Table 3, the order-creation inclusion transfers $\Delta_G^{G+(H+W)}C_p^\infty$ and $\Delta_{G+I}^{G+(H+W)}C_p^\infty$ are governed by the release of water molecules from the interior of the α -CD cavity upon the inclusion of the 1-alcohol guest. On the other hand, the order-destruction transfers $\Delta_G^{G+I}C_p^\infty$, $\Delta_{G+W}^{G+I}C_p^\infty$, and $\Delta_{G+W}^{G+(H+W)}C_p^\infty$ have different origins. The $\Delta_G^{G+I}C_p^\infty$ transfer is exclusively determined by the rupture of H-bonds in the pure 1-alcohol,²² while the $\Delta_{G+W}^{G+I}C_p^\infty$ transfer is controlled by the dehydration of the alcohol hydrophobic chain. Finally, from Table 3, the $\Delta_{G+W}^{G+(H+W)}C_p^\infty$ inclusion transfer values are seen to be the result of a competition between the negative chain dehydration contribution that overshadows the positive contributions stemming from the formation of hydrophobic interactions between the interior of the CD and the 1-alcohol chain and from the release of water molecules from the CD cavity. In this context, note that the large negative values for the usual definition of the inclusion process, $\Delta_{\text{incl}}C_p^\infty$, in eq 9 are due to the significant contribution provided by the dissolution of the α -CD host (see footnote in Table 2).

The X-ray structures of many ligand–protein or protein–protein complexes indicate that water molecules are present in the interface formed by the components of the complex. These so-called structural water molecules are sequestered from bulk water and are effectively less mobile so that they become an integral part of the overall complex structure. The uptake of water molecules contributes significantly to the heat capacity change upon formation of complexes involving proteins.^{43–45} For this reason, the contribution to the heat capacity due to the transfer of water molecules from a hydrophobic environment to bulk water (or vice versa) in Table 3 is of relevance. In order to express this contribution per water molecule, it is necessary to consider the number of them present in the α -CD cavity (w_{cav}). The X-ray crystal structure indicates that $w_{\text{cav}} = 2$, these water molecules being located almost on the α -CD molecular axes.⁴⁶ From the estimated entropies for the inclusion reaction between α -CD and alcohols, it was concluded that $w_{\text{cav}} \leq 2$.⁴⁷ On the other hand, extensive molecular dynamics simulations showed that for α -CD in aqueous solution, w_{cav} fluctuates between 4 and 6, and that upon inclusion of the hydrocarbon tail of a nonionic carbohydrate surfactant, all of these water molecules are displaced toward the exterior of the cavity, that is, $w_{\text{cav}} = 0$ for the inclusion complex.⁴⁸ Considering that the hydrophobic tail of 1-hexanol occupies the whole α -CD cavity and that, for the systems studied here, the aqueous solution estimate for w_{cav} (equal to 5, on average) may be more realistic than that from the solid-state data, the heat capacity change due to the transfer of a single water molecule from bulk water to a hydrophobic environment is $-24.5(6/5) = -29.4 \text{ J K}^{-1} \text{ mol}^{-1}$. This value can also be considered a good estimate when the final state is a polar nonaqueous environment, as is often encountered in the section of the protein surface where the binding or complexation with a ligand or another protein occurs. The value obtained here is in good agreement with that obtained from the heat capacities of liquid water and ice ($-34.3 \text{ J K}^{-1} \text{ mol}^{-1}$) in ref 43, in reasonable agreement with that attained through the inhomogeneous fluid solvation theory applied to experimental data for two carbohydrate–protein complexes ($-41.8 \text{ J K}^{-1} \text{ mol}^{-1}$) in ref 49 but much smaller than that directly estimated from the same carbohydrate–protein data ($-71 \text{ J K}^{-1} \text{ mol}^{-1}$) in ref 50.

Conclusions

A detailed analysis of the formation host–guest complexes in water can be performed employing a series of experimentally

determined heat capacity changes for several transfer processes. The application of this scheme to the data for the inclusion complexes formed between α -CD and linear and branched alcohols allowed the evaluation of the four main contributions to the heat capacity of cyclodextrin complexation, namely, the dehydration of the hydrophobic section of the guest molecule, H-bond formation, the formation of hydrophobic interactions, and the release of water molecules from the cyclodextrin cavity. The reported experimental information and its analysis provide a better characterization of the molecular recognition process involved in the inclusion phenomena.

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Supporting Information Available: Apparent molar heat capacities of the α -cyclodextrin + water and alcohol + *n*-heptane binary solutions and molar heat capacities for the alcohol + α -cyclodextrin + water ternary mixtures. This material is available free of charge via the Internet at <http://pubs.acs.org>.

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