

The cavity elongation effect. Calorimetric studies of the complexes of long-chain carboxylic acids with methyl- α -cyclodextrin in aqueous solutions

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Abstract The formation of complexes between methyl- α -cyclodextrin (M α CD) and monocarboxylic acids from C₅ to C₁₂ or cycloalkanols has been studied calorimetrically at 298 K in aqueous phosphate buffer, pH 11.3. The forces involved in the association process are discussed according to the signs and values of the thermodynamic parameters obtained: association enthalpy, constant, Gibbs energy and entropy. Methyl- α -cyclodextrin forms 1:1 inclusion complexes with monocarboxylic acids, characterized by a monotonous increase in the values of enthalpies and association constants at increasing alkyl chain length. Association is characterized by negative enthalpies and by positive entropies: that determines large association constants. That behaviour is compared to the unusual trend in the values of the association constants shown by the parent α -cyclodextrin interacting with the same monocarboxylic acids. The model proposed to rationalize the present data provides a cavity elongation effect. Namely, because of the presence of the methyl groups on the outside, the cavity behaves as it were deeper than that of the parent cyclodextrin. The association with cycloalkanols—cyclohexanol, cycloheptanol, cyclooctanol and 1-cyclohexyl-ethanol—is characterized by lower entropies, as determined by the enhanced negative contribution originating from the tighter fit of the guest into the cavity.

Keywords Methyl- α -cyclodextrin · Monocarboxylic acids · Calorimetry · Inclusion complexes · Hydrophobic interactions

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Introduction

Natural cyclodextrins (CDs), cyclic oligomers of α -D-glucose, are characterized by a fairly polar exterior and by a cavity, which is non-polar as respect to the exterior and to the usual external aqueous environments. As they have a hydrophobic cavity of suitable dimension, CDs are able to form complexes with a great variety of organic substances either in solution or in the solid state [1–5]. Several non-covalent intermolecular forces determine the formation of the complexes: hydrophobic interactions, hydrogen bonds, van der Waals interactions, conformational energy, dipole–dipole and ion–dipole interactions [1, 6–9]. Another contribution originates, upon association, from the rearrangement of water molecules originally surrounding both cyclodextrin and guest molecule [10–12]. Understanding the relative role of these non-covalent interactions is of the utmost importance not only for the CD chemistry, but also for supramolecular chemistry as a whole. Inclusion alters the physicochemical properties of the included substances: often it enhances the aqueous solubility, stability and bioavailability of the complexed apolar drugs with serious problems of side effects [13–16]. In recent years, chemically modified CDs have been prepared with the aim of providing versatile carrier and delivery systems for drug molecules [6, 16]. The only obvious implication is that undesired biological effects (for example, hemolysis) of the employed CD derivative in solution should be eliminated or minimized.

Complexes of CDs are extensively described in the literature: however, it is still a matter of debate which of the afore-mentioned forces is mainly responsible for the overall Gibbs energy of association. In the last

years, we have been interested in the inclusion properties of native and chemically modified CDs towards a variety of organic substances [17–19]. The present work will examine the interaction between the chemically modified methyl- α -cyclodextrin (M α CD) and monocarboxylic acids from C₅ to C₁₂ in aqueous solution, pH 11.3, where they exist prevalingly as charged ions. The role of the methyl substitution on the α -cyclodextrin (α CD) will be analyzed together with the effect of the length of the alkyl chain of the guest in the formation of a complex. The data obtained will be compared with those relative to the association of the parent α CD with the same monocarboxylic acids, in the same experimental conditions [20]. The comparison will be useful to test the validity of the association model already proposed for the parent α CD/monocarboxylic acid interaction.

The association process will be followed through isothermal microcalorimetry at 298 K. Through that technique it is possible to detect the thermal effect and the association constant, and from that the Gibbs energy and the entropy of the process. Knowing the values and signs of the thermodynamic parameters obtained makes possible to suggest hypotheses about the forces involved in the interaction between CDs and the examined guest molecules. That is useful in designing new modified CDs having more suitable characteristics to include specific drugs.

Experimental

Materials

Methyl- α -cyclodextrin was purchased from Cyclolab: it is a cell culture tested product. Its mean substitution degree is reported to be 11 methyl groups/cyclodextrin molecule, as determined by NMR.

Monocarboxylic acids were purchased from Sigma or Aldrich: their purity is 98%–99% or more. All substances were used as received, without further purification. Aqueous solutions of known molalities were prepared by mass, using doubly distilled water. A 0.5 mol kg⁻¹ Na₂HPO₄–NaOH buffer was employed to prepare solutions at pH 11.3. The choice of this buffer is determined by the need to avoid anions interfering with the inclusion process. It is reported in the literature that phosphate and sulphate anions satisfy this requirement in the pH range 2–11 [21]. The initial concentration of carboxylic acids varied between 2.4 × 10⁻² mol kg⁻¹ and 5 × 10⁻⁴ mol kg⁻¹. The initial concentration of M α CD varied between 6.7 × 10⁻² and 1.9 × 10⁻² mol kg⁻¹.

Calorimetry

Measurements of the heats of mixing, ΔH_{mix} , of solutions of the cyclodextrin (titrant) with solutions of monocarboxylic acids (titrate) were made at 298.15 ± 0.03 K with a thermal activity monitor (TAM) from thermometric, equipped with a 3 mL titration vessel. Experimental details are described in preceding papers [17, 18].

Treatment of the data

Assuming that a 1:1 complex is formed when mixing two binary solutions, the standard molar enthalpy of association, ΔH_a^0 , and the apparent association constant, K_a' , are related to the actual molality of the cyclodextrin host molecule, m_{CD}^f , and to the enthalpy of interaction between two solutes, ΔH^* , as follows [22]:

$$\Delta H^*/m_L = (\Delta_a H^0 K_a' m_{\text{CD}}^f) / (1 + K_a' m_{\text{CD}}^f) \quad (1)$$

Equation 2 can be rewritten in a linear form, more useful for fitting the data:

$$m_L/\Delta H^* = 1/\Delta_a H^0 + 1/(\Delta_a H^0 K_a' m_{\text{CD}}^f) \quad (2)$$

where the actual concentration of the guest molecule is given by

$$m_L^f = m_L - [\Delta H^*/\Delta H^*(\text{sat})]m_{\text{CD}} \quad (3)$$

The standard enthalpy and the constant are obtained from Eqs. 2 and 3 by an iterative least square method, according to the procedure reported previously [17, 21]. In the absence of any information about the activity coefficients, only an apparent constant, K_a' , can be determined. Consequently, the standard Gibbs energy and entropy, $\Delta_a G^0$ and $\Delta_a S^0$, obtained through the usual thermodynamic relations, suffer the same limitations.

Results

With the aim of understanding the effect of the methyl substitution on the parent α CD, the thermodynamic association parameters were determined at 298 K for the complexation of M α CD with monocarboxylic acids from C₅ to C₁₂ in phosphate buffer, pH 11.3. The charged and uncharged forms of carboxylic acids behave very differently towards the interaction with a cyclodextrin [23]. Thus, using that pH ensures that carboxylate anions are predominant in solution.

Table 1 Thermodynamic parameters for the association between M α CD and carboxylic acids in phosphate buffer 0.5 mol kg⁻¹, pH 11.3, 298 K

Acid	K_a' (kg/mol)	$-\Delta H_a^{\circ(a)}$ (kJ/mol)	$-\Delta G_a^{\circ(a,b)}$ (kJ/mol)	$T\Delta S_a^{\circ(a,c)}$
Pentanoic			N.D. ^(d)	
Hexanoic	$(1.8 \pm 0.3)10^3$	5.4 ± 0.2	18.6 ± 0.5	13.2 ± 0.7
Heptanoic	$(1.07 \pm 0.05)10^3$	9.4 ± 0.1	17.3 ± 0.1	7.9 ± 0.2
Octanoic	$(2.7 \pm 0.6)10^3$	9.2 ± 0.3	19.6 ± 0.5	10.4 ± 0.8
Non-anoic	$(8.5 \pm 0.8)10^3$	15.2 ± 0.1	22.4 ± 0.3	7.2 ± 0.4
Decanoic	$(2.3 \pm 0.4)10^4$	17.5 ± 0.3	24.9 ± 0.5	7.4 ± 0.8
Undecanoic	$(7 \pm 1)10^4$	18.1 ± 0.1	27.7 ± 0.5	9.6 ± 0.6
Dodecanoic	$(1.3 \pm 0.2)10^5$	18.1 ± 0.1	29.1 ± 0.4	11.0 ± 0.5

^(a) Errors reported are the standard deviations as obtained by fitting the data to Eqs. 2 and 3

^(b) Errors are half the range of ΔG_a° calculated from the upper and lower error in K_a'

^(c) Errors are the sum of the errors on free energy and enthalpy

^(d) N.D. means that association heat is almost null, not detectable: the mixing enthalpy is similar to the dilution enthalpy

In Table 1, the thermodynamic parameters (association constant, enthalpy, free energy and entropy) are reported: higher-molecular-mass acids could not be studied because of their poor solubility in aqueous solution. For acids lower than hexanoic it was not possible to evaluate the binding constants and the standard enthalpies or because the least squares did not converge or because the values of those parameters are overwhelmed by their own errors. Stoichiometry was imposed to be 1:1. The values of the association constants increase at increasing alkyl chain length, reaching very high values for the longer terms. Enthalpies are negative: they increase regularly up to decanoic acid and then remain almost constant. The entropic contribution is positive: it varies in a limited range of values.

In Table 2, the literature values of the same thermodynamic parameters are reported for the association of the parent cyclodextrin, α CD, with the monocarboxylic acids from C₄ to C₁₂ [20]. The data were obtained in exactly the same experimental conditions presently employed, thus making possible the comparison between the two sets of data. The values reported in the table have been obtained imposing that association occurs with a simple 1:1 stoichiometry. While the enthalpies increase with increasing length of the alkyl chain, the association constants increase at first, then decrease beginning with C₉, and increase again at C₁₁. Entropy is positive up to C₈, and then becomes negative and very large for the longer terms of the series (for instance, for dodecanoic acid $T\Delta S = -81$ kJ mol⁻¹).

In Fig. 1, the thermodynamic parameters—enthalpies, association constants, Gibbs energies and entropies—are reported as a function of the number of carbon atoms, n_C , in the alkyl chain of the monocarboxylic acids for both α CD and M α CD.

In Table 3, the thermodynamic parameters are reported for some cycloalkanols interacting with M α CD: cyclohexanol, cycloheptanol, cyclooctanol and 1-cyclohexylethanol. Association constants are small, an indication that weak complexes are formed. Enthalpies are negative, while entropies are positive for all cycles but 1-cyclohexylethanol.

Discussion

From preceding studies carried out in this laboratory on the complexes formed by several alkylated substances with natural α CD, it was inferred that it is the

Table 2 Thermodynamic parameters for the association between α CD and carboxylic acids in phosphate buffer 0.5 mol kg⁻¹, pH 11.3, 298 K^(a)

Acid	K_a' (kg/mol)	$-\Delta H_a^{\circ(b)}$ (kJ/mol)	$-\Delta G_a^{\circ(b,c)}$	$T\Delta S_a^{\circ(b,d)}$
Butanoic	90 ± 10	0.71 ± 0.06	11.0 ± 0.4	10.3 ± 0.5
Pentanoic	$(1.45 \pm 0.07)10^2$	4.5 ± 0.1	12.3 ± 0.1	7.8 ± 0.2
Hexanoic	$(5.1 \pm 0.5)10^2$	6.1 ± 0.1	15.4 ± 0.3	9.3 ± 0.4
Heptanoic	$(1.2 \pm 0.7)10^3$	12.2 ± 0.1	17.6 ± 0.1	5.4 ± 0.2
Octanoic	$(1.3 \pm 0.1)10^3$	18.6 ± 0.1	17.9 ± 0.2	0.7 ± 0.3
Non-anoic	$(2.5 \pm 0.2)10^2$	38.9 ± 0.8	13.7 ± 0.2	-25 ± 1
Decanoic	$(2.53 \pm 0.06)10^2$	50.7 ± 0.3	13.7 ± 0.1	-37.0 ± 0.4
Undecanoic	$(8.4 \pm 0.2)10^2$	58.9 ± 0.2	16.7 ± 0.1	-42.2 ± 0.2
Dodecanoic	$(1.1 \pm 0.2)10^3$	98 ± 3	17.3 ± 0.4	-81 ± 3

^(a) All data reported are from Ref. 20

^(b) Errors reported are the standard deviations as obtained by fitting the data to Eqs. 2 and 3

^(c) Errors are half the range of ΔG_a° calculated from the upper and lower error in K_a'

^(d) Errors are the sum of the errors on free energy and enthalpy

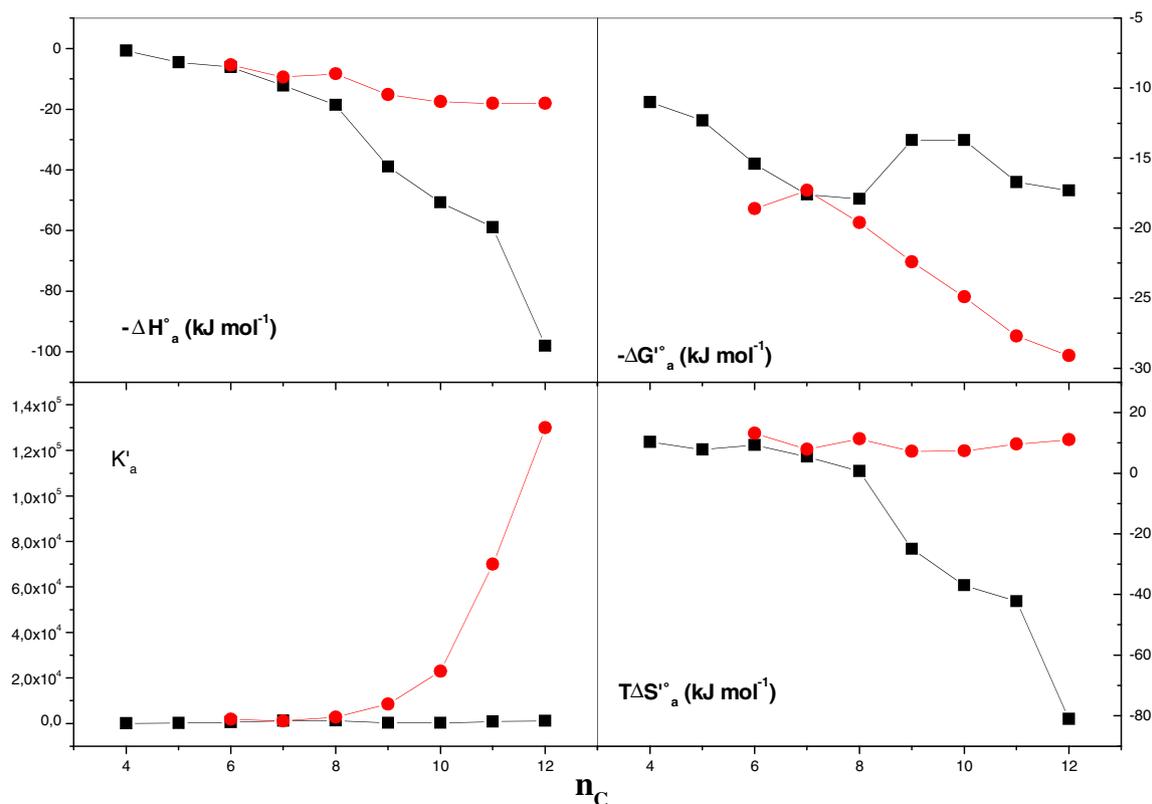


Fig. 1 Standard molar enthalpy of inclusion as a function of the number of carbon atoms, n_C , in the alkyl chain of carboxylic acids from C₄ to C₁₂ for α -CD (■) and for methyl- α CD (●)

alkyl chain which penetrates the cyclodextrin cavity, while the functional group forms hydrogen bonds with the external hydroxyl groups on the rim of the macrocycle cavity [24]. In general, the charged and hydrophilic functional groups of the guests, with the exception of the phenolic hydroxyl group, can be assumed to remain in the bulk solution before and after the association with the cyclodextrin. For what concerns the charged carboxylate group, the solvation requirements by water prevent the aliphatic chain from fully penetrating the cavity: the insertion of the charged carboxylate group of the guest into the cavity is probably energetically prohibitive [25].

The present data, relative to the interaction between M α CD and monocarboxylic acids as guests show that association occurs through the same mechanism. However, the presence of the external methyl groups causes the balance of the forces upon association to be different from that acting when the natural cyclodextrin, α CD, is involved. Association constants are very large: they increase passing from C₆ to C₁₂ terms (see Table 1). Enthalpies are negative: they increase up to undecanoic acid, probably for the enhanced van der Waals interactions of the increasingly longer alkyl chain with the cavity. Entropies are positive: upon inclusion, water molecules relax from an ordered

Table 3 Thermodynamic parameters for the association between M α CD and cycloalkanols in phosphate buffer 0.5 mol kg⁻¹, pH 11.3, 298 K

Cycloalkanol	K_a (kg/mol)	$-\Delta H_a^{\circ(a)}$ (kJ/mol)	$-\Delta G_a^{\circ(a,b)}$	$T\Delta S_a^{\circ(a,c)}$
Cyclohexanol	90 ± 10	8.3 ± 0.6	11.1 ± 0.3	2.8 ± 0.9
Cycloheptanol	(2.6 ± 0.2)10 ²	6.5 ± 0.1	13.8 ± 0.2	7.3 ± 0.3
Cyclooctanol	(1.8 ± 0.3)10 ²	10.2 ± 0.5	12.8 ± 0.4	3 ± 1
1-Cyclohexyl-ethanol	(1.8 ± 0.3)10 ²	15.2 ± 0.9	11.0 ± 0.2	-4.2 ± 0.9

(a) Errors reported are the standard deviations as obtained by fitting the data to Eqs. 2 and 3

(b) Errors are half the range of ΔG_a° calculated from the upper and lower error in K'_a

(c) Errors are the sum of the errors on free energy and enthalpy

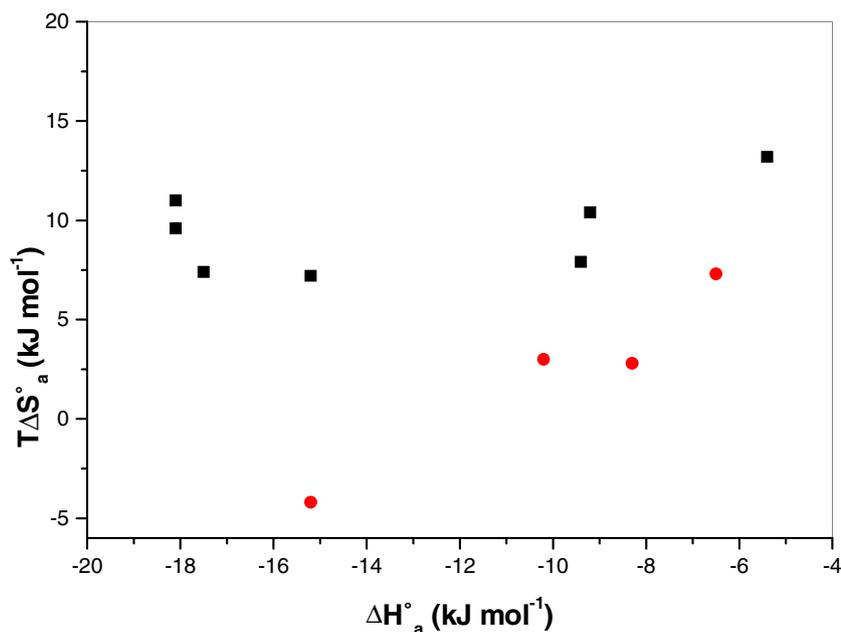
microenvironment, namely the cavity, and from the ordered hydrophobic hydration shells of the guests to a more disordered bulk. The negative enthalpies and the positive entropies concur in determining the large association constants. For M α CD/hexanoic acid complex, the association constant is higher than that for heptanoic acid, as determined by the largest entropic contribution found for this series of substances. The presence of the methyl groups on the exterior of the cavity makes this behaviour to be very different from that shown by monocarboxylic acids from C₃ to C₁₂ at pH 11.3 when interacting with the parent α CD [20]. In that case, complexation occurs with a much larger change in the enthalpy, while entropies pass from positive to largely negative starting with non-anoic acid (Table 2). Moreover, beyond 6 carbon atoms, free energy of association remains almost constant, while enthalpies keep increasing. Then, there must be a change in the interaction mechanism around $n_C = 6-7$. The hypothesis was that only one adduct forms for substances having an alkyl chain length up to about 6–7 CH₂ groups. For longer chains, a more complex model is necessary to get a better agreement between calculated and experimental data. For alkylated substances longer than C₆–C₇, experimental heats of association are better reproduced under the hypothesis that, because of the flexibility of the alkyl chain, two adducts form simultaneously having the included alkyl residue in a bent or in an extended form, whose concentration ratios depend on the alkyl chain length. For alkyl chains shorter than six or longer than nine carbon atoms, only one adduct is present, in an extended or bent form, respectively, while for intermediate alkyl chains, both adducts are present. The behaviour of alkanols in water resembles strictly that of monocarboxylic acids [26]. The analysis of the present data involving M α CD does not unravel any anomalous trend: the absence of any discontinuity in the values of the thermodynamic parameters means that the simple 1:1 model holds even for the longer terms. The whole thermodynamic frame leads to hypothesize that inclusion is ruled by a 1:1 stoichiometry, and only one type of adduct is present, the one having the alkyl chain in the extended form. As a fact, the plot in Fig. 1 indicates that Gibbs energy keeps increasing for $n_C = 12$. Then, methyl groups allow the cavity to behave as it were longer: that cavity elongation effect accounts for the formation of only one type of adduct, at least up to dodecanoic acid. Alkyl chains even longer than those required for the unsubstituted cyclodextrin would be needed for the formation of the adduct having a bent alkyl chain into the cavity. In that case, it would be possible to detect the jump in the

thermodynamic quantities, primarily enthalpies, that reflects the variation in the forces governing the association. Undecanoic and dodecanoic acids are characterized by the same values of the enthalpies, probably because the negative contribution due to the increased van der Waals interactions is balanced by the positive contribution originating from the dehydration of the more extended hydration shells of the guest molecule upon inclusion. For acids longer than C₆–C₇, a 2:1 association model, with two cyclodextrin molecules and one guest molecule, could account for the interaction with M α CD. However, that model must be rejected on the basis that only the uncharged form of the carboxyl group form 2:1 complexes [23, 27].

To verify that the formation of complexes having a bent alkyl chain accommodated in the M α CD cavity would be compatible with the cavity size, the interaction with some cycloalkanols, substances mimicking a bent alkyl chain, was studied in the same experimental conditions. Weak complexation occurs, as detected by the small values of the association constants, while association entropies are small and positive, or slightly negative as for cyclohexylethanol. For α CD interacting with octanoic to dodecanoic acids, the values [20] reported in Table 2 show that the entropic contributions pass from about zero to -81 kJ mol^{-1} . The bending of the alkyl chain inside the cavity makes entropies largely negative. Then, the large and positive inclusion entropies for M α CD interacting with monocarboxylic acids, evidences that, for the longer acids, the model providing the formation of two adducts does not describe the present association. In other words, M α CD behaves as a longer-cavity cyclodextrin, able to accept longer alkyl chains in their extended form. That cavity elongation effect, caused by the partial methylation of the external hydroxyl groups of the cyclodextrin with the formation of only one adduct, proves indirectly the validity of the model proposed for the parent α CD when interacting with the same monocarboxylic acids.

The formation of a complex between a cyclodextrin and a prevalingly hydrophobic guest molecule is a process ruled by the changes experienced by the solvent water upon association: dehydration of the guest molecule, desolvation of the cavity, formation of a hydration shell for the complex. For the methylated cyclodextrin, the positive entropies are an indication that hydrophobic interactions prevail. The relaxation of water molecules to the bulk, as a consequence of the interaction of the alkylated guest molecule with the hydrophobic exterior, is probably the effect that mostly determines the values of the association constants. The value of entropy is negative only for cyclohexylethanol: the alkyl chain allows the six-membered ring to

Fig. 2 Standard molar entropy of inclusion as a function of the ΔH_a° for carboxylic acid (■) and for cycloalkanols (●)



penetrate more deeply with a better adaptation to the cavity. For most complexes, a roughly linear trend is obtained when reporting ΔH° vs ΔS° [1–4, 28–30] or $T\Delta S^\circ$ vs ΔH° [30, 31]. These compensatory enthalpy–entropy relationships exist for all processes dominated by aquation phenomena due to the modifications of the solvent in the hydration cospheres of the interacting substances. In the $T\Delta S^\circ$ vs ΔH° plot, shown in Fig. 2, the lines roughly sketched through the data for cycloalkanols, and through the first four points for acids give $T\Delta S^\circ$, at $\Delta H^\circ = 0$, about 15 kJ mol^{-1} and about 16 kJ mol^{-1} , similar to the literature values for complexes formed by modified CDs. Thus, stabilization occurs even in the absence of enthalpic contributions, once more confirming that association is determined mainly by rearrangements of water molecules.

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