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Complexation forces in aqueous solution. Calorimetric studies of the association of 2-hydroxypropyl-β-cyclodextrin with monocarboxylic acids or cycloalkanols

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Abstract—The formation of complexes between 2-hydroxypropyl-β-cyclodextrin and monocarboxylic acids or cycloalkanols has been studied calorimetrically at 298 K in phosphate buffer, pH 11.3. The forces involved in the association process are discussed in the light of the signs and values of the thermodynamic parameters obtained: association enthalpy, binding constant, Gibbs free energy, and entropy.
From this study it was inferred that (i) for monocarboxylic acids, hydrophobic interactions are the primary force determining complexation, as indicated by the small enthalpies and by the high and positive entropies. For the cycloalkanols, instead, enthalpies are negative and entropies positive or negative, depending on the solvent medium employed, namely water or phosphate buffer; (ii) the most important requirement for the formation of the complex is a good spatial fit between the two interacting molecules. A cavity elongation effect occurs because of the presence of the hydroxypropyl groups on the rim of the macrocycle. The relative contribution of hydrophobic and van der Waals interactions varies with the dimensions of the guest molecules; (iii) a linear correlation exists between enthalpy and entropy of complexation, underlying that inclusion is a process dominated by hydration phenomena and ascribed to the modifications experienced by the solvent in the hydration shells of the interacting substances.

1. Introduction

Natural cyclodextrins (CDs), cyclic oligomers of α-D-glucose, are the most suitable host molecules for the recognition in aqueous media of hydrophobic guest molecules. They are characterized by a fairly polar exterior and by a cavity, which is nonpolar relative to the exterior and to the usual external aqueous environment. CDs are able to form complexes with a great variety of organic substances either in solution or in the solid state.[1–5] Complexation is determined by a series of noncovalent intermolecular forces: hydrophobic interactions, hydrogen bonds, van der Waals interactions, conformational energy, dipole–dipole and ion–dipole interactions.[1,6–9] In addition, another important effect determines inclusion: the rearrangement of water molecules originally surrounding both cyclodextrin and guest molecule.[10–12]

Complexation alters the physicochemical properties of the included substances: for instance, the aqueous solubility, stability, and bioavailability of apolar drugs are enhanced.[13–16] To modify the inclusion capacity, and to improve the physicochemical properties of the natural macrocycles as drug carriers,[6,16] cyclodextrin derivatives have been prepared. The only obvious implication is that undesired biological effects (for example, hemolysis) of the employed CD derivative in solution should be eliminated or minimized.

Notwithstanding the extensive studies about the complexes of cyclodextrins, it is still a matter of debate which of the afore-mentioned contributions is responsible for the overall free energy of association. We have already reported on the smallest cyclodextrin, αCD, and its methylated derivative interacting with various hydroxyalkylated substances.[10,17–21] in water and in mixed solvents. The thermodynamics of the interaction of parent or modified βCD with aromatic amino acids,[22] alkanols,[23] acids,[24] or substances of pharmacological interest[25] under different experimental conditions were also studied. The present contribution is aimed to further explore the factors determining the formation of the complexes by studying the interaction between 2-hydroxypropyl-β-cyclodextrin (HPβCD) and monocarboxylic acids or cycloalkanols in aqueous solution. The association process was followed through isothermal microcalorimetry at 298 K, in phosphate buffer 0.5 mol kg^{-1}, pH 11.3. Under these conditions, the acids exist predominantly as

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carboxylate anions. The role of the hydroxypropyl substitution on the cyclodextrin will be analyzed through the comparison of the data obtained with those for the association of the parent β-cyclodextrin (βCD) with the same monocarboxylic acids employed here.[24] Beyond that, the correlation between the complexation ability of the modified cyclodextrin and its degree of substitution (DS) will also be investigated. Knowledge of the values and signs of the thermodynamic parameters obtained—association enthalpy, binding constant, Gibbs energy, and entropy makes it possible to propose hypotheses about the forces involved in the interaction between CDs and the examined guest molecules. That is the basis for designing new modified cyclodextrins with more suitable characteristics for the inclusion of specific drugs.

2. Results

With the aim of understanding the effect of the hydroxypropyl substitution on the parent β-cyclodextrin, the thermodynamic association parameters were determined at 298 K in phosphate buffer 0.5 mol kg^{-1}, pH 11.3, for the complexation of HPβCD with monocarboxylic acids from C_5 to C_{12}. The charged and uncharged forms of monocarboxylic acids behave very differently toward the interaction with a cyclodextrin.[16,28] Using that pH value ensures that carboxylate anions predominate in solution. Concentrations of the acids have been chosen such that they are well below their critical micelle concentrations.

In the tables, the notation ND (not detectable) will be used to indicate that association was not detectable, either because the heat of association is very small or because the solubility of the interacting substances is so small that the corresponding thermal effect cannot be detected. In Table 1, the thermodynamic parameters (association constant, enthalpy, free energy, and entropy) are reported for the interaction of HPβCD (DS=6.3) with monocarboxylic acids from C_5 to C_{12}. Enthalpies, positive and small, increase up to heptanoic acid and then decrease remaining almost constant: they show a very small variability on increasing alkyl chain length. Association constants behave similarly, remaining almost the same with increasing dimensions of the guest molecule. Since the enthalpic contribution is positive, hence unfavorable to the inclusion, the process is mainly driven by the positive and large entropic contribution.

In Table 1, the thermodynamic parameters are also reported for the interaction between HPβCD (DS=3) and heptanoic, nonanoic, undecanoic, and dodecanoic acids. Heats of interaction were only detected for the lower acids. The association constants are higher for the smaller positive enthalpic contribution. The overall thermodynamic framework appears to be the same as for HPβCD with a higher substitution degree (DS=6.3).

In Table 2, the literature data are shown for the parent βCD interacting with the same acids in the same experimental conditions.[24] The enthalpies vary from small and positive to large and negative, passing from hexanoic to octanoic acid where it is not possible to determine a heat of interaction. On the other hand, entropies change their sign passing from positive to negative (dodecanoic acid). A jump occurs in the values of enthalpy and entropy between decanoic and undecanoic acids. Association constants for the higher molecular mass acids (decanoic to dodecanoic) have an irregular trend, and in general, they are higher than those for HPβCD as determined by the large and negative enthalpies. In Figure 1, enthalpies and entropies are reported for the formation of complexes between HPβCD or βCD and the carboxylic acids employed.

Table 3 reports the thermodynamic data for the interaction between HPβCD (DS=6.3) and cyclohexanol, cycloheptanol, 1-cyclohexylethanol, 3-cyclohexyl-1-propanol, and 4-cyclohexylbutanol in phosphate buffer, pH 11.3, and in water. Association constants are higher in buffer than in water, with enthalpies being negative in both solvents, larger in water. Inclusion differs mainly based on the entropic

Table 1. Thermodynamic parameters for the association between hydroxypropyl-β-cyclodextrin, DS=6.3 or 3, and monocarboxylic acids in phosphate buffer 0.5 mol kg^{-1}, pH 11.3, at 298 K

Acid	K_a'[a,b]	ΔH_a^0[b,c]	$-\Delta G_a^{0\prime}$[c,d]	$T\Delta S_a^{0\prime}$[c,e]
HPβCD (DS=6.3)				
Pentanoic	$(1.5\pm0.5)10^2$	2.0±0.5	12.4±0.8	14.0±1
Hexanoic	$(1.2\pm0.1)10^2$	4.4±0.4	12.0±0.3	16.4±0.7
Heptanoic	$(3.0\pm0.3)10^2$	6.8±0.4	14.1±0.2	20.9±0.6
Octanoic	$(2.9\pm0.2)10^2$	4.9±0.2	14.0±0.2	18.9±0.4
Nonanoic	$(3.4\pm0.4)10^2$	3.4±0.2	16.5±0.2	20.3±0.3
Decanoic	$(2.9\pm0.4)10^2$	4.2±0.4	14.0±0.3	18.2±0.7
Undecanoic	$(3.2\pm0.8)10^2$	3.7±0.4	14.3±0.6	18±1
Dodecanoic		ND[f]		
HPβCD (DS=3)				
Heptanoic	$(4.1\pm0.4)10^2$	5.2±0.2	14.9±0.2	20.1±0.4
Nonanoic	$(4.7\pm0.7)10^2$	3.1±0.1	15.2±0.1	18.3±0.2
Undecanoic		ND[e]		
Dodecanoic		ND[e]		

[a] kg/mol.
[b] Errors reported are the standard deviations as obtained by fitting the data to Eqs. 2 and 3.
[c] kJ/mol.
[d] Errors are half the range of $\Delta G_a^{0\prime}$ calculated from the upper and lower errors in K'_a.
[e] Errors are the sum of the errors on free energy and enthalpy.
[f] ND means that heat was very near to zero, hence, it was not detectable.

Table 2. Thermodynamic parameters[a] for the association between β-cyclodextrin and monocarboxylic acids, in phosphate buffer 0.5 mol kg^{-1}, pH 11.3, at 298 K

Acid	K_a'[b,c]	ΔH_a^0[c,d]	$-\Delta G_a^{0\prime}$[d,e]	$T\Delta S_a^{0\prime}$[d,f]
Pentanoic	(3.1±0.7)10	1.9±0.2	8.5±0.6	10.4±0.8
Hexanoic		ND[g]		
Heptanoic		ND[g]		
Octanoic		ND[g]		
Nonanoic	$(2.6\pm0.6)10^2$	−0.75±0.08	13.7±0.6	13.0±0.7
Decanoic	$(1.9\pm0.1)10^3$	−2.5±0.1	18.6±0.2	16.1±0.3
Undecanoic	$(5\pm1)10^2$	−13±2	15.1±0.7	2±3
Dodecanoic	$(2.4\pm0.5)10^3$	−21.1±0.6	19.3±0.5	−2±1

[a] All data in the table are from Ref. 24.
[b] kg/mol.
[c] Errors reported are the standard deviations as obtained by fitting the data to Eqs. 2 and 3.
[d] kJ/mol.
[e] Errors are half the range of $\Delta G_a^{0\prime}$ calculated from the upper and lower errors in K_a'.
[f] Errors are the sum of the errors on free energy and enthalpy.
[g] ND means that association heat is almost null, not detectable: the mixing enthalpy is similar to the dilution enthalpy.

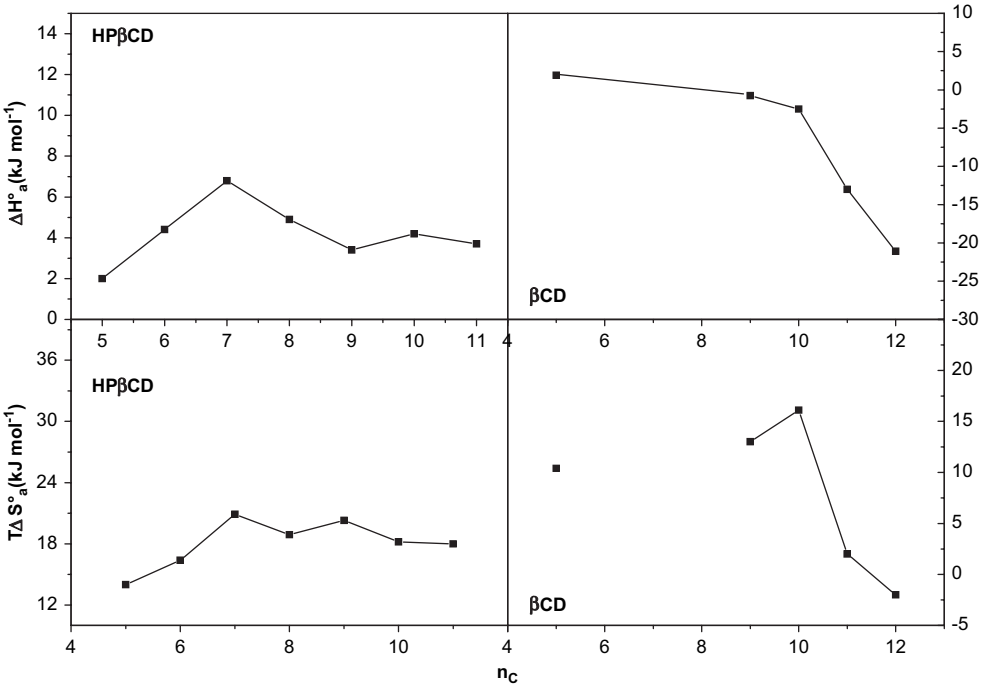

Figure 1. Enthalpies and entropies as a function of the number of carbon atoms, n_C, in the alkyl chain of the monocarboxylic acids for the formation of complexes with HPβCD (left) and βCD (right).

Table 3. Thermodynamic parameters for the association between hydroxypropyl-β-cyclodextrin and some cycloalkanols in phosphate buffer 0.5 mol kg^{-1}, pH 11.3, and in water pH 6.0

Cycloalkanol	K_a'[a,b]	ΔH_a^0[b,c]	$-\Delta G_a^{0\prime}$[c,d]	$T\Delta S_a^{0\prime}$[c,e]
Buffer phosphate				
Cyclohexanol	(4±3)10	−7±5	9±3	3±8
Cycloheptanol	(1.3±0.3)10^3	−3.0±0.1	17.8±0.6	14.8±0.7
1-Cyclohexylethanol	(1.5±0.4)10^3	−2.7±0.2	18.2±0.6	15.5±0.8
3-Cyclohexyl-1-propanol	(2.6±0.8)10^3	−4.2±0.2	19.4±0.8	15±1
4-Cyclohexyl-1-butanol	(2.0±0.4)10^4	−5.0±0.1	24.5±0.5	19.5±0.6
Water				
Cyclohexanol	(4±0.6)10	−16±2	9.1±0.1	−7±2
Cycloheptanol	(8±2)10	−13±2	10.9±0.6	−2±3
1-Cyclohexylethanol	(3.7±0.9)10	−19±4	8.9±0.6	−10±5
4-Cyclohexyl-1-butanol	(1.3±0.4)10^2	−18±2	12.1±0.8	−6±3

[a] kg/mol.
[b] Errors reported are the standard deviations as obtained by fitting the data to Eqs. 2 and 3.
[c] kJ/mol.
[d] Errors are half the range of $\Delta G_a^{0\prime}$ calculated from the upper and lower errors in K_a'.
[e] Errors are the sum of the errors on free energy and enthalpy.

contributions that are positive in buffer, increasing with increasing alkyl chain, and negative in water varying with a rather irregular trend. In Figure 2, the association parameters are reported for the cyclohexylalkanols as a function of the number of carbon atoms in the alkyl chain bound to the cyclohexyl group.

3. Discussion

According to the commonly accepted view, complexation of a cyclodextrin with an alkylated guest molecule occurs through the inclusion of the alkyl chain into the prevailingly hydrophobic cavity. The functional group forms hydrogen bonds with the external hydroxyl groups on the rim of the macrocycle cavity, acting as a hook, which prevents the further penetration of the alkyl chain.[17,18] The present data for the interaction between 2-hydroxypropyl-β-cyclodextrin and monocarboxylic acids show that association occurs through the same mechanism, namely the inclusion of the alkyl chain into the cavity. A 1:1 stoichiometry describes these complexes, and the formation of 2:1 complexes can be excluded. Preceding studies have, in fact, shown that the charged carboxyl group does not include, and that only the uncharged one can reside in the cavity.[17,28] However, the chemical modifications in the structure of the HPβCD macrocycle cause the forces determining the association process to be different from those acting when the natural βCD is involved.

The cyclodextrins employed have, on average, 6.3 or 3 hydroxyl groups substituted by hydroxypropyl groups per molecule of cyclodextrin. This makes the exterior of HPβCD more hydrophobic with respect to the parent β-cyclodextrin. The complexes formed with monocarboxylic acids are characterized by small association constants, probably because the association occurs through the interaction between the hydrophobic hydration shells of the alkyl chain of the guest and the hydrated external hydroxypropyl groups of the host. The relaxation to the bulk of the water molecules from these hydrated interacting groups upon inclusion determines the positive and large entropic contribution. That effect appears to be predominant, owing to the entropy invariance with increasing alkyl chain length. Enthalpies are positive and become larger with increasing length of the guest, reaching the largest value for heptanoic acid (6.8 kJ mol^{-1}). After that, they remain almost constant. The association process involving HPβCD is therefore mainly driven by the positive and large entropies, with the enthalpic contribution being

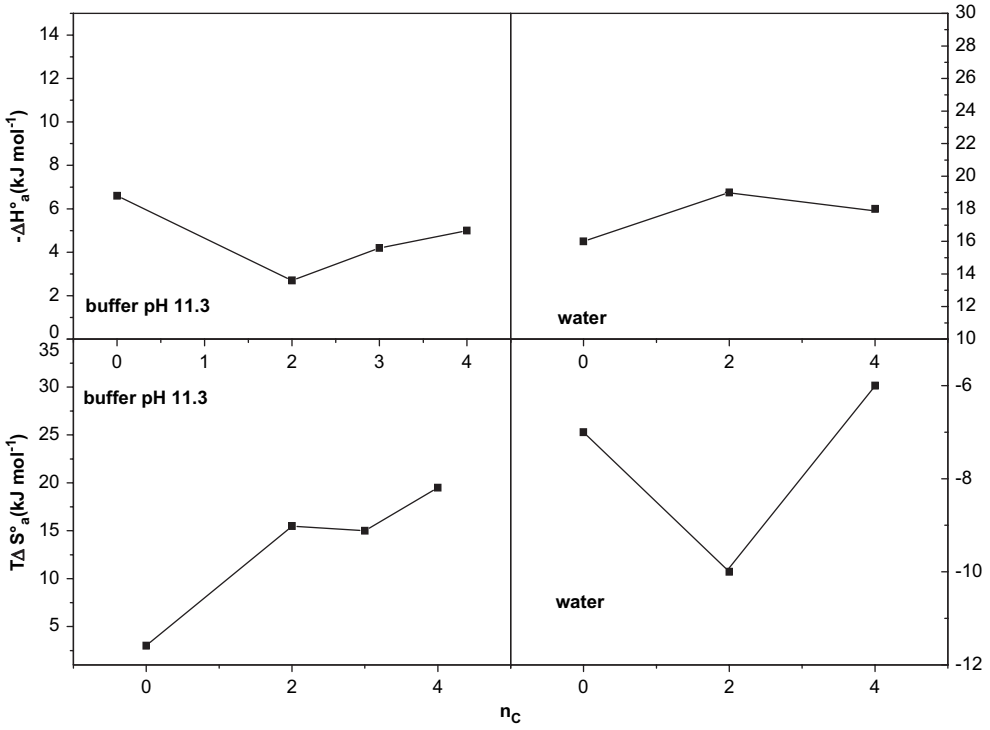

Figure 2. Enthalpies and entropies for the association of HPβCD with cyclohexanol, 1-cyclohexylethanol, 3-cyclohexyl-1-propanol, 4-cyclohexyl-1-butanol as a function of the number of carbon atoms, n_C, in the alkyl chain bound to the cyclohexyl group, in buffer (left) and in water (right). For cyclohexanol, n_C=0.

unfavorable to the complex formation. The value of enthalpy is determined by several effects, among them are the disruption of hydrogen bonds between water molecules in the cavity, the dehydration of the included hydrophobic guest molecule, and the adaptation of the guest molecule to the cyclodextrin cavity. The first two effects are endothermic, while the third one is exothermic. The cavity diameter of the modified cyclodextrin can safely be thought to be similar to that of the unmodified one, approximately 6.2 Å.[1] That means a loose adaptation of an alkyl chain upon the formation of the complex, with the consequent small negative contribution from van der Waals interactions and hydrogen bonds. That effect is even smaller for the lower-molecular-mass acids, the action of which would be confined mainly to the interaction with the hydrophobic exterior.

As pointed out before, the thermodynamic parameters for the inclusion process are determined mainly by the release of water molecules, either from the hydration shells of the interacting substances, or from the interior of the cavity. However, the thermodynamic framework describing the present data is remarkably different from that for the natural β-cyclodextrin (see Table 2),[24] a consequence of the substitution of hydroxyl groups with hydroxypropyl groups. The parent βCD forms 1:1 inclusion complexes characterized by an irregular variation of enthalpies, entropies, and association constants with increasing alkyl chain length. Association enthalpies are small and positive or even null. They change to negative beginning with nonanoic acid, with a sudden increase in absolute value passing from decanoic to undecanoic acids. Entropies vary from largely positive to slightly negative with a jump between the same two acids, an indication that van der Waals interactions are enhanced with the increasing size of the guests. The entropies, then, follow the increasingly better adaptation of the alkyl chain to the cavity, a process lowering the degrees of freedom. It can be hypothesized that, because of the flexibility of the alkyl chain, two adducts form simultaneously, bearing the included alkyl residue in a bent or in an extended form, the concentrations of which depend on the alkyl chain length. For alkyl chains shorter than 10 or longer than 11 carbon atoms, only one adduct would be present, in the extended or bent form, respectively, while for intermediate alkyl chains both adducts would form. The same model holds for α-cyclodextrin interacting with the charged form of monocarboxylic acids.[29] In that case, for alkyl chains shorter than 8 or longer than 10 carbon atoms, only one adduct is present, having the included chain in the extended or bent form, respectively. The absence of any jump in the values of the thermodynamic parameters characterizing the present data, relative to the hydroxypropylated cyclodextrin, indicates that only one type of complex forms, namely the one having the extended alkyl chain included into the cavity. Therefore, we propose that the hydroxypropyl substitution makes the cavity behave as if it were deeper than that of the parent cyclodextrin. This cavity elongation effect does not allow the alkyl chain to include fully, and most of the interaction would occur between the external hydroxypropyl groups and the alkyl chain of the acid. The limited variability of both enthalpies and entropies originates from that effect: even longer alkyl chains would be needed to detect significant variations, such as those occurring for natural cyclodextrins. For phenolphthalein interacting with HPβCD, literature reports that association constants increase with decreasing substitution degree, and attributes that to the attenuated steric hindrance.[30,31] The present data show a similar behavior. In fact, on passing from DS=6.3 to DS=3, association constants increase while enthalpies and entropies

become less positive. However, the differences between the two series of data are small, probably because, in both cases, the overwhelming effect is the relaxation to the bulk of water molecules from the hydrophobic hydrated shells of the alkyl chain of the guest and the external hydroxypropyl groups of the host.

Association between HPβCD and cycloalkanols differs markedly from that involving substances bearing linear alkyl chains. Cycloalkanols can only include through the cycle, since hydroxyl groups cannot reside in the cavity. The values of the thermodynamic parameters are affected by the different solvent media (phosphate buffer and water). Enthalpies are negative in both solvents, an indication of the prevalence of van der Waals forces: they are smaller in buffer, possibly because the increased dielectric constant of the medium attenuates hydrophilic interactions between the external hydroxyl groups of cyclodextrin and the guest molecule. In buffer, entropies are positive and large, making the association constants an order of magnitude higher than those for monocarboxylic acids. The large entropic contribution could be due to the chaotropic[19] action on water structure of the phosphate ions, which behave phenomenologically as urea.[24,32] Upon inclusion, water molecules are released from the hydrophobic hydration shells to a bulk which is more disordered than pure water. In water, instead, the association process is characterized by small and negative entropies (Table 3). Then, the positive entropic contribution originating from the release of water molecules from the hydrophobic hydration shells to the bulk is overwhelmed by the negative contribution due to the loss of degrees of freedom occurring upon association. This makes the value of the association constants small, notwithstanding the large and negative enthalpic contribution.

4. Conclusion

The changes experienced by the solvent water molecules on association control the formation of a complex between cyclodextrins and hydrophobic guest molecules. Dehydration of the guest molecule, desolvation of the cavity, and formation of a hydration shell for the complex are the most important processes common to all cyclodextrins. For 2-hydroxypropyl-β-cyclodextrin, an additional effect controls the values of the thermodynamic parameters: the relaxation of water molecules to the bulk, as a consequence of the interaction between the hydration shells of the guest molecule and the hydroxypropyl groups of the macrocycle. As for other alkyl-substituted β-cyclodextrins, that leads to large and positive entropic terms, and the overall inclusion process is therefore governed prevailingly by hydrophobic interactions.

For all processes dominated by hydration phenomena, compensatory enthalpy–entropy relationships exist.[1–4,17,33–35] In Figure 3 a $T\Delta S^{0\prime}$ versus ΔH^{0}[35,36] plot reports the data for all systems studied, including those for the parent βCD. Notwithstanding the limited number of data and their scattering, a roughly linear trend can be recognized that describes the changes in the forces governing the inclusion process. Enthalpies and entropies, both being negative, characterize systems where van der Waals interactions are dominant

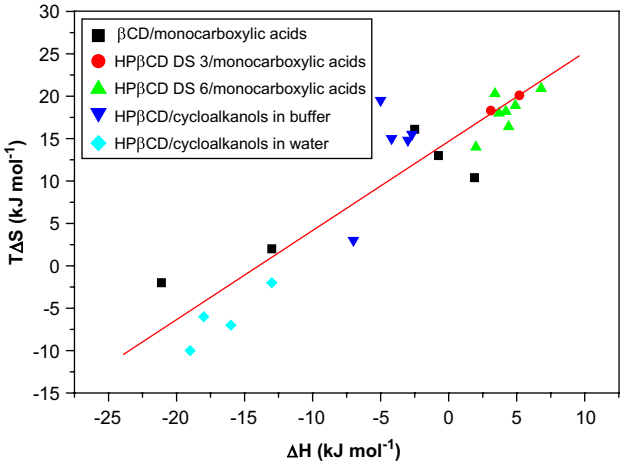

Figure 3. Entropy–enthalpy compensation plot for the formation of the complexes formed by β-cyclodextrin or 2-hydroxypropyl-β-cyclodextrin with monocarboxylic acids or cycloalkanols.

due to the tight fit of the included molecule to the cavity. This is the case for the association between βCD and long-chain acids, or between HPβCD and cycloalkanols in water. Negative, but smaller enthalpies and positive entropies describe systems where the release of water molecules to a more disordered bulk prevails or the fit of the included molecule to the cavity is loose. Cycloalkanols associating with HPβCD in phosphate buffer or βCD interacting with the lower acids (pentanoic to decanoic acids) are examples of this. The systems characterized by positive enthalpies and entropies, such as HPβCD interacting with monocarboxylic acids, are those dominated by classical hydrophobic interactions. If a line is forced to pass through all points (correlation coefficient=0.92), the $T\Delta S^{0\prime}$, at ΔH^{0}=0, and slope are 14.7±0.9 kJ mol^{-1} and 1.1±0.1, respectively, values not far from those reported in the literature for complexes formed by modified cyclodextrins with flexible sidearms.[1] The positive and large intercept suggests a stabilization of the complex even in the absence of enthalpic contributions, a confirmation that the association process is governed mainly by the changes experienced by water in the hydration shells of the interacting solutes.

5. Experimental

5.1. Materials

The two 2-hydroxypropyl-β-cyclodextrins (HPβCD) employed were purchased from Cyclolab. The average degrees of substitution (DS) are 6.3 and 3 hydroxypropyl groups per molecule, as determined by NMR. The purity is higher than 97%. Monocarboxylic acids from pentanoic to dodecanoic and cycloalkanols employed as guest molecules were purchased from Sigma and Aldrich. Solutions of known molalities were prepared by mass, using doubly distilled water. A 0.5 mol kg^{-1} Na_2HPO_4–NaOH buffer was employed to prepare solutions at pH 11.3. The choice of this buffer was determined by the need to avoid anions capable of interfering with the inclusion process. It is reported in the literature that phosphate and sulfate anions satisfy this requirement in the pH range 2–11.[26] The initial

concentration of carboxylic acids varied between 2.4×10^{-2} and 5×10^{-4} mol kg^{-1}. The initial concentration of HPβCD varied between 6.7×10^{-2} and 1.9×10^{-2} mol kg^{-1}.

5.2. 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.[24,25]

5.3. 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 formation of a complex, or in general the enthalpy of interaction between solutes, ΔH^*, as follows:[27]

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

ΔH^* is normalized to the total molality of the guest, m_L. Eq. 1 can be rewritten in a linear form, more useful for fitting the data:

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

where the actual concentration of the guest molecule is given by:

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

The standard enthalpy and the association constant are obtained from Eqs. 2 and 3 by an iterative least square method, according to the procedure reported previously.[24,25] 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, $\Delta G_a^{0\prime}$ and $\Delta S_a^{0\prime}$, obtained through the usual thermodynamic relations, suffer the same limitations.

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