Study of the Effects of Cosolvents on the Complexation of β-Cyclodextrin with Alkanols by Calorimetry at 298 K

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Abstract

The formation of complexes between β-cyclodextrin and 1-alkanols has been studied calorimetrically at 298 K in water and in concentrated aqueous solutions of ethanol or urea. When a complex is formed, calorimetry enables the calculation of both the enthalpy and the association constant, from which the free energy and the entropy of the process can be obtained. The effects of ethanol and urea on the hydration cospheres of the interacting substances have been investigated through the study of the binary solutions of the involved solutes in water and in the mixed solvents. The findings obtained are, then, related to the consequent changes in the association parameters. The forces involved in the association process are discussed in the light of the signs and values of the thermodynamic parameters obtained. The most important features coming out from this study are: (i) association in water is an entropy-driven process; (ii) in concentrated aqueous solutions of cosolvent, the enthalpic term contributes significantly to the Gibbs energy, while the entropic contribution is smaller; (iii) for every solvent medium employed, the invariance of the entropic contribution with increasing alkyl chain length of the alkanol is an indication that the relaxation of water molecules from the cavity of the macrocycle mainly determines the association process.

Introduction

The host–guest chemistry of inclusion complexes of cyclodextrins has been thoroughly studied [1–5], especially in relation to a number of biological mechanisms based on molecular recognition processes. Complexation processes result from the contribution of a series of noncovalent intermolecular forces: hydrophobic interactions, hydrogen bonds, van der Waals interactions, conformational energy, dipole–dipole and ion–dipole interactions [6–8]. Moreover, it is well known that inclusion leads to a substantial rearrangement of water molecules originally solvating both cyclodextrin and the guest molecule [9–11]. Cyclodextrins (CDs), the most suitable host molecules for the recognition in aqueous media of hydrophobic guest molecules, are cyclic oligomers of α-D-glucose. 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 environments. The most important property of CDs is their ability to form complexes with a great variety of organic substances either in solution or in the solid state [1–6]. Because of that, they are widely used for the enhancement of the aqueous solubility, stability and bioavailability of apolar drugs with serious problems of side effects [12, 13].

Despite the great number of papers dealing with the complexes of cyclodextrins, only a few hypotheses have been proposed concerning which of the afore-mentioned contributions is responsible for the overall free energy of association. In preceding papers, we have mainly reported on the smallest of the cyclodextrins, α-CD, having six glucose units, and its interaction with hydroxylated substances [9, 14–16], monocarboxylic acids [14, 15, 17], α,ω-dicarboxylic acids [18], aminoacids [19–21], and cycloalkanols [22] in water and/or in aqueous phosphate buffer, pH 11.3 and pH 1.3. The thermodynamics of the interaction of β-CD with aromatic amino acids was also studied [20]. Our present contribution continues the program aimed at understanding the factors determining the formation of the complexes between cyclodextrins and alkylated substances in aqueous solution. The role of a cosolvent and of the length of the alkyl chains in the complex formation will be analyzed through a calorimetric study at 298 K of the interaction of β-CD with 1-alkanols from C_5 to C_9 in water, in concentrated aqueous ethanol and in concentrated aqueous urea. These two substances have different effects on water structure: ethanol is a prevailingly hydrophobic structure maker, while urea is a well known chaotropic agent. Here, we shall analyze how the modifications induced in the structure of water by the two cosolvents alter the thermodynamic parameters characterizing the association process. Beyond the detection

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of the thermal effect, calorimetry shows whether association occurs and allows the evaluation of its equilibrium constant, from which the free energy and entropy of the process can be derived. Knowing the values and signs of the thermodynamic parameters, it is possible to propose hypotheses about the forces involved in the interaction between CD and the examined guest molecules.

Experimental

Materials

β-Cyclodextrin and the alkanols employed as guest molecules were purchased from Sigma and Aldrich. The optical rotation of β-CD was in agreement with that reported in the literature. Solutions were prepared by weight using doubly distilled water.

Calorimetry

Measurements of the heats of dilution and mixing were carried out using a Thermal Activity Monitor (TAM) from Thermometric, equipped with a GP 10 gradient programmer, a 500 μL mixing chamber, a PSV 50 electrovalve and a P3 peristaltic pump (all from Pharmacia) for the automatic preparation and for the pumping of solutions into the cells of the calorimeter. The following two kinds of experiments were arranged.

 (i) The determination of the heat of dilution from the initial (m^i) to the final (m^f) molality, $\Delta H_{dil}(m^i \rightarrow m^f)$, of binary aqueous solutions of β-CD and of the alkanols employed, in the various experimental conditions.

 (ii) The determination of the heat of mixing, ΔH_{mix}, of two binary aqueous solutions of the cyclodextrin and of an alkanol.

The values of the experimental heats (of dilution or of mixing) were obtained from

$$\Delta H = (dQ/dt)/P_w,$$

where (dQ/dt) is the heat flux and P_w is the total mass flow rate of solvent through the calorimeter. More details of the calorimetric experiments are reported in the literature [9].

Treatment of the data

The values of the experimental heats of dilution can be used to fit the following power-law expansion [23–25]:

$$\Delta H_{dil}(m^i \rightarrow m^f) = h_{xx}m^f(m^f - m^i) \\ + h_{xxx}m^f(m^{f2} - m^{i2}) + \cdots, \quad (1)$$

where ΔH_{dil} (J kg^{-1}) is the heat of dilution of a solute from the initial (m^i) to the final molality (m^f). The enthalpic interaction coefficients, h, appearing in Equation (1) are used to determine the contributions to the total enthalpy changes originating from the dilution of each of the solutes during the mixing process.

Assuming that a 1:1 complex is formed when mixing two binary solutions, the association process can be represented as follows:

$$\beta\text{-CD} + L = \beta\text{-CD} \cdot L,$$
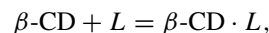
where L indicates the guest molecule. The enthalpy of formation of a complex, or in general the enthalpy of interaction between solutes, ΔH^*, is related to the heat of mixing two binary solutions, ΔH_{mix}, and to the heats of dilution experienced by the two solutes, ΔH_{dil}, as follows:

$$\Delta H^* = \Delta H_{mix}\{[(m_x^i)(m_y^i)] \\ \rightarrow (m_x^f, m_y^f)\} - \Delta H_{dil}(m_x^i \rightarrow m_x^f) \\ - \Delta H_{dil}(m_y^i \rightarrow m_y^f), \quad (2)$$

where m_x^i, m_y^i, m_x^f, and m_y^f are the initial and final molalities of the x and y solutes. ΔH^*, normalized to the total molality of the dextrin, m_{CD}, is a linear function of the actual molality of the guest molecule, m_L^f, of the standard molar enthalpy of association, ΔH_a^0, and of the apparent association constant, K_a', as follows [26]:

$$m_{CD}/\Delta H^* = 1/\Delta H_a^0 + 1/(\Delta H_a^0 K_a' m_L^f). \quad (3)$$

For each value of ΔH^*, the actual concentration of the guest molecule is given by:

$$m_L^f = m_L - [\Delta H^*/\Delta H^*(\text{sat})]m_{CD}, \quad (4)$$

where m_L is the total stoichiometric molality of the guest. The standard enthalpy and the constant are obtained from Equations (3) and (4) by an iterative least-squares method. The iterations are continued until two successive values of ΔH_a^0 differ by less than 2%. The values of the free energy and entropy are then obtained through the usual thermodynamic relations. The absence of any information about the activity coefficients leads to the evaluation of association parameters that are thermodynamically not exactly defined. Only an apparent constant, K_a', can be determined, and consequently the standard free energy and entropy, $\Delta G_a^{0'}$ and $\Delta S_a^{0'}$, suffer from the same limitations.

If the simple association model discussed above does not describe the studied systems, Equations (3) and (4) cannot be used: the least-squares iterative procedure does not converge, and saturation is not easily detected. All that is a clear indication of the inadequacy of the model. However, it is possible to obtain information about the weak interactions between solutes from the pair enthalpic cross interaction coefficients, which are related to the ΔH^* function, defined in Equation (1), as follows [23–25]:

$$\Delta H^* = 2h_{xy}m_x^f m_y^f + \text{higher terms.} \quad (5)$$

To fit the data of Equations (1) and (5), a least-squares method was employed, choosing the polynomial of highest degree, whose coefficients still exceed their own 95% confidence limits.

Results

With the aim of understanding the effect of the solvent medium on the association of alkanols with β-CD, the relative thermodynamic parameters were determined at 298 K in water and in the presence of constant amounts of ethanol or urea. Using aqueous alcoholic or urea solutions, the possible association of ethanol or urea molecules with the cyclodextrin must be considered, since they would be in competition with CD:alkanol complex formation. However, the constants reported in the literature for the association of β-CD to the shortest alcohols indicate that it is negligibly small [27–29]. The existence of an inclusion complex formed by urea with β-CD has been experimentally excluded.

Under the experimental conditions presently employed, 1-alkanols shorter than pentanol do not associate to β-cyclodextrin. In Table 1, the thermodynamic parameters (association constant, enthalpy, free energy and entropy) are reported for the interaction of β-CD with 1-alkanols from C_5 to C_9 in water. Higher-molecular-mass 1-alkanols could not be studied because of their poor solubility in aqueous solution. Constants increase from 1-pentanol up to 1-octanol: within the experimental error, the constant for 1-nonanol has the same value as that for 1-octanol. The enthalpic contribution is very small, even positive for 1-pentanol and 1-hexanol: thereafter it becomes negative reaching an almost constant value for the C_8 and C_9 alcohols. The association process is driven by entropy, whose values, positive and large, determine the values of the association constants, higher than those obtained in all other experimental conditions. Association of alkanols from propanol up to 1-octanol with β-CD has been studied previously by other authors [27–32]. In some cases, their results differ from ours, probably because measurements were carried out under different experimental conditions and by different techniques. In fact, the values of the constants were determined by spectrophotometric [27] or spectrofluorometric [28–32] methods or by inhibition kinetics [29]. Only in one case are enthalpies given, as obtained through van't Hoff plots [27]. In 3 mol kg^{-1} ethanol, 1-pentanol and 1-hexanol do not associate with the cyclodextrin (see Table 1). From 1-heptanol to 1-nonanol, enthalpies are negative and increase regularly, as do the constants, while entropies are positive and almost invariant at increasing alkyl chain length. In 9 mol kg^{-1} ethanol, complexation starts again from 1-pentanol, and it is characterized by the smallest association constants found in this work, that increase regularly up to 1-nonanol (see Table 1). Within the limits of the experimental errors, the association parameters for 1-nonanol are the same as those for 1-octanol, as in water. Enthalpies are negative, varying in a very limited range, and increase up to 1-heptanol, maintaining almost the same value for the other 1-alkanols. In 7 mol kg^{-1} urea, complexation starts from 1-hexanol, and it is characterized by association constants which increase regularly with increasing alkyl chain length (see Table 1). Enthalpies are negative and smaller than those in ethanol, while entropies are large and positive. Both quantities vary in a limited range. Figure 1 shows the complete thermody-

Table 1. Thermodynamic parameters for the association between β-CD and 1-alkanols, in water and in mixed aqueous solvents, at 298 K

1-Alkanol	K_a [a,b]	$\Delta H_a^{0\prime}$ [b,c]	$\Delta G_a^{0\prime}$ [c,d]	$T\Delta S_a^{0\prime}$ [c,e]
Water				
1-pentanol	276 ± 74	0.9 ± 0.2	13.9 ± 0.7	14.8 ± 0.9
1-hexanol	445 ± 112	0.7 ± 0.1	15.1 ± 0.6	15.8 ± 0.7
1-heptanol	1100 ± 268	-0.41 ± 0.04	17.4 ± 0.6	16.9 ± 0.7
1-octanol	3061 ± 418	-1.19 ± 0.03	19.9 ± 0.3	18.7 ± 0.4
1-nonanol	2453 ± 373	-1.21 ± 0.07	19.3 ± 0.4	18.1 ± 0.4
Ethanol				
3 mol kg^{-1}				
1-pentanol		N.A.[f]		
1-hexanol		N.A.[f]		
1-heptanol	410 ± 43	-6.9 ± 0.5	14.9 ± 0.3	8.0 ± 0.8
1-octanol	825 ± 138	-7.7 ± 0.6	16.6 ± 0.4	9 ± 1
1-nonanol	1560 ± 266	-10.9 ± 0.9	18.2 ± 0.4	7 ± 1
Ethanol				
9 mol kg^{-1}				
1-pentanol	35 ± 10	-5 ± 1	8.8 ± 0.7	4 ± 2
1-hexanol	95 ± 15	-5.5 ± 0.6	11.3 ± 0.4	6 ± 1
1-heptanol	158 ± 28	-6.8 ± 0.8	12.5 ± 0.4	6 ± 1
1-octanol	243 ± 103	-7 ± 2	13.6 ± 0.5	7 ± 2
1-nonanol	316 ± 101	-7 ± 2	14.3 ± 0.8	7 ± 3
Urea				
7 mol kg^{-1}				
1-pentanol		N.A.[f]		
1-hexanol	120 ± 38	-3.6 ± 0.8	11.9 ± 0.8	8 ± 2
1-heptanol	511 ± 71	-3.8 ± 0.2	15.4 ± 0.3	11.7 ± 0.5
1-octanol	881 ± 135	-4.6 ± 0.3	16.8 ± 0.4	12.2 ± 0.7
1-nonanol	1276 ± 221	-5.5 ± 0.4	17.7 ± 0.4	12.2 ± 0.8

[a] kg/mol.
[b] Errors reported are the standard deviations as obtained by fitting the data to Equation (3).
[c] kJ/mol.
[d] Errors are half the range of $\Delta G_a^{0\prime}$ calculated from the upper and lower error in K_a'.
[e] Errors are the sum of the errors on free energy and enthalpy.
[f] N.A. means that measurements have been performed, but no association was detected.

namic data for the association of 1-alkanols with β-CD in the different experimental conditions.

In Table 2, the enthalpic self-interaction coefficients are reported for the alkanols employed and for α- and β-cyclodextrin in water and in various mixed solvents. For both cyclodextrins, coefficients are negative in water and positive in 7 mol kg^{-1} urea. For β-cyclodextrin, the coefficient becomes increasingly negative at increasing concentrations of ethanol, then it reaches a minimum, and finally at 9 mol kg^{-1} ethanol its value is closer to that in water. Dilution of 1-alkanols in 3 and 9 mol kg^{-1} ethanol was also studied, and the relative enthalpic self-interaction coefficients are listed in Table 2. In the former solvent, alkanols larger than 1-hexanol could not be analyzed because of their very slight solubility: dilution is an exothermic process, so that coefficients are positive, higher than those in water, increasing with increasing length of the alkyl chain. In 9 mol kg^{-1} ethanol, instead, dilution is an endothermic process, so that coefficients are negative, very large for 1-octanol and 1-nonanol.
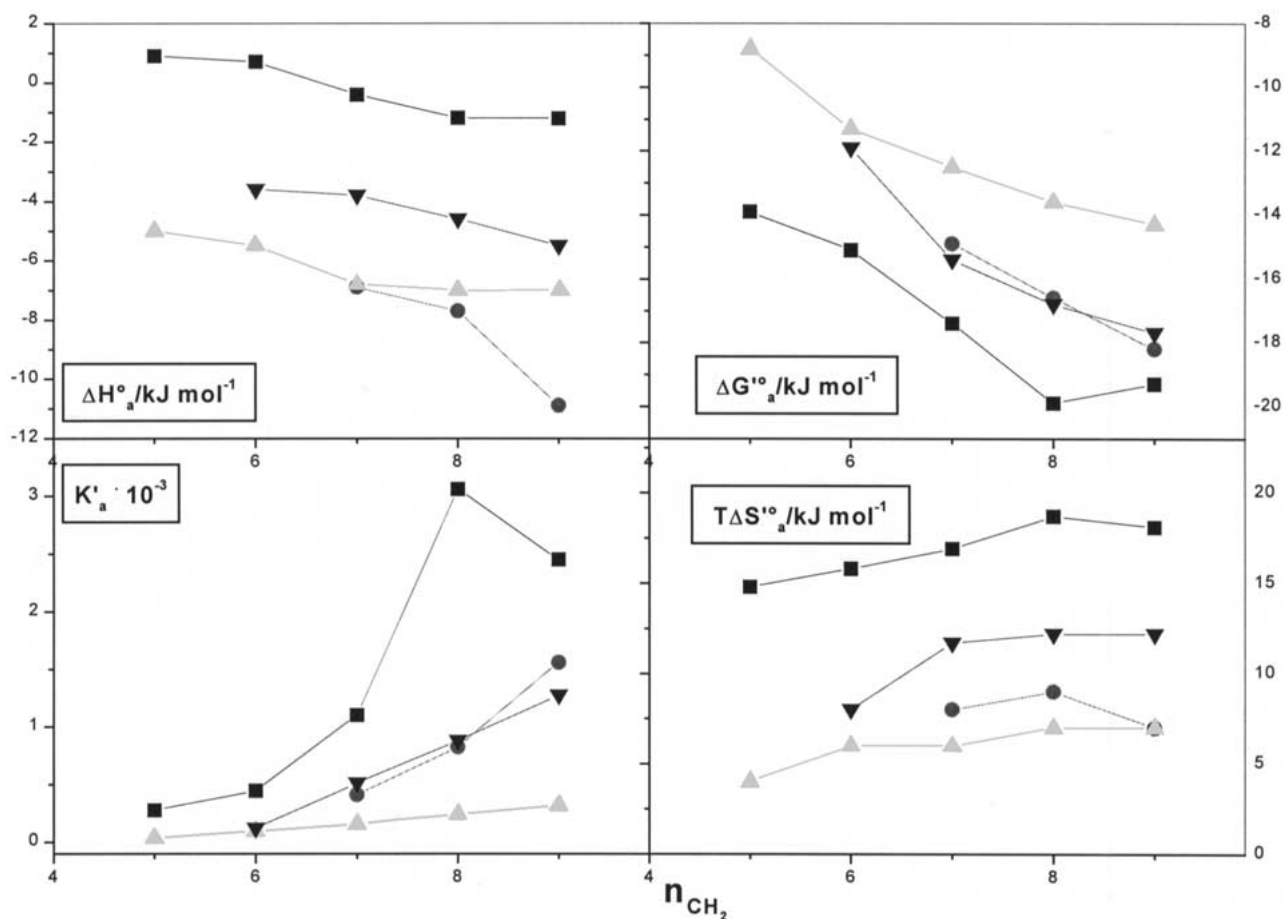
Figure 1. Thermodynamic association parameters – enthalpy, Gibbs free energy, constant and entropy – vs the number of methylene groups in the alkyl chain, n_{CH_2}, for 1-alkanols interacting with β-CD at 298.15 K under various experimental conditions: in pure water (■), in 3 mol kg^{-1} ethanol (●), in 9 mol kg^{-1} ethanol (▲), and in 7 mol kg^{-1} urea (▼).

Table 2. Pairwise enthalpic interaction coefficients for β-CD, α-CD, and 1-alkanols in water and in aqueous mixed solvents, at 298 K

Substance	h_{xx} [a]	c.r.[b]	n.p.[c]	Solvent medium
α-CD	-3920 ± 65[d]			water
α-CD	2760 ± 56	0.04–0.02	18	7 mol kg^{-1} urea
β-CD	-2754 ± 200	0.012–0.006	30	water
β-CD	1198 ± 27	0.05–0.0025	6	7 mol kg^{-1} urea
β-CD	-7379 ± 232	0.014–0.007	18	1 mol kg^{-1} ethanol
β-CD	-10333 ± 288	0.006–0.003	18	3 mol kg^{-1} ethanol
β-CD	-11190 ± 236	0.01–0.005	18	5 mol kg^{-1} ethanol
β-CD	-9018 ± 140	0.01–0.005	18	7 mol kg^{-1} ethanol
β-CD	-3593 ± 124	0.01–0.005	18	9 mol kg^{-1} ethanol
1-pentanol	2159 ± 56			water
1-pentanol	5146 ± 152	0.018–0.009	18	3 mol kg^{-1} ethanol
1-hexanol	8041 ± 186	0.02–0.01	17	3 mol kg^{-1} ethanol
1-heptanol	athermal	0.0005–0.00025		3 mol kg^{-1} ethanol
1-pentanol	-737 ± 60	0.1–0.05	18	9 mol kg^{-1} ethanol
1-hexanol	-5269 ± 102	0.04–0.02	18	9 mol kg^{-1} ethanol
1-heptanol	-16161 ± 442	0.0064–0.0032	18	9 mol kg^{-1} ethanol
1-octanol	-41585 ± 1260	0.009–0.0045	18	9 mol kg^{-1} ethanol
1-nonanol	-78527 ± 4628	0.006–0.003	18	9 mol kg^{-1} ethanol

Errors reported are the 95% confidence limits.
[a] J kg mol^{-2}.
[b] Concentration range, mol kg^{-1}.
[c] Number of experimental points.
[d] Ref. 9.

Table 3. Enthalpic cross-interaction coefficients for 1-pentanol/β-cyclodextrin in 3 mol kg^{-1} ethanol and 7 mol kg^{-1} urea, and for 1-hexanol/β-cyclodextrin in 3 mol kg^{-1} ethanol

System	h_{xy}[a]	Solvent medium
1-pentanol/β-CD	230 ± 6	3 mol kg^{-1} ethanol
1-hexanol/β-CD	659 ± 10	3 mol kg^{-1} ethanol
1-pentanol/β-CD	81 ± 2	7 mol kg^{-1} urea

Errors reported are the 95% confidence limits.
[a] J kg mol^{-2}.

In Table 3, pair enthalpic cross-interaction coefficients are reported for those systems not forming complexes. In 3 mol kg^{-1} ethanol, the coefficients for β-CD/1-pentanol and β-CD/1-hexanol systems are positive, increasing by about 400 J kg mol-1 passing from the shorter to the longer alkanol. The coefficient for β-CD/1-pentanol in 7 mol kg^{-1} urea is positive and very small.

Discussion

Binary aqueous solutions

The enthalpic coefficient for β-CD is less negative than that for α-CD (see Table 2), thus indicating that the larger macrocycle is a structure breaker less effective than α-CD. It is reported in the literature that α-CD undergoes a tense $\rightarrow$ relaxed transition upon formation of a complex [33]. β-CD, however, does not experience that transition, and it would present a relaxed conformation even in the absence of a guest, with the large cavity more exposed to bulk solvent. Thus, the value of the pairwise enthalpic interaction coefficient should be composed of two contributions, one originating from the overlapping of the hydrated hydrophilic exterior and the other from the displacement of structured water present in the hydrophobic cavity. The former contribution is negative for the prevalence of hydrophilic-hydrophilic interactions, while the latter is positive. That would make the pairwise interaction coefficient less negative than that for α-CD, notwithstanding the larger size of β-CD. As a conclusion, the cavity of β-CD, unlike that of α-CD, would participate in the interaction between two hydrated molecules.

The enthalpic coefficient for β-CD becomes more negative at increasing concentrations of ethanol, reaching a minimum at about 5 mol kg^{-1} ethanol, and thereafter increasing toward less negative values. This large variability could be an indication of conformational changes experienced by the macrocycle induced by the different solvent media. The addition of ethanol lowers the relative permittivity of the aqueous medium: hydrophilic interactions between the hydroxyl groups of ethanol and the external ones of the dextrin are enhanced, and at the same time, the bulk becomes more structured, lowering its energetic level. As a result, the coefficient is more negative than in water, attaining the most negative value at 5 mol kg^{-1} ethanol. A further increase in the concentration of cosolvent causes the shift of the coef-

ficient towards less negative values, though more negative values would be expected for the enhanced structuring effect in the bulk. Probably, the external cosphere of the dextrin becomes ethanolated for the increased favourable interactions between the hydroxyl groups of the two interacting substances. The resulting species shows properties quite different from those in water: for instance, it could adapt better to the new solvent.

At 3 mol kg^{-1} ethanol, the enthalpic interaction coefficients for 1-alkanols, prevailingly hydrophobic solutes, are positive and larger than those in water (see Table 2); then, they decrease with the increasing structuring effect of the cosolvent on water, reaching negative values at 9 mol kg^{-1} ethanol. At first, the presence of the cosolvent, which lowers the relative permittivity of the medium, enhances hydrophilic interactions, making hydrophobic interactions more cooperative for a better juxtaposition of alkyl groups. After that, the increased concentration of ethanol induces a new phenomenological behaviour: alkanols, typical hydrophobic structure maker solutes ($h_{xx} > 0$ in water), are described by negative enthalpic coefficients, which usually characterize typical hydrophilic structure breaker solutes ($h_{xx} < 0$ in water). In some way, when the increase in the structure of the medium becomes relevant, alkanols behave as *hydrophobic structure breaker solutes*. The same occurs for 1,2-diols and α-ω-diols in concentrated aqueous ethanol [34]. In that case, evidence is reported that at low concentration of ethanol the solvation cospheres are preferentially hydrated, while at higher concentrations of ethanol, they are, probably, to some extent "ethanolated". Then, in 9 mol kg^{-1} ethanol the solvation cospheres of alkanols presently studied, are ethanolated. The value of the enthalpic interaction coefficient for 1-nonanol in 9 mol kg^{-1} ethanol is particularly intriguing because it is negative and very large in magnitude (-78527 J kg mol^{-2}), thus indicating that the alkanol tends preferentially to self-association.

In concentrated urea, the coefficient for β-CD passes from negative to positive, thus reproducing the behaviour shown by glycine, formamide and other hydrophilic solutes, whose pair enthalpic interaction coeffcients become positive or less negative at increasing urea concentration [35]. According to studies on ternary aqueous solutions of hydroxylated substances, urea interacts mainly with the hydrophilic domains. Here, urea solvates prevailingly the external hydroxyl groups of cyclodextrin and the resulting increased steric hindrance leads to attenuated hydrophilic interactions. This transition to a thermochemically unfavourable behaviour could be partially ascribed to the enhanced dielectric constant of the medium determined by urea, an effect reducing the polar hydrophilic interactions.

The pair enthalpic interaction coefficients for alkanols in 7 mol kg^{-1} urea, are reported in the literature: they are positive and generally lower than those in water [36]. As before, the conclusion was that urea mainly solvates the hydroxyl groups causing also the reduction of the hydrophobic shells of the alkanols. That makes hydrophobic interactions less effective than in water.

As a conclusion, the presence of the cosolvent greatly modifies the character of the solvent medium, thus influencing the behaviour of the substances under consideration. Knowing the behaviour of the interacting substances in water and in the mixed solvents allows a deeper insight into the forces ruling the complexation of β-CD with alkanols.

Complexation thermodynamics in water

Preceding studies carried out in this laboratory on the complexes formed by mono and polyhydroxylated substances with α-CD confirmed the commonly accepted view that it is the alkyl chain which penetrates the cyclodextrin cavity. The hydroxyl group forms hydrogen bonds with the external hydroxyl groups on the rim of the macrocycle cavity [15]: it acts as a hook which prevents the further penetration of the alkyl chain. The association is ruled prevailingly by enthalpy, while entropy becomes increasingly smaller, even negative, at increasing alkyl chain length. Then, the shape-matching between the host cavity and the guest inserting group is a major factor determining the association between the two molecules. This picture is rather different from that coming out from the present data relative to β-CD/1-alkanol association in water: association constants are determined prevailingly by entropy, because enthalpies are very small, even positive for the first terms of the series. In fact, association enthalpies range from 0.9 kJ mol^{-1} to -1.21 kJ mol^{-1}, and entropies from 14.8 kJ mol^{-1} to 18.1 kJ mol^{-1}, passing from 1-pentanol to 1-nonanol. The small values of the enthalpies would result from several contributions. Among them, the endothermic contributions from the disruption of hydrogen bonds between water molecules in the cavity and the dehydration of the including hydrophobic guest molecule, and the exothermic one from interactions between the cyclodextrin cavity and the guest. The β-CD cavity diameter is approximately 6.2 Å, and about 4.9 Å for α-CD [1]: that causes a loose adaptation of an alkyl chain upon the formation of a complex, and consequently a less negative contribution from the binding forces, namely van der Waals interactions and hydrogen bonds [1]. In particular, owing to their small dimensions, the lower terms are statistically disordered in the β-CD cavity, and the resulting negative contribution is too small to overwhelm the positive one. For the higher terms, the negative contribution originating from the interactions with the cavity increases with increasing alkyl chain length, balancing the contribution due to the relaxation of water molecules both from the structured hydration cospheres of the alkanols and from the cavity. The resulting enthalpies become negative, but they remain small. The values of entropies are positive and large: they increase slightly in going from pentanol to nonanol, showing an almost constant contribution to Gibbs free energy. The β-CD cavity is rather large, so the alkanols need to be dehydrated only partially to be included. Hence, the contribution due to the dehydration of the hydrophobic alkyl chain upon inclusion is probably small, and the entropic term is mainly determined by the relaxation of water molecules from the cavity.

Complexation in mixed solvents

The presence of ethanol lowers the energetic level of the bulk. Upon association, water molecules released from the alkyl chain hydration cospheres, or displaced from the cavity, relax to a more structured medium. That causes the entropic contribution to become smaller with respect to water. Enthalpies are negative and larger than those in water, as a consequence of the decrease in the dielectric constant of the solvent, an effect that enhances hydrophilic interactions. Independently of the amount of ethanol, enthalpies and entropies vary in a limited range of values. Association constants increase with increasing length of the alkyl chain, but are smaller than those in water for the reduced favorable entropic contribution. Inclusion starts from heptanol in 3 mol kg^{-1} ethanol, and from pentanol in 9 mol kg^{-1} ethanol. In the latter solvent, the values of the association constants are the lowest among those determined in the various solvents. The study of the binary solutions of the interacting substances indicate that at this concentration of cosolvent, the solvation cospheres of alkanols and β-CD are probably ethanolated. The consequent steric hindrance is a factor that opposes the association. Moreover, the values of entropies become, on average, even smaller than those in 3 mol kg^{-1} ethanol for the relaxation of water molecules to a more structured medium. Both factors account for the small association constants.

In 7 mol kg^{-1} urea, bulk is less structured than pure water due to the presence of the chaotropic cosolvent. The relative permittivity of the medium increases, with the consequent attenuation of hydrophilic interactions, while water molecules relax to a less structured bulk: then, with respect to water, smaller enthalpies and higher entropies would be expected. Actually, enthalpies are larger and entropies smaller. Studies on binary aqueous solutions of alkanols have shown that, in concentrated urea, the hydration cospheres of alkanols are smaller [36]. Then, when the guest includes into the cavity, a smaller number of water molecules relaxes from the hydration cosphere to the bulk. The endothermic contribution, smaller for the reduced dehydration, causes the enthalpies to become more negative, with respect to water. As a conclusion, the association constants are smaller than those in water for a diminished favorable entropic term, notwithstanding the larger, favorable enthalpic term.

As shown in Table 1, whatever the experimental conditions, the entropic contributions for the association in mixed solvents are almost invariant with increasing length of the alkyl chain. Again, this is strong evidence that the relaxation of water molecules from the cavity is the common and major factor determining the entropic term.

Non-associating systems

The systems reported in Table 3 do not associate: hence, they have been treated according to the McMillan–Mayer approach for real solutions [23–25]. The heats of mixing of two binary solutions allow one to evaluate the enthalpic cross-interaction coefficients through Equation (5): these coefficients are positive and fall in the range of the homogen-

eous coefficients for β-CD and pentanol or hexanol. Their values could be ascribed to a kind of weak, prevailingly hydrophobic interaction, that does not lead to the formation of an adduct. In 7 mol kg^{-1} urea, the β-CD/1-pentanol interaction is characterized by an enthalpic interaction coefficient much smaller than that in ethanol. When interacting with a substance containing both polar and hydrophobic groups, such as an alkanol, urea solvates preferentially the polar group and reduces the hydrophobic hydration cosphere [35, 36]. The overall result of the two combined effects is a less effective hydrophobic interaction, characterized by a less positive coefficient.

Conclusions

In water, association between β-CD and 1-alkanols is characterized by large and positive entropies, an indication that hydrophobic interactions act in the complexation. On the contrary, for the same alkanols associating with α-CD entropies vary from positive (+2.1 kJ mol^{-1}) for pentanol to negative (−20.9 kJ mol^{-1}) for nonanol, thus indicating the prevalence of van der Waals interactions at increasing alkyl chain length [16]. The entropic contributions stem from the changes experienced by solvent water upon the desolvation of the cavity and dehydration of the including substance. The association parameters are mainly ruled by the former effect, namely the relaxation of water molecules that were originally residing within the cavity. In the presence of a cosolvent, complexation is characterized by enthalpy and entropy changes which depend on the extent of alteration induced by the cosolvent on the structure of water and on the hydration cospheres of the interacting substances.

A compensatory enthalpy-entropy relationship exists [1–4, 14, 37, 38], as for all processes dominated by aquation phenomena. The rough linear trend obtained by plotting $T\Delta S^0$ vs ΔH^0 for all data reported in Table 1 has intercept $T\Delta S_0^0$, obtained at $\Delta H^0 = 0$, and slope of 16 ± 1 kJ mol^{-1} and 1.1 ± 0.2, respectively. These values are in agreement with those reported in the literature for complexes formed by natural cyclodextrins [1]. Accordingly, the slope indicates to what extent the enthalpic gain is cancelled by entropic loss, while the positive intercept indicates that the complex is stabilized even in the absence of enthalpic contribution. Both values are higher for β-CD than for α-CD, an indication of a greater ring flexibility and of a larger number of associated water molecules in and around the cavity.

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