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Factors determining the formation of complexes between α-cyclodextrin and alkylated substances in aqueous solutions: a calorimetric study at 25 °C

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Abstract

The formation of complexes of α-cyclodextrin with cycloalkanediols, monoalkylamines and 1-alkanols has been studied calorimetrically at 25 °C in water, in phosphoric acid, pH 1.3, and in phosphate buffer, pH 5.5, respectively. 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. A model is proposed to explain the unusual trend of the association parameters for substances having alkyl chains longer than six–seven carbon atoms. The main role played by the different functional groups, and the forces involved in the association process, are discussed in the light of the signs and values of the thermodynamic parameters obtained. The effect of the variation of the aqueous medium on the hydration of the interacting substances and the consequent changes in the association parameters have been investigated. To this end, the thermodynamic parameters for the formation of the complexes between the cyclodextrin and 1-pentanol were determined at increasing concentrations of phosphate buffer. There is an increase in the association constant due to a positive entropy contribution originating from the relaxation of water molecules from the hydrophobic hydration cosphere of the alkanol to an increasingly disordered bulk. Deaquation of the interacting substances is the main factor determining the stability of the inclusion complex.

Keywords: α-Cyclodextrin; Calorimetry; Inclusion complexes; Alkanols; Monoalkylamines; Cycloalkanols

1. Introduction

Cyclodextrins (CDs), cyclic oligomers of α-D-glucose, are characterized by a fairly polar exterior and by a cavity that is nonpolar relative to the exterior and to the usual external environments, water in particular. 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]. The smallest of cyclodextrins (α-CD), having six glucose units in the solid state, has two water molecules entrapped in the cavity, hydrogen bonded to each other and to two glucopyranose rings [7]. In solution, these two water molecules diffuse to the medium when a complex is formed. At the same time, α-CD undergoes a conformational transition from a 'tense' to a 'relaxed' conformation [8]. There are few hypotheses concerning the forces involved in these processes, and many prob-

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lems are still unsolved about the mechanism and the changes experienced by water in the hydration shells of the 'guest' and 'host' molecules [9,10]. In preceding papers, we have reported on the interaction of α-CDs with hydroxylated substances [11–13], monocarboxylic acids [12,14], α,ω-dicarboxylic acids [15], aminoacids [16–18], cycloalkanols [19] and other small molecules [20–22] in water and/or in aqueous phosphate buffer, pH 11.3 and 1.3. Our present contribution continues the program aimed at understanding the factors determining the formation of complexes between cyclodextrins and alkylated substances in aqueous solution. A calorimetric study at 25 °C is reported on the interaction of α-CD with 1-alkanols from C_3 to C_9 in aqueous phosphate buffer, pH 5.5, with monoamines from C_3 to C_8 in phosphoric acid, pH 1.3, and with cycloalkanediols in pure water. The role of the different functional groups and of the length of the alkyl chains in the complex formation have been analyzed. For these association processes, a large variation of $\Delta H°$ and $\Delta S°$ has been observed. A linear trend is commonly obtained when reporting ΔH versus ΔS; this enthalpy–entropy compensation is a phenomenon frequently observed in water and ascribed to the modifications experienced by the solvent in the hydration shells of the interacting host and guest molecules [1,4,12,23–25]. To investigate the importance of this contribution, binary solutions of ethanol, 1-pentanol and α-CD were studied, as well as the interaction of 1-pentanol with α-CD, varying the concentration of phosphate buffer, at pH 5.5. Beyond the detection of the thermal effect, calorimetry shows whether association occurs and allows the evaluation of its equilibrium constant, from which the free energy and entropy can be derived. Knowing the thermodynamic parameters characterizing the association process, it is possible to form hypotheses about the forces involved in the interaction between α-CD and the studied organic substances.

2. Experimental

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

To prepare aqueous solutions at pH 1.3 and 5.5, phosphoric acid and dihydrogen phosphate–HCl buffer were employed, respectively. The choice of the phosphate buffer was determined by the need to avoid anions interfering with the inclusion process. Phosphate and sulfate anions satisfy this requirement in a wide pH range [26]. The concentration of 1-alkanols, cycloalkanediols and monoamines varied between 3×10^{-3} and 2×10^{-4} mol kg^{-1}, while that of α-CD was between 2 and 8×10^{-2} mol kg^{-1}.

Calorimetry.—The values of the experimental heats of mixing, ΔH_{mix}, of two binary solutions containing any one of the solutes and of the heats of dilution, ΔH_{dil}, of binary solutions were determined at 25 °C by means of a thermal activity monitor (TAM) from Thermometric, according to the experimental details reported previously [12].

Treatment of the data.—The enthalpy of formation of a complex, 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°, and of the apparent association constant, K'_a, as follows [27]:

$$m_{CD}/\Delta H^* = 1/\Delta H_a^\circ + 1/(\Delta H_a^\circ K'_a m_L^f) \qquad (1)$$

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

$$m_L^f = m_L - [\Delta H^*/\Delta H^* \text{ (sat)}]m_{CD} \qquad (2)$$

where m_L is the total stoichiometric molality of the guest. The standard enthalpy and the constant are obtained from Eqs. (1) and (2), according to the procedure reported in preceding papers [12–15]. The values of the free energy and entropy are then obtained through the usual thermodynamic relations.

The pairwise interaction coefficients of the excess enthalpies characterizing binary solutions are derived from the following relation [28–30]:

$$\Delta H_{\text{dil}}(m^{\text{i}} \rightarrow m^{\text{f}}) = h_{\text{xx}} m^{\text{f}}(m^{\text{f}} - m^{\text{i}}) + h_{\text{xxx}} m^{\text{f}}(m^{\text{f}2} - m^{\text{i}2})^{+} \qquad (3)$$

where ΔH_{dil} (J kg^{-1}) is the dilution enthalpy of a solute from the initial (m^{i}) to the final molality (m^{f}). To fit the data, a least-squares method was employed choosing the polynomial of highest degree, whose coefficients still exceed their own 95% confidence limits.

3. Results and discussion

From preceding studies carried out in this laboratory on the complexes formed by mono and polyhydroxylated substances with α-CD, it was inferred that it is the alkyl chain that penetrates the cyclodextrin cavity, while the hydroxyl group forms hydrogen bonds with the external hydroxyl groups on the rim of the macrocycle cavity [13]. When the hydroxyl group occupies a more central position, as in 2- or 3-alkanols, it acts as a hook, which prevents the further penetration of the alkyl chain [13]. Moreover, from thermodynamic and spectroscopic studies, it was inferred that for α,ω-diols the interaction involves mainly the exterior of the cyclodextrin. The diol caps the base of α-CD with the hydroxyl groups hydrogen-bonded to two hydroxyl groups on the rim of the macrocycle [13]; the mechanism is similar to that found for the interaction of cyclodextrins with other bifunctional compounds [34]. These and many other data reported in the literature [6] are consistent with the assumption that the charged and hydrophilic groups of the guests, with the exception of the phenolic hydroxyl group, remain in the bulk solution before and after association with cyclodextrin.

The thermodynamic parameters (association constant, enthalpy, free energy and entropy) for the interaction of α-CD with some cycloalkanediols are reported in Table 1. The complexes are weak, being characterized by low association constants, similar to those derived for substances bearing very short alkyl chains. Then, the shape-matching between the host cavity and the guest inserting group is rather poor; the failure of α-CD in discriminating between cis and trans isomers arises from this. However, it has been found before that association constants increase as the ring increases its distance from the functional group. In fact, the association constant for 4-cyclohexylbutan-1-ol, also reported in Table 1, is much higher than that for 1-cyclo-

Table 1
Thermodynamic parameters for the association in water between α-CD and cycloalkanols at 25 °C

Cycloalkanol	K'_{a} [a,b]	$-\Delta H^{\circ}_{\text{a}}$ [b,c]	$-\Delta G^{\circ\prime}_{\text{a}}$ [c,d]	$T\Delta S^{\circ\prime}_{\text{a}}$ [c,e]
cis-1,2-Cyclopentanediol	84 ± 7	1.0 ± 0.1	11.0 ± 0.2	10.0 ± 0.3
trans-1,2-Cyclopentanediol	69 ± 16	0.7 ± 0.1	10.5 ± 0.6	9.8 ± 0.7
cis-1,2-Cyclohexanediol	39 ± 2	3.6 ± 0.1	9.1 ± 0.1	5.5 ± 0.2
trans-1,2-Cyclohexanediol	41 ± 11	4.4 ± 0.9	9.2 ± 0.7	5 ± 2
cis-1,2-Cyclooctanediol	81 ± 8	2.7 ± 0.2	10.9 ± 0.2	8.2 ± 0.4
(*cis*/*trans*)-1,4-Cyclooctanediol		N.A. [f]		
Cyclopentanol [g]	63 ± 2	5.5 ± 0.1	10.3 ± 0.1	4.8 ± 0.1
Cyclohexanol [g]	83 ± 4	8.8 ± 0.3	10.9 ± 0.2	2.1 ± 0.5
Cycloheptanol [g]	25 ± 14	32 ± 15	8 ± 2	−24 ± 17
Cyclooctanol [g]	28 ± 19	40 ± 21	8 ± 2	−32 ± 23
1-Cyclohexylethanol [g]	86 ± 7	11.2 ± 0.7	11.0 ± 0.2	−0.2 ± 0.9
4-Cyclohexylbutan-1-ol [g]	983 ± 159	64 ± 6	17.1 ± 0.4	−47 ± 6

[a] kg mol^{-1}.
[b] Errors reported are the standard deviations as obtained by fitting the data to Eq. (2).
[c] kJ mol^{-1}.
[d] Errors are half the range of $\Delta G^{\circ\prime}_{\text{a}}$ 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.
[g] Ref. [19].

hexylethanol, probably because the former cycle can penetrate deeply into the cavity [19]. Its large complexation enthalpy could, then, be due to a better adaptation of the ring to the cavity. In contrast to 1,4-butanediol ($K' = 8$ kg mol^{-1} and $\Delta H^\circ_a = -10$ kJ mol^{-1} [13]), α-CD does not form a complex with 1,4-cyclooctanediol, even though the domain involved in the interaction should be the same. The stronger rigidity of the cycle with respect to the flexibility of the linear alkyl chain should cause hindrance of the cyclic compound in capping the cyclodextrin cavity. In contrast, 1,2-cyclooctanediol forms a complex because the two adjacent hydroxyl groups do not interfere with the adaptation of the remaining part of the cycle to the cavity. The comparison between the data for cycloalkanols [19], reported in Table 1, and those for 1,2-cycloalkanediols shows that the values of the constants are small and similar for both classes of substances, an evidence that a common domain includes poorly into the cavity. Instead, enthalpies for 1,2-cycloalkanediols are smaller than those for cycloalkanols, probably because favorable intramolecular hydrophilic interactions between the two adjacent hydroxyl groups reduce their capability to interact with the external hydroxyl groups of cyclodextrin.

The thermodynamic parameters for the association process involving α-CD and 1-alkanols from C_3 to C_9 in 0.5 M phosphate buffer, pH 5.5, are shown in Table 2. Higher-molecular-mass 1-alkanols could not be studied because of their poor solubility in aqueous solution. The association data, when treated according to a simple 1:1 model postulating the presence of only one adduct, give constants increasing regularly up to 1-heptanol, and maintaining almost the same value for the C_8 and C_9 terms. Enthalpies, instead, keep increasing, with a relevant jump passing from C_7 to C_8; the same occurs for entropies. In Table 2 the data are also reported for alkanols interacting with α-CD in water and in phosphate buffer, at pHs 1.3 and 11.3. Some of these data, already reported in Ref. [12], have been recalculated in the course of the present work due to a fault in the software used there; however, the relative variation of the parameters obtained is the same, so that the interpretation given before has not changed. At pH 1.3, the values of the constants are in agreement with those reported by other authors [31] up to 1-hexanol, while they differ for 1-heptanol and 1-octanol. Fig. 1 shows the complete thermodynamic frame for the association of these substances with α-CD. It is apparent that whatever the experimental conditions, there is a common trend, namely an increase in the association constants up to the C_6–C_7 terms and then an irregular variation. Enthalpies always increase at increasing alkyl chain, with a jump in correspondence of the C_6 term in water and at pH 1.3, and of the C_7 term at pH 5.5 and 11.3. In general, the experimental data for heptanol, octanol and nonanol are badly reproduced by the parameters calculated through Eq. (2); then, the hypothesis that only one adduct forms holds only for alkanols having an alkyl chain length up to about six to seven CH_2 groups. For longer chains, it is necessary to assume a more complex model to get a better overlap between calculated and experimental data. From Table 2 and Fig. 1, it can be observed that, beyond six carbon atoms, the free energy of association remains almost constant, enthalpies keep increasing, while entropies become negative. Then, there must be a change in the interaction mechanism around $n_C = 6$–7. Actually, for alkanols longer than C_6–C_7, 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, as inferred from studies on the association between α-CD and monocarboxylic acids from C_3 to C_{12} at pH 11.3 [14]. For intermediate alkyl chains, both adducts are present. The question is whether a bent alkyl chain could be accommodated in the small volume of the α-CD cavity. To verify this point, the interaction with a substance simulating a bent alkyl chain, 4-cyclo-

Table 2
Thermodynamic parameters for the association between α-CD and 1-alkanols at 25 °C, in water and at pH 11.3, 1.3 and 5.5

1-Alkanol	K'_a [a,b]	$-\Delta H^\circ_a$ [b,c]	$-\Delta G^{\circ\prime}$ [c,d]	$T\Delta S^{\circ\prime}_a$ [c,e]
pH 5.5				
1-Propanol			N.A. [f]	
1-Butanol	9 ± 11	43 ± 49	5.4	−38
1-Pentanol	359 ± 16	13.5 ± 0.5	14.6 ± 0.2	1.1 ± 0.6
1-Hexanol	791 ± 31	18.9 ± 0.4	16.5 ± 0.2	−2.4 ± 0.5
1-Heptanol	898 ± 45	22.0 ± 0.7	16.8 ± 0.1	−5.2 ± 0.8
1-Octanol	872 ± 49	39 ± 1	16.8 ± 0.2	−22 ± 1
1-Nonanol	1049 ± 227	51 ± 4	17 ± 1	−34 ± 5
Water				
1-Ethanol [g]	6.7	2.5	4.7	2.2
1-Propanol [g]	27	6.1	8.2	2.1
1-Butanol [g]	99.9	9.9	11.4	1.5
1-Pentanol [h]	275 ± 15	11.8 ± 0.2	13.9 ± 0.1	2.1 ± 0.3
1-Hexanol	523 ± 7	13.9 ± 0.1	15.5 ± 0.1	1.6 ± 0.2
1-Heptanol	377 ± 22	20.6 ± 0.8	14.7 ± 0.1	−5.9 ± 0.9
1-Octanol	220 ± 27	22 ± 1	13.4 ± 0.3	−9 ± 2
1-Nonanol	480 ± 37	36.2 ± 0.5	15.3 ± 0.2	−20.9 ± 0.7
pH 11.3				
1-Propanol [i]	94 ± 5	5.0 ± 0.2	11.3 ± 0.1	6.3 ± 0.3
1-Butanol [i]	110 ± 3	8.9 ± 0.1	11.6 ± 0.1	2.7 ± 0.2
1-Pentanol [i]	376 ± 11	11.3 ± 0.1	14.7 ± 0.1	3.4 ± 0.2
1-Hexanol	669 ± 58	11.8 ± 0.3	16.1 ± 0.2	4.3 ± 0.7
1-Heptanol	330 ± 65	11.2 ± 0.7	14.4 ± 0.5	3 ± 1
1-Octanol	197 ± 33	16 ± 1	13.1 ± 0.4	−3 ± 1
pH 1.3				
1-Propanol	67 ± 7	3.3 ± 0.2	10.4 ± 0.3	7.1 ± 0.5
1-Butanol	94 ± 4	7.2 ± 0.1	11.2 ± 0.1	4.0 ± 0.2
1-Pentanol	316 ± 6	10.8 ± 0.1	14.3 ± 0.1	3.4 ± 0.2
1-Hexanol	436 ± 32	15.8 ± 0.2	15.0 ± 0.2	−0.8 ± 0.4
1-Heptanol	306 ± 40	24.9 ± 0.9	14.2 ± 0.3	−11 ± 1
1-Octanol	421 ± 40	27.1 ± 0.7	15.0 ± 0.2	−12.1 ± 0.9

[a] kg mol^{-1}.

[b] Errors reported are the standard deviations as obtained by fitting the data to Eq. (2).

[c] kJ mol^{-1}.

[d] Errors are half the range of $\Delta G^{\circ\prime}_a$ 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.

[g] Ref. [11].

[h] Ref. [13].

[i] Ref. [12].

hexylbutan-1-ol, (see Table 1) was studied; the large complexation constant and enthalpy support the hypothesis that a long alkyl chain can bend in the interior of the dextrin. The same model describes the association, at pH 1.3, of α-CD with monoalkylamines, the thermodynamic parameters of which are shown in Table 3. Under these experimental conditions, monoalkylamines are mostly in the protonated form. It is impossible to obtain the thermodynamic parameters for the association of α-CD with uncharged monoalkylamines, because the necessary pH conditions can determine the dissociation of the external hydroxyl groups of cyclodextrin. For propylamine and butylamine least-squares converge, but the association parameters are characterized by very large errors, thus meaning that the complex does not form. The association constant and enthalpy regularly increase from the C_5 up to the C_7 compound; then, there is a jump in both parameters passing to the C_8 compound, whose association is well described by the bent-chain model described previously. The comparison between alkanols at pH 1.3 and monoalkylamines shows that a shift occurs from the C_6 to the C_7 term up to which only one adduct is supposed to form, an indication that the protonated amino group, with its stable hydration cosphere, does not allow the alkyl chain to penetrate fully into the α-CD cavity. The same happens for the charged carboxylate and zwitterionic groups [14,16]. As a conclusion, association depends on the nature of the functional group and, for all substances, it is an unsubstituted alkyl chain of about six carbon atoms that can include the α-CD cavity without giving any conformational change. Another model is reported in the literature for α-CD interacting with 1-alkanols longer than C_6; namely complexes with two α-CDs and one guest molecule can be formed in addition to the 1:1 complexes [35]. This is a reasonable hypothesis, but only if it does not provide a complexation occurring through the penetration of the alkyl chain and of the hydroxyl group into the cavities of two different α-CD molecules. An alternative model might take into consideration that long chains can pass through the cyclodextrin ring and protrude from the other side. The protruding part would, then, be caged by water molecules. However, it would be impossible to distinguish mathematically this model from the simple 1:1 association, and, besides, it would not account for the increasing $\Delta H/n_{CH2}$ at increasing alkyl chain length. Enthalpy, in fact, should remain almost constant since the negative contribution for the formation of the water cage would be balanced by the positive contribution originating from the dehydration of the guest molecule when passing through the cyclodextrin.

The possibility that cyclodextrin also undergoes a conformational transition favoring the formation of such complexes cannot be excluded. Support comes from studies about α-CD–alkanol interaction; on the basis of CPK models it has been shown that, for unbranched chains longer than about six carbons, some changes in conformation of both the alkanol and α-CD must occur to provide a fit [36]. With the aim of analyzing this point more deeply, binary solutions of α-CD have been studied under different experimental conditions. In Table 4 the pairwise enthalpic interaction coefficients are reported for α-CD under different experimental conditions. These coefficients are extremely dependent on pH and buffer concentration. For instance, in 0.5 M phosphate buffer h_{xx} is 1365 J kg mol^{-2} at pH 11.3, -1792 J kg mol^{-2} pH 5.5 and -3929 J kg mol^{-2} pH 1.3. That large variability could be ascribed to a conformational change of the macrocycle. This hypothesis is strengthened by the observation that, at pH 5.5, α-CD does not associate with 1-propanol and 1-butanol (see Table 2), and that a shift occurs in the term up to which the association occurs with the presence of only one adduct. Moreover, the values of the association en-

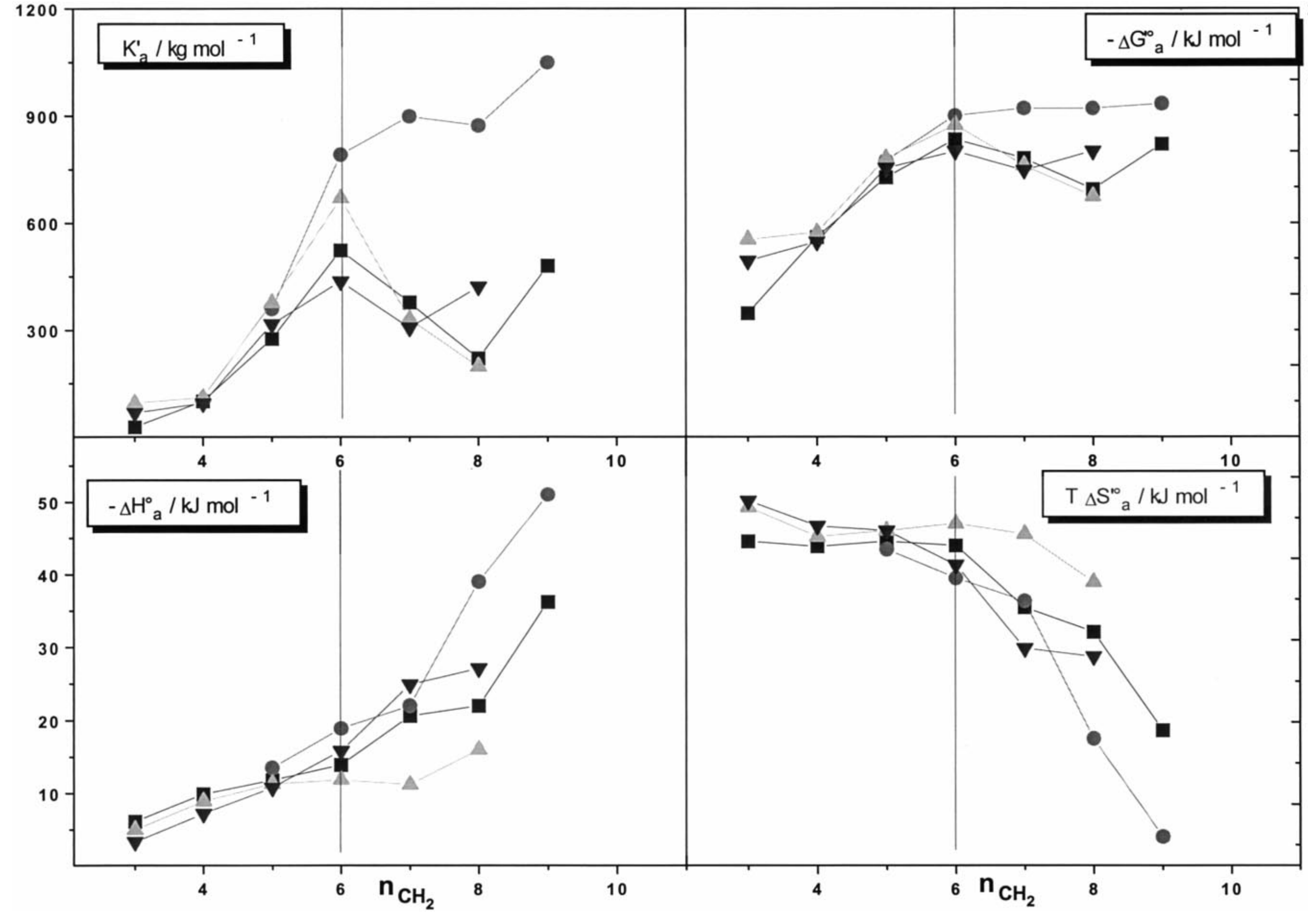

Fig. 1. Thermodynamic association parameters — association constant, Gibbs free energy, enthalpy and entropy — vs. the number of methylene groups in the alkyl chain, n_{CH_2}, for 1-alkanols interacting with α-CD at 298.15 K under various experimental conditions: in pure water (■), and in phosphate buffer at pH 5.5 (●), pH 11.3 (▲), pH 1.3 (▼).

Table 3
Thermodynamic parameters for the association between α-CD and 1-alkylamines at 25 °C, in phosphate buffer 0.5 mol kg^{-1}, pH 1.3

1-Amine	K'_a [a,b]	$-\Delta H^\circ_a$ [b,c]	$-\Delta G^{\circ\prime}_a$ [c,d]	$T\Delta S^{\circ\prime}_a$ [c,e]
1-Propylamine	46 ± 32	13 ± 8	10 ± 4	−3 ± 12
1-Butylamine	51 ± 110	1 ± 2	10	9
1-Pentylamine	102 ± 4	9.9 ± 0.3	11.4 ± 0.1	1.5 ± 0.4
1-Hexylamine	394 ± 5	12.5 ± 0.1	14.8 ± 0.1	2.3 ± 0.2
1-Heptylamine	1179 ± 27	14.1 ± 0.2	17.5 ± 0.1	3.4 ± 0.3
1-Octylamine	484 ± 36	26.7 ± 0.6	15.3 ± 0.2	−11.4 ± 0.8

[a] kg mol^{-1}.

[b] Errors reported are the standard deviations as obtained by fitting the data to Eq. (2).

[c] kJ mol^{-1}.

[d] Errors are half the range of $\Delta G^{\circ\prime}_a$ calculated from the upper and lower error in K'_a.

[e] Errors are the sum of the errors on free energy and enthalpy.

thalpies are higher than those obtained in the other experimental conditions. Hence, at this pH, the cavity should be wider, giving a looser fit with the included molecule. The more negative values for enthalpies could, then, originate from a smaller dehydration contribution when the hydrophobic guest molecule penetrates into the cavity.

The values of the enthalpies characterizing these complexes are negative, as for most of the adducts reported in the literature, spread over a wide range, and, in general, varying regularly with the alkyl chain length [1,4,6]. Entropies are positive or negative, an indication that hydrophobic interactions do not always play the major role in the inclusion process. On the basis of the large variation of ΔH° and ΔS°, some authors proposed that the stability of the complexes relies on a combined hydrophobic interaction [37]. The data for the association between α-CD and 1-pentanol, reported in Table 5, show that the favorable enthalpic contribution to the free energy decreases at increasing phosphate concentration. The competition with phosphate ion–hydroxyl group interactions could be the cause of attenuated hydrophilic interactions between the hydroxyl groups of the guest and the external ones of the host. This effect, however, does not play a fundamental role in the formation of the complexes, since the as-

Table 4
Pairwise enthalpic interaction coefficients for α-CD, 1-pentanol and ethanol in water and in phosphate buffer at different concentrations and pH, at 25 °C [a]

Substance	h_{xx} [b]	c.r. [c]	n.p. [d]	Phosphate buffer (mol kg^{-1}, pH)
α-CD	−3348 ± 219 [e]			0.2, 11.3
α-CD	1365 ± 80	0.07–0.035	16	0.5, 11.3
α-CD	2860 ± 152	0.04–0.02	16	0.8, 11.3
α-CD	−3929 ± 179	0.04–0.02	16	0.5, 1.3
α-CD	−1792 ± 100	0.03–0.015	10	0.5, 5.5
α-CD	−1223 ± 46	0.03–0.015	11	1, 5.5
α-CD	0	0.03–0.015	10	2, 5.5
1-Pentanol	1935 ± 67	0.06–0.030	10	0.5, 11.3
1-Pentanol	1996 ± 52	0.06–0.030	10	0.5, 1.3
1-Pentanol	1746 ± 70	0.07–0.035	20	0.5, 5.5
1-Pentanol	1536 ± 50	0.07–0.035	20	1, 5.5
1-Pentanol	100 ± 6	0.05–0.02	20	2, 5.5
Ethanol	136 ± 2	0.15–0.07	21	0.5, 5.5
Ethanol	87 ± 5	0.16–0.08	10	1, 5.5
Ethanol	−115 ± 6	0.15–0.07	10	2, 5.5

[a] Errors reported are the 95% confidence limits.

[b] J kg mol^{-2}.

[c] Concentration range, mol kg^{-1}.

[d] Number of experimental points.

[e] Ref. [17]. Coefficient in water for α-CD is −3920 ± 65 J kg mol^{-2}, Ref. [11], for 1-pentanol it is 1766 ± 68 J kg mol^{-2}, Ref. [32], and for ethanol it is 243 ± 10 J kg mol^{-2}, Ref. [33].

Table 5
Thermodynamic parameters for the association between α-CD and 1-pentanol at 25 °C, at different concentrations of phosphate buffer pH 5.5 [a]

mol kg^{-1}	K'_a [b,c]	$-\Delta H^\circ_a$ [c,d]	$-\Delta G^{\circ\prime}_a$ [d,e]	$T\Delta S^{\circ\prime}_a$ [d,f]
0.200	222 ± 7	14.0 ± 0.3	13.4 ± 0.1	-0.6 ± 0.4
0.500	359 ± 16	13.5 ± 0.5	14.6 ± 0.1	1.1 ± 0.6
1.00	715 ± 48	11.4 ± 0.3	16.3 ± 0.2	4.9 ± 0.5
2.00	2089 ± 359	10.6 ± 0.5	18.9 ± 0.4	8.3 ± 0.9

[a] For thermodynamic parameters in water, see Table 1.

[b] kg mol^{-1}.

[c] Errors reported are the standard deviations as obtained by fitting the data to Eq. (2).

[d] kJ mol^{-1}.

[e] Errors are half the range of $\Delta G^{\circ\prime}_a$ calculated from the upper and lower error in K'_a.

[f] Errors are the sum of the errors on free energy and enthalpy.

sociation constant keeps increasing. That must necessarily be attributed to a favorable entropic contribution which, indeed, becomes increasingly positive as buffer concentration increases. To rationalize this behavior, the binary solutions of the substances involved were analyzed. Pair enthalpic interaction coefficients for α-CD, ethanol and 1-pentanol are smaller in buffer than in pure water and decrease at increasing phosphate concentration (Table 4). This behavior is similar to that shown by glycine [38], hexane-1,2-diol and ethane-1,2-diol [39] in concentrated aqueous urea. Then, phosphate buffer behaves phenomenologically as this last substance, which is known to have a chaotropic effect on water structure. Accordingly, at increasing concentration of phosphate ions, the hydrophobic hydration cosphere of alkanols becomes smaller and the bulk more destructured. Upon inclusion, water relaxation occurs from the reduced hydrophobic hydration cosphere of the alkanol to an increasingly disordered bulk; this is the cause of the positive entropy contribution. As usually occurs in the formation of these complexes, a linear trend is obtained from plotting ΔH versus ΔS for all data presented in this study, independently of the experimental conditions employed; the slope, called the 'compensation temperature', is 301 ± 15 K, a value consistent with the $250 \div 320$ K range characteristic of processes dominated by aquation phenomena [1,4,6,12, 23–25]. Thus, deaquation of both guest and host molecules is in effect determining the stability of the inclusion complex. The ratio between the compensation temperature and the actual temperature of experiments has been used as a quantitative measure of the conformational changes upon complex formation [6]. The value of this ratio, close to unit for α-cyclodextrin [12,40], is unexpected when considering the rigid skeleton of the cyclic acceptor alone. However, it could be interpreted as a confirmation that the inclusion complexation implies the reorganization of the original hydrogen-bond network within the α-CD molecule.

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