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Role of the functional group in the formation of the complexes between α-cyclodextrin and alkanols or monocarboxylic acids in aqueous solutions. A calorimetric study at 25 °C

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Abstract

The interaction of α-cyclodextrin with 1-alkanols, monocarboxylic acids and α,ω-diols has been studied calorimetrically at 25 °C in water, in phosphoric acid, pH 1.3, and in phosphate buffer, pH 11.3. 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. Inclusion complexes are formed by 1-alkanols and monocarboxylic acids. For alkanols, a model is proposed to explain the unusual trend of the association constants at increasing alkyl chain length. The association occurs through the insertion of the guest's alkyl chain into the host's cavity. However, for terms longer than C_6, two forms of the guest can exist, each one associating to αCD with a different constant and enthalpy. α,ω-Diols associate through a mechanism which involves prevailingly the exterior of α-cyclodextrin. For terms longer than C_7, another mechanism is proposed which provides the inclusion of the alkyl chain, with the hydroxyl groups both laying outside the cavity. The main role played by the different functional groups, and the forces involved in the association process are discussed in the light of the analysis of the signs and values of the thermodynamic parameters obtained. © 1998 Elsevier Science Ltd. All rights reserved.

Keywords: α-Cyclodextrin; Calorimetry; Inclusion complexes; Alkanols; Monocarboxylic acids

1. Introduction

The most important property of cyclomalto-oligosaccharides (cyclodextrins) is their ability to form complexes with a great variety of organic substances either in solution or in the solid state [1–3].

The smallest of these cyclodextrins, cyclomaltohexaose (αCD), is especially interesting. In the solid state, it has two water molecules entrapped in the cavity, hydrogen bonded to each other and to two glucopyranose rings [4]. These two water molecules

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diffuse to the medium when a complex is formed. At the same time, αCD undergoes a conformational transition from a 'tense' to a 'relaxed' conformation [5]. There are few hypotheses concerning the forces involved in these processes, and many problems are still unsolved about the mechanism and the changes experienced by water in the hydration shells of the 'guest' and 'host' molecules [6,7].

In preceding papers, we have reported on the binary aqueous solutions of αCD [8] and on its interaction with low-molecular-mass hydroxylated substances [8,9], monocarboxylic acids at pH 11.3 [10], α,ω-dicarboxylic acids at pH 1.3 and 11.3 [11], amino acids [12–14], and other small molecules [15–17]. Our present contribution continues the program aimed at understanding the forces involved in the interaction of cyclodextrins with some higher-molecular-mass substances in aqueous solution. Here, we report a calorimetric study at 25 °C of the interaction of αCD with 1-alkanols from C_3 to C_9, α,ω-diols from C_4 to C_{10}, and monocarboxylic acids from C_3 to C_9. 1-Alkanols and α,ω-diols have been studied in water, in aqueous solutions of phosphoric acid, pH 1.3, and in aqueous phosphate buffer, pH 11.3. Monocarboxylic acids have been investigated in aqueous phosphoric acid, pH 1.3. The role of the hydroxyl group in the complex formation will be analyzed and compared to that of the charged and uncharged carboxyl groups. As well as 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 all thermodynamic parameters characterizing the association process, it is possible to make an analysis of the forces involved in the interaction between αCD and the organic substance.

2. Experimental

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

To prepare aqueous solutions of pH 1.3 and 11.3, 0.5 mol/kg phosphoric acid and 0.5 mol/kg sodium dihydrogen phosphate–NaOH buffer were employed, respectively. The choice of a phosphate buffer is determined by the need to avoid anions interfering with the inclusion process. It is reported that phosphate and sulphate anions satisfy this requirement in a wide pH range [18]. The concentration of 1-alkanols and α,ω-diols varied between $4.93 \cdot 10^{-3}$ and $9.35 \cdot 10^{-4}$ mol/kg; that for monocarboxylic acids between $2.7 \cdot 10^{-3}$ and $5.0 \cdot 10^{-4}$ mol/kg.

Calorimetry.—The values of the experimental heats of mixing, ΔH^{mix}, of two binary solutions containing any one of the solutes, were determined at 25 °C by means of a Thermal Activity Monitor (TAM) (Thermometric) equipped with a titration vessel. A microcomputer controlled the injections and collected the titration data. Approximately 30 injections of the titrating solution were made in each experiment. At least two experiments were performed for each substance. Enthalpies of dilution of the added substance in the appropriate solvent were determined, using the same number of injections and concentrations as in the titration experiments, and were subtracted from the enthalpies of the mixing process. The dilution of the component present in the cell was considered to be negligible. As an example of the calorimetric response, in Fig. 1, the experimental power–time plot is presented for octane-1,8-diol titrated with αCD in water.

Treatment of the data.—Assuming that a 1:1 complex is formed, the association process can be represented as follows:

$$\mathrm{CD} + \mathrm{L} = \mathrm{CD} \cdot \mathrm{L} \tag{1}$$

where CD indicates α-cyclodextrin and L any of the guest substances employed. The enthalpy of formation of the complex, ΔH^*, is related to the heat of mixing of two binary solutions, ΔH^{mix}, and to the heats of dilution experienced by the two solutes, ΔH^{dil}, as follows [19]:

$$\Delta H^* = \Delta H^{\text{mix}}\left\{\left[(m_{ix})(m_{iy})\right] \to (m_x, m_y)\right\} - \Delta H^{\text{dil}}(m_{ix} \to m_x) - \Delta H^{\text{dil}}(m_{iy} \to m_y) \tag{2}$$

where m_{ix}, m_{iy}, m_x, and m_y are the initial and final molalities of the x and y solutes. ΔH^*, normalized to the total molality of the dextrin, m_{CD}, can be expressed as a function of the actual molality of the guest molecule, m_{L}^{f}, of the standard molar enthalpy of association, $\Delta H_{\text{a}}^{\circ}$, and of the apparent association constant, K_{a}', as follows [20]:

$$\Delta H^* / m_{\text{CD}} = m_{\text{L}}^{\text{f}} \Delta H_{\text{a}}^{\circ} K_{\text{a}}' / \left(1 + K_{\text{a}}' m_{\text{L}}^{\text{f}}\right) \tag{3}$$

or in a linear form, useful for fitting the data:

$$m_{\text{CD}} / \Delta H^* = 1/\Delta H_{\text{a}}^{\circ} + 1/\left(\Delta H_{\text{a}}^{\circ} K_{\text{I}}' m_{\text{L}}^{\text{f}}\right) \tag{4}$$

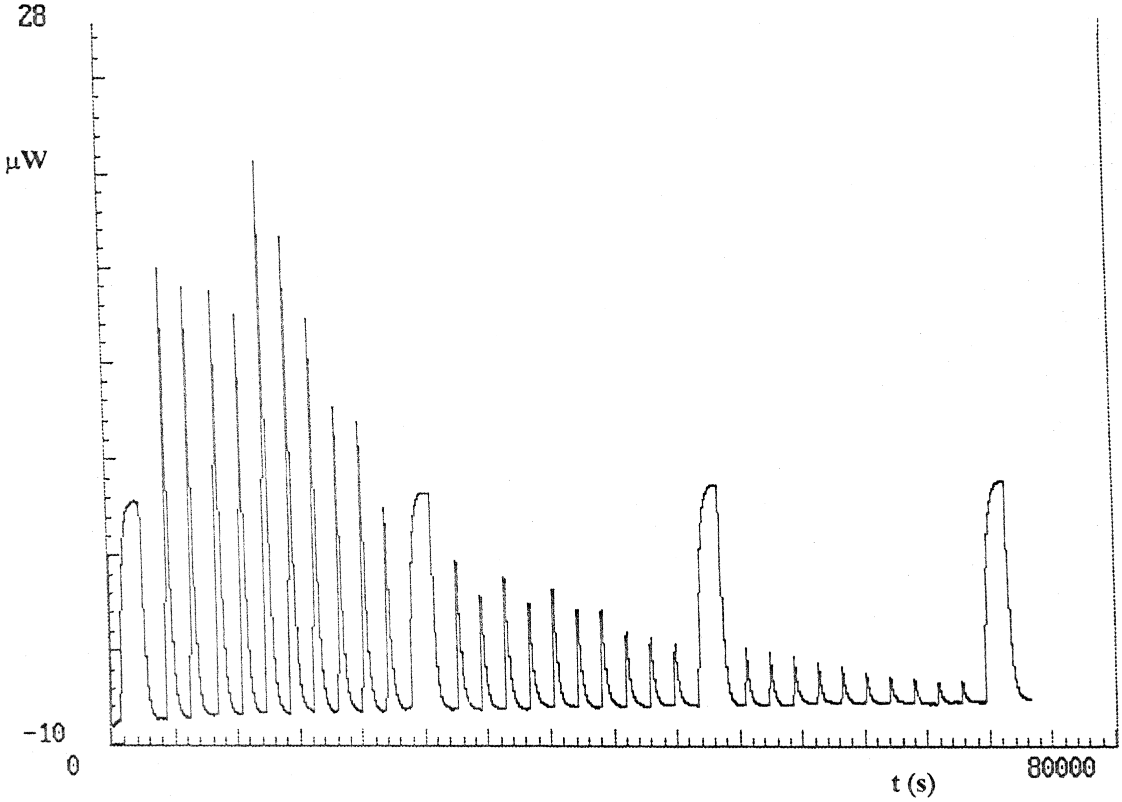

Fig. 1. Experimental power–time plot for the calorimetric titration of octane-1,8-diol with α-cyclodextrin in water at 25 °C.

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

$$m_L^f = m_L - [\Delta H^* / \Delta H^* (\text{sat})] m_{CD} \quad (5)$$

where m_L is the total stoichiometric molality of the guest. The standard enthalpy and the constant are obtained from Eqs. (4) and (5) by an iterative least square method. The iterations are continued until two successive values of ΔH_a° differ by less than 2%. The values of the free energy and entropy are then obtained through the usual thermodynamic relations.

3. Results

In Table 1, the thermodynamic parameters (constant, enthalpy, free energy and entropy) are shown for the association process involving αCD and 1-alkanols from C_3 to C_9 in water, in 0.5 mol/kg phosphate buffer, pH 11.3, and in 0.5 mol/kg phosphoric acid, pH 1.3. Because of their slight solubility in aqueous solution, higher 1-alkanols could not be studied. The association is hypothesized to occur through a 1:1 stoichiometry, in the presence of only one conformation of the alkanol. Whatever the experimental conditions are, there is a common trend in the values of the association constants: they increase regularly up to 1-hexanol and, then, vary irregularly. This is evident from Fig. 2, where the $\Delta G^{\circ\prime}$ values for 1-alkanols in water are reported vs. the total number of carbons in the alkyl chain. The standard enthalpies, being negative, generally increase at increasing length of the alkyl chain. Alkanols up to 1-octanol in acidic solution have been studied previously by Matsiu and Mochida [21], and the values of the constants were determined by spectrophotometric examination of the inhibitory effect of ROH on the association of αCD with a dye. The latter results are in agreement with our results at pH 1.3 for 1-alkanols up to 1-hexanol, while they differ for 1-heptanol and 1-octanol. The enthalpies obtained through a Van ’t Hoff plot are, instead, systematically higher.

In Table 2, the thermodynamic parameters are given for the association of αCD with monocarboxylic acids from C_3 to C_9 at pH 1.3. Constants increase regularly up to the C_6 compound, then they vary irregularly. There is a jump in the enthalpy passing from the C_6 to the C_7 compound. Owing to the slight solubility of the acids at pH 1.3, it has been impossible to study substances higher than C_9, while at pH 11.3 compounds up to C_{12} were investigated,

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

1-Alkanol	$K'^{a,b}$	$-\Delta H^{ob,c}$	$-\Delta G^{\circ\prime c,d}$	$T\Delta S^{\circ\prime c,e}$
Water				
1-Ethanol	6.7	2.5	4.7	2.2
1-Propanol	27	6.1	8.2	2.1
1-Butanol	100	9.9	11.4	1.5
1-Pentanol	275 ± 15	11.8 ± 0.2	13.9 ± 0.2	2.1 ± 0.4
1-Hexanol	1331 ± 10	13.8 ± 0.1	17.8 ± 0.1	4.0 ± 0.2
1-Heptanol	774 ± 43	20.2 ± 0.1	16.5 ± 0.1	−3.7 ± 0.2
1-Octanol	433 ± 52	22 ± 1	15.0 ± 0.3	−7 ± 1
1-Nonanol	748 ± 68	40 ± 1	16.4 ± 0.5	−24 ± 2
pH 11.3				
1-Propanol	94 ± 5	5.0 ± 0.2	11.3 ± 0.1	6.3 ± 0.3
1-Butanol	110 ± 3	8.9 ± 0.1	11.7 ± 0.1	2.8 ± 0.2
1-Pentanol	376 ± 11	11.3 ± 0.1	14.7 ± 0.1	3.4 ± 0.2
1-Hexanol	1162 ± 96	11.9 ± 0.2	17.5 ± 0.2	5.6 ± 0.4
1-Heptanol	469 ± 72	11.5 ± 0.3	15.2 ± 0.4	3.7 ± 0.7
1-Octanol	1323 ± 34	20.0 ± 0.3	17.8 ± 0.1	−2.2 ± 0.4
pH 1.3				
1-Propanol	147 ± 13	3.1 ± 10.2	12.4 ± 0.2	9.3 ± 0.4
1-Butanol	186 ± 7	6.7 ± 0.1	12.9 ± 0.1	6.3 ± 0.2
1-Pentanol	567 ± 11	10.6 ± 0.1	15.7 ± 0.1	5.1 ± 0.2
1-Hexanol	834 ± 58	15.5 ± 0.2	16.7 ± 0.2	1.2 ± 0.4
1-Heptanol	402 ± 49	25.8 ± 0.1	14.9 ± 0.3	−10.9 ± 0.4
1-Octanol	665 ± 62	26.8 ± 0.1	16.1 ± 0.2	−10.7 ± 0.3

[a] kg/mol.
[b] Errors reported are the standard deviations as obtained by fitting the data to Eq. (4).
[c] kJ/mol.
[d] Errors are half the range of $\Delta G^{\circ\prime}$ calculated from the upper and lower error in K'.
[e] Errors are the sum of the errors on free energy and enthalpy.
[f] Ref. [8].
[g] Ref. [9].

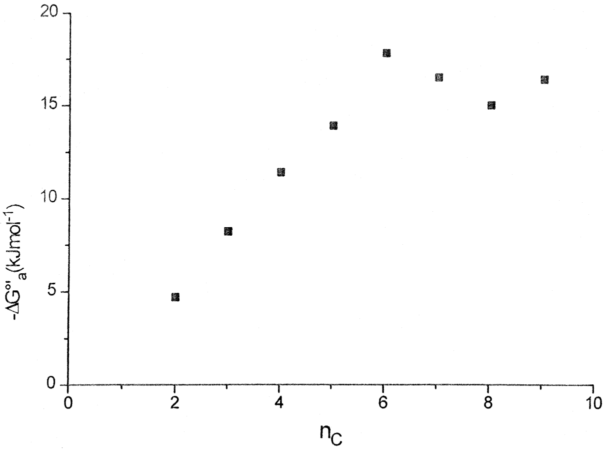

Fig. 2. Molar standard free energies, $\Delta G^{\circ\prime}$, of inclusion for 1-alkanols in water as a function of the total number of carbon atoms in the alkyl chain, n_C.

Table 2
Thermodynamic parameters for the association between αCD and monocarboxylic acids at 25 °C, pH 1.3 and 11.3

Acid	$K'^{a,b}$	$-\Delta H^{ob,c}$	$-\Delta G^{\circ\prime c,d}$	$T\Delta S^{\circ\prime c,e}$
pH 1.3				
Propanoic	55 ± 1	12.1 ± 0.2	9.9 ± 0.1	−2.2 ± 0.3
Butanoic	177 ± 8	15.3 ± 0.3	12.8 ± 0.1	−2.5 ± 0.4
Pentanoic	602 ± 26	25.1 ± 0.2	15.9 ± 0.1	−9.2 ± 0.3
Hexanoic	904 ± 7	26.5 ± 0.1	16.9 ± 0.1	−9.6 ± 0.2
Heptanoic	592 ± 42	40 ± 1	15.8 ± 0.2	−24 ± 1
Octanoic	1344 ± 109	42 ± 1	17.9 ± 0.2	−24 ± 1
Nonanoic	981 ± 48	47 ± 1	17.1 ± 0.1	−30 ± 1
pH 11.3[f]				
Propanoic		N.A.[g]		
Butanoic	86 ± 14	0.7 ± 0.1		
Pentanoic	145 ± 7	4.5 ± 0.1		
Hexanoic	511 ± 54	6.1 ± 0.1		
Heptanoic	1234 ± 68	12.2 ± 0.1		
Octanoic	1353 ± 111	18.6 ± 0.1		
Nonanoic	253 ± 20	38.4 ± 0.8		
Decanoic	253 ± 6	50.7 ± 0.3		
Undecanoic	845 ± 17	58.9 ± 0.2		
Dodecanoic	1066 ± 186	98 ± 3		

[a] kg/mol.
[b] Errors reported are the standard deviations as obtained by fitting the data to Eq. (4).
[c] kJ/mol.
[d] Errors are half the range of $\Delta G^{\circ\prime}$ calculated from the upper and lower error in K'.
[e] Errors are the sum of the errors on free energy and enthalpy.
[f] All data at this pH are taken from Ref. [10].
[g] Means that measurements have been performed, but no association was detected.

and their parameters are included in Table 2 [10]. The value of the constant for propanoic acid is in substantial agreement with that reported in the literature [22]; the enthalpy, instead, is different, probably because it was not measured directly, but obtained through a Van 't Hoff plot.

In Table 3, the thermodynamic parameters are reported for the interaction of αCD with the following cycloalkanols: cyclopentanol, cyclohexanol, cycloheptanol, and cyclooctanol. Here, the constants are much lower than those for the corresponding linear isomers. They are similar for cyclopentanol and cyclohexanol, and decrease at increasing dimensions of the ring structures. Enthalpies increase at increasing dimensions of the ring structures.

In Table 4, the association parameters are reported for the interaction between αCD and α,ω-diols, in water and in phosphate buffer, pH 11.3. Association constants increase up to the C_8 diol in water and, then, they remain almost invariant within the experi-

Table 3
Thermodynamic parameters for the association between αCD and cycloalkanols in water, at 25 °C

Cycloalkanol	$K'^{\mathrm{a,b}}$	$-\Delta H^{\circ \mathrm{b,c}}$	$-\Delta G^{\circ\prime \mathrm{c,d}}$	$T\Delta S^{\circ\prime \mathrm{c,e}}$
c-Pentanol	128 ± 5	5.0 ± 0.2	12.0 ± 0.2	7.0 ± 0.4
c-Hexanol	157 ± 9	7.9 ± 0.3	12.5 ± 0.3	4.6 ± 0.6
c-Heptanol	38 ± 3	23 ± 1	9.0 ± 0.4	− 14 ± 1
c-Octanol	38 ± 7	31 ± 4	9.0 ± 0.9	− 22 ± 5

[a] kg/mol.
[b] Errors reported are the standard deviations as obtained by fitting the data to Eq. (4).
[c] kJ/mol.
[d] Errors are half the range of $\Delta G^{\circ\prime}$ calculated from the upper and lower error in K'.
[e] Errors are the sum of the errors on free energy and enthalpy.

mental error. At pH 11.3, the constant increases up to the C_9 compound, then decreases. Enthalpies increase at increasing length of the alkyl chain with the exception of the C_8 compound in water, whose enthalpy is lower than that for the C_7 compound. Errors on the values of the association constants for the C_8–C_{10} diols in both experimental conditions are large when compared to those for the lower diols: the calculated curves do not describe well the experimental points.

4. Discussion

In a recent paper concerning the interaction of αCD with monocarboxylic acids from C_3 to C_{12} at pH 11.3, a model has been proposed to rationalize the unusual trend of the association constants for substances longer than C_7 [10]. According to this model, association occurs through the insertion of the alkyl chain into the cavity of the dextrin. Starting with the C_8 compound, the acid molecule can exist in two conformations, an extended one and a bent one, each having an association site for αCD. These two conformations are supposed to be in a frozen equilibrium, namely, they remain in their original proportions in the absence of cyclodextrin. Both associate to the cyclic acceptor with a different constant and enthalpy. The two parameters for each form were calculated and used to obtain ΔH as a function of the ratio between the concentration of αCD and that of the acid. For alkyl chains shorter than C_8 or longer than C_{10}, only one conformation associates to αCD, thus, indicating that, in these cases, the binding equilibrium is shifted towards a unique, prevailing form of the adduct.

The interaction of αCD with the present long chain 1-alkanols, when treated according to a simple

Table 4
Thermodynamic parameters for the association between αCD and alkane-α,ω-diols at 25 °C, in water and in 0.5 mol/kg phosphate buffer pH 11.3

Alkane-α,ω-diol	$K'^{\mathrm{a,b}}$	$-\Delta H^{\circ \mathrm{b,c}}$	$-\Delta G^{\circ\prime \mathrm{c,d}}$	$T\Delta S^{\circ\prime \mathrm{c,e}}$
Water				
Propane-1,3-diol[f]	4.3	6.7	3.6	− 3.1
Butane-1,4-diol[f]	8	10	5.2	− 4.8
Pentane-1,5-diol[f]	31	14.3	8.5	− 5.8
Hexane-1,6-diol[f]	94	16.1	11.3	− 4.8
Heptane-1,7-diol	275 ± 5	26.7 ± 0.2	13.9 ± 0.2	− 12.8 ± 0.4
Octane-1,8-diol	1888 ± 248	19.1 ± 0.6	18.7 ± 0.3	− 0.4 ± 0.9
Nonane-1,9-diol	1559 ± 90	29.0 ± 0.9	18.2 ± 0.1	− 11 ± 1
Decane-1,10-diol	1544 ± 336	35 ± 2	18 ± 1	− 17 ± 3
pH 11.3				
Butane-1,4-diol		N.A.[g]		
Pentane-1,5-diol	140 ± 2	9.7 ± 0.1	12.2 ± 0.1	2.5 ± 0.2
Hexane-1,6-diol	320 ± 6	12.3 ± 0.1	14.3 ± 0.1	2.0 ± 0.2
Heptane-1,7-diol	1004 ± 7	14.5 ± 0.1	17.1 ± 0.1	2.6 ± 0.2
Octane-1,8-diol	1680 ± 87	18.7 ± 0.2	18.4 ± 0.1	− 0.3 ± 0.3
Nonane-1,9-diol	2015 ± 136	24.5 ± 0.8	18.9 ± 0.2	− 6 ± 1
Decane-1,10-diol	1436 ± 480	30 ± 2	18 ± 2	− 12 ± 4

[a] kg/mol.
[b] Errors reported are the standard deviations as obtained by fitting the data to Eq. (4).
[c] kJ/mol.
[d] Errors are half the range of $\Delta G^{\circ\prime}$ calculated from the upper and lower error in K'.
[e] Errors are the sum of the errors on free energy and enthalpy.
[f] Ref. [9].
[g] N.A. means that measurements have been performed, but no association was detected.

1:1 model postulating that only one conformation of the alkanol is present, shows the same unusual trend as monocarboxylic acids at pH 11.3. The association constants increase up to 1-hexanol, then vary irregularly (see Table 1). Hence, the hypothesis of a simple 1:1 association holds only for alkanols having an alkyl chain length up to about 6 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. The hypothesis of an association occurring through the penetration of the alkyl chain and of the hydroxyl group into the cavities of two different αCD molecules, can be disregarded on the basis of preceding results on lower-molecular-mass 1-alkanols [8,9]. Briefly, these substances have been found to form inclusion complexes through the penetration of the alkyl residue into the cavity of αCD. As the length of the alkyl chain increases, the cavity is filled more effectively, and the resulting complex is characterized by larger association constants and enthalpies. The hydroxyl group lays outside the cavity, probably forming hydrogen bonds with the external hydroxyl groups of αCD. The functional hydroxyl group in more central positions, as in 2- or 3-alkanols, acts as a hook which prevents the further penetration of the alkyl chain into the αCD cavity [9]. Interpolation of the experimental data for 1-alkanols longer than C_6 with a 2:1 association model is reported in the literature, but no hypotheses are proposed about how the three molecules associate [23]. Other studies [24] about the αCD-alkanols interaction have shown, on the basis of CPK models, that for unbranched chains longer than about six carbons, some changes in conformation of both the alkanol and αCD must occur to provide a fit. The formation of these complexes can be monitored through the plot reported in Fig. 2: the trend obtained shows that, beyond 6 carbon atoms, the free energy remains almost constant. On the contrary, ΔH keeps increasing at increasing length of the alkyl chain, thus, indicating that there are still interactions between the alkanol and cyclodextrin. Moreover, the entropy change becomes negative, and the interaction is prevailingly enthalpy-driven (Table 1). Then, there must be an inversion in the interaction mechanism around $n_C = 6$–7. As a fact, starting with 1-hexanol, experimental heats of association are better reproduced using a model postulating a frozen equilibrium between two forms of the alkanols. In Fig. 3, ΔH is reported as a function of the ratio $m_{\alpha CD}$:m_{alc} for 1-heptanol at pH 1.3. The calculated points have been obtained employing a simple 1:1 association model at first, and then considering that the alcohol exists in two conformations in a frozen equilibrium. The good agreement obtained, by using the latter model, between experimental and calculated values is apparent. Probably, because of the flexibility of the alkyl chain, a bent form of the alkanol could exist together with an extended one: both would form 1:1 complexes with αCD. The question is

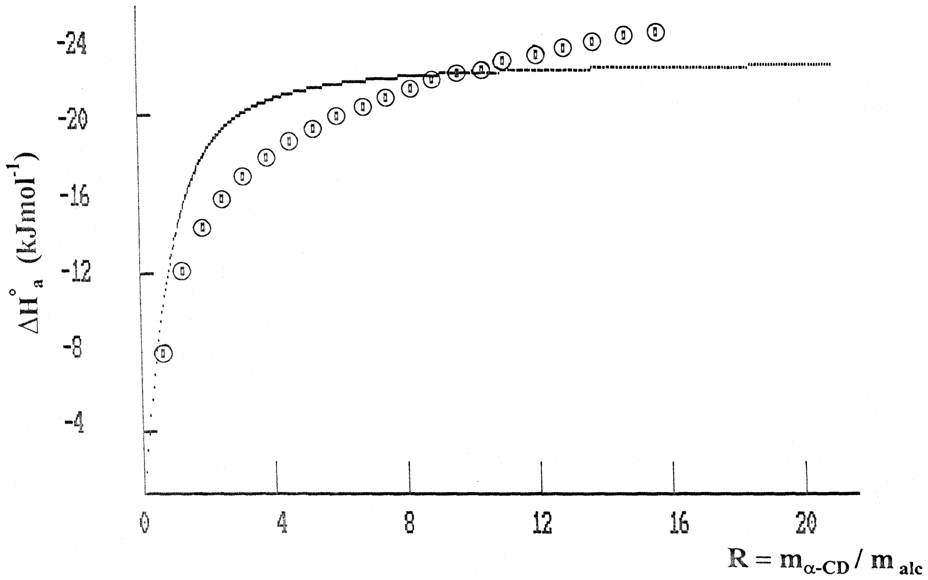

Fig. 3. Enthalpies of association, ΔH°, as a function of the ratio between the molalities of α-cyclodextrin, $m_{\alpha CD}$, and those of 1-heptanol, m_{alc}, at pH 1.3, 25 °C; experimental points (○); the calculated points were obtained by employing a simple 1:1 association model (solid curve), and the frozen equilibrium model (□).

whether the αCD cavity has dimensions that could accommodate a bent alkyl chain. To verify this point, we studied the interaction of αCD with the cycloalkanols reported in Table 3. Complexes were formed, characterized by association constants smaller than those obtained for the corresponding linear isomers. At increasing dimensions of the rings, the formation of the complexes becomes enthalpy-driven, as for linear alkanols. These cyclic substances can simulate bent alkyl chains, even though a free alkyl chain is much more flexible than a cycloalkanol, since the ring formation determines a more rigid structure. The greater flexibility of a bent alkyl chain would enable it to adapt better to the cavity. Thus, long chain alkanols could associate to αCD in a bent or an extended conformation, depending on the alkyl chain length. The possibility that the cyclodextrin also undergoes a conformational transition favoring the formation of such complexes cannot be excluded. The assumption that alkanols exist in a frozen equilibrium between two conformations may appear rather artificial, since other conformers and adducts in solution cannot be excluded. However, the proposed model must be intended only as a first effort to explain results that are unexplainable through other known models. Nevertheless, the very good consistency of the experimental data with this interpretation in the case of long-chain alkanols, as well as for monocarboxylic acids at pH 11.3, may be the basis for the proposal of more sophisticated studies concerning the mechanistic implications of complexation.

Monocarboxylic acids at pH 1.3 interact with αCD with constants and enthalpies greater than those at pH 11.3. Association occurs starting from propanoic acid (Table 2), while the propanoate anion does not form complexes. This is an indication that the uncharged carboxyl group allows the chain to penetrate better the cavity. The interaction is enthalpy-driven for all acids: constants show a regular trend up to hexanoic acid, and then an irregular variation, less pronounced as compared to alkanols and charged acids. However, differently from what occurs at pH 11.3, the frozen equilibrium model does not describe the experimental data at pH 1.3. The formation of 2:1 complexes could occur starting from heptanoic acid, a hypothesis based on preceding studies where evidence was given for the presence of such kind of complexes for higher-molecular-mass α,ω-dicarboxylic acids at pH 1.3 [11]. Hence, association should occur through the inclusion of the alkyl chain and of the uncharged carboxyl group into the cavities of two different molecules of cyclodextrin. The two association sites, however, would be not independent for the small length of the alkyl chain. That makes the treatment of the experimental data difficult, lacking the literature of models describing the association to this kind of sites.

Preceding thermodynamic and NMR spectroscopic studies on the interaction of αCD with lower-molecular-mass α,ω-diols support the hypothesis that the interaction involves mainly the exterior of cyclodextrin [9]. The molecule of an α,ω-diol caps the base of αCD with the alkyl chain pointing towards the cavity and the hydroxyl groups hydrogen-bonded to two hydroxyl groups on the rim of αCD. This capping mechanism, similar to that found for the interaction of cyclodextrins with other bifunctional compounds [25], seems the only suitable to describe the interaction between αCD and the low-molecular-mass diols. For C_8, C_9 and C_{10} compounds, instead, the fitting parameters do not reproduce well the experimental data. It is reported elsewhere that the formation of complexes with higher-molecular-mass α,ω-diols occurs through a 2:1 stoichiometry [26]. However, as discussed before, the association through the insertion of the hydroxyl groups into the cavity is not probable. More interesting, instead, is the mechanism proposed for the interaction of the diaminohexaethylene cation, DAHE, with αCD in aqueous solutions [27]: the alkyl chain lays in the interior of αCD, while the positively charged amino groups stay outside the cavity. Then, longer chain α,ω-diols could give this kind of complexes in addition to those formed through the capping mechanism.

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 [28]. Enthalpies are the sum of several and contrasting effects. For αCD, water molecules included in the cavity are displaced to the medium, whereas rearrangements in the external hydration shell exist. At the same time, the hydration shell of the hydrophobic part of the guest molecule loses some water molecules on entering the cavity. Both effects are endothermic. However, the reconstitution of the hydration shell of the complex, dipole-induced dipole and 'host–guest' interactions, hydrogen bonds, and the decrease in energy when a hydrophobic residue fills the cavity make the value of the enthalpy negative. A plot of the $\Delta H°$ values for the compounds up to C_5 vs. the number of carbon atoms in the alkyl chains of alkanols in the different experimental con-

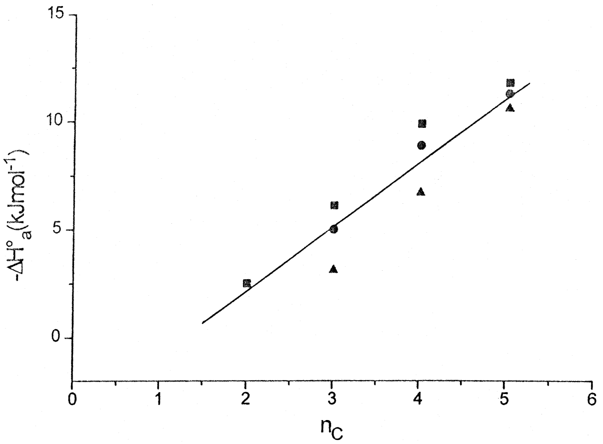

Fig. 4. Enthalpies of inclusion, ΔH°, for 1-alkanols as a function of the total number of carbon atoms in the alkyl chain, n_C, in water (■), at pH 1.3 (▲) and pH 11.3 (●), 25 °C.

ditions (Fig. 4) shows that all data roughly group around a line, thus, indicating that the interaction of a methylene group with the αCD cavity is scarcely influenced by the medium. Then, any differences in solute–solvent interactions of the isolated guest molecules before reaction do not contribute significantly to the enthalpy of association, in agreement with other findings reported in the literature [29]. From Fig. 4, it can be observed also that enthalpies in water are slightly but constantly higher than those at pH 1.3 and 11.3. At these pHs, the dielectric constant of the medium increases, thus weakening hydrophilic interactions between the hydroxyl group of the alkanols and the external hydroxyl functions of cyclodextrin, making the ΔH° values less negative. This effect is more pronounced for diols (see Table 4), probably because of the importance of external hydrophilic interactions. 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 [30]. A linear trend is obtained when reporting ΔH vs. 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 substances [28,31–33]. For the data shown here, the slope, called the ‘compensation temperature’, is 6 ± 1 °C, a value consistent with the $-23 \div 47$ °C range characteristic of processes dominated by aquation phenomena. Then, deaquation of both guest and host molecules is an effect determining the stability of the inclusion complex. The empirical linear correlation between ΔH and ΔS means that, whatever the cause, the resulting change in $T\Delta S$ is proportional to the consequent change in ΔH:

$$\Delta H = a + T_C \Delta S$$

$$\Delta(\Delta H) = T_C \Delta(\Delta S)$$

$$\Delta(\Delta S) = (1/T_C)\Delta(\Delta H)$$

where T_C is the compensation temperature. Multiplying both terms of the last equation by the temperature of the actual measurements, T, we obtain

$$T\Delta(\Delta S) = (T/T_C)\Delta(\Delta H)$$

$$T\Delta(\Delta S) = \alpha\Delta(\Delta H)$$

where $\alpha = T/T_C$. It is reported in the literature that α values can be used as quantitative measures of the conformational changes upon complex formation [33]. Large α values (0.76–0.86) for acyclic glymes/podands and cyclic crown ethers were related to substantial or moderate conformational change exhibited by these substances. Instead, the small α value for bicyclic cryptands ($\alpha = 0.51$) was related to the more rigid skeleton that cannot greatly change the original conformation upon complexation. The α value for cyclodextrin, obtained in the present study, is close to unity ($\alpha = 1.07$), in agreement with the literature [33]. This is unexpected when considering the rigid skeleton of the cyclic acceptor alone, but could be interpreted as a confirmation that the inclusion complexation implies the reorganization of the original hydrogen bond network within the αCD molecule.

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