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Thermodynamics of the interaction of α-cyclodextrin with α,ω-dicarboxylic acids in aqueous solutions. A calorimetric study at 25°C.

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Abstract

The interaction in water of α-cyclodextrin with α,ω-dicarboxylic acids from C_5 to C_{11} has been studied calorimetrically at 25°C in phosphate buffer at pH 11.3 and 1.3. When a complex forms, calorimetry enables the calculation of both enthalpy and association constant, from which the free energy and the entropy of the process can be obtained.

At pH 11.3, 1 : 1 complexes are formed, the association occurring through the interaction of the charged carboxylate groups with the hydroxyl groups on the exterior of the dextrin. The alkyl chain should point toward the interior of the cavity. This 'capping' mechanism relies on the impossibility of the carboxylate group to reside within the cavity. At pH 1.3, the values of the association constants do not follow a regular trend with increasing alkyl chain length. Evidences are presented for a variation of the stoichiometry of association for longer chain substances. A 2 : 1 stoichiometry would be possible because of the ability of the uncharged carboxyl group to be included in the cavity.

The forces involved in the association process are discussed in the light of the analysis of the signs and values of the thermodynamic parameters. © 1997 Elsevier Science B.V.

Keywords: Calorimetry; Capping; α-Cyclodextrin; α,ω-Dicarboxylic acids; Inclusion

1. Introduction

The most important property of cyclomalto-oligosaccharides (cyclodextrins) is their ability to form complexes with a wide variety of organic substances either in solution or in the solid state [1–3]. However, notwithstanding the great number of papers on these complexes, much remains to be clarified about the forces involved in these interactions [4,5].

The smallest of these cyclodextrins, cyclomaltohexose (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 [6]. These two water molecules diffuse to the medium when an inclusion complex forms. At the same time αCD undergoes a conformational transition from a 'tense' to a 'relaxed' conformation [7]. There are few hypotheses concerning the forces involved in these inclusion processes, and many problems are still unsolved regarding the mechanism and the changes experienced by water molecules in the hydration shells of the 'guest' and 'host' molecules.

In preceding papers we have reported on the binary aqueous solutions of αCD [8,9] and on its interaction with hydroxylated substances [8,10], alkylureas [11], aminoacids [9,12,13], monocarboxylic acids [14] and

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other small molecules [15,16]. Our present contribution reports a calorimetric study on the association of αCD with α,ω-dicarboxylic acids from C_5 to C_{11} at 25°C, in phosphate buffer, at pH 11.3 and 1.3. The aim of this study is to analyze the role of the functional group in the association process, to understand the forces involved in this interaction, and to verify whether a stoichiometry different from 1 : 1 holds for longer chain acids. As well as the detection of the thermal effect, calorimetry shows whether an association process occurs and allows the evaluation of its equilibrium constant, from which the free energy and entropy of the process can be derived.

2. Experimental

2.1. Materials

α-Cyclodextrin and the acids employed were purchased from Sigma. The optical rotations of αCD were in agreement with those reported in the literature. Solutions were prepared by weight, using doubly distilled water.

Solutions at pH 1.3 were prepared by dissolving 0.5 m phosphoric acid in water. For solutions at pH 11.3, a 0.5 m NaH_2PO_4/NaOH buffer was employed. The choice of this buffer is determined by the need of avoiding anions interfering with the inclusion process. It is reported [17] that phosphate and sulfate anions satisfy this requirement in a wide pH range. The concentration of α,ω-dicarboxylic acids varies between 2.0×10^{-3} m and 3.0×10^{-3} m for solutions at pH 11.3, and between 5.2×10^{-4} m and 2.0×10^{-3} m for solutions at pH 1.3.

2.2. Calorimetry

The values of the experimental heats of mixing, $\Delta_{\mathrm{mix}}H$, of two binary solutions containing any one of the solutes, were determined at 25°C by means of a thermal activity monitor (TAM) from 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 phosphate buffer were determined using the same number of injections and concentrations as in the titration experiments, and subtracted from the enthalpies of the mixing process.

2.3. Treatment of the data

Under the assumption that a 1 : 1 complex forms, the association process can be represented as follows:

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

where CD indicates α-cyclodextrin and L any of the guest substances employed. The heats of mixing of the two binary solutions, subtracted from the heats of dilution experienced by the two solutes [18], gives the enthalpy of formation of the complex, ΔH^*, that can be expressed as a 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 [8,19]:

$$\Delta H^*/m_{\mathrm{CD}} = m_L^{\mathrm{f}}\Delta H_{\mathrm{a}}^0 K_{\mathrm{a}}'/(1 + K_{\mathrm{a}}' m_L^{\mathrm{f}}) \tag{2}$$

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

$$m_{\mathrm{CD}}/\Delta H^* = 1/\Delta H_{\mathrm{a}}^0 + 1/\Delta H_{\mathrm{a}}^0 K_{\mathrm{a}}' m_L^{\mathrm{f}} \tag{3}$$

The standard enthalpy and the constant are obtained from Eq. (3) by an iterative least squares method. The iterations are continued until two successive values of ΔH_{a}^0 differ within 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 (association constant, enthalpy, free energy and entropy) are shown for the association process involving αCD and the α,ω-dicarboxylic acids from C_7 to C_{11} in phosphate buffer at pH 11.3. These values have been obtained under the hypothesis that the association occurs through a simple 1 : 1 stoichiometry. Terms lower than heptanedioic acid do not form complexes. Enthalpies and constants increase with increasing length of the alkyl chain. Within the limits of the experimental errors, the constants for the C_{11} and C_{10} terms are the same. It is to be noted that the lack of

Table 1

Thermodynamic parameters for the association between α-cyclodextrin and α,ω-dicarboxylic acids reported at 25°C in 0.5 m phosphate buffer, pH 11.3

α,ω-Acid	K' [a,b]	$-\Delta H^0$ [b,c]	$-\Delta G^0$ [b,d]	$T\Delta S^0$ [b,e]
Heptanedioic [f]	24±1	10.1±0.3	7.9±0.1	−2.2±0.4
Octanedioic	93±3	11.8±0.1	11.2±0.1	−0.6±0.2
Nonanedioic	629±21	14.0±0.1	16.0±0.1	2.0±0.2
Decanedioic	1786±83	16.2±0.1	18.6±0.1	2.4±0.2
Undecanedioic	1580±256	22.7±0.6	18.3±0.4	−4±1

[a] In kg mol^{-1}; [b] Errors are standard deviations as obtained by fitting the data to Eq. (3); [c] In kJ mol^{-1}; [d] Errors are half the range of the extreme values of the association constants; [e] Errors are the sum of the errors on free energy and enthalpy; [f] Terms lower than C_7 do not give association.

Table 2

Thermodynamic parameters for the association between α-cyclodextrin and α,ω-dicarboxylic acids reported at 25°C, in 0.5 m phosphoric acid, pH 1.3

α,ω-Acid	K' [a,b]	$-\Delta H^0$ [b,c]	$-\Delta G^0$ [b,d]	$T\Delta S^0$ [b,e]
Pentanedioic [f]	257±11	25.4±0.6	13.8±0.1	−11.6±0.7
Hexanedioic	280±5	26.8±0.2	14.0±0.1	−12.8±0.3
Heptanedioic	728±5	28.1±0.1	16.3±0.1	−11.8±0.2
Octanedioic	290±8	54.6±0.7	14.1±0.1	−40.5±0.8
Nonanedioic	432±8	70.7±0.5	15.0±0.1	−55.6±0.6
Decanedioic	2281±267	79±1	19.2±0.3	−60.0±1.3

[a] In kg mol^{-1}; [b] Errors are standard deviations as obtained by fitting the data to Eq. (3); [c] In kJ mol^{-1}; [d] Errors are half the range obtained from the extreme values of the association constant; [e] Errors are the sum of the errors on free energy and enthalpy [f] Terms lower than C_5 do not give association.

information about activity coefficients leads to the evaluation of apparent association parameters.

In Table 2, the same thermodynamic parameters are reported for α,ω-dicarboxylic acids from C_5 to C_{10} at pH 1.3. Association occurs from the C_5 term, while at pH 11.3 it begins from the C_7 term. The C_{11} term could not be studied, owing to its very low solubility at this pH. As an example, in Fig. 1 the experimental and calculated data are shown for the hexanedioic acid–αCD system. In the upper panel the experimental ΔH^*s, normalized to the total molality of the acid, are reported as a function of the ratio between the final molality of cyclodextrin and that of the acid. In the lower panel, $m_{\rm acid}/\ \Delta H^*$ vs. $1/m^{\rm f}_{\alpha{\rm CD}}$ is shown. The solid lines through the experimental points have been obtained using the association constant and the standard enthalpy as evaluated through Eq. (3). The constants follow a very complex trend. At first they increase, then decrease beginning with C_8, and then increase again at C_9. There is a jump in the association enthalpy passing from the C_7 to the C_8 term. That is shown also in Fig. 2, where the standard enthalpies at both pHs are reported as a function of the number of methylene groups between the carboxyl groups. That jump is an indication that the mechanism and/or the stoichiometry of complex formation is changing. It is possible to verify experimentally the formation of complexes having a stoichiometry different from 1 : 1 through an inverse titration, namely the concentration of acid and cyclodextrin are in the inverse ratio compared to the direct titration. When stoichiometry is different from 1 : 1, the evaluated enthalpies are different. In the present case the inverse titration for both octanedioic and nonanedioic acids gives values of enthalpies about half those calculated through the direct experiment. That constitutes a strong indication of an association occurring through a 2 : 1 stoichiometry. For decanedioic acid, the inverse titration was impossible to perform because of the slight solubility of this substance.

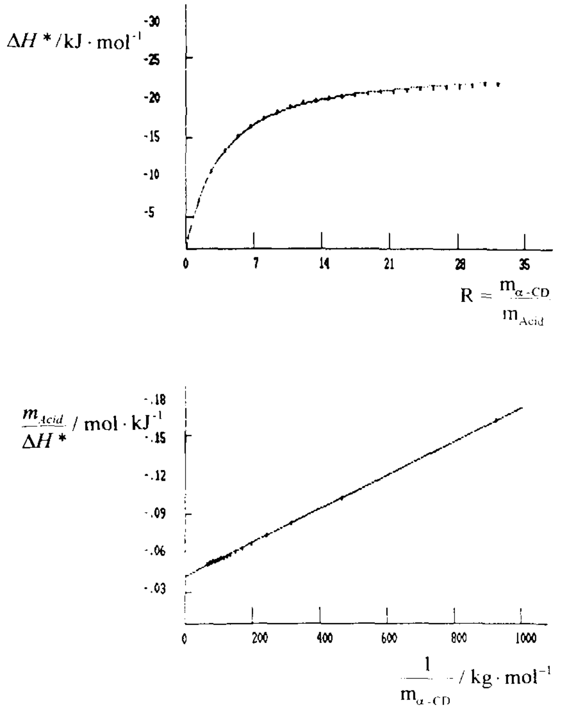

Fig. 1. Calorimetric data relative to the hexanendioic acid–α-cyclodextrin system at 25°C, in 0.5 m phosphoric acid pH 1.3. In the upper panel, ΔH^* normalized to the acid concentration is reported as a function of the ratio between the final molalities of cyclodextrin and acid. In the lower panel, $m_{acid}/\Delta H^*$ is reported vs. $1/\alpha$CD. The solid lines through the points are obtained using the association constant and standard enthapy evaluated through Eq. (3).

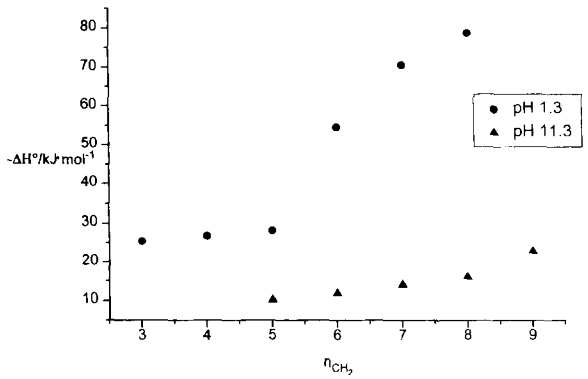

Fig. 2. Standard enthalpies of association for α,ω-dicarboxylic acids vs. the number of methylene groups between the carboxyl groups. Data at pH 1.3 (●) and at pH 11.3 (▼) are reported.

4. Discussion

From the preceding studies carried out in this laboratory on the complexes formed by mono- and polyhydroxylated substances with αCD [8,10], it was inferred that it is the alkyl chain which penetrates the cyclodextrin cavity, while the functional group forms hydrogen bonds with the external hydroxyl groups of the macrocycle. When the hydroxyl group occupies a more central position, it prevents the remainder of the alkyl chain from further penetrating the cavity. Studies on monocarboxylic acids at pH 11.3 [14] have established that inclusion occurs through the alkyl chain, while the charged carboxylate group cannot penetrate the cavity. Solvation requirements of the charged carboxylate group by water prevent the aliphatic chain from fully penetrating the cavity [20]. In contrast, the alkyl chain can penetrate deeper into the cavity when the carboxylic acid group is neutral, while this functional group may also form hydrogen bonds with the hydroxyl groups on the rim of the αCD cavity.

When the functional groups are confined to the extremities of the alkyl chain, as in the case of α,ω-diols and α,ω-aminoacids, a more complex process takes place. In fact, association cannot occur through the inclusion of the hydroxyls or charged amino and carboxyl groups in the cavity. In a preceding paper [10], calorimetric and NMR spectroscopic data concerning 1,2- and α,ω-diols interacting with αCD were rationalized proposing, for the latter substances, an interaction mechanism involving mainly the exterior of the macrocycle, namely the α,ω-diol caps the cavity, with the two hydroxyl groups forming hydrogen bonds with the external hydroxyl groups of cyclodextrin. The alkyl chain between the functional groups would point toward the interior of the cavity. This capping mechanism holds also for α,ω-aminoacids [13] – other examples are reported in the literature for the interaction of these macrocycles with some bifunctional compounds [21].

The data reported in Table 1, relative to the α,ω-dicarboxylic acids at pH 11.3, show that association occurs starting from the C_7 term. Association constants for the lower terms are smaller when compared to those for monocarboxylic acids having the same number of carbon atoms [14]. The presence of the charged carboxylate groups at the extremities of the alkyl chain could make the capping mechanism to be the only possible one, since the inclusion of this group in the cavity of the dextrin is probably energetically prohibitive [20]. At increasing length of the alkyl chain the association constants increase, indicating the optimization of the interactions between the alkyl chain and the cavity. When the alkyl chain is not long enough, as for the C_6 term, interactions are so weak that association does not occur. The association parameters for these systems strictly resemble those relative to the interaction of αCD with α,ω-aminoacids [13] and α,ω-diols [10] having the same number of CH_2 between the functional groups. Both 5-aminopentanoic and hexanedioic acids do not associate detectably with the cyclodextrin, while for the next term of both series the values of the association constants are similar. Pentane-1,5-diol and hexane-1,6-diol are characterized by association constants very similar to those for heptanedioic and octanedioic acids, respectively. Since these α,ω-substances are characterized by functional groups which do not enter into the cavity, association must occur predominantly through interactions with the exterior of the cyclodextrin. The association of undecanedioic acid with αCD is characterized by a constant similar, within the limits of the experimental error, to that for decanedioic acid. The longer molecule could undergo a distortion in adapting on the base of αCD, thus lessening favorable interactions with the cavity. On the other hand, it is reported in the literature that the complexation of diammoniohexaethylene cation with αCD is not possible in the crystalline state because of the positively charged ammonio groups at the ends [22]. However, the same cation forms a 1 : 1 complex with αCD in aqueous solutions, with three ethylene units threaded through one molecule of the macrocycle, and the two charged ends outside the cavity. The same association mechanism could hold for decanedioic and undecanedioic acids: therefore, the similar values of the two constants should be determined by the inclusion of the same portion of the alkyl chain in the cavity.

At pH 1.3, where the carboxyl group is present in neutral form, association is characterized by enthalpies negative and larger than those at pH 11.3, as shown in Table 2. This means that the uncharged carboxyl group induces more favorable interactions of the whole molecule with the cavity and the hydroxyls on the rim of cyclodextrin. An analogous increase in enthalpy has been observed also for the interaction of monocarboxylic acids with αCD passing from pH 11.3 to pH 1.3 [23]. The trends of both constants and enthalpies for the first three terms reported in Table 2 are similar to those obtained at pH 11.3 for heptane-, octane-, and nonanedioic acids, thus underlining that the association probably occurs through the same capping mechanism. There is a discontinuity passing from heptanedioc to octanedioic acid in the values of both enthalpies and constants. In fact, the enthalpy for octanedioic acid almost doubles that relative to heptanedioic acid, while the constant drops to the values characterizing the association with the smaller terms. Then, another mechanism must be proposed to describe this association. Owing to the possibility of the uncharged carboxyl group to be included in the cavity, the formation of the complex can be hypothesized to occur through a 2 : 1 stoichiometry. Two carboxyl groups, together with parts of the alkyl chain, could be included in the cavities of two different molecules of cyclodextrin. The inverse titration carried out for octanedioic and nonanedioic acids gave enthalpy values about half those derived in the direct experiment. This is a strong experimental indication that the complex has a 2 : 1 stoichiometry. Then, the acid molecule should have two sites available for the association to the macrocycle: these two sites, however, would be neither equivalent nor independent. In fact, the association with the first molecule of αCD influences the association on the second site. Only on lengthening the alkyl chain beyond a certain limit would the sites become independent and equivalent. In the case of decanedioic acid the formation of 2 : 1 complexes could be also hypothesized – the high value of the constant, then, could be explained as due to an improved inclusion of the extremities of the molecule in the cavities of two molecules of αCD. However, for this substance it was impossible to perform the inverse titration. The formation of 2 : 1 complexes is widely reported in the literature. For instance, for the αCD–adamantanecarboxylate system the formation of 2 : 1 complexes is proposed, with the acid molecule squeezed between two molecules of α-cyclodextrin [20]. Other authors report that, in the case of α,ω-diols, 2 : 1 complexes are formed starting from 1,8-octanediol [24], without proposing any hypothesis about the association mechanism.

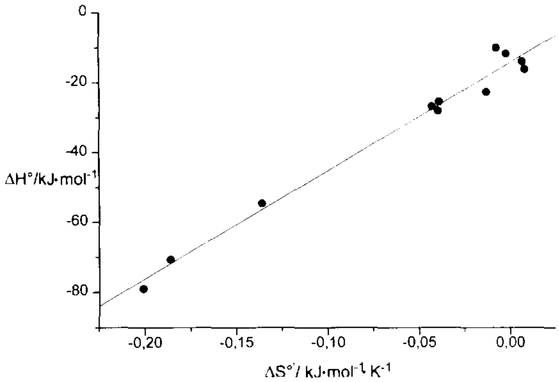

Fig. 3. Standard enthalpies of association vs. standard entropies for all systems reported in Tables 1 and 2, at 25°C.

In general, the values of the enthalpies characterizing these complexes vary regularly with the alkyl chain length: some discontinuities are noted, as at pH 1.3 passing from heptanedioic to octanedioic acid. ΔH^0 values are negative for most of the complexes reported in the literature. They are the sum of several contrasting effects determined primarily by the changes of water upon the inclusion process. For αCD water molecules included in the cavity are displaced to the medium, whereas there are rearrangements in the external hydration shell. 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. Thus, there are several effects involved in the formation of these complexes. Hydrophobic interactions do not always play the major role, as indicated by the positive or negative values of the entropies. At pH 1.3, only negative ΔS^0 values are found, and that could be ascribed to the different desolvation of the charged and uncharged carboxyl groups. The jump in the ΔS^0 values passing from heptandioic to octanedioic acid could be explained assuming that 2 : 1 complexes are formed with the C_8 to C_{10} terms. The acid molecule, squeezed between two macrocycles, would experience a large decrease of degrees of freedom. A plot of ΔH^0 vs. ΔS^0 for the systems here studied gives a linear trend (see Fig. 3): then, there is an enthalpy-entropy compensation, a phenomenon frequently observed in water, and ascribed to the modifications experienced by the solvent water in the hydration shells of the interacting substances [25–27]. The slope of the graph called the 'compensation temperature' gives 298 ± 11 K, a value consistent with the 250–320 K range characteristic of processes dominated by solvation phenomena. It can be concluded that changes in solvation of both the guest and host molecules play an important role in the formation of the complex.

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