The Effects of Cosolvents on the Complexation of α-Cyclodextrin with Alkylated Substances. Calorimetric Studies at 25 °C

GIUSEPPINA CASTRONUOVO*,   VITTORIO ELIA, MARCELLA NICCOLI and FILOMENA VELLECA
Department of Chemistry, University Federico II of Naples, Complesso Universitario di Monte S. Angelo – via Cintia-80126 Naples, Italy

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Abstract

The formation of complexes of α-cyclodextrin with 1,2-alkanediols, α,ω-alkanediols and some cycloalkanols has been studied calorimetrically at 25 °C in water, in 7 mol kg^{-1} aqueous urea and in 3 mol kg^{-1} aqueous glucose. 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 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. As respect to water, complexes are less stable in urea and more stable in glucose. The analysis of the data shows that this is the result of a different enthalpy-entropy balance in the two solvent media. Deaquation of the interacting substances plays a major role in determining the stability of the inclusion complexes.

Introduction

Cyclodextrins (Cds), cyclic oligomers of α-D-glucose, are characterized by a fairly polar exterior and by a cavity which 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, αCD, 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, αCD 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 problems 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 αCD's interaction with hydroxylated substances [11–14], monocarboxylic acids [12, 15], α,ω-dicarboxylic acids [16], aminoacids [17–19], cycloalkanols [20] and other small molecules [21–23] in water and/or in aqueous phosphate buffer, pH 11.3, pH 1.3, and pH 5.5. 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. To that, a calorimetric study at 25 °C is reported of the interaction of αCD with 1,2- and α,ω-alkanediols from C$_3$ to C$_{10}$ and with some cycloalkanols in aqueous 7 mol kg^{-1} urea and 3 mol kg^{-1} glucose. The role of the two cosolvents will be analyzed: these two substances act differently on water structure, since the former is the most common hydrophilic structure breaker, while the latter is a hydrophilic structure maker. For association processes involving CDs and a variety of guest molecules, a linear trend is commonly 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 host and guest molecules [1, 4, 6, 24–26]. Here, we shall analyze how the presence of urea and glucose alters the thermodynamic parameters characterizing the association process and whether enthalpy-entropy compensation still holds in the mixed solvents. 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 make hypotheses about the forces involved in the interaction.

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*   Author for correspondence.
E-mail: castronuovo@chem.stuy.umina.it

Experimental

Materials

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

The concentration of diols varied between 3.5×10^{-4} and 5.3×10^{-3} mol kg^{-1}, while that of αCD was between 1.6×10^{-4} and 3.9×10^{-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, 20].

Treatment of the data

Under the hypothesis of a 1:1 stoichiometry, 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^o, and of the apparent association constant, K_a', as follows [27]:

$$m_{CD}/\Delta H^* = 1/\Delta H_a^o + 1/\Delta H_a^o K_a' m_L^f). \tag{1}$$

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

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

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 a least-squares procedure reported in preceding papers [12–15, 20]. 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]:

$$\Delta H_{dil} (m^i \rightarrow m^f) = h_{xx}m^f(m^f-m^i) \\ + h_{xxx} m^f(m^{f2}-m^{i2}) + \dots \tag{3}$$

where ΔH_{dil} (Jkg^{-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.

Results and discussion

From preceding studies carried out in this laboratory on the complexes formed by mono and polyhydroxylated substances with αCD, it was inferred that it is the alkyl chain which 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]. Beyond that, 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 αCD 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 [31]. These and many other data reported in the literature [6] are consistent with the assumption that the hydrophilic groups of the guests, with the exception of the phenolic hydroxyl group, remain in the bulk solution before and after the association with the cyclodextrin.

The thermodynamic parameters for the association process involving αCD and 1,2-alkanediols from C$_5$ to C$_8$ in 7 mol kg^{-1} aqueous urea are reported in Table 1. Higher-molecular-mass diols could not be studied because of their poor solubility in this solvent, while for lower-molecular-mass diols association was not detected. Constants and enthalpies increase at increasing alkyl chain length. That is in agreement with an association process occurring through the inclusion of the alkyl chain of the guest: enthalpies increase along the series for a progressively better adaptation of the hydrophobic alkyl chain into the macrocycle cavity. The presence of the caotropic cosolvent modifies markedly the association parameters as respect to those in water (data shown in the same Table). In fact, enthalpies and constants are smaller, while entropies, negative in water, become positive. Moreover, the formation of a stable complex starts from 1,2-pentanediol in urea, and from 1,2-propanediol in water. For α,ω-alkanediols, the formation of a stable complex starts from the C$_6$ term in urea and from the C$_3$ term in water. In the mixed solvent, it occurs with a very pronounced decrease in the values of the enthalpies.

Several factors can determine the influence of the cosolvent on the intermolecular interactions acting in the association process: among them, the changes in the dielectric constant of the medium, in the structure of bulk water and in the hydrophobic hydration of the alkanediol. As a consequence of the increased dielectric constant of the medium owing to the presence of urea, enthalpies are less negative than in water, because of the attenuation of hydrophilic interactions between the hydroxyl groups of the alkanediol and the external ones of the cyclodextrin. This effect is much more evident for α,ω-diols which cap α-cyclodextrin forming hydrogen bonds with the hydroxyl groups of the macrocycle [13]. The attenuation of hydrophilic interactions probably determines the failure in associating with α,ω-diols shorter than 1,6-hexanediol, while in water that

Table 1. Thermodynamic parameters for the association between αCD and 1,2-alkane-diols or α,ω-alkanediols at 25 °C, in 7 mol kg^{-1} aqueous urea and in water

1,2-alkanediol	K_a' [a,b]	$-\Delta H_a^o$ [b,c]	$-\Delta G_a^{o'}$ [c,d]	$T\Delta S_a^{o'}$ [c,e]
7 mol kg^{-1} urea		1,2-alkanediols		
1,2-pentanediol	53 ± 5	2.0 ± 0.2	9.8 ± 0.3	7.8 ± 0.5
1,2-hexanediol	63 ± 7	5.3 ± 0.4	10.3 ± 0.3	5.0 ± 0.7
1,2-octanediol	231 ± 23	12.6 ± 0.6	13.5 ± 0.3	0.9 ± 0.9
		α,ω-alkanediols		
1,6-hexanediol	70 ± 10	2.1 ± 0.2	10.5 ± 0.3	8.4 ± 0.5
1,7-heptanediol	321 ± 27	2.9 ± 0.1	14.3 ± 0.1	11.4 ± 0.2
1,8-octanediol	158 ± 6	12.5 ± 0.1	12.5 ± 0.1	0.3 ± 0.4
1,9-nonanediol	382 ± 44	13.1 ± 0.9	14.7 ± 0.3	2 ± 1
1,10-decanediol	541 ± 17	13.8 ± 0.3	15.6 ± 0.1	1.8 ± 0.4
Water		1,2-alkanediols		
1,2-propanediol[f]	3 ± 2	2.0 ± 1	3 ± 2	1 ± 3
1,2-butanediol[f]	12.8 ± 0.4	7.7 ± 0.1	6.3 ± 0.1	$- 1.4 \pm 0.2$
1,2-pentanediol[f]	78 ± 5	11.5 ± 0.2	10.8 ± 0.2	$- 0.7 \pm 0.4$
1,2-hexanediol[f]	185 ± 43	14.0 ± 0.4	12.9 ± 0.6	$- 1 \pm 1$
		α,ω-alkanediols		
1,3-propanediol[f]	4.3 ± 0.4	6.7 ± 0.5	3.6 ± 0.2	$- 3.1 \pm 0.7$
1,4-butanediol[f]	8 ± 1	10 ± 1	5.2 ± 0.3	$- 4.8 \pm 1.4$
1,5-pentanediol[f]	31 ± 1	14.3 ± 0.3	8.5 ± 0.1	$- 5.8 \pm 0.4$
1,6-hexanediol[f]	94 ± 7	16.1 ± 0.4	11.3 ± 0.2	$- 4.8 \pm 0.6$
1,7-heptanediol	275 ± 5	26.7 ± 0.2	13.9 ± 0.2	-12.8 ± 0.4
1,8-octanediol	1188 ± 174	19.1 ± 0.7	17.5 ± 0.4	$- 2 \pm 1$
1,9-nonanediol	844 ± 51	29.0 ± 0.9	16.7 ± 0.1	-12 ± 1
1,10-decanediol	790 ± 79	29 ± 1	16.5 ± 0.2	-12 ± 1

[a] kg/mol.
[b] Errors reported are the standard deviations as obtained by fitting the data to Eq. (2).
[c] kJ/mol.
[d] Errors are half the range of $\Delta G_a^{o'}$ calculated from the upper and lower error in K_a'.
[e] Errors are the sum of the errors on free energy and enthalpy.
[f] Ref. 13.

Table 2. Thermodynamic parameters for the association between αCD and cycloalkan-ols in water and in 7 mol kg^{-1} aqueous urea at 25 °C

Cycloalkanol	K_a' [a,b]	$-\Delta H_a^o$ [b,c]	$-\Delta G_a^{o'}$ [c,d]	$T\Delta S_a^{o'}$ [c,e]
Water				
Cyclohexanol[f]	83 ± 4	8.8 ± 0.3	10.9 ± 0.2	2.1 ± 0.5
1-cyclohexylethanol[f]	86 ± 7	11.2 ± 0.7	11.0 ± 0.2	$- 0.2 \pm 0.9$
4-cyclohexylbutan-1-ol[f]	983 ± 160	64 ± 6	17.1 ± 0.4	-47 ± 6
7 mol kg-1 urea				
Cyclohexanol	98 ± 11	0.6 ± 0.1	11.4 ± 0.3	10.8 ± 0.4
1-cyclohexylethanol	32 ± 1	2.1 ± 0.1	8.6 ± 0.1	6.5 ± 0.2
4-cyclohexylbutan-1-ol	201 ± 13	47 ± 1	13.1 ± 0.2	-34 ± 1

[a] kg/mol.
[b] Errors reported are the standard deviations as obtained by fitting the data to Eq. (2).
[c] kJ/mol.
[d] Errors are half the range of $\Delta G_a^{o'}$ calculated from the upper and lower error in K_a'.
[e] Errors are the sum of the errors on free energy and enthalpy.
[f] Ref. 20.

Table 3. Thermodynamic parameters for the association between αCD and 1,2-alkanediols and α,ω-alkanediols, in 3 mol kg^{-1} aqueous glucose at 25 °C

1,2-alkanediol	K'_a [a,b]	$-\Delta H^o_a$ [b,c]	$-\Delta G^{o'}_a$ [c,d]	$T\Delta S^{o'}_a$ [c,e]
	1,2-alkanediols			
1,2-butanediol	70 ± 8	2.1 ± 0.2	10.5 ± 0.3	8.4 ± 0.5
1,2-pentanediol	93 ± 3	10.8 ± 0.2	11.2 ± 0.1	0.4 ± 0.3
1,2-hexanediol	332 ± 5	12.5 ± 0.1	14.4 ± 0.1	1.9 ± 0.2
	α,ω-alkanediols			
1,4-butanediol	18 ± 2	2.6 ± 0.2	7.1 ± 0.3	4.6 ± 0.5
1,5-pentanediol	170 ± 26	4.8 ± 0.5	12.7 ± 0.4	7.9 ± 0.9
1,6-hexanediol	231 ± 7	13.5 ± 0.1	13.5 ± 0.1	0 ± 0.2
1,7-heptanediol	555 ± 7	18.6 ± 0.1	15.6 ± 0.1	– 2.9 ± 0.2
1,8-octanediol	1349 ± 37	25.0 ± 0.1	17.8 ± 0.1	– 7.1 ± 0.2
1,9-nonanediol	1587 ± 61	32.2 ± 0.5	18.3 ± 0.1	–13.7 ± 0.6
1,10-decanediol	1297 ± 49	42.5 ± 0.5	17.7 ± 0.1	–24.7 ± 0.6

[a] kg/mol.
[b] Errors reported are the standard deviations as obtained by fitting the data to Eq. (2).
[c] kJ/mol.
[d] Errors are half the range of $\Delta G^{o'}_a$ calculated from the upper and lower error in K'_a.
[e] Errors are the sum of the errors on free energy and enthalpy.

is possible starting from 1,3-propanediol. Upon the formation of a complex, the release of water molecules from the ordered hydration shell of the hydrophobic guest to a less structured bulk makes a positive contribution to the overall entropy. However, that effect is more significant in urea than in water for the chaotropic effect of the cosolvent on water structure, as detected by the change in the sign of entropies that pass from negative to positive. The entropic gain, however, does not balance the decrease in the enthalpy: hence, the corresponding complexes are less stable than in water, being characterized by smaller association constants.

A discontinuity in the values of enthalpies and constants exists, in water and in concentrated urea, for 1,8-octanediol, while for C_9 and C_{10} terms those quantities remain almost unchanged. This trend suggests that, in correspondence of C_8, there must be a change in the interaction mechanism proposed for α,ω-diols. The thermodynamic parameters reported in Table I have been obtained through a 1:1 model postulating the presence of only one adduct. It is reported elsewhere that the formation of complexes with higher-molecular-mass α,ω-diols occurs through a 2:1 stoichiometry, with two αCD and one guest molecule [32]. This is a reasonable hypothesis, but only if it does not provide a complexation occurring through the penetration of the hydroxyl groups into the cavities of two different αCD molecules. More plausible, instead, could be the mechanism proposed for the interaction of the diaminohexaethylene cation, DAHE, with αCD in aqueous solution: the alkyl chain lays in the interior of αCD, while the positively charged amino groups stay outside the cavity [33]. Starting from C_8, longer-chain α,ω-diols could give this kind of complexes in addition to those formed through the capping mechanism.

The thermodynamic parameters (association constant, enthalpy, free energy and entropy) for the interaction of αCD with some cycloalkanols in urea are reported in

Table 2. Constants increase as the ring increases its distance from the functional group. In fact, the constant for 4-cyclohexylbutan-1-ol is much higher than that for 1-cyclohexylethanol, probably because the cycle of the former substance can penetrate deeply into the cavity: the better adaptation, then, determines the jump in the complexation enthalpy and constant. The values of the association parameters are very different from those in water [20] (data shown in the same table), and the differences in the two media are similar to those found for the two series of alkanediols described before.

As a conclusion, the large decrease in the enthalpies, when going from water to urea, is a confirmation of the attenuation of hydrophilic interactions induced by the hydrophilic structure breaker. The magnitude of that effect is such that the resulting complexes are destabilized, notwithstanding the increase in the association entropies.

In contrast to urea, glucose has a different effect on water structure. In fact, it is a hydrophilic structure maker [34]. When reacting with hydroxylated substances, it shows a very peculiar behaviour, being similar to urea in attenuating both hydrophilic and hydrophobic interactions [35]. Therefore, it appeared interesting to study how it influences the interactions involved in the association process under investigation. The parameters for the interaction of αCD with the two classes of diols in the presence of 3 mol kg^{-1} aqueous glucose are reported in Table 3: in all cases, association is stronger than in water. However, the stability of the complexes with 1,2-diols up to 1,2-hexanediol and with the lower terms of α,ω-diols is mainly determined by a favourable entropic contribution, while enthalpies are smaller than in water. On the contrary, the stability of the complexes with the higher α,ω-diols depends on the enthalpies, more negative than in water. The standard enthalpy of association is the sum of several contributions, the most important among them being (i) van der Waals interactions between the alkyl

Table 4. Pairwise enthalpic interaction coefficients for αCD at 25 °C

h_{xx} [a]	solvent
–3920 ± 65[d]	water
2760 ± 56	7 mol kg^{-1} urea
–1254 ± 112	3 mol kg^{-1} glucose

[a] Errors reported are the 95[b] Concentration range, mol kg^{-1}.
[c] Number of experimental points.
[d] Ref. 17.

chain of the guest and the macrocycle cavity, (ii) hydrophilic interactions between the hydroxyl groups of the guest and those of αCD, and (iii) the dehydration of the guest molecule. The first contribution depends essentially on the nature of the guest molecule: it is almost unaffected by the change in the solvent medium when a guest includes into the cavity. The presence of a cosolvent, instead, strongly influences the remaining two contributions. Studies of the binary aqueous solutions of saccharides show that these substances have a greater affinity for the solvent molecules than for other solutes present in solution [34]. That leads to the reduction of the hydrophobic hydration shells of the solutes and, consequently, to the attenuation of hydrophobic interactions. The discontinuity observed also in glucose, in correspondence of 1,8-octanediol, could be evidence of the transition from a capping to an inclusion mechanism. For the latter one, the reduction of the hydration shells makes smaller the endothermic contribution resulting from the dehydration of the including diol, leading to association enthalpies more negative than in water. As a conclusion, for lower-molecular-mass diols, the prevailing effect is the attenuation of hydrophilic interactions. For higher-molecular mass diols, a reduced hydrophobic interaction makes the enthalpies more favourable to the association. The association in glucose, then, is a complex process, where the overall enthalpy-entropy balance of the different effects is such to determine always an increase in the association constants.

The possibility that, in the different solvent media, α-cyclodextrin undergoes a conformational transition upon the formation of complexes cannot be excluded. In the aim to analyze this point, binary solutions of αCD have been studied in concentrated aqueous solutions of urea and glucose. In Table 4, the pairwise enthalpic interaction coefficients are reported. These coefficients are strongly dependent on the experimental conditions, as they are negative in water and in glucose, and positive in urea. That large variability could be an indication of conformational changes induced in the macrocycle by the different solvent media. This hypothesis is strengthened by the observation that the first term giving association is different for the three solvents employed.

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^{o} and ΔS^{o}, some authors proposed that the stability of the complexes relies on a combined hydrophobic interaction [36]. As usually occurs in the formation of these complexes, a linear trend is obtained from plotting ΔH vs ΔS for all data presented in this study, independently of the experimental conditions employed. This enthalpy-entropy compensation is a phenomenon characteristic of processes dominated by aquation phenomena [1, 4, 6, 12, 24–26]. Then, even in mixed solvents, deaquation of both guest and host molecules is an effect determining the stability of the inclusion complex. The ratio, α, between the compensation temperature and the actual temperature of experiments has been used as a quantitative measure of the conformational changes occurring upon complex formation [6]. The α value obtained in the present study for α-cyclodextrin is close to unit ($\alpha = 1.2$), in agreement with the literature. That is unexpected when considering the rigid skeleton of αCD alone, since it indicates a ring flexibility [12, 26]. However, it could be interpreted as a confirmation that the inclusion complexation implies the reorganization of the original hydrogen bond network within the αCD molecule. The large variation of the h_{xx} coefficient could just measure the ring flexibility in adapting to the different media.

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