Study at a Molecular Level of the Transfer Process of a Cationic Surfactant from Water to β-Cyclodextrin

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A high-precision technique for the simultaneous measurement of the speed of sound and density has been used to characterize the inclusion of decyltrimethylammonium bromide (DTAB) in the cavity of cyclodextrin (β-CD) in water. The partial derivatives of the density, speed of sound, volume, and compressibility with respect to the molality of the guest at fixed moles of water and β-CD have been obtained at 298.15 K, for different concentrations of the host molecule. The associated thermodynamic properties, molar volumes and compressibilities, are very different in the presence or in the absence of CD, when extrapolated to infinite dilution. This can only be explained in terms of drastic changes in the hydration state of the host and guest in the reaction. A model involving hydration molecules of water for the reaction has been proposed, yielding 6.5 water molecules within the CD in solution, as in solid state. The compressibility results can be explained in terms of the differences in hydrophobicity of the water and the surfactant in the process. ^{1}H NMR together with molecular modeling have been used to characterize the microscopic structure of the complex, with results consistent with those from analysis of the thermodynamic properties.

Introduction

Cyclodextrins (CDs) are cyclic oligosaccharides with six, seven, or eight glucopyranose units linked by glucosidic bonds α-1,4 (α-, β-, and γ-cyclodextrins, respectively). They have a toroidal or hollow, truncated, cone shape, with an apolar, hydrophobic interior and two hydrophilic rims, formed by the primary (narrower rim) and secondary (wider rim) OH groups. Because of their unusual structure, the CDs can form inclusion complexes through noncovalent interactions with molecules that fit into the cavity. Cyclodextrins are consequently of great interest in a variety of fields.[1]

There are many studies in the bibliography concerning the encapsulating properties of CDs with many different compounds,[2] together with the calculation of stoichiometries and equilibrium constants.[3] However, little attention has been paid to the role that water molecules have in these reactions. Volumetric properties of solutes are known to be sensitive to the degree and nature of the solute hydration, and many measurements have been done on more or less simple compounds containing hydrophobic and hydrophilic groups, such as alcohols,[4] carboxylic acids,[5] carbohydrates,[6] nucleotides,[7] aminoacids,[8] etc. Since the formation of an inclusion complex with CDs involves changes in the hydration water of both host and guest molecule, it must be reflected in thermodynamic properties related to the volume and compressibility of the species involved. To the best of our knowledge there is only the work of De Lisi and co-workers in which apparent molar properties of β-CD in the presence of dodecyltrimethylammonium bromide ($C_{12}TAB$) have been measured.[9] Despite the precision of the techniques employed by them, the study of the process requires a higher number of values below the stoichiometric point. This is the most interesting zone to understand the complexing process and the role of the water molecules.

As changes in the thermodynamic properties take place in a rather small and low concentration range, it is necessary to obtain values at very close intervals, making the relative change in the property even more important than its absolute value. Apparent molar properties, the most commonly studied, are not very useful in studying these systems and it is necessary to obtain the molar properties.

In this work we have measured the speed of sound and density for the ternary system β-CD + DTAB + water, and from these, the molar volumes and adiabatic compressibilities have been calculated. To obtain these properties with the required precision, a very precise technique has been developed to measure simultaneously density and speed of sound. It has the advantage, in relation to common experiments of this kind, that the sweep in concentration is performed continuously, so that between two consecutive points of very close concentration the system is not perturbed and the property and its derivative can be obtained with higher precision. These experiments give us information at a molecular level of the nature of the complex and the effect that the CD has on the micellization. A molecular modeling and ^{1}H NMR study has been done together with the thermodynamic study to reinforce the conclusions about the microscopic structure of the complex.

Experimental Section

Materials. β-CD was obtained from Aldrich and DTAB from Kodak. The purity of the β-CD is 99.5% and for the DTAB better than 99%. The water content of the cyclodextrin, determined by thermogravimetric analysis, was 13.5%. All the products were used as received, without further purification. For the NMR measurements deuterium oxide was employed as the solvent, from Merck, with a deuteration degree not less than 99.95%. The hydration water of the β-CD was taken into account in the concentration of the solutions, that were prepared by weight.

Speed of Sound and Density. Measurements of the speed of sound and density were performed simultaneously with a technique designed in this laboratory.[10] The measurement of

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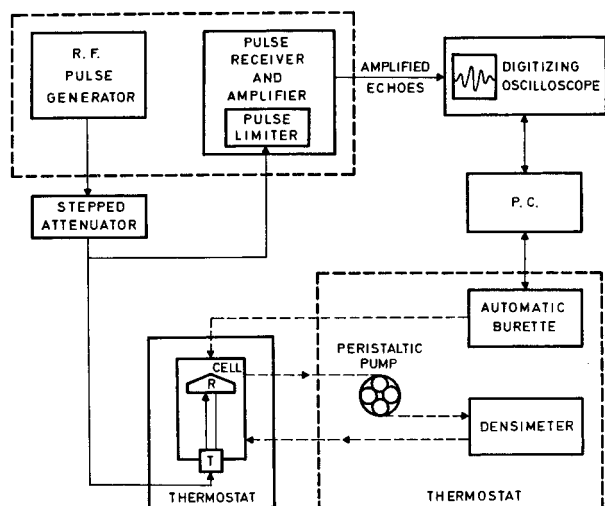⊗ Abstract published in *Advance ACS Abstracts,* April 15, 1997.

Figure 1. Block diagram of the technique.

both properties is carried out in a continuous way, as described below, thus permitting higher precision in the partial molar properties. The part of the technique related to the speed of sound is described extensively in a previous report.[11] It works by measuring the time that a wave packet of defined ultrasonic frequency takes to travel a certain distance between a piezoelectric transducer and a reflector. A digitizing oscilloscope of high sampling rate (20 Msamples/s) counts the time between two consecutive reflections and the speed of sound is obtained directly from the travel time of the wave packet and the known distance between the transducer and the reflector, which is calibrated in each experiment using a reference liquid (pure water). The ultrasonic cell is immersed in a thermostat, controlled by a temperature controller Tronac PTC41 and a cryostat. The stability in the temperature is better than 1 mK (all the experiments were carried at 298.15 K). Densities are measured with a vibrating tube densimeter Anton Paar DMA 601 HT, calibrated with water and air in each run of measurements, and thermostated by recirculation of the water of the thermostat. A peristaltic pump sucks the liquid to the densimeter from the ultrasonic cell, where a magnetic stirrer produces, together with the recirculation, the adequate homogenization of the medium. When the recirculation is judged to be complete, the pump is turned off. Once the properties are stable, the vibration period of the densimeter and the time of flight of the wave packet are registered (the complete process of stirring and stabilization of the measurements took about 15 min). After the measurement, an automatic buret Metrohm 665 Dosimat changes the concentration in the cell by adding volumes of a more concentrated solution, and the process of recirculation is repeated. A PC controls both the oscilloscope and the buret and it is programmed for following the evolution of the wave packets with the concentration. It calculates the volumes to be added to keep the increments of concentration constant and takes the measurements of added volume, time, and period. These data are stored on the hard disk and sent to the printer. The densimeter, peristaltic pump, and buret are contained in a polymethacrylate box at 298 K to avoid temperature gradients. Under these conditions, the precisions in the measurements of the speed of sound and density are 2×10^{-3} m s^{-1} and 1.5×10^{-3} kg m^{-3}, respectively. A block diagram of the technique is shown in Figure 1.

For all the experiments a stock solution of β-CD in water was prepared by weight. Part of this solution was introduced into the measurement cell. With the rest, another solution was prepared by weighing the surfactant, with which the buret was

filled. In this way, the molality of the β-CD is kept constant and so are the moles of water.

Molecular Modeling. Calculations were done with the Insight II program,[12] implemented in an IRIS 4D/310VGX workstation of Silicon Graphics. The molecular structure of the β-CD has been generated linking seven units of α-D-glucopyranose, and that of the DTAB ion by means of the Sketch utility from the main module Builder. Energy minimization of the isolated host and guest molecules was performed with the Discover program, employing the CVFF force field,[13] and with several algorithms (at first steepest descents, finishing with a modified Newton−Raphson to refine the structures), until the rms of the derivatives were less than 0.0001 kcal Å^{-1}. Afterwards, molecular dynamics of the system were performed at 298 K and the process of minimization was repeated to find the absolute minimum of energy. The structure of the CD thus obtained is highly symmetric, with the O4 atoms almost coplanar, and it is more regular than the crystalline structure obtained from X-ray and neutron diffraction data, available from the CSD.[14] We have chosen this highly symmetric structure rather than the crystalline one, which is slightly distorted because of the water molecules located inside and outside the cavity.

To fit the ion in the cavity and to obtain the contour energy plots, rigid docking experiments were carried out with the refined structures. An *XY* plane was defined by the O4 atoms of the CD, and the origin as the mass center of the seven O4. The *Z*-axis is perpendicular to this plane and with positive orientation to the wider rim. The N atom of the head group is considered as the center of the DTAB and the tail parallel to the *Z*-axis. Interaction energies were calculated with the Docking module of the program. The guest molecule is approximated along a vector in the *Z* direction by the head toward the wider rim of the CD with steps of 0.5 Å starting in 8 Å from the center of the CD and rotated each 30° around the *Z*-axis. The cutoff distances for the Coulomb and van der Waals energies were 100 Å in order to include all the possible interactions.

To account roughly for the solvent effects, a relative dielectric constant of 80 depending on inverse of the distance was used in the Coulombic sumand of the force field. It is preferable to use this approximation instead of assuming that the molecules are in the vacuum because, as we have said previously, the solvent plays a decisive part in these complexes.

^{1}H NMR Measurements. The samples for NMR were prepared in D$_2$O as solvent, at several molar ratios DTAB:β-CD, and keeping fixed the β-CD concentration at 0.015 M. The NMR spectra were recorded in a VARIAN VXR 300S, at 300 MHz, fitted with a thermostatization unit. All the records were carried out at 293 ± 0.2 K. The chemical shifts are relative to the HDO signal at 4.63 ppm.

Results and Discussion

Speed of Sound and Density. The u values versus the molality of DTAB in water and at three different constant molalities of β-CD are plotted in Figure 2. It is observed the critical micellar concentration (cmc) of the pure surfactant, at 0.068 m, in good agreement with the literature values,[15] as well as the formation of the inclusion complex at a stoichiometry 1:1. These results are similar to those previously published by us,[16] but now the simultaneous measurement of density allows us to express the concentration in molality and, given that the precision in the velocity is 1 order of magnitude higher, it is possible to obtain the derivative $(\partial u / \partial m_s)_{CD,w}$ between consecutive points[17] with better reliability (s, CD, and w stand for surfactant, β-CD, and water). Such values versus the molality
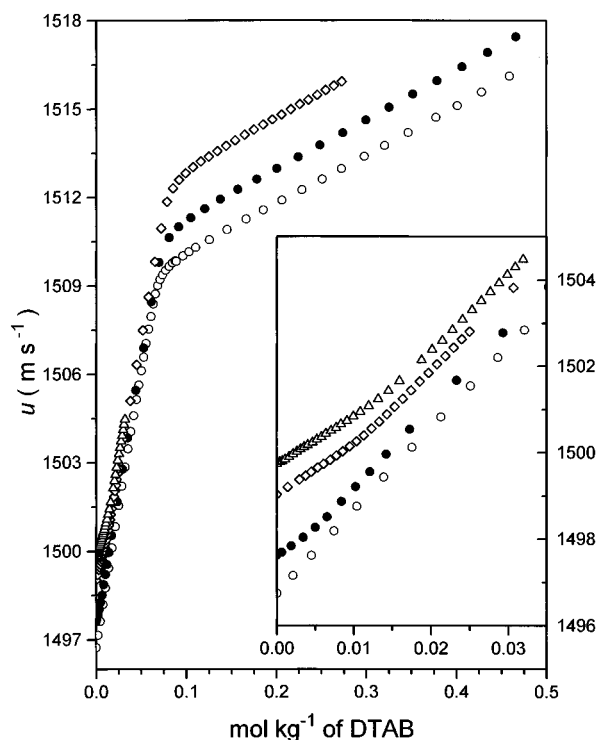
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Figure 2. Speed of sound, u, for pure DTAB in water and mixtures with β-CD versus DTAB molality: (○) β-CD 0.000 m; (●) β-CD 0.004601 m; (◇) β-CD 0.011462 m; (△) β-CD 0.014615 m.
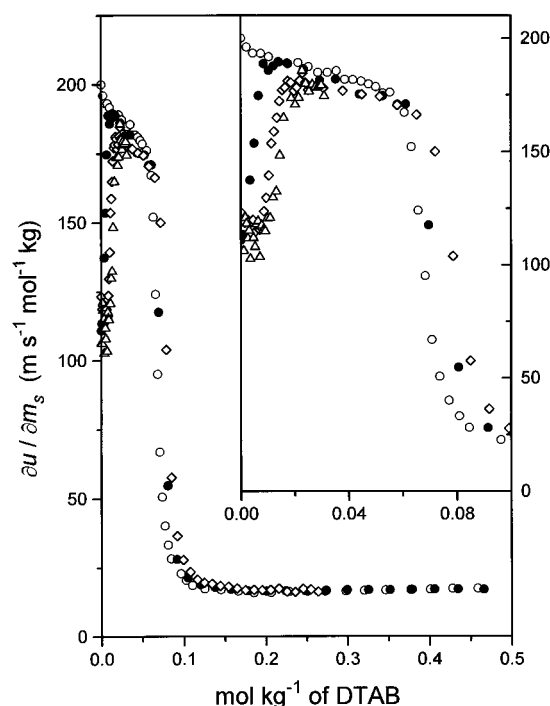

Figure 3. Derivatives of u with m_s for pure DTAB and mixtures with β-CD.

of surfactant are plotted in Figure 3. The cmc, in the absence or in the presence of β-CD (cmc*) corresponds with the maximum change in the derivative, and it is displaced by an equal amount to that of the molality of the β-CD. The stoichiometric point for the complex appears as well as a maximum change in the derivative.

For the pure surfactant, the derivative is far from being a constant in the premicellar region, going from 196 m s^{-1} mol^{-1} kg (infinite dilution) to 171 (at the beginning of the micellization), as would be expected if we assume a linear dependence

TABLE 1: Infinite Dilution Parameters for Pure DTAB and DTAB + β-CD at 298 K

Y	DTAB + H$_2$O	DTAB + β-CD + H$_2$O	ΔY_r^0
$(\partial u/\partial m_s)^0$ (m s^{-1} mol^{-1} kg)	197	110,^{a} 123,^{b} 111^c	82
$(\partial \rho/\partial m_s)^0$ (kg^2 m^{-3} mol^{-1})	24.4	$-3,^a$ 0,^{b} 5^c	23.4
$10^6 v_s^0$ (m^3 mol^{-1})	256.48	274.4,^{a} 275.6,^{b} 277.0^c	19.22
κ_s^0 (PPa^{-1} m^3 mol^{-1})	-16.52	53.4,^{a} 51.2,^{b} 53.9^c	69.32

^{a} $m_{CD} = 0.004601$ mol kg^{-1}. ^{b} $m_{CD} = 0.011462$ mol kg^{-1}. ^{c} $m_{CD} = 0.014615$ mol kg^{-1}. ΔY_r^0 calculated with the Y property mean value.

of the speed of sound with the concentration.[18] The negative slope in the monomeric zone is due to the solute−solute and solute−solvent interactions.

The limiting values at infinite dilution (Table 1), $(\partial u/\partial m_s)^0_w$ and $(\partial u/\partial m_s)^0_{CD,w}$, are different and, regardless of the CD concentration, the $(\partial u/\partial m_s)^0_{CD,w}$ limiting slopes are the same. Since there is an excess of CD, this limiting value will correspond, in a general case, to the $(\partial u/\partial m_s)^0_{CD,w}$ for an inclusion complex with the maximum possible relation of CD/DTAB, which in this work is assumed to be 1:1. The great difference with the value in the absence of CD is the consequence of the complexation between the host (CD) and guest molecule.

It can be observed that, after a certain value of m_s, all the differentiated curves for any fixed molality of CD are displaced in an amount equal to the CD concentration. This critical value has to depend of the equilibrium constant of the complex. The relation that is followed for all the curves is

$$\frac{\partial u}{\partial m_s}(m_s + m_{CD}, m_{CD}, w) = \frac{\partial u}{\partial m_s}(m_s, 0, w) \quad (1)$$

or the more general, for two CD concentrations with CD$_2$ > CD$_1$

$$\frac{\partial u}{\partial m_s}(m_{s+CD_2}, m_{CD_2}, w) = \frac{\partial u}{\partial m_s}(m_{s+CD_2-CD_1}, m_{CD_1}, w) \quad (2)$$

which is, taking into account the significance of these partial derivatives, a clear indication that after the complex is fully formed the system behaves like the one containing only pure surfactant.

Equations 1 and 2 are obeyed with a critical value of surfactant $m_{s,0}$. If the equilibrium constant were infinity, then $m_{s,0} = m_{CD}$. Integration of eq 1 between $m_{s,0}$ and m_s leads to the following result:

$$u(m_s + m_{CD}, m_{CD}, m_w) = u(m_{s,0}, m_{CD}, m_w) + u(m_s, 0, w) - u(m_{s,0}, 0, w) \quad (3)$$

Equation 3 sets a simple additivity relation for u from a point $(m_{s,0}, m_{CD}, m_w)$. The last result is because, for this system and from a certain surfactant concentration, the change in the speed of sound per mole of added surfactant is the same in the absence or presence of CD, and therefore the system behaves as ideal, in the sense that there is no interaction of the added surfactant with the complex. It is common practice to use the increments of u with respect to the origin divided by the molality, that is $(u - u_0)/m_s$, as a description of the system, instead of the partial derivatives. Indeed the errors for the increments are lower than for the derivatives. The values of $(u - u_0)/m_s$ versus the molality of surfactant for two CD molalities are plotted in Figure 4. The corresponding derivatives are also displayed for the same concentration. If there are successive changes in the system, as a cmc or a complex formation, reflected in a sharper variation
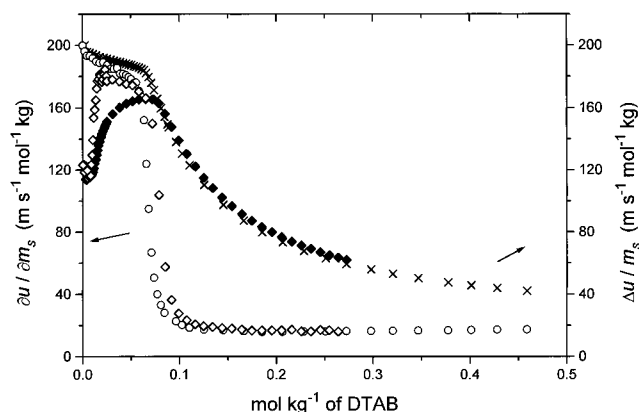
Figure 4. Comparation between increments of u and derivatives versus concentration for pure DTAB and with β-CD: ($\bigcirc$) and ($\times$) β-CD 0.000 m; ($\diamondsuit$) and ($\blacklozenge$) β-CD 0.011462 m.
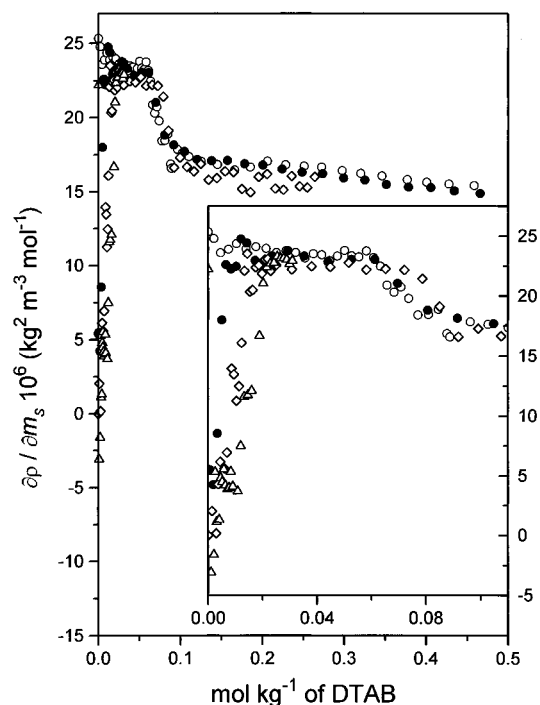
Figure 5. Derivatives of ρ with m_s for pure DTAB and mixtures with β-CD: ($\bigcirc$) β-CD 0.000 m; ($\bullet$) β-CD 0.004602 m; ($\diamondsuit$) β-CD 0.011462 m; ($\triangle$) β-CD 0.014615 m.

of the property with the molality, only the increments at very high concentrations would be coincident with the derivatives.

The differentiated values of density plotted in Figure 5 show a similar trend for $(\partial u/\partial m_s)_{CD,w}$ with the formation of the 1:1 complex and the shift of the cmc. The $(\partial\rho/\partial m_s)_{CD,w}$ at infinite dilution is lower than for pure DTAB in water. It is worth noting that the dependence of the density of the solution in the presence of CD versus the surfactant concentration is almost a constant, and when the stoichiometric point has been reached the slope increases. This behavior is not common, because if the concentration increases, we expect an increasing density. However it diminishes; that is, the overall effect is as if the solvent volume is increasing. This is precisely what is happening: the water from the interior of the cavity is being expelled when the surfactant enters, a fact that can be explained in quantitative terms by calculation of the associated apparent and partial properties.

Apparent and Partial Molar Properties. The apparent molar volume and apparent molar adiabatic compressibility of a solute i in a mixture where the molality of the other

components is kept constant can be calculated using the usual definitions:

$$\nu_{\phi,i} = (V - V_0)/m_i \qquad (4)$$

$$\kappa_{S,\phi,i} = -\frac{1}{m_i}\left\{\left(\frac{\partial V}{\partial P}\right)_S - \left(\frac{\partial V_0}{\partial P}\right)_S\right\} = \frac{1}{m_i}(\beta_S V - \beta_{S,0} V_0) \qquad (5)$$

where $\beta_S = (\rho u^2)^{-1}$ is the adiabatic compressibility, and the zero subindex stands for the initial state when the molality m_i is zero. In this paper, the molality is defined as moles of solute per kilogram of solvent according to the IUPAC, where the solvent, w, is pure water. According to the above definition of molality the resulting expressions for the apparent molar properties are:

$$\nu_{\phi,i} = M_i/\rho - (1 + m_jM_j)(\rho - \rho_0)/m_i\rho\rho_0 \qquad (6)$$

$$\kappa_{S,\phi,i} = \beta_S\nu_{\phi,i} + (1 + m_jM_j)(\beta_S - \beta_{S,0})/m_i\rho_0 \qquad (7)$$

where ρ is the density of the solution, ρ_0 is the density when $m_i = 0$, M_i and M_j are the molar mass of solutes i and j, and m_i and m_j are the molalities. The partial molar properties can be obtained from the apparent ones by using

$$\nu_i = \left(\frac{\partial V}{\partial n_i}\right)_{n_w,n_j} = \frac{d}{dm_i}(\nu_{\phi,i}m_i) \qquad (8)$$

$$\kappa_{S,i} = -\left(\frac{\partial}{\partial n_i}\left(\frac{\partial V}{\partial P}\right)_S\right)_{n_w,n_j} = \frac{d}{dm_i}(\kappa_{S,\phi,i}m_i) \qquad (9)$$

It is possible to define another molality scale, where the molality of i would be moles of i per kilogram of mixed solvent $w + j$, although in this case, in which i and j are solid solutes, it is more appropriate to use the IUPAC definition of molality. In any case, the conversion between both scales is straightforward and, for dilute systems, differences are minimal. The difference between eqs 6 and 7 and those usually found in the literature is that m_j (the molality of the third component) does not appear in the above expressions.

In Figure 6 are plotted the apparent molar volumes of the surfactant versus its molality at different CD concentrations and in Figure 7 the molar partial properties. The partial molar volume of the pure surfactant at infinite dilution, ν_s^0, has been obtained by adjusting the apparent values below the cmc to an expression of the form

$$\nu_{\phi,s} = \nu_s^0 + A_\nu m_s^{1/2} + B_\nu m_s \qquad (10)$$

where A_ν is the Debye–Hückel parameter for the apparent volume[19] and B_ν takes into account solute–solute interactions. The resulting value (256.48×10^{-6} m^3 mol^{-1}) agrees with the literature data,[20] and it is lower than the partial molar volume at infinite dilution in the presence of CD, $\nu_{S,CD}^0$. This is even higher than ν_S at high m_S (surfactant in micellar form). Since at infinite dilution interactions between DTAB molecules are negligible, the change in the molar volume at infinite dilution, $\Delta\nu_r^0$ (Table 1), corresponds to the interaction between the CD and the surfactant, that is, to the formation of an inclusion complex. This big change is only possible if the water is involved in the process.

The first maximum change in the derivative corresponds to the stoichiometric point (1:1 complex). With respect to the micellization, the curves from a given concentration are displaced, but the values of the micellization volumes are the same in the presence or absence of CD, proving that the complex
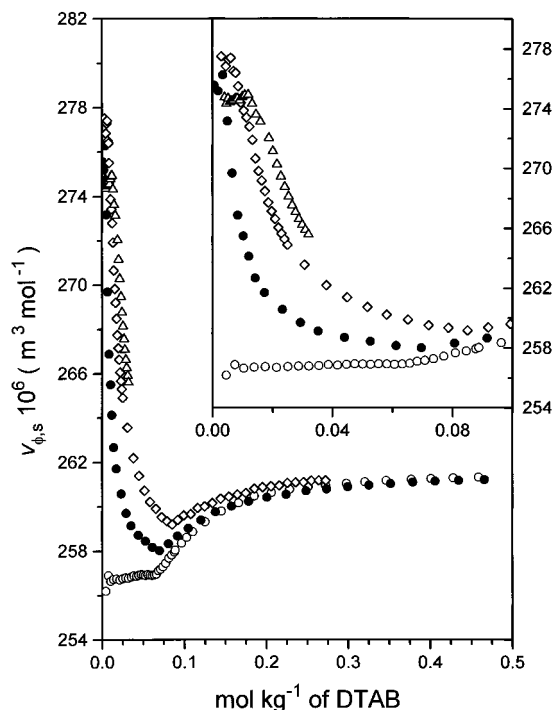
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Figure 6. Apparent molar volumes for pure DTAB and mixtures with β-CD: (○) β-CD 0.000 *m*; (●) β-CD 0.004601 *m*; (◇) β-CD 0.011462 *m*; (△) β-CD 0.014615 *m*.

Figure 8. Apparent molar compressibilities for pure DTAB and mixtures with β-CD: (○) β-CD 0.000 *m*; (●) β-CD 0.004601 *m*; (◇) β-CD 0.011462 *m*; (△) β-CD 0.014615 *m*.

Figure 7. Partial molar volumes for pure DTAB and mixtures with β-CD: (○) β-CD 0.000 *m*; (●) β-CD 0.004601 *m*; (◇) β-CD 0.011462 *m*; (△) β-CD 0.014615 *m*.
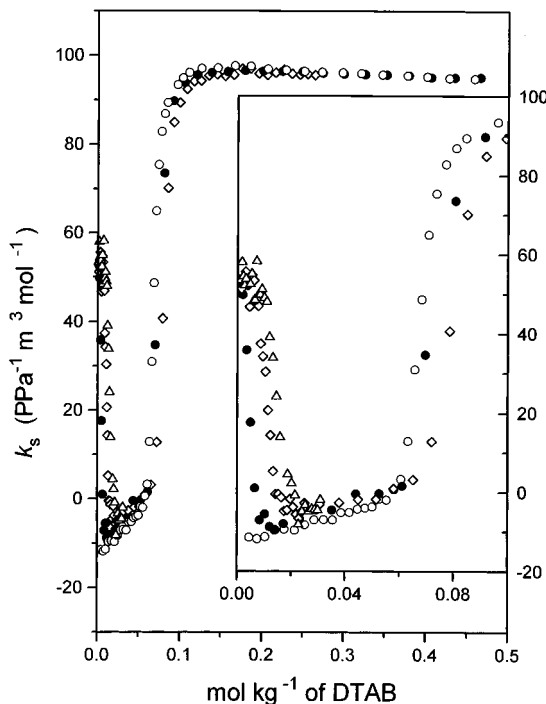
Figure 9. Partial molar compressibilities for pure DTAB and mixtures with β-CD: (○) β-CD 0.000 *m*; (●) β-CD 0.004601 *m*; (◇) β-CD 0.011462 *m*; (△) β-CD 0.014615 *m*.

does not have any influence on the micelles. $\Delta\nu_{mic} = 4.8 \times 10^{-6}$ m³ mol⁻¹ has been obtained as the difference between the initial plateau of the curves, where the micellization is completed, and that of the beginning of the micellization.

In Figures 8 and 9 are plotted respectively the apparent and partial compressibilities versus the DTAB molality. These graphs are less noisy than the properties obtained from the densities, since changes in the speed of sound with the concentration are about 10 times higher than the density. Compressibility of pure DTAB at infinite dilution was obtained
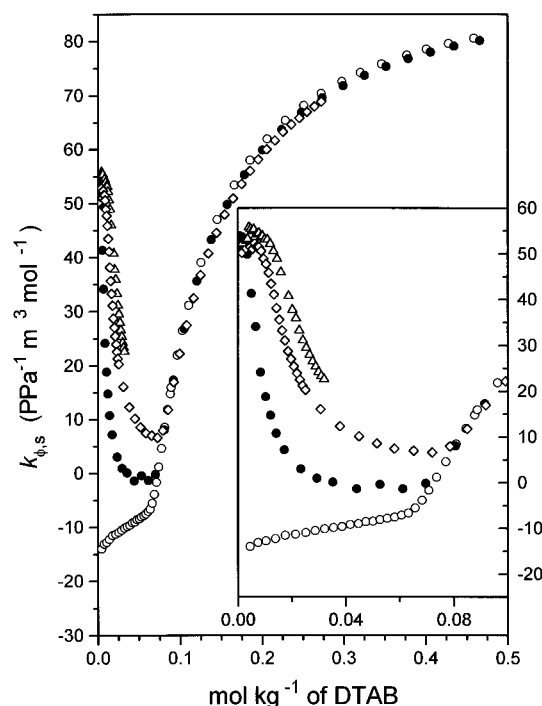
using a similar equation to the one used for the volumes (eq 10), leading to a value of -16.5 PPa⁻¹ m³ mol⁻¹, in good agreement with the bibliography data.[20] Compressibility curves show the same features as the volumes. At infinite dilution all the curves with CD go to the value of 52.8 PPa⁻¹ m³ mol⁻¹, well above the pure surfactant, but less than when the surfactant is forming micelles. In the same way as with the molar volumes, micelle compressibilities are the same in the presence or absence of CD, being $\Delta k_{mic} = 99.5$ PPa⁻¹ m³ mol⁻¹. The positive values for $\Delta\nu_{mic}$ and $\Delta\kappa_{mic}$ reflect that the inside of a

micelle resembles that of the pure alkane, resulting in higher volumes and compressibility values.

It is worth mentioning that in the graphs for the apparent properties, the curves for the ternary system reach the curve corresponding to the pure surfactant above its cmc, that is, at the point where the micelles have begun to form. If we want to calculate the micellization property of the DTAB with the CD as the difference between the value at high concentrations and at the cmc, it is not possible to give a well-defined difference if an apparent property is considered. However, by plotting the partial molar property there is no problem in obtaining the value, since for all the CD concentrations the curves come together in the monomeric region, or at the very beginning of the micelles, giving always the same increments. That is why very good precision in the speed of sound and/or densities is required for the study of these systems, precise enough to obtain the partial properties instead of the apparent ones.

All the given properties are derivatives either of magnitudes that are independent of the size of the system (u and ρ) or dependent on it (V and $-(\partial V/\partial P)_S$). As the properties are obtained with respect to the surfactant molality at a constant number of moles of the other component, e.g., water or water + CD, they represent the variation of u, ρ, V, and $-(\partial V/\partial P)_S$ per mole of added surfactant. If there is no interaction between DTAB and CD, all the derivatives should show the same value irrespective of the cyclodextrin concentration. Instead, remarkable differences are observed. The use of incremental values, $(X - X_0)/m_s$, where X is u, ρ, V, or $-(\partial V/\partial P)_S$, can lead to incorrect interpretations and the analysis has to be done with partial molar magnitudes.

The partial molar properties offer information on the complexation process at a molecular level. Thus, the big changes in the transfer volumes, Δv_r^0, and compressibilities, $\Delta \kappa_r^0$, are an indication that the molecular environment of the surfactant when the CD is present is much more different than in water, denoting that complexation has taken place. The resulting values of molar properties, assuming that all the water of the cavity is expelled, can be explained according to the following reaction scheme:

$$CD(m+n) + S(l) \rightarrow CD(m):S(l-s) + n \qquad (11)$$

where m is the number of outer water molecules of hydration, n represents the molecules of water of the cavity, l is water of hydration of the surfactant, and s is the water molecules that the surfactant loses when it is included in the cavity. Due to the geometry of the CD, we can assume that the only water which is going to be modified will be the hydration water of the cavity, and the part of the shell covering the surfactant which will be lost in the inclusion. The change in volume of the reaction according to this model, or transfer volume, Δv_r^0, is the difference between the volume of water expelled from the cavity (incorporated to the bulk) and the hole occupied by the part of the surfactant that is going to be included. Crystallographic data for the height of the cavity give a value of 7.9 Å, which is going to be the surfactant tail length included. This length corresponds to 6.3 CH_2 groups, as determined by considering the length of a C–C bond with C in sp³ hybridization[21] and by CPK space-filling model.[22] Given that the volume in water of a CH_2 group, v_{CH_2}, can be considered constant and equal to 15.8×10^{-6} m³ mol⁻¹ (ref 23), the inclusion leaves a hole in the water of 98.1×10^{-6} m³ per mole of included surfactant, while n_w molecules of water from the cavity are incorporated in the bulk water. That is

$$\Delta v_r^0 = v_w^0 n_w - n_{CH_2} v_{CH_2} \qquad (12)$$

where v_w^0 is the volume of 1 mol of pure water and n_{CH_2} is the number of CH_2 groups buried into the CD. The number of water molecules released, n_w, was found of 6.5, which is exactly the number of molecules found by XRD[24] and neutron diffraction[25] for the solid β-CD. This would indicate that the hydration water of the cavity is structured as in the solid state, and it remains within the CD when it is dissolved.

The compressibility should confirm these results, although a careful analysis of the inclusion process must include more contributions. The next equation can be proposed:

$$\Delta \kappa_r^0 = n_w \kappa_w^0 - n_{CH_2} \kappa_{CH_2} + (\kappa_{CD}^{as} - \kappa_{CD}^w)_{cavity} \qquad (13)$$

That is, the change in compressibility of the reaction, $\Delta \kappa_r^0$, is the difference between the compressibility of the water expelled from the cavity, with the same value of the bulk water ($\kappa_w^0 = 8.081\,09$ PPa⁻¹ m³ mol⁻¹), and the compressibility of the included surfactant moiety in water, $n_{CH_2} \kappa_{CH_2}$. The last contribution accounts for the different compressibility of the cavity when it is filled with the alkyl chain or with water.

If the amount of water released is known from the volumes through eq 12, and also the compressibility of a CH_2 group in water, it is possible to obtain the difference in compressibility of the CD filled with different guests. The literature value for κ_{CH_2} measured for alkyltrimethylammonium bromides[23] is -5.0 PPa⁻¹ m³ mol⁻¹, which when substituted in eq 13 gives for $(\kappa_{CD}^{as} - \kappa_{CD}^w)_{cavity}$ a negative value of -15.2 PPa⁻¹ m³ mol⁻¹. However, this term should be positive, since the free volume in the cavity is higher when the CD is filled with the guest than with water, as the high Δv_r^0 indicates. It is expected that the higher the free volume, the larger the compressibility.[26] One could think that, although the free volume is larger, it would be less compressible. This can only happen if the interactions are less favorable when the cavity is filled with the surfactant than with water. However, this cannot be possible, because the complex exists precisely because the interaction between the surfactant and the cavity is more favorable for the surfactant than for the water.

The compressibility per CH_2 group, in the monomeric form in water, given in the literature (ref 23) has been obtained for alkyltrimethylammonium bromides using a group additivity scheme, assuming that for higher homologues the values at the cmc are the same as at infinite dilution. On the other hand, the values obtained for another homologous series like alkanecarboxylates give a value close to zero.[27] Because of this inconsistency we have revised the compressibility for the alkyltrimethylammonium bromides. With the precision of our technique we have been able to make measurements as a function of the chain length up to the cetyltrimethylammonium bromide (C_{16}TAB) and below the cmc, obtaining without extrapolations a group CH_2 contribution of -1.3 PPa⁻¹ m³ mol⁻¹. Using this value in eq 13, we obtain a $(\kappa_{CD}^{as} - \kappa_{CD}^w)_{cavity}$ of 8.1 PPa⁻¹ m³ mol⁻¹. The last positive value is an indirect demonstration of how a favorable interaction between two moieties results in a higher compressibility than when the interaction is unfavorable. It is also a confirmation, although well-known, of the hydrophobic character of the inner part of the cyclodextrin.

Apparent Molar Properties of the β-CD. From ρ and u measurements it is possible to obtain the apparent molar properties not only for the surfactant but also for the CD. The
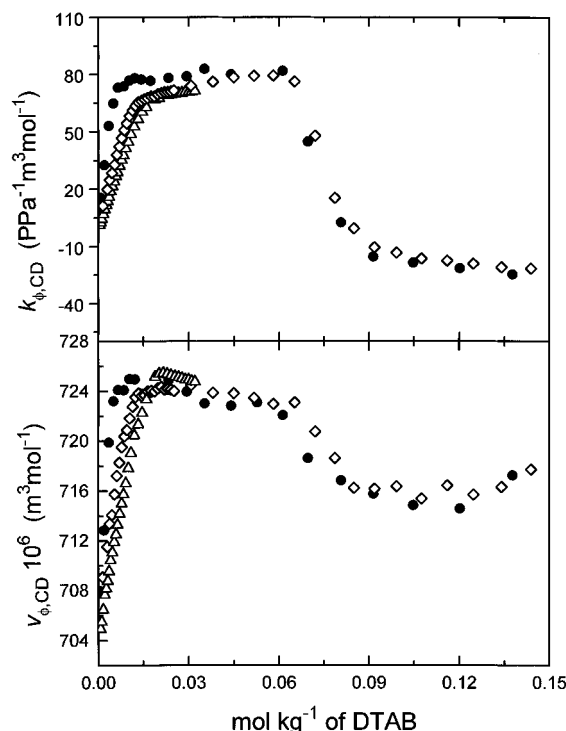
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Figure 10. Apparent molar volume and compressibility for β-CD in presence of DTAB: (○) β-CD 0.000 m; (●) β-CD 0.004601 m; (◇) β-CD 0.011462 m; (△) β-CD 0.014615 m.

apparent molar volume, $v_{\phi,CD}$, calculated through eq 6, where now i stands for the CD and j for the surfactant, ρ is the density of the solution at constant m_{CD} and at a certain m_s, and ρ_0 the initial state where the molality of the CD is zero. As this initial state is changing with m_s, ρ_0 has been calculated by interpolation in the curve of density versus molality for the pure surfactant ($m_{CD} = 0$).

The results for the apparent molar volumes are plotted versus the molality of surfactant in Figure 10. In this case it is not possible to obtain the molar properties given that the variable concentration is not the molality of the CD.

Equation 7 gives the apparent molar adiabatic compressibilities of the CD, $\kappa_{\phi,CD}$, β_S being the adiabatic compressibility of the solution of β-CD at variable surfactant molality and $\beta_{S,0}$ the compressibility of the initial state where the molality of the CD is zero. As with the density, it has been necessary to interpolate these values in the corresponding graph for the pure surfactant. The resulting values of $\kappa_{\phi,CD}$ are plotted versus m_S in the same figure.

Curves in Figure 10 are quite similar, and we will analyze the results simultaneously. At infinite dilution, where $m_s = 0$, the values of apparent volumes and compressibilities extrapolate to the molar volumes and compressibilities of the pure CD. Thus, the extrapolated values are 7.04×10^{-4} m^3 mol^{-1} and -2.6 PPa^{-1} m^3 mol^{-1}, which correspond with those obtained for pure CD in water.[28] The infinite dilution concept in this case and that of the previous section have different meanings. Here it stands only for the pure CD in water. When all the CD is complexed, at around $m_s = m_{CD}$, the apparent values are that of the pure CD plus the Δv_r^0 given in Table 1. This is what is observed for the maximum of the curves. The curve that corresponds to the lower concentration of CD reaches the maximum first and with a higher slope. After this maximum there is a plateau, because all the added CD will be complexed and there is almost no change in the apparent properties for the surfactant up to the cmc. After the plateau, both properties decrease. This is a consequence of the breaking of the micelles
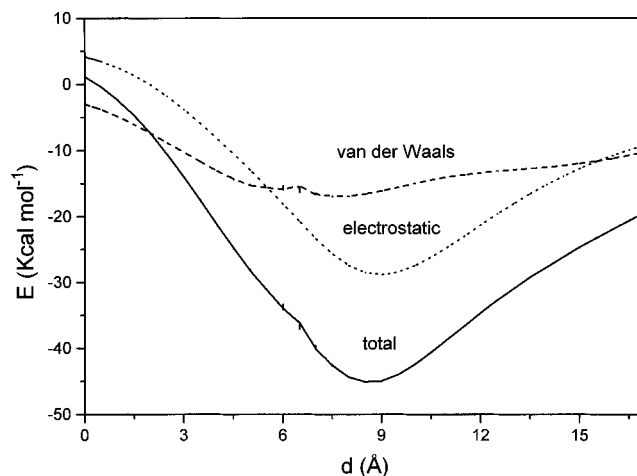

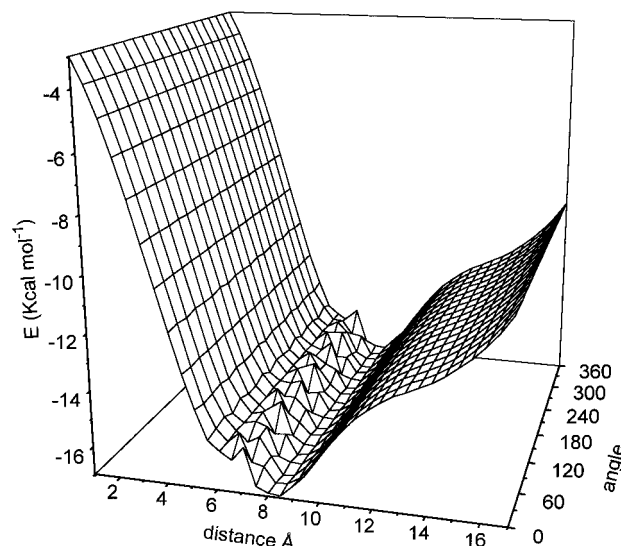**Figure 11.** Different contributions to the interaction energy between DTA$^+$ and β-CD.

Figure 12. Van der Waals energy surface for the interaction between DTA$^+$ and the β-CD.

that occurs when β-CD is added to a micellar solution since the equilibrium is more favorable for the complexation than for the formation of micelles. The volumes and compressibilities are the sum of those of the pure β-CD reaction values and micellization values.

Molecular Modeling and ¹H NMR. The potential energy curve and its different contributions is represented in Figure 11, according to the method described in the Experimental Section. The energy well is almost independent of the rotation angle of the molecule and there is no hindrance for the DTA$^+$ to go through the CD. Only the effect is more remarkable near the minimum, due to the contribution of the van der Waals energy (Figure 12), since steric repulsions arise between the bulky trimethyl group and the H5 protons of the narrower rim of the CD, the most protuberant ones. The minimal energy conformation is shown in Figure 13. Note how the cavity is filled with the surfactant, thus avoiding the existence of water molecules inside. The head is at the border of the primary hydroxyl rim, leaving about five methylene groups buried in the cavity. This structure would permit a possible 2:1 complex (2 CD:DTAB) that has not been observed with the thermodynamic measurements.

As for the cationic head, no complex formation was observed by ¹H NMR studies for N(CH₃)₄Br with β-CD in deuterium oxide. The low tendency of the CD's for complexing ions is a
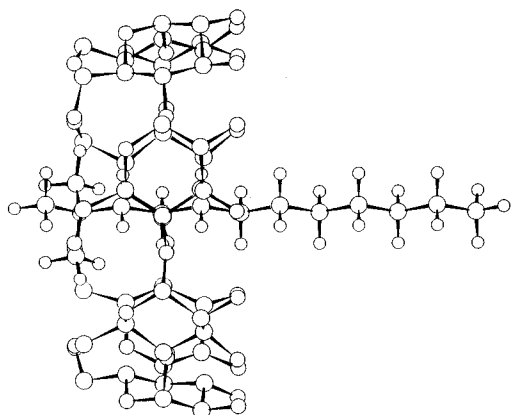
Figure 13. Docking conformation of minimum energy for the complex. Hydrogens of the β-CD are omitted for best visualization.
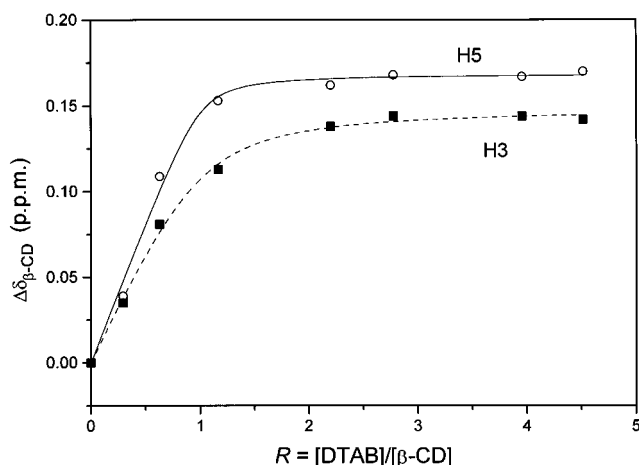

Figure 14. Chemical shifts of the H3 and H5 β-CD protons versus the molar ratio, $R = m_{DTAB}/m_{CD}$, and the corresponding fitted curves according to the Benesi−Hildebrand method.

common feature, given the hydrophobic character of the cavity.[29] Thus we can expect the cationic head to protrude outside the cavity even further as compared with Figure 13. This may be a consequence of the effect of formal molecules of water which were not considered in the calculation.

From the ^{1}H NMR spectra, it is possible to identify the resonances corresponding to the six types of protons of the β-CD.[30] When DTAB is present, upfield shifts of H5 and H3 are observed (0.17 and 0.15 ppm, respectively). H1, H2, and H4, that is, the protons located in the outer face of the CD, are scarcely shifted (less than 0.025 ppm). The plot of $\Delta\delta$ values (the chemical shift of the considered proton minus the value in the absence of guest molecule) against the quotients DTAB:β-CD for several R values proves the 1:1 stoichiometry (Figure 14). The shift in the resonances of the DTAB protons are not so marked as for the host molecule, the most relevant changes being those of the methylene protons of the tail $-(C^*H_2)(CH_2)-(CH_2)(CH_2)N^+-$ of 0.070 ppm, and $-(CH_2)(C^*H_2)(CH_2)-(CH_2)-N^+-$ of 0.060 ppm (the star indicates the resonance of the protons bonded to that C). The methyl protons of the head suffer less interaction (0.030 ppm) and the interaction of the terminal CH$_3$ is negligible. This suggests that the head is located outside the cavity, making a 2:1 stoichiometry (which has been observed for surfactants with longer alkyl chains[31]) less probable. This would give around 6.5 methylene groups included, rather than the 5 of Figure 13.

It is worth mentioning the broadening in the resonance of the methylene groups CH$_3$(C*H$_2$)$_6$(CH$_2$)− with molar ratio,

which suggest certain freedom of the hydrophobic tail to move through the cavity.

$\Delta\delta$ versus R plots permit us to estimate the binding constant for the reaction, K, by application of the Benesi−Hildebrand method modified for NMR applications,[32] assuming a 1:1 complex. We have obtained an equilibrium constant $K = 1000 \pm 200$ M^{-1} using the H5 proton and 750 ± 150 M^{-1} for the H3. The results are in fair agreement with the values of the literature obtained by NMR for alkyl sulfates.[33] The value is typical of surfactant guests, and it is high enough to resolve the competitive equilibrium between micellization and complexation in favor of the latter, producing the observed shift in the cmc.

Conclusions

The transfer process of decyltrimethylammonium bromide to β-cyclodextrin in water at 298.15 K has been studied using different experimental techniques: speed of sound, density, molecular modeling, and ^{1}H NMR.

The derivatives of u, ρ, V, and $-(\partial V/\partial P)_S$ with the molality of the surfactant at constant moles of the other components have been obtained. All of them show, above a certain value of surfactant molality, a shift equal to the fixed β-CD concentration. This indicates that, after the complex is fully formed, the system behaves like the pure surfactant and there are no further associations between the complex and the surfactant, neither with the surfactant micelles.

At infinite dilution, the partial molar volume and compressibility of the surfactant in the presence of β-CD is much higher than in pure water, having the same values independent of the total amount of cyclodextrin. The differences can be explained in terms of drastic changes in the hydration state of the host and guest in the reaction.

For the volume, the difference at infinite dilution, Δv_r^0, offers information at a molecular level of the complexation process, including the water expelled from the cavity as a new variable of the reaction. The number of water molecules that leave the inside of the CD results to be 6.5, the same as in crystalline state.

The surfactant compressibility at infinite dilution passes from negative values to positive values. By application of the same scheme as for the volume, we have proved that the compressibility of the cavity is higher when it is filled with the surfactant than with water. This is explained in terms of the different hydrophobicity of the guest: water (initial state) and the hydrophobic moiety of the surfactant (complexed state).

The molecular modeling study shows the existence of an energy well along the CD axis, with almost no angular dependence of the guest position. The cavity is completely filled with the alkylic chain, excluding any water molecule. ^{1}H NMR experiments confirm the 1:1 stoichiometry and give a mean equilibrium constant of 900 M^{-1}. The analysis of the host and guest chemical shifts suggests that the cationic head is located outside the β-CD, with the hydrophobic moiety of the surfactant buried in the cavity.

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