In Search of Fully Uncomplexed Cyclodextrin in the Presence of Micellar Aggregates

ARTICLE *in* THE JOURNAL OF PHYSICAL CHEMISTRY B · AUGUST 2006

Impact Factor: 3.3 · DOI: 10.1021/jp0626871

In Search of Fully Uncomplexed Cyclodextrin in the Presence of Micellar Aggregates

C. Cabaleiro-Lago,[†] L. García-Río,*[,‡] P. Hervés,[†] J. C. Mejuto,[†] and J. Pérez-Juste[†]

Departamento de Química Física, Facultad de Química, Universidad de Vigo, 36310 Vigo, Spain, and Departamento de Química Física, Facultad de Química, Universidad de Santiago, 15782 Santiago, Spain

Received: May 2, 2006; In Final Form: June 9, 2006

The chemical behavior of β-cyclodextrin/nonionic surfactant mixed systems has been investigated using the basic hydrolysis of *N*-methyl-*N*-nitroso-*p*-toluenesulfonamide as a chemical probe. The experimental results prove that at the cmc, there are significant quantities of uncomplexed β-CD in equilibrium with the micellar aggregates. In contrast to the expected situation, the percentage of uncomplexed β-CD in equilibrium with the micellar system increases on increasing the hydrophobicity of the surfactant molecule. This behavior is due to the existence of two simultaneous processes: complexation of surfactant monomers by cyclodextrin and the process of self-assembly to form micellar aggregates. The autoaggregation of surfactant monomers is expected to be more important than the complexation process in this mixed system. Varying the hydrophobicity of the surfactant monomer enabled us to determine that the percentages of uncomplexed cyclodextrin in equilibrium with the micellar system were in the range of 5−95%.

Introduction

Cyclodextrins (CDs) are a group of well-known cyclic sugars that are capable of forming reversible noncovalent complexes with a wide variety of guests.[1] These macrocycles are structurally based on glucose and consist of several α-D-glucopyranose residues (six, seven, or eight rings, named α-, β-, and γ-CD, respectively) linked by α-1,4 glycoside bonds. These compounds have a doughnut-shaped structure in which the cavity has a hydrophobic character but the rims, in which the primary and secondary OH groups are inserted, are hydrophilic. The cavity size and nature of the substituents can be modulated, depending on the nature of the particular guest (mainly its shape, hydrophobicity, or electronic density), to obtain the most suitable binding, stoichiometries, etc.[2,3] It is well-documented[2,4] that cyclodextrins form inclusion complexes with a variety of inorganic and organic molecules in solution. The formation of host−guest complexes occurs through desolvation of both species. Nevertheless, the stability of the complex is related to the amount of water that can be released by the cyclodextrin upon encapsulation of the guest molecule.[5,6] Connors[7] reported that amphiphilic compounds such as surfactants form highly stable complexes. As a consequence of the binding process, some properties of the target molecule can be dramatically changed. This is the case for amphiphiles that form micelles or any other type of aggregate. In this situation, the presence of CDs introduces a new equilibrium into the medium, and this competes with the self-assembly process, normally causing the destruction of the aggregates.[8,9]

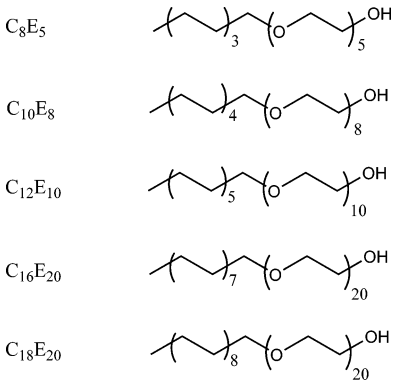
Surfactant inclusion complexes have been characterized by a wide variety of techniques including conductance,[10] NMR chemical shift,[11,12] fluorescence probe methods,[13,14] surfactant selective electrodes,[15] surface tension,[16] potentiometry,[17] sound velocity,[18] calorimetry,[5,17,19] density,[19b,20] heat capacity,[20a,c] and kinetic methods.[21] The reported binding constants for equivalent systems often vary considerably. A few studies have concerned complex formation between double alkyl chain surfactants[22−25] and nonionic heterogemini surfactants[26,27] with CDs. In such systems, the stoichiometry, the structure of the complex, and the binding constants are different from those observed with single chain surfactants. The majority of the studies carried out on these mixed systems is focused on analyzing the stoichiometry of the CD−surfactant complexes and also the calculation of their complexation constants. For this purpose, authors mainly use surfactant concentrations that are smaller than those corresponding to the start of the micellization process.

Our group has developed a kinetic model that accounts for reactivity in mixed surfactant−CD systems[28] well below and above the micellization point. This model has enabled us to highlight certain characteristics of mixed CD−surfactant systems: (i) at surfactant concentrations lower than the micellization point, a complexation equilibrium between the surfactant and the cyclodextrin is established. As the surfactant concentration increases, a situation is reached in which the concentration of the uncomplexed surfactant monomers in equilibrium with the CD is sufficient for the micellization process to begin. (ii) The critical micelle concentration has been found to shift to higher values in the presence of CD. The critical micelle concentration of a micellar system in the presence of cyclodextrin is equivalent to the combined concentrations of surfactant monomers complexed to the CD and of free dissolved monomers in equilibrium with the micellized surfactant. The concentration of free monomers remains essentially the same,[29] increases slightly,[30] or decreases slightly[30,31] depending on the surfactant. (iii) Once the micellization process has begun, interactions will not be established between the CD and the micellar system. The aggregation number is the same whether the micelles are in the presence or in the absence of cyclodextrins.[29a] Moreover, the volume of surfactant in the micelle form will be the same irrespective of the presence of β-CD with alkyltrimethylammonium bromides;[18c] sodium alkanoates;[8] bolaform surfactants;[18d] hydrogentad alkanoates;[20a] and fluorinated alkanoates.[20c] Ultrasonic studies of micelles in the presence of β-CD show that

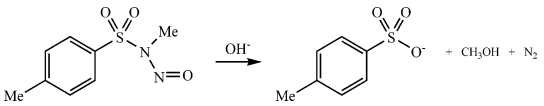
* Corresponding author. Phone: +34 981563100 ext. 14280; fax: +34 981595012; e-mail: qflgr3cn@usc.es.
[†] Universidad de Vigo.
[‡] Universidad de Santiago.

10.1021/jp0626871 CCC: $33.50
Published on Web 07/22/2006

SCHEME 1



SCHEME 2



the surfactant monomer−micelle exchange process appears to be unaffected by the presence of a β-CD−surfactant.[32] Other studies on the aggregation number as well as the degree of dissociation of the micelles are the same whether the micelles are in the presence or in the absence of cyclodextrins.[29a,33]

Previous studies have shown that at the micellization point, an appreciable concentration of uncomplexed CD must exist.[34] This conclusion contradicted the widely accepted view that considers the existence of a competitive equilibrium due to the affinity of the monomer for the micelle or the CD, an equilibrium that must be resolved in favor of the latter. In other words, only when all the available cavities are occupied can the monomers aggregate to form micelles. Previous results have identified mixed systems in which changes in the hydrophobicity of the surfactant monomers result in changes in the percentage of uncomplexed CD in equilibrium with the micellar system of between 5 and 30%. The aim of the work described here was to confirm quantitatively the existence of uncomplexed CD in equilibrium with the micellar system and, by modulating the hydrophobicity of the surfactant, to be able to increase to 100% the amount of uncomplexed CD in equilibrium with the micellar system. Our objective was to obtain a mixed system in which the addition of CD would not disturb the micellar system. We chose polyoxyethyleneglycol-based nonionic surfactants with different hydrophobicity: polyoxyethylene 20 stearyl ether ($C_{18}E_{20}$); polyoxyethylene 20 cetyl ether ($C_{16}E_{20}$); polyoxyethylene 23 lauryl ether ($C_{12}E_{23}$); polyoxyethylene 10 lauryl ether ($C_{12}E_{10}$); polyoxyethylene 8 decyl ether ($C_{10}E_8$); and polyoxyethylene 5 octyl ether (C_8E_5) (Scheme 1).

To study these systems, we used as a chemical probe the basic hydrolysis of *N*-methyl-*N*-nitroso-*p*-toluenesulfonamide (MNTS), a molecule whose geometry and polarity is suitable for complex formation with β-cyclodextrin and whose basic hydrolysis occurs by nucleophilic attack of hydroxyl ions on the SO_2 group of the MNTS (Scheme 2).[35]

The results obtained confirm that, contrary to expectations, the percentage of uncomplexed CD increases with the hydrophobic character of the surfactant. This result is a consequence of the dynamic behavior shown by the mixed cyclodextrin−surfactant systems, where the concentration of uncomplexed CD is the result of the balance between the complexation processes of the surfactant with the CD and the autoassociation (micellization) processes of the surfactant. The results demonstrate that on decreasing the surfactant cmc, the percentages of uncomplexed CD can increase to almost 95%. In these cases, the addition of moderate concentrations of CD to the micellar aggregate will not lead to the destruction of the micelles.

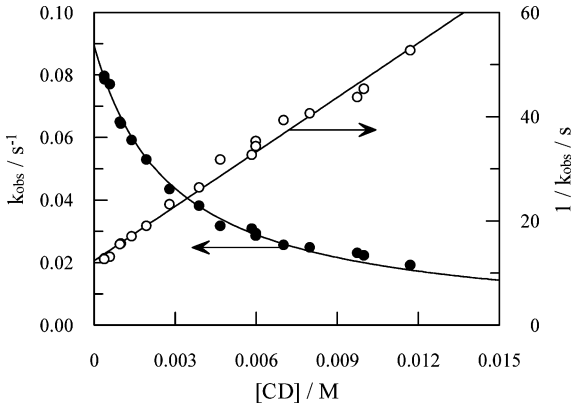


Figure 1. (●) Influence of CD concentration on the pseudo-first-order rate constant, k_{obs}, for the basic hydrolysis of MNTS at 25.0 °C. [NaOH] = 0.10 M. (○) Experimental data linearized according to eq 1.

Experimental Procedures

The surfactants, *N*-nitroso-*p*-toluenesulfonamide and β-cyclodextrin, were supplied by Sigma in the highest available purity and used without further purification. Owing to the low solubility of *N*-nitroso-*p*-toluenesulfonamide (MNTS) in water, stock solutions were prepared in acetonitrile. The percentage of acetonitrile in the reaction mixtures was always below 1% (v/v). CD solutions were made taking into account that commercial β-CD has a water content of 8 mol mol^{-1}. Under the alkaline conditions used, all CD was deprotonated (to give the −1 anion) since $pK_a^{\beta-CD} = 12.2$.[36] All hydroxyl ion concentrations were obtained by subtracting the CD concentration from the total concentration of NaOH.

The reaction kinetics was monitored by measuring the MNTS absorbance at 250 nm using an Agilent 8453 spectrophotometer thermostated at (25.0 ± 0.1) °C. The substrate concentration used was always 7.0×10^{-5} M, and that of hydroxyl ion was 0.10 M. The absorbance−time data of all kinetic experiments were fitted by pseudo-first-order integrated equations, and the values of the pseudo-first-order rate constants, k_{obs}, were reproducible to within 3%.

The critical micelle concentration of the surfactants both in the absence and in the presence of β-CD was obtained from surface tension measurements at 25.0 °C. The surface tension, σ/mNm^{-1}, was measured with a Kruss tensiometer (K9) using the Wilhelmy plates procedure.

Results

Basic Hydrolysis of MNTS in the Presence of β-CD. The addition of cyclodextrin to the reaction media inhibited the basic hydrolysis of MNTS, as can be seen from Figure 1. The formation of an unreactive complex between cyclodextrin and MNTS is responsible for the observed decrease in k_{obs} on increasing the oligosaccharide concentration.

If the binding constant of MNTS to β-CD is defined as K_{CD} = [MNTS − CD]/[CD][MNTS], we can derive the following expression for k_{obs}. Eq 1 predicts the existence of a linear dependence between $1/k_{obs}$ and CD concentration.

$$k_{obs} = \frac{k_w[OH^-]}{1 + K_{CD}[CD]} \text{ or } \frac{1}{k_{obs}} = \frac{1}{k_w[OH^-]} + \frac{K_{CD}[CD]}{k_w[OH^-]} \quad (1)$$

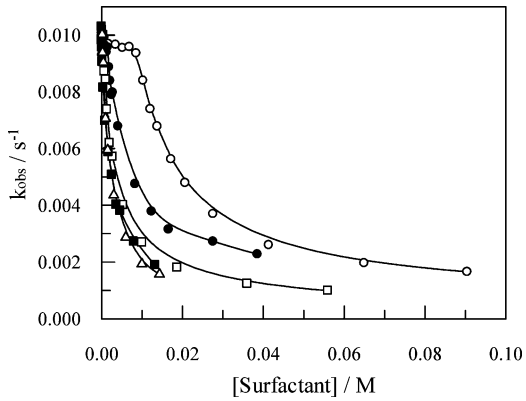
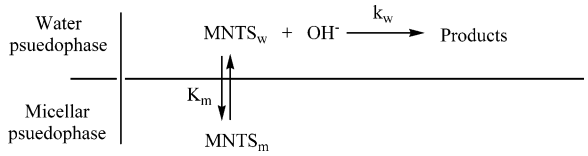


Figure 2. Influence of surfactant concentration on k_{obs} for the basic hydrolysis of MNTS at 25.0 °C. [NaOH] = 0.10 M. (○) C_8E_5; (●) $C_{10}E_8$; (□) $C_{12}E_{10}$; (■) $C_{16}E_{20}$; and (△) $C_{18}E_{20}$.

SCHEME 3



Values of $K_{CD} = (350 \pm 15)\ M^{-1}$ and $k_w = (9.5 \pm 0.5) \times 10^{-2}\ M^{-1}\ s^{-1}$ can be obtained.

Basic Hydrolysis of MNTS in the Presence of Nonionic Surfactants. Micellar systems also have the ability to alter chemical reactivity.[37] In an attempt to understand the kinetic behavior of the alkaline hydrolysis of MNTS in the presence of mixed systems formed by nonionic surfactants and β-CD, it is necessary to analyze the effect of the micellar system on this reaction. The influence of the concentration of nonionic surfactants has been studied in a wide interval that includes both the regions prior to the cmc, where the molecules of the surfactant are like unimers dispersed in the solution, and the regions after the cmc, where the surfactant molecules are associated to form micelles. The effect of the surfactant concentration on k_{obs} for the basic hydrolysis of MNTS is shown in Figure 2.

As can be seen from Figure 2, the pseudo-first-order rate constant remains practically unchanged on increasing the surfactant concentration up until the cmc. At surfactant concentrations higher than the cmc, a clear decrease in k_{obs} can be observed due to the presence of micellar aggregates. The formalism of the micellar pseudo-phase was applied to obtain a quantitative interpretation of the experimental results. Two well-differentiated environments were considered: water and a micellar pseudo-phase between which the MNTS is distributed. Provided that the OH^- ions do not associate with the micellar pseudo-phase, it can be considered that the reaction takes place only in the water pseudo-phase (Scheme 3).

On the basis of the micellar pseudo-phase approach, it is possible to derive the following equation, which relates the observed rate constant with the surfactant concentration.

$$k_{obs} = \frac{k_w[OH^-]}{1 + K_m[D_n]} \qquad (2)$$

where K_m is the distribution constant of MNTS between the water and the micellar pseudo-phases, $K_m = [MNTS]_m/[MNTS]_w[D_n]$; $[D_n]$ is the concentration of micellized surfactant, $[D_n] = [surfactant]_T - cmc$; and $[surfactant]_T$ is the total concentration of the surfactant. The values of cmc are required to fit eq 2 to the experimental results. The critical micelle concentration can be obtained kinetically as the minimal surfactant concentration necessary to observe an appreciable change in k_{obs}. Nevertheless, this method is not particularly accurate to determine very small cmc values, as in the cases of $C_{12}E_{10}$, $C_{16}E_{20}$, and $C_{18}E_{20}$. In these cases, the cmc values were obtained from surface tension measurements.

TABLE 1: Critical Micelle Concentrations for the Nonionic Surfactants Used in the Present Study and Binding Constants of MNTS to Nonionic Micelles

surfactant	cmc[a] (M)	cmc (M)	K_m (M^{-1})
C_8E_5	9.1×10^{-3}	9.0×10^{-3}	69 ± 3
$C_{10}E_8$	9.2×10^{-4}	1.34×10^{-3}	143 ± 12
$C_{12}E_{10}$	9.0×10^{-5}	1.58×10^{-4}	264 ± 17
$C_{16}E_{20}$	7.7×10^{-5}	8.0×10^{-5}	366 ± 25
$C_{18}E_{20}$	8.0×10^{-6}	1.6×10^{-6}	362 ± 33

[a] Literature values. See refs 38−41.

The distribution constants of the MNTS between the water and the micellar pseudo-phase (K_m) are given in Table 1 along with the cmc values obtained experimentally. The bibliographical cmc values are also given for the surfactants used. Small discrepancies are observed between the cmc values obtained in this work and the bibliographic ones. For C_8E_5 and $C_{16}E_{20}$, bibliographic cmc values are compatible with those obtained in this work under the presence of [NaOH] = 0.10 M. For the more hydrophobic surfactant, $C_{18}E_{20}$, the cmc value decreases as a consequence of the presence of NaOH as is well-documented in the bibliography for salt effects on nonionic surfactant micellization. However, for $C_{10}E_8$ and $C_{12}E_{10}$, the cmc value obtained in the presence of [NaOH] = 0.10 M is slightly larger than in the absence of additives, which can be attributed to the fact that the generation of a micellar phase may require a surfactant concentration slightly larger than the cmc. The binding constants of MNTS to the micellar pseudo-phase are also shown in Table 1. As can be seen, K_m increases with the length of the surfactant hydrocarbon chain. This behavior is well-documented in the bibliography, and it is considered to be due to the higher hydrophobic character of the micelles on increasing the length of the surfactant hydrophobic chain.

Basic Hydrolysis of MNTS in the Presence of Mixed Systems: Nonionic Surfactant and β-CD. It is well-known that the addition of CDs to micellar systems produces changes in its physicochemical properties, such as the cmc, due to the formation of CD−surfactant inclusion complexes. The observed rate constant for the basic hydrolysis of MNTS shows a clear inhibition as a consequence of the addition to the reaction media of both β-CD and nonionic surfactants. The mixed system was investigated by carrying out experiments in which the β-CD concentration was kept constant and the surfactant concentration was varied from values clearly lower than the cmc to values beyond the micellization point. As an example, the results obtained using C_8E_5 and $C_{12}E_{10}$ both in the presence and in the absence of different cyclodextrin concentrations are shown in Figure 3. From a qualitative point of view, the observed behavior is the same in both cases. When the surfactant concentration is zero, the observed rate constant diminishes as the concentration of CD increases. This result is consistent with that found for the β-CD/water system and is due to the formation of an unreactive inclusion complex.

The value of k_{obs} increases to a maximum as the concentration of surfactant increases. The increase in the observed rate constant is due to the competitive formation of inclusion complexes between the CD and the nonionic surfactant. The formation of these inclusion complexes displaces the MNTS toward the

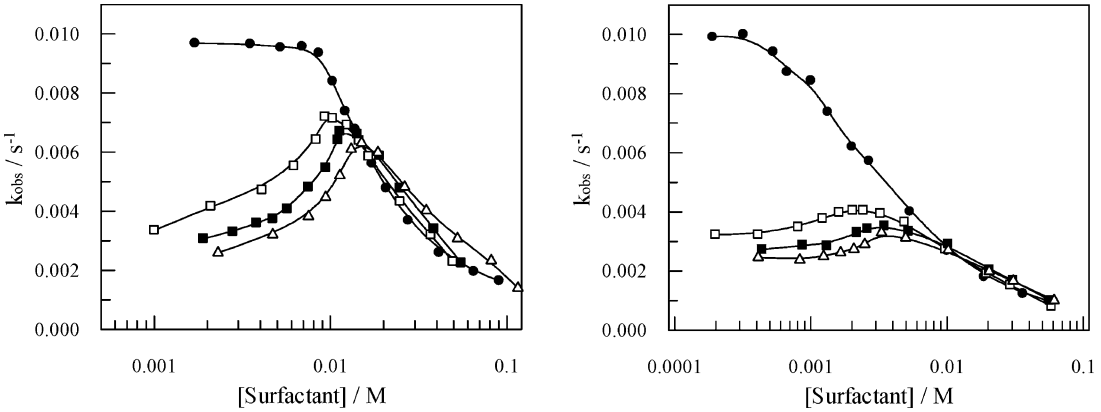


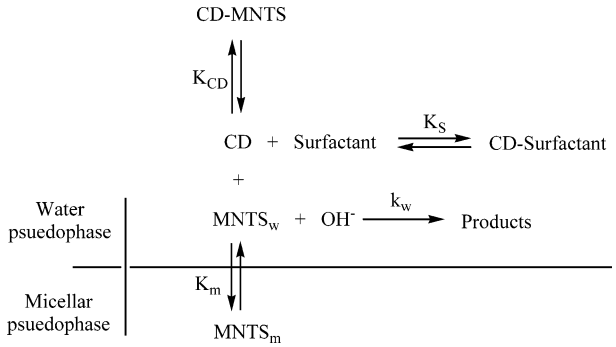
Figure 3. Influence of C_8E_5 (left) and $C_{12}E_{10}$ (right) concentration on the observed rate constant for the basic hydrolysis of MNTS at 25.0 °C, [NaOH] = 0.10 M. (●) [CD] = 0; (□) [CD] = 5.5×10^{-3} M; (■) [CD] = 7.5×10^{-3} M; and (△) [CD] = 1.0×10^{-2} M.

aqueous medium, and as a consequence, the rate constant of the reaction increases. The competitive formation of the CD−surfactant inclusion complexes occurs until the surfactant concentration reaches the value at which the micellization process begins. Once nonionic micelles have been formed, the typical inhibiting effect that they have on the basic hydrolysis of MNTS is observed. Therefore, the maximum observed in the plot of k_{obs} versus surfactant concentration can be attributed to the micellization point, where the kinetic effects caused by the formation of an inclusion complex between the surfactant and the CD (catalytic effect on k_{obs}) and for the formation of the micelles (inhibitory effect on k_{obs}) are compensated.

In an effort to develop a kinetic model, we considered that once the micellization process begins, interactions of any sort are not established between the CD and the micellar system.[32,33] Recent results from the study of the enthalpy of transfer of cyclodextrin form water to the aqueous surfactant solutions suggest the existence of interactions between micelles and cyclodextrins in systems using hydrogenated[5,42] and fluorinated[43] alkanoates. Quantitative analysis of the postmicellar region indicates that the cyclodextrin−micelle forces are ion−dipole (carboxylate head/hydroxylic group) in nature. However, the existence of this kind of interaction can be questioned on the basis of self-diffusion NMR studies of the host−guest interaction between β-CD and several surfactants.[44] The self-diffusion values for the β-CD decrease slightly with surfactant concentration after micellization instead of reaching a plateau value. This deviation could be related to the influence of the micelles (which cause an obstruction) in the solution on cyclodextrin self-diffusion. This deviation was observed with cationic, anionic, and nonionic surfactants where there is no electrostatic interaction present between micelles and cyclodextrins (or CD−surfactant complexes). Moreover, kinetic results previously obtained by our group show that there is no interaction between β-CD and SDS or TTABr micelles once the micellization process has started.[28c] However, it is important to note that this study is focused on the behavior of these mixed systems at the micellization point. Hence, the presence or absence of interactions between CD and micelles is not significant in this study, and the main conclusions drawn from these results will not be influenced by this aspect.

On considering the absence of interactions between micelles and cyclodextrins, the maximum of the plot of k_{obs} against the surfactant concentration coincides with the minimal surfactant concentration necessary to begin the micellization process in the presence of cyclodextrins. Once micellization begins, it is believed that the concentration of monomeric surfactant remains constant and that this addition only causes an increase in the concentration of micellized surfactant. This implies, in turn, that the concentration of the CD−surfactant complex remains unchanged after the cmc. These processes are represented in Scheme 4, which shows the distribution of the MNTS between the aqueous and the micellar pseudo-phases as well as the processes for the formation of the inclusion complexes of MNTS and the nonionic surfactant with the CD. As indicated previously, the only route for reaction is in the aqueous pseudophase through the uncomplexed MNTS.

SCHEME 4



The following equation can be obtained from Scheme 4 for the observed rate constant:

$$k_{obs} = \frac{k_w[OH^-]}{1 + K_{CD}[CD]_f + K_m[D_n]} \quad (3)$$

where $[CD]_f$ is the concentration of uncomplexed cyclodextrin that is available to form an inclusion complex with MNTS. The behavior of mixed surfactant−cyclodextrin systems is usually explained in terms of a mechanism involving stages, where the micellization does not begin until the surfactant has saturated the complexation capacity of the cyclodextrin. This assumption implies that when the micellization process begins, the cyclodextrin must be forming inclusion complexes with surfactant monomers. Previous studies carried out in our laboratory and by others[45] revealed that, rather than being two competitive processes, the associations with the cyclodextrin and the micellization are simultaneous processes, and the competition between them causes the existence of free cyclodextrin in equilibrium with the surfactant−cyclodextrin complexes and micelles.

For any surfactant concentration, it is possible to obtain the concentration of free cyclodextrin from the following equation:

$$[CD]_f = \left(\frac{k_w[OH^-]}{k_{obs}} - 1\right)\frac{1}{K_{CD}} \quad (4)$$

Eq 4 is easy to derive from eq 1, and the curve shown in Figure 1 can be used as a calibration curve to obtain the concentration of uncomplexed cyclodextrin in the mixed system formed by β-CD and a nonionic surfactant.

Once the micellization begins, both the concentration of monomeric surfactant and the concentration of the CD−surfactant complex—and therefore the concentration of uncomplexed cyclodextrin—remain constant. To solve eq 3, it is necessary to know, in addition to the concentration of uncomplexed cyclodextrin, the cmc to calculate the concentration of micellized surfactant, D_n. This value can be obtained kinetically from the plots of k_{obs} versus the surfactant concentration in the presence of cyclodextrin and is the surfactant concentration at which k_{obs} has a maximum value. These kinetically obtained critical micelle concentration values were corroborated by surface tension measurements. In the process of fitting eq 3 to the experimental results, the value of the association constant of MNTS to the micelles, K_m, was optimized. The good adjustment of the experimental results to eq 3 is reflected in the curves in Figure 3. In all cases, the optimized K_m values are compatible with those obtained in the absence of cyclodextrins (Table 1).

Micelle Decomposition by the Addition of Cyclodextrin? At low concentrations, the surfactants form a variety of low-molecular weight aggregates in solution and monolayers at the surface of the solvent, a situation that reduces the surface tension. The detergent molecules become more water soluble upon the inclusion complexation with cyclodextrins and are extracted from the micelles or from the surface into the bulk aqueous solvent. This process clearly interferes with the aggregation of the detergent molecules into micelles, thereby shifting the cmc to a higher concentration and, as indicated by the large rise in surface tension, also removes the surfactant molecules from the surface monolayer. As a result, the addition of cyclodextrins to surfactant solutions can be used to destroy micelles or to increase the surface tension (e.g., to avoid foaming).[46]

The influence of the β-CD concentration on the surface tension of different surfactant solutions is shown in Figure 4. In all cases, the surfactant concentration is 3.0×10^{-3} M and is higher than the cmc. The observed behavior shows that for the SDS, the surface tension increases as a consequence of the addition of β-CD. The complexation of surfactant monomers by cyclodextrin causes the monomers to dissolve in the aqueous medium, and consequently, destruction of the micellar system occurs. For the less hydrophobic nonionic surfactants ($C_{10}E_8$ and $C_{12}E_{23}$), an increase in the surface tension is observed as [β-CD] increases. It is important to analyze the influence of the nature of the surfactant on the concentration of β-CD necessary for the destruction of the micellar system. In the case of SDS, it is necessary to add [β-CD] = 2.81×10^{-3} M, while for $C_{10}E_8$ and $C_{12}E_{23}$, concentrations of [β-CD] = 3.23×10^{-3} M and [β-CD] = 1.06×10^{-2} M need to be added.

When more hydrophobic surfactants are used (i.e., $C_{16}E_{20}$ and $C_{18}E_{20}$), there is hardly any variation in the surface tension on the addition of β-CD (see Figure 4). To increase the surface tension for $C_{16}E_{20}$, it is necessary to use [β-CD] = 2.75×10^{-2} M. It is important to note that this concentration of β-CD is approximately 9 times greater than the total concentration of $C_{16}E_{20}$ present in the system. As the hydrophobic character of the surfactant increases (i.e., $C_{18}E_{20}$), an effect derived from the addition of β-CD could not be observed, despite having reached an approximately 12-fold excess in the concentration of β-CD with respect to surfactant concentration.

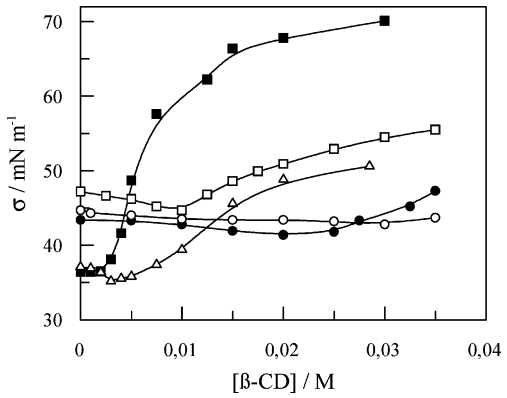


Figure 4. Influence of the [β-CD] on the surface tension for different surfactant solutions. [Surfactant] = 3.00×10^{-3} M; T = 25 °C; [NaOH] = 0.10 M. (○) $C_{18}E_{20}$; (●) $C_{16}E_{20}$; (□) $C_{12}E_{23}$; (△) $C_{10}E_8$; and (■) SDS.

Discussion

The results outlined in the previous section allow us to explain the experimental behavior observed in the mixed systems formed by cyclodextrins and surfactants. The results also show the validity of the kinetic method as a chemical probe to explore the behavior of complex systems. In this investigation, we focused on analyzing the existence of uncomplexed cyclodextrin in balance with the micellar system.

Evidence of Uncomplexed Cyclodextrin from the Critical Micelle Concentration. The experimental results shown in Figure 3 show that the cmc, identified as the maximum in the curve of k_{obs} versus surfactant concentration, increases with cyclodextrin concentration. The cmc values obtained for the different systems studied are shown in Table 2.

The cmc increases in all cases on adding cyclodextrin to the micellar system. Nevertheless, this increase is not equal for all the surfactants, nor is it of the expected magnitude. The widely accepted view is that the micellar aggregate would form only after saturating the complexation capacity of the cyclodextrin. Therefore, the critical micelle concentration would be the sum of the free monomer concentration plus the concentration of surfactant monomers complexed by the cyclodextrin, which is equal to the cyclodextrin concentration. In other words, cmc = [CD−surfactant] + [monomer] = $[CD]_T$ + [monomer]. The use of the cmc values and CD concentrations shown in Table 2 would give negative values for the monomer concentrations in equilibrium with the micellar system. In fact, in most cases, the cmc is lower than the cyclodextrin concentration. This result suggests that the traditional view must be ruled out, and it is therefore necessary to consider the formation of CD−surfactant complexes and the micellization process to be competitive processes that take place simultaneously. As shown later, the fact that the cmc is lower than the cyclodextrin concentration is indicative of the existence of a high percentage of uncomplexed cyclodextrin in balance with the micellar system.

Evidence of Uncomplexed Cyclodextrin from Surface Tension Measurements. The results shown in Figure 4 indicate that the destruction of the micellar system occurs due to complexation of the surfactant by β-CD. Therefore, the total concentration of β-CD will be equal to the sum of the concentration of uncomplexed β-CD plus the concentration of β-CD complexed by the surfactant: $[CD]_T$ = $[CD]_f$ +

TABLE 2: Influence of Cyclodextrin Concentration on the cmc for Mixed Systems Studied

surfactant	[CD] = 0 M	[CD] = 3.5 mM	[CD] = 5.0 mM	[CD] = 7.5 mM	[CD] = 1.0 mM
C_8E_5	9.0×10^{-3}	1.0×10^{-2}	1.1×10^{-2}	1.2×10^{-2}	1.3×10^{-2}
$C_{10}E_8$	1.34×10^{-3}	2.6×10^{-3}	4.0×10^{-3}		
$C_{12}E_{10}$	1.58×10^{-4}	1.0×10^{-3}	2.0×10^{-3}	2.6×10^{-3}	2.7×10^{-3}
$C_{16}E_{20}$	8.0×10^{-5}	1.1×10^{-4}	1.8×10^{-4}	4.5×10^{-4}	6.9×10^{-4}
$C_{18}E_{20}$	1.6×10^{-6}	3.0×10^{-5}	3.0×10^{-5}		

[CD−surfactant]. Likewise, the total concentration of the surfactant at the point of destruction of the micelle will be the sum of the concentration of surfactant complexed with β-CD plus the concentration of free monomers: $[\text{surfactant}]_T = [\text{CD−surfactant}] + [\text{surfactant}]_f$. In a good approximation, we can assume that the concentration of free surfactant will be equal to the cmc in the absence of β-CD. Therefore, $[\text{surfactant}]_T = [\text{CD−surfactant}] + \text{cmc}$. The combination of the mass balances for the total concentration of β-CD and surfactant gives the following expression for the concentration of noncomplexed β-CD in equilibrium with the micellar system: $[\text{CD}]_f = [\text{CD}]_T - [\text{surfactant}]_T + \text{cmc}$.

On applying the previous equation, and given the cmc values, the $[\text{surfactant}]_T$, and the $[\beta\text{-CD}]_T$ necessary to cause the destruction of the micellar system, we can obtain $[\text{CD}]_f$ in equilibrium with each surfactant. The values obtained show that as the breakdown of SDS micelles occurs, there is 18% of uncomplexed β-CD. This percentage increases for $C_{10}E_8$ (38%), $C_{12}E_{23}$ (73%), $C_{16}E_{20}$ (89%), and $C_{18}E_{20}$ (>92%). The results obtained show that there is a clear dependency between the percentage of uncomplexed β-CD in equilibrium with the micellar system and the hydrophobicity of the surfactant. As this hydrophobicity increases, the percentage of uncomplexed β-CD also increases.

It can be seen that as the hydrophobicity of the surfactant increases, the free Gibbs energy of micellization decreases. At the same time, we would expect a reduction to occur in the free energy of complexation of the surfactant by β-CD due to the lower solubility of the surfactants in an aqueous medium. However, the results obtained when studying the influence of the length of the surfactant hydrocarbon chain on its complexation by cyclodextrins shows that the capacity for complexation tends to reach a limiting value for hydrocarbons with more than 12 carbon atoms. This result is due to the fact that, according to Tanford,[47] a fully extended alkyl chain consisting of four CH_2 groups can span the β-CD cavity, whereas Park and Song[14] indicated that eight CH_2 groups can be accommodated in the β-CD cavity if allowances are made for carbon chain coiling due to the occurrence of gauche links. As a consequence of the balance between the free Gibbs energies of micellization and the cyclodextrin complexation, an increase occurs in the concentration of uncomplexed β-CD in equilibrium with the micellar system.

Evidence of Uncomplexed Cyclodextrin from the Rate Constants. The observed rate constants, k_{obs}, show a complex dependence on the surfactant concentration in the presence of β-CD (Figure 3). As discussed previously, the maximum of the k_{obs} versus surfactant] curve corresponds to the micellization point. The values of k_{obs} in the maximum of the aforementioned curve are shown in Figure 5, along with the value obtained in bulk water (dashed line).

Several aspects of Figure 5 should be highlighted. First, the values obtained for k_{obs} in the maximum of the curves (i.e., at the point of micellization) are always lower than those observed in bulk water. Provided that the point of micellization is when the micelles begin to exist, the difference between k_{obs} in the maximum and that obtained in bulk water cannot be attributed

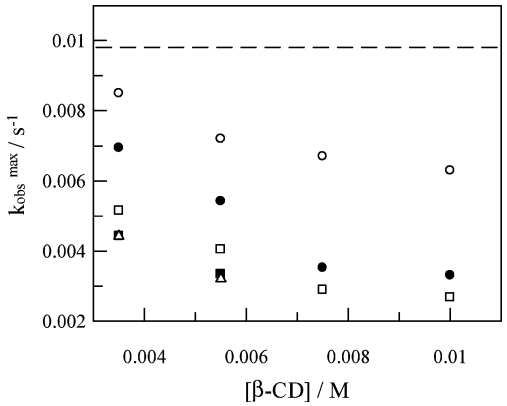


Figure 5. k_{obs} values in the maximum of the plots k_{obs} vs [surfactant] at different cyclodextrin concentrations for (○) C_8E_5; (●) $C_{10}E_8$; (□) $C_{12}E_{10}$; (■) $C_{16}E_{20}$; and (△) $C_{18}E_{20}$ at 25.0 °C.

TABLE 3: Percentage of Uncomplexed Cyclodextrin in Equilibrium with the Micellar System for Different Nonionic Surfactants and Cyclodextrin Concentrations

$[\beta\text{-CD}]$ (M)	C_8E_5	$C_{10}E_8$	$C_{12}E_{10}$	$C_{16}E_{20}$	$C_{18}E_{20}$
3.5×10^{-3}	14	35	58	80	91
5.0×10^{-3}	17	36	59	81	92
7.5×10^{-3}	16		62	80	
1.0×10^{-2}	17		58	83	
mean value	16 ± 2	35 ± 1	60 ± 2	81 ± 2	92 ± 1

to the micellar system. Rather, it must be attributed to the existence of uncomplexed cyclodextrin that exerts an inhibiting effect on the basic hydrolysis of MNTS (see Figure 1). Second, it is important to mention that the value of k_{obs} in the maximum diminishes as the β-CD concentration increases, which indicates that the concentration of uncomplexed cyclodextrin increases on increasing the total concentration of cyclodextrin. Nevertheless, it will be shown here that the percentage of uncomplexed cyclodextrin does not depend on the total concentration of cyclodextrin. Third, it is important to emphasize that the value of k_{obs} in the maximum diminishes as the hydrophobic character of the surfactant increases (i.e., increasing the hydrophobic character of the surfactant increases the concentration of uncomplexed cyclodextrin).

Evidence for the existence of uncomplexed cyclodextrin obtained from the values of k_{obs} is consistent with the results obtained from the values of the critical micelle concentration and the surface tension measurements. Nevertheless, the advantage of using the values of k_{obs} is that it allows us to quantify the concentration of uncomplexed cyclodextrin in balance with the micellar system. The concentration of uncomplexed cyclodextrin in equilibrium with the micellar system can be calculated using eq 4 in conjunction with the k_{obs} value at the maximum of the plot of k_{obs} versus [surfactant]. The percentages of uncomplexed cyclodextrin were obtained for each of the surfactants under investigation for all cyclodextrin concentrations (Table 3). It can be seen that the percentage of uncomplexed cyclodextrin is independent of the cyclodextrin concentration in the medium. Likewise, it is possible to verify quantitatively that the percentage of uncomplexed cyclodextrin increases with increasing chain length of the surfactant.

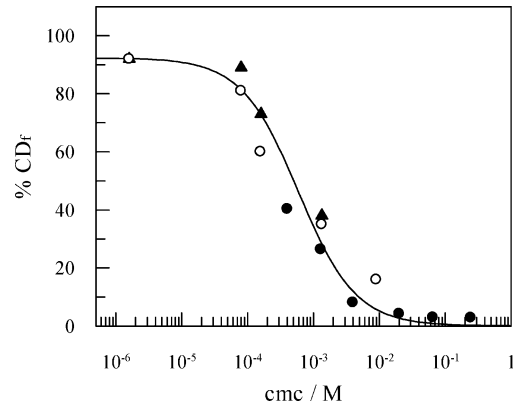


Figure 6. Influence of cmc on the percentage of uncomplexed β-CD in equilibrium with the micellar system at 25.0 °C. (○) Nonionic surfactants (uncomplexed cyclodextrin from kinetic data), (▲) nonionic surfactants (uncomplexed cyclodextrin from surface tension data), and (●) alkyltrimethylammonium halide surfactants (ref 34b).

An increase in the hydrophobic character of the surfactant favors the association to the cyclodextrin but at the same time implies an increase in its tendency to micellize. Having increased the nonpolar character of a surfactant, the tendency to form micelles is higher. Therefore, for surfactants with similar polar headgroups, an increase in the length of the hydrocarbon chain will decrease the cmc. The balance between these two processes governs the concentration of free CD balanced in the mixed system. Because of the fact that the formation of the inclusion complex is in equilibrium, even though the association constant with the CD is very high, free surfactant will always exist in the medium. The association of the surfactant with the CD will take place until the concentration of free surfactant in equilibrium with the free cyclodextrin and the complex CD−surfactant reaches the minimum value necessary to begin the micellization process.

There is a clear relationship between the cmc value of each surfactant and the percentage of noncomplexed cyclodextrin. Varying the cmc by 5 orders of magnitude changes the free cyclodextrin from ∼5 to ∼95%. If we consider Figure 6, we can highlight general trends in the behavior observed for nonionic, anionic, and cationic surfactants. However, in quantitative terms, there are slight differences in that the cationic surfactants exhibit a lower percentage of free cyclodextrin. The electrostatic repulsions between cationic headgroups hinder micellization. Hence, for a given hydrocarbon chain, the cmc values of such surfactants are higher than those for corresponding anionic and nonionic headgroups. Cationic and nonionic surfactants with the same chain length can be compared. In this case, the nonionic surfactant has a higher tendency to micellize than the cationic surfactant and, therefore, a higher value for noncomplexed cyclodextrin.

The widely accepted ideas concerning mixed CD/surfactant systems consider that the addition of cyclodextrins to micellar systems causes their destruction. Our results indicate that this view needs to be modified. We should consider that the complexation equilibrium of the surfactant with the CD and the autoassociation of the surfactant take place simultaneously. The balance between these two processes will give rise to the existence of uncomplexed CD in equilibrium with the micellar system and its variation with the nature of the surfactant. As a consequence, the addition of cyclodextrins to micellar solutions formed by very hydrophobic surfactants will not cause their destruction. Precautions should therefore be taken when attempting to modify the detergent properties of surfactants by adding cyclodextrins.

Acknowledgment. Financial support from the Xunta de Galicia (PGIDIT04TMT209003PR) and Ministerio de Ciencia y Tecnología (CTQ2005-04779 and MAT2004-0299) is acknowledged. C.C.L. thanks FPU for a fellowship.

References and Notes

(1) D'Souza, V. T.; Lipkowitz, K. B. *Chem. Rev.* **1998**, *98*, 1741.
(2) Connors, K. A. *Chem. Rev.* **1997**, *97*, 1325.
(3) Raymo, F. M.; Stoddart, F. J. *Chem. Rev.* **1999**, *99*, 1643.
(4) Rekharsky, M. V.; Inoue, Y. *Chem. Rev.* **1998**, *98*, 1875.
(5) De Lisi, R.; Milioto, S.; Muratore, N. *Langmuir* **2000**, *16*, 4441.
(6) Inoue, Y.; Liu, Y.; Tong, L. H.; Shen, B. J.; Jin, D. S. *J. Am. Chem. Soc.* **1993**, *115*, 10637.
(7) Connors, K. A. *J. Pharm. Sci.* **1996**, *85*, 796.
(8) Gonzalez-Gaitano, G.; Sanz-Garcia, T.; Tardajos, G. *Langmuir* **1999**, *15*, 7963.
(9) Gonzalez-Gaitano, G.; Compostizo, A.; Sanchez-Martin, L.; Tardajos, G. *Langmuir* **1997**, *13*, 2235.
(10) (a) Palepu, R.; Richardson, J. E.; Reinsborough, V. C. *Langmuir* **1989**, *5*, 218. (b) Rafati, A. A.; Bagheri, A.; Iloukhani, H.; Zarinehzad, M. *J. Mol. Liq.* **2004**, *116*, 37.
(11) (a) Ahmed, J.; Yamamoto, T.; Matsui, Y. *J. Inclusion Phenom. Macrocyclic Chem.* **2000**, *38*, 267. (b) Guo, W.; Fung, B. M.; Christian, S. D. *Langmuir* **1992**, *8*, 446. (c) Wilson, L. D.; Siddall, S. R.; Verrall, R. E. *Can. J. Chem.* **1997**, *75*, 927. (d) Wilson, L. D.; Verrall, R. E. *Langmuir* **1998**, *14*, 4710.
(12) (a) Funasaki, N.; Ishikawa, S.; Neya, S. *J. Phys. Chem. B* **2003**, *107*, 10094. (b) Funasaki, N.; Ishikawa, S.; Neya, S. *J. Phys. Chem. B* **2004**, *108*, 9593.
(13) Patonay, G.; Rollie, M. E.; Warner, I. M. *Anal. Chem.* **1985**, *57*, 569.
(14) Park, J. W.; Song, H. J. *J. Phys. Chem.* **1989**, *93*, 6454.
(15) (a) Rafati, A. A.; Bagheri, A. *Bull. Chem. Soc. Jpn.* **2004**, *77*, 485. (b) Jezequel, D.; Mayaffre, A.; Letellier, P. *Can. J. Chem.* **1991**, *69*, 1865.
(16) Saito, Y.; Watanabe, K.; Hashizaki, K.; Taguchi, H.; Ogawa, N.; Sato, T. *J. Inclusion Phenom. Macrocyclic Chem.* **2000**, *38*, 452.
(17) Mwakibete, H.; Crisantino, R.; Bloor, D. M.; Wyn-Jones, E.; Holzwarth, J. F. *Langmuir* **1995**, *11*, 57.
(18) (a) Junquera, E.; Gonzalez Benito, J.; Pena, L.; Aicart, E. *J. Colloid Interface Sci.* **1994**, *163*, 355. (b) Gonzalez Gaitano, G.; Crespo, A.; Compostizo, A.; Tardajos, G. *J. Phys. Chem. B* **1997**, *101*, 4413. (c) Gonzalez-Gaitano, G.; Crespo, A.; Tardajos, G. *J. Phys. Chem. B* **2000**, *104*, 1869. (d) Gonzalez-Gaitano, G.; Guerrero-Martinez, A.; Ortega, F.; Tardajos, G. *Langmuir* **2001**, *17*, 1392.
(19) (a) Rekharsky, M. V.; Myhew, P.; Goldberg, N.; Ross, P. D.; Yamashoji, Y.; Inoue, Y. *J. Phys. Chem. B* **1997**, *101*, 87. (b) Wilson, L. D.; Verrall, R. E. *J. Phys. Chem. B* **1998**, *102*, 480.
(20) (a) De Lisi, R.; Milioto, S.; Pellerito, A.; Inglese, A. *Langmuir* **1998**, *14*, 6045. (b) Wilson, L. D.; Verrall, R. E. *J. Phys. Chem B* **1997**, *101*, 9270. (c) De Lisi, R.; Milioto, S.; De Giacomo, A.; Inglese, A. *Langmuir* **1999**, *15*, 5014. (d) Wilson, L. D.; Verral, R. E. *J. Phys. Chem. B* **2000**, *104*, 1880.
(21) (a) Bravo Diaz, C.; Gonzalez Romero, E. *Langmuir* **2005**, *21*, 4888. (b) Maeso, M. H.; Gonzalez, S. P.; Bravo Diaz, C.; Gonzalez Romero, E. *Colloids Surf., A.* **2004**, *249*, 29. (c) Ghosh, K. K.; Sharma, P.; Taramkar, S.; Sar, S. K. *React. Kinet. Catal. Lett.* **2004**, *81*, 161. (d) Iglesias, E.; Fernandez, A. *J. Chem. Soc., Perkin Trans 2* **1998**, 1691. (e) Iglesias, E. *J. Am. Chem. Soc.* **1998**, *120*, 13057. (f) Okubo, T.; Kuroda, M. *Macromolecules* **1989**, *22*, 3936. (g) Hersey, A.; Robinson, B. H.; Kelley, H. C. *J. Chem. Soc., Faraday Trans 1* **1986**, *82*, 1271.
(22) Ishikawa, S.; Neya, S.; Funasaki, N. *J. Phys. Chem. B* **1998**, *102*, 2502.
(23) Funasaki, N.; Neya, S. *Langmuir* **2000**, *16*, 5343.
(24) Isnin, R.; Yoon, H. R.; Vargas, R.; Quintela, P. A.; Kaifer, A. E. *Carbohydr. Res.* **1989**, *192*, 357.
(25) Funasaki, N.; Ishikawa, S.; Neya, S. *Langmuir* **2002**, *18*, 1786.
(26) Abrahmsen-Alami, S.; Alami, E.; Eastoe, J.; Cosgrove, T. *J. Colloid Interface Sci.* **2002**, *246*, 191.
(27) Alami, E.; Abrahmsen-Alami, S.; Eastoe, J.; Grillo, I.; Heenan, R. K. *J. Colloid Interface Sci.* **2002**, *255*, 403.
(28) (a) García-Río, L.; Leis, J. R.; Mejuto, J. C.; Pérez-Juste, J. *J. Phys. Chem. B* **1997**, *101*, 7383. (b) García-Río, L.; Leis, J. R.; Mejuto, J. C.; Pérez-Juste, J. *J. Phys. Chem. B* **1998**, *102*, 4581. (c) Alvarez, A. R.; García-Río, L.; Hervés, P.; Leis, J. R.; Mejuto, J. C.; Pérez-Juste, J. *Langmuir* **1999**, *15*, 8368. (d) García-Río, L.; Leis, J. R.; Mejuto, J. C.; Navarro-Vazquez, A.; Pérez-Juste, A.; Rodríguez-Dafonte, P. *Langmuir* **2004**, *20*, 606.
(29) (a) Junquera, E.; Tardajos, G.; Aicart, E. *Langmuir* **1993**, *9*, 1213. (b) Junquera, E.; Tardajos, G.; Aicart, E. *J. Colloid Interface Sci.* **1993**, *158*, 388.
(30) Peña, L.; Junquera, E.; Aicart, E. *J. Solution Chem.* **1995**, *24*, 1075.

(31) Junquera, E.; Peña, L.; Aicart, E. *Langmuir* **1995**, *11*, 4685.

(32) (a) Jobe, D. J.; Verrall, R. E.; Junquera, E.; Aicart, E. *J. Phys. Chem.* **1993**, *97*, 1243. (b) Jobe, D. J.; Verrall, R. E.; Junquera, E.; Aicart, E. *J. Phys. Chem.* **1994**, *98*, 10814.

(33) (a) Junquera, E.; Peña, L.; Aicart, E. *Langmuir* **1997**, *13*, 21. (b) Jobe, D. J.; Reinsborough, V. C.; Wetmore, S. D. *Langmuir* **1995**, *11*, 2476.

(34) (a) Dorrego, B.; García-Río, L.; Hervés, P.; Leis, J. R.; Mejuto, J. C.; Pérez-Juste, J. *Angew. Chem., Int. Ed.* **2000**, *39*, 2945. (b) Dorrego, B.; García-Río, L.; Hervés, P.; Leis, J. R.; Mejuto, J. C.; Pérez-Juste, J. *J. Phys. Chem. B* **2001**, *105*, 4912.

(35) Castro, A.; Leis, J. R.; Peña, M. E. *J. Chem. Soc., Perkin Trans. 2* **1989**, 1861.

(36) Bender, M. L.; Komiyama, M. *Cyclodextrin Chemistry*; Springer: Berlin, 1978.

(37) Bunton, C. A.; Savelli, G. *Adv. Phys. Org. Chem.* **1986**, *22*, 213.

(38) Samaha, M. W.; Naggar, V. F. *Int. J. Pharm.* **1988**, *42*, 1.

(39) Mukerjee, P.; Mysels, K. J. *Critical Micelle Concentration of Aqueous Surfactant Solutions*; National Bureau of Standards: Washington, DC, 1971.

(40) Meguro, K.; Takasawa, Y.; Kawahashi, N.; Tabata, Y.; Ueno, M. *J. Colloid Interface Sci.* **1981**, *83*, 50.

(41) Kokol, V. *Carbohydr. Polym.* **2002**, *50*, 227.

(42) (a) De Lisi, R.; Lazzara, G.; Milioto, S.; Muratore, N.; Terekhova, I. V. *Langmuir* **2003**, *19*, 7188. (b) De Lisi, R.; Lazzara, G.; Milioto, S.; Muratore, N. *J. Phys. Chem. B* **2003**, *107*, 13150.

(43) De Lisi, R.; Milioto, S.; Muratore, N. *J. Phys. Chem. B* **2002**, *106*, 8944.

(44) (a) Cabaleiro-Lago, C.; Nilsson, M.; Söderman, O. *Langmuir* **2005**, *21*, 11637. (b) Valente, A. J. M.; Nilsson, M.; Söderman, O. *J. Colloid Interface Sci.* **2005**, *281*, 218.

(45) Lima, S.; Goodfellow, B. J.; Teixeira-Dias, J. J. C. *J. Phys. Chem. B* **2003**, *107*, 14590.

(46) Saenger, W.; Müller-Fahrnow, A. *Angew. Chem., Int. Ed. Engl.* **1988**, *27*, 7, 393.

(47) Tanford, C. *The Hydrophobic Effect: Formation of Micelles and Biological Membranes*, 2nd ed.; Wiley: New York, 1980.