Chemical Physics Letters 499 (2010) 70–74

Contents lists available at ScienceDirect

Chemical Physics Letters

journal homepage: www.elsevier.com/locate/cplett

Cyclodextrin-surfactant binding constant as driven force for uncomplexed cyclodextrin in equilibrium with micellar systems

M. Cepeda [1], R. Daviña, L. García-Río *, M. Parajó

Departamento de Química Física, Facultad de Química, Universidad de Santiago, 15782 Santiago, Spain

ARTICLE INFO

Article history:
Received 7 May 2010
In final form 5 September 2010
Available online 9 September 2010

ABSTRACT

Mixed systems formed by surfactants, sodium alkylsulfonates, and β-cyclodextrin have been studied by using the solvolysis of 4-methoxybenzenesulfonil chloride (MBSC) as a chemical probe. The kinetic analysis allows us to obtain the percentage of uncomplexed cyclodextrin in equilibrium with the micellar media and its variation with the alkyl chain length of the surfactant. Competition between surfactant complexation by the cyclodextrin and self-aggregation to form micelles is the driving force for the percentage of uncomplexed cyclodextrin in equilibrium with the micellar system and its variation with the surfactant chain length.

1. Introduction

Since their discovery, cyclodextrins have been the objective of a large number of studies, specially focused on their ability to form inclusion complexes [1,2]. The formation of the inclusion compounds greatly modifies the physical and chemical properties of the guest molecule, mostly in terms of water solubility. This is the reason why cyclodextrins have attracted much interest in many fields, especially pharmaceutical applications: because inclusion compounds of cyclodextrin with hydrophobic molecules are able to penetrate body tissues, these can be used to release biologically active compounds under specific conditions [3]. Of particular interest is the effect of cyclodextrins on the self-organization processes involving surfactants in which the presence of these macrocycles introduces a new equilibrium, which in turn competes with aggregation [4]. Traditionally, supramolecular complexes, of which CDs are a simple class of host molecules, have been characterized by X-ray crystallography or by determining thermodynamic parameters. These structural measurements provide information on the system when it is equilibrium but do not convey any kinetic understanding of the association and dissociation processes [5].

Our group has developed a kinetic model that accounts for reactivity in mixed surfactant-CD systems [6]. This model has enabled us to highlight certain characteristics of mixed surfactant-CD 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, the concentration of uncomplexed surfactant monomers in equilibrium with the cyclodextrin is sufficient for the micellization process to begin. (ii) The critical micelle concentration has been found to shift to higher values in 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. (iii) Once the micellization process has begun, interactions will not be established between the CD and the micellar system.

Previous studies have shown that the percentage of uncomplexed CD in equilibrium with the micellar system increases with the chain length of the surfactant [7–9]. This behaviour has been explained by considering simultaneous competitive equilibria: (i) surfactant complexation by the cyclodextrin yields a higher uncomplexed cyclodextrin in equilibrium with the micellar system on decreasing the binding constant of the surfactant by β-CD. This can be achieved by decreasing the alkyl chain length of the surfactant. (ii) Surfactant self-association yielding micelles. As higher is the tendency of surfactants to form micelles (smaller the *cmc*) higher is the percentage of uncomplexed cyclodextrin. It should be noted that both factors are present simultaneously. In previous studies [7–9] we have used surfactants where the main factor is its self-association yielding a higher percentage of uncomplexed cyclodextrin on decreasing the *cmc*. In the present study we are searching for surfactants where the surfactant binding by the β-CD is dominant in reporting the uncomplexed cyclodextrin. In this way we need to use surfactants with very large *cmc* (i.e. short alkyl chains). Therefore we studied mixed systems formed by anionic surfactants with different chain lengths and β-CD. As chemical probe we used the hydrolysis of the 4-methoxybenzenesulfonil chloride (MBSC), a molecule whose geometry and polarity is suitable for complex formation with β-CD and whose basic hydrolysis has been previously studied in water and water:organic solvent

* Corresponding author. Fax: +34 981595012.
E-mail address: luis.garcia@usc.es (L. García-Río).
[1] Permanent address: Facultad de Química, Pontificia Universidad Católica de Chile, Casilla 306, 6094411 Santiago, Chile.

0009-2614/$ - see front matter © 2010 Elsevier B.V. All rights reserved.
doi:10.1016/j.cplett.2010.09.017

mixtures [10]. The results obtained confirm that, contrary to the expectations, the percentage of uncomplexed CD decreases with the number of carbons of the chain, meaning that the percentage of uncomplexed CD decreases with the hydrophobic character of the surfactant.

2. Experimental section

Sodium decane sulfonate ($C_{10}SO_3Na$), sodium octane sulfonate (C_8SO_3Na), sodium hexane sulfonate (C_6SO_3Na) and sodium butane sulfonate (C_4SO_3Na) were Aldrich products of the highest available purity and were used without further purification. β-CD was supplied by Cyclolab. Stocks solutions of MBSC were prepared in acetonitrile due to its low solubility in water. The final acetonitrile concentration in the reaction medium was 1% (v/v). Surfactant-CD systems were prepared by mixing appropriate volumes of stock aqueous solutions of CD and surfactant. Kinetics runs were initiated by injecting a stock solution of MBSC into the mixed system in a 1 cm cuvette.

Reaction kinetics were recorded by measuring absorbance due to MBSC at 270 nm in a Cary 100 UV–Vis spectrophotometer with a cell holder thermostated at (25.0 ± 0.1)°C. The MBSC concentration was always approximately 1.2×10^{-4}M. The absorbance-time data of all kinetic experiments were fitted by 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 mixed system was obtained kinetically.

3. Results and discussion

3.1. Solvolysis of MBSC in the presence of anionic micelles

The influence of the concentration of C_4SO_3Na; C_6SO_3Na; C_8SO_3Na and $C_{10}SO_3Na$ on the solvolytic rate constant of MBSC has been studied in a wide interval of concentrations that includes both the regions prior to the *cmc*, where the molecules of surfactant are presented as monomers 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 the pseudo-first-order rate constant, k_{obs}, for the hydrolysis of the MBSC is shown in Figure 1.

As can be seen from Figure 1, 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. These inhibitions are due to the substrate incorporation into the micelles where the rate of solvolytic reaction is smaller than in bulk water. The formalism of the micellar pseudophase [11,12] was applied to obtain a quantitative interpretation of the experimental results. Two well-differentiated environments were considered: water and a micellar pseudophase between which the MBSC is distributed.

By considering that the solvolysis can take place simultaneously in water, k_w, and at the micellar pseudophase, k_m, it is possible to derive the following equation, which relates the observed rate constant with the surfactant concentration. (Eq. (1)).

$$k_{obs} = \frac{k_w + k_m K_m [D_n]}{1 + K_m [D_n]} \quad (1)$$

where K_m is the distribution constant of MBSC between the water and the micellar pseudophase, $K_m = [MBSC]_m/([MBSC]_w[D_n])$; $[D_n]$ is the concentration of micellized surfactant, $[D_n] = [Surfactant]_T - cmc$; and $[Surfactant]_T$ is the total concentration of the surfactant. If we consider that the solvolysis reaction takes place only in the aqueous medium we should simplify Eq. (1) to Eq. (2)

$$k_{obs} = \frac{k_w}{1 + K_m [D_n]} \quad (2)$$

Critical micelle concentration values 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}. Obtained values are shown in Table 1. Fitting the experimental results to Eq. (2) (lines showed in Figure 1 left) by a nonlinear regression method provided the value of the distribution constant of the MBSC between the water and the micellar pseudophase (K_m). These values along with the *cmc* values obtained experimentally are given in Table 1.

The binding constant of MBSC to the micellar system increases with the length of the surfactant hydrocarbon chain so does its hydrophobity too. Likewise, as the length of the surfactant hydrocarbon chain increases the critical micelle concentration decreases.

3.2. Solvolysis of MBSC in presence of cyclodextrins

The influence of β-CD concentration on the rate of solvolysis of MBSC was studied. This effect is shown in Figure 1-right. As can be observed, addition of β-CD to the reaction medium inhibits the

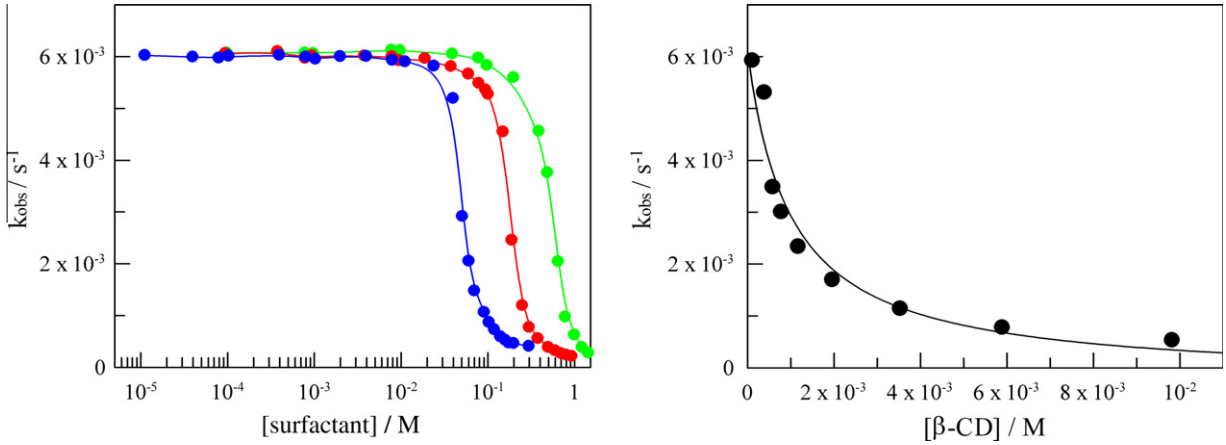


Figure 1. Left: Influence of the alkyl sulfonate concentration on the pseudofirst order rate constant for solvolysis of MBSC at 25.0 °C. (●)C_6SO_3Na; (●)C_8SO_3Na and (●)$C_{10}SO_3Na$. Lines correspond to the fit of Eq. (2) to the experimental data. Right: Influence of β-CD concentration on the pseudo-first-order rate constant, k_{obs}, for the hydrolysis of MBSC at 25.0 °C. Curves represent the fits of the experimental data to Eq. (3).

Table 1
Critical micelle concentration obtained experimentally and results obtained by fitting the experimental data to Eq. (2) and Eq. (4) for the hydrolysis of MBSC in the presence of surfactant and in mixed systems surfactant: β-CD. $k_w = (6.0 \pm 0.1) \times 10^{-3} s^{-1}$; $k_{CD} = (1.43 \pm 0.03) \times 10^{-4} s^{-1}$; $K_{CD} = (1.89 \pm 0.01) \times 10^{3} M^{-1}$; [$\beta$-CD] = 2.6×10^{-3}M.

Surfactant	*cmc*/M	cmc_{CD}/M	K_N/M^{-1}	K_m/M^{-1}	$\%CD_f$
C_4SO_3Na	0.75			1.1 ± 0.1	
C_4SO_3Na + β-CD		0.8	7 ± 1	1.1 ± 0.1	31.8
C_6SO_3Na	0.20			4.1 ± 0.8	
C_6SO_3Na + β-CD		0.3	200 ± 25	4.1 ± 0.8	7.5
C_8SO_3Na	0.13			25 ± 3	
C_8SO_3Na + β-CD		0.12	1500 ± 100	25 ± 3	3.6
$C_{10}SO_3Na$	0.04			55 ± 5	
$C_{10}SO_3Na$ + β-CD		0.04	$(10 \pm 2) \times 10^3$	55 ± 5	3.2

hydrolysis of MBSC. The experimental behaviour can be explained by considering a mechanistic behaviour where MBSC bind the cyclodextrin and the solvolytic reaction takes place simultaneously in water, k_w, and through the MBSC-CD complex [13], k_{CD}. The dependence of k_{obs} on the concentration of β-CD is expressed by (Eq. (3)).

$$k_{obs} = \frac{k_w + k_{CD} K_{CD}[CD]}{1 + K_{CD}[CD]} \tag{3}$$

where K_{CD} is the equilibrium binding constant of the substrate to the cyclodextrin, k_{CD} is the rate constant for the reaction in the cyclodextrin complex, and k_w is the rate constant for the hydrolysis in the aqueous medium. The good fit of the experimental data to this last equation (Figure 1-right) allows us to obtain the binding constant of MBSC to the cavity of the cyclodextrin: $K_{CD} = (1.89 \pm 0.01) \times 10^3 M^{-1}$. and the solvolytic rate constant inside the cavity of the CD, $k_{CD} = (1.43 \pm 0.03) \times 10^{-4}\ s^{-1}$.

3.3. Solvolysis of MBSC in surfactant/cyclodextrin mixed systems

The study of the mixed system was carried out with experiments in which the β-CD concentration was kept constant (2.6×10^{-3}M) and the surfactant concentration was varied from values clearly lower than the *cmc* to values beyond the micellization point. The influence of the mixed system on the hydrolysis of MBSC rate constant is shown in Figure 2.

From a qualitative point of view, the observed behaviour is the same in all cases; the value of k_{obs} increases to a maximum as the concentration of surfactant increases. This increase is due to the competitive formation of inclusion complexes between the cyclodextrin and the surfactant. The formation of these inclusion complexes displaces the MBSC towards the aqueous medium, where the reaction rate is higher than inside the CD cavity and, as a consequence, the observed rate constant of the reaction increases. The competitive formation of the CD-surfactant inclusion complexes occurs until the concentration of surfactant monomers reaches the value at which the micellization process begins. Once micelles have been formed, the typical inhibiting effect that they have on the hydrolysis of MBSC 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 micelles (inhibitory effect on k_{obs}) are compensated.

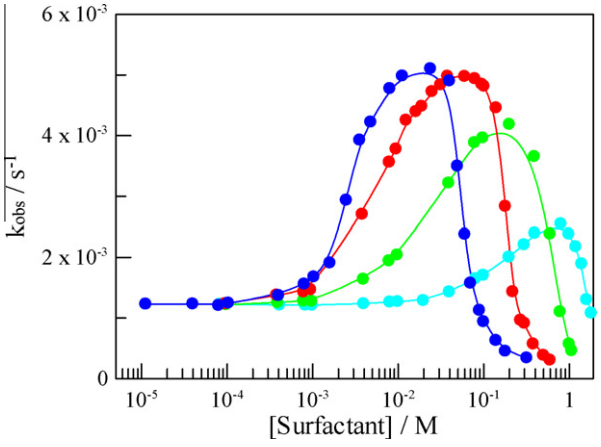


Figure 2. Influence of the surfactant concentration on the observed rate constant for the hydrolysis of MBSC at 25.0 °C in the presence of β-CD. (●) $C_{10}SO_3Na$, (●) C_8SO_3Na, (●) C_6SO_3Na, (●) C_4SO_3Na.

In order to explain the experimental behaviour we considered that the solvolysis proceeds exclusively through the free substrate in aqueous medium (Scheme 1). As we have seen before the rate constants for the reaction in the micelles (k_m) are negligible compared to k_w. We assume also that there is uncomplexed cyclodextrin coexisting with the micellar system and that there are no interactions of any sort between the CD and the micellar system once the micellization process begins.

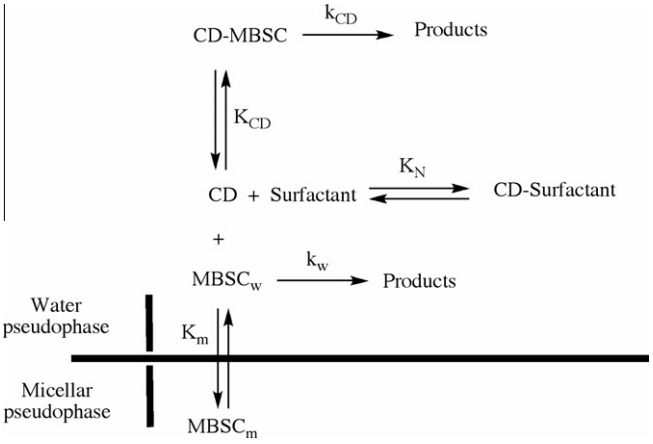
This mechanistic scheme allows us to derive the following expression for the rate constant.

$$k_{obs} = \frac{k_w + k_{CD} K_{CD}[CD]_f}{1 + K_{CD}[CD]_f + K_m[D_n]} \tag{4}$$

To solve Eq. (4) it is necessary to obtain the concentration of uncomplexed cyclodextrin, $[CD]_f$, for each surfactant concentration as well as the values of $[D_n]$. The concentration of free CD can be obtained by means of a simulation procedure, supposing that the complex formed between the surfactant molecules and the CD has a stoichiometric ratio [14,15] of 1:1, as well as for the CD-MBSC complex. The complexation constant for binding of the substrate by CD, K_{CD}, surfactant molecules by the cyclodextrin, K_N, and substrate by the micellar system, K_m, are expressed as.

$$K_{CD} = \frac{[MBSC - CD]}{[MBSC]_w [CD]_f} \quad K_m = \frac{[MBSC]_m}{[MBSC]_w [D_n]}$$
$$K_N = \frac{[Surf - CD]}{[Surf_{mon}][CD]_f} \tag{5}$$

The mass balances for the total concentrations of cyclodextrin, surfactant and substrate: [{CD}]_T = [{CD}]_f + [{MBSC - CD}] + [{Surf - CD}]; [{Surf}]_T = [{Surf_{mon}}] + [{D_n}] + [{Surf - CD}]



Scheme 1.

and [{MBSC}]_T = [{MBSC}]_w + [{MBSC - CD}] + [{MBSC}]_m are combined with binding constants to give a third-order equation for the concentration of uncomplexed cyclodextrin:

$$\alpha[CD]_f^3 + \beta[CD]_f^2 + \gamma[CD]_f - [CD]_T = 0 \quad (6)$$

$$\alpha = K_N K_{CD} \quad (7)$$

$$\beta = K_N + K_{CD} + K_N K_{CD}([Surf]_T - [CD]_T + [MBSC]_T) \quad (8)$$

$$\gamma = 1 + K_N([Surf]_T - [CD]_T) + K_{CD}([MBSC]_T - [CD]_T) \quad (9)$$

These equations were solved for different values of K_N allowing us to obtain the concentration of uncomplexed cyclodextrin for each surfactant concentration. Using the $[CD]_f$ values and with the $[D_n]$ values, we can fit the experimental k_{obs} values to Eq. (4). The value of K_N for which we obtain the best root-mean-square deviation (χ^2) values in fitting Eq. (4) to the experimental results was taken as optimal. The validity of this model was tested by fitting Eq. (4) to the experimental data by means of a two-tier optimization process in which the optimized variable was K_{CD}, and the values obtained in the simple systems were taken as constants. As can be seen in Table 1 the binding constant of MBSC to the cyclodextrin is independent of the presence of surfactants. Moreover the binding constant of MBSC to the micelle, K_m, is strongly dependent on the hydrophobicity of the surfactant but independent on the presence or absence of β-CD. The insensitivity of K_m to the presence of β-CD is in agreement with the absence of interaction between the cyclodextrins and micelles once they have been formed.

The most important aspect of the results obtained in the present study that should be remarked is the k_{obs} value in the maximum of the plot k_{obs} *vs.* surfactant concentration (Figure 2). This value is lower than the value obtained in bulk water and is due to the presence of uncomplexed cyclodextrin at the micellization point. The difference between k_{obs} in bulk water and in the mixed system increases on decreasing the alkyl chain length of the surfactant. In Table 1 we present the percentage of uncomplexed cyclodextrin obtained from a calibration procedure. For any surfactant concentration, it is possible to obtain the concentration of uncomplexed cyclodextrin from a calibration curve. The calibration curve can be obtained by regrouping Eq. (3) and using previously obtained values for $K_{CD} = (1.89 \pm 0.01) \times 10^3\ M^{-1}$; $k_{CD} = (1.43 \pm 0.03) \times 10^{-4}\ s^{-1}$ and $k_w = (6.0 \pm 0.1) \times 10^{-3}\ s^{-1}$.

$$[CD]_f = \frac{k_w - k_{obs}}{K_{CD}(k_{obs} - k_{CD})} \quad (10)$$

Results in Table 1 show that the percentage of uncomplexed cyclodextrin in equilibrium with the micellar system increases on decreasing the hydrophobic character of the surfactant. This behaviour is contrary with that previously reported in our laboratory [7–9] where the percentage of uncomplexed cyclodextrin increases on increasing the alkyl chain length of the surfactant for surfactants with alkyl chain larger than ten carbon atoms. Traditional ideas on mixed CD-surfactant systems consider that the micellization process only begins once the complexation capacity of the cyclodextrin has been saturated. Thus supposition implies the absence of uncomplexed CD in equilibrium with the micellar system. Our results indicate that this vision should be modified. We should consider that the complexation equilibrium of the surfactant by the CD and the autoassociation of the surfactant (micellization) take place simultaneously. The balance between both processes will be the cause of the existence of uncomplexed CD in equilibrium with the micellar system and its variation with the nature of the surfactant.

The total free energy per aggregated molecule of surfactant [16] in the micelles can be evaluated from the experimental *cmc* values, using the following equation:

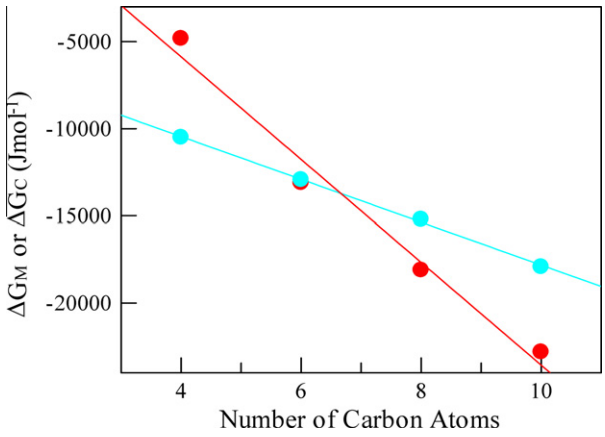


Figure 3. Influence of the surfactant alkyl chain length on the free energy per aggregated molecule of surfactant (ΔG_M, ●) and on the free energy of surfactant complexation by β-CD (ΔG_C, ●) at 25.0 °C.

$$\Delta G_M = RT \ln cmc' \quad (11)$$

where *cmć* is the critical micelle concentration in mole fraction units. Moreover, from the binding constants of the alkyl sulfonate surfactants to the cavity of the cyclodextrins we can evaluate the complexation free energy, ΔG_C. Figure 3 shows the variation of ΔG_M and ΔG_C with the alkyl chain length of the surfactant. As can be observed for alkylsulfonates with very short alkyl chain length, C_4SO_3Na, micellization is favored against of surfactant-CD complexation. Because the percentage of uncomplexed cyclodextrin is a consequence of the balance between micellization and CD-surfactant complexation, on increasing the weight of micellization *vs.* CD-surfactant complexation we expect to increase the percentage of uncomplexed cyclodextrin. If we increase the alkyl chain length of the surfactant, CD-surfactant complexation is energetically more favorable than micellization and as a consequence the percentage on uncomplexed cyclodextrin decreases on increasing the alkyl chain length on going from C_4SO_3Na to $C_{10}SO_3Na$.

4. Conclusions

Mixed systems formed by surfactants and cyclodextrins are characterized by the presence of a non-negligible amount of uncomplexed cyclodextrin in equilibrium with the micellar system once the micelles have been formed. In this way traditional ideas that micelles are formed only once the complexation ability of cyclodextrins have been saturated should be removed. The existence of an appreciable percentage of uncomplexed cyclodextrin is a consequence of the competitive equilibria of CD-surfactant complexation and surfactant self-assembly to form micelles. The balance between both equilibria determines the influence of the hydrophobic character of the surfactant on the percentage of uncomplexed cyclodextrin. In this study we have shown that on decreasing the alkyl chain length of the surfactant micellization is more important than complexation by the cyclodextrin and the precentage of uncomplexed cyclodextrin increases.

Acknowledgments

This work was supported by the Ministerio de Ciencia y Tecnología (Project CTQ2008-04420/BQU) and Xunta de Galicia (PGIDIT07-PXIB209041PR).

References

[1] M.L. Bender, M. Komiyama, Cyclodextrin Chemistry, SpringerVerlag, New York, 1978.
[2] W. Saenger, Angew. Chem. Int. Ed. Engl. 19 (1980) 344–362.
[3] G. Becket, L.J. Schep, M.Y. Tan, Int. J. Pharm. 179 (1) (1999) 65.
[4] G.M. Nicolle, A.E. Merbach, Chem. Commun. 7 (2004) 845.
[5] L.T. Okano, T.C. Barros, D.T.H. Chou, A.J. Bennet, C. Bohne, J. Phys. Chem. B 105 (2001) 2122.
[6] L. García-Río, J.R. Leis, J.C. Mejuto, A. Navarro-Vazquez, A. Pérez-Juste, P. Rodríguez-Dafonte, Langmuir 20 (2004) 606.
[7] B. Dorrego, L. Garcia-Rio, P. Herves, J.R. Leis, J.C. Mejuto, J. Perez-Juste, Angew. Chem. Int. Ed. Engl. 39 (2000) 2945.
[8] B. Dorrego, L. Garcia-Rio, P. Herves, J.R. Leis, J.C. Mejuto, J. Perez-Juste, J. Phys. Chem. B 105 (2001) 4912.
[9] C. Cabaleiro-Lago, L. Garcia-Rio, P. Herves, J.C. Mejuto, J. Perez-Juste, J. Phys. Chem. B 110 (2006) 15831.
[10] R.M. Forbes, H.J. Maskill, J. Chem. Soc., Chem. Commun. 13 (1991) 854.
[11] C.A. Bunton, G. Savelli, Adv. Phys. Org. Chem. 22 (1986) 213.
[12] C.A. Bunton, J. Phys. Org. Chem. 18 (2005) 115.
[13] L. Garcia-Rio, M. Mendez, M.R. Paleo, F.J. Sardina, J. Phys. Chem. B 111 (2007) 12756.
[14] C. Cabaleiro-Lago, M. Nilsson, O. Söderman, Langmuir 21 (2005) 11637.
[15] X. Shen, M. Belletete, G. Durocher, Langmuir 13 (1997) 5830.
[16] S. Pavvada, D. Blankschtein, J. Phys. Chem. 96 (1992) 5567.