Arabian Journal of Chemistry (2020) 13, 2318–2330

King Saud University

Arabian Journal of Chemistry

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ORIGINAL ARTICLE

Influence of the surfactant degree of oligomerization on the formation of cyclodextrin: surfactant inclusion complexes

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Received 8 January 2018; accepted 19 April 2018
Available online 5 May 2018

KEYWORDS

Surfactants;
Cyclodextrins;
Inclusion complexes;
Oligomerization degree;
Conductivity;
NMR

Abstract Supramolecular complexation is an attractive strategy to modulate the performance of surfactants, e.g., by host-guest interactions. Here, we investigate the interaction of single-chained, di-, tri-, and tetrameric cationic surfactants with cyclodextrins by conductivity and ^{1}H NMR measurements, exploring the effect of increasing the number of the surfactant hydrophobic tails on the stability of cyclodextrin:surfactant inclusion complexes. The stoichiometry and the binding equilibrium constants of the different inclusion complexes were elucidated. Under the working conditions, the number of hydrophobic chains was found not to affect stoichiometry and 1:1 inclusion complexes were formed for all the surfactants investigated. The stability of the host-guest complexes decreases from single-chained to dimeric ("gemini") surfactants, the binding following a non-cooperative mechanism. This result may be rationalized by taking into account steric constraints and electrostatic effects as well as the need to overcome the hydrophobic interactions between the chains of the same surfactant molecule. However, a further increase in the number of hydrophobic tails, from two to three to four, results in an increase in the equilibrium binding constant, K_1. In

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Peer review under responsibility of King Saud University.

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https://doi.org/10.1016/j.arabjc.2018.04.015

this case, an increment in the number of chains capable of interaction with the cyclodextrin molecules seems to be the main factor responsible for the increase in K_1. ROESY spectra show the coexistence of different types of 1:1 host-guest complexes for tri- and tetrameric surfactants.

1. Introduction

Cyclodextrins, CDs, are cyclic oligosaccharides made up of six to eight (α-, β-, and γ-CD) α(1-4) ether linkages of glucopyranoside units (Szejtli, 1998; Crini, 2014). CDs are shaped like a truncated cone with internal cavities which are relatively hydrophobic. As a result, CDs have the ability to form inclusion complexes with a variety of organic and inorganic molecules in aqueous solution. The molecular encapsulation may positively affect properties of the entrapped molecules such as solubility enhancement, stabilization of labile guests, etc. (Yuan et al., 2013; Singh et al., 2011; Polyakov et al., 2005; Chun et al., 2012) thus providing a number of possible benefits.

Among guest molecules surfactants play an important role in the understanding of the driving forces involved in CD inclusion complexes since they provide the possibility of changing the balance between several intermolecular forces by varying both hydrophobic and hydrophilic regions of the surfactant molecules. Besides, the wide range of applications of both CDs and surfactants can be increased by taking advantage of the CD-surfactant complex formation (Bilensoy, 2007; Bilensoy, 2011; Dodziuk, 2006; Huang et al., 2017; Adeoye and Cabral-Marques, 2017). Oligomeric surfactants are made up of two or more amphiphilic moieties connected at the level of the head group (Menger and Keiper, 2000; Laschewsky, 1995; Wattebled et al., 2007). Compared with conventional single-chained surfactants, oligomeric surfactants show lower critical micelle concentrations, better wetting properties, higher surface activity, unusual viscosity changes, a higher solubility for organic compounds, etc. They are useful for several applications such as drug formulations, waste water treatment, gene delivery vectors, and analytical methods (Shukla and Tyagi, 2006; Kirby et al., 2003; Silva et al., 2014; Wuang and Hu, 2008; Song et al., 2012). However, as Valente and Söderman (2014) pointed out in their recent review on CD:surfactant host:guest complexes, despite the potential applications of CD:oligomeric surfactant complexes, studies on their interactions are scarce in the case of dimeric surfactants and really limited for tri- or tetrameric surfactants. The main goal of this study was to investigate the effect of increasing the surfactant degree of oligomerization (the number of the surfactant hydrophobic tails) on the stability of CD:surfactant inclusion complexes. Additionally, the influence of the spacer group separating the hydrophobic tails as well as the effect of the size of the CD cavity on the inclusion complex formation were also examined.

The surfactants studied in this work are: (i) single-chained surfactants: *N*-benzyl-*N,N*-dimethyl-*N*-(1-dodecyl)ammonium bromide and chloride (P1) and *N*-cyclohexylmethyl- *N,N*-dimethyl-*N*-(1-dodecyl)ammonium chloride and bromide (C1); (ii) dimeric surfactants: *N,N′*-(1,3-phenylenebis(methylene))bis(*N,N*-dimethyl-*N*-(1-dodecyl)ammonium dibromide and dichloride (M-P-2), *N,N′*-(cyclohexane-1,3-diylbis(methylene))bis(*N,N*-dimethyl-*N*-(1-dodecyl)ammonium dibromide (M-C-2); (iii) linear trimeric surfactants: bis(3-(N′,N′-dimethyl-N′-dodecylammoniomethylene)phenylenemethylene)-N-dodecyl-N-methylammonium trichloride (M-P-3) and bis(4-(N′,N′-dimethyl-N′-dodecylammoniomethylene)phenylenemethylene)-N-dodecyl-N-methylammonium trichloride (P-P-3); and (iv) linear tetrameric surfactants: 1,3-Bis(N-(3-(N′-dodecyl-N′,N′-dimethylammoniomethyl)phenylenemethylene)-N-dodecyl-N-methylammoniomethyl)benzene tetrachloride (M-P-4) (see Scheme 1). We also prepared the star-like trimeric surfactant *N,N′,N″*-(1,3,5-phenylenebis(methylene))tris(*N,N*-dimethyl-*N*-(1-dodecyl)ammonium tribromide, TP3. However, the low solubility of TP3 in water precluded several of the experiments necessary to obtain conclusive information about its inclusion complexes. In order to help the discussion of the results, the binding of the single-chained references dodecyltrimethylammonium bromide and chloride, DTAB and DTAC, and of the frequently studied dimeric surfactant ethanediyl-α-ω-bis(dodecyldimethylammonium)bromide, 12-2-12,2Br$^-$, to cyclodextrins was also investigated.

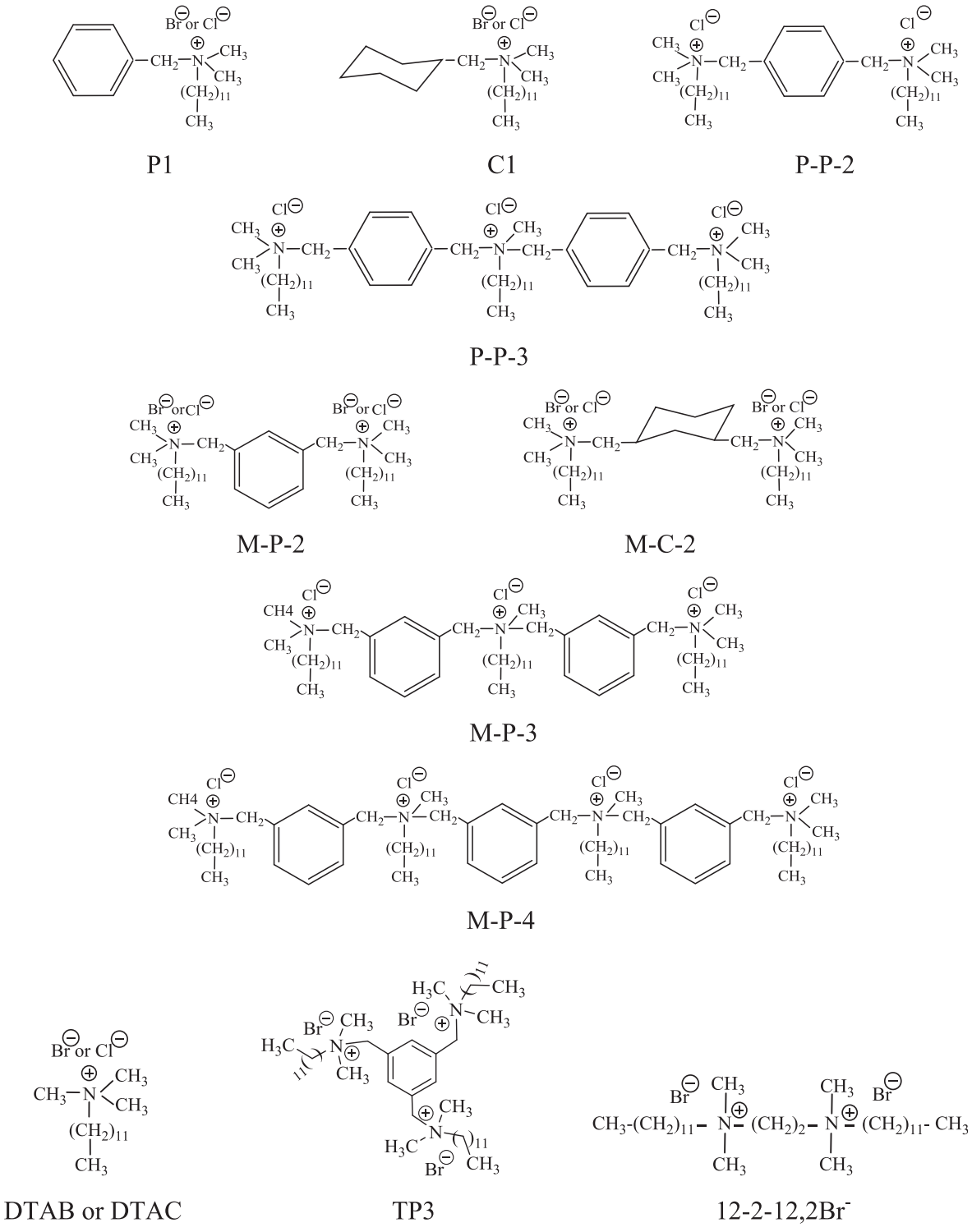
To the authors' knowledge, the effect of an increase in the surfactant degree of oligomerization on the stability of cyclodextrin:surfactant host-guest complexes has not been studied yet. The results of our study will thus foster the understanding of cyclodextrin:surfactant interactions. This is important for a wide range of applications of both CDs and surfactants, which can be broadened by taking advantage of the CD-surfactant complex formation.

2. Materials and methods

2.1. Materials

Dodecyltrimethylammonium bromide and chloride, DTAB and DTAC, were from Sigma-Aldrich. α-, β-, and γ-cyclodextrins of the highest purity available were purchased from Aldrich (>99% purity, according to the manufacturer) and were kept under vacuum. The syntheses of the surfactants C1, P1, M-P-2, and M-C-2, with bromide counterions, were done as described by Martín et al. (2011) and those of the surfactants P1, M-P-2, M-P-3, P-P-3, and M-P-4, as well as C1 and M-C-2, with chloride counterions, were carried out following the methods described by Laschewsky et al. (2005) and Martín (2014), respectively. Dimer 12-2-12,2Br$^-$ was prepared as reported by Menger et al. (2002). D_2O was supplied by Sigma. Water was MilliQ (resistivity > 18 MΩ cm).

The synthesis of the trimeric surfactant TP3 was carried out by displacement with *N,N*-dimethyl-*N*-(1-dodecyl)amine of 1,3,5-tris(bromoethyl)benzene. The synthetic route is similar to that of M-P-2 (Martín et al., 2011). The new compound was characterized by NMR, mass spectrometry and micronalysis.



Scheme 1 Structure of the surfactants used in this work.

2.2. Conductivity measurements

Conductivity was measured with a Crison GLP31 conductimeter calibrated with KCl solutions of the appropriate concentration range. The conductimeter was connected to an external water circulator (Heto) and the whole system was placed in a room in which the temperature was kept constant within 303 ± 0.5 K. Temperature was maintained at 303 ± 0.01 K. Solutions were used within 5 h after preparation. In a typical experiment a surfactant solution was placed in the thermostated conductivity cell; then, aliquots of the CD solution, in the presence of the same surfactant concentration, were added in a stepwise manner using a programmable dispenser Crison Burette 1S (±0.1 μL). The specific conductivity of

the solution was measured 10 min after each addition, after checking that the specific conductivity remained constant with time. Each experiment was repeated at least twice.

The formation of the inclusion complexes of M-C-2 and M-P-2, with chloride and bromide, with γ-CD was not investigated due to the small conductivity variation observed, which would have resulted in too large errors in the estimated equilibrium binding constants. In the case of the tri- and tetrameric surfactants the conductivity changes were even smaller, given that the surfactant concentrations used (below the critical micelle concentration, cmc) were rather small. Since for the single-chained surfactants the differences between the equilibrium constant values for α- and β-CD were not large, only the binding of the di-, tri-, and tetrameric surfactant to β-CD was investigated.

2.3. NMR measurements

The NMR spectra were performed in CITIUS (Research General Services for the University of Seville). NMR samples were prepared by dissolving the corresponding amount of the surfactant and/or the CD in D_2O followed by a brief sonication. The solutions were kept thermostated at 303 K for at least 5 h before carrying out the NMR experiments. NMR experiments were recorded on a Bruker Avance III 500 MHz spectrometer (500.2 MHz for ^1H) equipped with a 5 mm TCI cryoprobe operating at 303 K. All ^1H chemical shifts are referenced to the residual HDO signal set to 4.71 ppm (Gottlieb et al., 1997).

Two-dimensional, 2D, rotating frame nuclear Overhauser effect experiments were performed using the Bruker standard pulse sequence (EASY-ROESY version, Thiele et al., 2009). 2048×256 data points were acquired with 16 transients per increment and a relaxation delay of 1.5 s. A mixing time of 250 ms was used. Data processing was performed on a 1024×1024 data matrix. Cosine-squared window functions were used along F1 and F2.

3. Results and discussion

In order to avoid the effect of micellization surfactant concentrations were kept below the cmc. Cmc values in aqueous solution for the different surfactants investigated can be found in the literature (Martín et al., 2010, 2011; Laschewsky et al., 2005; Martín, 2014; Ostos, 2014). Conductivity and pyrene fluorescence emission measurements showed that TP3 does not self-aggregate in water.

A preliminary investigation of the formation of the inclusion complexes between the surfactants and the cyclodextrins was carried out using conductivity measurements. Figure S1 (Supplementary Material) shows the dependence of the specific conductivity on surfactant concentration for P1,Br^- aqueous solutions in the absence and in the presence of a fixed concentration of β-CD. The cmc was taken as the breakpoint of the conductivity vs. surfactant concentration plots and it was estimated by using Carpena's method (Carpena et al., 2002). An increase in the apparent cmc is observed in the presence of β-CD, which indicates the formation of the inclusion complex between the macrocycle and the surfactant. As the complexed surfactant monomers are not available to form the micelles, self-aggregation occurs at higher surfactant concentrations (Liang et al., 2011). The same behavior was observed for all the surfactants investigated.

The ^1H NMR spectra of α-, β-, and γ-CD in D_2O are well known. Some of the ^1H NMR spectra of the surfactants used in this work, which were not previously published, are shown in Figure S2 (Supplementary Material). The presence of bromide or chloride as counterion showed no differences in the ^1H NMR spectra of the surfactants. As expected, for P-P-3,3Cl^- and M-P-3,3Cl^- these spectra revealed the presence of two set of signals corresponding to two different kinds of hydrophobic tails. Thus, for these surfactants, the methylene groups of the hydrophobic tail in alpha and beta position to the ammonium nitrogen gave, each of them, two different signals in the ^1H NMR spectrum, corresponding to the central and the flanking tails. These differences in the spectra were crucial for the ROESY study (see below), as they allowed to clarify the interaction of the cyclodextrins with both types of tails.

Two-dimensional rotating frame nuclear Overhauser effect spectroscopy, ROESY, can provide information about the CD:surfactant inclusion complexes. Fig. 1 shows the ROESY spectra of D_2O solutions containing M-P-3,3Cl^- or M-P-4,4Cl^- and β-CD (1:1) at 303 K. The incorporation of the hydrophobic tail of the guest molecule into the cavity of the host can be inferred from the observation of NOE cross-peaks between the protons of the methylene ($(CH_2)_n$) groups of the alkyl chain of the surfactant and the internal protons (H-3 and H-5) of the cyclodextrin. Furthermore, the observed pattern of intermolecular NOE cross-peaks, which are stronger for H-3 than for H-5 of the CD, suggest that the hydrophobic tails of the surfactant enter into the CD cavity from the wide rim. This conclusion is further supported by the observation of very low intensity NOE contacts between the methylene protons in beta position to the ammonium nitrogen (cf. Fig. 1, position 2) and H-3 of the CD, which are not observed for H-5. As showed in Fig. 1a, these NOE contacts are observed for both, the central and the flanking tails, indicating that the CD ring interacts with both types of tails. The later intermolecular NOEs were not observed for M-P-4 (see Fig. 1b), most probably due to the lower concentration used for this surfactant.

Similar conclusions can be drawn from the analysis of these ROESY spectra taken for the other CD:surfactant complexes investigated, as exemplified in Figure S3 in the Supplementary Material.

The binding stoichiometry of the CD-surfactant host-guest complexes was estimated by using the Job method (Djedaini et al., 1990). This method is based on the analysis of a measurable physical parameter, P, proportional to the complex formation, for a series of CD:surfactant mixtures, in which the total concentration of the two species is kept constant, while the molar fractions of each component are varied from 0 to 1. It is assumed that the quantity ΔPś[CD] (or ΔPś[surfactant]), where ΔP = P(mixture) – P(free), is proportional to the CD:surfactant complex concentration, and its maximum as a function of X_{CD} (or $X_{Surfactant}$) corresponds to the stoichiometry of the inclusion complex. As the surfactants investigated are ionic, conductivity measurements were carried out for obtaining the desired information. Fig. 2 shows exemplarily the Job plots obtained for selected surfactants, where the dependence of $(\Delta\kappa_{obs}) \times [CD_T]$ on the CD molar

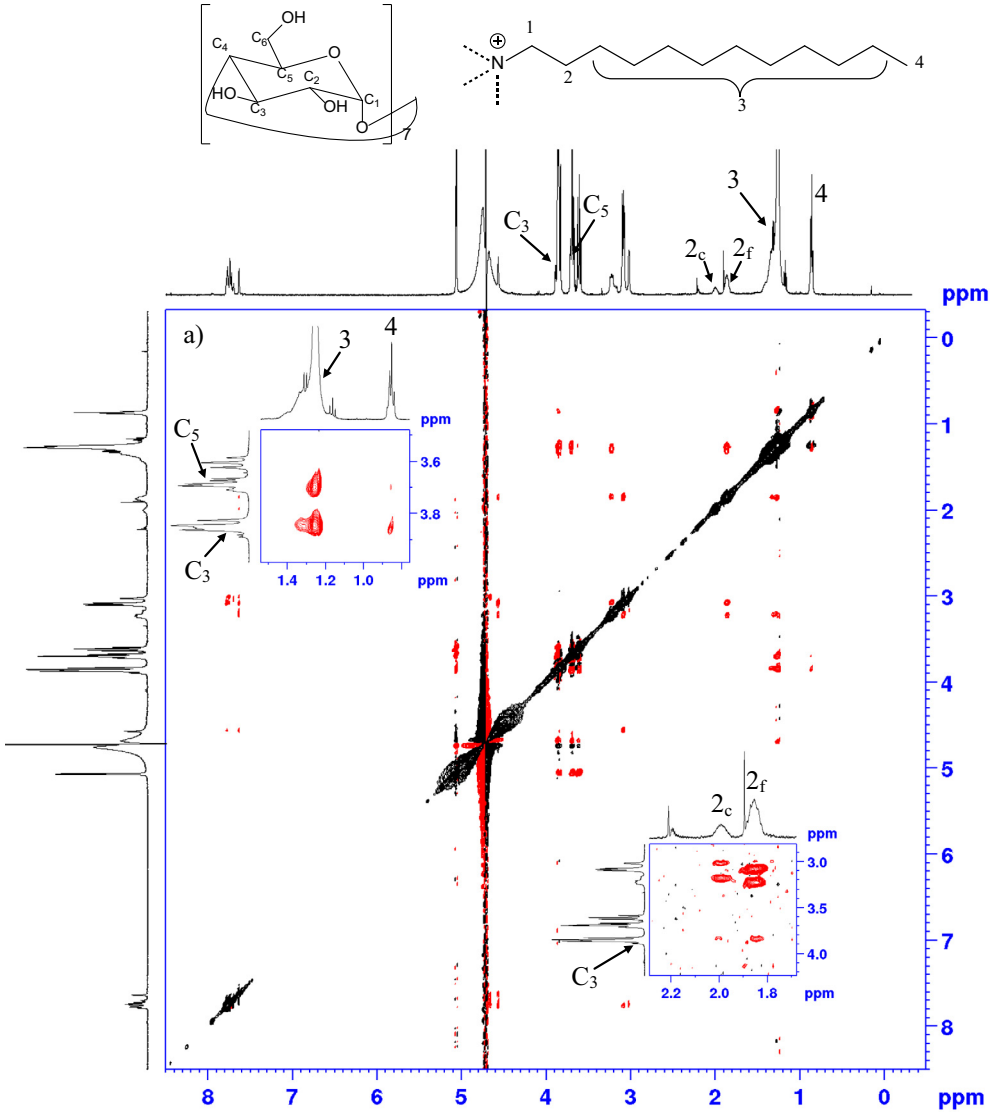


Fig. 1 2D-ROESY spectra of D_2O solutions containing: (a) [M-P-3,3Cl$^-$] = 5.00×10^{-4} M and [β-CD] = 5.00×10^{-4} M and (b) [M-P-4,4Cl$^-$] = 5.50×10^{-5} M and [β-CD] = 5.50×10^{-5} M at 303 K. The subscripts c and f refers to central and flanking tails, respectively. (Note: to facilitate the interpretation of the NMR spectra, only a schematic representation of a hydrophobic tail of the surfactant has been drawn in the upper part of the figure).

fraction is shown, κ_{obs} being the experimental specific conductivity. It was found that 1:1 complexes, CDS, are formed under the working conditions for all the surfactants investigated, independently of the number of hydrophobic chains. The stoichiometry was also independent of the counterions' nature. In order to check the method, we studied also the stoichiometry of the inclusion complexes formed between the-cationic surfactants DTAB, DTAC, and 12-2-12,2Br$^-$ and β-CD at 298 K, in order to compare our results with those obtained by other methods. Figure S4 shows that DTAB (as well as DTAC) forms a 1:1 complex, whereas the stoichiometry of CD:dimeric surfactant was 1.6:1. Both results are in agreement with literature data (Valente and Söderman, 2014; Lu et al., 1997; Nilsson et al., 2006). The estimated stoichiometry of both inclusion complexes at 303 K was similar to that reported at 298 K.

The stability of the inclusion complexes can be described in terms of the equilibrium binding constants, K. For a 1:1 complex one can write:

$$CD_f + S_f \leftrightarrows CDS \quad K_1 = \frac{[CDS]}{[CD_f][S_f]} \tag{1}$$

The subscript f stands for the free, non-associated, species in solution. The mass conservation law equations for the above equilibrium can be written for the total surfactant and cyclodextrin concentrations, indicated by subscript T, as:

$$[CD_T] = [CD_f] + [CDS] \tag{2}$$

$$[S_T] = [S_f] + [CDS] \tag{3}$$

In this case, the observed specific conductivity could be expressed by Eq. (4):

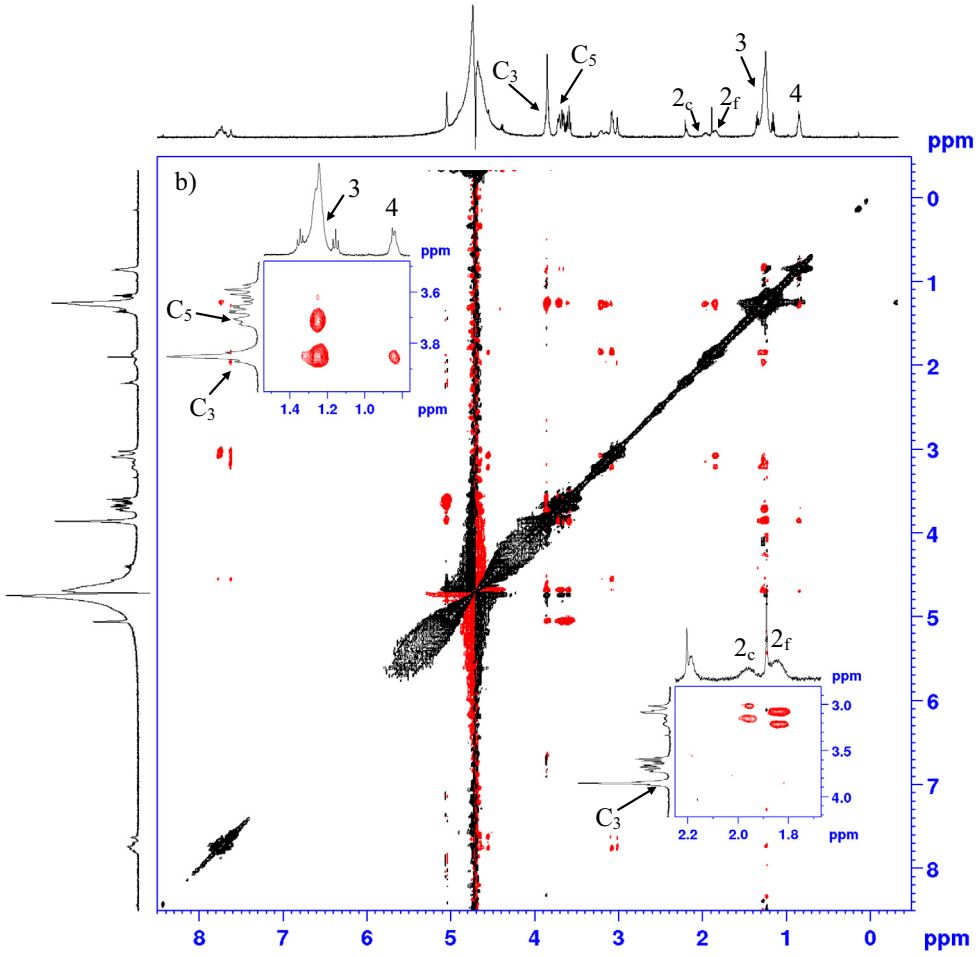


Fig. 1 (*continued*)

$$\kappa_{obs} = \kappa_S + \kappa_{Br^-\ or\ Cl^-} + \kappa_{CDS} \tag{4}$$

This equation can also be written in terms of the molar ionic conductivities, λ_i, in the form:

$$\kappa_{obs} = \lambda_S \times [S_f] + \lambda_{Br^-\ or\ Cl^-} \times [Br^-\ \text{or}\ Cl^-] + \lambda_{CDS} \times [CDS] \tag{5}$$

which takes into account that bromide or chloride ions are the surfactant counterions. The molar conductance of each species can be defined in terms of the specific conductivity as follows:

$$\Lambda_i(\Omega^{-1}\ m^2\ mol^{-1}) = \frac{\kappa_i}{1000\ [C_i]} \tag{6}$$

Taking Eqs. (1)–(6) into account it is possible to write:

$$\Delta\Lambda_{obs} = \frac{\Delta\lambda}{2K_1[S_T]}\{K_1([S_T]+[CD_T]) + 1 - ((K_1\ ([S_T] + [CD_T]) + 1)^2 - 4K_1^2\ ([S_T]+[CD_T]))^{1/2}\} \tag{7}$$

where $\Delta\Lambda_{obs}$ is the observed decrease in the molar conductance of the surfactant aqueous solutions due to the addition of CD, $\Delta\lambda$ is the difference in the ionic conductivities of the unassociated, λ_S, and associated, λ_{CDS}, surfactant ions, and $[S_T]$ and $[CD_T]$ are the total surfactant and cyclodextrin concentrations in the solutions. Fig. 3 shows some examples of the dependence of $\Delta\Lambda_{obs}$ on the total cyclodextrin concentration. Solid lines in this figure show the result of the fittings using Eq. (7). Experiments with different surfactant concentrations were carried out, and the results showed that $[S_T]$ does not affect the estimated K_1 values. For each surfactant concentration, at least three sets of experiments were carried out, for all the CD:surfactant systems. In order to increase the accuracy of the calculated equilibrium constants, global fits were done using the three sets of experimental data. The association equilibrium constants are listed in Table 1.

Figure S5 (Supplementary Material) shows the data for the system β-CD:12-2-12,2Br$^-$. One can clearly see that Eq. (7) cannot fit the experimental data, as was expected since both 1:1 and 2:1CD:surfactant complexes are formed (Valente and Söderman, 2014). For this system the observed specific conductivity can be expressed as:

$$\kappa_{obs} = \kappa_S + \kappa_{CDS} + \kappa_{CD2S} + \kappa_{Br-} \tag{8}$$

In this case, besides the formation of the CDS complex, the following equilibrium has to be considered:

$$CDS + CD_f \leftrightarrows CD_2S \quad K_2 = \frac{[CD_2S]}{[CDS][S_f]} \tag{9}$$

Following the steps described by Valente and Söderman (2014), one can write:

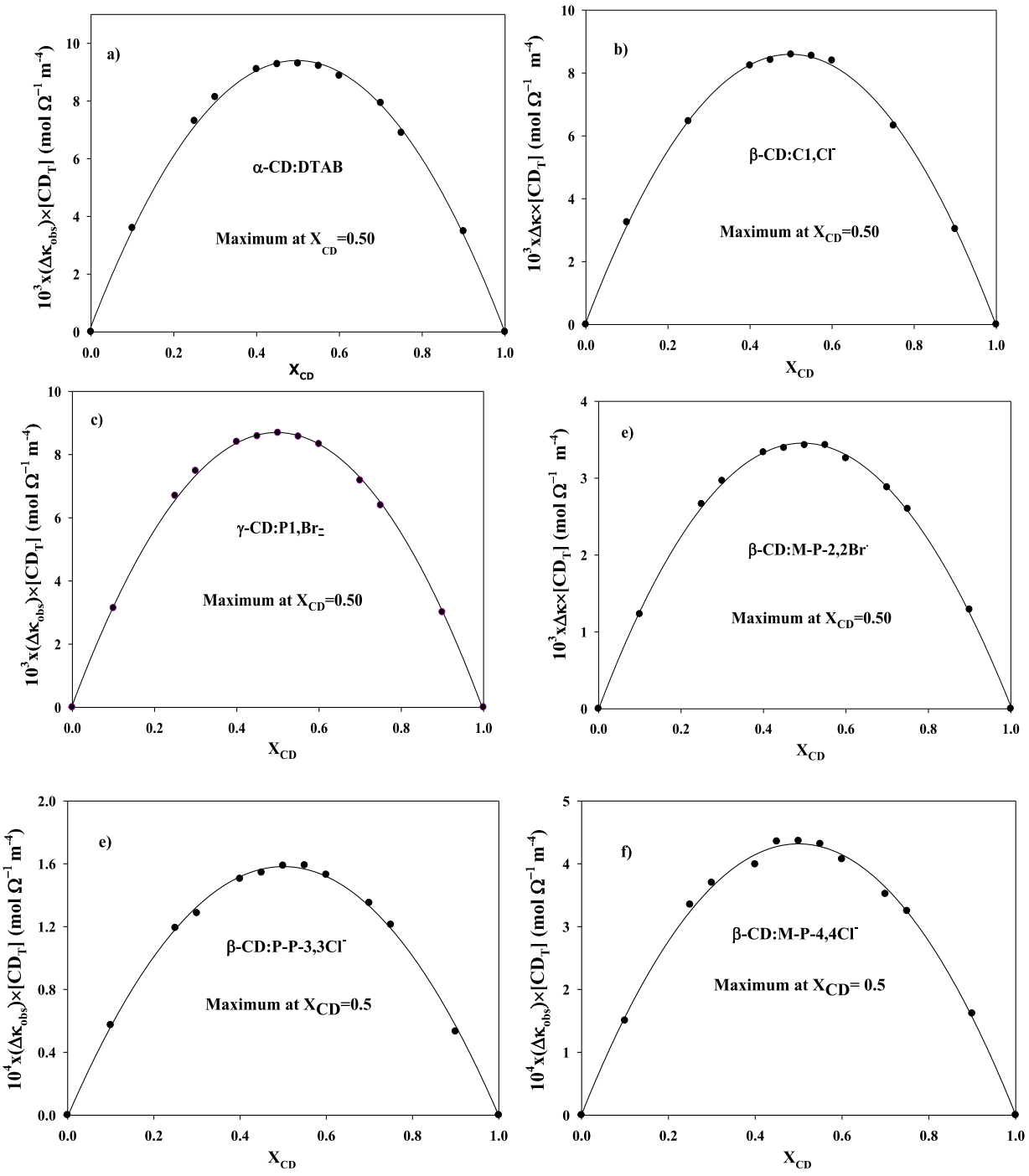


Fig. 2 Job's plots at 303 K. (a) α-CD:DTAB; (b) β-CD:C1,Cl^-; (c) γ-CD:P1,Br^-; (d) β-CD:M-P-2,2Br^-; (e) β-CD:P-P-3,3Cl^-; (f) β-CD:M-P-4,4Cl^-.

$$\Delta\Lambda_{obs} = \frac{\lambda_S + \lambda_{SCD}K_1[CD_f] + \lambda_{SCD2}K_1K_2[CD_f]^2}{\left(1 + K_1[CD_f] + K_1K_2[CD_f]^2\right)} \quad (10)$$

and:

$$K_1K_2[CD_f]^3 + (K_1 - K_1K_2[CD_T] + 2K_1K_2[S_T])[CD_f]^2 + (1 + K_1[S_T] - K_1[CD_T])[CD_f] - [CD_T] = 0 \quad (11)$$

The free cyclodextrin concentration was obtained from solving Eq. (11) using standard procedures. The binding equilibrium constants were obtained from a least-squares fit of Eqs. (10) and (11) to the experimental molar conductivities by using in-house written software based on the Matlab package. As was mentioned above, global fits using the experimental data from the different surfactant concentrations studied were done. The equilibrium binding constants obtained for

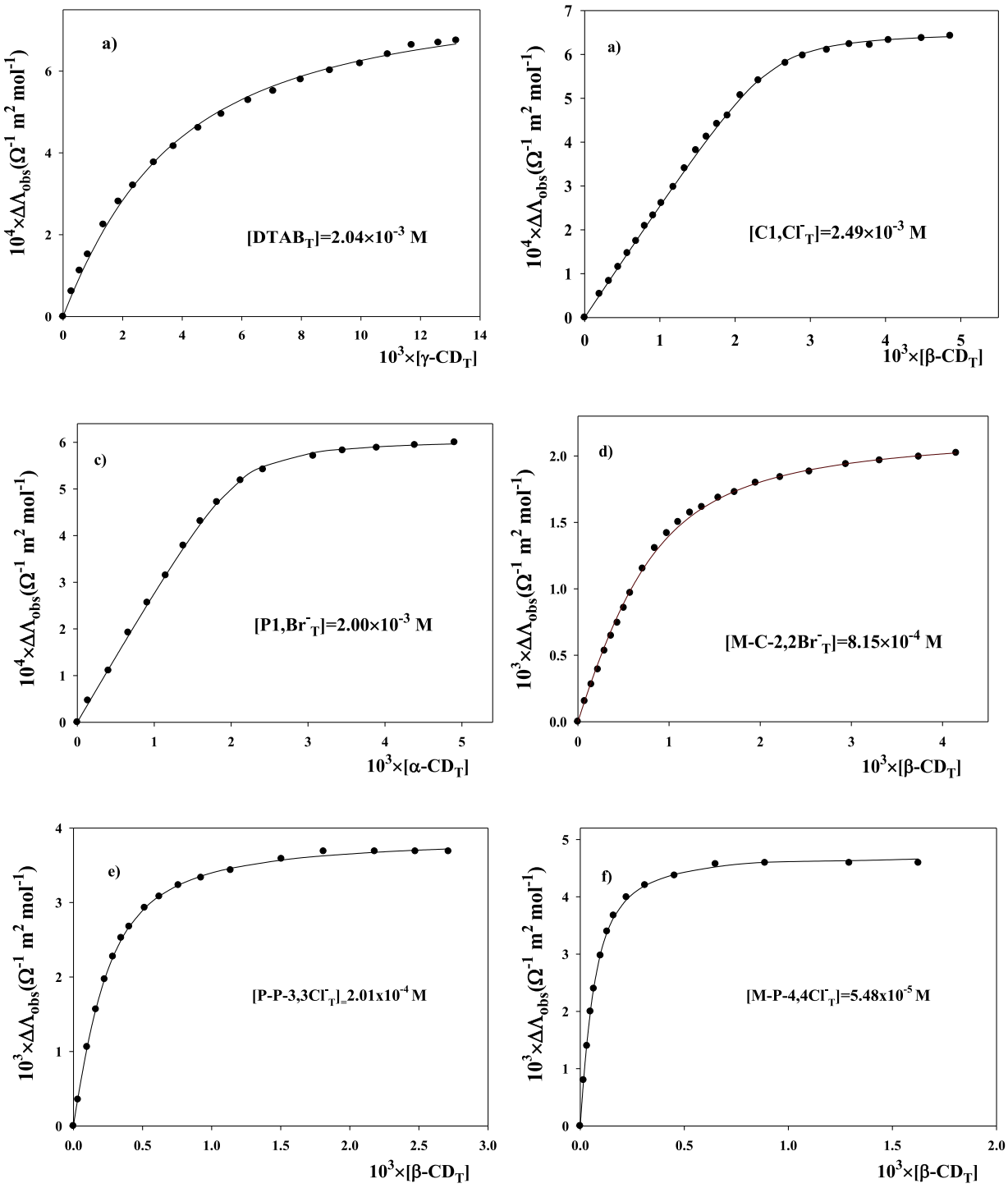


Fig. 3 Dependence of $\Delta\Lambda_{obs}$ on the total cyclodextrin concentration for the surfactants investigated at 303 K. Solid lines show the fitting of the experimental data by using Eq. (7).

the system β-CD:12-2-12,2Br$^-$ were $K_1 = (2.5 \pm 0.5) \times 10^3$ M^{-1} and $K_2 = (1.3 \pm 0.4) \times 10^3$ M^{-1}, in good agreement with previous results within experimental errors (Valente and Söderman, 2014; Nilsson et al., 2006).

For the trimeric surfactant TP3 it was observed that its solubility in water increases upon adding β-CD to the aqueous solution, which could indicate that CD:surfactant inclusion complexes are formed. Solubility problems precluded to carry out conductivity measurements at constant [CD] + [TP3], and varying the molar fractions of both CD and TP3 from 0 to 1, or at constant [TP3] and increasing [CD]. As a consequence, neither the stoichiometry nor the equilibrium binding constant could be calculated.

The formation equilibrium constants of the inclusion complexes can also be estimated from ^{1}H NMR measurements. In order to do so, the surfactant concentration was kept constant

Table 1 Values of equilibrium binding constants, K_1, for the different cyclodextrin:surfactant systems investigated. T = 303 K.

CD:surfactant	K_1 (M^{-1}) Conductivity measurements	K_1 (M^{-1}) ^{1}H NMR measurements
α-CD:DTAB	$(2.5 \pm 0.8) \times 10^4$	
β-CD:DTAB	$(1.5 \pm 0.3) \times 10^4$	$(1.7 \pm 0.4) \times 10^4$
β-CD:DTAC	$(1.2 \pm 0.4) \times 10^4$	
γ-CD:DTAB	$(3.9 \pm 0.2) \times 10^2$	
α-CD:C1,Br^-	$(2.3 \pm 0.4) \times 10^4$	
β-CD:C1,Br^-	$(1.7 \pm 0.3) \times 10^4$	$(1.6 \pm 0.3) \times 10^4$
β-CD:C1,Cl^-	$(1.9 \pm 0.3) \times 10^4$	
γ-CD:C1,Br^-	$(3.6 \pm 0.5) \times 10^2$	
α-CD:P1,Br^-	$(2.3 \pm 0.2) \times 10^4$	
β-CD:P1,Br^-	$(1.5 \pm 0.3) \times 10^4$	$(1.5 \pm 0.3) \times 10^4$
β-CD:P1,Cl^-	$(1.2 \pm 0.4) \times 10^4$	
γ-CD:P1,Br^-	$(4.1 \pm 0.4) \times 10^2$	
β-CD:M-C-2,2Br^-	$(3.1 \pm 0.3) \times 10^3$	$(3.3 \pm 0.4) \times 10^3$
β-CD:M-C-2,2Cl^-	$(3.5 \pm 0.5) \times 10^3$	
β-CD:M-P-2,2Br-	$(3.6 \pm 0.5) \times 10^3$	$(3.3 \pm 0.5) \times 10^3$
β-CD:M-P-2,2Cl^-	$(3.4 \pm 0.4) \times 10^3$	
β-CD:P-P-2,2Cl^-	$(2.7 \pm 0.4) \times 10^3$	
β-CD:M-P-3,3Cl^-	$(8.9 \pm 0.4) \times 10^3$	
β-CD:P-P-3,3Cl^-	$(8.5 \pm 0.4) \times 10^3$	
β-CD:M-P-4,4Cl^-	$(2.5 \pm 0.2) \times 10^4$	

and below <cmc, while [CD] was varied to obtain different molar ratios [CD]/[Surfactant]. Only the inclusion complexes formed by selected single-chained and dimeric surfactants with β-CD were investigated using NMR measurements. The low surfactant concentrations used for tri- and tetrameric surfactants resulted in too large experimental errors to derive meaningful data. Representative results of the ^{1}H NMR spectra for the CD:surfactant mixtures are shown in Fig. 4 (see also S6-S8, Supplementary Material). Assuming that the condition of fast exchange on the NMR time scale applies, the measured frequency is a weighted average of the frequencies in each site, and the chemical shift can be used to measure the extent in which the equilibrium is displaced (Connors, 1987). For a 1:1 inclusion complex, the observed chemical shift can be expressed as (Valente and Söderman, 2014):

$$\delta_{obs} = X_{Sf}\delta_{Sf} + X_{CDS}\delta_{CDS} = (1 - X_{CDS})\delta_{Sf} + X_{CDS}\delta_{CDS} \quad (12)$$

where XS = [Sf]/[ST] and XCDS = [CDS]/[ST]. In this case:

$$\delta_{obs} = \delta_{Sf} + X_{CDS}(\delta_{CDS} - \delta_{Sf}) \quad (13)$$

$$\delta_{obs} - \delta_{Sf} = X_{CDS}(\delta_{CDS} - \delta_{Sf}) \quad (14)$$

$$\Delta\delta_{obs} = X_{CDS}\Delta\delta_o \quad (15)$$

The concentration of the complex is given by the mass action law and the formation equilibrium constant K_1 of the 1:1 inclusion complex can be written:

$$K_1 = \frac{[CDS]}{[S_f][CD_f]} = \frac{[CDS]}{([S_T] - [CDS])([CD_T] - [CDS])} = \frac{X_{CDS}}{(1 - X_{CDS})([CD_T] - X_{CDS}[S_T])} \quad (16)$$

After some algebraic manipulation and simplification one can write (Valente and Söderman, 2014):

$$\Delta\delta_{obs} = \frac{\Delta\delta_0}{2K_1[S_T]}\left(K_1([S_T] + [CD_T]) + 1 - \left((K_1([S_T] + [CD_T]) + 1)^2 - 4K_1^2[S_T][CD_T]\right)^{1/2}\right) \quad (17)$$

Figure S9 (Supplementary Material) shows examples of the dependence of $\Delta\delta_{obs}$ on the total cyclodextrin concentration for some nuclei of C1,Br^-. Two different procedures can be used in order to estimate the equilibrium binding constants from the NMR experimental data. One method fits the experimental chemical shifts to eq. 17 using a non-linear least-square algorithm for all the protons in the system that are shifted with CD concentration, or at least with those than undergo the larger changes. In this way, K_1 will be estimated as the average of the values obtained independently for each proton. Another procedure is to use multivariable analysis by fitting all the protons under study and considering that the association binding constant must be the same for all of them. When using the two methods, no substantial differences between the equilibrium binding constants obtained were found. The K_1 values calculated from NMR measurements are summarized in Table 1. One can see that the K_1 values estimated by conductivity and ^{1}H NMR measurements are in good agreement.

The driving forces leading to the formation of CD:surfactant inclusion complexes include electrostatic interactions, van der Waals interactions, hydrophobic interactions, hydrogen bonding, release of conformational strain of the CD, exclusion of cavity-bound high-energy water from the CD cavity and charge-transfer interactions (Liang et al., 2011; Liu and Guo, 2002). However, due to enthalpy-entropy compensation, release of conformational strain and exclusion of cavity-bound high-energy water usually do not play an important role in the complex formation. K_1 values in Table 1 show that, within experimental errors, similar binding equilibrium constants are estimated for chloride and bromide surfactants, this

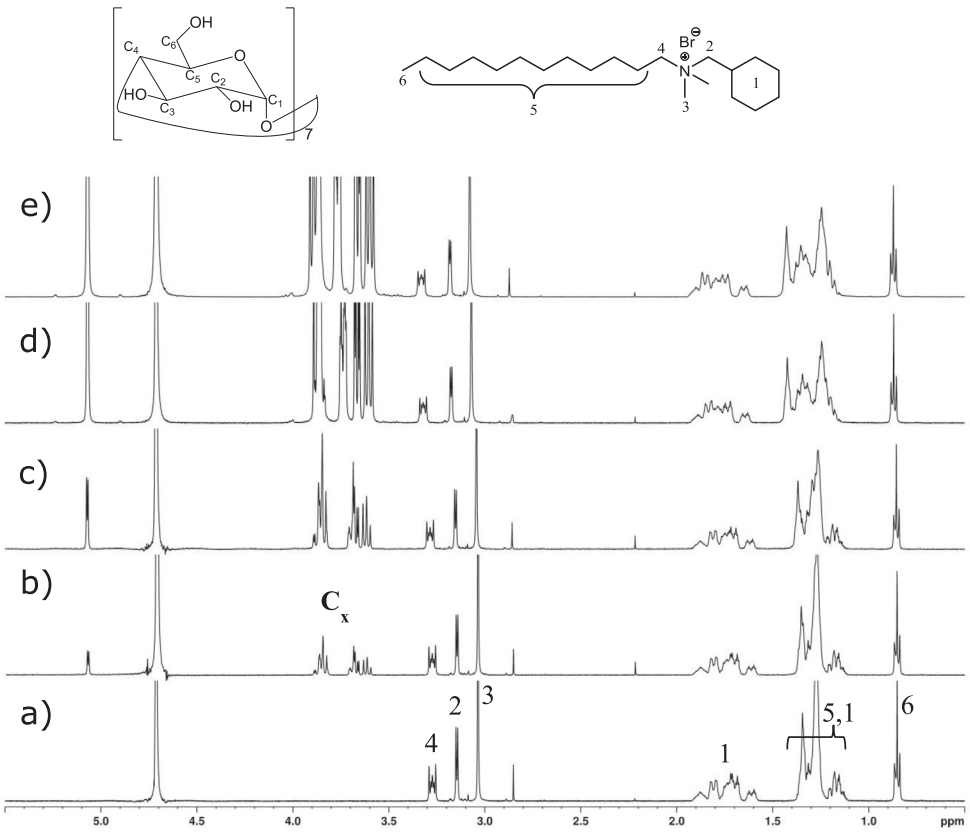
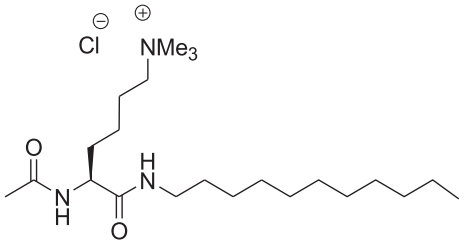


Fig. 4 ^{1}H NMR spectra of β-CD:C1,Br$^-$ in D_2O solutions at 303 K, with [C1,Br$^-$] = 2.00×10^{-3} M. (a) [β-CD] = 0 M; (b) [β-CD] = 2.00×10^{-4} M; (c) [β-CD] = 1.00×10^{-3} M; (d) [β-CD] = 2.80×10^{-3} M; (e) [β-CD] = $5.00 \cdot 10^{-3}$ M. More β-CD concentrations were investigated but the spectra are not included in the figure for the sake of clarity.



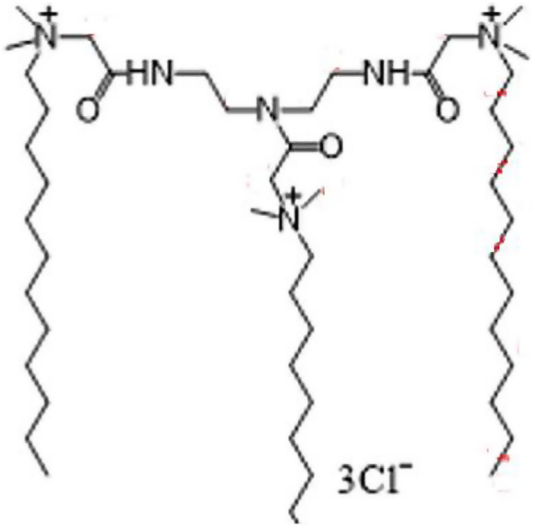
Scheme 2 Molecular structure of the amino acid-based surfactant LYCl.

indicating the negligible effect of the counterion nature on K_1. This finding is in agreement with previous results (Valente and Söderman, 2014). Data in Table 1 also show that the binding of the bromides of C1 and P1, as well as that of DTAB to α-, β-, and γ-CD depends on the CD nature, but not on the surfactant. The equilibrium association constant of the lysine-based surfactant (*S*)-5-acetamido-6-(dodecylamino)-*N,N, N*-trimethyl-6-oxohexan-1-ammonium chloride, LYCl (Scheme 2), with a bulky head group, to β-CD is $(1.9 \pm 0.4) \times 10^4$ M^{-1} (Martín et al., 2015), similar to those obtained in this work for the single-chained surfactants. Accordingly, the size and nature of the surfactant head group are of little importance in the formation of the inclusion complexes. Also the nature of the counterion hardly affects the value of the equilibrium binding constants. Given that the common structural feature for these surfactants is the dodecyl hydrocarbon chain, the results indicate that the key structural surfactant feature influencing K_1 is the hydrocarbon tail length. That is, hydrophobic interactions constitute the major driving force for the CD:single-chained surfactant complexation. This statement is in agreement with experimental results previously obtained, which show that for both single-chained and dimeric surfactants, an increase in the hydrophobic chain length results in an increase in K_1 (Valente and Söderman, 2014). For instance, the equilibrium binding constants K_1 between the alkyltrimethylammonium surfactants, and β-CD, at 303 K, for decyltrimetylammonium bromide, DeTAB, DTAB, and tetradecyltrimethylammonium bromide, TTAB, are 2.9×10^3 M^{-1}, 1.5×10^3 M^{-1}, and 4.8×10^3 M^{-1}, respectively (Valente and Söderman, 2014).

With regard to the effect of the cyclodextrin's nature on the formation of the CD:C1,Br$^-$, CD:P1,Br$^-$, and CD:DTAB complexes, the binding seems slightly stronger for α-CD than for β-CD. In the case of γ-CD:surfactant complexes, the binding is much weaker than for either α- or β-CD. This observation can be explained by considering the size of the CD cavity and the fact that the better the fitting in the cavity is, the stronger the CD:surfactant interactions will be (Ostos, 2014; Liu and Guo, 2002; Saenger et al., 1998; Xing et al., 2008; Funasaki et al., 2004; Piñeiro et al., 2008; Ghoreishi et al., 2008).

It is important to note that an increase in the cyclodextrin concentration in the working medium will favor the formation of 2:1 inclusion complexes. That is, the average number of CDs per surfactant molecule could augment for the surfactants studied, if the CD concentration is substantially increased. With regard to this, data summarized in the review of Valente and Söderman (2014) show that the stoichiometry and binding equilibrium constants can depend considerably on the experimental method, the working conditions and the method used to interpret data. Therefore, the association equilibrium constants estimated by different authors for a CD:surfactant system at a given temperature can differ by one or even two orders of magnitude.

Under the working conditions, the stoichiometry found for the inclusion complexes formed between β-CD and the single-chained, di-, tri-, and tetrameric surfactants investigated was 1:1. This stoichiometry seems typical for CD:single-chained surfactant complexes (Valente and Söderman, 2014). In the case of dimeric surfactants, various stoichiometries are reported in the literature, depending on the surfactant nature and the working conditions (Valente and Söderman, 2014). For instance, the average number of CD molecules per alkyl-α,ω-bis(dodecyldimethylammonium bromide surfactant molecule in the inclusion complexes β-CD:12-s-12,2Br$^-$ increases by increasing the length of the spacer from 1.6, for s = 2, to 2, for s = 12 (Nilsson et al., 2006; Carvalho et al., 2011). In contrast, a 1:1 stoichiometry was found for the surfactants bis(alkyldimethylammonium)-2-hydroxypropyl dichloride ($(C_nN)Cl_2$, n = 12, 14, and 16) (Sun et al., 2006), and for bis-(dodecyldimethylammonium)diethylether dibromide, 12(EO1)12, the latter at low and moderate CD concentrations (Guerrero-Martínez et al., 2006). Still, despite the potential applications of CD:dimeric surfactant complexes, studies on the complexation mechanism and complex properties have been rare. Recently, Zhou et al. studied exceptionally the interaction between a star-shaped cationic trimeric surfactant, DTAD (see Scheme 3), and α-, β-, and γ-CD (Zhou et al., 2016). Under their working conditions, and using calorimetric measurements, the trimeric surfactant forms 1:1 inclusion complexes with β-CD. To our knowledge, no results for linear trimeric and tetrameric surfactants have been reported so far.



Scheme 3 Structure of the trimeric surfactant, DTAD.

With regard to the stability of the host-guest complexes, K_1 values are similar for M-C-2, M-P-2, and P-P-2, and they are also similar, within experimental errors, to those found for the β-CD:12-2-12,2Br$^-$ and β-CD:12(EO1)12,2Br$^-$ complexes (Nilsson et al., 2006; Carvalho et al., 2011; Guerrero-Martínez et al., 2006). No influence of the counterion nature on K_1 was found. In contrast to the results for β-CD:12-s-12,2Br$^-$ complexes (Nilsson et al., 2006; Carvalho et al., 2011), our experimental results indicate that, for the dimeric surfactants studied the spacer nature does practically not affect the formation of the inclusion complexes. This could be explained by the similar lengths of the spacer groups of the dimeric surfactants investigated. The observed K_1 value for dimeric surfactants is nearly 5 times smaller than that of the single-chained surfactants. That is, the presence of a second hydrophobic chain makes the formation of the inclusion complexes less favorable, This indicates that the binding follows a non-cooperative mechanism. This result can be rationalized by taking into account steric constraints and electrostatic effects. Once the first CD molecule has bound to the dimeric surfactant, the space available for the second CD molecule to associate with the remaining free chain is limited. Also, if the two chains are complexed to CD molecules, the positively charged ammonia groups will be confined in an environment rich in methyl groups (a more hydrophobic surrounding), which is electrostatically unfavorable. Besides, the hydrophobic interactions between the two dodecyl hydrophobic tails of the dimeric surfactant molecules have to be overcome in order to form the inclusion complex (Valente and Söderman, 2014).

The presence of a third and fourth hydrophobic chain results in increased equilibrium binding constants for the inclusion complex formation upon increasing the number of hydrophobic chains. Zhou et al. (2016) estimated a value of K_1 for the inclusion complex β-CD:DTAD equal to 1.36×10^5 M^{-1}, which is about 15-fold higher than those found for M-P-3 and P-P-3. This could be explained by considering that DTAD has longer spacer groups than M-P-3 and P-P-3 as well as by its star-like architecture. Both factors result in the hydrophobic chains being more distant than in the case of the linear trimeric surfactants studied, which makes the formation of the inclusion complexes more favorable. Equilibrium binding constants in Table 1 show that the increase by one hydrophobic chain, from two to three to four, increases K_1 approximately by a factor of ~2.5. This could be explained by a higher probability for the inclusion complex formation since the number of hydrophobic chains capable of interacting with the cyclodextrin molecules augments. In fact, ROESY spectra show that more than one type of 1:1 inclusion complex is formed for trimeric and tetrameric surfactants, depending on the flanking or the central hydrophobic chains being incorporated into the cavity of the host.

To the author's knowledge, this is the first work investigating the influence of the surfactant degree of oligomerization on the formation of CD:surfactant inclusion complexes.

4. Conclusions

The binding of single-chained, di- tri-, and tetrameric cationic surfactants with dodecyl hydrophobic chains to cyclodextrins was investigated. The experimental results show that:

(i) Under the working conditions, all the surfactants form 1:1 inclusion complexes.
(ii) Bromide and chloride surfactants render similar stoichiometry and equilibrium binding constants.
(iii) For single-chained surfactants the trend K_1(α-CD) > K_1(β-CD) > > K_1(γ-CD) was observed. This result can be explained by considering that the better the surfactant tail fits into the CD cavity, the stronger the host–guest interactions will be.
(iv) From the comparison of the equilibrium binding constants obtained in this work with those taken from the literature, one can conclude that neither the size nor the nature of the head group does influence the CD: single-chained surfactant complexation. For the di- and trimeric surfactants investigated in this work, no effect of the spacer group nature on the equilibrium constant values was observed. This could be explained by the similar length of the spacer groups.
(v) The stability of the CD:single-chained surfactant complexes is higher than that of the CD:dimeric surfactants, the binding following a non-cooperative mechanism. This result could be rationalized by taking into account steric constraints and electrostatic effects as well as the need to overcome the hydrophobic interactions between the chains of the same surfactant molecule. However, the further increase by one hydrophobic chain, from two to three to four, increases K_1 approximately by a factor of ~ 2.5. This can be explained by a higher probability for the inclusion complex formation since the number of hydrophobic chains which can interact with the cyclodextrin molecules augments. In this regard, ROESY spectra show that more than one type of 1:1 inclusion complex is formed for trimeric and tetrameric surfactants.

Acknowledgements

This work was financed by the Consejería de Innovación, Ciencia y Empresa de la Junta de Andalucía (P12-FQM-1105), FQM-274 and FQM-206, University of Seville (2017/1004), and FEDER funds.

Appendix A. Supplementary material

Supplementary data associated with this article can be found, in the online version, at https://doi.org/10.1016/j.arabjc.2018.04.015.

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