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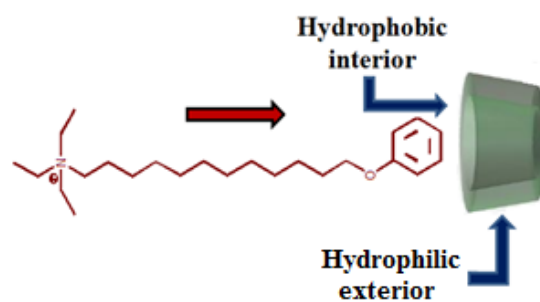

In this work the influence of the incorporation of aromatic substituents at the end of the hydrophobic tail on the binding of cationic surfactants to cyclodextrins was studied.

HOST-GUEST INTERACTIONS BETWEEN CYCLODEXTRINS AND SURFACTANTS WITH FUNCTIONAL GROUPS AT THE END OF THE HYDROPHOBIC TAIL

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Abstract

The aim of this work was to investigate the influence of the incorporation of substituents at the end of the hydrophobic tail on the binding of cationic surfactants to α-, β-, and γ-cyclodextrins. The equilibrium binding constants of the 1:1 inclusion complexes formed follow the trend $K_1(\alpha\text{-CD}) > K_1(\beta\text{-CD}) >> K_1(\gamma\text{-CD})$, which can be explained by considering the influence of the CD cavity volume on the host-guest interactions. From the comparison of the K_1 values obtained for dodecyltriethylammonium bromide, DTEAB, to those estimated for the surfactants with the substituents, it was found that the incorporation of a phenoxy group at the end of the hydrocarbon tail does not affect K_1, and the inclusion of a naphthoxy group has some influence on the association process, slightly diminishing K_1. This makes evident the importance of the contribution of hydrophobic interactions to the binding, the length of the hydrophobic chain being the key factor determining K_1. However, the presence of the aromatic rings does influence the location of the host and the guest in the inclusion complexes. The observed NOE interactions between the aromatic protons and the CD protons indicate that the aromatic rings are partially inserted within the host cavity, with the cyclodextrin remaining close to the aromatic rings, which could be partially intercalated in the host cavity. To the authors´ knowledge this is the first study on the association of cyclodextrins with monomeric surfactants incorporating substituents at the end of the hydrophobic tail.

1. Introduction

Cyclodextrins, CD, are cyclic oligosaccharides formed through α(1-4) ether linkages of glucopyranoside units [1,2]. The most common CDs, α-, β-, and γ-CD, are composed of six, seven and eight glucose units, respectively. CDs are shaped like a truncated cone with internal cavities ranging from 5 to 8 Å. The hydroxyl functions are oriented to the exterior of the cavity, with the secondary hydroxyl groups located on the wider edge, and the primary

ones on the narrow edge. The C-H bonds on the ring and the nonbonding electron pairs of the glycosidic oxygen bridges point inward. As a result of this spatial arrangement of the functional groups, the cavity shows a relatively hydrophobic character while the external surfaces are hydrophilic. This is responsible for both their water solubility and their ability to form inclusion complexes with molecular guests of suitable size. This capacity to form inclusion complexes with a wide variety of molecules, together with the non-toxicity towards humans, has been the basis for the CDs large range of applications [3-9].

The understanding of the driving forces involved in the CD inclusion complex formation is fundamentally important not only in CD chemistry, but also for supramolecular chemistry as a whole. In a recent review Valente and Söderman [10] pointed out that surfactants are ideal guests for fundamental studies on the complexation with CDs since both hydrophobic and hydrophilic regions of the surfactant molecules can be systematically varied. These authors examined the effect of different surfactant architectures on the formation of inclusion complexes by considering the results obtained by several authors for single tailed, double tailed, gemini and bolaform surfactants, with special emphasis on cationic surfactants. However, to the authors´ knowledge, the influence of the incorporation of a functional group at the end of the hydrophobic surfactant tail on the surfactant:CD interactions has not been investigated. With this in mind, the surfactants triethyl(1-phenoxydodecyl)ammonium bromide (Phenoxy12) and triethyl(2-naphthoxydodecyl)ammonium bromide (Naphthoxy12) were prepared in this work and their interactions with α-, β-, and γ-cyclodextrins studied. In order to help the discussion of the results, the formation of host:guest complexes between dodecyltriethylammonium bromide (DTEAB) and CDs was also investigated. Since there is not much information about surfactants with functional groups at the end of the hydrophobic tail in the literature, a brief discussion of the physicochemical properties of Phenoxy12 and

Naphthoxy12 aqueous solutions was done before considering the formation of the inclusion complexes.
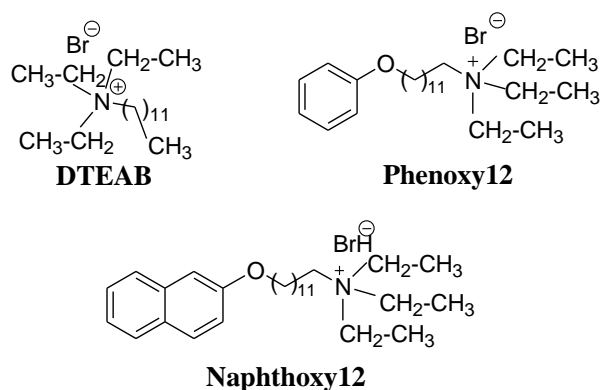
Scheme 1.- Structure of the surfactants used in this work.

The results obtained in this work will contribute to the understanding of the surfactant:cyclodextrin interactions. This is important in relation to the wide range of applications of both CDs and surfactants, which can be increased by taking advantage of the CD-surfactant complex formation.

2. Experimental section

2.1. Materials and chemicals

Dodecyltrymethylammonium bromide, DTAB, was from Sigma-Aldrich. α-, β-, and γ-cyclodextrins of the highest purity available were also purchased from Aldrich (>99% purity, according to the manufacturer) and were kept under vacuum. DTEAB was prepared in a previous work [11] and its synthesis is briefly described in the Supplementary Material. The preparation of Phenoxy12 and Naphthoxy12 is described below. The surfactants were characterized by ^{1}H NMR, ^{13}C NMR and elemental analysis (CITIUS, University of Seville). D$_2$O was supplied by Sigma. Water was MilliQ (resistivity >18 MΩ cm).

2.2. Preparation of the surfactants

### 2.2.1. Preparation of Phenoxy12

The synthesis of Phenoxy12 was performed according to Scheme 2. Starting from commercial 1,12-dibromo-dodecane, the phenoxy group, PhO, was introduced at the end of the fatty alkyl chain by nucleophilic substitution reaction with sodium phenoxide in acetone, thus giving compound **1** (12-bromo-1-phenoxydodecane) in 29% yield. Finally, a nucleophilic displacement reaction with acetonitrile and triethylamine gave the compound **2** (triethyl(1-phenoxydodecyl) ammonium bromide) in 75% yield. Its ^{1}H NMR spectrum indicated the appearance of a triplet and a quartet signals integrating for nine and six protons, respectively, corresponding to the new three ethyl groups. Procedures for the preparation of the surfactant and intermediates are described in detail in Supplementary Material.
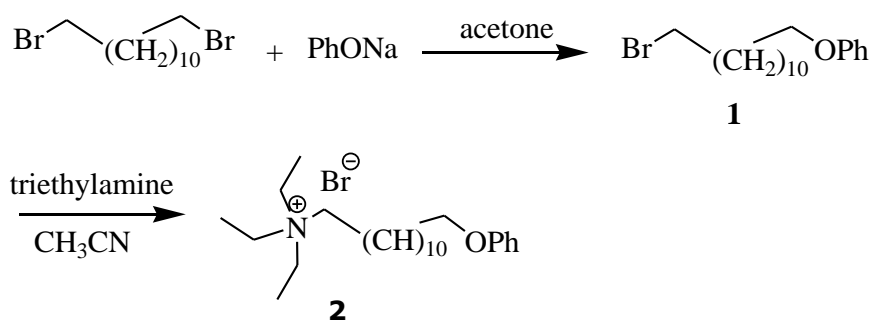
Scheme 2.- Synthesis of Phenoxy12

2.2.2. Preparation of Naphthoxy12

The synthesis of Naphthoxy12 was similar to that of Phenoxy12, as it is shown in Scheme 3. In this scheme the naphthoxy group is represented by NaphO. Commercial 1,12-dibromo-dodecane and sodium naphthoxide were used in the nucleophilic substitution reaction to render compound **3** (12-bromo-1-naphthoxydodecane), in 52% yield. Finally, the nucleophilic displacement reaction with acetonitrile and triethylamine gave the compound **4** (triethyl(1-naphthoxydodecyl) ammonium bromide) in 97% yield. Similarly to Phenoxy12,
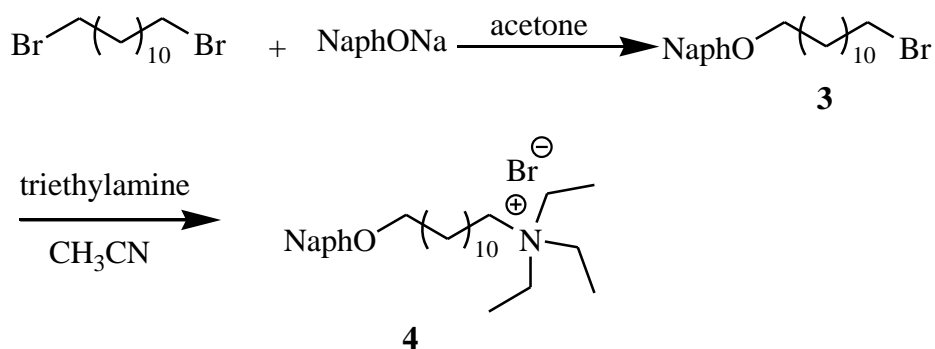
Scheme 3.- Synthesis of Naphthoxy12

^{1}H NMR spectrum of Naphthoxy12 indicated the appearance of a triplet and a quartet signals integrating for nine and six protons, respectively, corresponding to the new three ethyl groups. Procedures for the preparation of the surfactants and intermediates are also described in detail in Supplementary Material.

2.3. Methods

2.3.1. 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 ±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 critical micellar concentrations of Phenoxy12 and Naphthoxy12 were estimated by means of conductivity measurements as described in ref. 12.

2.3.2. Surface tension measurements

Surface tension was measured by a du Noüy ring method using a KSV 703 digital tensiometer (Finland) as described in ref. 12.

2.3.3. 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 hours before carrying out the NMR experiments. NMR experiments were recorded on a Bruker Avance III 500 MHz spectrometer (500.2 MHz for ^{1}H) equipped with a 5 mm TCI cryoprobe operating at 303 K. All ^{1}H chemical shifts are referenced to the residual HDO signal set to 4.71 ppm [13].

Two-dimensional, 2D, rotating frame nuclear Overhauser effect experiments were performed using the Bruker standard pulse sequence (EASY-ROESY version [14]). 2048 x 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 x 1024 data matrix. Cosine-squared window functions were used along F1 and F2.

3. Results and discussion

3.1. Physicochemical properties of the Phenoxy12 and Naphthoxy12 aqueous solutions

The critical micellar concentration, cmc, and the micellar ionization degree, α, of Phenoxy12 and Naphthoxy12 in aqueous solutions were determined using conductivity measurements. Figure S1 (Supplementary Material) shows the dependence of the specific conductivity on Phenoxy12 and on Naphthoxy12 concentrations at 303 K. The Carpena method [15] was used in order to obtain the cmc and α values from the experimental results. These data are summarized in Table 1, together with that corresponding to DTEAB. The Gibbs energy of micellization, ΔG^o_M, can be calculated by using eq. 1 [16]:

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$$\Delta G^{o}_{M} = RT(2-\alpha) \ln cmc \qquad (1)$$

where cmc is expressed in mole fraction and R and T have their usual meaning. ΔG^{o}_{M} values are listed in Table 1. Comparison of the ΔG^{o}_{M} values obtained for the three surfactants shows

Table 1.-Critical micellar concentration, cmc, micellar ionization degree, α, and Gibbs energy of micellization, ΔG^{o}_{M}, for the cationic surfactants studied in this work, at 303 K.

Surfactant	Cmc/mM	α	ΔG^{o}_{M}/kJ mol^{-1}
DTEAB[a]	14.3±0.4	0.35±0.02	-34.3±1.8
Phenoxy12[b]	3.7±0.2	0.40±0.03	-38.8±1.7
Naphthoxy12[b]	0.641±0.015	0.43±0.03	-45.0±1.9

[a]Ref. 11; [b]This work.

that the introduction of a phenoxy and a naphthoxy group at the end of the surfactant hydrophobic tail substantially favors micellization. The experimental observations can be explained by taking into account the transfer Gibbs energy contribution, ΔG^{o}_{transf}, to the Gibbs energy of micellization, ΔG^{o}_{M}. ΔG^{o}_{transf} considers the transfer of the hydrophobic surfactant chains from the aqueous phase to the micellar interior and it is the driving force for the self-association process of surfactants [17]. The surfactants listed in Table 1 have a dodecyl hydrophobic chain and the corresponding ΔG^{o}_{transf} contribution would be the same for all of them. The 4-fold and a 22-fold diminution in the cmc, with respect to that of DTEAB, caused by the incorporation of a phenoxy group, C_6H_5O-, and of a naphthoxy group, $C_{12}H_7O$-, at the end of the hydrophobic tail can be rationalized by considering the additional hydrophobic contribution to ΔG^{o}_{transf} due to the transfer of the C_6H_5O- and $C_{12}H_7O$- groups into the micelles. The large difference found between the cmc´s of Phenoxy12 and Naphthoxy12 could be accounted for by the different hydrophobicity of these two aromatic substituents. As an example, the logarithm of the octanol/water partitition coefficient, logP, is 1.46 and 2.70 for phenol and naphthol, respectively [18].

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With regard to the micellar ionization degrees listed in Table 1, these values could be rationalized with the help of surface tension measurements if it is assumed that the optimum head group area per surfactant molecule at the micellar surface, A_o, can be approximately estimated by the minimum area per surfactant molecule at the air/solution interface, A_{min} [19]. Figure S2 (Supplementary Material) shows the dependence of the surface tension on ln(Surfactant concentration) for Phenoxy12. The surface excess concentration, Γ_{exc}, was calculated by using the Gibbs equation, with the Gibbs prefactor n equal to 2. A_{min} was estimated by the equation $A_{min} = (N_A \Gamma_{exc})^{-1}$, where N_A is Avogadro´s number. Thomas et al. [20-23] and Eastoe et al. [24, 25] found large discrepancies between surface excess concentrations determined for ionic surfactants by surface tension and neutron reflection. This discrepancy was described in terms of the value of the pre-factor n necessary to reconcile the coverage determined from application of the Gibbs equation to surface tension data and from neutron reflection and it was shown to be mainly the result of the presence of impurities. The surfactants studied have been thoroughly purified and NMR experiments did not show any trace of impurities. Even though, dynamic surface tension effects must be taken into account and, in the case of the cationic surfactants, the possibility of specific adsorption on the oxide layer of the platinum du Noüy ring can also affect the surface tension measurements [25]. With this in mind, A_{min} have to be taken as approximate and they are going to be used for comparison purposes. The A_{min} values obtained were 99×10^{-20} m^2 and 110×10^{-20} m^2 for Phenoxy12 and Naphtoxy12, respectively. These values can be compared to that corresponding to DTEAB, which is 72×10^{-20} m^2 [11]. $A_{min}(DTEAB) < A_{min}(Phenoxy12) < A_{min}(Naphthoxy12)$ and taking into account that the smaller A_{min} is, the higher the charge density at the micellar surface will be, the expected trend for the micellar ionization degree would be $\alpha(DTEAB) < \alpha(Phenoxy12) < \alpha(Naphthoxy12)$, in agreement with the experimental results.

The micellization process was also studied by means of ^{1}H NMR measurements. Two different surfactant concentrations were prepared, one below the cmc and one above the cmc. Figure 1 shows the ^{1}H NMR spectra for the Phenoxy12 D$_2$O solutions at 303 K. One can observe in this figure that the self-aggregation process is accompanied by substantial changes in the ^{1}H NMR spectrum. Micellization leads to line broadening and decrease in the chemical shifts of most of the protons, with the strongest upfield changes shown by the signals corresponding to the methylene protons H8, and the aromatic protons H1', H2', and H3'. Besides, the initially overlapped peaks of the aromatic H1' and H3' protons become well resolved as a result of the self-aggregation process, due to the higher change observed for H1' than for H3' ($\Delta\delta$(H1')>$\Delta\delta$(H2')>$\Delta\delta$(H3')). These variations in the ^{1}H NMR spectrum can be explained by the shielding process due to the proximity of the hydrophobic tails in the micelle
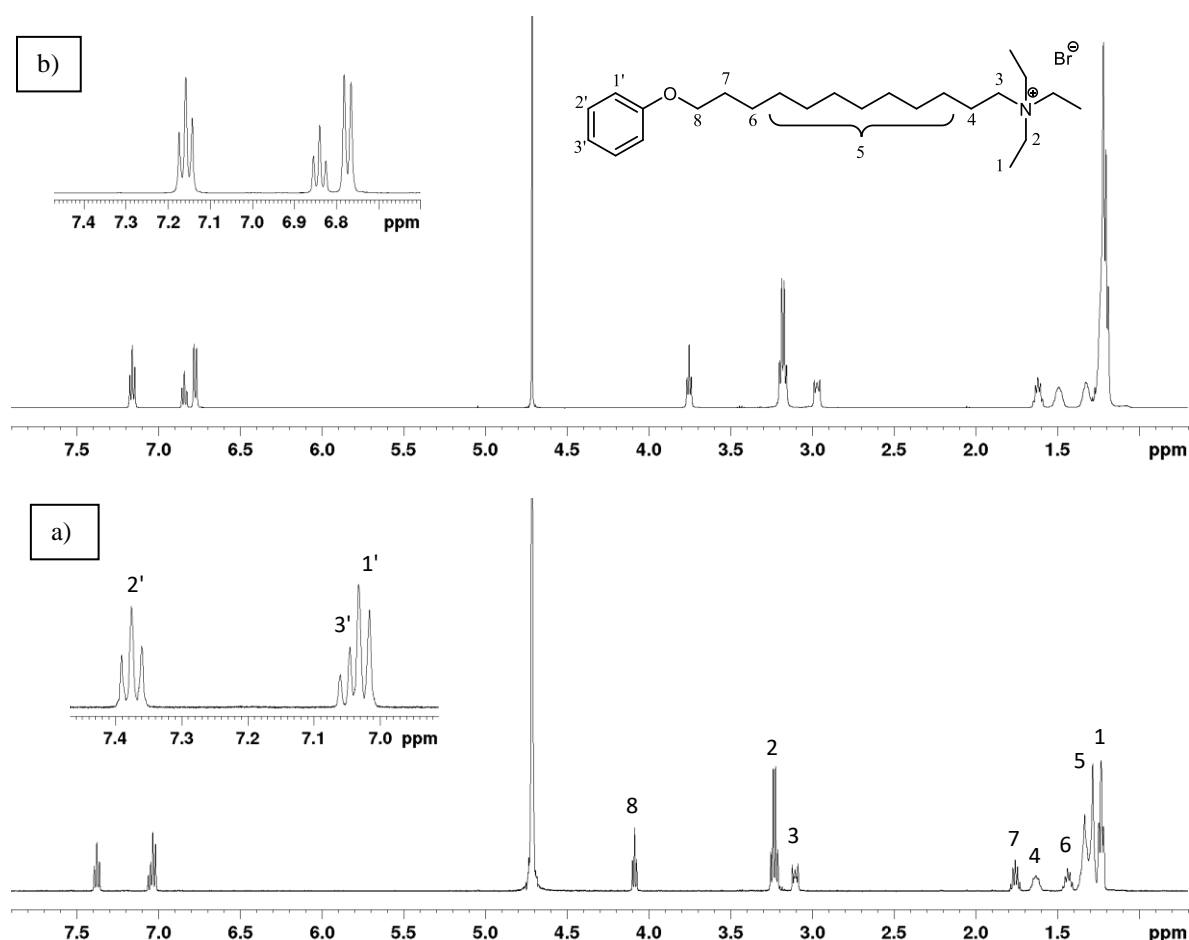
**Fig. 1.-** Concentration dependence of ^{1}H NMR spectrum of Phenoxy12, in D$_2$O, on surfactant concentration. a) [Phenoxy12]=2.00x10^{-3} M; b) [Phenoxy12]= 0.010M. T=303 K.

interior, together with a contribution, in this case, of the strong anisotropy in the magnetic susceptibility around the aromatic ring. The ^{1}H NMR spectra for the Naphthoxy12 in D_2O solutions at 303 K is shown in Figure S3 (Supplementary Material). As in the case of Phenoxy12, micellization leads to line broadening and decrease in the chemical shifts of most of the protons. Figure S3 shows that for Naphthoxy12 the initially overlapped peaks of the aromatic H1' and H3' protons become well resolved as a result of the self-aggregation process. The observed variations in the ^{1}H NMR spectrum can be explained similarly to those found for Phenoxy12.

3.2. Formation of inclusion complexes CD:Surfactant

A preliminary investigation of the formation of the inclusion complexes between the surfactants and the cyclodextrins was carried out using conductivity measurements. It was found that an increase in the apparent cmc is observed in the presence of CDs, which indicates the formation of the inclusion complexes between the macrocycle and the surfactant. The complexed surfactant monomers are not available to form the micelles and so the self-aggregation process occurs at higher surfactant concentrations.

Two-dimensional rotating frame nuclear Overhauser effect spectroscopy, ROESY, can provide information about the influence of the surfactant structure on the formed surfactant:CD inclusion complexes. Figure 2 shows the ROESY spectra of D_2O solutions of Phenoxy12 and either α-, β-, or γ-CD, at 303 K. In the case of Naphthoxy12, the low surfactant concentration present in the D_2O solutions makes the observation of the signals in the ROESY spectra difficult and the precision of the measurements decreases. The ROESY spectrum of Naphthoxy12:β-CD can be seen in Figure 4S (Supplementary Material). For all the inclusion complexes investigated, the presence of cross-peaks due to NOE contacts between the protons of the methylene $((CH_2)_n)$ groups of the alkyl chain of the surfactant and

a) α-CD
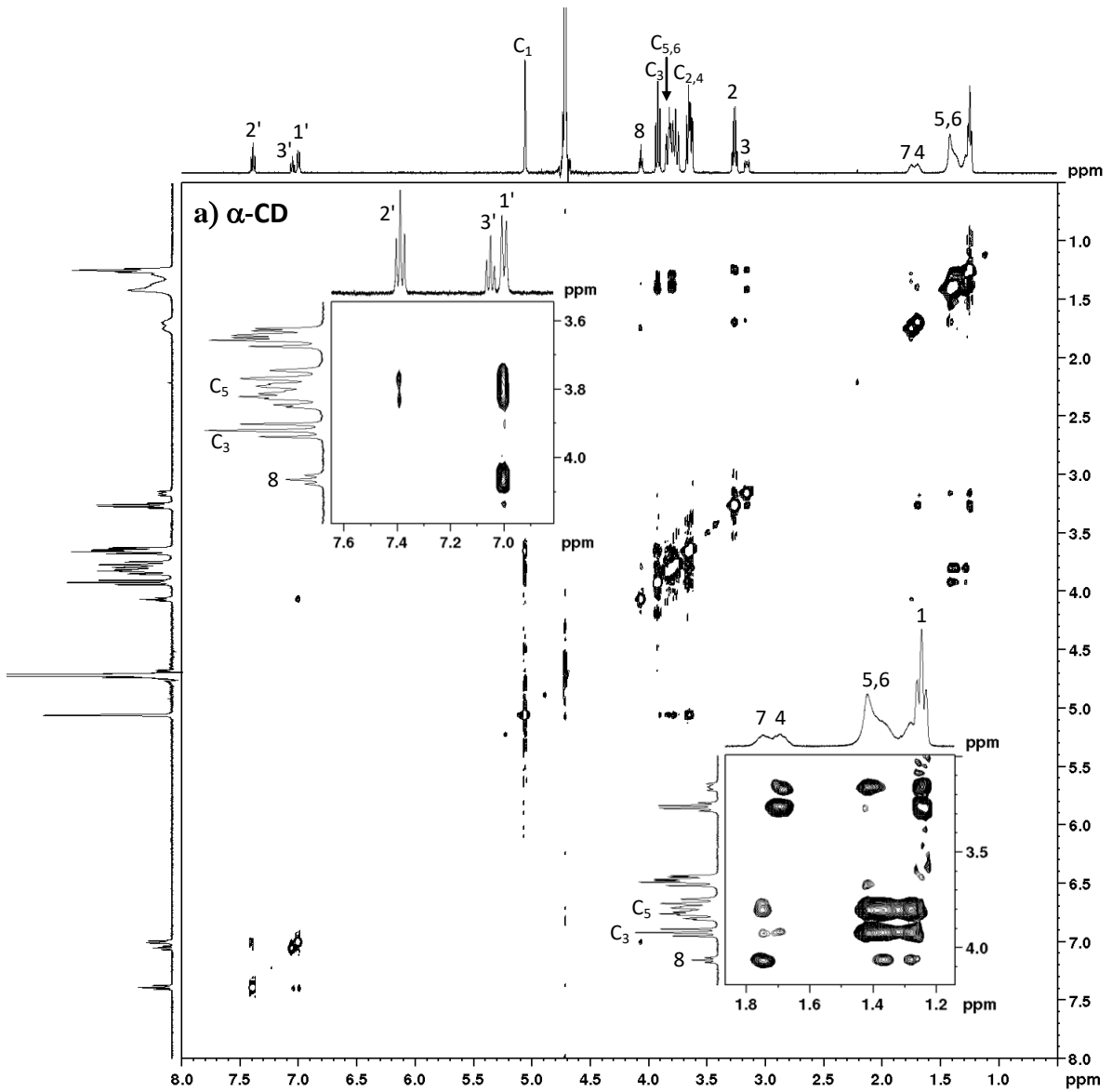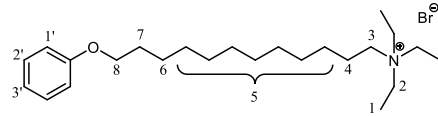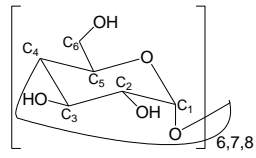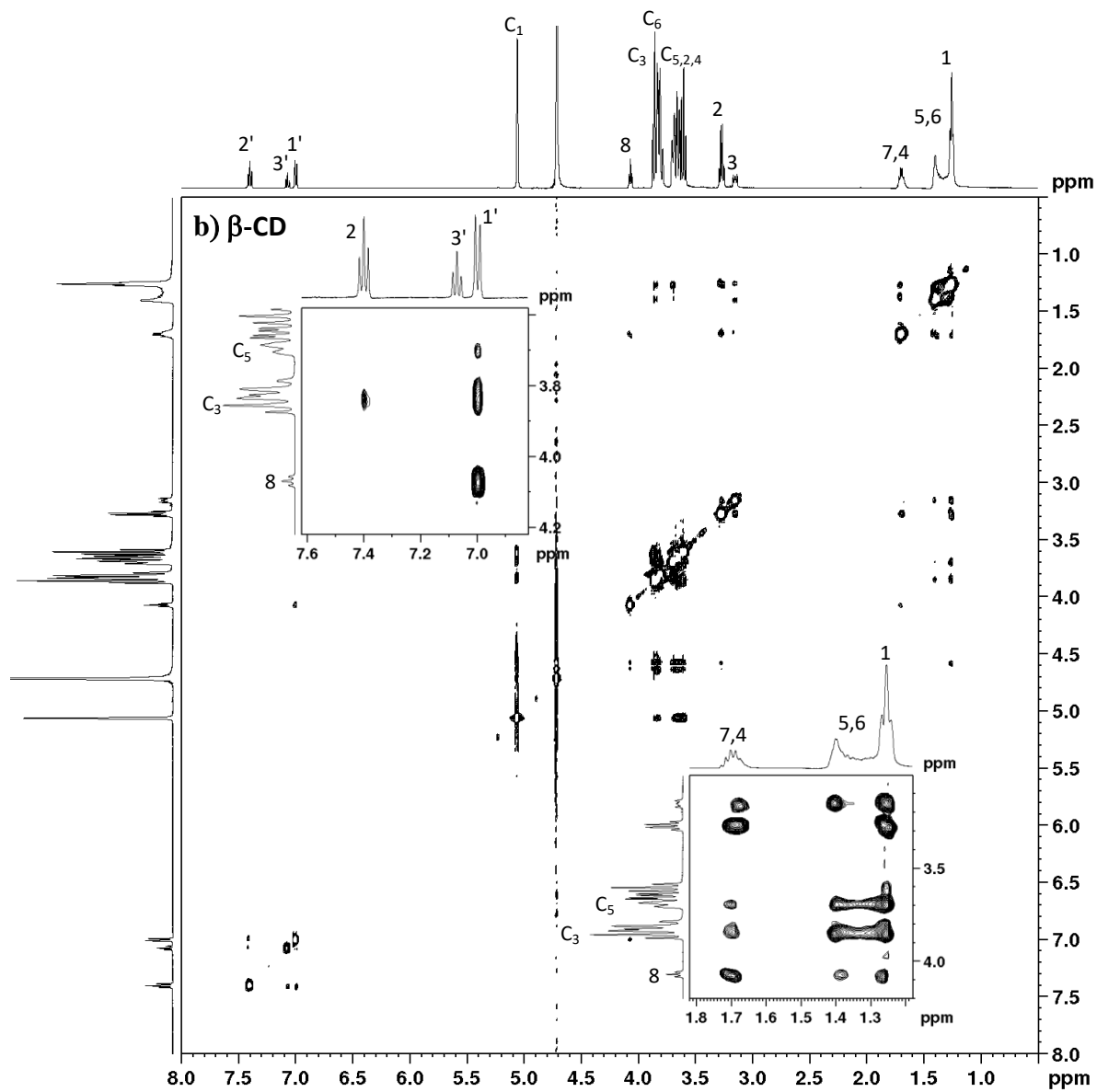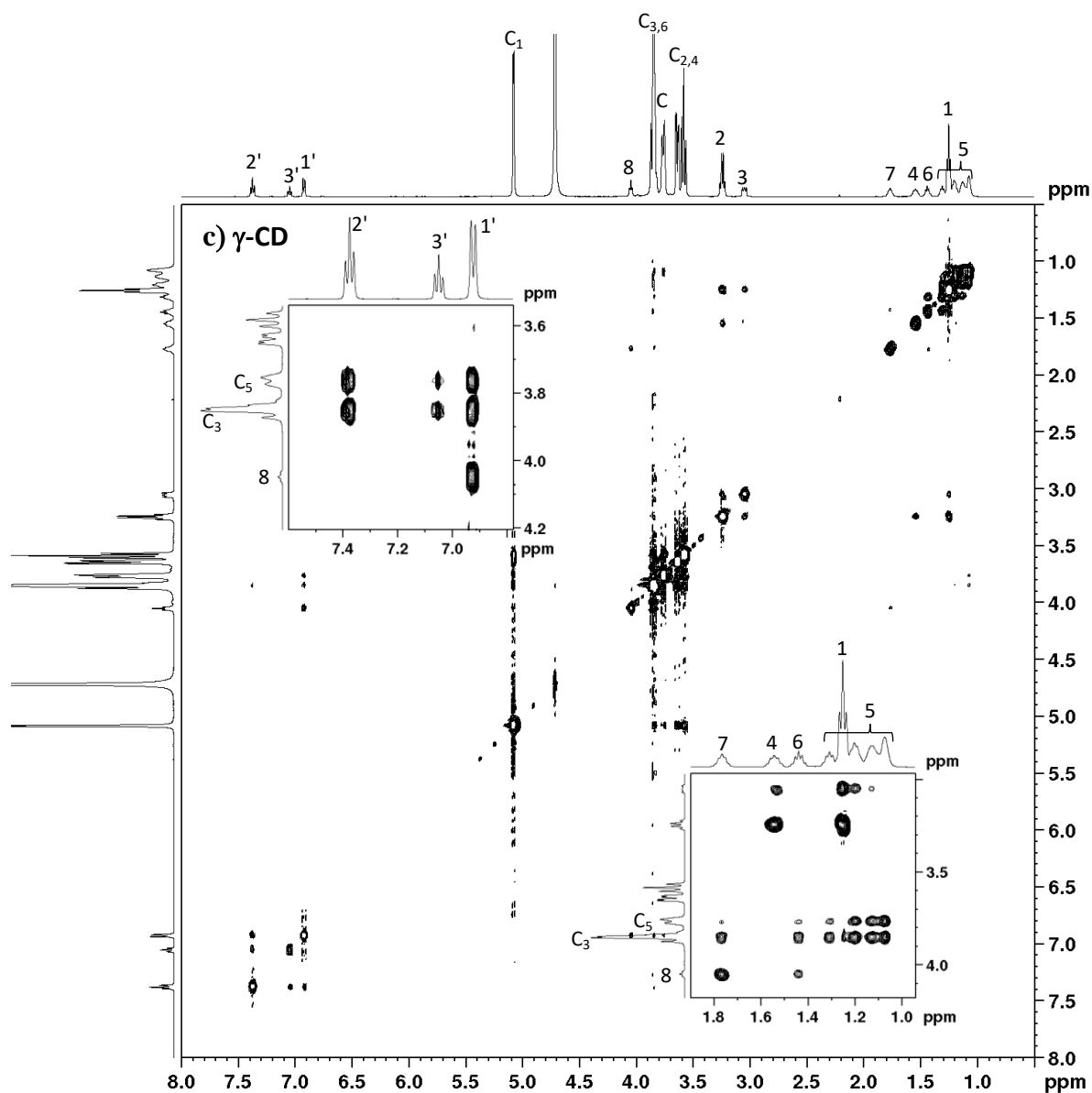
Fig. 2.- ROESY spectra of D_2O solutions containing [Phenoxy12]=2.05×10^{-3} M and [CD]=2.00×10^{-3} M at 303 K. a) α-CD; b)β-CD; c)γ-CD.

the internal protons of the cyclodextrin are observed. This indicates that the hydrophobic tail of the guest molecule is incorporated into the cavity of the host. Furthermore, the largest observed chemical shift changes in the CD molecule upon complexation corresponded to protons C3 and C5, which are facing the cavity of the CD, something which is also in agreement with the inclusion of the surfactant into the CD. In the case of Phenoxy12 and α-CD, the pattern of intermolecular NOEs observed between both molecules suggests a specific

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orientation of the surfactant, with the aromatic moiety located close to the narrower rim of the cyclodextrin.

Interactions between the CD protons and the aromatic surfactant protons are observed for Phenoxy12 and Naphthoxy12. Considering the ROESY spectra of the Phenoxy12 surfactant, one can see NOE interactions between the aromatic H1' and H2' protons (stronger for H1') of the surfactant and protons of the cyclodextrins for α-, β-, and γ-CD. For Naphthoxy12 (see Figure 4S, Supplementary Material) NOE interactions between the protons H1', H3´, H4´, and H8´ (stronger for H1´and H3´) and protons of the CDs are observed. These findings point out that in the formed inclusion complexes the **cyclodextrin remains close to the aromatic rings, which could be partially intercalated in the host cavity**. They also show the dynamic character of the inclusion complex formation, which associates and dissociates with a frequency that would depend, for a given guest, on the CD nature. This dynamic character could explain the really interesting fact that the interaction between the CD protons and all the aromatic protons of Phenoxy12 is only observed in the case of γ-CD. This cyclodextrin has the largest cavity volume of the three CDs, which would make the dissociation easier than for α- and β-CD, increasing the probability of interactions between the CD and the aromatic protons. The estimated equilibrium binding constants obtained in this work support this assumption (see below).

3.3. Stoichiometry

Prior to the calculation of the equilibrium binding constants of the inclusion complexes, the binding stoichiometry of the CD:Surfactant host-guest complexes has to be estimated. In order to do so Job´s method was used [26]. It is observed that when CDs are added to an aqueous ionic surfactant solution, at constant surfactant concentration, an increase in CD concentration could result in a decrease in the experimental specific conductivity. This decrease can be ascribed to the formation of CD:Surfactant, CDS, inclusion complexes, which

have considerably smaller ionic equivalent conductivity than those of surfactant monomers [27]. For this reason, conductivity measurements can be used in order to get information about ionic surfactants/CD interactions. Figure 3 shows some of the Job´s plots obtained for the different surfactants and cyclodextrins investigated, where the dependence of $(\Delta\kappa_{obs}) \times [CD_T]$ on the CD molar fraction was shown, κ_{obs} being the experimental specific conductivity. In all cases only 1:1 complexes, CDS, are formed under the working conditions.
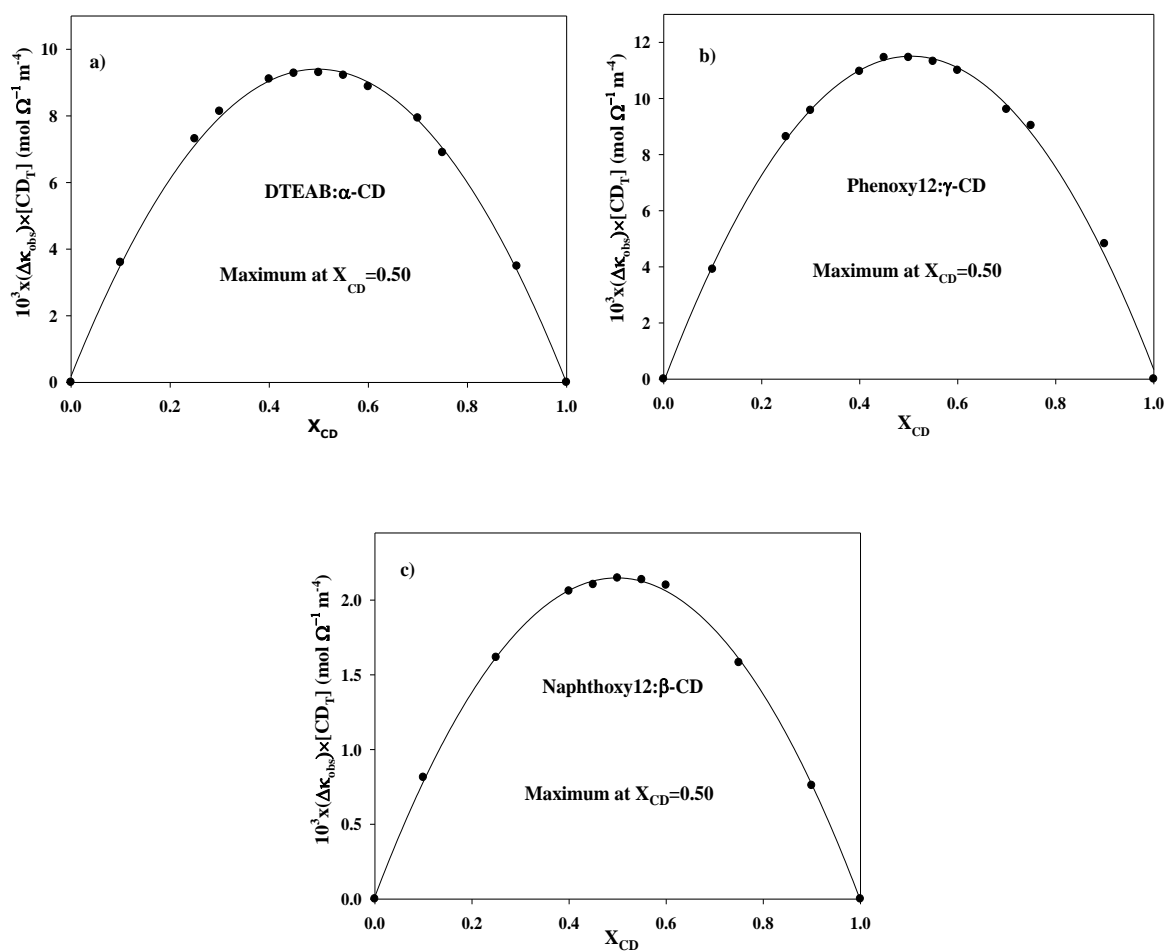

Fig. 3.-Job´s plots at 303 K. a)DTEAB:α-CD; b)Phenoxy12:γ-CD; c)Naphthoxy12:β-CD.

3.4. Formation equilibrium constants for the inclusion complexes

The association process between the surfactants and the cyclodextrins has been studied by varying the CD concentration, for a constant surfactant concentration lower than the cmc.

The stability of the inclusion complexes can be described in terms of the equilibrium binding constants, K_1. For a 1:1 complex K_1 can be defined as:

$$CD + S \leftrightarrows CDS \qquad K_1 = \frac{[CDS]}{[CD][S]} \qquad\qquad (2)$$
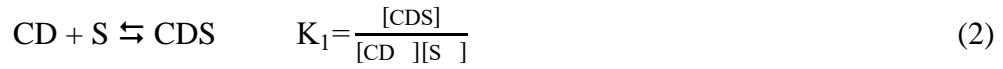
From the mass conservation law equations and taking into account that the experimental specific conductivity is the sum of the contributions coming from the surfactant free ions, the bromide counterions and the CDS inclusion complexes, the observed decrease in the molar conductance of the surfactant aqueous solutions due to the addition of CD, $\Delta\Lambda_{obs}$, can be expressed as [28]:

$$\Delta\Lambda_{obs} = \frac{\Delta\lambda}{2K_1[S_T]}\{K_1([S_T] + [CD_T]) +$$

$$+1 - \left((K_1([S_T] + [CD_T]) + 1)^2 - 4K_1^2([S_T] + [CD_T])\right)^{1/2}\}$$

$$(3)$$

where, $\Delta\lambda$ 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. Figure 4 shows some examples of the dependence of $\Delta\Lambda_{obs}$ on the total cyclodextrin concentration. Eq. 3 was fitted to the experimental data using a non-linear least-square algorithm. Solid lines in Figure 4 show the result of the fittings. One can see that the agreement between the experimental and theoretical data is good. The values of the binding equilibrium constants, K_1, obtained from the fittings are summarized in Table 2. Experiments with different surfactant concentrations were carried out and the results showed that $[S_T]$ does not influence the estimated K_1 value. The method was also checked by determining K_1 for the 1:1 inclusion complex formed between dodecyltrimethylammonium bromide, DTAB, and β-cyclodextrin at 298 K. The K_1 value obtained for this inclusion complex was 1.9×10^4 M^{-1}, in good agreement with literature data [10]. K_1 values summarized in Table 2 are the average of at least four different experiments.
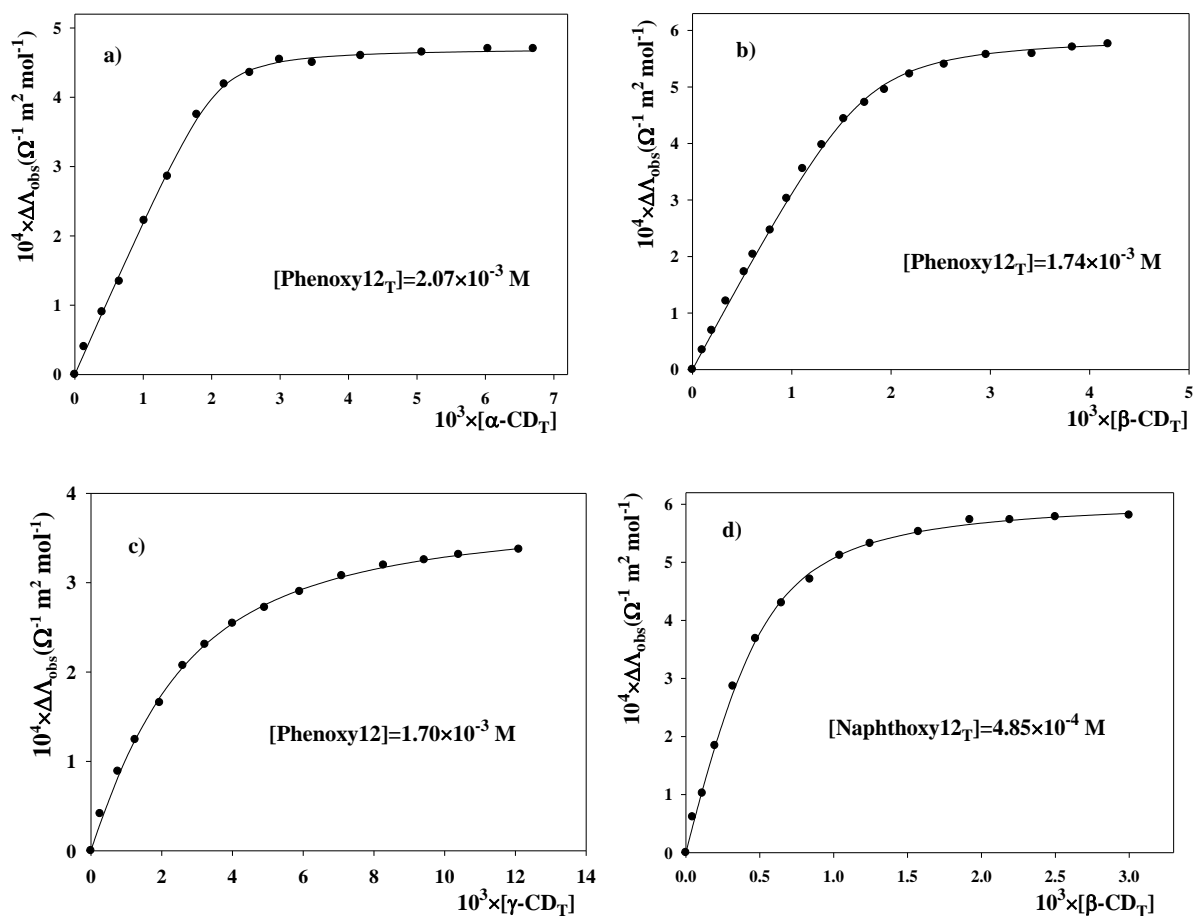
Fig. 4.-Dependence of $\Delta\Lambda_{obs}$ on the total cyclodextrin concentration for the surfactants investigated at 303 K. Solid lines show the fitting of the experimental data by using eq. 3.

Table 2.- Values of equilibrium binding constant, K_1, estimated from the fittings of the observed molar conductance variations of the aqueous surfactant solutions upon increasing the total CD concentration, by using eq. 3. T= 303 K.

Surfactant:CD	K_1 (M^{-1})
DTEAB:α-CD	$(2.4\pm0.5)\times10^4$
DTEAB:β-CD	$(1.6\pm0.4)\times10^4$
DTEAB:γ-CD	$(3.8\pm0.3)\times10^2$
Phenoxy12:α-CD	$(2.2\pm0.5)\times10^4$
Phenoxy12:β-CD	$(1.3\pm0.2)\times10^4$
Phenoxy12:γ-CD	$(6.9\pm0.5)\times10^2$
Naphthoxy12-α-CD	$(2.9\pm0.7)\times10^4$
Naphthoxy12-β-CD	$(8.2\pm0.8)\times10^3$
Naphthoxy12-γ-CD	$(4.0\pm2.2)\times10^2$

It is worth noting that the estimation of the equilibrium binding constants for the inclusion complexes Naphthoxy12:CDs was carried out in the presence of [surfactant]~5×10^{-4}

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M, due to the low cmc of this surfactant (cmc=6.7×10^{-4} M). As a consequence, the precision of the estimated K_1 values is poor, particularly for the Naphthoxy12:γ-CD system.

The formation equilibrium constants of the inclusion complexes can also be estimated by using ^{1}H NMR measurements. The effect of micellization in the chemical shifts of the surfactant resonances has been avoided using a fixed surfactant concentration below the cmc. The concentration of cyclodextrin was varied to obtain different molar ratios [CD]/[Surfactant]. Representative results of the ^{1}H NMR spectra for the CD/surfactant mixtures are shown in Figure 5 for the system Phenoxy12:β-CD. The ^{1}H NMR spectra of α-,

$C_x=C_2$, C_3, C_4, C_5, and C_6
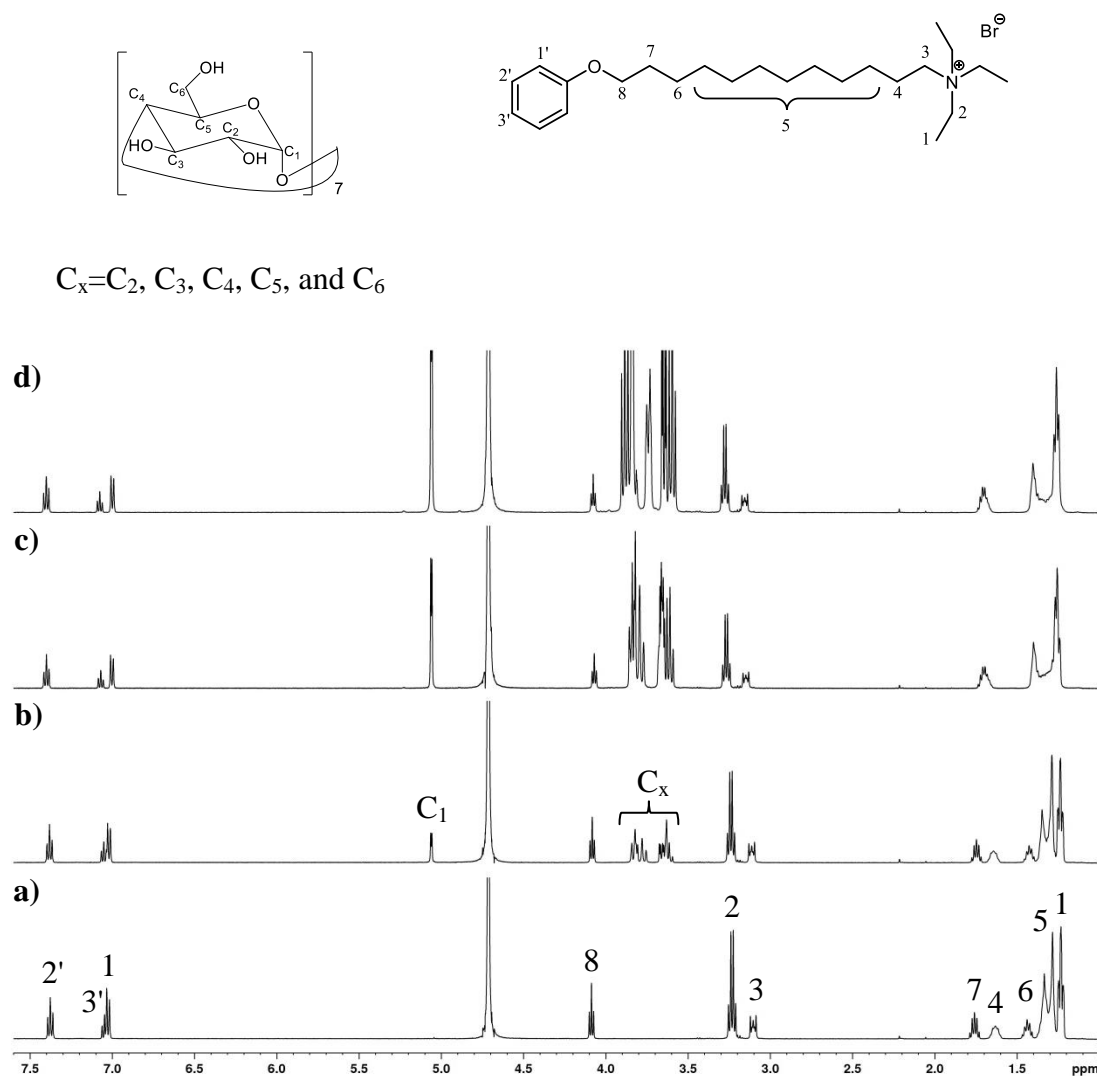
Fig. 5.- ^{1}H NMR spectra of Phenoxy12:β-CD solutions in D$_2$O at 303 K, with [Phenoxy12]=2.05×10^{-3} M. a) [β-CD]=0 M; b) [β-CD]= 4.0×10^{-4} M; c) [β-CD]=2.0×10^{-3} M; d) [β-CD]=4 x10^{-3} M; More β-CD concentrations were investigated but the spectra are not included in the figure for the sake of clarity. T=303 K.

β-, and γ-CD are shown in Figure S5 (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 [28]. The observed chemical shift, for a 1:1 inclusion complex is [10]:

$$\delta_{obs} = X_S\,\delta_S + X_{SCD}\delta_{SCD} = (1 - X_{SCD})\delta_S + X_{SCD}\delta_{SCD} \tag{4}$$

where $X_S = [S]/[S_T]$ and $X_{SCD} = [SCD]/[S_T]$. In this case:

$$\Delta\delta_{obs} = \delta_{obs} - \delta_S = X_{SCD}(\delta_{SCD} - \delta_S) = X_{SCD}\Delta\delta_o \tag{5}$$

For a 1:1 inclusion complex, one can write [10]:

$$K_1 = \frac{[SCD]}{[S][CD]} = \frac{[SC]}{([S_T] - [SCD])([CD_T] - [SCD])} =$$
$$= \frac{X_{SCD}}{(1 - X_{SCD})([CD_T] - X_{SCD}[S_T])} \tag{6}$$

After some algebraic manipulation and simplification [10]:

$$\Delta\delta_{obs} = \frac{\Delta\delta_0}{2K_1[S_T]}\left(K_1([S_T] + [CD_T]) + 1 - \right.$$
$$\left. - ((K_1([S_T] + [CD_T]) + 1)^2 - 4K_1^2[S_T][CD_T])^{1/2}\right) \tag{7}$$

Eq. 7 was fitted to the experimental data using a non-linear least-square algorithm. Figure 6 shows two examples of the dependence of $\Delta\delta_{obs}$ on the total cyclodextrin concentration for some nuclei. The experiments were done at least twice for each surfactant-cyclodextrin system. Since these measurements were done in order to check the reliability of the equilibrium constants values listed in Table 2, only β-cyclodextrin was used. The equilibrium constant for the Naphthoxy12:CD complexes could not be calculated from ^{1}H NMR experiments because of the large errors due to the low surfactant concentration present in the deuterated solutions. The values of the binding equilibrium constants, K_1, obtained from NMR measurements are summarized in Table 3. One can see that the K_1 values listed in Tables 2 and 3 are in good agreement.
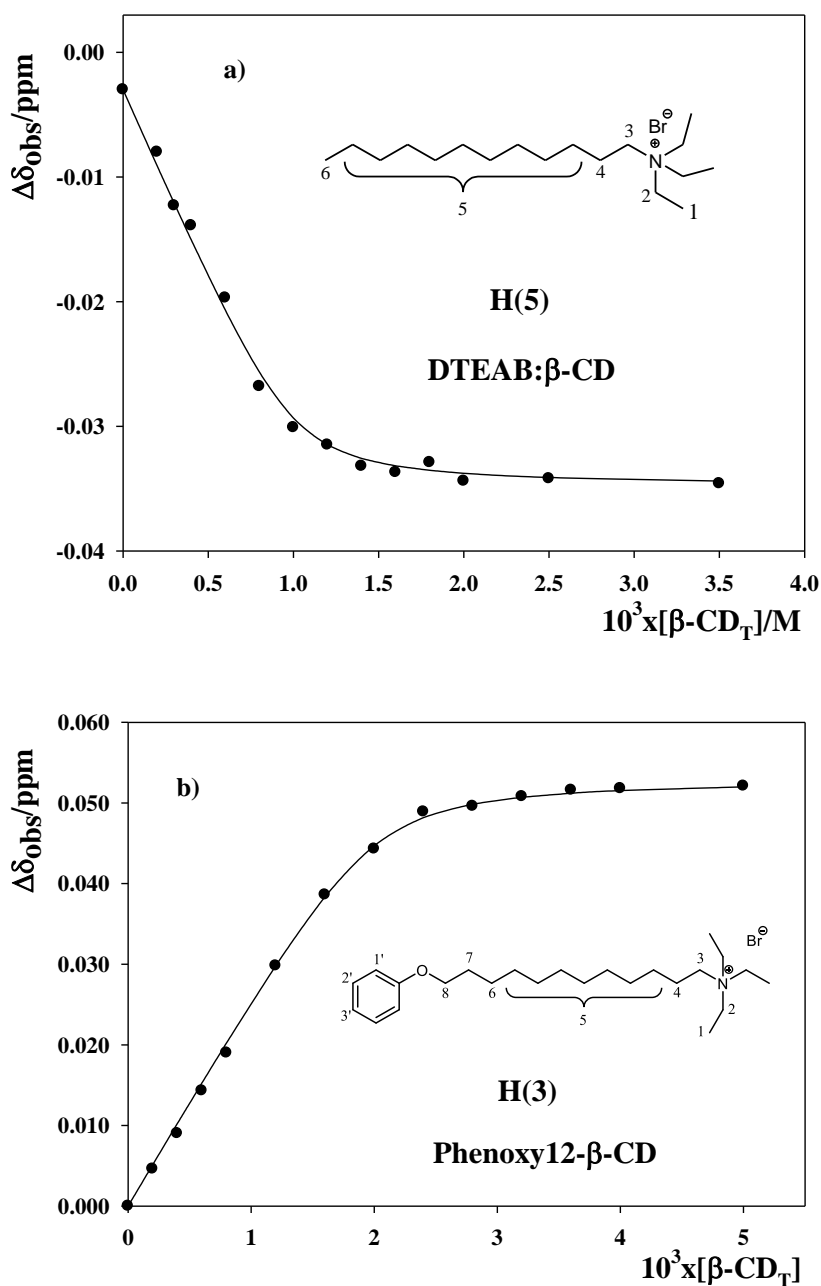
Fig. 6.- Dependence of the chemical shift $\Delta\delta_{obs}=\delta_{obs}-\delta_S$ on total β-cyclodextrin concentration for selected protons of the surfactants. Solid lines are the best fit to eq. 14.

Table 3.- Values of equilibrium binding constant, K_1, estimated from the fittings of the observed chemical shift variations of surfactant protons upon increasing the total CD concentration, by using eq. 14. T= 303 K.

Surfactant:CD	[Surfactant$_T$](M)	K_1 (M^{-1})
DTEAB:β-CD	1.95×10^{-3}	$(1.6\pm0.5)\times10^{4}$
Phenoxy12:β-CD	2.05×10^{-3}	$(1.4\pm0.4)\times10^{4}$

The experimental results have shown that inclusion complexes are formed between the CDs and the surfactants investigated. At this point, it is interesting to consider how they are formed. The surfactants are quaternary ammonium derivatives, with identical cationic head groups and a hydrocarbon tail with twelve carbon atoms. The volume of the $-N(C_2H_5)_3^+$ head group is large and, besides, it is charged and to push it through the relatively non polar cavity of the CDs will be energetically expensive. As a consequence, it would be expected that the intercalation of the surfactant tail into the host cavity occurred as is shown in Figure 7. The
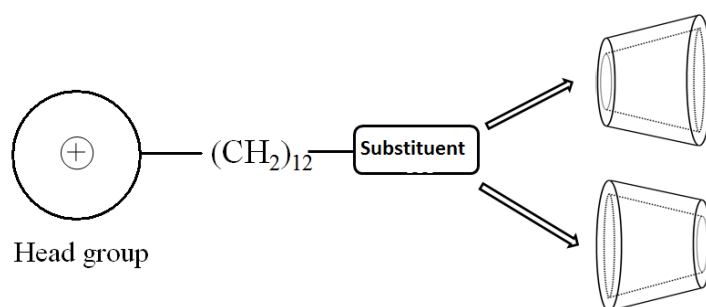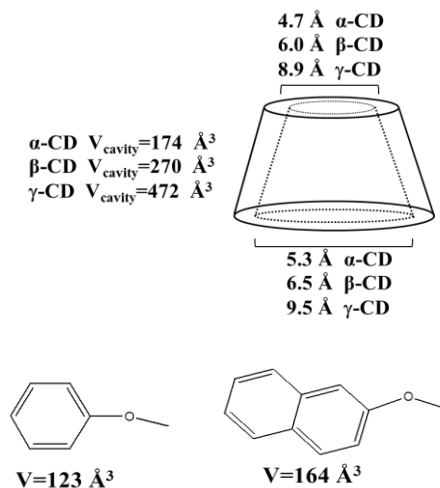

Fig. 7.-Formation of the inclusion complexes

work of Lyon et al. [29] supported this hypothesis. These authors investigated the formation of inclusion complexes between the bolaform surfactants $[(CH_3)_3N(CH_2)_nN(CH_3)_3]Br_2$ ($n=8$, 10, 12) and $((CH_3)_2EtN(CH_2)_{10}NEt(CH_3)_2)Br_2$, and α-CD. They found that the replacement of one methyl by an ethyl in each of the end groups on the $((CH_3)_3N(CH_2)_{10}N(CH_3)_3)^{2+}$ surfactant results in a strong decrease in the equilibrium binding constant. Replacements of two or all of the methyls by ethyls prevent the formation of the inclusion complexes even after prolonged heating.

The geometries of the aromatic substituents were optimized with a RHF wavefunction using 6-81g(d) basis set with the Gaussian 09 suit of programs [30] and their volumes were calculated. As is shown in Figure 8, the bulk of the two aromatic substituents permits the insertion of the hydrophobic tail into the host cavity of either α-, β- or γ-CD to form the inclusion complexes. Figure 7 shows that two possible inclusion complexes could be formed due to the truncated cone shape of the CD molecule. Only in the case of the α-CD:Phenoxy12

system, the ROESY spectrum suggests that the surfactant is preferentially oriented with the aromatic moiety located close to the narrower rim of the cyclodextrin. The experimental data would give information about the average equilibrium binding constant.

Fig. 8.- Some structural information about the host molecules and the two aromatic substituents.

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 [31]. Tables 2 and 3 show that the equilibrium binding constants follow the trend $K_1(\alpha\text{-CD})>K_1(\beta\text{-CD})>>K_1(\gamma\text{-CD})$. These observations can be explained by considering the volume of the cyclodextrin cavity (α-CD(V=174 Å^3 [32]), β-CD (V=270 Å^3 [32]) and γ-CD(V=472 Å^3 [32]), and taking into account that the smaller the cavity is, the stronger the surfactant-CD interactions will be [10, 33-36]. Due to enthalpy-entropy compensation, release of conformational strain and exclusion of cavity-bound high-energy water do not usually play an important role in the complex formation. Van der Waals interactions and hydrophobic interactions constitute the major driving forces for cyclodextrin complexation, together with electrostatic interactions and hydrogen bonding. This is in agreement with the no substantial effects of the substituents

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on K_1. One can see that the incorporation of a phenoxy group, C_6H_5-O-, at the end of the dodecyl chain does not significantly affect the binding of the surfactant molecules to the three CDs investigated. On the other hand, the presence of a naphthoxy group, $C_{10}H_7$-O-, makes the association of the surfactant to the α-CD somewhat stronger, whereas the association to the β-CD is made a little weaker. The binding of Naphthoxy12 to γ-CD also seems to be weaker, although the large experimental errors do not permit to reach any conclusion. This makes clear that the hydrocarbon chain length is the key structural surfactant feature determining the stability of the inclusion complexes investigated, which can be taken as evidence of the importance of the hydrophobic interactions contribution to the binding [10, 31]. A similar result was found by other authors in the study of inclusion complexes formed between anionic, cationic and non-ionic surfactant homologs and cyclodextrins [10, 37, 38]. The presence of the aromatic rings at the end of the hydrophobic tail does not substantially affect K_1, however, it **does influence** the location of the host and the guest in the inclusion complexes. The observed NOE interactions between the aromatic protons and the CD protons indicate that the aromatic rings are partially inserted within the host cavity, with the macrocycle preferentially located at the end of the hydrocarbon tail of the surfactant, in contrast with the structure of the inclusion complexes formed with DTEAB. It was also found than in the case of the phenoxy substituent, the pattern of intermolecular NOEs observed suggests a specific orientation of the surfactant in the inclusion complex formed with α-CD, with the aromatic moiety located close to the narrower rim of the cyclodextrin.

4. Conclusions

In the study of the complexation between cyclodextrins and surfactants the influence of several factors in the stability of the host-guest complexes has been investigated. The effects on the formation of the inclusion complexes of changing the size of the host cavity [10, 33-36, 39], the hydrophobic chain length of the surfactant [10, 37, 38], the nature of the

surfactant head group [10, 39, 40], and the number of hydrophobic chains and head groups of the surfactants [10, 41-44] have been examined. Nonetheless, to the authors´ knowledge, the influence of incorporating a functional group at the end of the hydrophobic surfactant chain on the formation of cyclodextrin-surfactant complexes has not been studied. With the goal of investigating this issue, in this work the binding of cationic surfactants with a dodecyl hydrocarbon chain, a triethylammonium head group and aromatic substituents incorporated at the end of the surfactant tail to α-, β-, and γ-cyclodextrins has been studied by conductivity and ^{1}H NMR measurements. A 1:1 stoichiometry was found for all the cyclodextrin-surfactant systems. The stability of the inclusion complexes increases when the size of the host cavity augments, as is observed for surfactants with no functional groups present in their hydrophobic tails. From the comparison of the equilibrium binding constants obtained for dodecyltriethylammonium bromide, DTEAB, to those estimated for the surfactants with the aromatic substituents, it was found that the substituents studied do not substantially affect the equilibrium binding constant. This result shows that the main factor controlling the stability of the complexes are the hydrophobic interactions, the length of the hydrocarbon chain being the main structural feature determining K_1. Nonetheless, the intercalation of the aromatic rings at the end of the hydrocarbon tail **does influence** the location of the host and the guest in the inclusion complexes. ROESY spectra show that the cyclodextrins are preferentially located at the end of the surfactant hydrophobic chain, with the aromatic rings partially inserted within the host cavity. A different structure to that found for DTEAB. Besides, the pattern of intermolecular NOEs observed for the α-CD-Naphthoxy12 system suggests a specific orientation, with the aromatic moiety located close to the narrower rim of the cyclodextrin. That is, the structure of the inclusion complex could be tuned by changing the nature of the substituent.

The control of the stability and structure of the inclusion complexes by intercalating new substituents in the hydrophobic tail is worth further investigation. In order to do so, new surfactants need to be prepared. The peaks corresponding to the protons of the substituents have to appear in a region of the ^{1}H NMR spectrum which would permit a good observation of the chemical shifts caused by the cyclodextrin-surfactant interactions. Besides, a difficult compromise between the substituent nature/size and the cmc of the surfactant in aqueous solution has to be reached. On one hand the inclusion complexes have to form, but on the other hand the experimental errors associated to the equilibrium constants determination should be lowered. Good candidates would be adamantane, pyridinium or imidazolinium derivatives.

The results in this work provide new physical insights into the topic of surfactant:cyclodextrins interactions, which are important in relation to the wide range of applications of both CDs and surfactants. It has been shown that cyclodextrins are efficient decompacting agents of DNA-cationic surfactants complexes [45-49] on account on the stronger and more specific surfactant:cyclodextrin hydrophobic interactions. The reversibility of the DNA compaction process is of importance since DNA compaction and decompaction are required for successful gene delivery [50].

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Figure captions

Figure 1.- Concentration dependence of ^{1}H NMR spectrum of Phenoxy12, in D$_2$O, on surfactant concentration. a) [Phenoxy12]=2.00x10^{-3} M; b) [Phenoxy12]= 0.010M. T=303 K.

Figure 2.- ROESY spectra of D$_2$O solutions containing [Phenoxy12]=2.05×10^{-3} M and [CD]=2.00×10^{-3} M at 303 K. a) α-CD; b)β-CD; c)γ-CD.

Figure 3.-Job´s plots at 303 K. a)DTEAB:α-CD; b)Phenoxy12:γ-CD; c)Naphthoxy12:β-CD.

Figure 4.-Dependence of ΔΛ$_{obs}$ on the total cyclodextrin concentration for the surfactants investigated at 303 K. Solid lines show the fitting of the experimental data by using eq. 3.

Figure 5.- ^{1}H NMR spectra of Phenoxy12:β-CD solutions in D$_2$O at 303 K, with [Phenoxy12]=2.05x10^{-3} M. a) [β-CD]=0 M; b) [β-CD]= 4.0x10^{-4} M; c) [β-CD]=2.0x10^{-3} M; d) [β-CD]=4 x10^{-3} M;   More β-CD concentrations were investigated but the spectra are not included in the figure for the sake of clarity. T=303 K.

Figure 6.- Dependence of the chemical shift Δδ$_{obs}$=δ$_{obs}$-δ$_S$ on total β-cyclodextrin concentration for selected protons of the surfactants. Solid lines are the best fit to eq. 14.

Figure 7.-Formation of the inclusion complexes

Figure 8.- Some structural information about the host molecules and the two aromatic substituents.

Tables

Table 1.-Critical micellar concentration, cmc, micellar ionization degree, α, and Gibbs energy of micellization, ΔG^o_M, for the cationic surfactants studied in this work, at 303 K.

Surfactant	Cmc/mM	α	ΔG^o_M/kJ mol^{-1}
DTEAB[a]	14.3±0.4	0.35±0.02	-34.3±1.8
Phenoxy12[b]	3.7±0.2	0.40±0.03	-38.8±1.7
Naphthoxy12[b]	0.641±0.015	0.43±0.03	-45.0±1.9

[a]Ref. 11; [b]This work.

Table 2.- Values of equilibrium binding constant, K_1, estimated from the fittings of the observed molar conductance variations of the aqueous surfactant solutions upon increasing the total CD concentration, by using eq. 3. T= 303 K.

Surfactant:CD	K_1 (M^{-1})
DTEAB:α-CD	$(2.4\pm0.5) \times 10^4$
DTEAB:β-CD	$(1.6\pm0.4)\times 10^4$
DTEAB:γ-CD	$(3.8\pm0.3)\times 10^2$
Phenoxy12:α-CD	$(2.2\pm0.5)\times 10^4$
Phenoxy12:β-CD	$(1.3\pm0.2)\times 10^4$
Phenoxy12:γ-CD	$(6.9\pm0.5)\times 10^2$
Naphthoxy12-α-CD	$(2.9\pm0.7)\times 10^4$
Naphthoxy12-β-CD	$(8.2\pm0.8)\times 10^3$
Naphthoxy12-γ-CD	$(4.0\pm2.2)\times 10^2$

Table 3.- Values of equilibrium binding constant, K_1, estimated from the fittings of the observed chemical shift variations of surfactant protons upon increasing the total CD concentration, by using eq. 14. T= 303 K.

Surfactant:CD	[Surfactant$_T$](M)	K_1 (M^{-1})
DTEAB:β-CD	1.95×10^{-3}	$(1.6\pm0.5) \times 10^4$
Phenoxy12:β-CD	2.05×10^{-3}	$(1.4\pm0.4)\times 10^4$

HOST-GUEST INTERACTIONS BETWEEN CYCLODEXTRINS AND SURFACTANTS WITH FUNCTIONAL GROUPS AT THE END OF THE HYDROPHOBIC TAIL

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Preparation of dodecyltriethylammonium bromide, DTEAB

The DTEAB was prepared in a previous work (ref.11) following the method of Guo et al. (J. Polym. Sci. A 2009, 47, 434-449). Briefly, stoichiometric amounts of 1-bromododecane and trietylamine were heated, under reflux, in acetone for 20 h at 75ºC. The crude product was recrystallized 5 times from acetone and washed with ether. The product was obtained as a white solid (26.7%). The purity of DTEAB was checked by NMR measurements and mass spectrometry.

Experimental procedures for triethyl(1-phenoxydodecyl)ammonium bromide, Phenoxy12 and triethyl(2-naphthoxydodecyl)ammonium bromide, Naphthoxy12.

General techniques. The characterization of the compound was performed by its spectral data. ^{1}H and ^{13}C-NMR spectra were obtained for solutions in D_2O on a Bruker Avance III 500 MHz spectrometer (500.2 MHz for ^{1}H) equipped with a 5 mm TCI cryoprobe operating at 303 K. All ^{1}H NMR chemical shifts are referenced to the residual HDO signal set to 4.71 ppm; J values are given in Hz and δ in ppm. The NMR spectra for all compounds were performed in CITIUS (Research General Service for the University of Seville). The completion of the reactions were monitored by TLC (silica gel HF254 (Merck) hexane and DCM:MeOH=3:1) with detection by UV light and charring with Pancaldi. Elemental analysis of the surfactant was also carried out.

12-Bromo-1-phenoxydodecane (1)

A solution of 1,12-dibromo-dodecane (1g, 3.05 mmoles) and sodium phenolate (0.71g, 6.12 mmol) in dry acetone (70 mL), was stirred under Ar and heated at 62 °C for 30 min and then concentrated to dryness at reduced pressure. The residue was dissolved in dichloromethane and extracted successively with water (4x15 mL). The organic phase was dried with Na_2SO_4 and concentrated to dryness under reduced pressure. The residue was purified using column chromatography with silica gel and hexane. Product **1** was obtained as a white amorphous solid (0.3 g, 29%).

Triethyl(1-phenoxydodecyl)ammonium bromide (2), Phenoxy12

A solution of 12-bromo-1-phenoxydodecane (0.246g, 0.79 mmol) and triethylamine (2.5mL, 17.9 mmol) in acetonitrile (19 mL), was stirred under Ar and heated at 90 °C for 1 day. The progress of the reaction was controlled by TLC (DCM:MeOH=3:1). The reaction mixture was then concentrated to dryness at reduced pressure. Subsequently, 10 ml of hexane was added and the mixture was stirred for 15 min and then filtered under vacuum (this

procedure was repeated three times). Product **2** was obtained as a white amorphous solid (0.24 g, 75%).

^{1}H RMN (500 MHz, D$_2$O): δ(ppm)=7.45 (t, 2H, Ph), 7.15-7.07 (m, 3H, Ph), 4.16 (t, 2H, Ph-O-C$\underline{H}_2$-(CH$_2$)$_{11}$), 3.36-3.26 (m, 6H, N$^+$(C$\underline{H}_2$)$_3$(CH$_3$)$_3$), 3.21-3.13 (m, 2H, C$\underline{H}_2$-N$^+$(CH$_2$)$_3$(CH$_3$)$_3$), 1.88-1.79 (m, 2H, Ph-O-CH$_2$-C$\underline{H}_2$), 1.76-1.66(m, 2H, C$\underline{H}_2$-CH$_2$-N$^+$(CH$_2$)$_3$(CH$_3$)$_3$), 1.56-1.47 (m, 2H, Ph-O-(CH$_2$)$_2$-C$\underline{H}_2$), 1.47-1.34 (m, 14H, (C$\underline{H}_2$)$_7$), 1.31 (t, 9H, ^3J = 7 Hz, N$^+$(CH$_2$)$_3$(C$\underline{H}_3$)$_3$).

^{13}C RMN (75.4 MHz, CDCl$_3$): δ (ppm) = 157.1, 129.24, 127.65, 123.63, 118.7, 106.7 (Ph), 67.9 (Ph-O-$\underline{C}$H$_2$-(CH$_2$)$_{11}$), 56.5 ($\underline{C}$H$_2$-N$^+$(CH$_2$)$_3$(CH$_3$)$_3$), 52.7 (N$^+$($\underline{C}$H$_2$)$_3$(CH$_3$)$_3$), 29.6, 26.4, (Ph-O-CH$_2$-($\underline{C}$H$_2$)$_9$), 21.3(C$\underline{H}_2$-CH$_2$-N$^+$(CH$_2$)$_3$(CH$_3$)$_3$, N$^+$(CH$_2$)$_3$(C$\underline{H}_3$)$_3$)

12-Bromo-1-naphthoxydodecane (3)

A solution of 1,12-dibromo-dodecane (2g, 6.10 mmoles) and sodium naphtholate (2.03g, 12.19 mmol) in dry acetone (140 mL), was stirred under Ar and heated at 65 °C for 30 min and then concentrated to dryness at reduced pressure. The residue was purified using column chromatography with silica gel and cyclohexane. Product **1** was obtained as a white amorphous solid (2.11 g, 52.26%).

### Triethyl(2-naphthoxydodecyl)ammonium bromide (4), Naphthoxy12

A solution of 12-bromo-1-naphthoxydodecane (0.640g, 1.64 mmol) and triethylamine (2.73mL, 19.62 mmol) in acetonitrile (50 mL), was stirred under Ar and heated at 90 °C for 1 day. The progress of the reaction was controlled by TLC (DCM:MeOH=3:1). The reaction mixture was then concentrated to dryness at reduced pressure. Subsequently, 10 ml of cold cyclohexane was added and the mixture was stirred for 30 min and then filtered under vacuum (this procedure was repeated three times). Product **2** was obtained as a white amorphous solid (0.624 g, 97.43%).

^{1}H NMR (500 MHz, D$_2$O, 303 K): δ(ppm)=7.38 (m, 2H, Naph), 7.05 (m, 1H, Naph), 7.02 (m, 2H, Naph), 4.09 (t, 2H, Naph-O-C$\underline{H}_2$-, 6.5 Hz), 3.23 (q, 6H, N$^+$(C$\underline{H}_2$CH$_3$)$_3$, 7.3 Hz), 3.10 (m, 2H, -C$\underline{H}_2$-N$^+$(CH$_2$CH$_3$)$_3$), 1.76 (m, 2H, Naph-O-CH$_2$-C$\underline{H}_2$-), 1.63 (m, 2H, -C$\underline{H}_2$-CH$_2$-N$^+$-), 1.44 (m, 2H, Naph-O-(CH$_2$)$_2$-C$\underline{H}_2$-), 1.38-1.26 (m, 14H, -(C$\underline{H}_2$)$_7$-(CH$_2$)$_2$-N$^+$-), 1.23 (bt, 9H, -N$^+$(CH$_2$C$\underline{H}_3$)$_3$).

^{13}C NMR (75.4 MHz, CDCl$_3$): δ= 134.72 (C4', C5'and C8'), 129.40-127.72 (C4', C5'and C8'), 126.79-126.41 (C6'), 123.58 (C7'), 119.12 (C1' and C3'), 106.68 (C1'and C3') 68.12 (C8), 57.74 (C3), 53.74 (C2), 29.59-29.25 (C7, C6 and C5), 26.60-26.19 (C6 and C5), 22.23(C4), 8.27 (C1).
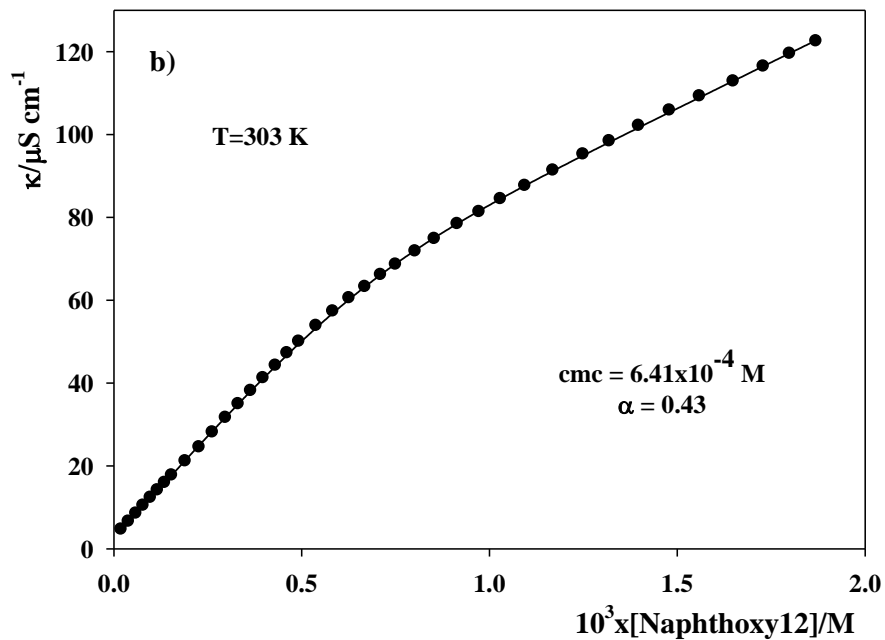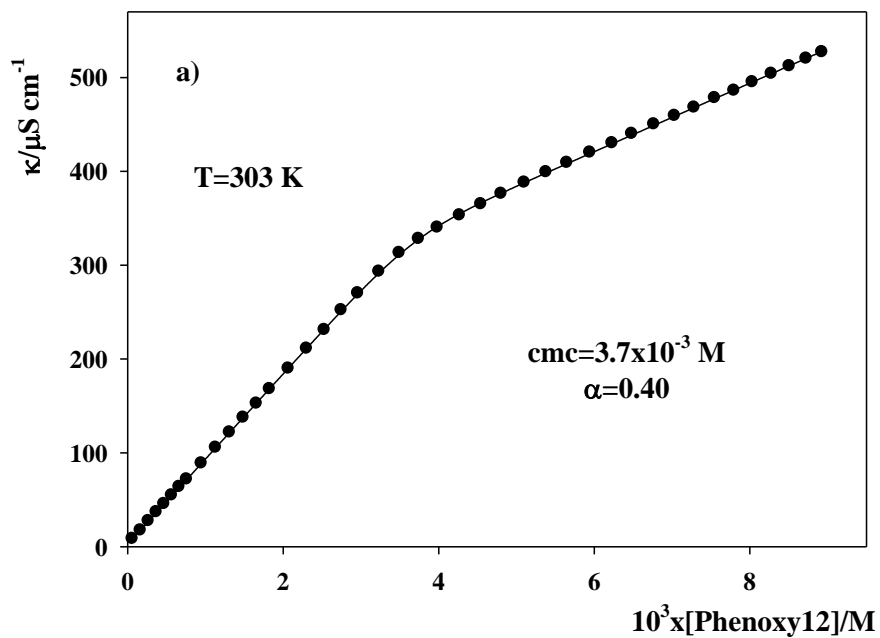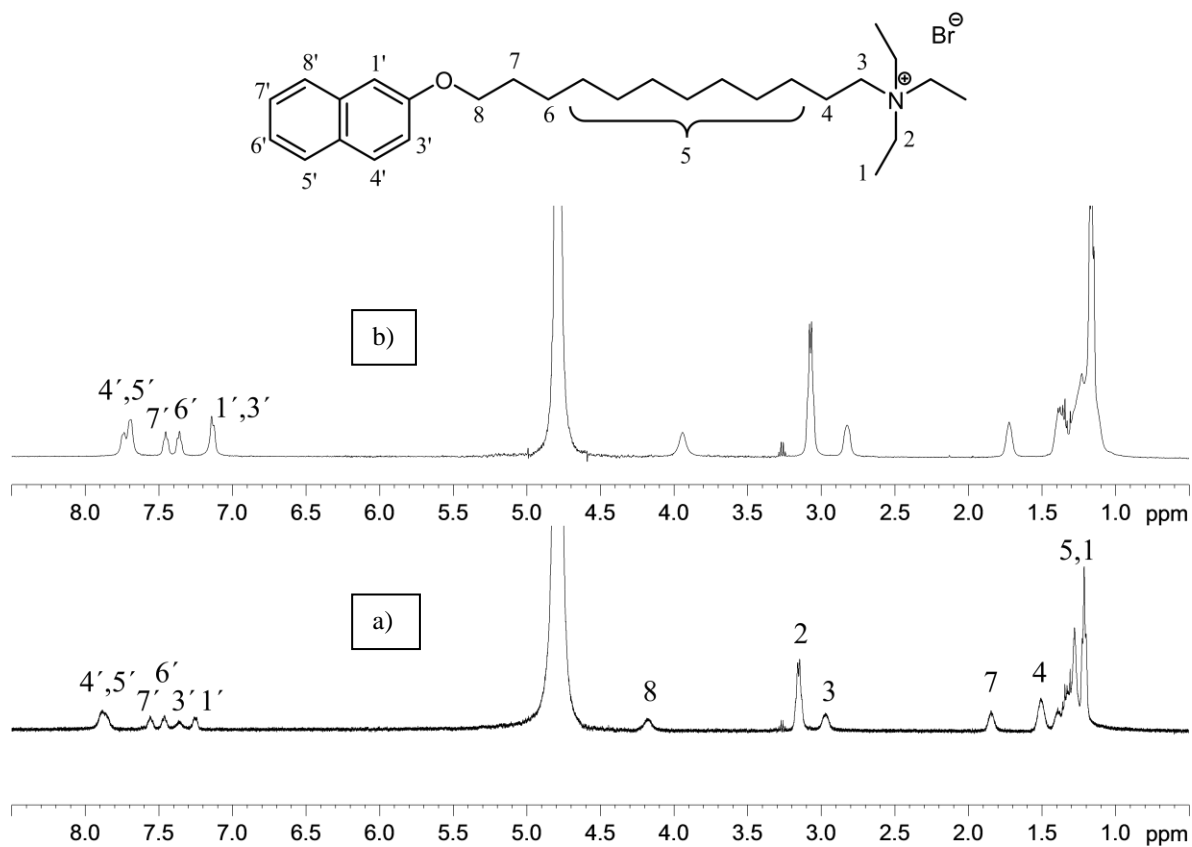
Figure S1.- Dependence of the specific conductivity, $\kappa/\mu S\ cm^{-1}$, on surfactant concentration. a)Phenoxy12; b)Naphthoxy12. T=303 K. The solid lines correspond to the Carpena fittings.
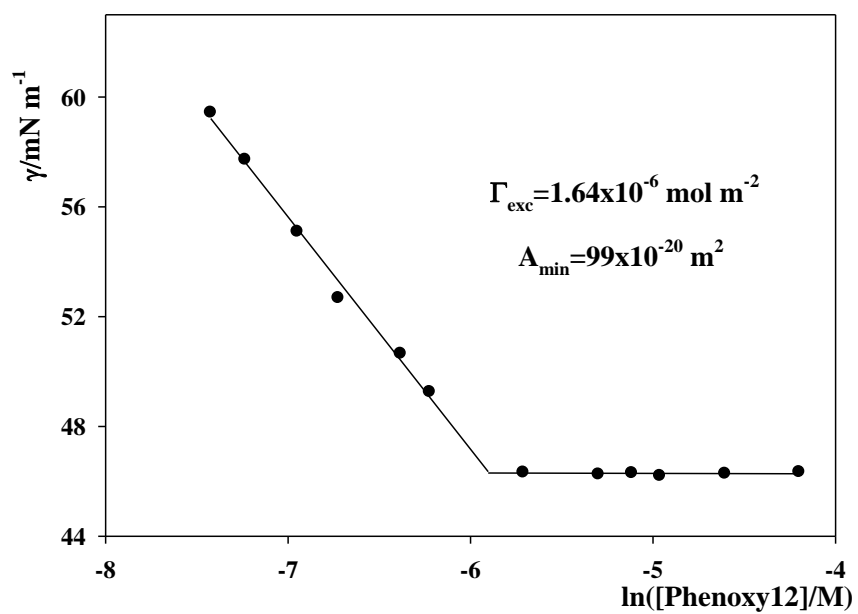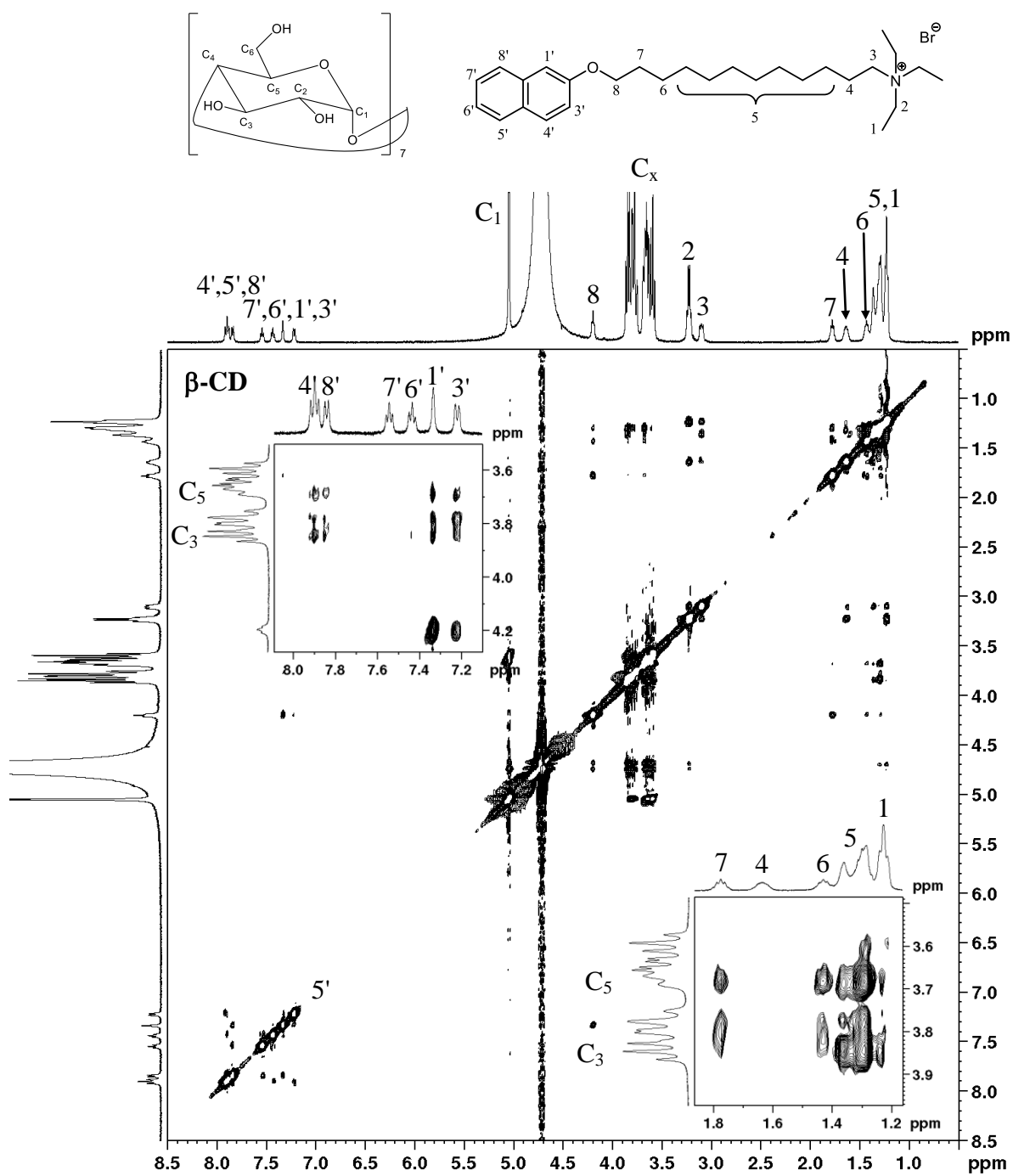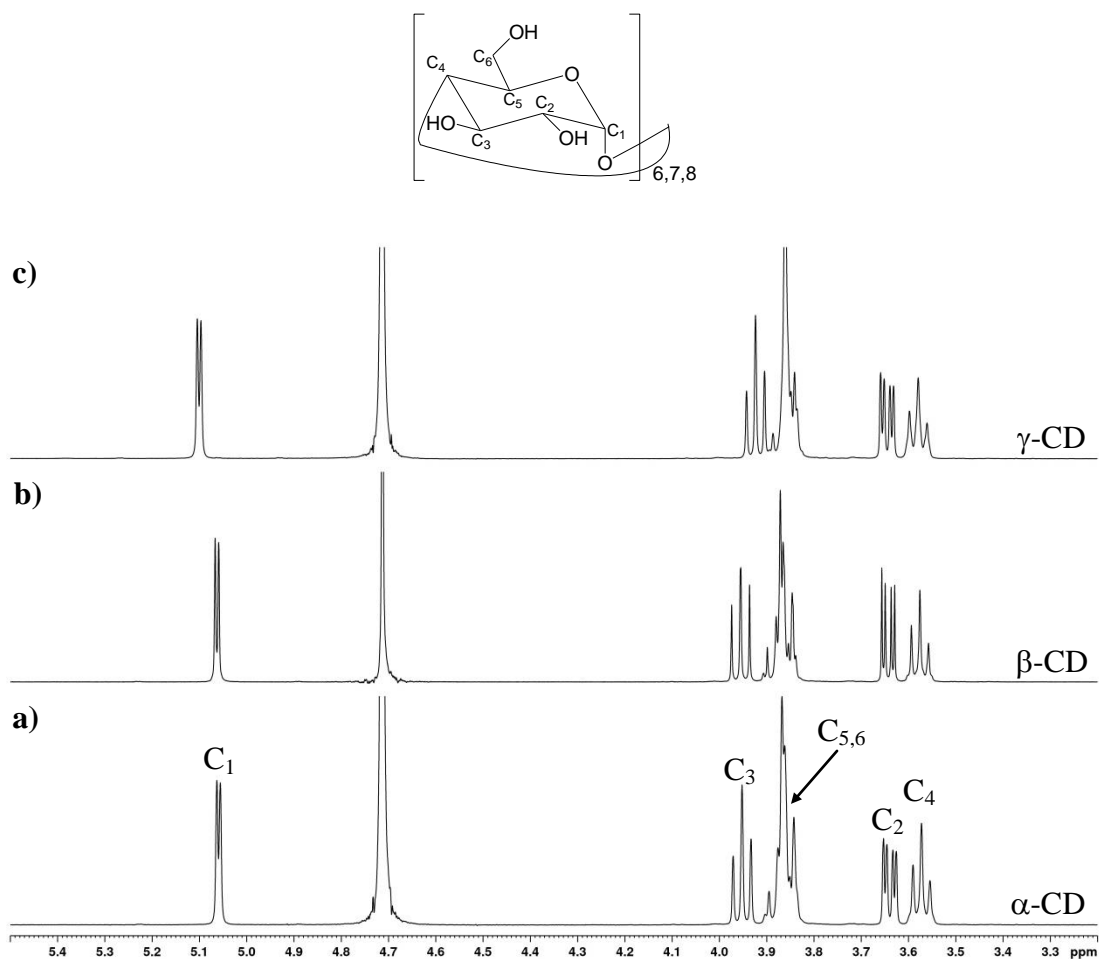
Figure S2.- Dependence of the surface tension, γ, on ln([Phenoxy12). T=303 K.

Figure S3.- Concentration dependence of ^{1}H NMR spectrum of Naphthoxy12, in D_2O, on surfactant concentration. a) [Naphthoxy12]=5.00x10^{-4} M; b) [Naphthoxy12]=1.00x10^{-3} M. T=303 K.

Figure S4.- ROESY spectrum of an aqueous solution containing 5.02×10^{-4} M of Naphthoxy12 and 5.00×10^{-4} M of β-CD. T=303 K.

Figure S5.- ^{1}H NMR spectra of 2.00×10^{-3} M cyclodextrins in D_2O at 303 K. a) α-CD; b) β-CD; c) γ-CD.