Journal of Colloid and Interface Science 354 (2011) 725–732

Contents lists available at ScienceDirect

Journal of Colloid and Interface Science

www.elsevier.com/locate/jcis

The effect of the head-group spacer length of 12-*s*-12 gemini surfactants in the host–guest association with β-cyclodextrin

R.A. Carvalho [a], H.A. Correia [a,b], A.J.M. Valente [b,*], O. Söderman [c], M. Nilsson [c]

[a] Department of Life Sciences and Center of Neurosciences, University of Coimbra, 3001-401 Coimbra, Portugal
[b] Department of Chemistry, University of Coimbra, 3004-535 Coimbra, Portugal
[c] Physical Chemistry 1, Lund University, P.O. Box 124, SE 22100 Lund, Sweden

ARTICLE INFO

Article history:
Received 9 September 2010
Accepted 11 November 2010
Available online 16 November 2010

Keywords:
Gemini surfactants
Cyclodextrins
^{1}H NMR spectroscopy
Supramolecular structures
Binding constants

ABSTRACT

NMR spectroscopy has been used to study and characterize the interactions in solution between β-CD and alkyl-α,ω-bis(dodecyldimethyl ammonium bromide) gemini surfactants with the following head-group spacer lengths: 2, 4, 6, 8, and 10. The application of the method of continuous variation gives as a result that 1:1 and 2:1 (β-cyclodextrin-gemini) complexes are formed; the association stoichiometry is dependent on the spacer chain length, varying from 1.5 (for $s = 2$) to 1.8 (for $s = 10$). Assuming a two-step mechanism, the binding constants have been computed. In general, the overall binding constant slightly increases with an increase of the number of methylene groups in the spacer. The ^{1}H NMR spectra of the N-$(CH_3)_2$ groups in β-cyclodextrin/gemini mixed solutions are split into two peaks for 12-10-12, suggesting that the gemini spacer can thread the β-cyclodextrin so that the latter is positioned between the gemini head-groups. Inspection of the ROESY spectra allowed the establishment of several spatial proximities between the protons from the β-CD and the gemini and for a spacer length of 10, the data indeed indicate that complexes are formed with the CD molecule positioned between the two charged head groups with the spacer passing through the CD molecule.

1. Introduction

Cyclodextrins (CDs) are torus-shaped oligosaccharides [1,2] with the primary hydroxyl groups at the narrow side and the secondary hydroxyl groups at the wide side of the glucose units, making it hydrophilic as a whole. However, the interior surface of the truncated cone, normally considered as the site of the guest molecules, is hydrophobic. These hydrophobic cavities provide a potential for the formation of inclusion complexes with a large variety of organic, and inorganic compounds [3–5].

CDs are often used in is pharmaceutics, where CDs are used to entrap a wide variety of drugs [6,7] into their hydrophobic cavity under noncovalent interactions, in both solution and solid state. This inclusion improves the drug chemical stability, membrane permeability, taste, apparent aqueous solubility, dissolution rate and bioavailability [2].

The mode of binding consists of inclusion of the less polar part of the guest within the cavity while its hydrophilic part remains solvent-exposed. An important prerequisite for preparation and use of formulations based on CD inclusion complexes is an understanding of the interaction mechanisms between the guest molecule and the macrocycle during complexation. Structural information, such as the stoichiometry and the geometry of the complex, and also thermodynamic parameters, such as binding constants, are necessary to clarify the complexation mechanism and the driving forces governing the interaction. In this study the inclusion complex between gemini surfactants with different spacer lengths (but constant tail lengths) and β-CD have been studied.

Gemini (G) surfactants are made up of two amphiphilic moieties connected at the level of the head group [8–10]. Gemini surfactants typically have low critical micelle concentrations (cmc) [11]. The properties of gemini surfactants are influenced by the length of the spacer group [12], hydrophobic chain length and dissymmetry [13]. For a fixed length of both hydrophobic tails the cmc increases with spacer length until it reaches a maximum value, and then the value decreases [12,14,15]. Aqueous solutions of some dimeric cationic surfactant with short spacers show a very high viscosity at relative low concentrations and/or display viscoelasticity and shear induced viscoelasticity [16]. They also have a high surface activity, better foaming properties, and the ability to make organic compounds soluble in water [17], which make them useful for applications in different fields such as in waste water treatment [18] and in the context of DNA compaction [19].

Inclusion complexes between CD (alfa, beta and gamma) and surfactants in aqueous solution have been studied and characterized by a wide battery of techniques: conductometry [20,21],

---

* Corresponding author. Fax: +351 239 827703.
E-mail address: avalente@ci.uc.pt (A.J.M. Valente).

0021-9797/$ - see front matter © 2010 Elsevier Inc. All rights reserved.
doi:10.1016/j.jcis.2010.11.024

measurement of speed of sound [22,23], isothermal calorimetry [24], chemical shift NMR [25], self-diffusion NMR [5,26,27], fluorescence [28], surfactant selective electrode [29], surface tension [30], and kinetic methods [31]. However, relatively few studies deal with gemini surfactants and their interactions with cyclodextrins.

Abrahmsén-Alami et al. [32,33] studied the interaction between hydroxypropenyl-β-cyclodextrin and a heterogemini surfactant (NIHG750) with self-diffusion NMR, chemical shift and surface tension and found that both the hydrophobic (CH_2-groups) and hydrophilic part (EO-groups) appeared to interact. Guerrero-Martinez et al. [34] studied the interaction between the gemini (dodecyl dimethylammonium)diethyl ether dibromide and β-CD with chemical shift NMR, self-diffusion NMR and two-dimensional Rotating frame Overhauser Enhancement SpectroscopY (ROESY). They found that the stoichiometry (β-CD:gemini) was 2:1 at high β-CD concentrations with the first equilibrium constant ($K_1 = (8 \pm 5) \times 10^3\ M^{-1}$) lower than the second ($K_2 = (2.8 \pm 0.9) \times 10^4\ M^{-1}$), indicating a co-operative process. Based on the ROESY data they proposed structures for the 1:1 and 2:1 β-CD-gemini surfactant complexes.

Recently, we have reported the association of the gemini, alkyl-α,ω-bis(dodecyldimethyl ammonium bromide), 12-*s*-12 (*s* = 2, 8 and 10) with β-CD by using electrical conductance [21]. The highest stoichiometry was shown to be 2:1 (CD:G) for the three gemini spacer lengths investigated. The values of the first and second binding constants, K_1 and K_2, respectively, increased with increasing spacer length. For geminis with a spacer $s = 2$ and 8, $K_1 > K_2$, whilst at $s = 10$, the binding constants were the same. The non co-operativity for $s = 2$ and 8 was justified by the hydrophobic interactions between the hydrocarbon tails on the gemini and steric constraints and electrostatic effects, whilst for 12-10-12, it was suggested that the two tails are independent of each other.

In the present work, the binding stoichiometry and the binding constants for β-CD:12-*s*-12 geminis ($2 \leqslant s \leqslant 10$) aqueous systems, at 25 °C, have been determined. The analysis of the chemical shifts of CDs, when varying the G concentrations, shows that 1:1 and 2:1 (β-CD:G) complexes are formed. The role of the experimental method in the computation of *K* values, as well as on the assessment of the interaction mechanism, is evaluated.

On account of the dependence of the binding constants on the spacer length, we decided to further characterize the interaction mechanism between gemini (12-*s*-12) surfactants and β-CD by ^1H NMR and ROESY which allowed the establishment of spatial proximities between 12-*s*-12 hydrogen's of the guest and the β-CD protons.

2. Experimental

2.1. Chemicals and solutions

β-cyclodextrin (CD) was purchased from Aldrich with a water content of 13.1 wt.% (molar ratio of H_2O to CD is 17:2) as determined from thermal analysis.

Gemini surfactants: ethyl-α,ω-bis(dodecyldimethylammonium bromide) (12-2-12), butyl-α,ω-bis(dodecyldimethylammonium bromide) (12-4-12), hexyl-α,ω-bis(dodecyldimethylammonium bromide) (12-6-12), octyl-α,ω-bis(dodecyldimethylammonium bromide) (12-8-12), and decyl-α,ω-bis(dodecyldimethylammonium bromide) (12-10-12) were kindly provided by Prof. Jason Keiper (Emory University, Atlanta, GA) and were used without further purification.

The NMR samples were prepared using D_2O (99.8%), supplied by Dr. Glaser AG (Basel, Switzerland), as solvent, and containing 3-(trimethylsilyl)propionic-2,2,3,3-d4 acid sodium salt (TSP), purchased from Sigma, at tracer concentration (below 3 μM). Solutions were prepared by weighing the proper amount of solutes (CD and surfactant) and solvent. The gemini concentrations were kept below the cmc, as reported in Refs. [21,34], in order to avoid micellization effects on the chemical shifts of the gemini resonances [35].

2.2. ^1H NMR studies

^1H NMR spectra for different [β-CD]/G ratios, *r*, were recorded at 25.0 (±0.1) °C on a Varian 500 MHz spectrometer using a 5 mm NMR probe. Spectra were obtained with residual solvent (HOD) presaturation and the experimental parameters were: 24 k data points covering a spectral width of 8 kHz were acquired, the radiofrequency excitation pulse was 45° and the scan repetition time was 15 s to allow for full relaxation. The resonance at 0 ppm, due to $Si{-}(CH_3)_3$ signal from trimethylsilyl propionate-D4 (TSP) was used as internal reference.

2.3. ROESY experiments

Two-dimensional ROESY experiments were acquired in the phase sensitive mode with residual solvent (HOD) presaturation using the same spectrometer and NMR probe as described above. Each spectrum consisted of a matrix of 2048 (F2) by 1024 (F1) points covering a spectral width of 4000 Hz in each dimension. Spectra were obtained on samples of β-CD:12-*s*-12 systems at different concentration ratios, using spin-lock mixing periods of 300 ms. Before Fourier transformation, the matrix was zero filled to 4096 (F2) by 2048 (F1) and Gaussian apodization functions were applied in both dimensions. Cross-peak volumes were measured using the "ll2d" subroutine of the Varian NMR software.

3. Results and discussion

3.1. ^1H NMR spectra of gemini cationic surfactants and β-cyclodextrin

Although the assignment of ^1H NMR for gemini cationic surfactants and cyclodextrins has been reported in the literature [34,36,37], for convenience we will briefly discuss the ^1H NMR spectra of solutions of 12-10-12 (0.604 mM) and β-CD (0.247 mM). The symbols used in the proton assignment of these two compounds are defined in Fig. 1. For 12-10-12 in D_2O solution, an upfield well-defined triplet at $\delta H_\omega = 0.890$ ppm is assigned to the $-CH_3$ groups of the hydrophobic chains. Proceeding downfield, three different broad resonances appear in the 1.3–1.4 ppm chemical shifts range: $\delta H_\lambda = 1.300$ ppm (br, 28H $(CH_2)_{14}$), $\delta H_{\lambda'} = 1.228$ ppm (4H $(CH_2)_2$) and $\delta H_\gamma = 1.372$ ppm (br, 8H $(CH_2)_4$). The β-methylene protons of the hydrophobic tails present a broad resonance at $\delta H_\beta = 1.690$ ppm (br, 4H $(CH_2)_2$). The two methyl groups of each nitrogen (label n in Fig. 1) show a strong singlet at $\delta H_n = 3.074$ ppm (12H $(CH_3)_4$). Further downfield, a broad peak at 3.255 ppm results from the overlapping of α and α′ protons.

The ^1H NMR spectrum of β-CD in D_2O shows a triplet (assigned to the H_4 protons) at $\delta H_4 = 3.573$ ppm (7H $(CH)_7$). The H_2 protons are located at the outside of the cavity but near the wide side and are characterized by a doublet of doublets at $\delta H_2 = 3.637$ ppm (7H $(CH)_7$). The H_1 protons are located between those two (H_4 and H_2) showing a downfield doublet at $\delta H_1 = 5.058$ ppm (7H $(CH)_7$). The H_3 protons are located at the wide side of the cavity, and are less shielded, showing a strong triplet at $\delta H_3 = 3.952$ ppm (7H $(CH)_7$). The H_5 protons are located inside the cavity and overlap with the H_6 protons of the C_6–OH group sitting on the outside of the cavity on the primary face (the narrow side). The H_6 protons split up to $H_{6'}$ and $H_{6''}$ due to the chiral nature of CD [36,38]. The overlapping resonances for the protons of H_5, $H_{6'}$ and $H_{6''}$ are found