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Aggregation Process of a Benzyl Ammonium Chloride: Molecular Dynamics Simulation

Proceso de agregación del surfactante catiónico cloruro de N-dodecil-N,N-dimetil-N-bencilamonio (BC-R12) mediante Simulaciones de Dinámica Molecular

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● Resumen

En el presente trabajo se estudia mediante simulaciones de Dinámica Molecular el proceso de agregación del surfactante catiónico cloruro de N-dodecil-N,N-dimetil-N-bencilamonio (BC-R12). Para este fin, se evaluaron micelas de diferentes tamaños y se compararon con los sistemas análogos donde las moléculas se encuentran distribuidas aleatoriamente, con el objetivo de encontrar el número de agregación de este surfactante. Los resultados obtenidos en las simulaciones sugieren que los agregados pequeños de 6 a 10 moléculas son los más favorecidos. El análisis de las diferentes conformaciones indica una fuerte interacción entre el grupo fenilo y las colas hidrocarbonadas. En una molécula de BC-R12 el grupo fenilo puede interaccionar con su propia cola y con las colas de las moléculas vecinas.

Palabras clave: Dinámica Molecular, cloruro de N-dodecil-N,N-dimetil-N-bencilamonio.

● Abstract

The aggregation process of the cationic surfactant N-dodecyl-N,N-dimethyl-N-benzylammoniumchloride (BC-R12) has been simulated, by the first time, using molecular dynamics. Micelles with different sizes were evaluated and compared with the analogue systems, where the molecules were randomly distributed in water, in order to provide an aggregation number. The results obtained at 5ps, and reconfirmed in simulations of 55 ps in selected systems, evidenced that small aggregates formed by 6-10 molecules are favoured. The analysis of the different conformations indicates a strong interaction between the benzyl group and the hydrocarbons tails. Benzyl group could interact with its own tail ("folds back") and with the neighbouring tails.

Keywords: Molecular Dynamics simulations, N-dodecyl-N,N-dimethyl-N-benzylammonium chloride.

● Introduction

Surfactants are molecules with regions of different polarity. This fact defines their properties and applications. In solution, above certain concentration, the surfactants tend to form micelles. The size and shape of these micelles depend on the structure and chemical composition of the surfactant molecules, as

well as the concentration in solution. Different tools -like NMR methods, light scattering and theoretical simulations- have been used to determine the characteristics of surfactant micelles [1-5]. The aggregation number of surfactants (N_{agg}), that is the number of molecules forming the micelle, is an important parameter for the determination of other thermodynamic magnitudes like the equilibrium

constant, enthalpy and hence the Gibbs free energy of the micelle formation process.

Benzalkonium chloride (BC) is a cationic surfactant that has been widely used in the pharmaceutical industry. BC is a mixture of three surfactants, which differ in the length of the aliphatic chain: N-dodecyl-N,N-dimethyl-N-benzylammonium chloride (BC-R12), N-tetradecyl-N,N-dimethyl-N-benzylammonium chloride (BC-R14), and N-hexadecyl-N,N-dimethyl-N-benzylammonium chloride (BC-R16). BC-R12 is the main component in the mixture. The critical micellar concentration (cmc) of BC-R12 is 8,19 mmol L⁻¹ /6/.

Some authors have studied the micellization process of cationic surfactants based on quaternary ammonium chlorides /1, 3-5, 7-9/. Molecular Dynamics simulations (MD) of the n-decyltrimethylammonium chloride micelles in water suggested an aggregation number of 30 /10/. However, it is known that the Nagg of the alkyl ammonium chlorides is bigger than the reported for phenyl ammonium chlorides. On the other hand, static and dynamic light scattering studies reported the Nagg for some of the last ones.

They estimated an aggregation number of 10 for BC-R12 /3/. Also, some NMR studies suggest that the molecule geometry changes when BC-R12 passes from monomer to micelle /11/. In the micelle, it seems to be that the molecule does not remain linear, which should be taken into account to estimate the micelle dimensions.

In the present paper we have simulated by the first time, using molecular dynamics, the self aggregation process of BC-R12 molecules in water in order to know the size of the aggregates, as well as the nature of the interactions present in the system. Although the initial self aggregation process of surfactants takes place at very short time scale, of the order of nanoseconds, the equilibrium is achieved between 10-6 s and 1s. This time scale is too long for an atomistic MD simulation.

Taking into account this fact we decided to model two different states of the process: the initial one, where the surfactant molecules are randomly oriented in water; and the final one, where the spherical micelle is surrounded by water molecules. The number

of BC-R12 molecules was changed in order to explore micelles of different sizes and to determine the most stable one. Although some MD simulations of surfactant aggregation have been reported in the literature /12-14/, even for alkyl ammonium chlorides /5, 10/, we have not found any simulation of this process for the phenyl ammonium chlorides.

The details of the simulations are presented in the next section and the obtained results are discussed in the following section.

● Methodology

Interatomic Potentials

Simulations were performed with DL_POLY molecular dynamics simulation package version 2.0 /15/ and the force field used to model the interaction present in BC-R12 molecules was the consistent force field 91 (cff91) /16/. This force field is based in the Class II force field (CFF), and it was developed in order to describe organic and biological molecules. That is why it was chosen to reproduce the interactions of surfactant molecules used in the present work.

The total energy of the system was calculated as the sum of the intramolecular and intermolecular interactions. For the surfactant, the intramolecular interaction included the harmonic bond stretching ($\epsilon_{stretch}$), the bond angle bending (ϵ_{bend}) and, in order to keep the planarity in the aromatic ring, we used a dihedral angle term ($\epsilon_{torsion}$).

$$\epsilon_{intra} = \sum \epsilon_{stretch} + \sum \epsilon_{bend} + \sum \epsilon_{torsion} \quad (1)$$

The forms of the terms of the equation (1) are given in equations (2)-(4). The bond stretching term is given by:

$$\epsilon_{stretch} = U(r) = \frac{1}{2} k_r (r - r_o)^2 \quad (2)$$

where k_r is the bond stretching force constant, r_o is the equilibrium bond length and r is the actual bond length. The bond bending term is given by:

$$\epsilon_{stretch} = U(r) = \frac{1}{2} k_r (r - r_o)^2 \quad (3)$$

where k_ϕ is the bending force constant, ϕ_0 is the equilibrium bond angle and ϕ is the actual bond angle. The torsion term used for the atoms of the benzyl groups is represented by:

$$\varepsilon_{\text{torsion}} = U(\phi) = A[1 + \cos(m\phi - \delta)] \quad (4)$$

where A is the torsional force constant, ϕ is the dihedral angle, m is an integer number and δ is an angular shift.

The charges of the atoms of the BC-R12 molecules were obtained from AM1 semiempirical calculations for this molecule reported in a previous work /17/. Water molecules are modeled using the potentials reported by de Leeuw and Parker /18/.

The other intermolecular interactions were calculated as the sum of the van der Waals interactions, modeled by a Lennard-Jones potential (), and coulombic interactions ($\varepsilon_{\text{coul.}}$) between all atoms:

$$\varepsilon_{\text{inter}} = \sum \varepsilon_{\text{vdw}} + \sum \varepsilon_{\text{coul.}} \quad (5)$$

Molecular Dynamics Details

The first step was the geometry optimization of BC-R12 molecule used in the simulations. This was performed at MP2 level using the 6/31G** basis set implemented in GAUSSIAN98 program /19/. This is the surfactant starting geometry used to build the different initial distributions.

Two different initial configurations were explored. In the first one, the surfactant molecules and 500 water molecules were randomly distributed in a cubic box. In the second one, the BC-R12 molecules were placed in a spherical micelle at the center of the cubic box surrounded by the same number of water molecules.

We have modelled the random distribution of surfactants and water in order to see the development of the early stages of the aggregation process. And it was modelled the spherical micelle to detect any deformation of the ideal sphere. In this case, the polar head groups are located on the micelle surface and are in direct contact with the water molecules; the hydrocarbon tails are directed to the hydrophobic core. In order to know the size of the most stable micelle different numbers of BC-R12 molecules were tested. The number of surfactant molecules tested was 6, 16, 22, 33 and 46. The edge length of the cubic boxes was approximately 110 Å.

The simulations were done in the NVE ensemble at 300 K. The time step was 0.1 fs. An initial equilibration run of 0.3 ps were performed and the total simulation time was 5ps. Larger simulations of 55 ps were done for both distributions of 22 BC-R12. Periodic boundary conditions were applied in the three spatial directions.

The Verlet algorithm was used to integrate the Newton's motion equations. A cut off radius (r_{cut}) of 6 Å was used for short-range interactions due to Lennard-Jones potential decay to 0 at distances lower than 5 Å. The Ewald summations were used to handle the long-range coulombic interactions.

• Results and Discussion

The average total energies reported at 5 ps for all simulated systems are presented in Table 1. As can be seen, the micelle distributions have lower energies than the random distributions. This result is coherent with the known fact that surfactant molecules in solution aggregate to form micelles. The detailed results of both the two initial distributions are discussed below.

TABLE 1. AVERAGE TOTAL INTERNAL ENERGY (x105 kcal mol⁻¹) AT 5PS

Number of BC-R12 molecules	6	16	22	33	46
Random distributions	-1,412 6	-1,402 3	-1,394 9	-1,379 5	-1,373 4
Micelle distributions	-1,418 0	-1,403 6	-1,406 2	-1,396 5	-1,373 5

Random Distributions

In the random distributions, when the BC-R12 molecules number increase on the simulation box, the molecules begins to aggregate.

At the beginning of the simulation, six surfactant molecules randomly distributed with 500 waters are at distances larger than 20 Å. At 5 ps we do not observe any cluster formation in this system, because they need more time to diffuse or a bigger number of surfactant molecules to form aggregates. When the number of BC-R12 increases to 16, some molecules are aggregated in small clusters formed by 2 and 3 molecules. This fact was not observed in the system of 22 BC-R12 as could be expected in a system with more surfactant molecules. In the last one, the molecules are dispersed on the solution, i.e., they do not associate.

In the most concentrated systems, those formed by 33 and 46 BC-R12, it is possible to observe the association of molecules as dimers. These dimers approach one another forming aggregates of 3 and 4 molecules in the 33 BC-R12 system, and up to 4 and

6 molecules in the 46 BC-R12 system. These aggregates lack any well defined organization.

Figure 1 shows the radial distribution function, $g(r)$, of N-N atoms and C5-C5 atoms (the carbon of the terminal methyl group). The main maxima are around 5 and 7 Å, which could be considered as the distances of the molecules in the clusters. In earlier MD simulations of self-assembly process of alkylammonium bromide /14/, the author considered that two molecules belong to the same aggregates if the distances between the neighboring tail atoms are lower than 6.4 Å. In addition, the signals corresponding to $g(r)$ N-N and C5-C5 appear at the same distance, in particular for the system of 33 BC-R12. It indicates that molecules, in the final configuration, are oriented parallel to each other.

The driving forces responsible of the diffusion of BC-R12 in the aqueous solutions to form small clusters are the electrostatic interactions. The van der Waals (vdW) interactions begin to play a role when molecules are as near as in the clusters. When the distances are bigger than 6 Å, the vdW potential tends to zero.

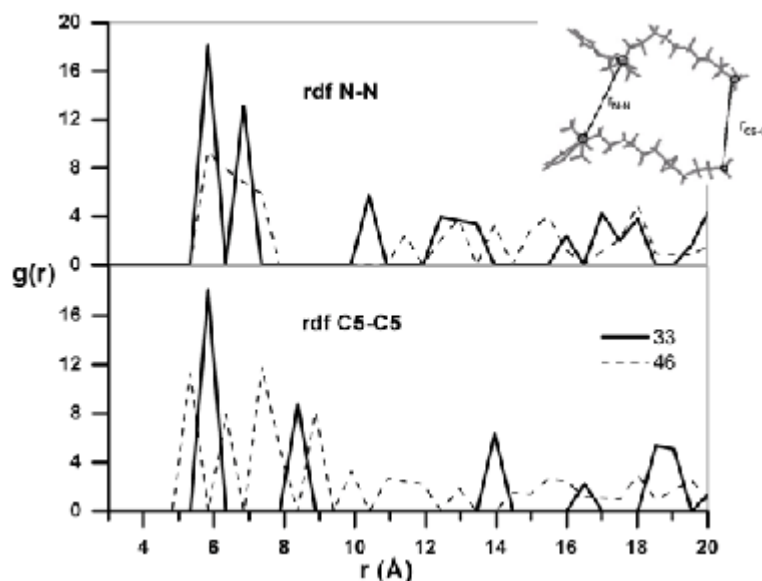


Fig. 1 Radial distribution functions N-N and C5-C5 at 5 ps in the 33 and 46 BC-R12 random distributions

Micelle Distributions

The most stable micelle is the smallest, formed by 6 BC-R12 molecules. At 5 ps this micelle keeps the spherical form, only one molecule changed its initial position and migrated to the surface of the sphere. The radius of the micelle was 20 Å and the radius of the hydrophobic core was 10 Å. This result is in good agreement with experimental studies [3], which suggest $N_{agg}=10$ for this surfactant.

For the micelle of 6 BC-R12 we did not observe that water molecules entered the hydrophobic core of the micelle. However, some water molecules interact with the surfactant at distances of the order of the hydrogen bonds. Analyzing the radial distribution function, $g(r)$, between the hydrogens of BC-R12 and the oxygens of water (see figure 2), we observe a maximum at 2.79 Å that corresponds to the interactions with 6 aromatic hydrogens (H1) and with 3 aliphatic hydrogens (H2).

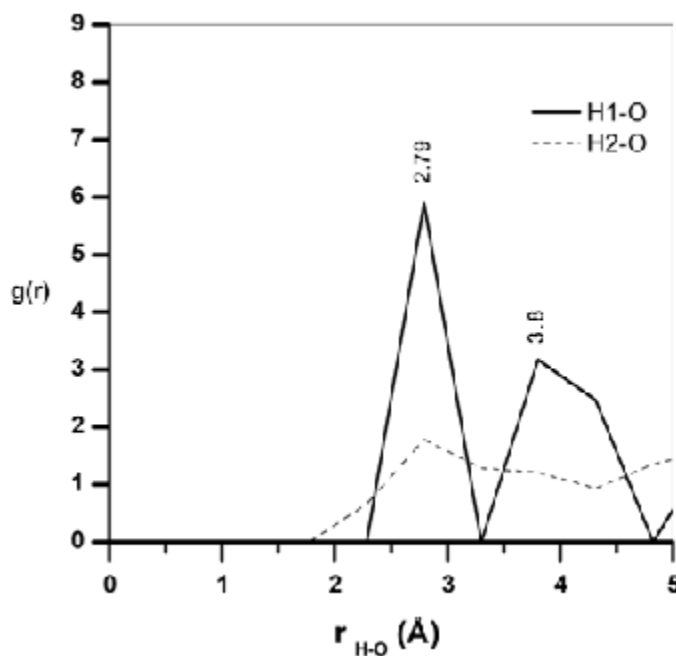


Fig. 2 Radial distribution function HBC-R12 – Owater at micelle of 6 BC-R12.

In the medium size micelles, those formed by 16 and 22 BC-R12, a reorganization process takes place. The surfactant molecules migrate to the surface and form small aggregates. The formation of these aggregates is more evident in the micelle of 22 BC-R12.

Furthermore, in this system strong interaction between the oxygen of water and the hydrogens of BC-R12 could be found (we have found 18 O-H distances smaller than 2.8 Å, 7 with the aromatic hydrogens and 11 with the aliphatic hydrogens). These reasons could be the cause

that the energy of this system is lower than the micelle of 16 BC-R12.

Figure 3 shows the final configuration obtained at 5 ps in the micelle of 22 BC-R12. Water molecules are not included in order to have a more detailed structure of the system. In the final configuration we can define two aggregates, the former one with 8 BC-R12 molecules and another with 4 molecules. In addition, another group of 8 BC-R12 molecules are almost parallel with the polar head oriented to the surface. The other two monomers of BC-R12 are among the clusters.

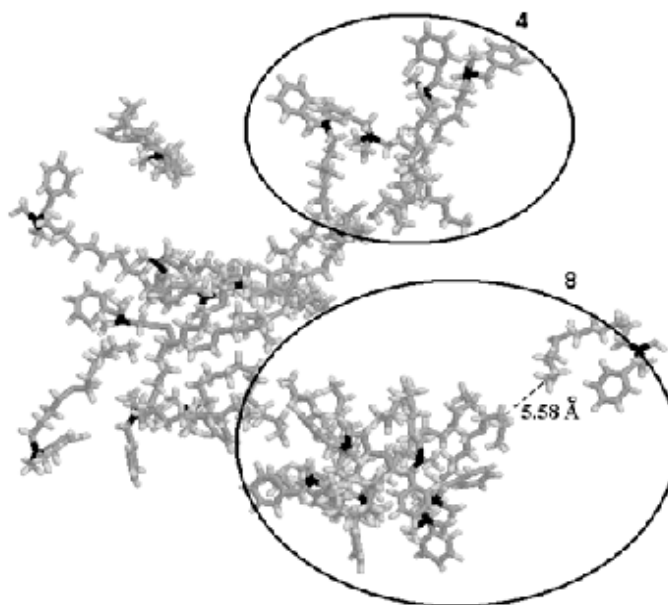


Fig. 3 Micelle of 22 BC-R12 at 5 ps. Water molecules were not included. In the picture the small clusters are marked with circles and the number of monomers is indicated.

In the largest micelles, those formed by 33 and 46 BC-R12, we also observed the migration of molecules to the surface. In the micelle of 33 BC-R12 all molecules could migrate to the surface. However, in the micelle of 46 BC-R12, due to the increase of the number of particles, the motion to the surface is limited.

In the largest micelles, at 5 ps, we could not define the formation of smallest aggregates. This fact also limited the interaction of the surfactant molecules with the water molecules. That is why the energy difference between the random and micelle organization is small. It is important to note that in the system with 46 BC-R12 randomly distributed the surfactant molecule can organize forming aggregates of 4-6 molecules and also it is present a strong interaction with water molecules.

Longer Simulations in the Systems of 22 BC-R12

Longer simulations, of 55 ps, were carried out in the systems formed by 22 BC-R12, random and micelle distributions. We have selected this middle size micelle because at 5ps it has begun to split in

different aggregates. It is interesting to continue the evolution of the fragmentation process in order to know the Nagg of the new aggregates.

The average total energies reported at 55 ps for the systems with 22 molecules of BC-R12 are presented in Table 2. As in the simulation at 5ps, the micelle distribution has lower energy than the random distribution. And the energies obtained at 55ps are lower than the obtained at 5ps for the all systems (Table 1).

In the reorganization of the micelle of 22 BC-R12, the strong water-water interactions self-organize the system. At 55ps, water molecules have penetrated into the micelle and it is split in three clusters, see Figure 4. The biggest is formed by ten molecules, there is another formed by seven molecules and the third has three surfactants. Another two surfactant molecules are isolated and just interact with water molecules. These clusters have diameters of 45, 40 and 30 Å, respectively. The N-N distances of the surfactant molecules in the new aggregates are between 5 and 6.5 Å, see figure 5. This fact supports our previous results, where we suggest that BC-R12 aggregates in small micelles.

TABLE 2. AVERAGE TOTAL INTERNAL ENERGY ($\times 10^5$ kcal mol⁻¹) AT 55PS FOR THE SYSTEMS WITH 22 MOLECULES OF BC-R12

Number of BC-R12 molecules	22
Random distributions	-1,429 7
Micelle distributions	-1,443 0

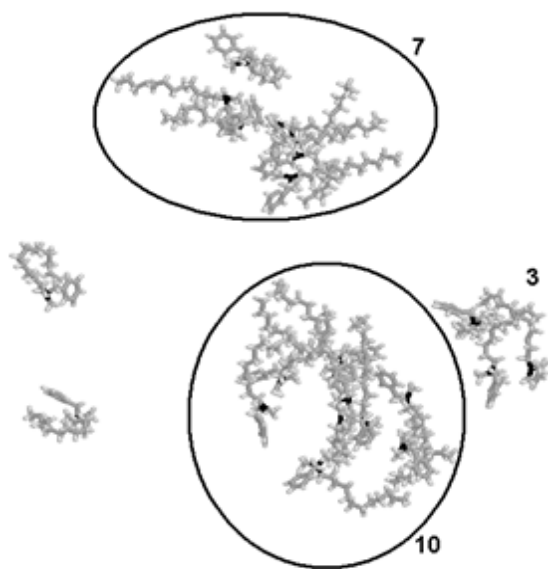


Fig. 4 Micelle of 22 BC-R12 without water at 55ps. As in the previous picture, water molecules were not included.

On the other hand, at 55ps in the random distribution of 22 BC-R12 molecules in water, the molecules just were associated in pairs. Six pairs were found and also one cluster formed by three surfactant molecules. The others seven surfactant molecules only interact with the surrounding water. In the final geometry the surfactants are more separated, which can be seen if we analyze the N-N distance of the neighbor surfactant molecules which are between 5.5 and 7 Å, see figure 5. This fact suggests that the aggregation process is not well observed in this distribution. Simulations in another time scale would be needed in order to observe the formation of the aggregates from the random distribution of this surfactant in water.

Conformations of BC-R12

When the geometry of BC-R12 molecule is optimized using ab-initio calculations, the hydrocarbon tail is extended and the N-C5 distance is 12.5 Å. However, one of the most remarkable findings from our simulation is that the BC-R12 hydrocarbon tail was *folded up*. This fact was observed in both distributions -micelle and random-. The N-C5 distance is shortened down to 5 Å when the molecules fold up, except for the system with 6 BC-R12 molecules, see radial distribution functions N-C5 in figure 6. A similar behavior was previously suggested by proton NMR studies for different cationic surfactants in water /1, 11/.

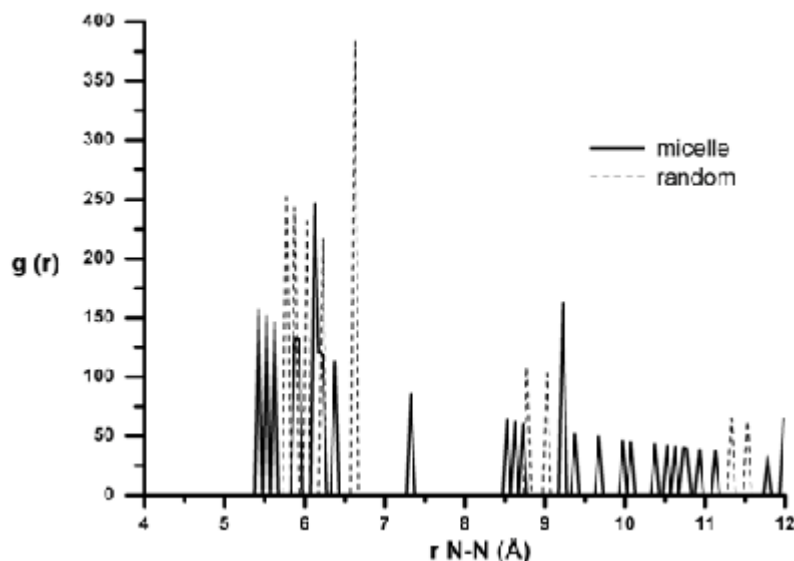


Fig. 5 Radial distribution function N-N in the micelle and random distribution of 22 BC-R12 at 55 ps.

One of the potentially useful products of this study is the N-N distance predicted in our simulation, which we have not found in the literature for BC-R12. It gives rise to the area per surfactant molecule at the micelle. This spacing can be measured using small angle neutron scattering (SANS), and sometimes estimated based on surface tension vs. concentration curves.

The simulations performed here provide useful data that could be corroborated by experimental determinations in the future. The Nagg obtained (6-10) for the micelles is associated to the folding of the benzyl group, which produces an increase in the area of the polar head, i.e. in the distance between surfactant molecules. In the case of a straight cationic surfactant, without the presence of a phenylene substituent in the molecule, the spacing between neighboring surfactants decreases, and the Nagg increases. For example, the value of Nagg for dodecyltrimethylammonium chloride, as determined by light scattering, amounts to 44 /20/ .



Conclusions

We have simulated by molecular dynamics the aggregation process of the BC-R12 cationic surfactant in water. We observed that the micelle distribution is more stable than the random one.

The most stable micelle is the smallest, formed by 6 surfactant molecules. In the middle micelles, like the micelle with Nagg=22, the initial spherical micelle splits in smaller aggregates formed by 7-10 molecules, supported by experimental results. In the clusters, the BC-R12 can be found in different intra- and inter- molecular conformations, where important interactions between the benzyl group and the hydrocarbons tails were observed. Also, the N-N distance between surfactant molecules in the micelle was determined; it could be a useful parameter for future experimental determinations.

The simulations presented in this work have allowed to confirm the preferential existence of small micelles in this type of surfactant, contrary to the reported for alkyl ammonium chlorides.

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