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ORIGINAL PAPER

Interaction of the interleukin 8 protein with a sodium dodecyl sulfate micelle: A computer simulation study

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Abstract Molecular simulations were carried out to study the sodium dodecyl sulfate (SDS) surfactant with the interleukin 8 (IL8) protein as a model to investigate the influence of amphiphilic molecules on proteins. Simulations for an SDS micelle with an IL8 protein show that both aggregates, which were initially separated, eventually approach each other to form a single complex. The results showed that the protein was attached to the SDS micelle by the charged positive amino acids whereas less contacts were observed for the negatively charged amino acids. Structural protein properties, such as amino acid contacts and pair correlation functions were conducted between the micelle and the protein groups and they showed greater interactions between the surfactant headgroups and the positively charged residues in the protein. Moreover, hydrogen bonds were also calculated between both structures and a greater number of bonds among the SDS headgroups and the charged positive amino acids in the protein was found.

Keywords Protein structure · Surfactant structure · Protein–surfactant complex · Protein–surfactant interaction · Molecular dynamics

Introduction

Studies of protein–surfactant systems have been the matter of several investigations for many years not only for their scientific interest but also for their applications in industries such as the food industry, pharmaceutical industry, or detergent industry [1]. Those investigations can reveal new issues about the conformational changes that proteins may undergo as response of the protein–surfactant interaction. Moreover, surfactants can promote protein aggregation depending on their polar groups and sizes [2]; for instance, it has been recognized that cationic surfactants promote protein aggregation whereas anionic surfactants reduced it, i.e., it seems that surfactants could be used to modulate protein conformation and protein properties [1]. On the other hand, due to ionic–hydrophobic interactions, it has been observed that ionic surfactants may denature proteins at low surfactant concentrations whereas no further unfolding occurs at concentrations above the critical micelle concentration (cmc) [3–5].

In order to understand such complex systems, computer simulations have played an important role in the last years and currently it is feasible to conduct studies from a molecular level. For instance, studies of protein conformations in the presence of different surfactants have been conducted where it is possible to observe new trends about protein unfolding and denaturation as a function of surfactant concentration [6–9]; moreover, an increment of small surfactant clusters in the presence of proteins has been observed [10].

In this paper, we study the surfactant–protein interaction of a particular system using a protein related with inflammation. Inflammation is a response of body tissues to harmful stimuli including damaged cells or irritants. Chemokines, in particular, are small proteins produced in cells as a response to inflammatory stimuli and among those proteins interleukin 8 (IL8) is present in several inflammatory disorders. In fact, an inflammatory response could be altered by the inhibition of chemokines mediators [11, 12]. Therefore, studies of chemokines and how they interact with other

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macromolecules could help us to understand such complex problems. For instance their structure and behavior with glycosaminoglycans, which have the ability to bind proteins, have been investigated by experiments [13–15] and by computer simulations [16, 17]. Moreover, the interaction of chemokine proteins with model membranes such as SDS detergent micelles and lipid bilayers have also been studied [18, 19].

In the present work, we study whether surfactant molecules can be used to modify the structure of a chemokine protein or its properties. For this purpose, we work a system composed of sodium dodecyl sulfate surfactants (SDS), which have a sulfate group similar to those of glycosaminoglycans, interacting with an interleukin 8 protein (IL8).

Model

Simulations of molecular dynamics were carried out to study the protein–SDS micelle system. Firstly, simulations were conducted for a SDS micelle where each surfactant molecule was composed of 12 united carbons attached to a headgroup, SO_4. Moreover, the micelle was prepared with 60 SDS molecules (the aggregation number [20, 21]) and it was equilibrated for 50 ns. The SDS simulation parameters were taken from the literature [22].

For the protein, we took the initial structure from the research data bank (PDB 1IL8) using CHARM27 force field. Interleukin IL8 is a chemokine composed of two identical chains, i.e., it is an homodimer protein, however, since we are interested in how the surfactant interacts with the protein, for the purpose of this investigation we used only one chain. The protein was also equilibrated in an independent simulation for 50 ns. Then, the chemokine and the micelle were placed close to each other (see Fig. 1) and the whole system was solvated with 55,867 water molecules using the TIP3P model. The initial separation distance between the SDS micelle and the protein was 50 Å from their center of masses. Simulations with different initial configurations were tested, i.e., different initial orientations between the SDS micelle and the protein, and for all of them it was observed that the protein approached the SDS micelle. Simulations were conducted in the NPT ensemble at a temperature of $T = 300$ K and a pressure $P = 1$ bar. The Parrinello–Rahman barostat was used to maintain the pressure, whereas the velocity rescaling thermostat was used to keep the temperature, this thermostat is essentially a Berendsen thermostat with a stochastic term to keep the correct kinetic energy [23]. Temperature and pressure relaxation time constants of $\tau_T = 0.1$ ps and $\tau_P = 2.0$ ps were used, respectively. The nonbonded interactions were cut off at 10 Å and the long-range electrostatic interactions were handled by the particle mesh Ewald method. Then, simulations were performed for 300 ns after 50-ns equilibration with a timestep of dt = 0.002 ps using GROMACS 4.5.6 software [24]. Calculations were analyzed in blocks of 50 ns each for the last 150 ns, i.e., an average over three blocks were taken for the results.

Results

Structure

As stated above, the initial configuration of the surfactant–protein system consisted of a micelle, of SDS molecules, separated from the protein IL8 (left of Fig. 1). Initially, the alpha helix was the face of the protein close to the SDS micelle and the beta strands were farther (left of Fig. 1). For the first nanoseconds of the simulation, the SDS micelle preserved its spherical shape and both structures remained separated until they eventually approached each other and they gathered together forming a single complex (right of Fig. 1). Once the protein was attached to the micelle, it was observed by calculation of the amino acids distances to the micelle center of mass, that the alpha helix was now farther way than the beta strands suggesting that the protein rotated

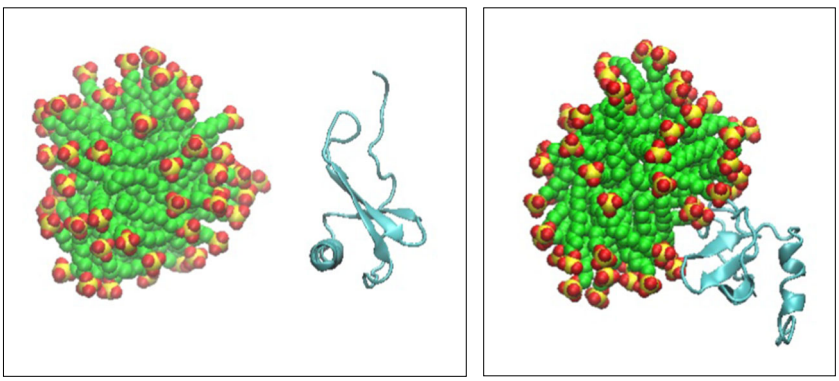

Fig. 1 *Left*: Initial configuration of the surfactant micelle (SDS) - protein (IL8) system. *Right*: Final configuration. SDS headgroups are in *red* and *yellow* and tail groups in *green*

from its original position (right of Fig. 1). It was also seen that all the SDS molecules remained in the micelle, i.e., no penetration of any surfactant into the protein was observed. For this particular configuration, once both structures (SDS micelle and protein) were joined, the whole complex was analyzed. The average distance between the micelle and the protein center of masses was calculated and a value of 2.62 nm was calculated. It is worth to mention that simulations were conducted for a SDS concentration above the critical micelle concentrations and then we did not expect the protein to be unfolded [3]. The structure of the micelle and the protein was also characterized by their moments of inertia and their average radii. From the radius of gyration (Fig. 2), it was possible to estimate the average radius of the SDS micelle and the protein where radii of 2.09 nm and 1.75 nm for the SDS and protein were found, respectively. In fact, those radii did not change significantly from their initial structures, 2.16 nm and 1.58 nm for the SDS and protein, respectively. The eccentricity of both structures were also calculated as $\epsilon = 1 - I_{min}/I_{av}$, where I_{min} is the moment of inertia with minimum magnitude and I_{av} is the average over three moment of inertia. For a sphere, this value should be zero. In our case, the values were $\epsilon = 0.0165$ for the SDS and $\epsilon = 0.1413$ for the IL8, i.e., the SDS micelle presented more spherical-like shape than the IL8 protein. Initially, the eccentricities of both structures were $\epsilon = 0.0179$ and $\epsilon = 0.236$ for the SDS micelle and the IL8 protein, respectively. It seems, from the above calculations, that the SDS micelle did not change significantly its initial shape whereas the protein was just attached to that micelle. When different initial configurations were taken the average distances calculated between the center of masses of the SDS micelle and the protein were similar to that obtained above.

The SDS–protein complex

To know where the protein attaches the SDS micelle, we determined which residues were closer to that micelle by calculating the number of atoms in each amino acid next to the SDS structure. In Fig. 3 (top figure) the ratio of atoms close to the SDS micelle is shown. The ratio is defined as NR_i/TR_i where NR_i is the number of atoms in amino acids "i" which are at a distance less than 2.6 nm (the distance between the micelle and the protein) from the center of mass of the micelle and TR_i is the total number of atoms in all amino acids "i".

From the top of Fig. 3 it was observed that CYS and TYR amino acids were the ones with more atoms next to the SDS micelle, suggesting that the protein was attached to the micelle by the side where the two disulfides are (formed by the CYS amino acids). There were also amino acids which half of their atoms were close to the micelle, such as ALA, GLN, GLY. On the other hand, residues PHE, PRO, and VAL had just few atoms close to the micelle whereas amino acid TRP did not have any atom next to the micelle.

The attraction of the interleukin protein with the SDS micelle was also evaluated by calculating the minimum distance of each residue in the protein to the surfactant headgroups (sulfur atoms of the SDS) and the results were plotted in Fig. 3 (bottom). The largest minimum distances were for amino acids with a small number of atom residue ratios, e.g., PHE, PRO, and VAL with distances greater than 0.5 nm, and for TRP where its minimum distance was $\approx$ 1 nm, suggesting that this amino acid was farther away from the SDS headgroups. On the other hand, residues with large atom ratios (Fig. 3) had smaller minimum distances. It is interesting to note that the positively charged chains of

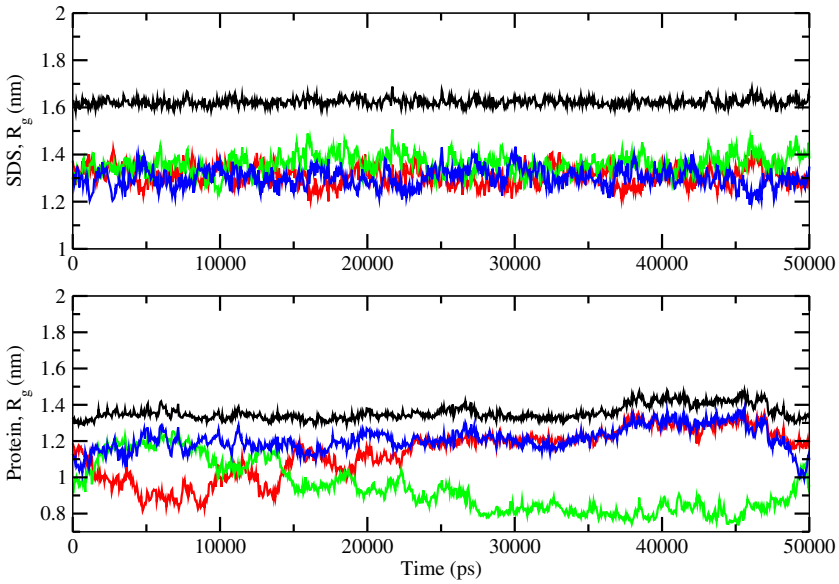

Fig. 2 Radius of gyration for the SDS micelle (*top*) and for the protein (*bottom*) for the last 50 ns. *Black lines* are the total average radius of gyration whereas *red*, *blue*, and *green* are the radius of gyration in the *X*-, *Y*-, and *Z*-axis, respectively

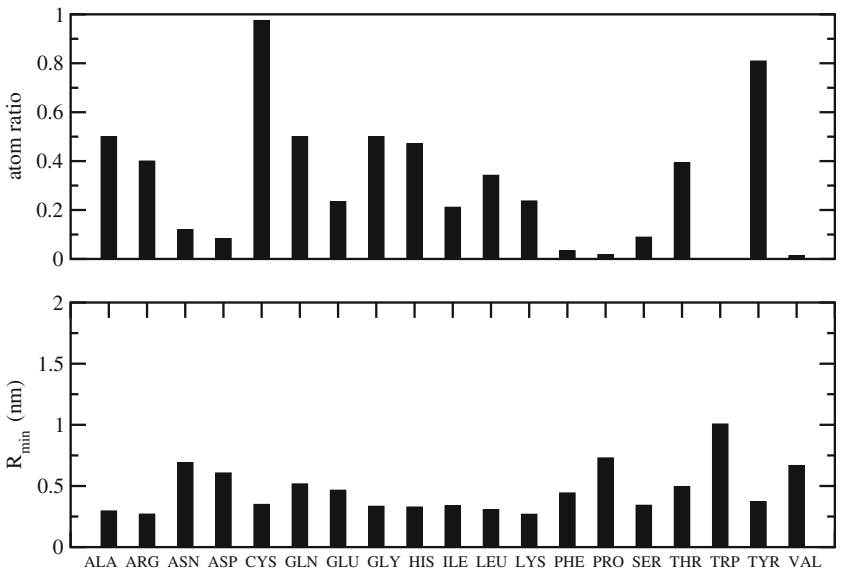

Fig. 3 Ratio of atoms in the different amino acids close to the SDS micelle (*top*). Minimum distance of each amino acid in the IL8 protein with respect to the SDS headgroup (*bottom*)

amino acids ARG, HIS, and LYS were closer to the negative SDS headgroups than the negatively charged chain's amino acids, such as ASP and GLU, which were slightly farther from those headgroups. It is worth mentioning that the average minimum distance of the amino acids with the SDS headgroups did not change significantly over time. On the other hand, once the protein–SDS micelle were joined, the rotational diffusion was calculated from the rotational correlation function [25]. The value of 0.0414 ns^{-1} was obtained, which is of the order of other small proteins [25]. The last results suggested that the protein remained attached to the micelle, by the positive amino acids, and it hardly rotated over it. It is also important to note that the ratio of atoms of the protein amino acids close to the micelle could change for different micelle–protein initial configurations, indicating that the protein approaches the micelle from a different side, however, the minimum residue distances were always for the positively charged amino acids.

SDS–protein interaction

The affinity of the protein with the SDS micelle was also studied in terms of pair distribution functions (g(r)). However, based on the above results, we studied particularly the g(r) of the SDS headgroups with the electrically charged amino acids. Figure 4 shows the functions for the positively charged chain's amino acids, ARG, HIS, and LYS, with the SDS headgroup. In all of those g(r), it was possible

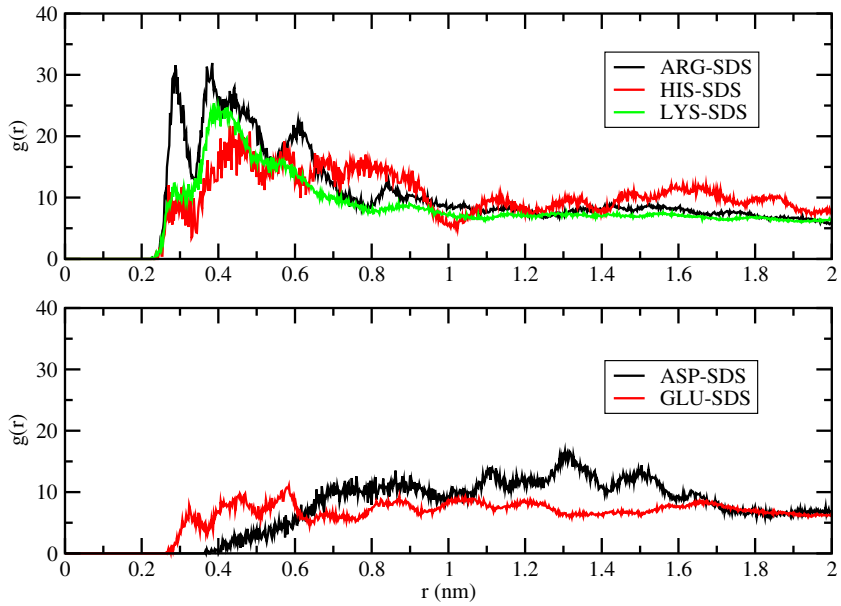

Fig. 4 Pair correlation functions of SDS headgroups with positively charged amino acids (*top*) and with negatively charged amino acids (*bottom*)

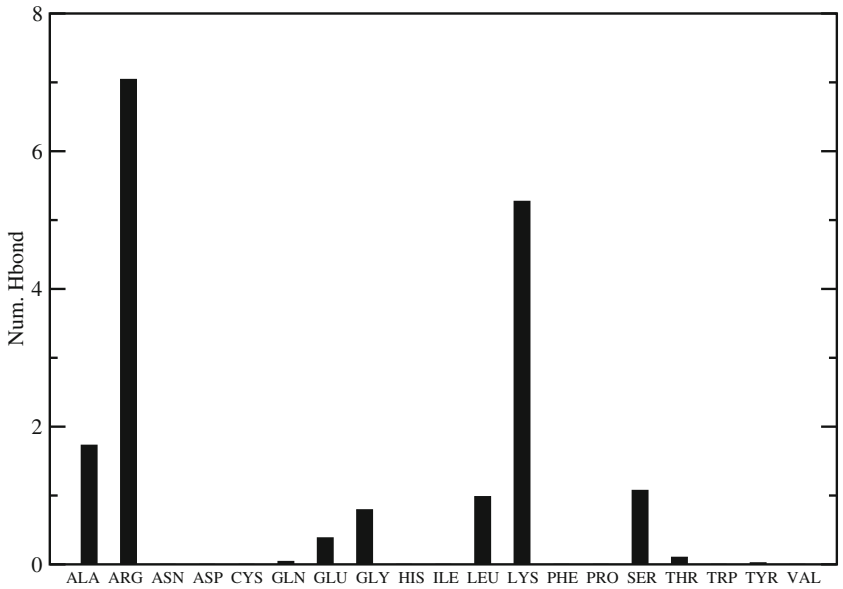

Fig. 5 Number of hbonds between the protein (IL8) and the surfactant (SDS)

to observe several peaks, suggesting a strong structure of those amino acids in the vicinity of the SDS, i.e., first, second, and even third nearest neighbors were depicted from the plots. In fact, the first peaks for all the plots were about ≈ 0.3 nm in agreement with the minimum distance of those residues with the SDS (top of Fig. 4). When the g(r) of the negative amino acids, ASP and GLU, with SDS headgroups were analyzed, different features were noted, for instance those functions did not show any structure (any peaks were observed), i.e., those amino acids did not seem to interact with the SDS headgroups. It is worth mentioning that the system SDS and protein are not homogeneous and nonsymmetric in the simulation box and therefore, the g(r) of the surfactant-amino acids do not go to unity as usual g(r) of bulk systems. From these results, it is noted that there is a strong interaction of the SDS headgroups with the positively charged amino residues as suggested by previous works [5].

It was also possible to know how the protein interacted with the SDS micelle by looking at the hydrogen bonds. In Fig. 5, the average number of hydrogen bonds per amino acid in the IL8 protein with the SDS surfactant are plotted. From that figure, we viewed that most of the amino acids did not form hydrogen bonds with the surfactant molecules, however, there were a few of them that had a large number of bonds, for instance the positively charged amino acids ARG and LYS presented the largest number of hydrogen bonds, however it was interesting to note that the HIS-positive amino acid did not show any hydrogen bonds.

The configurational energy per amino acid was calculated and plotted in Fig. 6 where the energy was divided

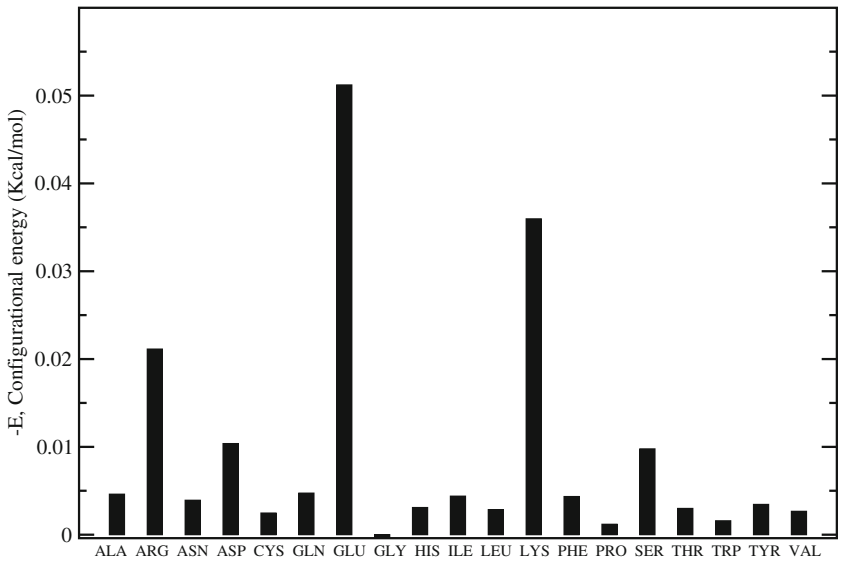

Fig. 6 Configuration energy per each amino acid in the protein

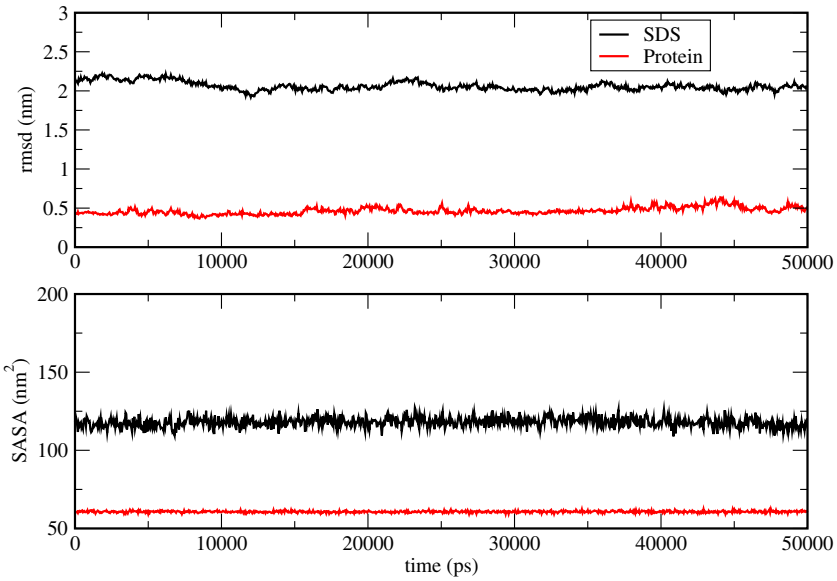

Fig. 7 The root mean square deviation (RMSD) respect to the initial configuration (*top*) and the average solvent accessible surface area (SASA) (*bottom*). The *black lines* are for the surfactant (SDS) and *red* for the protein (IL8)

by the total number of water molecules. Here the energy was calculated with all the contributions of the Lennard–Jones and electrostatic interactions of each residue with the rest of the molecules. From that figure, interesting features were depicted. The configurational energy for the positively charged, ARG and LYS, amino acids was high, however, the highest configurational energy was on the negative amino acid GLU. Intermediate values were also found for the negative amino acid ASP and the polar no charged amino acid SER. The rest of the amino acids, including residue HIS, did not have high configurational energy. Therefore, it is noted that the main configurational energy was obtained for the charged amino acids in the protein, which it seemed to be the ones with high interaction with the SDS micelle.

To know how the final structure of the SDS micelle and the protein deviates from their initial configurations, we calculated the root mean square deviations (RMSD) and solvent accessible surface area (SASA) of both structures. In Fig. 7 the RMSD with respect to the initial configuration is shown where it was observed, because of the small value, that the protein did not change significantly from its initial structure. On the other hand, the RMSD value for the SDS micelle indicated that the micelle was slightly modified from its initial configuration, however, this result can be explained due to the random movements of the SDS tails inside the micelle.

Estimation of the contact area of the micelle–protein complex was calculated by the average solvent accessible surface area (SASA) of the whole complex and the areas of the SDS and IL8 protein before they were attached. The values that we found were 155.0 nm^2, 117.7 nm^2, and 54.7 nm^2 for the total complex, the SDS micelle, and the protein, respectively. Therefore, by calculating the difference in the areas it was possible to evaluate the touching surface between the two structures and it was 17.4 nm^2. Then, from those results, it was estimated that the exposed surface of the protein was nearly 70% (37.3 nm^2), indicating that 30% of the protein surface was interacting with the SDS micelle.

Conclusions

In the present work, we studied the surfactant–protein interaction using sodium dodecyl sulfate surfactant and IL8 protein. Moreover, we focus on the interaction of an spherical SDS micelle with the protein. It was observed that both structures, which were initially separated, eventually became a single complex, i.e., the SDS micelle and the chemokine assembly each other to form a single aggregate. The attachment of the SDS with the protein was produced mainly by the positively charged amino acids, ARG (6, 47), HIS (18), and LYS (3, 11, 15). In fact, those residues also presented higher attractions with the SDS headgroups, as suggested by the pair correlation functions. It was also possible to depict that the N-terminal residue was closer to the SDS micelle than the C-terminal as also observed in previous experiments of a similar system, IL8α with SDS micelles [18]. It was also noted that residue HIS-18 approaches the micelle as observed in a glycosaminoglycan - IL8 system [16]. In those studies, it was found that amino acid ARG-68 binds with the glycosaminoglycan, however, in the present study amino acids ARG-6 and ARG-47 seem to bind better with the micelle.

The smallest attractions between both, SDS and protein, structures were obtained for the negatively charged amino acids, ASP and GLU. Even though the structure of the protein did not change significantly from its initial configuration, it was observed that the presence of the surfactant

reduced the protein's accessible surface area up to 30%, whereas higher configurational energy was detected on the charged amino acids. Therefore, the results suggest that the principal interactions of the SDS micelle with the protein are mainly conducted by the polar headgroups of the surfactant molecules, i.e. the repulsive and attractive coulombic forces are the main interactions between the surfactants and the protein. It is possible that a cationic (or non-ionic) surfactant micelle behaves differently with the same protein and the complex might have a different shape (those simulations are currently conducted). It is also important to note that the simulations were carried out with an SDS micelle already formed, therefore, it was unlikely that the protein suffered any unfolding. However, it is also possible that single surfactant molecules might have different effects on the protein that could modify its structure or its behavior (those studies are also currently conducted).

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