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Journal:	*Physical Chemistry Chemical Physics*
Manuscript ID	CP-ART-07-2018-004505.R1
Article Type:	Paper
Date Submitted by the Author:	12-Sep-2018
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Coarse-Grained Molecular Dynamics Simulation of interface behaviour and self-assembly of CTAB Cationic Surfactant [†]

Sílvia Illa-Tuset[a], David C. Malaspina[a] and Jordi Faraudo[*a]

In this work we study the behaviour at interfaces and the micelle self-assembly of a cationic surfactant (CTAB) by Molecular Dynamics (MD) simulations of coarse-grain models. We consider both the standard (with explicit water) Martini force field and the implicit solvent version of the Martini force field (Dry Martini). First, we study the behaviour of CTAB at a water vacuum/interface, at a water/organic solvent interface and a pre-assembled CTAB micelle using both standard and Dry Martini and all-atomic simulations. Our results indicate that there are significant quantitative differences between the predictions of the two models. Interestingly, implicit solvent simulations with Dry Martini show good quantitative agreement with all-atomic MD simulations, better than explicit solvent Martini MD simulations. The computational efficiency of the Martini and Dry Martini models allowed us to study the self-assembly of CTAB in a large system with many micelles. We observe the self-assembly of CTAB into micelles and also we observe exchange of CTAB molecules between micelles by events such as micelle fusion and fission which are difficult to observe in all-atomic MD simulations due to the involved time and length scales involved. In the studied conditions, both Martini models predict rather different self-assembly behaviour. The standard Martini model predicts a final equilibrium state with spherical micelles with an average size of ≈ 70 CTAB molecules. On the contrary, the Dry Martini model predicts the formation of large tubular micelles with ≈ 330 CTAB molecules. Compared with experiments, standard Martini and Dry Martini underestimate and overestimate respectively the micelle size.

1 Introduction

Surfactants (by definition, surface active agents) are amphiphilic molecules with an hydrophobic tail and hydrophilic headgroup[1]. In aqueous solution and above a certain concentration (the critical micelle concentration, cmc), they self-assemble in a variety of structures (spherical or rod-like micelles, vesicles, ...) depending on thermodynamic conditions and on the presence of other components (such as added salt, other amphiphilic molecules, ...). This self-assembly ability makes surfactants very useful molecules, employed in a variety of applications, ranging form their classical use as detergents to nanotechnology. Despite the large amount of experimental and theoretical studies, a full molecular-level theoretical understanding of surfactant self-assembly is still lacking. Even simple questions such as the actual shape of the micelles (spherical or elongated) are still under dis-

cussion[2,3]. From the practical point of view, it should be very important to be able to predict basic features of micelles features directly from the knowledge of the chemical structure of the surfactant molecule, so one could do a rational design of tailored, for example, new surfactant molecules. In principle, Molecular Dynamics (MD) simulations seem to be a tool of choice to investigate this phenomena at the molecular level. However, the length and time scales needed to study the formation of micelles and their interactions (exchange of surfactants, fusion and rupture of micelles) are still far from those that are feasible in all-atomic MD simulations (AA). This has motivated the use of MD simulations of coarse-grain (CG) model[4]. CG models focus on essential features, averaging over less important atomistic details. In that way, these models provide substantial advantages respect to more detailed, fully atomistic models, both from computational (faster calculations, possibility of reaching longer time scales and larger length scales) and conceptual (easier to interpret) perspectives[4,5]. Combined with advances in computational power, CG models allow the possibility of performing molecular simulations in problems that were previously inaccessible. There are many CG models suitable for simulation of soft matter systems and or-

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ganic molecules (see[4] for a review). Between these models, the Martini CG model[5], is gaining increasing popularity due to its efficiency. The Martini model is based on a building block principle, in which groups of atoms are replaced by a single bead which interacts with other beads with an effective interaction designed to maintain the chemical specificity[5,6]. This model has been employed mostly in simulations of properties of lipid membranes and proteins in membranes[5]. Recent works also employ the Martini model to simulate systems involving diverse surfactants such as anionic SDS micelles[7], zwitterionic poly(ethylene oxide) surfactant micelles[8], the effect of salt in micelles[9]and lipid self-assembled nanoparticles capped with zwitterionic surfactants[10]. Here our interest is to consider an example of a cationic surfactant of a different nature, in particular the popular cationic CTAB surfactant.
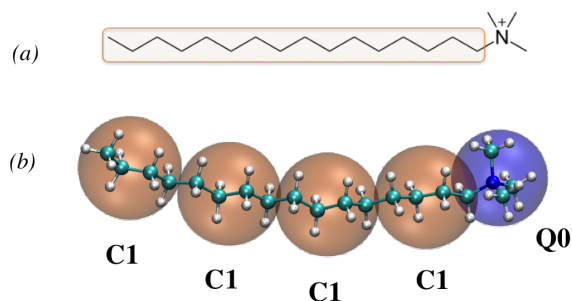

Fig. 1 (a) structural formula of CTA^+ surfactant (its hydrophobic tail is highlighted) (b) Correspondence between the atomistic and coarse-grained (Martini) model of CTA^+. In the atomistic model, all atoms are shown in CPK representation. The coarse-grain beads of the Martini model are shown as large spheres including all atoms subsumed into the same bead. The hydrophobic beads of type C_1 beads are shown in orange and the hydrophilic charged bead of type Q_0 is shown in blue.

The surfactant $[N(CH_3)_3]^+Br^-$ known as CTAB (cetrimonium bromide or cetyltrimethylammonium bromide or hexadecyltrimethylammonium bromide, see Fig.1) is a quaternary ammonium cationic surfactant, which has a bromide anion as counterion. It is used in many commercial products such as hair conditioning products or antiseptic chemicals. Also, we have been employing CTAB as an essential component in novel highly stable mixed vesicles[11,12]. CTAB in water self-assemble in micelles with a cmc of ≈ 0.9 mM at 25°C[3,13]. At the cmc, the micelles have an average aggregation number of $61-66$ molecules[13,14] in absence of added salt. As the concentration of CTAB increases, the aggregation number increases[14,15] and the micelles become more elongated[13,16]. CTAB has also a second cmc concentration (an abrupt increase of aggregation number as a function of concentration) at a concentration of about[3] 240 mmol/kg which corresponds to elongated micelles with an average aggregation number of ≈ 150 surfactants. The nature of this second cmc concentration as well as the actual shape of micelles are still controversial issues[3]. Given the wealth of previous experimental results with this surfactant, the relevance of the molecule and the fact that there are still open questions related to supramolecular organization, the study of the CTAB self-assembly with the Martini forcefield seems particularly pertinent.

In this paper, we will consider both the explicit solvent Martini force field (W-Martini) and the implicit solvent version of the Martini force field ("dry" Martini, D-Martini) for CTAB. First, we compare the predictions of MD simulations of CTAB between explicit and implicit solvent coarse-grain models and also with all-atomic MD simulations when possible. In particular, we consider the predictions for the potential mean force (PMF) of transfer of CTAB in different situations (water/vacuum interface, water/organic solvent interface and pre-formed CTAB micelle in water). Then, we consider MD simulations of both coarse-grain models for the self-assembly of CTAB in a large system with many micelles, so we are able to observe micelle formation, micelle fusion and surfactant exchange which are events that are rarely observed in all-atomic MD simulations.

2 Computational Methods

2.1 All-atomic and coarse-grain models

CTAB is a surfactant with a very simple structure, it has a hydrophilic cationic headgroup and a hydrophobic tail (see Fig.1). In our simulations, we have considered CTAB molecules in water, described at three different levels of approximation: all-atomic, coarse-grain with explicit solvent and coarse-grain in implicit water solvent.

In the case of all-atomic simulations, we have described the CTA^+ surfactant and the Br^- counterion with a force-field compatible with CHARMM[17], employed in our previous work[11]. Water was described using the TIP3P model, as usual in CHARMM force field.

In the case of coarse-grain with explicit solvent simulations, we have considered the Martini model and force field[5,6]. Typically, the model maps 4-5 heavy atoms (C,N,O) and their associated hydrogen atoms to a single bead, although some specific cases (e.g. molecules with rings) require a treatment with higher resolution. In the Martini model, there are four generic types of beads (Q = charged, P =polar, N=nonpolar and C = apolar) and, within each main type, subtypes are distinguished by a letter denoting the hydrogen bonding capabilities (d=donor, a=acceptor, da=both, 0=none) or by numbers indicating the degree of polarity (1 to 5). Each bead has a mass of 72 amu, irrespective of its type.

According to the definition of Martini beads[6], we have mapped the alkylic tails to 4 hydrophobic beads of type C_1 (the most apolar bead type allowed in Martini) and the headgroup to one Q_0 bead, as shown in Fig.1-(b). Using this coarse-grain procedure, we have replaced the atomic model of CTA^+ with 62 atoms by a CG model with only 5 beads. The Br^- counterion is mapped to a Q_a bead, which corresponds in Martini to a hydrated anion.

For water molecules, we have employed the standard Martini CG water model[5]. The complexity of liquid water (with substantial anisotropic hydrogen bonding interactions) cannot be simulated by a single bead. For this reason, the CG model of water is composed by a mixture of P_4 spherical beads and special AF (anti-freezing) beads. One P_4 bead corresponds to 4 water molecules and the number of AF beads is one for each ten P_4 beads. The highly interacting P_4 beads, when let alone, tend to form isotropic crystals at room temperature, which are disrupted

Table 1 Summary of simulations performed in this work. We indicate a code for each kind of system and type of model, number of molecules of each type, total number of atoms or CG beads in each simulation, equilibrium size of the system and temperature.

	System and Model	CTAB molec.	Water molec.	AF molec.	Organic molec.	Total atoms or CG beads	Size	T
S1-A	interface - AA	1	2984	-	-	9015	$22 \text{ nm}^2 \times 20 \text{ nm}$	298 K
S1-M	interface - W-Martini	1	724	70	-	800	$18 \text{ nm}^2 \times 20 \text{ nm}$	298 K
S2-M	interface - W-Martini	1	3574	397	200	5777	$29 \text{ nm}^2 \times 14 \text{ nm}$	303 K
S2-D	interface - D-Martini	1	-	-	200	1806	$20 \text{ nm}^2 \times 15 \text{ nm}$	303 K
S3-A	micelle - AA	72	21176	-	-	68064	$6 \times 13 \times 9 \text{ nm}^3$	298 K
S3-M	micelle - W-Martini	72	14637	1554	-	16723	$12 \times 13 \times 14 \text{ nm}^3$	298 K
S3-D	micelle - D-Martini	72	-	-	-	432	$12.5 \times 13.5 \times 13 \text{ nm}^3$	298 K
S4-M	micelles - W-Martini	1000	115000	13000	-	134000	$24 \times 24 \times 32 \text{ nm}^3$	303 K
S4-D	micelles - D-Martini	1000	-	-	-	6000	$30 \times 30 \times 40 \text{ nm}^3$	303 K

by the AF beads. With this mixture of two beads one obtains a highly interacting liquid at room temperature which resembles water. More details on Martini water model can be found in Refs.[5,6].

In the case of Martini implicit solvent simulations, we employed the recently developed Dry Martini ForceField[18]. In Dry Martini, one considers the same bead types as in standard Martini except for water, which is not included explicitly. The equations for the force field are the same as in standard Martini but the strength of the interactions is modified to take into account the fact that water is considered implicitly[18]. Therefore, the same model of CTAB with the same bead definitions developed for standard Martini (Fig. 1) can be used for Dry Martini without any modification.

2.2 Methodology for MD Simulations

Using the models described in the previous subsection, we have performed a series of Molecular Dynamics (MD) simulations, summarized in Table 1. Simulations S1-A, S1-M, S2-M and S2-D correspond to a comparison of the different models in the case of a single CTAB molecule adsorbed at an interface. We consider a water/vacuum interface for S1-A and S1-M and water/organic solvent interface in the case of S2-M and S2-D. Simulations S3-A, S3-M and S3-D correspond to the simulation of a single CTAB micelle in water using the three models described in the previous subsection. Finally, in simulations S4-M and S4-D we study the self-assembly of many CTAB molecules in multiple micelles using both Martini forcefields. All MD simulations reported in Table 1 were performed using either NAMD[19] or GROMACS[20,21], as indicated in the following subsections. Snapshots and analysis of the results were obtained using VMD program[22] with home-made analysis scripts and for the simulations done with GROMACS we also used the analysis tools available with this package[21].

Interface simulations

In simulations S1-A and S1-M, we study the adsorption of CTAB at a water/vacuum interface considering all-atomic (S1-A) and CG Martini model with explicit water (S1-M). The simulation system consists of a single CTA^+ molecule, its Br^- counterion and a water slab in contact with a large vacuum (see Table 1).

In the case of S2-M and S2-D simulations, we have considered CG models (with explicit and implicit solvent respectively) for the adsorption of a CTAB molecule at a water/organic solvent

interface. The organic solvent considered here is the same as considered in Ref[8] for the comparison of surfactant adsorption in standard and Dry Martini CG models. Each organic solvent molecule is a linear alkyl chain with 9 Martini CG beads of C_1 type. The simulated system consists of a single CTA^+ molecule, its Br^- counterion, an organic solvent slab with 200 organic solvent molecules and a water slab (which has explicit water molecules in the S2-M case and a vacuum in the S2-D case, see Table 1).

It should be noted that this choice of the solvent is unrealistic in the sense that 9 CG Martini beads correspond to 36 carbon atoms, so this chain will correspond to hexatriacontane ($C_{36}H_{74}$) which is solid at room conditions (melting point 348K). Unfortunately, it is not possible to use solvents corresponding to smaller number of Martini CG beads because they do not maintain a stable condensed liquid phase, particularly in the Dry Martini case. It seems that the Martini force field has limitations to model organic solvents, probably because cohesion molecular energies in a real condensed phase are higher than those considered by the simplified Martini and Dry Martini force field. Therefore, we employ here this model for an organic solvent as in previous works[8] only as a technical tool for comparison between standard and Dry Martini models but we should keep in mind that this Martini organic solvent does not really correspond to a model for any real liquid n-alkane.

The MD simulations of these systems (S1-A, S1-M, S2-M and S2-D) were performed using the NAMD 2.12 program[19]. In all cases, we employed a Langevin thermostat to maintain the temperature constant. In simulation S2-M we also employed a Langevin piston to maintain the pressure at 1 atm. The time step was 2 fs in all-atomic MD simulations (S1-A) and 20 fs in CG MD simulations (S1-M, S2-M, S2-D). All other parameters of the simulation were standard for all-atomic or Martini MD simulations with NAMD. The objective of these NPT or NVT simulations was to obtain equilibrated interfaces for subsequent free energy calculations. Due to the small size of the simulated systems, short runs were enough to obtain equilibration. In the case of the water/vacuum interface, we considered 4 ns for S1-A and 2 ns for S1-M. In the case of the water/organic solvent interface, we used longer times due to the presence of the organic solvent. We considered 10 ns for the explicit water case (S2-M) and 7 ns for the implicit solvent case (S2-D).

Starting from the results of these NVT or NPT MD simulations, we have performed free-energy calculations using the Adaptive Biasing Force (ABF) technique as implemented in NAMD[23]. In these biased MD simulations we obtain the free energy profile (the potential of mean force, PMF) predicted by each model for the adsorption of the CTAB molecule at the interfaces and its transfer to the different phases. In these simulations, we selected as a generalized "reaction coordinate" the position of the CTAB headgroup in the direction perpendicular to the interface (z axis) so the origin ($z = 0$) is located at the equilibrium position of the CTAB headgroup at the interface. In the MD-ABF simulations, the CTAB molecule is forced to sample a large interval of values of z, entering into each of the bulk phases. The force constant employed in the ABF calculation was 50 kcal/mol/Å^2. PMF of CTAB in each case was obtained with a 0.1 Å resolution. The simulation time for each MD-ABF run (S1-A, S1-M, S2-M and S2-D), is 28, 400, 100 and 800 ns respectively.

Single Micelle simulations

In this case, we compare simulations for the three models (all-atomic and CG using standard Martini and Dry Martini) in the case of a pre-assembled micelle of CTAB in water. The all-atomic MD simulations (S3-A) correspond simply to an extension (a simple continuation of the MD trajectory) of a previous all-atomic simulation of a single CTAB micelle reported in our previous work[11]. Simulation S3-M corresponds to a coarse-grain MD simulation using the Martini model with explicit water. The initial configuration for this simulation was obtained using VMD[22] to coarse-grain the equilibrated all-atomic configuration of the CTAB micelle obtained in S3-A. CG Water and AF beads were added using the Gromacs solvate tool[21]. The initial configuration for S3-D simulation (Dry Martini force field) was obtained by simply removing all water (P4 and AF beads) from an equilibrated S3-M configuration. MD simulations of all these single micelle models (S3-A, S3-M, S3-D) were performed using the NAMD program[19] version 2.9 (as in the original all-atomic study[11]) using a Langevin thermostat to maintain the temperature at 298K. In S3-A and S3-M simulations we also employ the Langevin piston (NPT simulations) as implemented in NAMD to maintain the pressure at 1 atm. The production run for S3-A, S3-M and S3-D simulations has 65 ns, 47 ns and 1049 ns respectively.

From the simulation results, we have computed the radius of gyration R_g of the micelles and its principal moments of inertia averaged over all configurations from the equilibrated MD trajectory. The diameter D of the micelles was computed from the average radius of gyration R_g with the formula[24]:

$$D = 2\sqrt{\frac{5}{3}}R_g = 2\sqrt{\frac{5}{3}\frac{1}{\sum\limits_{i=1}^{N}m_i}\sum_{i=1}^{N}m_i\left(\vec{r}_i(t) - \vec{r}_{CM}(t)\right)^2}, \quad (1)$$

where $\vec{r}_i$ and m_i are the position and mass of the headgroup of each surfactant, $\vec{r}_{CM}$ is the centre of mass of the N CTAB molecules and the numerical factor accounts for the geometrical relation between the radius of a sphere and the radius of gyration of a sphere with uniform density. The eccentricity of the micelle was

computed from the moments of inertia using the equation[24]:

$$e = 1 - \frac{I_{min}}{I_{av}}, \quad (2)$$

where I_{min} is the minimum principal moment of inertia and I_{av} is the average of the three principal moments of inertia. We have also computed the degree of ionization α of the CTAB molecules in the following way. We have first computed the radial distribution function between the Br$^-$ ions and the CTA$^+$ headgroup[25]. The ions in the first coordination shell of the CTA$^+$ headgroup were considered as adsorbed ions so we can obtain the number of adsorbed ions N_{ads} for all the configurations in the production run. Hence, the degree of ionization α was computed from the average number of adsorbed ions $< N_{ads} >$ (averaged over all the production run) as:

$$\alpha = 1 - \frac{< N_{ads} >}{N_{CTAB}}, \quad (3)$$

where N_{CTAB} is the number of surfactant molecules.

As in the previous subsection, starting from the equilibrium simulations of the micelle systems, we have performed free energy calculations using biased MD simulations with the ABF technique[23]. In these simulations, we selected as a generalized "reaction coordinate" the distance between a selected CTAB headgroup and the centre of the micelle. In the MD-ABF simulations, the selected CTAB molecule is forced to leave the micelle, sampling different values of the radial distance r from the centre of the micelle until it enters completely the water phase, leaving the micelle. The force constant employed in the calculation was 10 kcal/mol/Å^2. PMF of CTAB in each case was obtained with a 0.1 Å resolution. The simulation time for each MD-ABF run (S3-A, S3-M, and S3-D), is 48, 36, and 100 ns respectively.

Simulation of the self-assembly of many micelles

Self-assembly of a large number of CTAB molecules into micelles was studied using both standard and Dry Martini forcefields (simulations S4-M and S4-D). Those MD simulations were performed using GROMACS[21] v5.1.4 and v2018 respectively. The integration time step was 20 fs and short range coulomb interactions were calculated using a reaction field with a cut off of 1.2 nm and 1.1 nm for Dry -Martini and standard Martini respectively. The parameters for the simulations were chosen following the published implementations of both standard[5] and dry[18] Martini force fields. The relative permittivity was $\varepsilon_r = 15$. The non-bonded Lennard-Jones interactions for Dry Martini (S4-D) were shifted at 0.9 nm with a cut off 1.2 nm, while for standard Martini (S4-M) the Lennard-Jones interactions were modified using potential shift verlet option of Gromacs with a cut off of 1.1 nm.

The NPT ensemble was used for S4-M simulation with explicit solvent, using a Nose-Hoover thermostat and the Parrinello-Rahman barostat (pressure P=1 bar). The equilibrium size obtained for the simulation cell is reported in Table 1. With this equilibrium volume, simulation S4-M correspond to a concentration of CTAB about $\approx$ 110 mM. The NVT ensemble was used for implicit solvent simulations (S4-D), using the Bussi-Donadio-Parrinello thermostat[26]. The size of the simulation box for S4-D

(Table 1) was chosen as the same employed in the initial conditions of simulation S4-M. In fact, also the initial coordinates of the CTAB molecules were the same, so both simulations started from the same initial conditions. The values for all parameters not detailed above (decay times for the thermostat and barostats,...) were those listed as the default values suggested when using Martini forcefield on GROMACS. The number of clusters (micelles) was monitored during the simulation using the *clustsize* tool of GROMACS. These simulations were performed until we observed that the number of clusters remained stable during a substantial time (much larger than the initial time of formation of the clusters). The length of the production run was 334 ns for S4-M and 780 ns for S4-D.

3 Results
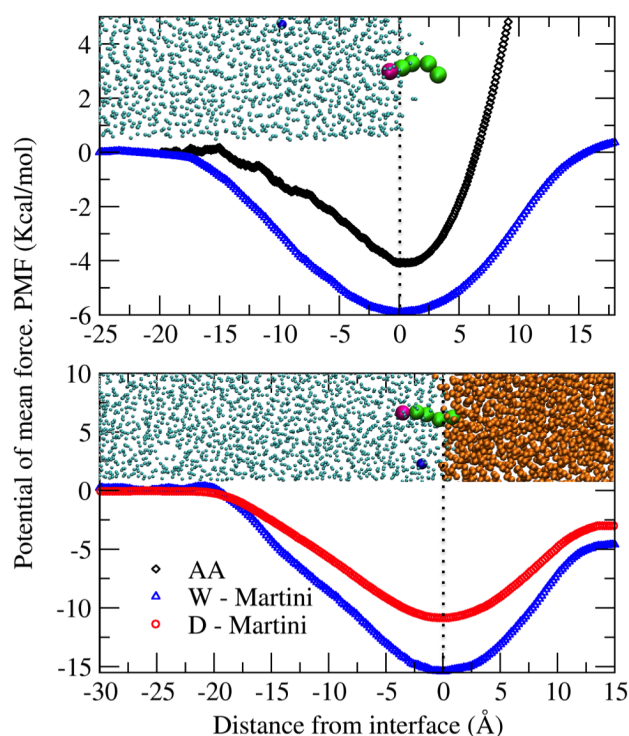
Fig. 2 Potential of mean force (PMF) of a CTA$^+$ surfactant as function of the distance from the interface in two situations: a water slab in contact with vacuum (top panel) and a water slab in contact with a organic solvent slab (bottom panel). The origin of coordinates is taken at the interface, with $z < 0$ corresponding to the water phase and $z > 0$ to the vacuum or organic phase. In both cases we include a representative snapshot with the CTAB molecule emphasized (CTA$^+$ tail and headgroup are shown in green and pink respectively, Br$^-$ is shown in dark-blue). The water slab is always on the left side and the dashed line indicates the interface.

3.1 Interface simulations

We first study the behaviour of a single CTAB amphiphilic molecule at two different interfaces, in order to compare the predictions of the different models (all-atomic and coarse-grain) and different force fields (with implicit or explicit water).

We first consider a water/vacuum interface with a single adsorbed CTAB molecule with two different models: all-atomic and Martini CG with explicit water, which correspond to simulations S1-A and S1-M in Table 1, respectively (obviously, in this case it is not possible to consider implicit solvent simulations). In both cases, the CTA$^+$ molecule adsorbs at the water/vacuum interface (the polar headgroup is solvated with water and the apolar tail is in the vacuum region). The Br$^-$ counterion remains solvated inside the water region.

In Fig.2-(top), we show the PMF associated to the transfer of CTA$^+$ to each phase. In the all-atomic simulation (S1-A), the transfer of the molecule from the interface to the water phase has a cost of about 4 Kcal/mol, whereas in the Martini CG model (S1-M) we obtain a significantly larger value of about 6 Kcal/mol. The most important difference between the two models corresponds to the transfer of the molecule from the interface to the vacuum region. In the case of the coarse-grain (S1-M) simulation, the free energy cost of transfer of the molecule from the interface to vacuum is only slightly larger than the cost of transferring the molecule from the interface to the water phase (see Fig.2(top). However, in the case of the all-atomic simulation (S1-A), this transfer is much more difficult as indicated by the steep increase in the PMF. In the all-atomic simulation, when moving the CTA$^+$ from the interface, the molecule tries to retain the solvation water of its polar headgroup and deforms the interface(this is, in fact, a realistic feature of the all-atomic simulations). This tendency to retain the solvation water is not observed in the S1-M simulation and it is probably due to the simplicity of the Martini water model and the simplified surfactant-water interactions employed in this case. In a second simulation (Fig.2, bottom) we compare the predictions of the CG models with implicit and explicit water for a CTAB molecule at an interface (see Methods section for details). In this case, we consider a water-organic solvent interface, which contains explicitly both phases in the case of the S2-M simulation but only contains explicitly the organic phase in the case of the S2-D simulation (Table 1). In both simulations, the preferred location of the surfactant molecule is with its head group at the interface and the tail immersed in the hydrocarbon slab. In Fig.2-(bottom), we compare the PMF for transfer of a single surfactant from the interface to any of the phases using both force fields (S2-M and S2-D simulations). The resulting PMFs have similar shapes but the energies required to transfer the surfactant to the water or the organic phase are higher for simulation S2-M which employs standard (explicit solvent) Martini forcefield. According to the results in Fig.2, the standard Martini force field gives larger adsorption free energies for CTAB at interfaces than all-atomic and implicit solvent Martini models.

It is also interesting to compare the results for both interfaces with the same model (S1-M and S2-M, which employ standard Martini force field). According to Fig.2, the adsorption of CTAB to the water/organic solvent interface is substantially more favourable than the adsorption at the water/vacuum interface (6 Kcal/mol as compared to 10 Kcal/mol).

Table 2 Results of single micelle simulations. D is the diameter of the micelle, e its eccentricity and α the degree of ionization of CTAB molecules (see Methods section for details)

Simulation	D	e	α
S3-A (all-atomic)	4.79 nm	0.29	0.63
S3-M (Martini)	4.54 nm	0.14	0.78
S3-D (Dry Martini)	4.42 nm	0.12	0.73

3.2 Single Micelle simulations

In these simulations (S3-A, S3-M and S3-D in Table 1), we consider a pre-formed micelle of 72 CTAB molecules in water. According to the experimental data [14], this number of surfactants in a micelle corresponds to the average aggregation number found for CTAB concentrations 5-10 mM. The objective here is to compare the results obtained by all-atomic (S3-A), standard Martini model with explicit solvent (S3-M) and implicit solvent Dry Martini force field (S3-D) for a simple system which can be simulated using the three models. In all cases, the pre-assembled micelles were stable during the simulations. In the all-atomic simulation (S3-A), we observe a CTAB molecule leaving the micelle, whereas in the CG simulations all molecules remain in the micelle.

The results of the simulations, including size, shape, and structure of the micelle are summarized in Table 2 and in Fig.3. First of all, we note that all three models predict very similar diameters for the micelles (Table 1).

The shape of the micelle is almost spherical for CG simulations (see eccentricity e in Table 2) but it has a significant eccentricity in the case of all-atomic simulations (S3-A), indicating a spheroidal shape. This can also be seen in the snapshots shown in Fig.3a). In Table 2 we also report the degree of ionization α of the micelle for the three models. The obtained values are very similar, although in the all-atomic (S3-A) simulation we observe a lower ionization (higher condensation of ions) as compared with S3-M and S3-D simulations.

Concerning the structure of the micelles, the three models predict very similar distributions for the hydrocarbon tail inside the micelle (see Fig.3), although the all-atomic model predicts a more structured profile with a peak absent in Martini models. The profiles corresponding to polar headgroup and the counterions are very similar in the case of the standard and Dry Martini models. The all-atomic model shows a more broad distribution of headgroup and ions than the Martini models, probably due to the different shape of the micelle (as seen in Table 2, the micelle from the all-atomic model has substantially larger eccentricity).

We have also computed (Fig.4) the PMF associated to the removal of a single CTAB molecule from the micelle to the water phase. Interestingly, the Dry-Martini model predicts a free energy very close to that predicted by the all-atomic model (although the energy profile is a bit more steeper for all-atomic simulations). In contrast, the simulations using the standard Martini force field predict a lower free energy ($\approx$10 Kcal/mol as compared to $\approx$13Kcal/mol).
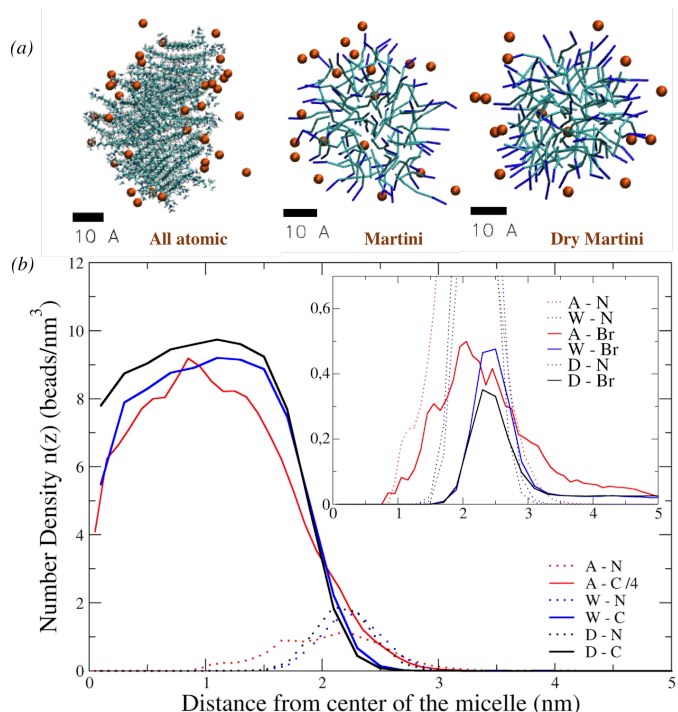

Fig. 3 (a) Snapshot of CTAB micelle from all-atomic (S3-A), W-Martini (S3-M) and D-Martini (S3-D) simulations. Carbon atoms or beads are colored in cyan with licorice representation and nitrogen and bromide atoms or beads are colored in blue and orange, respectively, with VdW representation. (b) Number density of beads (hydrocarbon tail beads are denoted by C, headgroup beads are denoted by N and ion bead by Br) as function of the distance from centre of the micelle (in the AA case we have divided the atom density between 4 to account for the equivalence between 1 bead to 4 heavy atoms). The inset shows a magnification to show more clearly the location of the headgroup and counterions.

3.3 Self-assembly of micelles

Self-assembly of a surfactant solution in multiple micelles is almost impossible to study using all-atomic models due to the large amount of atoms and the long time scales required. As we mentioned before coarse-grain (CG) models appear as an attractive alternative to explore these situations. In this subsection we present results from standard Martini and Dry-Martini corresponding to the self-assembly of multiple micelles (S4-M and S4-D in Table 1, respectively). The results are summarized in Fig.5 and 6. Movies of the simulations, showing the self-assembly process are also available in the Supporting Information.

In the case of the standard Martini force field simulation (S4-M), we observe the formation of micelles Fig.5a. As shown in Figure 5b, after 200 ns of simulation (see Fig.5) the number of micelles as a function of time fluctuates around $\approx$ 14 micelles which corresponds to an average aggregation number of $\approx$ 70 CTAB molecules per micelle. There is of course a distribution of sizes. For example, in the configuration shown in Fig.5a, we have a few small spherical micelles with only $\approx$ 20 − 30 surfactant molecules and big elongated micelles with $\approx$ 140 − 160 molecules. Unfortunately, with our small number of micelles at equilibrium, we do not have enough statistics to provide an accurate calculation of the size distribution of the micelles.
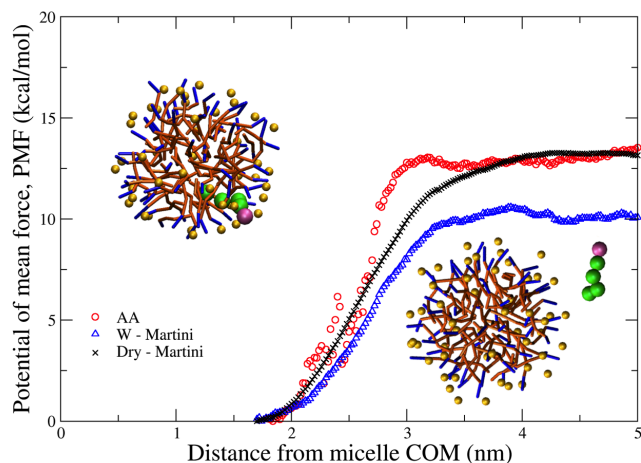
Fig. 4 Potential of mean force (PMF) of a CTAB surfactant as function of the distance (in nm) between the CTAB headgroup and the centre of mass of a CTAB micelle. We also show two simulation snapshots, corresponding to the situations of CTAB inside the micelle and CTAB extracted from the micelle. The CTAB molecule extracted from the micelle is emphasized (green sphere for the tail and pink for the head group). All other CTAB molecules are shown in bond representation (orange for the tails and blue for the headgroups). Bromide ions are shown as yellow spheres.
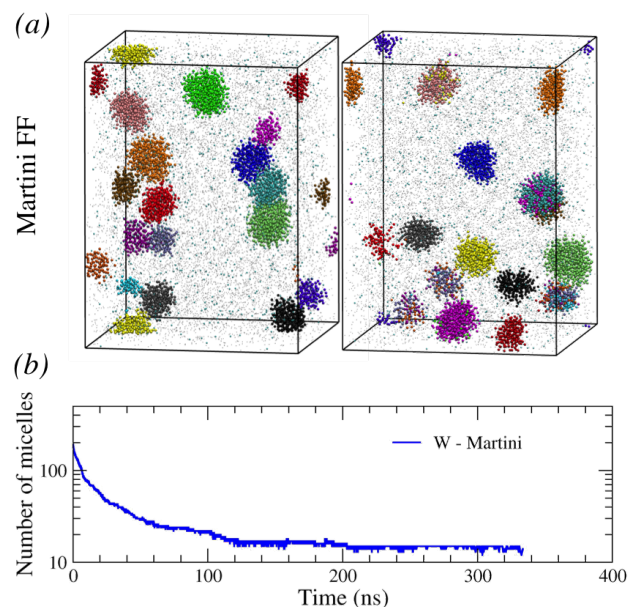

Fig. 5 (a) Snapshots from self-assembly simulations with Martini force field (S4-M in Table 1) at different times: $t = 260$ ns (left) and $t = 334$ ns (right). In order to track surfactant exchange and fission and fusion of micelles, we have coloured the surfactant molecules at short times in (a), left panel, according to the micelle to which they belong at that time. In the right panel, corresponding to a later time, we can observe a mixture of colours in individual micelles which indicates exchange of molecules and micelle fission and fusion. In all cases counterions are represented as cyan dots and in water and AF beads are represented as grey dots. (b) Plot of the number of micelles in simulation S4-M as a function of simulation time.

We also recall that in Fig.5b we observe fluctuations in the number of micelles. This is due to fusion and rupture of micelles and exchange of CTAB molecules between the micelles observed during the simulations, as illustrated in Fig.5a. Once the average number of micelles is stabilized, these processes are still observed in the time scales of the simulation in a way that maintain the average number of micelles. This is what it should be expected in a situation in which the simulations correctly reproduce a thermodynamic equilibrium situation.

As compared with experimental results, the micelles obtained from S4-M simulations have too low aggregation numbers. According to experimental data, the concentration corresponding to S4-M (see Methods section) is above the second micellar concentration of CTAB[3] and elongated micelles with aggregation numbers of ≈ 150 are expected.

In the case of the Dry Martini simulation (S4-D), the situation is completely different (see Fig.6). At short times (≈ 20 ns), we observe the formation of spherical micelles but at longer times ($\approx 100 - 200$ ns) these micelles coalesce to give only a few large, elongated micelles (see Fig.5). But at even longer times, the micelles fuse giving rise to three large, elongated micelles. These three surviving micelles also aggregate (at ≈ 500 ns of simulation), giving rise to a larger structure as seen in Fig.6. As seen in the Fig.6, the three remaining micelles maintain their identity inside this larger structure, without fusing into a larger micelle. This aggregated state is maintained until the end of the simulation (780 ns). Therefore, the Dry Martini forcefield predicts an unrealistic collapse of the system. This effect has been observed in previous works of a different (anionic) surfactant[7], in which

it was proposed a modification of the Dry Martini force field (an artificial increase of the dielectric constant, the use of PME electrostatics and a reparametrization) to correct for the excessive aggregation behaviour. We also tried to implement their modifications in the force field (results not shown) but without success (no improvements in the overall results and a substantial increase of computational time). Also, it is interesting to note that the results presented in the previous subsections indicate that the Dry Martini force field reproduces quite accurately the results from all-atomic MD simulations, including potentials of mean force (see Fig.2 and 4). At this point, and given the agreement between all-atomic and Dry Martini free energy calculations, we may wonder whether the excess of aggregation predicted by the Dry Martini self-assembly simulations is a problem to be attributed to some intrinsic defect of the Dry Martini model or is a more general problem which will also arise in all-atomic simulations if we had enough computational resources to perform self-assembly simulations with that model.

4   Conclusions

The two versions of the Martini CG model (standard with explicit solvent and Dry-Martini with implicit solvent) offer the possibility of performing semi-quantitative MD simulations of supramolecular self-assembly processes at length and/or time scales not accessible with fully atomistic models. The possibility of performing
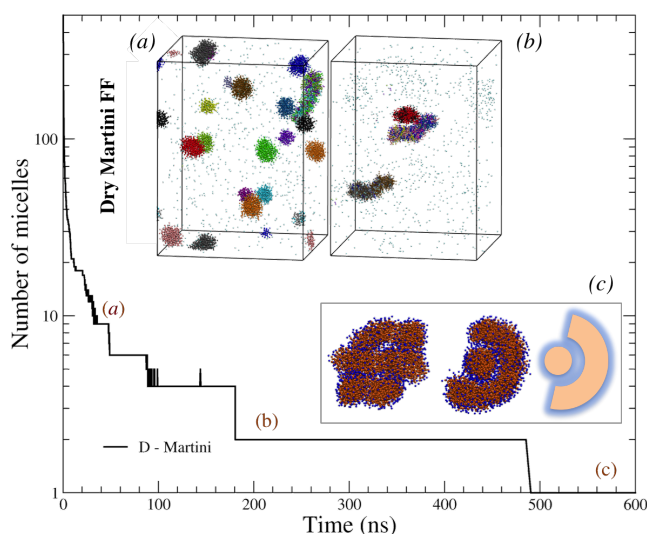
Fig. 6 Number of micelles as a function of simulation time for the Dry Martini model (D-Martini), simulation S4-D in Table 1. The insets (a) and (b) are snapshots corresponding to $t = 22$ ns and $t = 180$ ns respectively. In all cases counterions are represented as cyan dots. Inset (c) shows an image of the final structure obtained in the case of Dry Martini S4-D simulations in two different orientations (we also add a cartoon for the sake of clarity). The color codes employed here have the same meaning as in Figure 5.

fast simulations of large simulation boxes with large number of molecules will open the possibility to explore from a molecular point of view important questions such as the nature of the second critical micellar concentration or the evolution of the size and shape of the micelles as a function of concentration which are important questions still under discussion[2,3]. Before being able to address these questions with confidence, it is essential to test the performance and accuracy of these models for particular, relevant surfactants. Here, we have performed a relevant step in this direction by exploring the predictions of these models for the CTAB surfactant in various situations (at interfaces, in a pre-assembled micelle and in a self-assembly simulation).

Our results provide mixed conclusions about the ability or inability of these models to correctly predict the behaviour of surfactants.

The results of our simulations of a single CTAB molecule at a water/vacuum interface indicate a semi-quantitative agreement between the explicit solvent Martini model and all-atomic simulations. The Martini force field predicts a too large adsorption free energy (as compared with the all-atomic prediction) and neglects the high free energy needed to extract the surfactant molecule to the vacuum phase (associated to desolvation of the surfactant). In the case of the water/organic solvent interface, we obtain that the explicit solvent Martini model predicts larger adsorption free energy at the interface than the Dry Martini model.

Concerning the simulations of a single micelle with a given number of surfactants, we obtain a micelle of almost identical size for the three considered models (all-atomic, Martini and Dry Martini) and very similar internal structure. The shape of the micelles was spherical micelles for both Martini models and a

slightly elongated micelle (with a eccentricity ≈ 0.3) in the case of the all-atomic model. Quite remarkably, the free energy profiles predicted by Dry Martini and all-atomic models for a CTAB molecule in the micelle are extremely similar. In contrast, the standard Martini model with explicit solvent predicts a significantly lower value for the free energy.

Using the standard and Dry Martini force fields, we have been able to study the self-assembly of CTAB molecules into micelles. Using these models, we are able to observe not only micelle formation but also fission and fusion of micelles which leads to an exchange of surfactant molecules between different micelles. As compared with experiments, the simulations using the standard Martini force field predict micelles that are too small (about half of the expected experimental size). On the contrary, Dry Martini force field simulations, predict the formation of too large micelles (more than double the experimental size) and also the micelles tend to aggregate in a way that seems unphysical.

From our results, it seems clear that both Martini and particularly the Dry Martini model can be used to predict some properties of interest of surfactants at interfaces instead of costly all-atomic models. But it is also clear that the models have still limitations that prevent their systematic use to simulate large-scale self-assembly processes.

Micelles are the simplest example of a self-assembled colloid, but as we have seen here, detailed theoretical predictions of their self-assembly process are still a challenge.

Acknowledgments

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