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# MOLECULAR DYNAMICS SIMULATION STUDY OF CETYLPYRIDINUM CHLORIDE AND CETYLTRIMETHYLAMMONIUM BROMIDE MICELLES

**V.S. Farafonov, A.V. Lebed**

Properties of cetylpyridinum chloride and cetyltrimethylammonium bromide micelles were investigated by means of molecular dynamics simulation. The depth of water penetration into hydrocarbon micelle cores was inspected. The distribution and binding of counter-ions around micelles were examined. The all-atom potential models for surfactants studied were developed.

**Keywords:** cetylpyridinum chloride, cetyltrimethylammonium bromide, all-atom model, radius of gyration, hydration, degree of counter-ion binding, molecular dynamics simulation.

## Introduction

Alkylpyridinium surface active substances are extensively used in medicine as a component of drugs and hygienic agents. Usually they act as antiseptics, but in recent studies they were shown to enhance drug transport through skin [1] and to be able to deliver drugs to the central nervous system [2]. On the other hand, they are commonly employed as cationic surfactants in the experimental work in the field of colloid chemistry. These applications require deeper understanding of the properties of the systems containing alkylpyridinium salts. In this study we employ the method of molecular dynamics (MD), which would give an insight into the properties of these systems on the molecular level.

However, there are only few publications reporting MD studies of alkylpyridinium salts [3–5], in contrast to alkyl sulfate or alkylammonium surfactants. Moreover, among these publication there is only a single work devoted to a micellar solution [5]. To fill this gap we choose to employ the molecular dynamics method to investigate the properties of micelle of cetylpyridinium chloride (CPC) as the most important and widely used representative of this class of surfactants. Also we compare our findings with the properties of micelle of cetyltrimethylammonium bromide (CTAB) as an example of alkylammonium surfactants with the same length of hydrophobic tail.

Because the number of tested potential models of CPC or CTAB available in the literature appeared to be limited, we develop, as a preliminary step, a new consistent set of potential models for the surfactants. These models could be used in future simulations of systems containing CPC or CTAB.

## Potential models

The correctness of the results of MD simulations is mainly determined by the accuracy of the employed potential models. The models are generally divided in two groups, the all-atom models where each atom of the substance molecule is explicitly represented, and the united-atom models where hydrogen atoms are merged with neighbor weight atoms. The latter models allow saving a large amount of computational time and, at the same time, can well reproduce experimental properties provided proper parameterization is made.

We start with the analysis of the models available in literature. In [3,4] all-atom models were used, and in [5] a united-atom model was employed. This united-atom model was tested in order to reproduce the micelle properties; it was shown to perform well and be compatible with other models built within the framework of the GROMOS force field. A drawback of united-atom models is, however, that converting $CH_n$ groups to a single interaction sites completely removes the electrostatic contribution of the surfactant hydrocarbon chain to the interactions with other molecules. This could become a problem when interaction between surfactant and other molecule is of interest (e.g. in studies of adsorption or solubilization of a substance on a micelle). In such cases omitting large fraction of surfactant–substance electrostatic interaction could violate interactions balance and distort the results of the simulation. This argument limits applicability of the united-atom models.

On the other hand, all-atom models in the abovementioned studies have not been tested in micellar configurations. Moreover, they either used uncommon force field (CLAY FF) [3], or were developed with significant deviations from the parameterization methodology of used force field (namely, in the

 alebed@karazin.ua

atomic charges derivation stage) [4]. These drawbacks hinder compatibility with other potential models of other molecules. For these two reasons we did not use these all-atom models in our present study.

The number of MD simulation studies of cetyltrimethylammonium halogenides micellar solutions is also short [6–8], and in most of them united-atom models are used.

Therefore we have chosen to develop and test novel all-atom models for CPC and CTAB, which would reproduce micelle properties and, at the same time, would be versatile enough to be suitable for simulations together with other molecules. We chose OPLS-AA as the one of the most widely used and validated force fields [9]. At the same time, it was shown that original OPLS-AA parameters poorly reproduce properties of long hydrocarbons at room temperature. It is because the molecules become artificially ordered, which results in overestimated density and melting point. Naturally, this defect also distorts the properties of micelles consisting of the surfactants with long hydrocarbon tails. In an attempt to fix this defect some parameters were reconsidered in literature [10,11]. We employed the modification by Murzyn et al. [11], which provides updated C–C–C–C and H–C–C–H dihedral angle parameters. This improvement brings calculated properties of long alkanes close to the experimental values.

The next step is the derivation of atomic point charges. In accordance with the OPLS-AA fragment approach, the whole cetylpyridinium ion was divided into two fragments carrying integer charges: the neutral tetradecane, and the positively charged ethylpyridinium cation. Atomic charges of the tetradecane fragment were set equal to the force field charges of alkane C and H atoms. This is physically correct because of a fast fading of the *–I* effect of the pyridinium ring. However, OPLS-AA does not include atomic charges of either ethylpyridinium ion or protonated pyridine; therefore it became necessary to compute these charges. We employed the algorithm, which was recommended by OPLS-AA parameterization methodology. The first step was to perform the quantum chemical computation of the distribution of electrostatic potential around the ethylpyridinium ion on the RHF level of theory using the 6-31G(d) basis set. Then this distribution was fitted by point charges centered on each atom of the ion using CHELPG algorithm. Importantly, these steps should be repeated for several molecule orientations in order to obtain reliable values. We employed the RED server, which was specifically developed for this task to automate the process [12]. Finally, both fragments were merged and the charge on the C atom second from the N atom was slightly adjusted to make the charge of the whole cetylpyridinium ion equal to +1.

The final atomic charges as well as assigned atom types from OPLS-AA force field are represented on Fig. 1, positively charged atoms are colored red, negatively charged ones are colored blue. For other atoms the standard force field parameters are used.

In contrast, the potential model of cetyltrimethylammonium cation did not require additional parameterization because all the parameters including atomic charges were found in the force field. The model is also shown on Fig. 1.

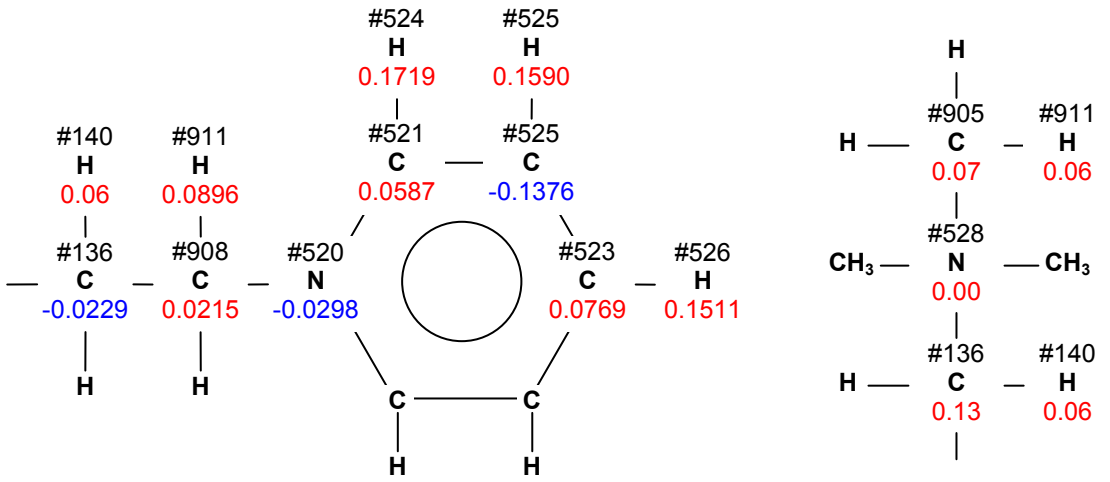


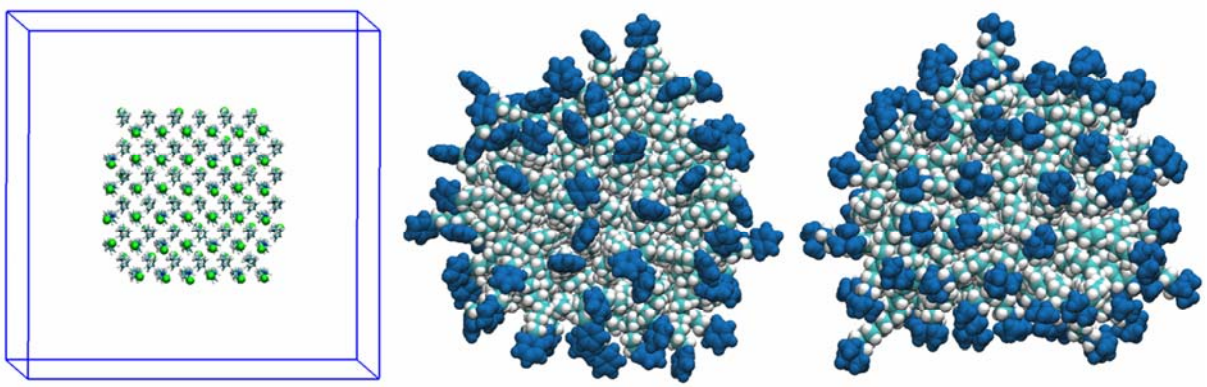

**Figure 1.** Atomic charges and types used in potential models of cetylpyridinium and cetyltrimethylammonium cations. Only parts with non-standard parameters are shown.

For chloride and bromide the standard OPLS-AA parameters were employed. The water model chosen was SPC.

### Simulation methodology

All simulations were carried using GROMACS 5 [13] software package. The following parameters were used: standard conditions, maintained using Berendsen couplings with the thermostat time constant of 1 ps and the barostat time constant of 1.5 ps, the time step of 2 fs, the 3D periodic boundary conditions, PME electrostatics, the cut-off length for van der Waals interactions of 1 nm. All bonds were constrained with the LINCS algorithm.

A 20 ns simulation was performed for CPC and CTAB. The initial structure for all cases was a nearly square bilayer consisting of 80 monomers together with their counter-ions. Starting with a pre-assembled compact structure is a common approach [5–8] that simultaneously allows testing the quality of the model, and requires much less computational time in comparison with the starting configuration with monomers uniformly distributed in solution. The bilayer was solvated in a cubic cell of water with the size 9.7 nm that contained about 30000 water molecules (Fig. 2A). The monomer count of 80 falls in the range of experimental aggregation numbers of both studied surfactants [14,15] therefore it is correct to study micelles of this size. Further, using equal monomer count for both micelles allows to investigate the net effect of head groups and counter-ions on the micelle properties. The obtained micelles are shown on Fig. 2BC.



**A** **B** **C**

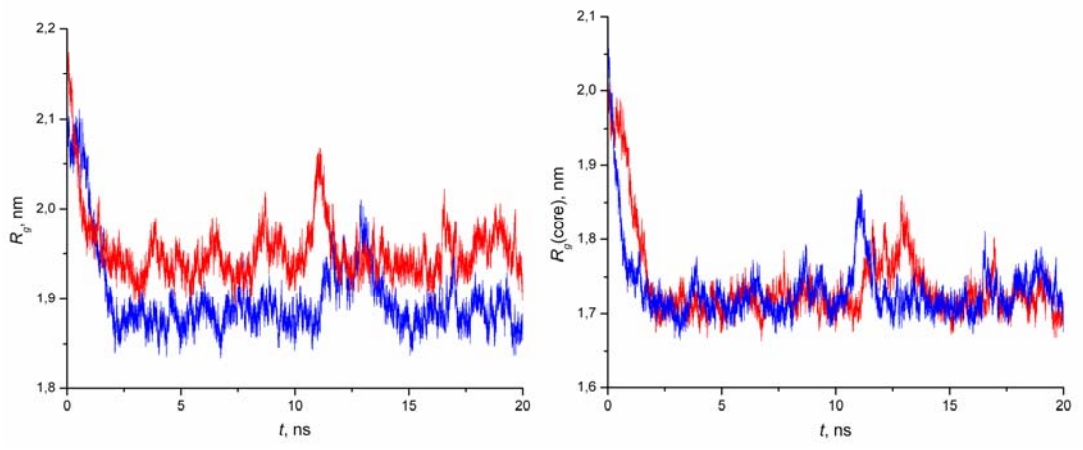
**Figure 2.** A: Initial configuration for CPC micellization. $Cl^-$ ions are shown as green orbs; B: Final CPC micelle; C: Final CTAB micelle. Head groups are colored blue.

### Results and discussion

First, size of obtained micelles was compared. The common measure of the size of the micelles, proteins as well as other macromolecules and supramolecular aggregates is the radius of gyration $R_g$. Because the surfactants studied have head groups of different sizes we also calculated $R_g$ taking into account only cetyl radical atoms (i.e. only the micelle hydrocarbon core). The results are shown on Fig. 3. It could be seen that the size of the CPC micelle is larger than that of the CTAB one; the difference is caused by the head groups, while the hydrocarbon cores of all micelles have the same size. The size reached the equilibrium value and fluctuates around it, except of the short-time deformation that occurred at 11–14 ns. The average values of $R_g$ are 1.95 nm for the CPC micelle, and 1.88 nm for the CTAB one. For both hydrocarbon cores $R_g$ equals 1.72 nm. We can estimate geometrical radii using the ratio between geometrical and gyration radii of homogeneous sphere: $R_g / R = \sqrt{3/5}$. This gives approximate $R$ values of 2.52 nm for CPC, 2.43 nm for CTAB, and 2.22 nm for hydrocarbon cores. Direct comparison with experiment is hindered because of polymorphism and aggregation number variability of micelles of these surfactants.

Next we examined the depth of water penetration into micelles. To estimate it we plotted radial distribution functions (RDF's) $g(r)$ for distances between water atoms and micelle center of mass (COM). For comparison RDF's micelle COM–N were plotted. Hereafter only last 10 ns of trajectories were used for computations. The plots are shown on Fig. 4A. It could be seen that RDF's are similar for

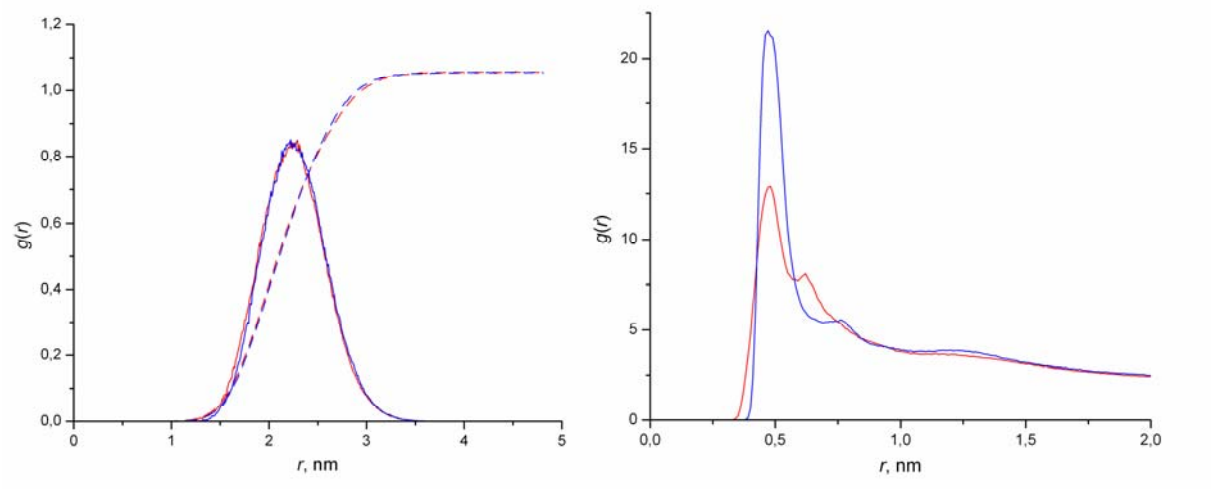
both surfactants that indicates smallness of impact of the head group on these properties in the studied case. Nitrogen atoms of the head groups of both surfactants are usually located at 1.7–2.8 nm from the micelle COM with the maximal probability at 2.2 nm. The density of water decreases by 2 times at roughly the same distance (2.1 nm) as compared to the bulk solution. This indicates that the layers of head groups and adjacent methylene groups of both micelles are strongly hydrated. Micelles become almost dry at 1.3 nm ($g(r)$ is 1% of the bulk value) and completely dry at 1 nm. This observation agrees well with the results of experimental measurements.




**A** **B**

**Figure 3.** Radii of gyration $R_g$ of whole CPC and CTAB micelles (A) and of their hydrocarbon cores (B). Red curves are for CPC, blue curves are for CTAB.

Further the distribution of counter-ions around micelles was inspected. We evaluated the radial distribution functions for distances between nitrogen atoms of surfactants and counter-ions, the results are shown on Fig. 4B. The distributions have the same general character, and consists of a well-defined high peak at 0.47 nm followed by a lower and smoother peak (CPC) or a short plateau (CTAB).




**A** **B**

**Figure 4.** Radial distribution functions micelle COM–N and micelle COM–water (A), N–$Cl^-$and N–$Br^-$ (B). Red curves are for CPC, blue curves are for CTAB.

Finally, the degree of counter-ion binding $\beta$ was calculated. Unfortunately, there is no strict criterion defining the position of the border between the ions considered as bound and those considered as free. Moreover, this position seemingly depends on the experimental technique employed because several $\beta$ values are usually reported for the same surfactant. Therefore we estimated a range of possible $\beta$ values by taking two limiting positions of the border. We took the end of the first peak on the RDF as the lower bound (0.58 nm for CPC and 0.7 nm for CTAB) and, somewhat arbitrary, 0.9 nm as

the upper bound. The fraction of the counter-ions located closer to the head groups than the lower (upper) bound was taken as the lower (upper) estimation of $\beta$, correspondingly. The ranges obtained are presented in Table 1 together with results of experimental measurements [16–19].

**Table 1.** Calculated and experimental values of degree of counter-ion binding of CPC and CTAB.

| Surfactant | MD | Experiment |
|---|---|---|
| CPC | 37–65% | 45–67% |
| CTAB | 59–69% | 74–84% |

It could be seen that the CPC model represents counter-ion binding well, while the CTAB model underestimates it by 5–15%, that is 6–19% of the average experimental value.

## Conclusions

MD simulation of micelles of common cationic surfactants cetylpyridinum chloride and cetyltrimethylammonium bromide with equal aggregation numbers was performed. The properties were found to be very similar despite of difference of the head groups. Both micelles have dry hydrocarbon cores with radius 1.0–1.3 nm, which agrees with available indirect experimental data. The developed surfactant models represent the experimental values of degree of counter-ion binding with good accuracy, which proves that the ion–surfactant and ion–water interactions balance is maintained. The models could be used in all-atom simulations studying the behavior of substances dissolved in micellar solutions or interactions of biomolecules with surfactant micelles within the framework of the OPLS-AA force field.

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В.С. Фарафонов, А.В. Лебедь. Изучение мицелл цетилпиридиний хлорида и цетилтриметиламмоний бромида методом молекулярно-динамического моделирования.

Определены свойства мицелл поверхностно-активных веществ цетилпиридиний хлорида и цетилтриметиламмоний бромида с помощью молекулярно-динамического моделирования. Оценена глубина проникновения воды в углеводородные ядра мицелл. Рассмотрены распределение и связывание противоионов вокруг мицелл. Разработаны полноатомные модели для изученных веществ.

**Ключевые слова:** цетилпиридиний хлорид, цетилтриметиламмоний бромид, полноатомная модель, радиус инерции, гидратация, степень связывания, молекулярно-динамическое моделирование.

В.С. Фарафонов, О.В. Лебідь. Вивчення міцел цетилпіридиній хлориду та цетилтриметиламоній броміду методом молекулярно-динамічного моделювання.

Визначені властивості міцел поверхнево-активних речовин цетилпіридиній хлориду та цетилтриметиламоній броміду за допомогою молекулярно-динамічного моделювання. Оцінена глибина проникнення води у вуглеводневі ядра міцел. Розглянуті розподіл та зв'язування протийонів навколо міцел. Розроблені повноатомні моделі для вивчених речовин.

**Ключові слова:** цетилпіридиній хлорид, цетилтриметиламоній бромід, повноатомна модель, радіус інерції, гідратація, ступінь зв'язування, молекулярно-динамічне моделювання.