

Micelle Formation Of Hexa(Sodium 10-Undecenoate) In Aqueous Solution: Molecular Dynamics

Clifford E. Larrabee, Jr., Timothy H. Dennison

University of Cincinnati Clermont College

Department of Science & Health

Batavia, Ohio, USA

cliff.larrabee@uc.edu; hayden@dennison7.com

Abstract –Ionic surfactants self-assemble in aqueous solution to form aggregates called micelles. The same hydrophobic interactions that drive micelle formation give surfactants their ability to solubilize hydrophobic substrates. Micelles are thermodynamically stable above their critical micelle concentration, CMC, but their existence is dynamic. Complete micelles form, disintegrate, and reform on a millisecond time scale. Individual surfactants can join or leave a micelle on an even faster time scale, microseconds or less. The dynamic nature of micelles causes problems in applications such as reaction templating for nanotechnology or targeted drug delivery but can be circumvented by covalently bonding the surfactants to form polymeric “surfmers”. While polymeric and oligomeric surfactants have been proven to have useful properties, the mechanism of their interactions with each other and with potential substrates are just beginning to be detailed. Here we show the results of molecular dynamics simulations of hexa(sodium 10-undecenoate) using the GROMOS 54A7 force field for the oligomeric surfactant and the simple point charge, SPC, model for water. Estimates of CMC, aggregation number, and degree of ionization derived from the simulation are in excellent agreement with their corresponding experimental values. This indicates that the approximations of the force fields used in this study do not limit the quality of the simulations and that more involved studies can proceed with confidence.

Keywords: micelle, oligomer, surfmer, CMC, degree of ionization, molecular dynamics

1. Introduction

Surfactants have been used for centuries as detergents and more recently in the fields of enhanced oil recovery (Rosen & Kunjappu, 2012), reaction templating in nanotechnology (Summers & Eastoe, 2003), and targeted drug delivery (Rangel-Yagui, Pessoa Jr, & Tavares, 2005). However, the dynamic nature of surfactant micelles can limit their effectiveness, especially as reaction templates or drug delivery systems. (Summers & Eastoe, 2003; Torchilin, 2001).

One approach to maintaining the advantages of micellar systems while eliminating their dynamic instability is to polymerize the surfactants, making covalently bonded polymers called “surfmers”. (Summers & Eastoe, 2003) One of the first examples of this approach was the polymerization of sodium 10-undecenoate by γ -irradiation of aqueous solutions above the critical micelle concentration, CMC. (Larrabee Jr. & Sprague, 1979) The product of the free-radical polymerization is a polydisperse oligomer. The oligomer is well characterized: it has a very low CMC of $0.006 \pm 0.003 \text{ mol kg}^{-1}$ (Larrabee Jr., Warmin, & Iles, 2014), and an aggregation number of 42 ± 2 effective monomer units with a degree of ionization of 0.33 ± 0.04 (Denton, Duecker, & Sprague, 1993). Both monomeric and oligomeric sodium 10-undecenoate micelles are capable of solubilizing a hydrophobic substrate; the monomeric micelles have a higher solubilization power for the hydrophobic substrate, oil blue n, while the oligomeric micelles form a more stable complex. (Larrabee Jr. et al., 2014) However, little is known about the details of their molecular interactions or the mechanism of their formation and solubilization.

The overall goal of the research described in this paper was to develop a better understanding of the factors affecting micelle formation and solubilization of a simple oligomeric micelle. The specific

objective of the current project was to validate appropriate force fields and simulation parameters for the molecular dynamics modelling of hexa(sodium 10-undecenoate) in water at 300 K.

2. Methods

Molecular dynamics simulations were performed using the GROMACS 5.0 package. (Abraham, Van Der Spoel, Lindahl, & Hess, 2014) The molecular interactions for sodium, 10-undecenoate, and hexa(10-undecenoate) ions were calculated according to the parameters and potential functions of the GROMOS 54A7 force field. (Schmid et al., 2011) United-atom, optimized-geometry structure files and topology files were generated by the Automated Topology Builder (ATB) version 2.1. (Koziara, Stroet, Malde, & Mark, 2014) The simple point charge, SPC, model was employed for the water molecules. (Berendsen, Postma, van Gunsteren, & Hermans, 1981) The steepest descent method was used to minimize the energies of the initial configurations. After minimization, a brief equilibration under NVT ensemble at 1 atm and 300 K using the V-rescale thermostat with a temperature coupling time constant of 0.1 ps was performed for each model system to make the system volume stable. Then an 80 ps NPT simulation was carried out at 300 K for each system to equilibrate pressure. Finally, a MD simulation under a Berendsen barostat and V-rescale thermostat was carried out at 300 K for each system, with barostat and thermostat time constants of 2.0 and 0.1 ps, respectively. Neighbor searching was performed every 40 steps, or every 200 fs. In the MD simulation, bond lengths were constrained using the LINCS algorithm, periodic boundary conditions were applied in all directions, and a time-step of 5 fs was used throughout the production simulation. The nonbonded potential truncation was performed with a cutoff distance at 1.17 nm for Lennard–Jones interactions. The particle mesh Ewald method was employed for the long-range electrostatic interactions, with a cut-off of 1 nm. During MD simulations the positions, energies, and velocities of all atoms were stored every 10 ps.

3. Results

3. 1. Simulation 1: Random Hexamers

Fifteen hexa(10-undecenoate) ions, 90 monomer equivalents, were randomly placed in a $9 \times 9 \times 9$ nm³ box. Water and sodium counterions were added, giving a concentration of 0.20 mol kg⁻¹ of monomer equivalents. This is approximately twice the CMC of the monomeric surfactant. The simulation was carried out for 250 ns.

Within 100 ns, the surfactants had self-assembled into six aggregates, five formed from two hexamers (12 monomer equivalents) and one formed from three hexamers (18 monomer equivalents). At about 200 ns, the aggregation distribution shifted to four two-hexamer aggregates and two three-hexamer aggregates. See figure 1. This distribution lasted through the 250 ns simulation.

3. 2. Simulation 2: Single Preformed Micelle

Initial conditions for this simulation were the same as simulation 1 except that the hexamers were packed into a single preformed micelle with Packmol software. (J. M. Martínez & Martínez, 2003; L. Martínez, Andrade, Birgin, & Martínez, 2009)

Almost immediately, the single micelle split into two aggregates, one of seven hexamers, and one of eight hexamers. This configuration was stable for 250 ns. See figure 2.

4. Discussion

Molecular dynamics simulations of micelle formation from randomly distributed monomers requires a microsecond (Wang & Larson, 2015) or longer (Poghosyan, Antonyan, Arsenyan, & Shahinyan, 2014) time scale. The simulations presented here were stopped after 250 ns and do not represent equilibrium configurations. Qualitatively, they point in the right direction. The random monomer initial configuration led to increasingly larger aggregates. The single, preformed micelle initial configuration separated into two aggregates almost immediately.

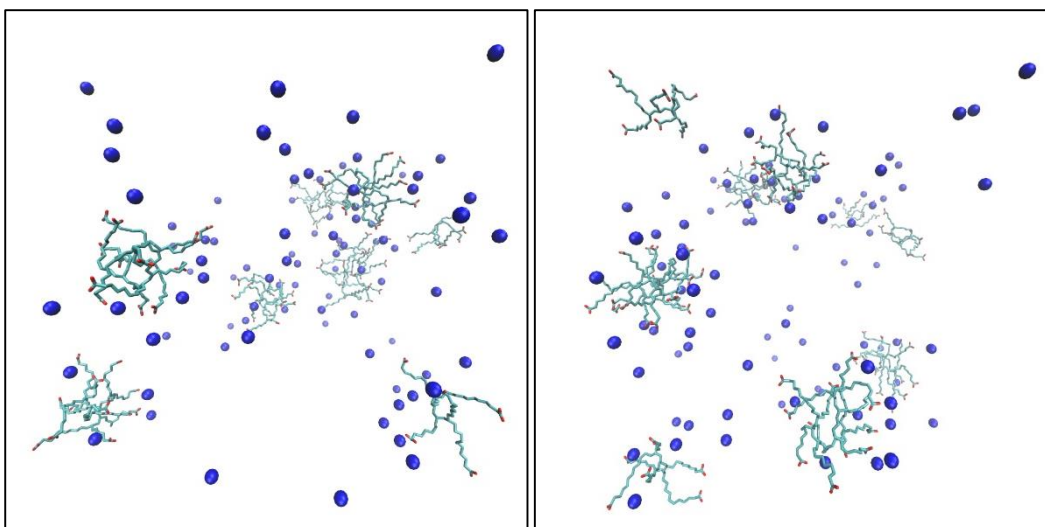


Fig. 1. Aggregation of random hexamers after 100 ns (left) and after 200 ns (right). Light blue lines represent hydrocarbon, red dots represent oxygen, and dark blue dots represent sodium ions.

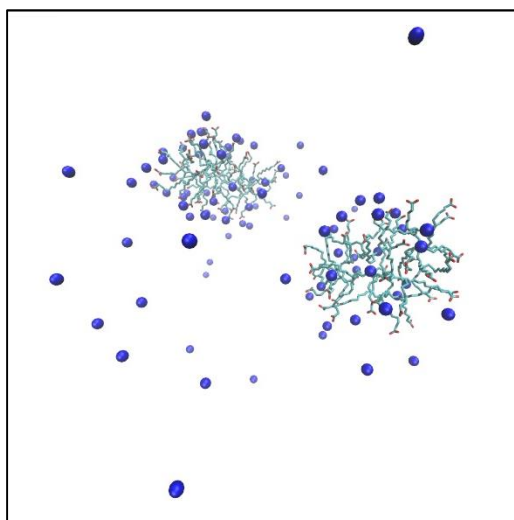


Fig. 2. Aggregates formed from the fragmentation of a single preformed micelle after 250 ns.

We have calculated the apparent CMC, micelle aggregation number, and degree of ionization for simulation 2 and compared them with the known experimental values. See table 1. We estimate the upper limit for CMC for this simulation to be the concentration of the solution, 0.20 mol kg^{-1} , divided by the number of hexamers, 15; this gives a limiting value of $0.013 \text{ mol kg}^{-1}$. The degree of ionization, β , is the ratio of ionized counterions to total counterions. It was determined by considering any sodium more than 0.5 nm from all hexamer atom to be ionized. This value stabilized after 50 ns at 0.34 ± 0.07 . See figure 3. The experimental CMC value is from (Larrabee Jr. et al., 2014). The experimental aggregation number and degree of ionization are from (Denton et al., 1993). The agreement is excellent.

Table. 1. Comparison of Experimental and Simulation Results.

	CMC (mol kg^{-1})	Aggregation number	Degree of Ionization
Simulation 2	< 0.013	45 ± 3	0.34 ± 0.07
Experimental	0.006 ± 0.003	42 ± 2	0.33 ± 0.04

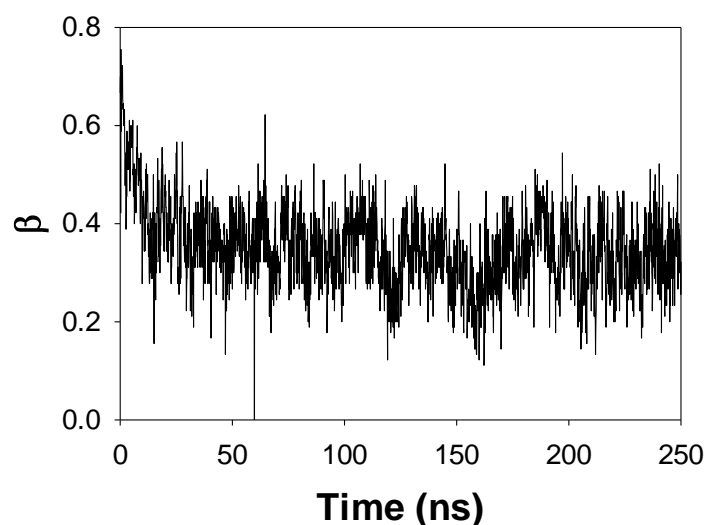


Fig. 3. Degree of ionization, β , as a function of time for simulation 2.

The overall goal of the research is to develop a better understanding of the process of micellization and solubilization. One surprising result was the extent and frequency of the fluctuations about a very stable average value for the degree of ionization shown in Figure 3. This is in sharp contrast to the relative stability of the surfactants within their respective aggregates. It is not clear whether this is the result of the 1 nm cutoff for the long-range electrostatic interactions in the simulations or if it gives an accurate reflection of the magnitude of the difference in exchange rates between the surfactant ions and counterions.

5. Conclusion

The specific objective of this project was to test the validity of the Gromos 54A7 force fields for an ionic, oligomeric surfactant in SPC water. Two 250-ns simulations were run: one starting with fifteen randomly distributed hexa(sodium 10-undecenoate) ions and the other starting with fifteen ions packed in a single micelle. The results reported here in section 3 and discussed in section 4, do not give any reason for concern with the force fields or their use in the investigation of the micellization of an ionic, oligomeric surfactant. Consequently, more involved studies can proceed with confidence.

The process of solubilization of a hydrophobic substrate is particularly important in the applications of reaction templating (Summers & Eastoe, 2003) and targeted drug delivery (Rangel-Yagui et al., 2005). Subtle changes in surfactant and counterion structure can lead to significant changes in solubilization power (Larrabee Jr, Warmin, & Howard, 2014) and consequently in the effectiveness of the application. Molecular dynamics studies of these interactions based on the Gromos 54A7 forces fields are expected to provide insight into the solubilization mechanisms of these systems.

References

- Abraham, M., Van Der Spoel, D., Lindahl, E., & Hess, B. (2014). *The GROMACS Development Team*. GROMACS User Manual Version 5.0. 2.
- Berendsen, H. J., Postma, J. P., van Gunsteren, W. F., & Hermans, J. (1981). Interaction Models For Water In Relation To Protein Hydration. In *Intermolecular Forces* (pp. 331-342). Springer.
- Denton, J. M., Duecker, D. C., & Sprague, E. D. (1993). Size And Solution Behavior Of Sodium 10-Undecenoate Oligomers. *The Journal of Physical Chemistry*, 97(3), 756-762.
- Koziara, K., Stroet, M., Malde, A., & Mark, A. (2014). Testing And Validation Of The Automated Topology Builder (ATB) Version 2.0: Prediction Of Hydration Free Enthalpies. *Journal of Computer-Aided Molecular Design*, 28(3), 221-233.

- Larrabee Jr, C. E., Warmin, M. R., & Howard, M. J. (2014). Clathrate Hydrate Formation and Micellization of Tetrabutylammonium 10-Undecenoate. *International Journal of Theoretical and Applied Nanotechnology*, 2, 40-45.
- Larrabee Jr., C. E., & Sprague, E. D. (1979). Radiation-Induced Polymerization Of Sodium 10-Undecenoate In Aqueous Micelle Solutions. *Journal of Polymer Science: Polymer Letters Edition*, 17(12), 749-751.
- Larrabee Jr., C. E., Warmin, M. R., & Iles, C. N. (2014). Effect of Oligomerization of Sodium 10-Undecenoate on the Solubilization of a Hydrophobic Substrate. *Proceedings of the International Conference on Nanotechnology, Fundamentals and Applications*, 194-191-194.
- Martínez, J. M., & Martínez, L. (2003). Packing Optimization For Automated Generation Of Complex System's Initial Configurations For Molecular Dynamics And Docking. *Journal of Computational Chemistry*, 24(7), 819-825.
- Martínez, L., Andrade, R., Birgin, E. G., & Martínez, J. M. (2009). PACKMOL: A Package For Building Initial Configurations For Molecular Dynamics Simulations. *Journal of Computational Chemistry*, 30(13), 2157-2164.
- Poghosyan, A., Antonyan, L., Arsenyan, L., & Shahinyan, A. (2014). Atomic Level And Coarse-Grained Simulation Of Long Chain Alkyl Sulfonate: Micelle self-assembly. *Colloids and Surfaces A: Physicochemical and Engineering Aspects*, 462, 99-106.
- Rangel-Yagui, C. O., Pessoa Jr, A., & Tavares, L. C. (2005). Micellar Solubilization Of Drugs. *J. Pharm. Pharm. Sci*, 8(2), 147-163.
- Rosen, M. J., & Kunjappu, J. T. (2012). *Surfactants And Interfacial Phenomena*. John Wiley & Sons.
- Schmid, N., Eichenberger, A., Choutko, A., Riniker, S., Winger, M., Mark, A., & van Gunsteren, W. (2011). Definition And Testing Of The GROMOS Force-Field Versions 54A7 And 54B7. *European Biophysics Journal*, 40(7), 843-856.
- Summers, M., & Eastoe, J. (2003). Applications Of Polymerizable Surfactants. *Advances in Colloid and Interface Science*, 100–102(0), 137-152.
- Torchilin, V. P. (2001). Structure And Design Of Polymeric Surfactant-Based Drug Delivery Systems. *Journal of controlled release*, 73(2), 137-172.
- Wang, S., & Larson, R. G. (2015). Coarse-Grained Molecular Dynamics Simulation of Self-Assembly and Surface Adsorption of Ionic Surfactants Using an Implicit Water Model. *Langmuir*, 31(4), 1262-1271.