J|A|C|S
ARTICLES

Published on Web 12/03/2008

Micelle Fission through Surface Instability and Formation of an Interdigitating Stalk

Maria Sammalkorpi,*,†,§ Mikko Karttunen,‡ and Mikko Haataja†

Department of Mechanical and Aerospace Engineering, Princeton University, Princeton, New Jersey 08544, and Department of Applied Mathematics, The University of Western Ontario, London, Ontario, N6A 5B8 Canada

Received October 4, 2008; E-mail: msammalk@princeton.edu

Abstract: We report on the first detailed atomic-scale studies of micelle fission in micellar systems consisting of anionic sodium dodecyl sulfate with explicit solvent. We demonstrate a new micelle fission pathway for ionic surfactants and show how micelle fission can be induced by varying the ionic concentration. We argue that this fission pathway proceeds through an initial Rayleigh instability driven by Coulombic interactions and show how the intermediate stages proceed through the formation of a highly interdigitated stalk. This pathway may facilitate easier compartmentalization and functionalization of micelles.

1. Introduction

The ability of amphiphilic surfactant aggregates to change their size, shape, and topology in response to a broad spectrum of physical, chemical, and mechanical cues lies at the heart of important phenomena in both the natural and synthetic worlds. In the former case, membrane fusion and fission are fundamental to cellular function and survival. For example, endo- and exocytosis, membrane recycling, and the cell entry of an enveloped virus all depend on such processes.[1,2] In the latter case, fusion and fission of amphiphilic aggregates control the behavior and feasibility of systems such as drug delivery vehicles and novel nanoscale soft materials.[3] As these processes are inherently dynamic and involve complex, collective kinetics at the molecular level, the details of their physical mechanisms and kinetic pathways remain controversial or unresolved.[4,5]

In the case of membranes, fusion/splitting processes have been suggested to take place through an intermediate stage, the fusion stalk, in which the inner leaflets remain separated but the outer leaflets connect to form a short neck between the two fusing or splitting membranes.[1,2,5] This process has indirect evidence through the formation of hemifused vesicles in which lipids are exchanged but whose contents remain unmixed.[1,2] X-ray studies have provided support for the existence of a short stalk,[6] and molecular simulations have suggested a pore-mediated fusion pathway.[7] Other interesting studies of vesicle and membrane fusion have been reported using mostly coarse-grained approaches.[8,9]

Although micelle/vesicle fusion has received a lot of attention, fission processes have been studied much less. That is most likely due to experimental difficulties and high computational demands. In this investigation we focus on fission, although we believe that our results have important implications for fusion processes as well, as will be discussed later in the paper in more detail.

As for fission, pioneering work was done by Rharbi and Winnik[10,11] on the experimental side, and by Pool and Bolhuis[12,13] by computer simulations. Rharbi and Winnik were able to study the fragmentation rates in sodium dodecyl sulfate (SDS) micelles, and they pointed out the crucial importance of electrostatic interactions and shape fluctuations in fragmentation. Pool and Bolhuis[12,13] were the first, to our knowledge, to simulate fission processes in the presence of solvent and study the transition paths. They employed a coarse-grained Lennard-Jones model and a Monte Carlo/free energy analysis-based approach, and demonstrated the possibility of different splitting paths. Earlier computational studies by Noguchi and Takasu[14,15] focused on splitting under a pulling force as in optical trap experiments. In addition, in another related study, Briels et al.[16] studied merging and splitting of wormlike micelles under applied tension. A recent notable computational study of micelle fission was performed by Markvoort et al.[17] By using a coarse-grained model they identified three vesicle fission pathways that had a close resemblance to the fusion mechanism with a short stalk.

In this paper, we report results from detailed atomic-scale molecular dynamics simulations of micelle fission in systems consisting of anionic SDS with explicit ions and water. SDS

† Princeton University.
‡ The University of Western Ontario.
§ Formerly M. Huhtala.

(1) Jahn, R.; Lang, T.; Südhof, T. C. *Cell* **2003**, *112*, 519.
(2) Gruner, S. M. *Science* **2002**, *297*, 1817.
(3) Hillmyer, M. A. *Science* **2007**, *317*, 604.
(4) Inaoka, Y.; Yamazaki, M. *Langmuir* **2007**, *23*, 720.
(5) Müller, M.; Katsov, K.; Schick, M. *J. Chem. Phys.* **2002**, *116*, 2342.
(6) Yang, L.; Huang, H. W. *Science* **2002**, *297*, 1877.
(7) Marrink, S. J.; Mark, A. E. *J. Am. Chem. Soc.* **2003**, *125*, 11144.
(8) Kasson, P. M.; Kelley, N. W.; Singhal, N.; Vrljic, M.; Brunger, A. T.; Pande, V. S. *Proc. Natl. Acad. Sci. U.S.A.* **2006**, *103*, 11916.
(9) Knecht, V.; Marrink, S.-J. *Biophys. J.* **2007**, *92*, 4254.
(10) Rharbi, Y.; Winnik, M. A. *J. Am. Chem. Soc.* **2002**, *124*, 2082.
(11) Rharbi, Y.; Winnik, M. A. *J. Phys. Chem. B* **2003**, *107*, 1491.
(12) Pool, R.; Bolhuis, P. G. *Phys. Rev. Lett.* **2006**, *97*, 018302.
(13) Pool, R.; Bolhuis, P. G. *J. Chem. Phys.* **2007**, *126*, 244703.
(14) Noguchi, H.; Takasu, M. *Biophys. J.* **2002**, *83*, 299.
(15) Noguchi, H.; Takasu, M. *Phys. Rev. E* **2002**, *65*, 051907.
(16) Briels, W. J.; Mulder, P.; den Otter, W. K. *J. Phys.: Condens. Matter* **2004**, *16*, S3965.
(17) Markvoort, A. J.; Smeijers, A. F.; Pieterse, K.; Vansanten, R. A.; Hilbers, P. A. J. *J. Phys. Chem. B* **2007**, *111*, 5719.

was chosen because it is one of the most commonly used surfactants and it has been extensively employed in chemistry and biochemistry for more than 60 years (see, e.g., refs 18, 19). Lately, the interactions of SDS, and charged micelles in general, with other molecules, water, and surfaces, and their dynamical behavior, have received a lot of attention due to applications in drug delivery and in design of tunable soft materials.[20−23] From the structural point of view, pioneering work on SDS micelles was performed by Cabane, who used nuclear magnetic resonance (NMR) to study the detailed structure of SDS micelles together with typical conformations of the SDS molecules.[24] Importantly, that work set a model for the water−micelle interface, which sparked excitement in the field. The determination of SDS micelle structure was continued further by Cabane et al., who subsequently employed X-rays to study shape fluctuations and their fundamental importance for the behavior of SDS micelles.[25] That study firmly established that micelles undergo strong fluctuations and the stereotypical picture of a perfectly round micelles was not accurate for SDS. A few years later, Cabane, Kékicheff et al. identified four different mesophases[26] when the morphology changed from planar to cylindrical, and a phase diagram for SDS−water systems was established.[27] Finally, in a series of pioneering experiments, SDS-based micelles were used to study micelle fusion and fission by Rharbi and Winnik.[10,11,28]

Our aim here is to identify the atomic-scale interactions and physical mechanisms behind electrostatically driven micelle fission in the case of anionic SDS micelles. Water and ions are taken explicitly into account. To our knowledge, this is the first time such simulations have been performed. As will be discussed later, our study confirms the importance of electrostatic interactions as suggested by Rharbi and Winnik,[10,11] and we demonstrate how shape fluctuations occur and drive the system toward splitting. In comparison with Pool and Bolhuis,[12,13] our study shows the detailed kinetics of the splitting process in a charged system; Pool and Bolhuis had a neutral coarse-grained system, and they used a probability-based Monte Carlo method rather than direct molecular dynamics. Furthermore, our study demonstrates the detailed atomic-level kinetic processes as was called for already by Pool and Bolhuis.

Our main results can be summarized as follows: We demonstrate a new micelle fission pathway and explain its physical mechanisms. Here, fission is induced by a sudden change in the ionic strength of the solution. Our main observation is that micelle fission progresses through a dumbbell-like morphology involving the formation of a *long and narrow stalk* in which the surfactants are *highly interdigitated*. The rod-like interdigitating structure allows the stalk/neck to elongate over a much longer distance while providing partial shielding of the hydrocarbon tails from the solvent and leading to a stable intermediate. Figure 1 shows representative snapshots from a simulation, while movies of fission processes are provided in the Supporting Information.

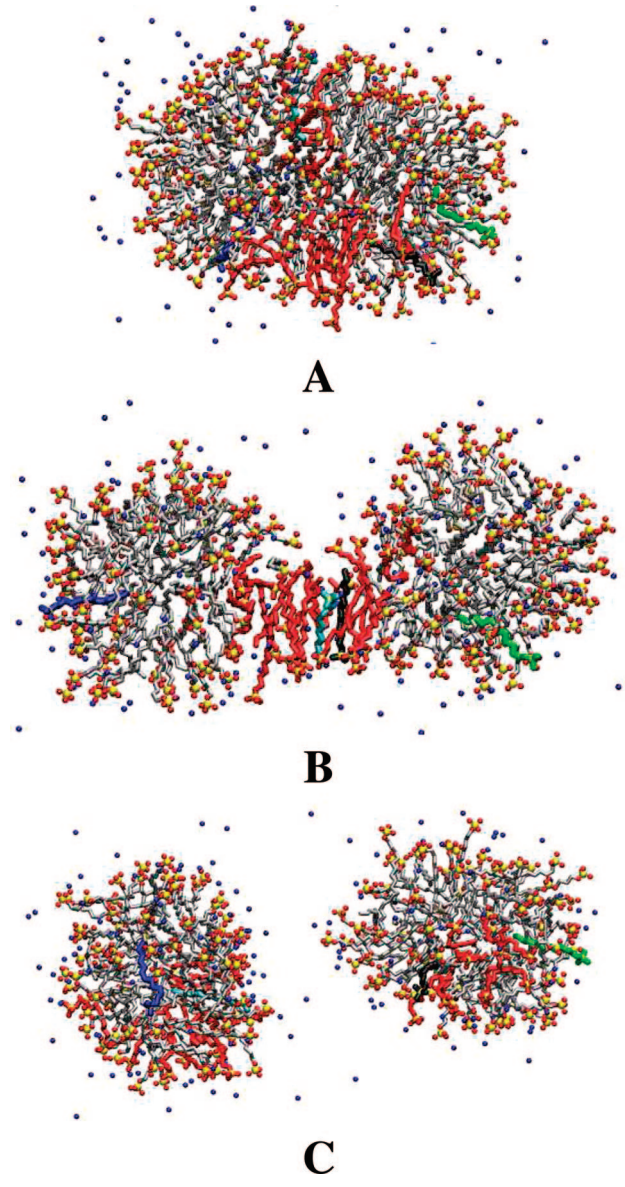

Figure 1. Simulated micelle splitting. The molecules regarded as the neck are colored in red. Highlighted molecules enable tracing of molecules from frame to frame; the cyan and black molecules are part of the neck. The other two highlighted molecules provide a comparison to the neck region dynamics. $T = 323$ K, $N_{SDS} = 186$. The snapshots are (A) at the beginning of the process (0 ns), (B) after 4 ns, and (C) after about 6 ns.

2. Methods

The study was performed using detailed atomic-level molecular dynamics simulations and a previously validated model[29] of anionic SDS surfactants in the presence of explicit solvent molecules (water), counterions (Na^+), and excess salt ($CaCl_2$ or NaCl). The simulation protocol was as follows. First, a micelle formed from an initially random SDS solution in the presence of 700 mMol of $CaCl_2$ was chosen. The salt concentration was then suddenly decreased, and the simulations were continued for up to an

(18) Putnam, F. W.; Neurath, H. *J. Am. Chem. Soc.* **1944**, *66*, 692.
(19) Armstrong, W. M. *Arch. Biochem. Biophys.* **1958**, *74*, 427.
(20) Sigal, G. B.; Mrksich, M.; Whitesides, G. *J. Am. Chem. Soc.* **1998**, *120*, 3464.
(21) Quina, F. H.; Nassar, P. M.; Bonilha, P. M.; Bales, B. L. *J. Phys. Chem.* **1995**, *99*, 17028.
(22) Bales, B. L.; Messina, L.; Vidal, A.; Peric, M.; Nascimento, O. R. *J. Phys. Chem. B* **1998**, *102*, 10347.
(23) Love, J. C.; Estroff, L. A.; Kriebel, J. K.; Nuzzo, R. G.; Whitesides, G. M. *Chem. Rev.* **2005**, *105*, 1103.
(24) Cabane, B. *J. Phys. (France)* **1981**, *42*, 847.
(25) Cabane, B.; Duplessix, R.; Zemb, T. *J. Phys. (France)* **1985**, *46*, 2161.
(26) Kékicheff, P.; Cabane, B. *J. Phys. (France)* **1987**, *48*, 1571.
(27) Kékicheff, P.; Grabielle-Madelmont, C.; Ollivon, M. *J. Colloid Interface Sci.* **1989**, *131*, 112.
(28) Rharbi, Y.; Chen, L.; Winnik, M. A. *J. Am. Chem. Soc.* **2004**, *126*, 6025.
(29) Sammalkorpi, M.; Karttunen, M.; Haataja, M. *J. Phys. Chem. B* **2007**, *111*, 11722.

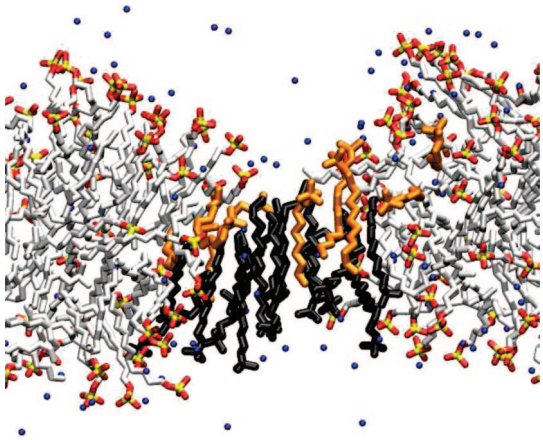

Figure 2. Close-up of the neck region. Interdigitation is almost complete, as the diameter of the cross-section is only slightly larger than the length of an SDS molecule.

additional 30 ns. In total, 20 runs with different initial conditions were performed to investigate the effects of temperature and ionic strength. Three different micelles of size $N_{SDS} = 181$, 186, and 188 were studied. Technical details are provided in the Supporting Information.

3. Results

At $T = 323$ K, the decrease in the ionic strength of the solution from 700 mMol of $CaCl_2$ to zero excess salt drives the micelles to split into two almost equally sized daughter micelles. This occurred for all three micelles corresponding to different initial conditions. In all three cases, fission occurred within about 6 ns after the sudden change in salt concentration; furthermore, the fission pathways were identical to the one shown in Figure 1: (1) Due to the sudden change in the ionic strength, and consequently in the screening length of Coulombic interactions, the surface experiences a strong deformation and a dumbbell is formed (Figure 1A–B). (2) The shapes of the dumbbell fluctuate and a long neck with strongly interdigitating rod-like structure forms between the heads (Figure 1B–C). The neck has a length of about 3.5−4 nm, which is comparable to the diameter of the head. The SDS molecules in the neck display almost complete interdigitation, which helps to provide a stretchable intermediate. (3) Finally, the stalk ruptures and the two daughter micelles quickly attain spherical shapes.

The detailed structure of the stalk is shown in Figure 2, and the nearest-neighbor intermolecular orientation distribution in Figure 3. The latter shows that the relative orientations of the SDS molecules are very different in the micellar regions and the stalk. Visual inspection of the configurations shows that there are areas of negative curvature and splay-like conformations, as well as almost gel-like ordering of the chains (see also Figures 1 and 2).

To examine the effect of temperature on fission kinetics, it was varied at 5 K intervals between T= 323 and 283 K for the $N = 181$ SDS system. At $T = 318$ K splitting took place with the same rate and pathway as at $T = 323$ K, but at lower temperatures the process halted at the formation of the dumbbell with a neck that oscillated in length. We suspect that a much longer simulation would have resulted in fission.

Interestingly, the counterions and excess salt ions play a dual role and help both destabilize and stabilize parts of the system at different stages of the fission process. First, as a result of the reduction in the ionic strength of the solution, the anionic SDS

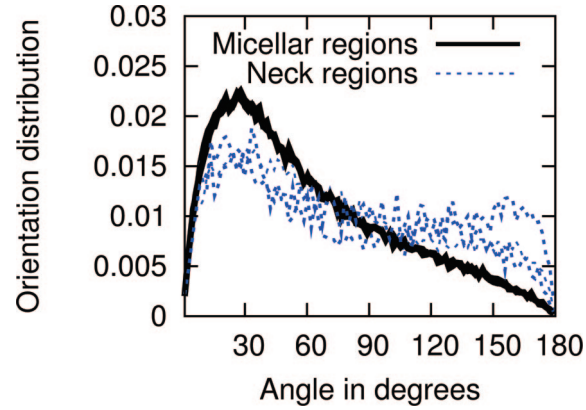

Figure 3. Nearest-neighbor intermolecular orientation distribution in micellar and neck regions. The three lines represent the $N = 181$, 186, and 188 SDS simulations at $T = 323$ K. In the micellar regions, the lines coincide.

becomes more loosely bound, leading to the initial Rayleigh instability.[30,31] Counterions and excess salt ions help, however, stabilize the stalk during the subsequent stages of the fission process. The presence of some excess salt at $T = 323$ K was observed to either slow down the fission process or *halt it to the dumbbell intermediate*, or if enough salt is present, to maintain the original elongated micellar form. While a concentration of 50 mMol of $CaCl_2$ was sufficient to maintain the original form of the micelle, 100 mMol of NaCl led to a fission event after 9 ns, and formation of the stalk was observed at 300 mMol of NaCl for up to 30 ns.

This stabilizing effect of counterions and excess salt can be understood via a simple argument based on the Poisson−Boltzmann equation.[32,33] Theory predicts that, in a dilute system, the (counter)ions are not bound to the charged sphere (micelle) but "escape" to the solution. To a first approximation, the (counter)ion distributions of the dumbbell heads overlap in the stalk region, leading to a larger localized (counter)ion density. It is precisely this cloud of condensed (counter)ions which helps stabilize the stalk. We attempted to quantify this argument by measuring the degree of counterion binding in the micellar and neck regions. While the data systematically suggest that the degree of counterion binding is higher in the stalk compared to the micellar regions for all cases studied, fluctuations in the data unfortunately prevent a more quantitative comparison.

The splitting process changes the dynamics of individual SDS molecules in a system undergoing fission by reducing the neighbor residence time by an order of magnitude in comparison to SDS molecules in a stable micelle, as shown by Figure 4. The graph plots the neighbor residence time distribution of the whole system for both the stable micelles and the splitting micelles—no difference was observed in the neighbor residence time distribution when the neck region molecules and the dumbbell heads were regarded separately in the splitting micelles. In the analysis, a neighboring SDS is defined as one with headgroup S−S distance less than 0.81 nm, which corresponds to the distance to the first minimum in the S−S radial distribution function. The data set used as stable micelles is described in detail in ref 29.

Finally, it is interesting to note that the gauche defect probability does not vary significantly between the neck region

(30) Strutt, J. W. (Lord Rayleigh) *Philos. Mag.* **1882**, *14*, 184.
(31) Deserno, M. *Eur. Phys. J. E* **2001**, *6*, 163.
(32) Deserno, M.; Holm, C.; May, S. *Macromolecules* **2000**, *33*, 199.
(33) Patra, M.; Patriarca, M.; Karttunen, M. *Phys. Rev. E* **2003**, *67*, 031402.

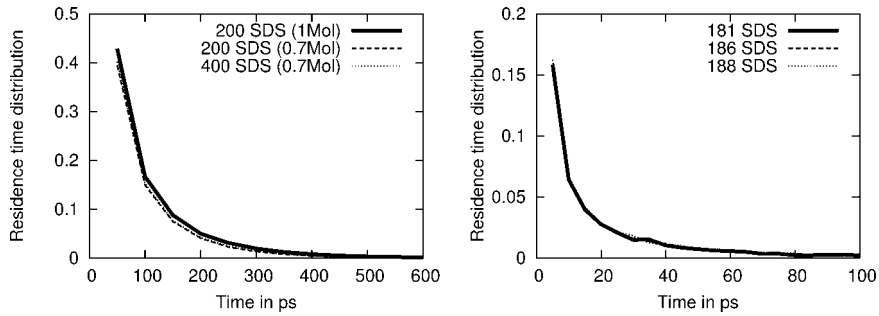

Figure 4. Neighbor residence time distributions in stable SDS micelles at different concentrations and system sizes (left) and in SDS micelles undergoing a fission (right). Note the order of magnitude difference in time axes between the two graphs. In both graphs, the different data sets coincide almost totally. The simulation details related to stable micelles are described in ref 29.

and the dumbbell heads. At first sight, this is surprising, as the semicrystalline nature of the neck region would seem to indicate a lower gauche defect probability for it in comparison to the dumbbell heads. On the other hand, the molecules are quite distorted in the neck region in order to protect the exposed hydrophobic chains, and this leads to an overall gauche defect probability very close to the value found in intact micelles.

4. Conclusions and Discussion

In this paper we have demonstrated a new micelle fission pathway which can be triggered by a sudden change in the excess salt concentration (or pK_a). This may provide a practical method to manipulate micelle sizes and contents. It may also be feasible to drive and control micellar fission events using an applied electric field to manipulate the (counter)ion concentration in the vicinity of micelles, allowing for easier compartmentalization and functionalization of micelles and vesicles. For example, it has been suggested that control of the stalk may be used as a conductivity microswitch in controlled release of vesicle contents in "kiss-and-run" exocytosis.[34,35] The observations reported here are in excellent agreement with experiments which have shown that an increase in excess salt is accompanied by a decrease in the observed fission rate,[10,11] and we provide a direct demonstration of the importance of electrostatic interactions and the appearance of large shape fluctuations. Perhaps more importantly, our simulations have provided a detailed microscopic view of the fission process in the case of the anionic SDS. We suspect that the observed stalk structure could also provide a low-energy pathway for bilayer fusion/fission in the case of charged lipids.

It is interesting to note that the fission events reported here take place within ~10 ns after the sudden change in the ionic strength of the solution. This is a very fast time scale relative to surfactant exchange processes which lead to the eventual equilibration of the surfactant−solvent system. Experimentally, such exchange processes occur over time scales ranging from milliseconds to minutes and have been found to be very sensitive to the ion concentration;[36] in vesicles the corresponding time scales are even longer.[37] Thus, direct molecular dynamics simulations offer a quantitative means to probe the fission pathways in which surfactant exchange kinetics are effectively "frozen-in" (and thus relatively unimportant). In our previous work, we have followed the time evolution of an initially random SDS system above the critical micelle concentration as micelles form, grow, and evolve over 200 ns.[29] The evolution includes fluctuations and deviations from the spherical shapes similar to those measured by Cabane et al.[25] (see also ref 29).

We would like to finish by pointing out the general importance of understanding micelle (and vesicle) fission. First, understanding the atomistic details and physical mechanisms behind fission, fusion, and fragmentation is key in designing soft nanostructures; see, e.g., ref 23. In this area, detailed atomistic simulations can provide important insight into the complex dynamics occurring during fission/fusion processes and their effects on the overall collective behavior, growth, and size selection of micelles. In addition to micelles and vesicles, it is important to understand electrostatic control and manipulation of molecules and assemblies in related systems such as dendrimers, which can be used in the transport of drugs and DNA into cells[38−41] or the packing of organic compounds using SDS micelles.[42]

Acknowledgment. We thank Markus Deserno for useful discussions. This work has been supported by Academy of Finland (M.S.), NSERC of Canada (M.K.), NSF-DMR Grant No. 0449184 (M.H.), and NSF-MRSEC Program, Grant No. DMR-0213706 (M.S. and M.H.). Computational resources from SharcNet (www.sharcnet.ca) are gratefully acknowledged.

Supporting Information Available: Simulation protocol and movies. This material is available free of charge via the Internet at http://pubs.acs.org.

JA8077413

(34) Frolov, V. A.; Lizunov, V. A.; Dunina-Barkovskaya, A. Y.; Samsonov, A. V.; Zimmerberg, J. *Proc. Natl. Acad. Sci. U.S.A.* **2003**, *100*, 8698.
(35) Ryan, T. A. *Proc. Natl. Acad. Sci. U.S.A.* **2003**, *100*, 2171.
(36) Rharbi, Y.; Winnik, M. A. *Adv. Colloid Interface Sci.* **2001**, *89*, 25.
(37) Zhdanov, V. P.; Kasemo, B. *Langmuir* **2000**, *16*, 7352.
(38) Langer, R. *Nature* **1998**, *392*, 5.
(39) Peer, D.; Karp, J. M.; Hong, S.; Farokhzad, O. C.; Margalit, R.; Langer, R. *Nature Nanotech.* **2007**, *2*, 751.
(40) Gurtovenko, A. A.; Lyulin, S. V.; Karttunen, M.; Vattulainen, I. *J. Chem. Phys.* **2006**, *124*, 094904.
(41) Pasupathy, K.; Lin, S.; Hu, Q.; Luo, H.; Ke, P. C. *Biotech. J.* **2008**, *3*, 1078.
(42) Badjić, J. D.; Kostić, N. M. *J. Phys. Chem. B* **2001**, *3*, 1078.