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Computer Study of Stimuli-Responsive Polyelectrolyte Micelles in Aqueous Media. Comparison of Monte Carlo and Self-Consistent Field Approaches

*Karel Jelínek, Filip Uhlík, Zuzana Limpouchová, Karel Procházka**

Summary: The behavior of polyelectrolyte micelles with kinetically frozen hydrophobic cores in aqueous solutions was studied by Monte Carlo (MC) simulations and self-consistent field (SCF) calculations. Some results have already been published. The structure of water-soluble shells formed by weak polyelectrolytes, both pure and containing a low fraction of strongly hydrophobic units arranged either in a short sequence or distributed uniformly in the shell-forming chains was studied in detail. In the case of sequenced system, the analysis of concentration profiles of individual species reveals strong segregation and important self-organization of hydrophobic units in the shell. A comparison and critical analysis of results of MC and SCF methods is presented.

Keywords: chain conformations; Monte Carlo simulations; polymeric micelles; self-consistent field calculations

Introduction

Aqueous solutions of self-assembled polymeric nanoparticles (micelles, vesicles, etc.) are interesting and practically important systems that offer a number of potential applications in different fields, e.g., as drug carriers in medicine.[1,2] It is why they have been amply studied by many research groups experimentally,[3–9] theoretically and by computer simulations for two last decades.[10–15] In our laboratory, we have been studying the behavior of kinetically frozen polyelectrolyte micelles by light scattering, fluorescence, different separation techniques, atomic force microscopy[16,17] and also by computer simulations[18–20] for more that ten years. The kinetically frozen micelles of high molar mass copolymers containing a long hydrophobic block, such as polystyrene, and a long weak polyelectrolyte block, such as poly(methacrylic acid), have to be prepared indirectly, e.g., by dialysis because the samples are insoluble in water. The sample is dissolved in a 1,4-dioxane-rich mixture with water and dialyzed against mixtures with increasing content of water. During dialysis, the quality of the solvent for PS deteriorates. The association number and the core density increase with increasing water content. At certain water content, the solvent is so bad for PS that the equilibrium exchange of unimers among micelles stops (because the cores are dense and very viscous and the concentration of free unimers virtually drops to zero). The micellization equilibrium kinetically freezes and with further increase in water content, the association number does not change any more, only the core shrinks and the shell expanses, because the quality for PMA improves. The final self-assembled nanoparticles can be regarded as glassy PS nanospheres decorated by the polyelectrolyte PMA brush which is tethered to their

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Department of Physical and Macromolecular Chemistry & Laboratory of Specialty Polymers, Charles University in Prague, Faculty of Science, Albertov 6, 128 43 Praha 2, Czech Republic
E-mail: prochaz@vivien.natur.cuni.cz

surface. However, their aqueous solutions are stable in a broad range of conditions and they represent important stimuli (pH and ionic strength)-responsive systems.

In our long-term research of nanoparticles with polyelectrolyte shells, we have been using computer simulations (Monte Carlo, self-consistent field and molecular dynamics) as a tool providing better insight in the studied problem. The combined multidisciplinary approach allows us to interpret experimental data unambiguously in detail. The comparison of experimental and computer data requires (i) good theoretical model that captures all essential features of the behavior and (ii) the use of appropriate parameters describing interactions. Because the use of coarse-grained models is indispensable for feasible and successful simulations of polymers, it is usually difficult to achieve a full quantitative agreement with experiment. We have always been interested in a semi-quantitative agreement only because it allows the analysis of the behavior at the coarse-grained level in detail providing that correct trends have been reproduced. Nevertheless, a proper parameter setting at this level is a delicate task and requires great care.

For studying the conformations of shell-forming chains, we have been using two independent approaches: Monte Carlo simulations combined with solving the radial Poisson-Boltzmann equation, MC-PB[20] and self-consistent field calculations, SCF (the spherical variant developed by Scheutjens and Fleer[21]). Both methods assume a rough spherical symmetry of micelles (i.e., the ‘‘ensemble-average symmetry’’). The MC-PB simulations strongly alleviate the symmetry burden, yield more detailed description of the shell structure, but they are very demanding from the computation point of view. The SCF approach is relatively fast and allows studying the conformational behavior in a broad range of pH, ionic strength and temperature, but it provides radial characteristics only. For an efficient analysis of experimental data and for predictions of properties of similar systems, it is desirable to combine both approaches. In this paper, we compare results of MC-PB and SCF methods for several systems differing in complexity. We analyze the data with the aim to identify and understand the most important sources of differences.

Model and Methods

Studied System

We use the parameters corresponding to kinetically frozen self-assembled spherical micelles that we recently studied by light scattering and by several other techniques.[16,17] The core is modeled as a hydrophobic sphere to which the shell-forming chains are tethered and the shell is modeled as a spherical polymeric brush. The shell-forming block is either a weak polyelectrolyte chain (E), or an amphiphilic chain, containing a high E content and a relatively low fraction (10%) of strongly hydrophobic units (H). The H units are distributed either uniformly or they are arranged in a short sequence inside the hydrophilic chain. Experimental studies of the latter system are in progress and results will be published in future. The studied systems are depicted in Figure 1. The

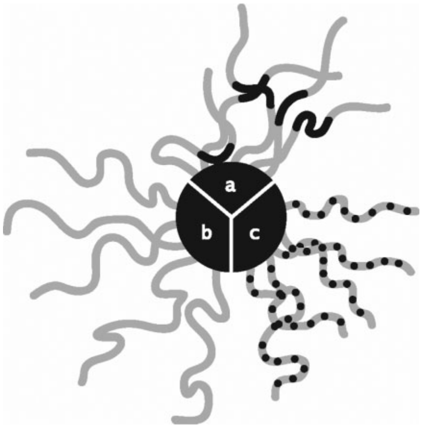

Figure 1.
Schematic depiction of studied systems with (a) one hydrophobic sequence, (b) unmodified chains and (c) alternating copolymer chains. Weak polyelectrolyte units are shown in gray, hydrophobic units and the core in black.

literature value of the dissociation constant for monomeric methacrylic acid, $pK_A = 4.69$[22] was used in both SCF and MC studies.[19,20] We study very dilute solutions and therefore we consider one micelle immersed in the solvent only.

The directly experiment-derived parameters are: association number, $N_{As} = 113$ and core radius, $R_C = 13$ nm.[16,17] The size of the spherical core was recalculated from the association number using the density of bulk polystyrene 1.05 g/cm^3.[23] Other parameters were obtained indirectly by the mapping procedure aimed at reproducing the most important structural features of the real system by the coarse-grained model, such as the experimental ratio of the contour length of shell-forming chains-to-the radius of the core and the flexibility of real and model chains (i.e., the same ratio C_∞ of the radius of gyration of real non-ionized linear chains and corresponding model E chains). The indirectly experiment-derived parameters are the lattice constant, $l = 1$ nm and the number of the Kuhn segments, $N = 100$. The coarse graining and the back-mapping procedure is a delicate task and was described and discussed in detail in our earlier studies.[18–20,26,27]

The parameters describing the short-range van der Waals interactions have been optimized in our earlier studies and are the following; χ-parameters (for SCF): $\chi_{EE} = 0.0$, $\chi_{EH} = 0.5$, $\chi_{ES} = 0.5$, $\chi_{HH} = 0.0$, $\chi_{HS} = 5.0$ and $\chi_{SS} = 0.0$,; ε-parameters (for MC): $(\varepsilon_{EE}/kT) = 0.8$, $(\varepsilon_{EH}/kT) = 0.6$ and $(\varepsilon_{HH}/kT) = -3.0$. They model a system in which the solvent is a θ-solvent for the non-ionized E units and a very strong precipitant for the core and for hydrophobic units (we assume the same value for the core-solvent and for H-solvent interaction). The solvent is an effective solvent, composed of H_2O, H_3O^+, OH^- and small ions Na^+ and Cl^- (the concentrations of which control pH and ionic strength). Its role is accounted for only implicitly, which means that the algorithm focuses on polymer chains and the solvent is assumed to occupy the lattice sites that are not occupied by the units of the polymer chain.

Self-Consistent-Field Calculations

Because the studied micelles are on average spherical nanoparticles, we performed simulations on a spherical lattice. Using the radial SCF developed by Scheutjens and Fleer,[21] we model the micellar shell as a brush tethered to the hydrophobic spherical core, i.e., we solve a "diffusion-like" master equation numerically on a spherical lattice. The fundamentals of this method (which allows the steps in all directions, including a back step) and pertinent computational schemes were described in a number of articles.[24,25]

Monte Carlo Simulation

We have been using configuration bias MC simulations on a simple cubic lattice. The shell-forming chains, which are tethered to the micellar core, are modeled as the fully inter- and intra-chain self-avoiding walks (in the geometrical sense, requiring that the chain does not intersect, i.e., each lattice site can be filled either by one polymer bead, or implicitly by the solvent). The Rosenbluth weights reflect not only geometrical restrictions, but also interaction energies, which are accounted for by the Boltzmann factor, $\exp(W/kT)$, where W is the interaction energy of the bead with all nearest neighbors. For the equilibration of the system, we employ two basic moves: (i) dissolution and random growth of a random part of a random chain and (ii) dissolution and random growth of a randomly chosen chain from a new randomly selected position at the core surface. The electrostatic contribution is treated indirectly by solving the radial Poisson-Boltzmann (PB) equation. A standard Metropolis criterion takes into account the short-range interactions (reflecting the solvent selectivity and compatibility of individual polymeric units) and the long-range electrostatic forces, which secures the self-consistency of the solution. Details of the simulation method were described earlier.[20]

Results and Discussion

In our earlier studies, we have found that both MC-PB and SCF reproduce all decisive features of kinetically frozen micelles with polyelectrolyte shells reasonably well.[18–20,26,27] The trends of measurable quantities compare satisfactorily with those observed in experiment at the semiquantitative level. However, we have found that MC-PB simulations underestimate and the SCF calculations overestimate the effect of pH and ionic strength. To demonstrate the differences between MC-PB and SCF, we compare global structural characteristics of core-shell micelles corresponding to PS-PMA experimental system.

In Figure 2 we collate the radii of gyration of micellar shells, R_g (i.e., the values of empty shells without cores) obtained by MC (dashed curves) and by SCF (full curves) as functions of pH for two values of ionic strength, $I = 0.01$ and 0.1, respectively. It is obvious that the mutually corresponding parameters characterizing the short-range van der Waals interactions between unionized groups have been set correctly because at low pH (at negligible ionization of -COOH), the gyration radii predicted by both methods compare well. With increasing pH, we witness quite pronounced divergence between MC-PB and SCF data, mainly at low I. The SCF curves increase more strongly than the MC-PB curves. "Experimental data" (not shown to yield a comprehensive graphics), i.e., the curves based on light scattering measurements for micelles and recalculated for empty shells, would be in between both corresponding curves (closer to MC-PB data).

The SCF approach inherently assumes the spherical symmetry of micelles. In complex micellar systems, the symmetry assumption can break down and reasonable results are no more guaranteed. Therefore, it is necessary to perform more severe tests of the applicability of SCF. For testing, we selected systems with complex internal structure - micelles with segmented shell-forming chains containing a relatively short H sequence inside the E chain, because one can expect some segregation and association of H units from different chains in shells leading to the symmetry perturbation.

We performed both SCF[6] and MC[7] studies and compared the data. We would like to point out that in the combined MC-PB approach we assume the spherical symmetry of the electric field only. We believe that the spherical field is an inherent feature of polyelectrolyte micelles with frozen spherical cores. As it is evident at the simulation snapshot (Figure 3) depicting a typical shell structure of the $E_{30}H_{10}E_{60}$ system for pH 7 and $I = 0.01$, this assumption does not prevent significant coiling of shell-forming E chains. The typical conformational behavior can be characterized as follows: The hydrophobic units from several chains partially adsorb at the core and partially self-assemble in small domains.

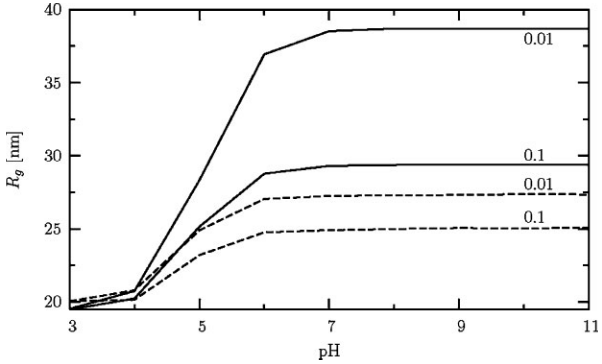

Figure 2.
Radii of gyration, R_g calculated by SCF (full lines) and by MC (dashed lines) as functions of pH; ionic strength indicated on the curves.

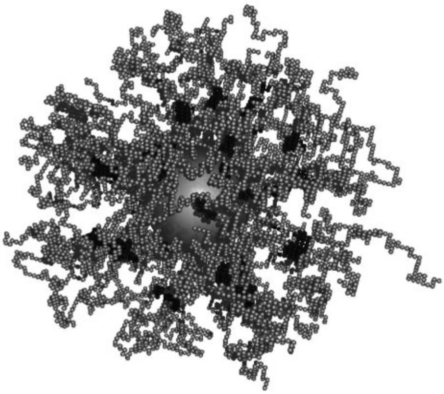

Figure 3.
A snapshot of $E_{30}H_{10}E_{60}$ system for pH 7 and $I = 0.01$. Polyelectrolyte units and the core are light grey, hydrophobic units are dark grey.

Figure 4 shows the probability densities $\pi_T(r)$ and $\pi_H(r)$ of all shell-forming units (thin curves) and of H units (bold curves) for $I = 0.01$ and pH 5. They are normalized by the formula: $\int_{r=R_C}^{R_{\max}} \pi_i(r)dr = 4\pi \int_{r=R_C}^{R_{\max}} \rho_i(r)r^2 dr = 1$, where $\rho_i(r)$ are number densities of units $i = \mathrm{T}$ or H, respectively. The MC data show that the domains are localized in relatively narrow radial regions forming spherical strips around the core, in which they are distributed uniformly in all directions. We can summarize that MC simulations confirmed our speculations concerning the shell structure.[26]

The formation of hydrophobic domains in two distinct spherical layers (immediately around the core and quite far from it) is a result of the enthalpy-to-entropy interplay. The adsorption of H units at the core is favorable from the enthalpy point of view, but it causes a partial collapse of chains or at least the formation of loops which lowers the entropy. The formation of small H domains does not almost affect the entropy, but the domains are not as compact as the core and their surface-to-volume ratio is quite high. Hence the minimization of the number of unfavorable interactions with water molecules is relatively low. The optimization of the enthalpy-to-entropy balance leads to a bimodal distribution of chain conformations. We observed a similar conformational behavior both experimentally and theoretically in fluorescently labeled systems.[17] The MC study shows that the conformational behavior depends on the position of the H sequence in the E chain, on pH and ionic strength.[26] An increase in pH promotes ionization and the counterion-mediated electrostatic force induces the stretching of polyelectrolyte chains. At high pH, a lower fraction of hydrophobic sequences returns back to the core and a higher fraction of hydrophobic sequences forms domains at larger distances from the core (not shown). In systems with H sequence

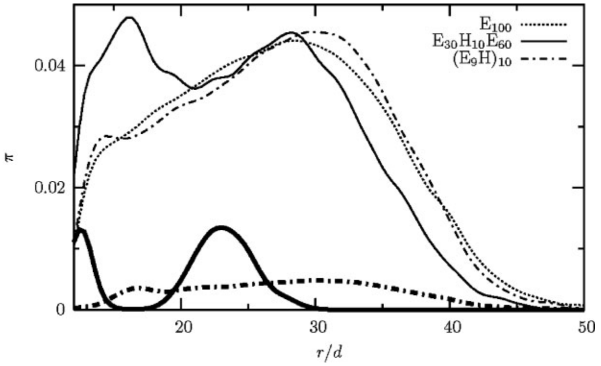

Figure 4.
Probability density functions of finding a bead, any one (upper thin curves) and the hydrophobic one (lower bold curves), at a distance from the core center r for pH 5 and $I = 0.01$ (the curves are normalized as follows: the integrated area below π_T curve equals 1 and that below π_H equals 0.1; hence the values plotted on the y-axis depend also on the total x-interval of the corresponding curve).

close to the middle of E chain, an almost complete conformational transition from the core-adsorbed to the domain-forming regime can be observed.[26]

The tests of the SCF applicability for micelles with nanosegregated shells are generally positive.[27] This method yields only radial functions, but it also predicts the formation of two layers containing increased concentrations of H units – one around the core and the other in a distance depending on the H sequence position in the E chain, further on pH and ionic strength. Figure 5 shows the comparison of probability densities $\pi_T(r)$, thin curves and $\pi_H(r)$, bold curves, predicted by both methods for the $E_{30}H_{10}E_{60,}$ $I = 0.01$ and (a) pH 5 and (b) pH 7. Besides the already mentioned difference in the pH-provoked shell-stretching, we see one other effect of electrostatics which differs in both methods. While the MC-predicted conformational transition is only partial in the relatively narrow pH region from 5 to 7 and the $\pi_H(r)$ curves are bimodal in both cases, a strong role of increasing dissociation results in a complete transition from the bimodal to the monomodal regime (containing only domains far from the core) in the SCF prediction.

The Analysis of Sources of Differences Between MC-PB and SCF

The comparison of fundamentals of SCF and MC approaches suggests that the observed differences are caused mainly by dissimilar treatment of chains in both methods. In our Monte Carlo simulations, the interaction energy of all units with all neighbors is taken into account in order to accept or to reject the conformation. The SCF approach treats an average "pseudo-chain" in a mean force field, which depends only of the radial position and hence it neglects details of the shell structure. In MC, the interaction energy of the unit under consideration depends on the instantaneous arrangement of all surrounding species while in SCF it is an effectively

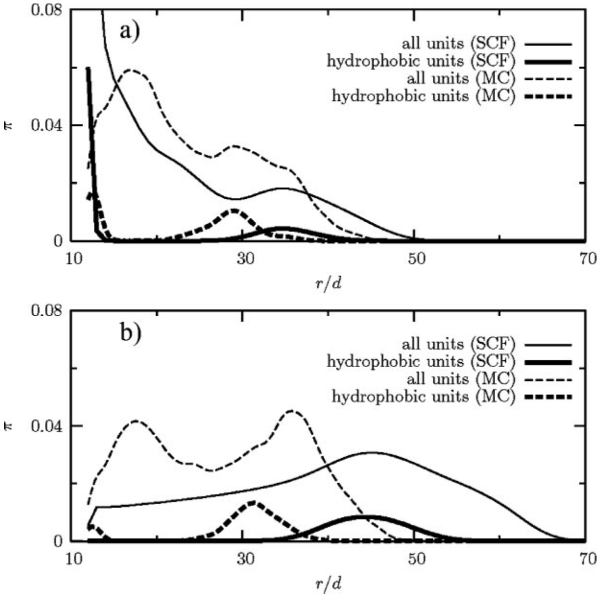

Figure 5.
Comparison of MC and SCF probability density functions of finding a bead, any one (thin upper curves) and the hydrophobic one (bold lower curves), at a distance from the core center r for $E_{30}H_{10}E_{60,}$ $I = 0.01$ and (a) pH 5, (b) pH 7.

angularly averaged function of the radial distance from the symmetry center.

The fact that the used SCF *a priori* assumes spherical symmetry of all properties represents other source of differences. The applied MC uses a simple cubic lattice and the Metropolis criterion does not prefer any direction during the self-avoiding growth of individual chains. Only the energies of instantaneous configurations count. In contrast to MC, the radial SCF assumes only radial characteristics and uses a spherical lattice. Hence it *a priori* differentiates between radial and tangential directions and treats the properties of chains in different directions unevenly.

The most severe discrepancies originate from different handling of the self-avoiding character and connectivity of chains. In the used MC, the fully connective self-avoiding chains are generated. The self-consistent field calculations do respect the self-avoiding character and connectivity of "pseudo-chains" only implicitly, i.e., only the global layer characteristics are important, and steps in all directions (including a reversal step) are allowed. The equivalency of all lattice points in a layer perturbs the connectivity of "pseudo-chains" in tangential directions. The difference between radial and tangential directions translates in a suppressed effect of the excluded volume, which is accounted for by the average layer density only. In summary, the SCF "pseudo-chains" are not strictly self-avoiding, not fully connective and effectively more flexible than the MC chains.

Different relevance of the self-avoiding character and connectivity of shell-forming chains in model systems results in higher sensitivity of "SCF shells" than "MC shells" to pH and ionic strength. The study suggests that the insufficient self-avoidance plays particularly important role in systems of weak polyelectrolytes, where all electric charges are "mobile". In the MC-PB approach, the forbidden intersection of chains is the "highest imperative" of the conformational behavior. Therefore many local conformations (favorable from the point of view of distribution of charges) are forbidden and charges (formed due to –COOH dissociation) redistribute on the chain in order to minimize the electrostatic energy. The SCF approach neglects the interchain correlations and the E sequences experience only the angularly averaged electric forces acting under θ conditions without any geometrical restrictions, while "MC chains" are strongly influenced by all types of correlation effects (similarly as chains in real systems). It is why in MC, the effect of electrostatic forces is rather weak and indirect.

The most important result of the MC study is a piece of information that the H domains are distributed (on average) uniformly in all directions in narrow spherical layers. This finding justifies the applicability of the spherically symmetrical SCF approach for the studied systems and proves that the SCF results are not invalidated due to major "symmetry collapse". The SCF itself does not reveal the true physical nature of hydrophobic layers that are in reality relatively narrow zones containing a number of small and compact hydrophobic domains, but a combination of fast SCF with detailed MC is very useful.

Conclusion

Both the MC and spherically symmetrical SCF provide reasonable predictions of the behavior of kinetically frozen micelles in aqueous buffers. The angularly averaged radial functions compare well at the semi-quantitative level, but in spite of a considerable effort in optimization of parameters, a good quantitative agreement between MC and SCF results was not achieved. In this respect, our conclusions agree with our earlier observations[8–20] and with those of many other authors.[8–35]

Monte Carlo simulations considerably suppress the symmetry limitations and provide more detailed description of the shell behavior. Information concerning the radial and angular distribution of hydrophobic domains provided by MC justifies the applicability of SCF for systems with nanoheterogeneous shells.

The SCF data are not self-explanatory, but their combination with MC is very useful. This finding is practically important: SCF is much faster than MC and allows for extensive studies of dependences on pH, I and on the type of distribution of H units in the shell-forming chains.

The excessive sensitivity of SCF results to pH and I can be, according to our opinion, explained by the following arguments. The SCF approach does not strictly respect the connectivity and the self-avoidance of individual chains, but the used MC variant does. Because some conformations of self-avoiding chains (even though favorable from the point of view of the charge distribution) cannot be achieved, the charges redistribute along the weak polyelectrolyte chains (i.e., the dissociation occurs at different positions) in order to minimize the Gibbs function. The redistribution of charges provides a feedback attenuating the effect of electrostatic forces in MC simulations. The same principle holds in real systems. As the SCF treatment does not capture this feature, the average response of SCF pseudo-chains is strongly influenced by electrostatic forces and the pH response is exaggerated.

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