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Dissipative Particle Dynamics Simulation Study of Poly(2-Oxazoline)-based Multicompartment Micelle Nanoreactor

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ABSTRACT

We investigate multicompartment micelle consisting of poly(2-oxazoline)-based triblock copolymers for nanoreactor application, using DPD simulation method to characterize the internal structure of micelle and the distribution of reactant. The DPD simulation parameters are determined from the Flory-Huggins interaction parameter (χ_{FH}). From the snapshots of the micellar structures and radial distribution function of polymer blocks, it is clearly presented that the micelle has the feature of the multicompartment. In addition, by implementing the DPD simulations in the presence of reactants, it is found that Reac-C4 and Reac-OPh are well associated with the hydrophilic shell of the micelle whereas other two reactants such as Reac-Ph and Reac-Cl are not incorporated into the micelle. From our DPD simulations, we confirm that the miscibility (solubility) of reactant with the micelle has strong correlation with the rate of hydrolysis kinetic resolution. Utilizing accurate methods evaluating accurate χ_{FH} parameters for molecular interactions in micelle system, this DPD simulation can have a great potential to predict the micelle structures consisting of designed multiblock copolymers for useful reactions.

Keywords: hydrolytic kinetic resolution, multicompartment micelle, dissipative particle dynamics simulation, Flory-Huggins interaction parameter

1. INTRODUCTION

Multicompartment micelle has gained intensive attention in recent catalysis chemistry community.[1-8] This material contains multiple well-defined spaces in nanoscale structure, which has shown great potentials for nanoreactor technology.[1-10] Owing to the successful progress in fine synthesis in polymer chemistry, well-defined architecture in multi-block copolymer chain leads to a highly controlled morphologies and functionalities of their aggregates.[6] Especially, the placement of reactive substrates or catalysts on the hydrophobic blocks results in highly localized compartmental space in the micellar core in aqueous solvent environment.[4, 6, 9-11] Besides, the hydrophilic shell of micelle can protect these sites from any undesirable environments such as solvents and impurities which can cause deactivation of chemical reaction or degradation of products.[2, 4, 7, 8, 11, 12]

According to the report from O'Reilly and coworkers,[3, 5, 13] smart micelle nanoreactor with a selectivity towards reactants can be generated through introducing specific interactions such as hydrogen bonding, ionic and hydrophobic interactions, implying that reactive catalysts can be embedded in such nanoreactors. Since catalysts are highly localized and encapsulated within the core of micelle, the accessibility of reactants to the reactive core is one of the most crucial factors in developing successful micelle-based nanoreactors. For instance, Weck and coworkers[4, 11] have studied the poly(2-oxazoline)s (POXs) based shell cross-liked multicompartment (SCM) micelle which can be utilized as nanoreactor for the hydrolysis kinetic resolution (HKR) of epoxides. Although the recyclability of catalysts was enhanced by cross-linking the shells in the micelle, it was observed that the HKR of some epoxides was carried out in the SCM micelle nanoreactor with unexpectedly slow rate: the HKR of epichlorohydrin with Co(III)-salen (catalyst) was completed within 5 hours without using micelle, whereas it was not completed in the micelle

even after 24 hours. This result might be due to the shell of micelle blocking the reactive sites as a structural barrier in the micelle. In this case, the transport or permeation of reactant through such structural barrier plays an important role for determining the rate of the HKR of epoxides.

In our previous study,[14] regarding the structural barrier as a permeation barrier, we investigated the correlation of Flory-Huggins parameter (χ) with the reaction rate of HKR using full-atomistic molecular dynamics (MD) simulation method. The Flory-Huggins parameter (χ) is a measure of the solubility (or miscibility) of reactants with the micelle, which is a main governing factor for the permeability of the reactants. Although our full-atomistic MD simulations successfully described the association of reactants and products with the micelle as observed in experiment,[14] it was not possible to characterize the distribution of reactants throughout the entire multicompartment micelle with large dimension using such full-atomistic MD simulation. Thus, the details of the reactant distribution in each compartment and at the interface between the compartments remains veiled up to date.

In this study, we investigated the structure of micelle consisting of POX-based triblock copolymers and its association with the reactants using dissipative particle dynamics (DPD) simulation method. DPD simulation method developed by Hoogerbrugge and Koelman[15, 16] has been successfully employed to study the microstructure and properties of polymer phases,[17, 18] the hydrodynamic behavior of complex fluids,[16, 19-22] the microphase separation of polymer mixtures.[23-26] Especially it is noted that the self-assembled structures of multicompartment micelles has been intensively characterized using DPD simulation method.[27-32] Inspired by these efforts, we implemented the DPD simulations to elucidate the structure of micelle as a self-assembly of triblock copolymers and the distribution of reactant

molecules within the micelle.

2. MODELS AND SIMULATION METHODS

2.1. Models

In the scheme of DPD simulation, the atomistic details of polymer structure are replaced by simplified bead-spring model, so-called coarse-grained model, whose individual beads corresponds to a group of atoms.[15, 16, 19] In this study, three POX derivatives were expressed using few number of particles as shown in Figure 1. This coarse-graining was carried out using molecular surface area of monomeric units which was evaluated from the solvation free energy as reported in our previous paper.[14] The ratio of surface area is almost PSCoX:PBOX:PMOX = 1:4:8. Then, we ran MD simulations for equilibrium conformations and found that PSCoX has more compact molecular structure. Thus, we decided to use 1:3:6 ratio, meaning that the numbers of monomers to have similar surface area are 6, 2, and 1 for PMOX, PBOX, and PSCoX, respectively. Similarly, the reactant and product molecules were also coarse-grained as presented in Table 1. Although the yellow block B has the reactive triple bond at the end of the side chain for the formation of cross-linked micelle, we simulated micelle without cross-linking in this study. However, we left the block B to keep its molecular interaction with reactants.

Here, we need to emphasize the nature of coarse-grained model for DPD simulation employed in this study: in addition to the structural coarse-graining by lumping atoms into large beads, the interactions between coarse-grained beads are described by Flory-Huggins χ parameters which implicitly reflect all the detailed atomistic interactions such as van der Waals, electrostatic and hydrogen bond interactions. Although the model loses most of the atomistic details via this aggressive simplification, the phase separation or segregation can be

efficiently simulated using DPD simulation compared to traditional MD simulation.

2.2. DPD Simulation Details

The momenta and position vectors of the DPD particles are governed by Newton's equations of motion:[15, 16, 19]

$$\frac{d\vec{r}_i}{dt} = \vec{v}_i, \qquad m_i \frac{d\vec{v}_i}{dt} = \vec{f}_i \tag{1}$$

where $\vec{r}_i, \vec{v}_i$ and m_i are the position, velocity, and mass of the *i*-th particle, respectively. The force $\vec{f}_i$ acting on each particle in the DPD simulation consists of three parts as shown by the following equation:

$$\vec{f}_i = \sum_{j \neq i} (F_{ij}^C + F_{ij}^D + F_{ij}^R) \tag{2}$$

where F_{ij}^C, F_{ij}^D, and F_{ij}^R are denoted for the conservative force, the dissipative force, and the random force. The three forces are considered within a certain cutoff radius r_c. The conservative force is a soft repulsion acting along the line of centers and is given by

$$F_{ij}^C = \begin{cases} a_{ij}(1 - r_{ij}/r_c)\hat{r}_{ij} & (r_{ij} < r_c) \\ 0 & (r_{ij} \geq r_c) \end{cases} \tag{3}$$

where a_{ij} and r_{ij} denote a maximum repulsion force and distance between particles *i* and *j*, respectively, and $\hat{r}_{ij}$ denotes a unit vector directing from particle *i* to particle *j*. The parameters for repulsion between particles of different types are obtained as a function of the Flory-Huggins interaction parameter χ_{ij} calculated from the Hildebrand solubility parameter (δ). The repulsive parameter (a_{ij}) is expressed as follows:[19]

$$a_{ij} = a_{ii} + 3.27\chi_{ij} \tag{4}$$

According to the regular solution theory, χ_{ij} can be calculated from Hildebrand solubility parameters:

$$\chi_{ij} = \frac{V_m(\delta_i - \delta_j)^2}{RT} \tag{5}$$

where δ_i, V_m, R and T are the Hildebrand solubility parameter of particle i, the mixed molar volume of particles, gas constant, and temperature (300 K). In order to evaluate the Hildebrand solubility parameters (δ_i), we prepared three pure systems for PMOX (DP=100, 2 chains), PBOX (DP=100, 2 chains) and PSCoX (DP=30, 2 chains) and ran NPT MD simulations for 5 ns in equilibrium state. From such equilibrium MD simulations, δ_i was calculated by $\delta = [(\Delta H_v - RT)/V_m]^{1/2}$ where ΔH_v is the heat of vaporization, and V_m is the molar volume.[33, 34]

The dissipative force F^D and the random force F^R are expressed by:

$$F_{ij}^{D} = -\gamma\omega^D(r_{ij})(\hat{r}_{ij}\cdot\vec{v}_{ij})\hat{r}_{ij} \tag{6}$$

$$F_{ij}^{R} = \sigma\omega^R(r_{ij})\theta_{ij}\hat{r}_{ij} \tag{7}$$

where ω^D and ω^R are weight functions vanishing for $r > r_c$, $\vec{v}_{ij} = \vec{v}_j - \vec{v}_i$, γ is the friction coefficient, σ is the noise amplitude, and θ_{ij} is a randomly fluctuating variable with Gaussian statistics. The two weight functions can be taken simply as

$$\omega^D(r) = [\omega^R(r)]^2 = \begin{cases} (1 - r_{ij}/r_c)^2 & (r_{ij} < r_c) \\ 0 & (r_{ij} \geq r_c) \end{cases} \tag{8}$$

$$\sigma^2 = 2\gamma k_B T \tag{9}$$

A simulated box size was fixed at 25×25×25 r_c^3 with periodic boundary conditions.

With the reduced bead density ρ $(=r_c^3/V_m)$ is 3, bead density of 3, the box contained about 47,000 DPD beads, 10% of which was used for the polymer molecules. The coarse-grained structure of POX triblock copolymer was drawn as Figure 1. The time step and harmonic spring constant were taken as 0.05 and 4, respectively. The simulation took a total of 2×10^5 DPD steps to guarantee the equilibration of the system. The equilibrium states were confirmed through monitoring pressure, temperature, density and radius of gyration of micelle. In Table 2, the repulsive parameters used in this DPD simulation are summarized. According to Groot and Warren,[19] $a_{ii}=25$ was determined to obtain a compressibility of liquid water and is broadly used for liquid systems in general. Three independent simulations were performed for each system and the results were averaged.

To quantitatively analyze the simulated micellar structures, radial distribution function (RDF) was utilized. The RDF, which is usually denoted by *g(r),* is calculated by the following equation:

$$g_{COM-polymer}(r)=\left(\frac{n_{polymer}}{4\pi r^2\Delta r}\right)/\left(\frac{N_{polymer}}{V}\right) \qquad (10)$$

where $n_{polymer}$, V, and $N_{polymer}$ denote the number of particle found in a shell ($4\pi r^2\Delta r$) apart from the center of mass of micelle by the distance (r), the total volume of simulated system, and the total number of particle in the simulated system, respectively.

3. RESULTS AND DISCUSSION

Total 5 systems were simulated to investigate how the reactant molecules were distributed through the multicompartment micelle. The block sequence of $A_{50}B_2C_2$ was employed: the block A, B and C represent PMOX, PBOX and PSCoX, respectively.

First, a bare micelle system was simulated without reactant molecules. From Figure 2a, it is observed that the hydrophobic blocks (red color) form the micelle core by minimizing the

undesirable contact with solvent phase and other types of blocks, while the hydrophilic shell is also formed to wrap the core from the external solvent phase. From the RDF of the polymer blocks (Figure 2b), it is also observed that each domain has shell structure within the micelle system: the core domain (block C, red color) is located from the center of the micelle up to $5r_c$, while the most of block A (blue color) is distributed in the outermost region ranging from $2r_c$ to $7r_c$. Clearly, the polymer block phases are significantly overlapped. However, it should be noted that such internal structure can be better-defined by increasing block length since the value of χN increases with increasing N and thereby the phase-separation will develop more.

In the following sections, the distribution of reactant molecules in the micellar structure is presented. In each case, total 450 molecules of reactant molecules were added to the micelle system (equivalent to 1.1 mol %).

3.1. Reac-OPh and Reac-C4

In Figure 3a, due to the weak repulsive interaction between Reac-OPh molecules and polymer blocks, numerous reactant molecules are associated in the hydrophilic domain (block A). In addition, some amount of reactant molecules are located around the core domain. According to the RDF shown in Figure 3b, it is confirmed that the reactant molecules are well accommodated in the hydrophilic shell consisting of block A from $3r_c$ and $8r_c$. It seems that there are a few reactant molecules in the hydrophobic core domain.

Figure 4a shows that Reac-C4 molecules are well dispersed in micelle, which is comparable to Reac-OPh. Both cases demonstrated a strong evidence (Figure 4b) confirming that the high solubility of reactant molecules enhances the molecular association of reactants with the hydrophilic shell of micelle, and results in the high accessibility of reactant to the

reactive sites in the micelle core.

The important finding from these simulations with two reactants is that these reactants have higher rate of HKR compared to other cases. From this, it is concluded that this higher rate of HKR is correlated with the miscibility of the reactants with the micelle. We think this is because the miscibility is a component of the permeation of reactants into the reactive core of micelle.

3.2. Reac-Ph and Reac-Cl

In our previous studies,[14] Reac-Ph and Reac-Cl were characterized to be less miscible in the micelle structure compared to Reac-OPh and Reac-C4, which is well described in our DPD simulations as illustrated in Figures 5 and 6. Figure 5a shows that Reac-Ph molecules form a cluster on the micelle surface, instead of being incorporated into the micelle due to the poor miscibility of Reac-Ph. Hence, the results observed from DPD simulations lead to the conclusion that the slow HKR of Reac-Ph is straightforwardly attributed to the poor miscibility between Reac-Ph and micelle.

Another reactant (Reac-Cl) with the slow rate also exhibits a poor incorporation into the micelle as similarly observed in the case of Reac-Ph. Unlike the system with Reac-Ph, Reac-Cl molecules are spread over the surface of the micelle and enter the hydrophilic shell to some extent, which is consistent with the observation in Figure 6b. We think that this difference is well explained by the repulsive interaction parameters reported in Table 1. With respect to PMOX, PBOX and PSCoX, the repulsive interaction parameters (a_{ij}) of Reac-Ph have greater values than those of Reac-Cl, which means that Reac-Ph undergoes more exclusion from the micelle. Besides, the larger value of a_{ij} of Reac-Cl against water phase plays a role in driving the Reac-Cl molecules into the hydrophilic shell more.

3.3. Comparison with Previous χ_{FH} Parameters

In our previous study,[14] The χ_{FH} parameters were calculated as a function of compositions. Moreover, the energy of mixing was independently calculated from the mixed systems. In contrast, the χ_{FH} parameters used for DPD simulations are calculated using the δ parameters without considering the concentration (or composition) as expressed by Equation (5). For this reason, it seems to be necessary to compare one set of parameters to another in order to identify any possible deficiency in the current scheme of χ_{FH} parameter calculation and its solutions to improve the quality of parameters.

Figure 7 shows the comparison of χ_{FH} parameters for variety of reactant with respsect to a polymer (Figure 7a) and variety of polymer with respect to a reactant (Figure 7b). First, it is found from the most cases that the values of χ_{FH} parameters calculated from the δ parameters for DPD simulations are smaller than those calculated from our previous MD simulation study. Although it seems to be obvious because the different χ_{FH} parameters can be resulted from the different theories, it is noted that the χ_{FH} parameters calculated from the MD simulations with the composition of 70 wt% reactant shows similar trend to those calculated from the δ parameters. We think that this is because the δ parameter is calculated from the condensed phase, and the composition of 70 wt% provides a similar condition of the condensed phase as used in the calculation of δ parameters. Considering that the phase separation or segregation are determined by relative miscibility or immiscibility among components, it is anticipated that that the phase segregation described using χ_{FH} parameters with the composition of 70 wt% reactant would be in agreement with the phase segregation usign δ -based χ_{FH} parameters.

Another point in Figure 7a is that the χ parameters for Reac-OPh and Reac-C4 are smaller than those for Reac-Cl and Reac-Ph with respect to PMOX, which confirms that our understanding based on the simulated χ parameters has a good predictability for HKR of

epoxides. This means that Reac-OPh and Reac-C4 have better miscibility with the micelle corona than Reac-Cl and Reac-Ph, which is in a good agreement with the observation of the previous publication.[14] In other words, Reac-OPh and Reac-C4 are expected to be associated more with the micelle corona compared to Reac-Cl and Reac-Ph.

Figure 7b presents the change of χ parameter of Reac-OPh with polymer blocks such as PMOX, PBOX and PSCoX, which provides an evaluation of χ parameter as Reac-OPh diffuses into the micelle from corona to core. First, at lower concentration conditions, namely, 15 wt% and 45 wt%, the value of χ parameter with the core is smaller, meaning that Reac-OPh is miscible with the core (PSCoX, the reactive site of HKR) more than with corona (PMOX) and mid-shell (PBOX). On the contrary, the χ parameter monotonously increases at higher concentration condition, meaning that diffusion of Reac-OPh towards the core of micelle becomes more difficult, which is also observed that the solubility-based χ parameter in DPD simulation. Here, please note that HKR occurs at the core of micelle, indicating that Reac-OPh will be consumed at the core. Then the concentration at the core will be reduced, which will facilitate new provision of Reac-OPh into the core.

By considering this χ parameter as well as the distribution through the micelle, it is conclusively clear that the HKR has strong correlation with the miscibility (or solubility) of reactant with micellar nanoreactor.

4. SUMMARY

DPD simulation method was employed to simulate the multicompartment micelle consisting of 71 POX-based triblock copolymers ($A_{50}B_2C_2$). The DPD parameters were determined according to the Flory-Huggins interaction parameter (χ_{FH}) calculated from the Hildebrand solubility parameters (δ). Both the coarse-grained molecular models and the

RDF data from DPD simulations confirm that the micelle has the feature of the multicompartment.

Next, the incorporation of reactant molecules into the multicompartment micelle was investigated. The simulations showed that Reac-C4 and Reac-OPh are well associated with the micelle, especially in the hydrophilic shell whereas Reac-Ph and Reac-Cl are not mixed with the hydrophilic shell. These findings are in a good agreement with the previous experiment[4] and simulation study,[14] reporting that the miscibility (solubility) of reactant with the micelle has strong correlation with the rate of HKR.

Using DPD method, the entire micelles with detailed internal multicompartment micelles feature were efficiently simulated in the presence of water phase, and the distributions of reactants through this multicompartment micelle were quantitatively characterized. By combining accurate method evaluating χ_{FH} parameters for molecular interactions in micelle system, this DPD simulation protocol can be applied for selecting promising candidates for higher rate of HKR.

5. ACKNOWLEDGMENTS

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Table 1. Chemical structures of reactant and product molecules and their coarse-grained model in DPD simulation. Water molecule was also coarse grained by single bead in this simulation scheme

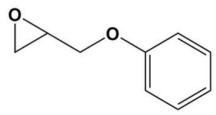
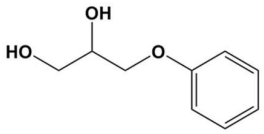
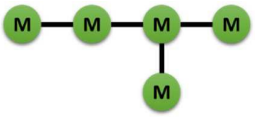
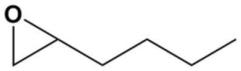
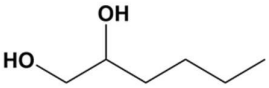
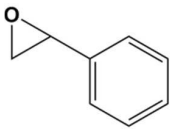
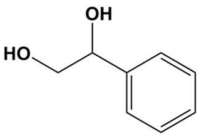
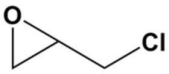
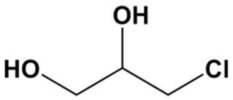
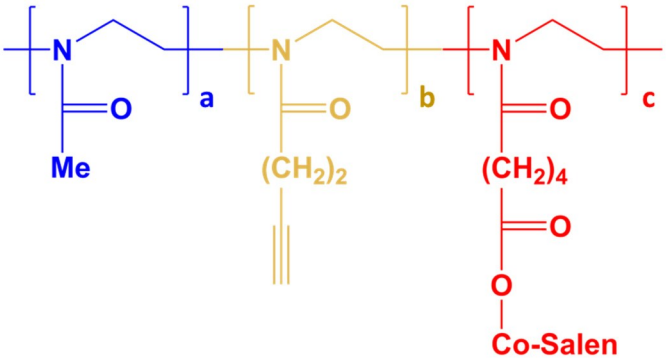
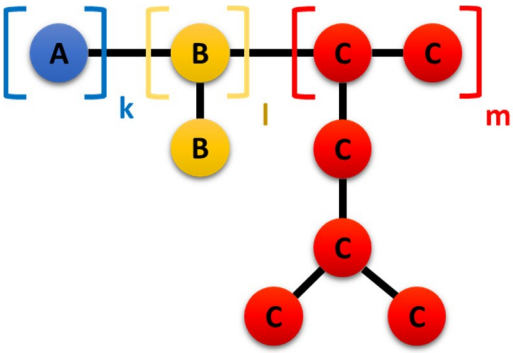
Entry	Atomistic Chemical Structure		Coarse-Grained Model
1			
	Phenyl glycidyle ether (Reac-OPh)	Phenol glycerol ether (Pro-OPh)	
2			
	Epoxyhexane (Reac-C4)	Hexane diol (Pro-C4)	
3			
	Styrene oxide (Reac-Ph)	Phenylethane diol (Pro-Ph)	
4			
	Epichlorohydrine (Reac-Cl)	Chloropropane diol (Pro-Cl)	

Table 2. Repulsive interaction parameters (a_{ij} in Equation (4)) among the components in DPD simulation system. A, B, C, and W denote PMOX, PBOX, PSCoX and water solvent, respectively. Since each simulation includes only one type of reactant or product molecules with the polymer micelle, there is no parameter among reactant and product molecules

	A (PMOX)	B (PBOX)	C (PSCoX)	W (Water)
A	25.00	-	-	-
B	25.01	25.00	-	-
C	26.60	26.34	25.00	-
W	83.57	85.23	104.56	25.00
Reac-OPh	25.84	26.17	32.93	136.35
Reac-C4	25.00	25.04	28.70	155.98
Reac-Ph	36.38	37.50	52.79	90.56
Reac-Cl	30.46	31.24	42.93	108.43

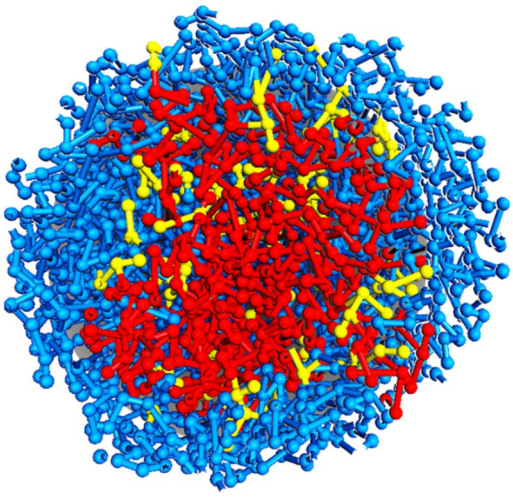


(a)

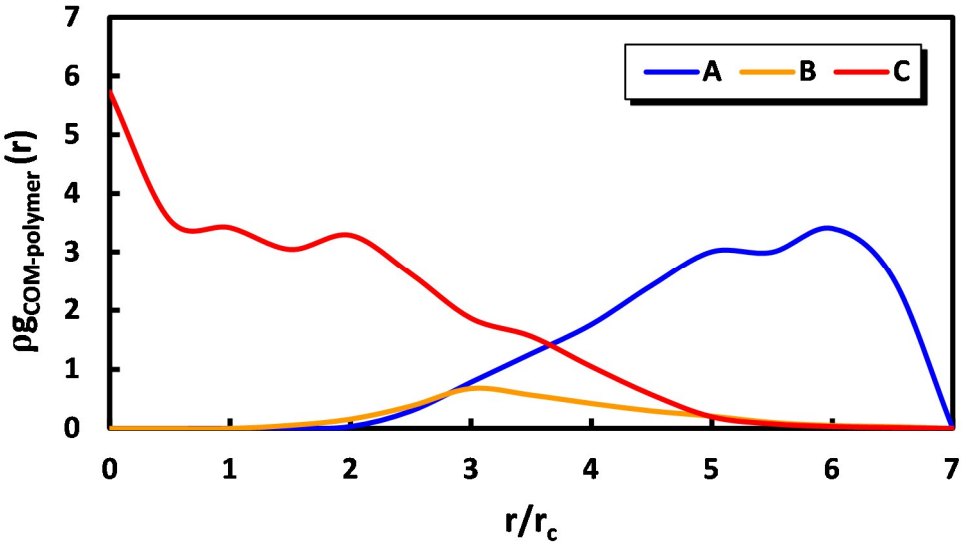


(b)

Figure 1. Chemical structures of POX derivatives and their coarse-grained models in DPD simulation: (a) Blue, yellow, and red colored structures represent poly(2-metyl-2-oxazoline) (PMOX), poly(2-(3-butinyl)-2-oxazoline) (PBOX), and poly(methyl-3-oxazol-2-yl) pentanoate with Co(III)-salen (PSCoX), respectively; (b) Likewise, blue, yellow, and red colored beads denote the coarse-grained PMOX, PBOX, and PSCoX, respectively.

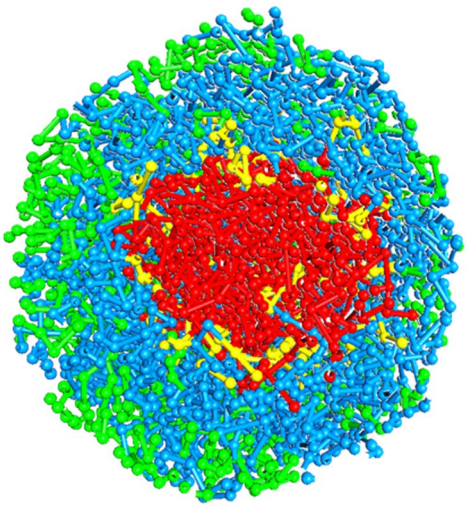


(a)

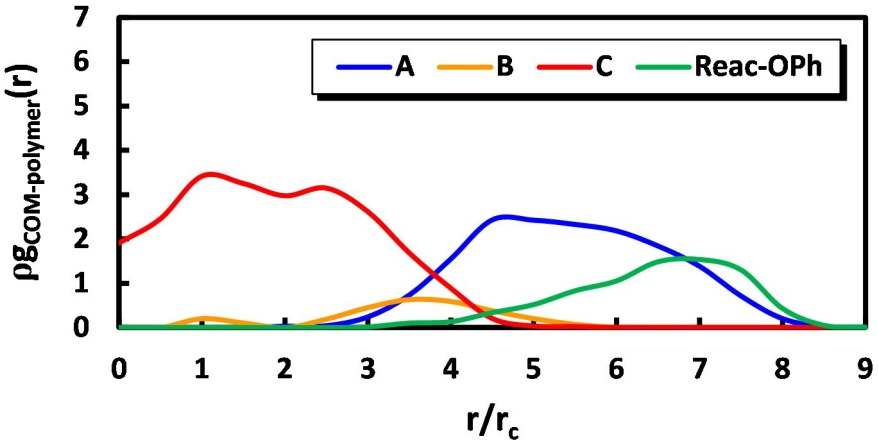


(b)

Figure 2. DPD simulation of bare micelle: (a) the cross-sectional view of micelle structure; (b) the RDF of three components from the center of the micelle. Blue, yellow, and red colored regions indicate block A, B, and C (the coarse-grained PMOX, PBOX, and PSCoX blocks), respectively

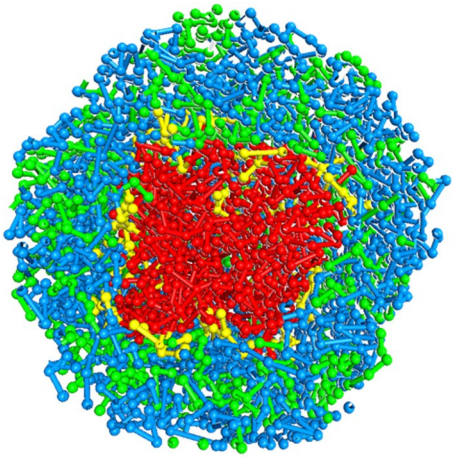


(a)

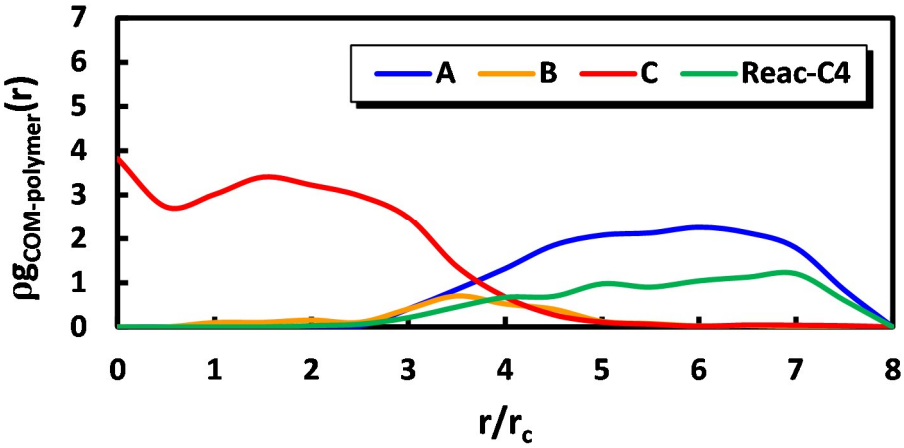


(b)

Figure 3. DPD simulation of micelle with Reac-OPh: (a) the cross-sectional view of micelle structure; (b) the RDF of four components from the center of the micelle. Blue, yellow, red, and green colored regions indicate bead A, B, C (the coarse-grained PMOX, PBOX, and PSCoX blocks), and Reac-OPh, respectively.

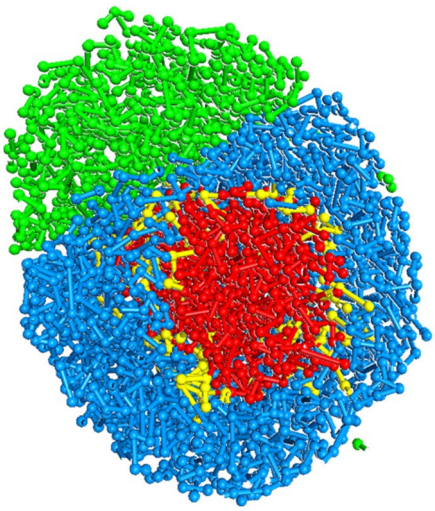


(a)

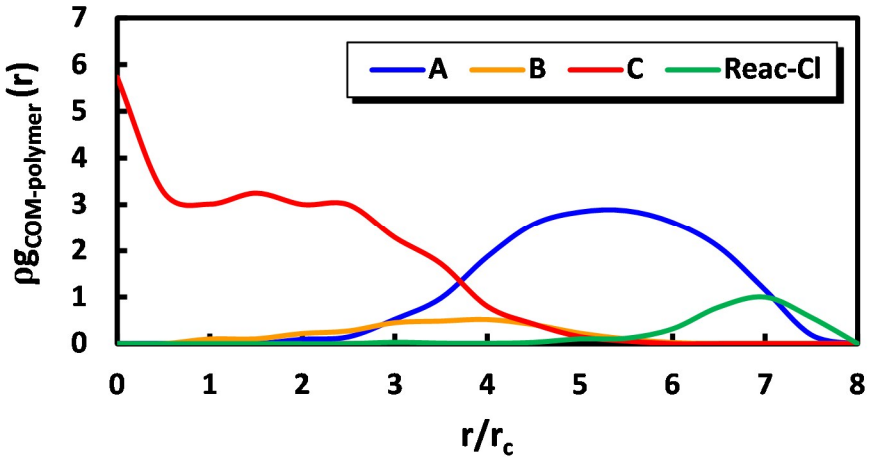


(b)

Figure 4. DPD simulation of micelle with Reac-C4: (a) the cross-sectional view of micelle structure; (b) the RDF of four components from the center of the micelle. Blue, yellow, red, and green colored regions bead A, B, C (the coarse-grained PMOX, PBOX, and PSCoX blocks), and Reac-C4, respectively.

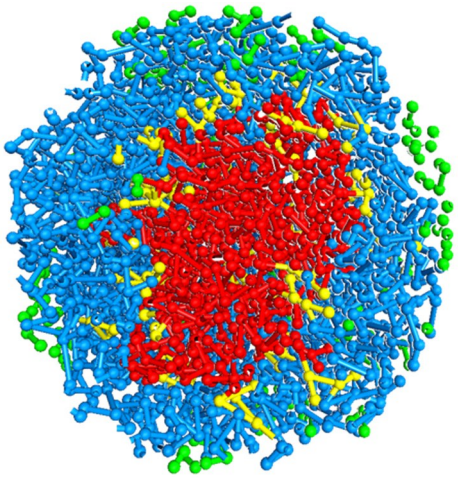


(a)

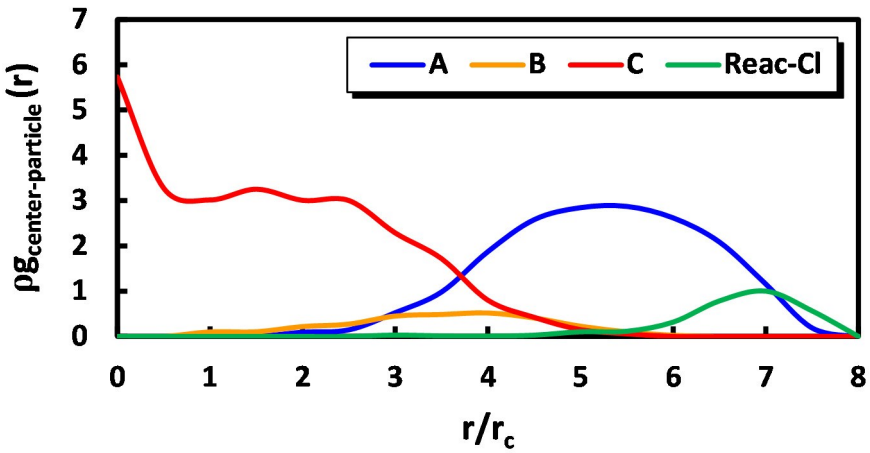


(b)

Figure 5. DPD simulation with Reac-Ph: (a) the cross-sectional view of micelle structure; (b) the RDF of four components from the center of the micelle. Blue, yellow, red, and green colored regions indicate bead A, B, C (the coarse-grained PMOX, PBOX, and PSCoX blocks), and Reac-Ph, respectively.

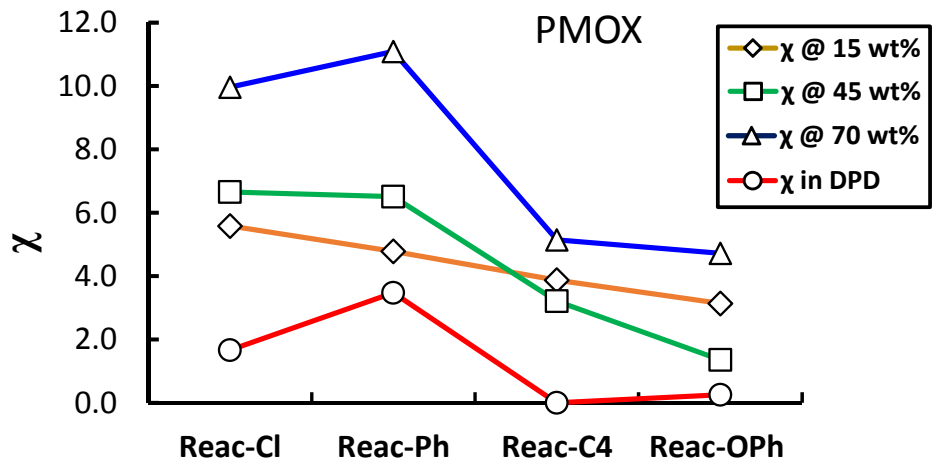


(a)

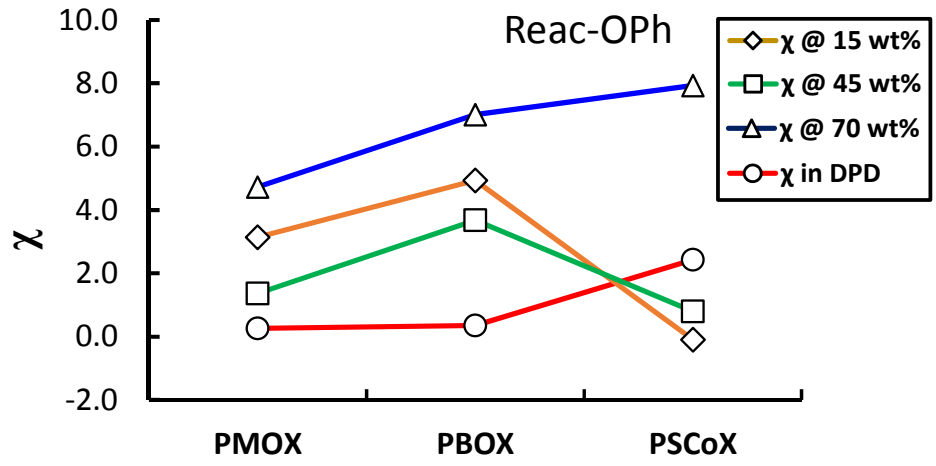


(b)

Figure 6. DPD simulation with Reac-Cl: (a) the cross-sectional view of micelle structure; (b) the RDF of four components from the center of the micelle. Blue, yellow, red, and green colored regions indicate bead A, B, C (the coarse-grained PMOX, PBOX, and PSCoX blocks), and Reac-Cl, respectively.



(a)



(b)

Figure 7. Comparison of χ_{FH} parameters: (a) for various reactants with respect to a common polymeric block (PMOX); (b) for various polymeric blocks with respect to a common reactant (Reac-OPh). Only "χ in DPD" is obtained from coarse-grained models while all others are from full-atomistic models.

GRAPHIC ABSTRACT