Formation and Regulation of Multicompartment Vesicles from Cyclic Diblock Copolymer Solutions: A Simulation Study

Yongbing Song, Run Jiang, Zheng Wang, Yuhua Yin,* Baohui Li, and An-Chang Shi

ABSTRACT: The self-assembly of a cyclic AB copolymer system with relatively long A blocks and short B blocks in B-selective solvents is investigated using a simulated annealing method. By investigating the effect of the lengths and solubilities of A and B blocks (N_A, N_B, ε_AS, and ε_BS), the incompatibility between A and B blocks (ε_AB), as well as the polymer concentration (C_p) and the conditions for the formation of multicompartment vesicles in cyclic diblock copolymer solutions, is predicted. The phase diagrams in terms of N_B, ε_AS, and C_p are constructed. The mechanism of the morphological transition is elucidated. It is shown that for cyclic copolymers the change in the above factors relating to the polymer and solvent properties all can lead to the transition from simple vesicles to multicompartment vesicles, but two different transition mechanisms are revealed. In addition, our simulations demonstrate that the self-assembly of cyclic copolymers could provide a powerful strategy for regulating the compartment number and the wall thickness of the multicompartment vesicles by adjusting the block solubilities and block lengths, respectively. These findings will facilitate the application of multicompartment architectures in cell mimicry, drug delivery, and nanoreactors.

1. INTRODUCTION

Compartmentalization is an essential feature found in living cells, most evidently in eukaryotes where different organelles can be identified, each surrounded by their own membrane. This structure allows the cell to separate in time and space the functional processes governing its survival. However, so far, most of the strategies that mimic cell function have focused on simple vesicles with one fluidic core; multicompartment vesicles (MCVs) with membranes that delineate distinct and multiple aqueous compartments have only recently caught attention. In fact, this multicompartment structure not only can promote the development of novel artificial cell-like systems but also provide a delivery system for specific drug applications by containing different drugs to be delivered simultaneously and safely.

In recent years, a growing effort has been made in experiments to design and construct vesicles with compartmentalized architectures, such as polymer-in-polymer and liposome-in-liposome structures. While these studies have produced many impressive results, the techniques to make these structures are rather complex. It is well known that the self-assembly of the copolymers is a simple and effective approach to various nanostructures. Recently, thermodynamically stable multicompartment vesicles, created by utilizing the self-assembly of mixtures of diblock copolymers with homopolymers or triblock copolymers have been reported. Additionally, large compound vesicles, considered as a result of kinetic control involving a secondary aggregation of individual vesicles, were also obtained from the self-assembly of a linear diblock copolymer via the addition of ions, or from the branched copolymers and hyperbranched multiarm copolymers. These studies indicate that a complex vesicular structure could directly form from the self-assembly of copolymer chains with different architectures.

Compared to traditional linear or branched polymers, the cyclic topology and a lack of chain ends impart unique physical properties to upon cyclic polymers. The topology effects by cyclic polymers could be amplified in their assembled aggregates in selective solvents. A reduced size and a longer degradation time of micelles formed by cyclic diblock copolymers have been observed in comparison with that from their linear diblock analogues. A more compact core and shell and the enhanced thermal and salt stability of the flowerlike micelles formed by cyclic block copolymers than their linear triblock counterparts were demonstrated. Due to the reduced size and unique properties of them, the cyclic copolymer aggregates could be advantageous for applications such as potential drug delivery carriers.

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Our previous simulation studies have demonstrated that the thermodynamic stable multicompartment vesicles can self-assemble from cyclic diblock copolymer solutions. Although such compartmentalized structures have been created in experiments as mentioned above, the theoretical and simulation reports on them are still very scarce. Especially, the formation conditions of MCV copolymer systems and the details of the equilibrium nature of them, which are important for applications using multicompartment vesicles for encapsulation, have not been investigated systematically. In the present study, we focus on the formation conditions and mechanism of multicompartment vesicles in cyclic diblock copolymer solutions. In addition, the characteristics of MCVs obtained, including their geometric shape, wall thickness, and the number of the compartments inside the multicompartment vesicles, are also investigated to facilitate the regulation of their structure.

The paper is arranged as follows. In the next section, we describe our model and provide details of the simulation technique. In the subsequent section, we discuss the results of our simulations for cyclic diblock copolymers in selective solvents. Finally, we summarize our conclusions from these studies.

2. MODEL AND METHODS

Lattice Monte Carlo simulations are carried out in a cubic box with a size of \( V = L_x \times L_y \times L_z = 60^3 \), where periodic boundary conditions are applied in all three directions. We note that to examine the stability and reproducibility for obtained morphologies, a number of additional simulations are performed in bigger simulation boxes (\( V = 72^3 \) or \( 96^3 \)). The cyclic AB copolymers are used in the study. The number of all of the segments in a copolymer chain is \( N \), while the numbers of A and B segments in a chain are \( N_A \) and \( N_B \), respectively. The copolymer concentration is defined by \( C_p = n_s V \), where \( n_s \) is the number of copolymer chains in the system. Each segment occupies one lattice site, and the excluded volume effect is dealt with by enforcing the rule that no two segments can simultaneously occupy one lattice site. The length of the bond connecting two consecutive segments in a chain is set to 1 and \( \sqrt{2} \) lattice spacing; thus, each lattice site has 18 nearest-neighbor sites.

In our simulation, only the nearest-neighbor interactions are considered. There are three types of effective pair interactions in the system, which are interactions of segment A and segment B, segment A and the solvent, segment B and the solvent. These interactions are modeled by assigning an energy \( E_{ij} = e_{ij} k_B T_{ref} \) to each nearest-neighbor pair of unlike components \( i \) and \( j \), where \( i, j = A, B, S \) (solvent), \( e_{ij} \) is the reduced interaction energy, \( k_B \) is the Boltzmann constant, and \( T_{ref} \) is a reference temperature. In this paper, we assume \( e_{AB} > 0 \), which ensures the immiscibility between the A and B segments; \( e_{AS} > 0 \) and \( e_{BS} < 0 \) mean that the solvent is assumed to be poor for A segments but good for B segments, respectively. Furthermore, we set \( e_{ss} = 0 \) with \( i = A, B, S \).

The computational simulations are carried out using a simulated annealing method. It is a well-known procedure for obtaining the lowest-energy "ground states" in disordered systems. In our previous studies, it has been demonstrated that simulated annealing is an appropriate method for studying the self-assembly morphologies of block copolymers with different architectures in a solution. To avoid chain self-knotting and concatenation, the starting configuration of the simulations is generated by putting an array of cyclic copolymer chains onto the lattice such that they are parallel to the z-axis, just like an extended linear chain folded once. After the desired number of chains has been generated, the remaining empty sites in the simulation box are assigned to solvent molecules. The evolution of chain configuration is achieved by exchange moves, where the partial reptation movement is included to accelerate the relaxation process of the chains. To avoid the formation of knottiness with each ring, bond crossing is always forbidden during the relaxation.

The acceptance or rejection of the attempted move is governed by whether it breaks the chain and further by the Metropolis rule. Starting from the initial state, the ground state of the system is obtained by a simulated annealing protocol with an initial temperature \( T = 70 T_{ref} \) which in our simulations is high enough to assure that the simulation results do not depend on the starting configurations, and decreasing \( T \) by a factor of 0.94 with each successive simulation until 70 annealing steps are reached. Then, the snapshots of the equilibrium morphologies are obtained. At each annealing step, 300 000 Monte Carlo steps are performed. One Monte Carlo step is defined as the average number of moves required for all of the segments to be visited one time.

3. RESULTS AND DISCUSSION

In this work, we focus on the key factors to control the formation of MCVs in cyclic copolymer solutions. This section consists of three parts. In the first part, the influence of the block length and the interaction parameters on the self-assembled morphologies from cyclic AB copolymers is mainly studied. In particular, the phase diagram as a function of the hydrophilic B block length \( N_B \) and the repulsive interaction between the hydrophobic A block and solvent \( (\epsilon_{AS}) \) is presented in this part to illustrate the dominant phase region (including MCVs) formed by the cyclic block copolymers at a fixed polymer concentration \( (C_p = 0.06) \). Additionally, the influences of other interaction parameters (including \( \epsilon_{BS}, \epsilon_{AB} \) ) and the length of A blocks \( (N_A) \) are also investigated. This is followed by the second part focusing on the influence of polymer concentration, where another phase diagram is presented as a function of \( C_p \) and \( \epsilon_{AS} \) for cyclic \( A_9B_2 \). At the same time, the morphological transition mechanism is elucidated in the above two parts by computing the average contact numbers between different species, the mean-square radius of gyration of the chains, the radial density profile of segments, and the solvent content in vesicular aggregate. Finally, the characteristics of the MCV are investigated in the third part.

3.1. Influence of the Block Length and Interaction Parameters. 3.1.1. Phase Diagram. The phase diagram of the cyclic diblock copolymer with \( N_A = 9, \epsilon_{BS} = -1.0, \) and \( \epsilon_{AB} = 1.0 \) at \( C_p = 0.06 \) in terms of \( \epsilon_{AS} \) and \( N_B \) is displayed in Figure 1, where six different dominant morphologies are presented: spherical micelles, cylindrical micelles, disklike micelles, simple vesicles, MCVs, and large compound micelles (LCMs). In addition, two mixed morphologies, i.e., spherical and cylindrical micelles or cylindrical and disklike micelles, are also present in the phase diagram. In this work, we focus on the MCV structures. It is clear from the phase diagram that the MCV structure can be obtained for cyclic \( A_9B_2 \) with a relatively wide range of hydrophilic block length \( (N_B = 1-5) \), generally at the interaction parameter \( \epsilon_{AS} \) between those associated with simple vesicles and LCMs. Also, the width of the \( \epsilon_{AS} \) window...
forming MCV increases with the increase of the hydrophilic block length when $N_B < 5$.

In addition, from Figure 1, we can see that the morphological transition sequence, spherical micelles $\rightarrow$ cylindrical micelles $\rightarrow$ disklike micelles $\rightarrow$ vesicles $\rightarrow$ MCVs, could be induced by increasing $\varepsilon_{AS}$ at fixed $N_B$ (such as $N_B = 4$, snapshots are given in Figure 2) or decreasing $N_B$ at fixed $\varepsilon_{AS}$ (such as $\varepsilon_{AS} = 2.5$, snapshots are given in Figure S1). For a more comprehensive description of this morphological transition sequence, we will take the morphological transformations of cyclic $A_9B_4$ with $\varepsilon_{AS}$ as an example (Figure 2).

- When $\varepsilon_{AS} \leq 1.5$, all of the aggregates are core–corona spherical micelles (Figure 2a).
- When $\varepsilon_{AS}$ increases to 1.6, some spherical aggregates become short rodlike micelles with two caps in the end (Figure 2b), so the mixed morphologies of spheres and rods are formed. With the further increase of interaction (1.8 $\leq \varepsilon_{AS} \leq 2.3$), some rods fuse into long cylinders (Figure 2c), so the mixed morphologies of spheres and cylinders are formed. When $\varepsilon_{AS} = 2.4$, all of the aggregates in the simulation system form cylindrical micelles. When $\varepsilon_{AS} = 2.5$, one end of some cylinders becomes flatten (Figure 2d), so the mixed morphology of cylinders and disks are observed.
- With the increase of the $\varepsilon_{AS}$, the disklike micelles with short rods at $\varepsilon_{AS} = 2.6$–2.9 (Figure 2e1,e2), then the conventional disklike micelles with a circular shape at $\varepsilon_{AS} = 3.0$–3.4 (Figure 2e3) are observed. Upon continuous increase of $\varepsilon_{AS}$, vesicles are formed. It is interesting to notice that the vesicles with different shapes (Figure 2f1–f4) are also observed for cyclic $A_9B_4$ at $\varepsilon_{AS} = 3.5$–3.7. In particular, the peanut-shaped vesicles with resembling morphologies shown in Figure 2f2 were reported in experiments of the amphiphilic linear diblock copolymer$^{48}$ and cyclic diblock copolymer in solution.$^{49}$ However, with the increase of $\varepsilon_{AS}$, a stable spherical vesicle, as seen in Figure 2g, is always observed (at $\varepsilon_{AS} = 3.8$–3.9).
- With the further increase of $\varepsilon_{AS}$ ($\varepsilon_{AS} = 4.0$–4.7), the vesicle becomes elongated (Figure 2h). Then, MCV is formed (at $\varepsilon_{AS} = 4.8$–8.0), which comprises two (Figure 2i) or more (Figure 2j).

Figure 1. Phase diagram of the cyclic copolymer $A_9B_n$ at $C_p = 0.06$ in B-selective solvents as a function of the interaction parameter $\varepsilon_{AS}$ and the B block length $N_B$. Similar morphologies are represented by the same symbols. The mixed morphologies are represented by overlapped two different symbols for each morphology.

Figure 2. Snapshots of typical morphologies for cyclic $A_9B_4$: spherical micelles at (a) $\varepsilon_{AS} = 1.5$; cylindrical micelles at (b) $\varepsilon_{AS} = 1.6$, (c) $\varepsilon_{AS} = 2.0$, and (d) $\varepsilon_{AS} = 2.5$; disklike micelles at (e1–e2) $\varepsilon_{AS} = 2.6$ and (e3) $\varepsilon_{AS} = 3.0$; vesicles at (f1–f4) $\varepsilon_{AS} = 3.5$, (g) $\varepsilon_{AS} = 3.8$, and (h) $\varepsilon_{AS} = 4.3$; and MCVs at (i) $\varepsilon_{AS} = 5.0$ and (j) $\varepsilon_{AS} = 6.0$. Only A domains are shown in red, which are transparent to make visible the aqueous core inside them.
2j) fluidic cores separated by a copolymer matrix inside one aggregate.

It should be mentioned that in our simulations, at a relatively wide parameter space, identical morphologies are obtained for simulations with different random number generator seeds. At some parameter space near the phase boundaries, however, different morphologies may coexist for the same parameters just with different random number seeds, such as the morphologies in Figure 2e1−e2, which are near to the boundaries between the cylindrical structures and the disklke structures, or those in Figure 2f1−f2, which are near to the boundaries between the disklke structures and vesicles. The coexistence of different morphologies may have resulted from the small energy difference between these morphologies. We have used dozens of random number seeds and found that the vesicles with different shapes in Figure 2f1−f3 can be formed with almost the same probability, which most likely correspond to metastable morphologies, while spherical vesicles in Figure 2f4 with a slightly higher probability should have a more stable morphology.

Just as shown in Figure 1, some or all morphologies of the sequence are also observed for other cyclic block copolymers with different compositions we studied, but the same morphological regions are shifted to the smaller $\varepsilon_{AS}$ for $N_B < 4$ and the bigger one for $N_B > 4$. In addition, we notice that for cyclic copolymers with short B blocks the width of the cylindrical micelle region is very narrow, for example, for the $N_B \leq 3$ case, we do not locate a cylindrical micelle state without mixing spheres. We also notice that there is a favorable morphology in the mixed morphologies in the phase diagram at different state points. For example, for copolymers with $N_B = 6$ at $\varepsilon_{AS} = 3.5$ (near to the spherical micelle region), spherical micelles are more favorable, only short cylinders are formed, while at $\varepsilon_{AS} = 4.5$ (near to the cylindrical micelle region), most of the aggregates are cylinders.

A morphology sequence similar to Figure 2, from spherical univesicular aggregates to tubular or elongated vesicles and then to large compound vesicles, was also observed in experimental studies of ion-induced morphological changes in solutions of crew-cut aggregates of amphiphilic linear diblock copolymers. However, the large compound vesicle obtained was thought of as a kinetic control morphology in that case. However, our results suggest that the multicompartment vesicles in our simulations should be or close to be thermodynamically stable using the simulation method involving an annealing process with a suitable annealing rate ($f = 0.94$) to obtain the equilibrium state.

Meanwhile, we also investigate the influence of other interaction parameters, such as $\varepsilon_{BS}$ and $\varepsilon_{ABA}$, on the morphology of the cyclic copolymer $A_B B_A$. Here, we take cyclic $A_B B_A$ and cyclic $A_A B_B$ as examples to demonstrate the conditions for MCV formation. The snapshots of typical morphologies are shown in the Supporting Information. We find that if the solubility of hydrophilic B blocks is decreased (Figure S2), or the incompatibility of the A and B segments weakens (Figure S3), the transition from simple vesicles to multicompartment vesicles occurs for both cyclic $A_B B_A$ and $A_A B_B$ and the number of the compartments increases greatly; otherwise, the transition from simple vesicles to micelles (disks, cylinders, or spheres) is preferable. Due to the relatively longer hydrophilic block for $A_B B_A$, the aqueous cores are connected together to form a network in the multicompartment vesicles with more than two cores when the solubility of hydrophilic B blocks is poor (Figure S2a). However, for a cyclic diblock copolymer with a shorter hydrophilic block, such as $A_A B_B$, the cores are separated by a hydrophobic wall in all cases.

On the other hand, our studies on the influence of the hydrophobic A block length on the morphologies demonstrate that, compared with above parameters, changing $N_A$ is not an effective way to promote the transition from simple vesicles to multicompartment vesicles (Figure S4). For cyclic copolymers with $N_A = 2$ when the $N_B$ is increased from 9 to 11, although the transition from simple vesicles to MCVs with two compartments is observed, the number of compartments remains unchanged until $N_A = 20$ (the longest A block length in this study). While for cyclic copolymers with $N_A = 4$, the transition from simple vesicles to MCVs does not occur even though the $N_A$ is increased to 20. However, the decrease of $N_A$ still has a significant effect on other morphologies from the cyclic block copolymers. For both cases of $N_B = 2$ and $N_B = 4$, as the $N_A$ is decreased, the transition from simple vesicles to disklke, to cylindrical micelles, and then to spherical micelles occurs.

3.1.2. Morphological Transition Mechanism. To understand the mechanism of the morphological transition mentioned above, we calculate the average contact numbers for the segments, corresponding to the average contact area between different species in our model. There are three species in contact with each segment: A segment, B segment, and the solvent. The average contact numbers for each A or B segment as a function of $\varepsilon_{AS}$ for cyclic $A_B B_A$ with $N_A = 9$, $\varepsilon_{BS} = -1.0$, and $\varepsilon_{ABA} = 1.0$ at $C_p = 0.06$ are shown in Figure 3a,b, where $N_{AA}$, $N_{AB}$, and $N_{AS}$ represent the average contact number for each A segment with A segments, B segments, and solvents, while $N_{BA}$, $N_{BB}$ and $N_{BS}$ represent the average contact number for each B segment with A segments, B segments, and solvents. From Figure 3a, we notice that $N_{AS}$ substantially decreases from a value close to 4 to near 0.5 when the morphology changes from spherical micelles to simple vesicles and then it still decreases slightly when MCVs are formed. We also notice that $N_{AB}$ always increases in the transition process from spherical micelles to MCVs, even more rapidly during the formation of MCVs. This indicates that the MCV formation can decrease the unfavorable contact between A segments and solvents mainly by increasing the contact between A and B segments. Although the increase of $N_{AB}$ during the transition from vesicle to MCV morphology is not energetically favorable, it is reasonable when considering the high value of repulsive interaction (greater than 4.5) between the A segment and the solvent than that between the A and B segments (1.0). On the other hand, Figure 3b shows that there is always a decrease in $N_{BS}$ with the increase of $\varepsilon_{BS}$, indicating the decrease in the surface area of the aggregate during the morphological transition from spherical micelles to MCVs. From the trends of the curves in Figure 3, we argue that poorer compatibility of A/S and B/S and better compatibility of A/B facilitate the formation of MCVs. This is consistent with the simulation results presented in Figures S2 and S3 mentioned above.

We have also calculated the total energy change during this morphological transition (Figure 3c), which includes the repulsive interaction of A/B and A/S and attractive interaction of B/S, i.e., $E_{\text{total}} = \varepsilon_{AS} (N_{AA} + N_{AB} + N_{BS}) + \varepsilon_{BS} (N_{AB} + N_{BA} + N_{BB})$. It is found that the total energy increases rapidly at first and then slows down when the bilayer disk morphology is formed, and when vesicular morphologies are formed (including vesicles and MCVs), the total energy increases rapidly again.
Especially, to understand the transition mechanism from disks to vesicles then to MCVs, we may assume that for cyclic A₉B₄ at each $\varepsilon_{AS}$ disklike (as in the case of $\varepsilon_{AS} = 3.0$, Figure 2e), vesicle (as in the case of $\varepsilon_{AS} = 3.8$, Figure 2g), and MCV (as in the case of $\varepsilon_{AS} = 5.0$, Figure 2i) morphologies can be formed, respectively, and we then compare the total energy of them. In Figure 3d, the total energies of the disks, vesicles, and MCVs (with two aqueous cores) are presented. From Figure 3d, we can see that the calculated energy in the assumed case of the disk micelles, vesicles, and MCVs is the lowest when $\varepsilon_{AS} \leq 3.0$, $3.0 > \varepsilon_{AS} > 6.0$, and $\varepsilon_{AS} \geq 6.0$, respectively. It can be seen that the assumed transition point from disks to vesicles occurs at almost the same value of $\varepsilon_{AS}$ as that from simulation results. However, for vesicular morphologies, the simulation results always do not correspond to the assumed morphologies. For example, the transition from vesicles to MCVs occurs at $\varepsilon_{AS} = 4.8$ from the simulation results, while the assumed MCVs would form at higher values of $\varepsilon_{AS}$. Hence, the resulted morphologies in our simulations should not only depend on the total energy.

Figure 4a shows the density profiles of the A segments for vesicular aggregates from cyclic A₉B₄ as a function of the distance from the center of mass of the aggregate, where the aggregate size can be estimated by the location of the peak value of $\rho_A(r)$. Besides, the number of solvent molecules inside the vesicular aggregates as a function of $\varepsilon_{AS}$ is shown in Figure 4b. From Figure 4, the decrease of the vesicular aggregate size and the reduction of the solvent content inside the aggregates with increasing $\varepsilon_{AS}$ can be observed. It indicates that in response to the increase in the interfacial energy for the vesicular aggregates from cyclic copolymers due to the increase of $\varepsilon_{AS}$, the total interfacial area is minimized by expelling a part of the solvents from the inside to the outside of the vesicles. Thus, their shape is changed from spherical to elongated (prolate) vesicles induced by the spontaneous curvature to minimize the free energy of the system, then, a further decrease of the solvents inside the aggregate leads to the vesicle structure become unstable. As a result, some A segments near the outer surface of the wall are pushed into the aggregate to form multicompartiment vesicles with a slightly smaller size.
Further decreasing the solvents inside the MCVs could result in the formation of LCMs, just as shown in the phase diagram (Figure 1).

It is noted that a decrease of the solvent content inside the vesicular aggregates formed by cyclic copolymers is also observed when the transition from simple vesicles to MCVs occurs by decreasing the strength of $\varepsilon_{BS}$ or $\varepsilon_{AB}$ (Figures S5 and S6), or by changing $N_A$ or $N_B$ (Figures S7 and S8), respectively.

### 3.2. Effect of the Polymer Concentration

#### 3.2.1. Phase Diagram

Figure 5 presents the phase diagram of the cyclic A9B2 in terms of the copolymer concentration $C_p$ and the interaction parameter $\varepsilon_{AS}$. The simulation results show that the morphological transition sequence, i.e., spherical micelles $\rightarrow$ cylindrical micelles $\rightarrow$ disklike micelles $\rightarrow$ vesicles $\rightarrow$ MCVs $\rightarrow$ LCMs, is always observed for A$_{9}$B$_{2}$ with increasing $\varepsilon_{AS}$ when $C_p \geq 0.01$. It should be noted that due to short B blocks ($N_B = 2$) most of the cylindrical micelles in this case have mixed morphologies of spheres and cylinders, consistent with the observations at small $N_B$ in the previous phase diagram (Figure 1). The proportion and length of cylinders in the mixed morphologies increase with the increase of $C_p$. In addition, the mixed morphologies of cylinders (or spheres) and disks are also presented in this phase diagram. At low concentrations such as $C_p = 0.005$, the cylindrical micelles are more like ellipsoids and the vesicle in the above morphological transition sequence is replaced by a semivesicle structure, which is similar to the vesicle but without or only small amounts of solvents inside the aggregate, while at $C_p \leq 0.003$, all of the aggregates obtained in the range of $\varepsilon_{AS}$ we investigated are spherical micelles.

When we increased the copolymer concentration at fixed $\varepsilon_{AS}$, however, three different morphological transition sequences were observed depending on the strength of $\varepsilon_{AS}$. As shown in Figure 5, when $\varepsilon_{AS} \leq 1.3$, the common sequence of morphologies, generally from spherical micelles to rodlike micelles, then to disklike micelles, and to vesicles, is observed with the increase of $C_p$, although not all of the morphologies are accessible for all of the $\varepsilon_{AS}$. Especially, when $1.3 < \varepsilon_{AS} \leq 3.0$, the morphological transition from spherical micelles to semivesicles, to vesicles, and then to multicompartments vesicles occurs as $C_p$ increases. In contrast, when $\varepsilon_{AS} > 3.0$, due to the strong repulsion of the hydrophobic A blocks and solvents, the spherical micelles directly change to LCMs with the increase of $C_p$. It seems that the MCVs only could be formed in the second morphological sequence occurring at a moderate $\varepsilon_{AS}$.

#### Figure 5. Phase diagram of the cyclic diblock copolymer A$_{9}$B$_{2}$ in selective solvents for the B block as a function of the interaction parameter $\varepsilon_{AS}$ and the copolymer concentration $C_p$. Similar morphologies are represented by the same symbols. The mixed morphologies are represented by two overlapped different symbols for each morphology.

#### Figure 6. Snapshots of typical morphologies formed by cyclic-A$_{9}$B$_{2}$ at (a) $\varepsilon_{AS} = 0.3$; (b) $\varepsilon_{AS} = 1.2$; (c) $\varepsilon_{AS} = 1.3$; (d) $\varepsilon_{AS} = 2.0$; (e) $\varepsilon_{AS} = 3.0$ as a function of $C_p$. Only A domains are shown in red.
To deeply understand the different scenarios of phase transformation in cyclic copolymer solutions, a detailed analysis of the morphologies in first and second transition sequences, observed for cyclic A_9B_2 as mentioned above, is performed. First, we focus on the former morphological sequence that occurred at \( \varepsilon_{AS} \leq 1.3 \). In our simulations of the cyclic block copolymer at \( \varepsilon_{AS} = 0.3 \), the dominant morphologies are spherical micelles with a similar size, only the number of which increases with \( C_p \), as shown in Figure 6a. This feature can be confirmed by the change of micelle aggregation number with the increase of copolymer concentration in Figure S9, which increases significantly at a very low concentration (\( C_p = 0.003-0.01 \)) and then remains unchanged until \( C_p = 0.06 \). At \( \varepsilon_{AS} = 0.8 \), the morphology changes from spheres to short rods, then to a mixture of spherical and cylindrical micelles, and finally to long cylindrical micelles with the increase of copolymer concentration, while for \( \varepsilon_{AS} = 1.0 \), the morphologies are spheres, short rods, a mixture of spherical or cylindrical and disklike micelles. When \( \varepsilon_{AS} = 1.2 \), the disklike micelles dominate the phase diagram, whereas the transition from disks to vesicles is observed for \( \varepsilon_{AS} = 1.3 \). We would like to point out that the disklike micelles show a similar thickness to that the hydrophobic wall, but the shapes of them are different with the copolymer concentration, as shown in Figure 6b. At low concentrations (e.g., \( C_p = 0.01 \)), a flat circular disk is formed, while at high concentrations (e.g., \( C_p = 0.07 \)), a bending ellipse disk is more favorable. It should be noted that the transition from the disklike micelles to vesicles is not observed in the concentration range we studied at \( \varepsilon_{AS} = 1.2 \). However, when \( \varepsilon_{AS} \) increases slightly (\( \varepsilon_{AS} = 1.3 \)), this transition has occurred at concentrations not high enough (\( C_p = 0.03 \)), as shown in Figure 6c.

When \( 1.3 < \varepsilon_{AS} \leq 3.0 \), the morphological transition sequence is different from the above case. Here, we take \( \varepsilon_{AS} = 2.0 \) as a typical example. As shown in Figure 6d, a spherical micelle is formed at very low copolymer concentrations (at \( C_p = 0.001 \)); then, with the increase of \( C_p \), semivesicles are formed with some hydrophilic blocks appearing in the center of spherical micelles (at \( C_p = 0.005 \)). Afterward, vesicles are observed with a lot of solvents appearing in the center (at \( C_p = 0.01 \)), then the vesicles become larger, and finally MCVs are formed (at \( C_p = 0.04 \)). For larger \( \varepsilon_{AS} \) such as \( \varepsilon_{AS} = 3.0 \) (Figure 6e), the transition from vesicles to MCVs occurs earlier and the number of the compartments in MCV increases for cyclic copolymers at the same concentration compared with that at \( \varepsilon_{AS} = 2.0 \). However, for smaller values of \( \varepsilon_{AS} \) such as \( \varepsilon_{AS} = 1.5 \), the vesicle morphology has been maintained in the \( C_p \) range we studied.

3.2.2. Morphological Transition Mechanism. To illustrate the mechanism of the above two morphological transition sequences, we calculate the average contact numbers for each A segment and the mean-square radius of gyration of the hydrophobic A blocks for cyclic A_9B_2 at \( \varepsilon_{AS} = 1.3 \) (first transition sequence) and \( \varepsilon_{AS} = 2.0 \) (second transition sequence) as a function of \( C_p \) in Figure 7. The mean-square radius of gyration is scaled in terms of the mean-square radius of gyration of the ideal ring Gaussian chain, i.e., \( 1/12 * N_A b^2 \), where \( b \) is the average value of all of the allowed bond lengths. For cyclic A_9B_2 at \( \varepsilon_{AS} = 1.3 \), a slower decrease of \( N_A \) with the increase of copolymer concentration can be seen when compared with that at \( \varepsilon_{AS} = 2.0 \). On the other hand, a faster decrease of the scaled mean-square radius of gyration at \( \varepsilon_{AS} = 1.3 \) than that at \( \varepsilon_{AS} = 2.0 \) with the concentration of the copolymer is observed. Therefore, from these figures, we can deduce that the strength of interaction between the hydrophobic blocks and the solvents may result in different morphological sequences induced by the copolymer concentration. When \( \varepsilon_{AS} \) is small, the first morphological transition sequence, spheres → rods → disks → vesicles, is preferred by the system because this sequence can release the stretching of the hydrophobic blocks of the copolymers more efficiently. However, when \( \varepsilon_{AS} \) is large, the interfacial energy between the hydrophobic A domains and the solvents dominates the morphological transition and the second morphological transition sequence, spheres → semivesicles → vesicles, is preferred by the system to minimize the total interfacial energy. Therefore, in this case, both the energy of the system and the conformational entropy of chains are important in determining the self-assembled morphologies. We notice that two typical morphologies are also labeled in the figure, where SM means spherical micelles, CM means cylindrical micelles, DM means disklike micelles, SV means semivesicles, V means vesicles, and MCV means multicompartiment vesicles. The labels in (c) for \( \varepsilon_{AS} = 1.3 \) are black and that for \( \varepsilon_{AS} = 2.0 \) are red.
mechanisms of vesicle formation as a result of different conditions, similar to our above studies, have been proposed for linear block copolymers.\textsuperscript{53,54}

In these two transition sequences, a further increase in the copolymer concentration result in an increase in the vesicle size to minimize the total interfacial area, as indicated by the radial density distribution of A blocks in vesicular aggregates formed by cyclic A_9B_2 at $\varepsilon_{AS} = 2.0$ in Figure 8a. At the same time, the added copolymers cause the vesicle wall to swell and they become thicker, which can be seen from the variation of the wall thickness (obtained by calculating the width at half-maximum of the peak of the A-segment distribution curve in Figure 8a,b) with $C_p$ in Figure 8c. Once the thickness of the wall reaches a critical size (about 5.90 for cyclic A_9B_2), a fraction of copolymers constitutes partitioning walls, which spans the internal solvent space of a vesicle, to form multiple hollow compartments and then MCVs are formed. After that, the thicknesses of the outside wall of the MCV, equal to the critical size of wall thickness of the simple vesicle, does not vary with the copolymer concentration, as shown in the inset in Figure 8b. The thickening of the vesicle wall with the $C_p$ for vesicles can also be seen clearly for cyclic A_9B_2 at $\varepsilon_{AS} = 1.5$ in Figure 8c, but the thickness of the wall is always smaller than the critical size even when $C_p = 0.06$. Therefore, the transition from vesicles to MCVs does not been observed in simulations when $\varepsilon_{AS} \leq 1.5$. It is noted that for cyclic A_9B_2 at $\varepsilon_{AS} = 1.5$ when $C_p = 0.07$ (the largest polymer concentration investigated in the current study) the vesicles become elongated, and for cyclic A_9B_2 at $\varepsilon_{AS} = 1.3$, the forming vesicles are always mixed with spheres or disks, so the data is not shown here.

The variation in the solvent content inside the vesicular aggregates at $\varepsilon_{AS} = 2.0$ is also calculated in Figure 9. In contrast to the decrease in the solvent content with the interaction parameter and copolymer composition in the process of the transition from simple vesicles to MCVs, in this case, a significant increase in the solvent content with the increase of $C_p$ can be seen. Therefore, changing only the copolymer concentration would not result in the further transition from MCVs to LCMs.

In this case, the formation mechanism of MCVs is different from that by adjusting the interaction parameter or changing the block length as discussed previously. We notice that a new mechanism for the formation of large compound vesicles proposed by He et al.\textsuperscript{55} is similar to the formation mechanism of MCVs with an increase of $C_p$ in our studies.

### 3.3. Regulation of Multicompartment Vesicles

From our simulation results, it can be seen that changing the interaction parameter, especially the interaction between the solvents and A or B blocks, is an effective way to obtain MCVs. It is interesting to find that the number of compartments (aqueous cores) in the vesicular aggregates can be accurately tuned via adjustment of the solubility of B blocks for cyclic copolymers with short B blocks, as shown in Figure 10, where the core number increases successively from 1 to 17 with the decrease of the attractive interaction between the B block and the solvent for A_9B_1 at $C_p = 0.06$, $\varepsilon_{AS} = 0.6$, and $\varepsilon_{AS} = 1.0$. In addition, from Figure 10, it is found that when the core number is about more than 8, one aqueous core appears at the center of the aggregate. Moreover, the regular hexagonal packing of the cores is observed in the cut section of the aggregate at $\varepsilon_{BS} = -0.25$. Our simulation results demonstrate that the compartment number of MCVs can be accurately tuned by adjusting $\varepsilon_{BS}$ for the cyclic copolymer A_9B_2 at different $C_p$ values ($C_p \geq 0.02$). For the systems with only different concentrations, lower $C_p$, and fewer compartment

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**Figure 8.** Radial density profiles of the A blocks in vesicular aggregates formed by cyclic A_9B_2 at $\varepsilon_{AS} = 2.0$: (a) $C_p = 0.01$--$0.03$ and (b) $C_p = 0.035$--$0.07$. For ease of comparison between the plot at different $C_p$ values, the shifted curves are shown in the corresponding inset. (c) Wall thickness of vesicles formed by cyclic A_9B_2 as a function of $C_p$.
increasing thicknesses of the outside wall increase with increasing shrinking of the outer surface of the wall. In contrast, the examples (the radial density profile) formed by cyclic AB with fixed $N_A = 1.0$, the compartment number is 3 at $C_p = 0.02$, 9 at $C_p = 0.04$, and 18 at $C_p = 0.07$ (Figure S10).

To characterize the geometric shape of the vesicular aggregates, we calculate the eccentricity $\eta$ of the aggregates (at the bottom of Figure 10) according to the equation

$$\eta = 1 - \frac{I_{\text{min}}}{I_{\text{avg}}}$$

(1)

where $I_{\text{min}}$ is the smallest principal moment of inertia and $I_{\text{avg}}$ is the average of all of the three components of the principal moment of inertia. We notice that when the core number of the MCVs is greater than 8, the value of $\eta$ is close to 0, indicating that the MCVs are nearly spherical, while those with the core number less than 8 are nonspherical, as indicated by $\eta \geq 0.1$. Therefore, the geometric shape of the MCV depends on the core packing inside it.

Furthermore, we also investigate the factors influencing the thicknesses of the hydrophobic wall of the MCVs. Here, we take MCVs with three compartments formed by cyclic AB with fixed $N_A = 9$ but changed $N_B$ and with two compartments formed by cyclic AB with fixed $N_B = 2$ but changed $N_A$ as examples (the radial density profiles of the A segments for these MCVs are presented in Figure S11). We find that the thicknesses of the outside wall of these MCVs decrease with increasing $N_B$ for copolymers with fixed $N_A$, mainly due to the shrinking of the outer surface of the wall. In contrast, the thicknesses of the outside wall increase with increasing $N_A$ with fixed $N_B$, mainly due to the expansion of the inner surface of the wall. Therefore, the wall thickness of the MCV can be tuned by adjusting the hydrophilic blocks or the hydrophobic wall-forming blocks. However, it should be noted that too large wall thickness is not helpful to the formation of multicompartment vesicles. This is supported in part by the frequent observation of simple vesicles when $N_A$ is more than 22 in the $N_B = 2$ case (not shown here).

4. CONCLUSIONS

We performed the simulated annealing procedure to investigate the self-assembly of amphiphilic cyclic AB diblock copolymers with much longer hydrophobic A blocks and shorter hydrophilic B blocks in B-selective solvents. Rich self-assembled morphologies, such as the spherical micelles, cylindrical micelles, disklike micelles, vesicles, multicompartment vesicles (MCVs), and large compound micelles (LCMs), from cyclic diblock copolymers are observed by varying the quality of the solvent, the block length, and the concentration of the polymer. The corresponding phase diagrams are constructed. Especially, the formation conditions and mechanisms of the MCVs are studied in detail.

As shown in the simulations, the MCVs can be formed spontaneously under a wide range of conditions for cyclic copolymers. For example, once the simple vesicles are formed, the MCVs always can be obtained by tuning the interaction parameter, such as by increasing the strength of $\varepsilon_{AB}$ or decreasing the strength of $\varepsilon_{BS}$ and $\varepsilon_{AB}$, or reducing the B block length, $N_{B}$, whereas changing $N_A$ is not a very effective approach. In the above cases, it has been suggested that during the transition from simple vesicles to MCVs a part of the solvents is expelled from the inside to the outside of the vesicles, resulting in a little shrinking of their size or changing of their geometric shape, so as to decrease the interfacial energy between the hydrophobic wall (both inner and outer) and the solvent. Therefore, a further morphological transition from the MCVs to LCMs may occur. On the other hand, an increase in the copolymer concentration $C_p$ can also result in the transition from simple vesicles to MCVs at mild $\varepsilon_{AS}$ (such as $2 \leq \varepsilon_{AS} \leq 3$ for $A_9B_2$). However, in this case, a significant increase in the solvents inside the vesicular aggregates during the transition has been confirmed. This indicates that the morphological transition mechanism is different in these two cases; for the latter, a further morphological transition from the MCVs to LCMs is not likely to happen.

Additionally, the control over the number and location of the compartments is an important fabrication challenge for applications of multicompartment architectures in nano-reactors, cell mimicry, and eventually drug delivery. Our simulations have shown that the self-assembly of cyclic copolymers could provide a powerful strategy for regulating the compartment number and the wall thickness of the multicompartment vesicles by adjusting the block solubility and the block length, respectively. Hopefully, our simulation studies will stimulate the future experiments and help to better understand, reconstruct, and apply natural compartmentalization strategies in soft matter science.

ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge at https://pubs.acs.org/doi/10.1021/acsomega.0c00374.

Snapshots of typical morphologies for cyclic A$_9$B$_4$ as a function of $N_B$ (Figure S1); snapshots of typical morphologies for cyclic A$_9$B$_4$ and A$_9$B$_2$ as a function of $\varepsilon_{BS}$, $\varepsilon_{AB}$, and $N_A$ (Figures S2−S4); number of solvent molecules in vesicular aggregates from cyclic A$_9$B$_4$ as a function of $\varepsilon_{BS}$, $\varepsilon_{AB}$, $N_A$, and $N_B$ (Figures S5−S8); aggregation number of spherical micelles formed by cyclic A$_9$B$_2$ at $\varepsilon_{AS} = 0.3$ as a function of $C_p$ (Figure S9); snapshots of typical morphologies as a function of $\varepsilon_{BS}$ for...
cyclic $A_B^C$ at different $C_p$ values (Figure S10); radial density profile of the A segments for MCVs with three cores formed by cyclic copolymers with $N_A = 9$ and for MCVs with two cores formed by cyclic copolymers with $N_B = 2$ (Figure S11) (PDF)

**AUTHOR INFORMATION**

**Corresponding Author**

Yuhua Yin – School of Physics, Nankai University, Tianjin 300071, China; orcid.org/0000-0003-1962-8167; Email: yinyh@nankai.edu.cn

**Authors**

Yongbing Song – School of Physics, Nankai University, Tianjin 300071, China

Run Jiang – School of Physics, Nankai University, Tianjin 300071, China

Zheng Wang – School of Physics, Nankai University, Tianjin 300071, China

Baohui Li – School of Physics, Nankai University, Tianjin 300071, China; orcid.org/0000-0002-8403-1220

An-Chang Shi – Department of Physics and Astronomy, McMaster University, Hamilton, Ontario L8S 4M1, Canada; orcid.org/0000-0003-1379-7162

Complete contact information is available at: https://pubs.acs.org/10.1021/acsomega.0c00374

**Notes**

The authors declare no competing financial interest.

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