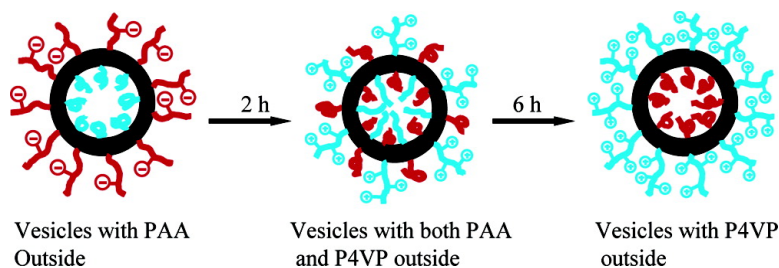Article

Preparation and pH Triggered Inversion of Vesicles from Poly(acrylic Acid)-*block*-Polystyrene-*block*-Poly(4-vinyl Pyridine)

Futian Liu, and Adi Eisenberg

Vesicles with PAA Outside → 2 h → Vesicles with both PAA and P4VP outside → 6 h → Vesicles with P4VP outside

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Preparation and pH Triggered Inversion of Vesicles from Poly(acrylic Acid)-*block*-Polystyrene-*block*-Poly(4-vinyl Pyridine)

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Abstract: The aggregate morphologies of the biamphiphilic triblock PAA_{26}-*b*-PS_{890}-*b*-$P4VP_{40}$ have been studied by TEM as a function of pH in $DMF/THF/H_2O$ mixtures. The outside surfaces of the aggregates were characterized by ζ potential measurements. Starting at the apparent pH (pH*) of 1, and increasing gradually to pH*14, the aggregate morphologies of this triblock change progressively from vesicles (pH*1), to solid spherical or ellipsoidal aggregates (pH*3~11), and finally back to vesicles (pH*14). Vesicles prepared at pH*1 contain P4VP chains on the outside and PAA chains on the inside, while those prepared from the same triblock at pH*14 contain PAA outside and P4VP inside. The segregation is based on the difference in repulsive interactions within the PAA or P4VP corona under different pH conditions. At low pH, the curvature is stabilized through increased repulsive interactions between the P4VP chains on the outside relative to the less repulsive interactions between the PAA chains on the inside. At pH*14, by contrast, the PAA is preferentially segregated to the outside and the P4VP to the inside because of the increased repulsive interaction between PAA chains and the decreased repulsive interaction between P4VP chains at high pH. Most importantly, vesicles with PAA on the outside can be inverted to P4VP on the outside by changing the pH while the vesicles have swollen cores and are under dynamic conditions. The conversion mechanism is suggested to involve a whole vesicle process because the CMC is far too low for single chain reassembly to be involved.

1. Introduction

The self-assembly of block copolymers in solution into aggregates of a range of morphologies has attracted considerable interests for several years.[1-9] Although such aggregates can be prepared from a wide range of block copolymers, amphiphilic blocks in selective solvents are perhaps the most versatile in that connection. If the soluble block in such aggregates, for example micelles, is very long, they are referred to as starlike, whereas if the corona block is short relative to the size of core, they are called crew-cut aggregates.[2] In 1995, Zhang and Eisenberg reported that, in solution, vesicles are a part of a morphological continuum of crew-cut aggregates, which includes spheres, rods, vesicles, inverse micellar aggregates, and, in some cases, also bicontinuous and hollow-rod structures.[3] The morphologies of crew-cut aggregates, including vesicles, are governed by a balance of contributions to the free energy, which involve the interfacial energy between the core and the outside solution, the stretching of the core forming blocks, and the repulsive interactions among corona chains.[3] Thus, morphologies can be controlled by many factors, such as relative block length, ion content, solvent composition, etc., all of which influence one or more of the free energy contributions.[3, 10-12]

Polymeric vesicles and other hollow spheres have many potential applications in areas such as microreactors, microcapsules, and drug delivery systems, in the context of encapsulation of various kinds of guest molecules. In addition to the work of the present investigators, many other groups have

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studied such structures in the past few years;[4,8,14–18] a few examples are given in the Supporting Information. It has been suggested by our research group that vesicles are equilibrium structures under some circumstances because of the reversibility of sizes in response to changes in solvent compositions.[13] Furthermore, the thermodynamic stabilization mechanism of diblock copolymer vesicles has been elucidated.[19] It was shown that the curvature in block copolymer vesicles is stabilized by preferential segregation of short hydrophilic blocks to the inside of the vesicles, and the long blocks to the outside. The repulsion among the longer corona chains is greater than that among the shorter chains. Therefore, segregation of the hydrophilic blocks by length, which allows the formation of an asymmetric lamella, stabilizes the curvature of the vesicles.

Very recently, we have shown that asymmetric vesicles with different chains on the inside and the outside can be prepared from a diblock copolymer mixture of PS_{300}-b-PAA_{11}/PS_{310}-b-$P4VP_{33}$ under acidic conditions.[20] The PAA blocks in PS_{300}-b-PAA_{11} are segregated into the inside of the vesicles because they are short, while the P4VP chains of the PS_{310}-b-$P4VP_{33}$ are segregated to the outside because they are long. Another factor which contributes to the curvature stabilization is that the P4VP chains are positively charged (which implies a repulsive interaction in acid solution), whereas the PAA chains are uncharged under the same conditions.

The one-step assembly of vesicles in which one hydrophilic species is attached to the inside wall of the vesicles and another to the outside has inspired us to design a new type of triblock copolymer. This new triblock has the composition of PAA_{26}-b-PS_{890}-b-$P4VP_{40}$, which contains hydrophobic PS blocks between the two short hydrophilic blocks (of similar block length), one of which is acidic, whereas the other is basic. Such a triblock might yield vesicles of different surface compositions (i.e., either PAA inside and P4VP outside or vice versa) from the same triblock by changing the preparation conditions, such as the pH.

Up to now, only a few publications described vesicle formation from ABC[21–23] and ABA triblock copolymers,[24,25] and a more detailed description is given in the Supporting Information. For example, vesicles from the ABC triblock, polystyrene-*block*-poly (methyl methacrylate)-*block*-poly (acrylic acid) (PS_{180}-b-$PMMA_{67}$-b-PAA_{37}), were prepared from a diox-ane-H_2O mixture by Yu et al.[21] Another example of vesicle formation from an ABC triblock, Poly (5-(N, N-dimethylamino) isoprene)-*block*-polystyrene-*block*-poly (methacrylic acid) (PAi-*b*-PS-*b*-PMAA), was given by Müller's group.[22] Vesicles from a poly (ethylene oxide)-poly (propylene oxide)-poly (ethylene oxide) (PEO-*b*-PPO-*b*-PEO) triblock copolymer have been studied by Schillén's group in dilute aqueous solution.[24] Following Luo and Eisenberg's idea that the curvature in block copolymer vesicles is stabilized by preferential segregation of short hydrophilic blocks to the inside of the vesicles and the long blocks to the outside,[19,20] Meier's group showed that ABC triblocks with two different nonionic hydrophilic blocks of different block lengths can self-assemble to vesicles with the shorter and longer hydrophilic blocks preferentially segregated into the inside and outside of the vesicles, respectively, with the hydrophobic blocks forming the wall.[23]

In the present paper, we report on a detailed study of the effect of pH on the morphology of a new type of asymmetric ABC triblock, PAA_{26}-b-PS_{890}-b-$P4VP_{40}$, with two different relatively short hydrophilic blocks, PAA and P4VP, i.e., one acidic and one basic, separated by a hydrophobic block (PS). From published acid or base strengths of PAA and P4VP, as well as from previous studies of the PS-*b*-PAA[3] and PS-*b*-P4VP systems,[26] one can expect different effects of pH on these two different hydrophilic blocks. At low pH, the P4VP blocks are quaternized, and therefore the repulsive interactions among P4VP chains are increased; the PAA blocks, however, are protonated at low pH and the repulsive interactions among the nonionic PAA blocks are low. Alternately, at high pH, the PAA blocks are neutralized, and the repulsive interactions among PAA coronas are high, whereas the repulsive interactions among the P4VP blocks are low. Asymmetric vesicles with preferentially segregated acidic and basic corona chains could thus be formed by control of the repulsive interaction among corona chains under different pH conditions, i.e., with PAA on the outside at high pH and P4VP outside at low pH. By using the triblock PAA_{26}-b-PS_{890}-b-$P4VP_{40}$, vesicles can, indeed, be are prepared with either P4VP or PAA on the outside under different pH conditions. Most interestingly, vesicles with PAA on the outside can be inverted to P4VP outside by a pH change, whereas the vesicles are under dynamic conditions, i.e., when the wall is swollen.

2. Experimental Section

Experimental details are given in the Supporting Information.

3. Results and Discussion

The results and discussion section consists of three parts. The first part describes the effect of solution pH* on the aggregate morphology of the triblocks. The preparation of vesicles with either PAA on the outside or P4VP on the outside is emphasized in this part. The second part is devoted to a discussion of the formation of aggregates. Finally, the inversion, triggered by a pH change, from vesicles with PAA on the outside to vesicles with P4VP on the outside, is described.

3.1. Aggregate Morphology of PAA_{26}-b-PS_{890}-b-$P4VP_{40}$.
3.1.1. pH* Effect. The aggregate morphologies of the triblock copolymer, formed under different pH* conditions for a polymer

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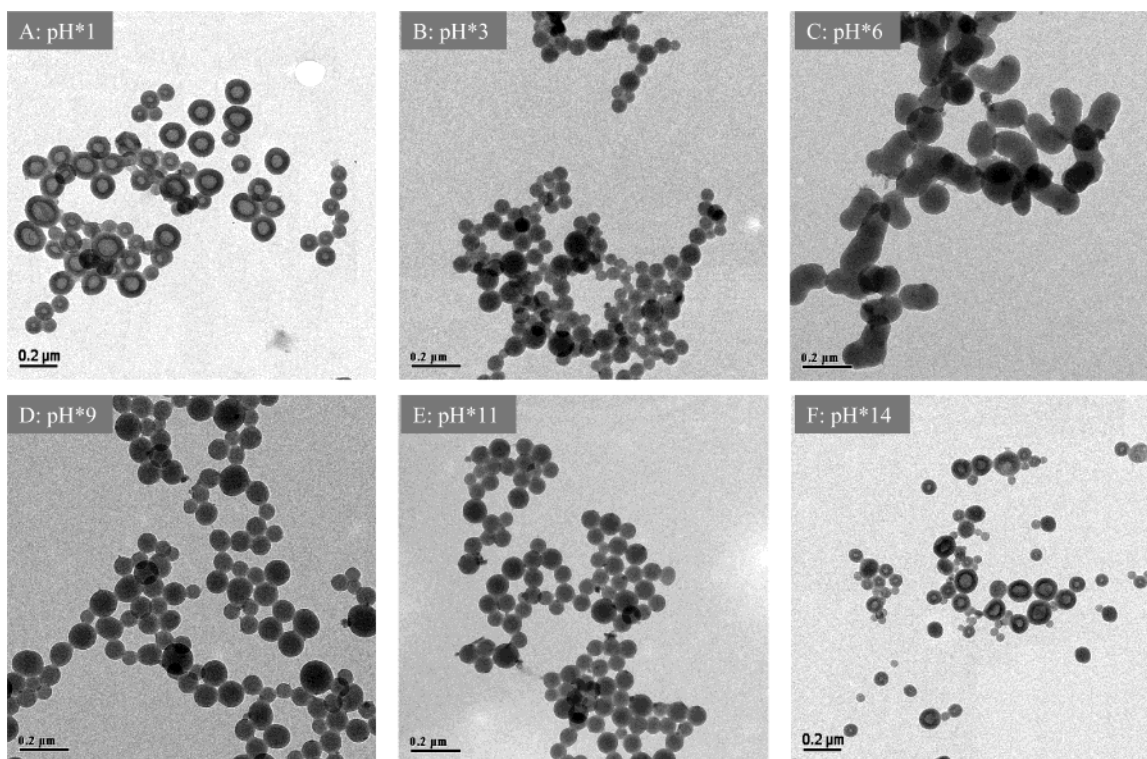(26) Shen, H.; Zhang, L.; Eisenberg, A. *J. Am. Chem. Soc.* **1999**, *121*, 2728−2740.

Figure 1. TEM pictures of aggregates prepared at different pH* (polymer concentration: 1 wt% in DMF-THF (85/15 wt/wt); water content before quenching, 30 wt%).

concentration of 1 wt % in DMF/THF (85/15 w/w) are shown in Figure 1. With increasing pH* of the solutions in which the aggregates are prepared, the morphology changes progressively from vesicles at pH*1 (Figure 1A, mole ratio of HCl/4VP, R = 5.6), to spheres at pH*3 (Figure 1B, mole ratio of HCl/4VP, R = 0.056), to ellipsoids or short rods at pH*6 (Figure 1C, mole ratio of HCl/4VP, $R = 5.6 \times 10^{-4}$), back to spheres at pH*9 (Figure 1D, mole ratio of NaOH/AA, $R = 4.8 \times 10^{-5}$), continuing as spheres at pH*11 (Figure 1E, mole ratio of NaOH/AA, $R = 0.048$), and finally vesicles at pH*14 (Figure 1F, mole ratio of NaOH/AA, $R = 4.8$).

The vesicles in Figure 1A have an average outside diameter of 118 ± 20 nm and an average wall thickness of 30 ± 2 nm, whereas for those in Figure 1F, the comparable values are 90 ± 24 nm and 28 ± 3 nm. Considering the length of the polystyrene block (890 units), the wall thickness of ca. 30 nm suggests that these vesicles are probably unilamellar monolayer structures, in contrast to the usual unilamellar diblock copolymer vesicles, which are bilayer structures. In the latter case, for example for PS_{500}-b-PAA_{58}, the vesicle wall thickness is ca. 37 nm.[12] The diameters of the aggregates in Figure 1B, 1D, and 1E are 62 ± 16 nm, 82 ± 18 nm and 75 ± 10 nm, respectively; while the structures in Figure 1C have an approximate diameter of ca. 100 nm.

3.1.2. Electrophoretic Mobility of the Vesicles. The outside surface of the vesicles was investigated by measuring the pH dependence of the ξ potential after dialysis of the vesicles against pure water. Figure 2 shows plots of the ξ potential versus pH for aggregates prepared under different pH conditions. Vesicles prepared at pH*1 show a positive potential at low pH. With increasing pH, the ξ potential decreases and even becomes negative in the pH range above 6.8. This plot is quite similar to that reported earlier for vesicles prepared from the diblock
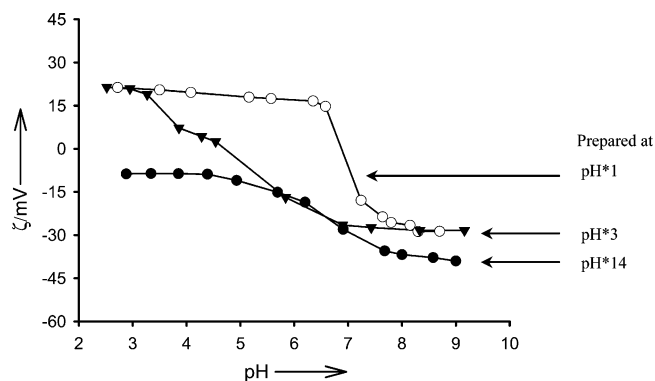

Figure 2. Plots of ζ potential versus pH for vesicles prepared at pH*1 (○), for spheres prepared at pH*3 (▼), and for vesicles prepared at pH*14 (●).

PS_{310}-b-$P4VP_{33}$ which has only P4VP chains in the corona.[20] The positive ζ potential at low pH shows that the surface of the vesicles is positively charged, which is evidently due to the protonation of P4VP at low pH. With increasing pH, the degree of protonation of the P4VP decreases; as a result, the ζ potential of the vesicles decreases. The ξ potential becomes negative above a pH of 6.8; most likely, this inversion of the ξ potential is caused by the adsorption of anions, i.e., OH⁻, as was suggested by several research groups.[27]

The outside surface of the vesicles prepared at pH*14 was again characterized by measurement of the ξ potential. The plot of the ξ potential versus pH for these vesicles is also shown in Figure 2. In contrast to the vesicles prepared under acid conditions, the ξ potential of this type of vesicles is negative at

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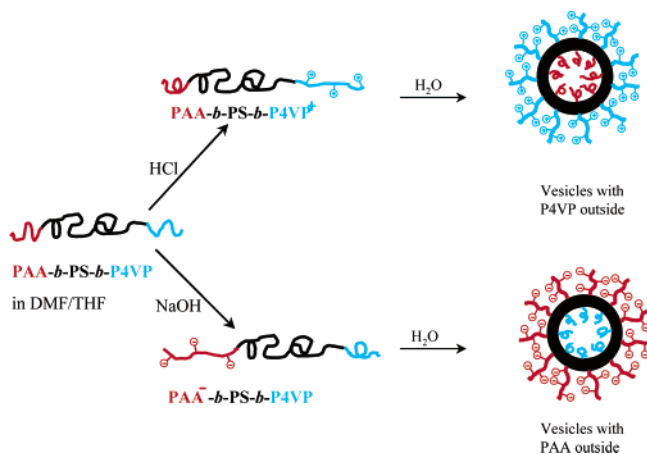
Figure 3. Schematic of the preparation of the two types of vesicles from the triblock. The charges are on the chains, not counterions.

Figure 4. Schematic of the inversion of vesicles from PAA outside to P4VP outside. The charge are on the chains, not counterions.

low pH and also decreases with increasing pH. This negative ζ potential at low pH is characteristic of vesicles with PAA chains on the outside, which are negatively charged because of the slight ionization of carboxylic acid groups. These results, again, parallel those obtained for vesicles prepared from only PS-*b*-PAA diblocks,[20] which suggests that the outside surface of the vesicles is composed of PAA blocks.

Compared with the behavior of the vesicles which were prepared at pH*1 and pH* 14, plots of the ξ potential versus pH for the solid aggregates prepared at pH*3 to 11 are quite different. An example of the ξ potential of such structures prepared at pH*3 is also shown in Figure 2. At low pH (<4.7), the ξ potential is positive, which shows that there is P4VP on the outside. However, the ξ potential decreases sharply with increasing pH and even becomes negative when the pH is above 4.7. The most likely explanation for this observation is that PAA chains are also on the outside because PAA chains become negatively charged with the increasing pH. This result indicates that the outside surface is composed of both P4VP and PAA chains.

3.2. Reasons for the Observed pH* Effects. From the ξ potential measurements described above, it is seen clearly that vesicles with either PAA or P4VP on the outside can be prepared from the same triblock PAA_{26}-*b*-PS_{890}-*b*-$P4VP_{40}$ under different pH* conditions, and that the solid aggregates contain a mixture of PAA and P4VP on the surface. The formation of various aggregates, especially the two types of vesicles, will now be discussed briefly.

3.2.1. Vesicle Formation at pH*1. The addition of acid to the triblock solution will have opposite effects on the PAA and P4VP chains, as shown schematically in Figure 3. Under acid conditions, both PAA and P4VP blocks are protonated. The protonation of the PAA blocks decreases or even eliminates their charge relative to that at neutral pH*, and thus decreases the repulsive interactions among them. As a result, the PAA chains undergo a conformational change, from a relatively extended chain to a coil as the pH* decreases.[28,29] The P4VP blocks, by contrast, become positively charged due to the quaternization under acidic condition which increases the
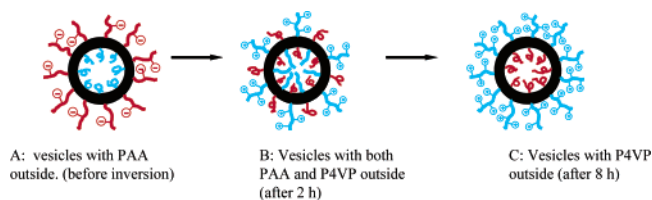
repulsive interactions. At pH*1 (at which the ratio of HCl/4VP is 5.6), vesicles with P4VP on the outside were therefore obtained (Figure 1A). The estimated degree of ionization of the P4VP at that pH* is ca. 95%,[26] and the electrostatic repulsive interactions among the P4VP chains are stronger than those among the uncharged PAA chains even in the presence of some shielding due to the H$^+$ and Cl$^-$ ions. Therefore, the curvature stabilization mechanism is based on segregation of the more highly stretched P4VP chains to the outside, whereas the PAA chains segregate to the inside of the vesicle.

3.2.2. Vesicle Formation at pH*14. At pH*14, the PAA chains are fully neutralized by NaOH; therefore, they are in a more extended form because of the increased electrostatic repulsion, again even in the presence of some shielding by the Na$^+$ and OH$^-$ ions. It should be recalled that the P4VP chains can also be ionized to some extent through the release of an α-H in the presence of NaOH.[26] However, the degree of ionization for the P4VP block is much lower than that of the PAA (i.e., below 20% when ratio of NaOH/P4VP is 4.8; however, for the same ratio of NaOH/PAA, the neutralization of the PAA is complete).[26] Therefore, the electrostatic repulsive interactions among the P4VP blocks are much lower than those among PAA blocks. In this case, the curvature stabilization mechanism favors segregation of the more stretched PAA to the outside while the P4VP chains are on the inside of the vesicle (as shown schematically in Figure 3).

3.2.3. Aggregate Formation at Intermediate pH* Values. At intermediate pH* values, aggregation may occur with the insoluble PS blocks forming the core and the soluble PAA and P4VP blocks forming the corona in the early stage of the self-assembly process, because some attractive interactions between the PAA blocks and the P4VP blocks are possible in the intermediate pH range (3~11). The interactions between PAA and P4VP can be electrostatic or due to hydrogen bonding. In such a case, the spherical aggregates (in Figure 1B, D, and E) would have both PAA and P4VP chains on the outside (as confirmed, for example, in the plot of the pH dependence of the ζ potential curve for pH*3 in Figure 2). The spherical aggregates, which are large and polydisperse, may be large compound micelles (LCMs), i.e., aggregates of primary reverse micelles, with a hydrophilic surface, as described previously.[3]

3.3. Inversion of Vesicles. In view of the control which can be exerted by pH* on the interior or exterior interfaces, i.e., whether PAA or P4VP is on the outside with the opposite block on the inside, it was of interest to see whether vesicles could be inverted from one state to the other by a change in the pH*. A Schematic representation for inversions of the vesicles from PAA outside to P4VP outside is shown in Figure 4. For greatest generality, it was of interest to start with the dry powder, although solutions of vesicles in the appropriate solvent mixtures could also be used.

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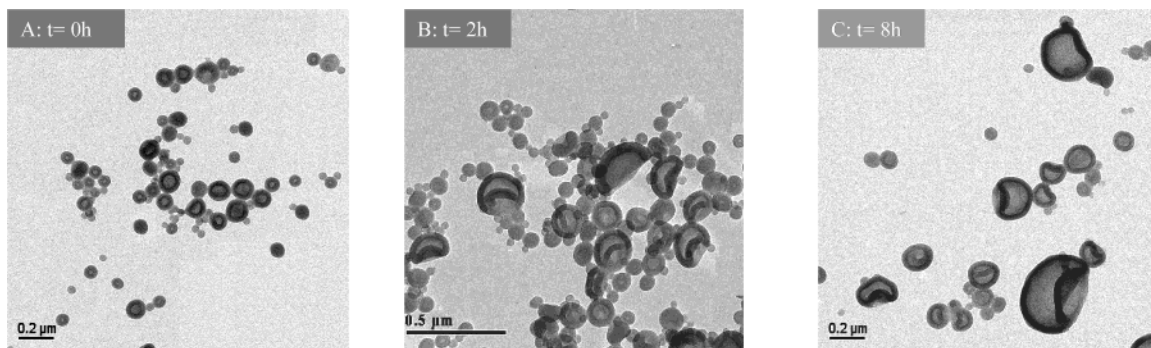(29) Chen, J.; Jiang, M.; Zhang, Y.; Zhou, H. *Macromolecules* **1999**, *32*, 4861−4866.

Figure 5. TEM images of the vesicles starting with PAA on the outside (A), after an inversion time of 2h (B), and after an inversion time of 8h (C).
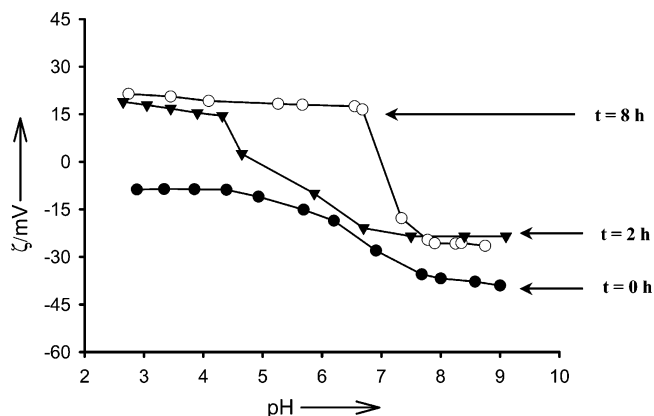

Figure 6. Plots of ζ potential versus pH for vesicles with PAA on the outside (●), after an inversion time of 2h (▼), and after an inversion time of 8h (○).

The dry powder of vesicles with PAA on the outside was first dispersed in a mixture of DMF, THF and water (50, 18, and 32 wt %, respectively); then an aqueous acid solution (4M HCl) was added. The presence of DMF and THF serves to soften the glassy PS wall and to make it dynamic so that diffusion at reasonable rates is possible. Also, 32 wt % water at ca. 1 wt % polymer locates the aggregate in the vesicle region of the phase diagram as suggested by the stability of the vesicles under dynamic conditions.

Figure 5 shows vesicles at various times during the inversion process. Figure 5A shows vesicles with PAA outside prior to drying. Figure 5B and Figure 5C show the vesicles 2 h and 8 h after redispersion and HCl addition. In all cases, polydisperse vesicles are seen in the presence of some spheres. Before the TEM pictures were taken, the vesicle solutions (for 2 and 8 h) were dialyzed against pH 4 water. The pH 4 solution was employed because when the vesicles were dialyzed against pure water, they precipitated. The precipitation at neutral pH constitutes a preliminary indication that P4VP chains are on now the outside.

To confirm the localization of P4VP chains, the pH dependence of ζ potential was measured before and after the inversion process. Figure 6 shows the result for the initial vesicles ($t = 0$ h; this plot is the same as that shown in Figure 2 for the vesicles prepared at pH*14 because these vesicles are also the starting point for the kinetic study), after 2 h and after 8 h; the $t = 0$ curve is typical for vesicles with PAA outside, because the ζ potential is negative over the entire pH range.[20] The curve for $t = 8$ h is typical for vesicles with P4VP outside because the ζ potential is positive until pH >7 and turns negative at high pH.

The negative ζ potential at high pH is most likely due to adsorption of OH^- ions, as has been mentioned above and described in the literature.[20] The $t = 2$ h plot presents an intermediate case. At low pH (<4.5), the plot resembles the vesicles with P4VP outside, but at intermediate pH (5∼7), it moves closer in shape to that for vesicles with PAA outside. The low pH behavior can be understood on the basis of partial inversion. At low pH (<4), the P4VP chains on the outside make the vesicles positive; however, between pH4.5 and 7, the PAA chains become dominant and the ζ potential reflects the increasingly negative charge on the vesicles. At pH >7, the vesicles remain negatively charged; however, not enough of the PAA chains are on the outside to give the vesicles the same level of negative charge as for the completely inverted vesicles with only PAA outside. This curve suggests that the inversion is a gradual process. Not surprisingly, the curve resembles that for vesicles prepared at pH*3 in Figure 2. Most importantly, the curves $t = 0$ and $t = 8$ h prove that a successful inversion has, indeed, occurred from vesicles with PAA outside to those with P4VP outside.

Several attempts were made to invert vesicles with P4VP outside to PAA outside. So far, these attempts were unsuccessful because in all of these it was necessary to place vesicles with P4VP chains on the outside into a basic solution, where, the vesicles precipitated. Attempts to achieve this inversion are continuing, however.

Several inversion mechanisms are conceivable for the inversion of vesicles with PAA outside to P4VP outside. These mechanisms can be classified into two groups. One involves inversion of vesicles without participation of single chains, the other involves single chains in the inversion. If HCl can pass through the swollen PS wall to quaternize the P4VP chains inside, then inversion of vesicles could be triggered by repulsive interaction among P4VP chains caused by quaternization. Naturally, the charged P4VP chains would have to diffuse through the wall. It has been shown before that uncharged PAA chains can do so.[19] More probably, P4VP and PAA chains with low or zero charge densities may be diffusing through the softened wall. Once the P4VP chains are on the outside, they become protonated, in which case the likelihood of back diffusion is much smaller. Simultaneously, uncharged PAA chains can move to the inside. At this time, we do not have proof as to which of the two mechanisms is operative, or whether possibly even partly protonated P4VP chains might be diffusing through the swollen PS wall, because we do not yet have quantitative information on the diffusion kinetics. However, because diffusion through the wall for chains of low or zero
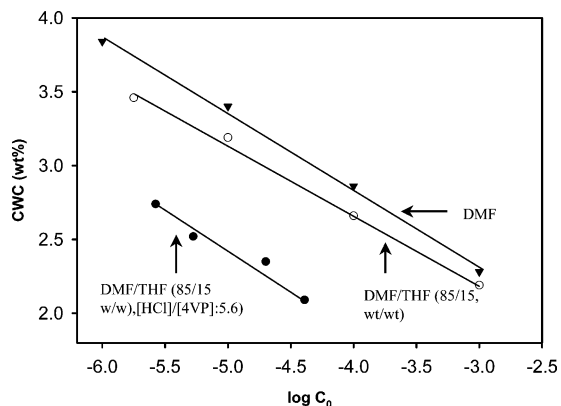
Figure 7. Critical water content vs logarithm of the polymer concentration in various solvents or solvent mixtures.

charge density is more likely than those of high charge density, the latter mechanism is preferred.

Finally, it is necessary to address the possibility that single chains might be involved in the inversion mechanism. Before doing so, it is most useful to explore the concentration of single chains (cmc) under the condition of inversion (32 wt % water). At that water content, the cmc is far too low to be measured directly. However, we can measure the critical water content as a function of polymer concentration at similar DMF−THF ratios as those used for the inversion. The results of the measurements in the accessible water content range are shown in Figure 7. For all of these solutions, the plots also represent the critical micelle concentration at different water contents, from which one can extrapolate to the region of interest (32 wt %). Although it is very risky to extrapolate over such long ranges, it is nevertheless instructive to do so to obtain a very approximate idea of the single chain concentration to be expected. The details of the extrapolation procedure are given in the supporting material. The single chain fraction (relative to total polymer content) at 32 wt % water is ca. 10^{-58}. Even if this number is off by 10 or even 20 orders of magnitude, and is meaningful only in terms of the very unfavorable thermo-dynamics for single chains, it is clear that the single-chain concentration is far too low for these to be involved in the inversion process.

4. Summary and Conclusions

The pH* under preparative conditions exerts a strong effect on the morphology of aggregates for PAA_{26}-*b*-PS_{890}-*b*-$P4VP_{40}$

systems in DMF/THF/H_2O mixtures. Starting with a pH*1, and moving gradually to pH*14, the aggregate morphology changes from vesicles (pH*1), to solid aggregates (pH*3∼11), and finally back to vesicles (pH*14). Vesicles prepared at pH*1 are composed of P4VP on the outside and PAA on the inside. At pH*14, the vesicles consist of PAA on the outside corona and P4VP on the inside. This segregation is based upon the difference in repulsive interaction of PAA and P4VP under different pH* conditions, with the more strongly repulsive block forming the outside. At intermediate pH* values, solid aggregates are formed which contain both PAA and P4VP blocks on the outside.

Vesicles are invertible from PAA outside to P4VP outside by a pH* change, whereas they are swollen and under dynamic condition. Because the CMC for this triblock is far too low for a single chain to be involved at 32 wt % water, the inversion mechanism, most likely, involves a whole vesicles process with diffusion of PAA or P4VP chains of low or zero charge density through the PS wall. It is likely that inversion processes for vesicles induced by an external chemical trigger, as described here, might find applications in various controlled release or delivery processes.

Supporting Information Available: A brief description of work on vesicles from other groups, a brief literature review of vesicles from ABC and ABA triblocks**,** the experimental details describing the polymer synthesis, preparation and characterization of aggregates, inversion of vesicles and the extrapolation of polymer critical micelle concentration (CMC). This material is available free of charge via the Internet at http://pubs.acs.org.

Note Added after ASAP Posting: This manuscript was originally published on the Web (11/14/2003) without the incorporation of the revised caption for Figure 1. The final Web version (published 11/18/2003) and the print version are correct.

JA038142R