One-Step Preparation of Block Copolymer Vesicles with Preferentially Segregated Acidic and Basic Corona Chains**

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Amphiphilic molecules, such as block copolymers,[1–10] phospholipids,[11, 12] synthetic surfactants,[13, 14] and other amphiphiles[15–18] can self-assemble to form vesicles in aqueous solutions. The equilibrium nature of vesicles has received considerable attention. It has been suggested that vesicles prepared from surfactant mixtures made by combining oppositely charged surfactants are equilibrium structures. The free energy is minimized in vesicles through different concentrations of the two surfactants on each side of the bilayer.[19–22] Alternatively, small-molecule vesicles can also be stabilized by grafting a polymer to the outer layer.[23] Very recently, the thermodynamic stabilization mechanism of diblock copolymer vesicles was elucidated by our research group.[24] In vesicles prepared from polystyrene-*b*-poly(acrylic acid) (PS-*b*-PAA) diblock copolymers, it has been shown that shorter PAA chains are segregated into the inside of the vesicles, while the longer PAA chains are segregated on the outside. The repulsions among the longer PAA chains on the outside are stronger than those among the shorter PAA chains on the inside, thus stabilizing the curvature of the vesicles. Preferential segregation of blocks of different lengths was proved by the use of fluorescently labeled diblock copolymers in which pyrene was located at the junction point between the hydrophilic and hydrophobic blocks. If the vesicles were prepared in a dioxane–water mixture (40% water content) with a labeled copolymer containing short hydrophilic segments, the pyrene was mostly inaccessible to the quencher because it was located on the inside of the vesicles. By contrast, pyrene molecules attached to the block copolymers with long hydrophilic chains were accessible to the quencher because they were on the outside. It was also shown that segregation is dependent on the size of the vesicles and that it is reversible in response to changes of size.[25] On the basis of this evidence it was suggested that vesicles are equilibrium structures in dioxane–water mixtures.

Since corona chains can be directed preferentially to either the inside or the outside of the vesicles, it is clear that the technique can, in principle, be utilized to locate chemically distinct groups on the inside or outside of the vesicles. Herein we show this is indeed possible by exploring the segregation of a mixture of polystyrene diblock copolymers containing both polystyrene-*b*-poly(acrylic acid) (PS-*b*-PAA) and polystyrene-*b*-poly(4-vinylpyridine) (PS-*b*-P(4-VP)). Although one of these blocks is acidic and the other one is basic, we show that they can be preferentially segregated on the inside and outside of the vesicles, respectively, by using different hydrophilic block lengths. One aspect of the proof of segregation consists of the use of a fluorescently labeled diblock of PS_{295}-Py-*b*-PAA_{12} (with a pyrene molecule (Py) located between the styrene and the acrylic acid blocks) mixed with unlabeled PS_{300}-*b*-PAA_{11} as the acidic component. If segregation occurs in this system we expect the pyrene to be largely inaccessible to the quencher. Another element of the proof of segregation consists of a comparison of the ζ potential of vesicles prepared from only PS_{310}-*b*-P(4-VP)$_{33}$ and others of only PS_{300}-*b*-PAA_{44} with that of vesicles prepared from the mixed copolymers.

It is worth noting that asymmetric diblock copolymers in solution can self-assemble into aggregates of a range of morphologies; vesicles are a part of a morphological continuum of crew-cut aggregates which include spheres, rods, vesicles, inverse micellar aggregates, and, in some cases, also bicontinuous and hollow-rod structures.[2] A balance of the free energy associated with the interfacial energy between the core and the outside solution, the stretching of the core-forming blocks, and the repulsive interactions among the corona chains controls the morphologies of the crew-cut aggregates.[26] Thus, morphologies can be controlled by many factors, such as relative block length,[2a,b] ion content,[2c,d] and solvent composition,[2f,h] all of which influence one or more of the three free-energy contributions.[26]

In our studies, five distinct block copolymers and mixtures were considered. Transmission electron microscopy (TEM) was used to investigate the morphologies of the aggregates. As shown in Figure 1a and b, PS_{300}-*b*-PAA_{11} self-assembles into large compound micelles (LCMs); while PS_{310}-*b*-P(4-VP)$_{33}$ self-assembles into vesicles under the conditions described in the experimental section. The vesicles have an average outside diameter ($\pm$standard deviation) of 102 ± 14 nm and an average wall thickness of 26 ± 2 nm. Only vesicles were observed in the mixture of the two diblock copolymers (Figure 1c). The average diameter and wall thickness are 90 ± 12 nm and 26 ± 2 nm, respectively. The sizes of vesicles prepared from the mixture are somewhat smaller than those prepared from the single component; the wall thickness, however, is the same. The pyrene-labeled diblock copolymer mixture also forms vesicles (Figure 1d). Both the average diameter (88 ± 11 nm) and wall thickness (26 ± 2 nm) are similar to those of vesicles prepared from unlabeled mixture. As reported previously, PS_{300}-*b*-PAA_{44} can self-assemble into vesicles with an average diameter of 98 ± 7 nm and a wall thickness of 26 ± 3 nm in a dioxane–water solvent mixture containing 1% polymer and 40% water.[24]

The outside surface properties of PS_{310}-*b*-P(4-VP)$_{33}$, PS_{300}-*b*-PAA_{44}, and PS_{300}-*b*-PAA_{11}/PS_{310}-*b*-P(4-VP)$_{33}$ vesicles were investigated by measurement of the ζ potential.[27] Figure 2 shows the plots of the ζ potential versus pH for vesicles prepared from these three different systems. The outside corona of the PS_{310}-*b*-P(4-VP)$_{33}$ vesicles consists of only P(4-VP) chains. The 4-VP units are protonated at pH 3 and, therefore, the PS_{310}-*b*-P(4-VP)$_{33}$ vesicles show a positive ζ potential. The degree of protonation of P(4-VP) decreases with increasing pH, and hence the ζ potential decreases.[28]

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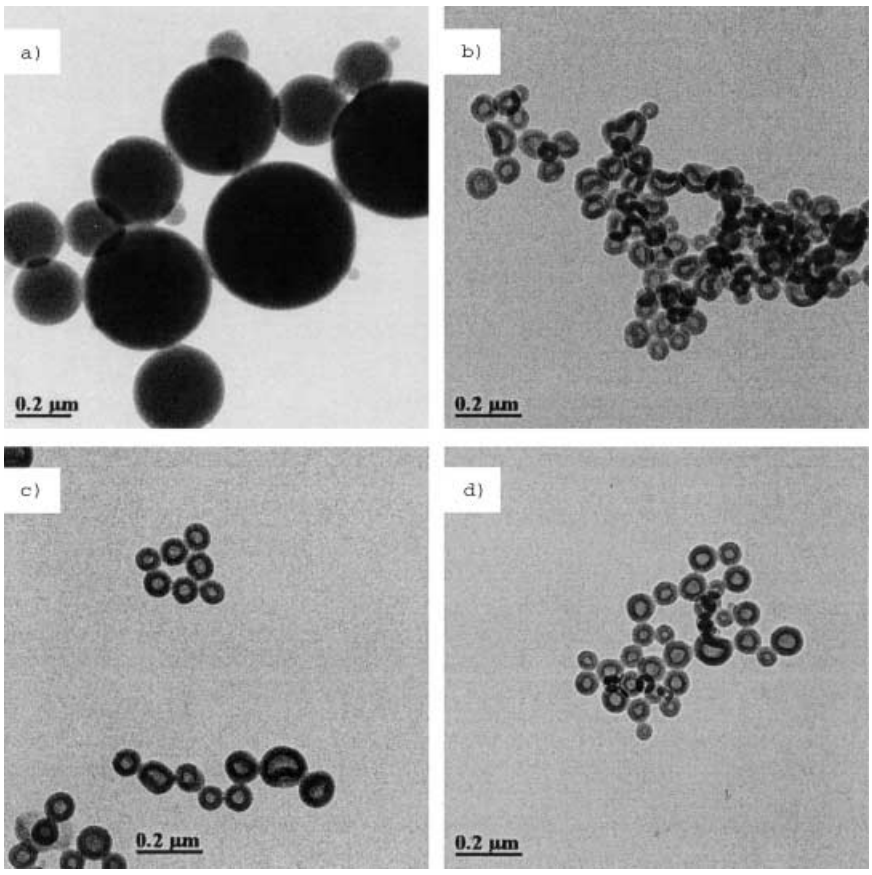

Figure 1. Transmission electron micrograph of aggregates prepared from DMF solution (pH 3.0) of a) PS_{300}-*b*-PAA_{11} (polymer weight: 0.49 %); b) PS_{310}-*b*-P(4-VP)$_{33}$ (polymer weight: 0.81 %); c) PS_{300}-*b*-PAA_{11}/PS_{310}-*b*-P(4-VP)$_{33}$ (polymer weight: 0.49/0.81 %; molar ratio: 2/3); d) PS_{300}-*b*-PAA_{11}/PS_{295}-Py-*b*-PAA_{12}/PS_{310}-*b*-P(4-VP)$_{33}$ (polymer weight: 0.43/0.06/0.81 % ; molar ratio: 7/1/12) by adding water to 50 %.

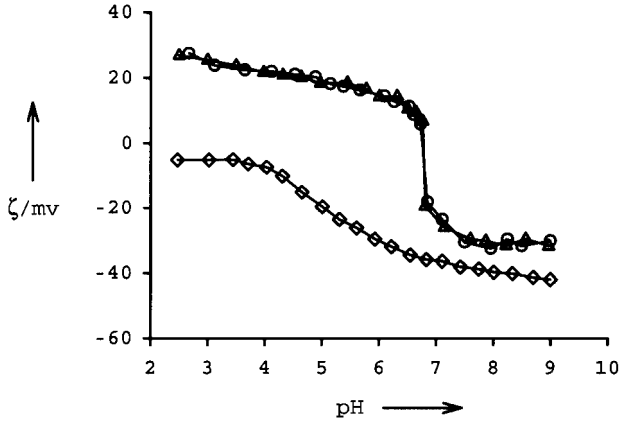

Figure 2. Plots of ζ potential versus pH of vesicles of PS_{310}-*b*-P(4-VP)$_{33}$ (△), PS_{300}-*b*-PAA_{44} (◇), and PS_{300}-*b*-PAA_{11}/PS_{310}-*b*-P(4-VP)$_{33}$ (molar ratio: 2/3, ○).

The zeta ζ potential becomes negative in the pH region above 6.8. As reported previously, the pK_a value of P(4-VP) at zero protonation is 5.0.[29] Thus, the H^+ ions can not play a role in determining the value of the ζ potential in the region above pH 6.8. The reason that the ζ potential becomes negative above pH 6.8 is, most likely, because of the adsorption of anions, that is, OH^-, as was suggested by several research groups.[30] In contrast to the vesicles prepared from PS_{310}-*b*-P(4-VP)$_{33}$, the outside corona of the PS_{300}-*b*-PAA_{44} vesicles consists only of PAA chains. The degree of ionization of PAA increases with increasing pH value.[31] Hence, the ζ potential of the PS_{300}-*b*-PAA_{44} vesicles is negative and decreases further with increasing pH value (Figure 2). The changes in the ζ potential with pH for mixed vesicles of PS_{300}-*b*-PAA_{11}/PS_{310}-*b*-P(4-VP)$_{33}$ in aqueous solution are also given in Figure 2. The plot is identical to that for PS_{310}-*b*-P(4VP)$_{33}$ vesicles. This result suggests that the outside corona of PS_{300}-*b*-PAA_{11}/PS_{310}-*b*-P(4-VP)$_{33}$ vesicles consists mainly of P(4-VP) chains.

It should be noted that poly(vinylpyridine) is not stable in aqueous solution above pH 5.0. Nevertheless, it is possible to determine the pH dependence of the ζ potential above pH 5.0 using our instrumentation (see below), because the vesicles precipitate very slowly. The speed of precipitation was studied semi-quantitatively by monitoring the turbidity as a function of time for both PS_{310}-*b*-P(4VP)$_{33}$ vesicles as well as those prepared from the mixture of PS_{300}-*b*-PAA_{11}/PS_{310}-*b*-P(4-VP)$_{33}$ after changing the pH value of the solutions from 3.0 to 7.0 (Figure 3). The decrease in the turbidity results from the settlement of vesicles under the force of gravity. The slow rate of settling shows that over the time scale used for measuring the ζ potential (less than 10 seconds for the measurement of the ζ potential itself and less than 5 minutes for the preparation of the solution). The turbidity is essentially constant. More importantly, the results obtained for the settlement rates at pH 7.0 (Figure 3) confirm that the extended surfaces of the vesicles prepared from PS_{310}-*b*-P(4VP)$_{33}$ and the mixture of PS_{300}-

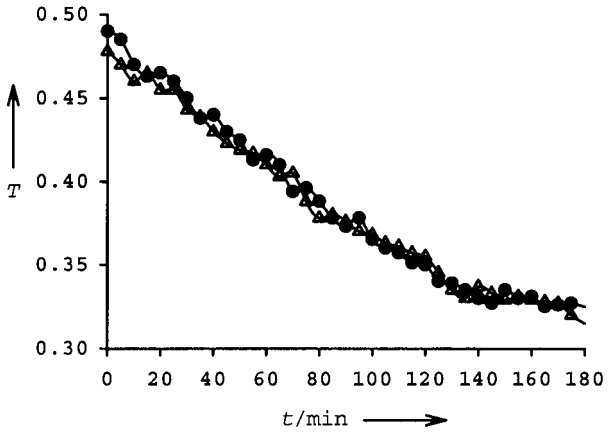

Figure 3. Change of turbidity *T* versus time for solutions of PS_{300}-*b*-PAA_{11}/PS_{310}-*b*-P(4-VP)$_{33}$ (△) and PS_{310}-*b*-P(4-VP)$_{33}$ (●) vesicles (pH 7.0, 7.5 mM NaCl, 0.05 % polymer concentration).

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b-PAA_{11}/PS_{310}-*b*-$P(4\text{-}VP)_{33}$have the same properties. The slowness of the precipitation process in the micelles, relative to what is observed in the homopolymer, is probably a result of the presence of the hydrophobic surface in the vesicles which can adsorb ions and thus extend considerably the length of time the vesicles remain in solution at pH > 5.0.

The location of the PAA chains was explored using a mixture of block copolymers consisting of PS_{300}-*b*-PAA_{11}/PS_{295}-Py-*b*-PAA_{12}/PS_{310}-*b*-$P(4\text{-}VP)_{33}$ (molar ratio: 7/1/12). The location of the pyrene molecules in the vesicles can be determined by fluorescence quenching experiments using Tl^+ ions as a quencher. Once the vesicles were prepared, they were quenched in water and dialyzed against water. Subsequently, various amounts of Tl^+ ions were added to the solutions of the vesicles and the fluorescence was measured. If pyrene molecules were located on the outside of the vesicles they would be exposed to the Tl^+ ions, and would thus experience efficient quenching. By contrast, the pyrene molecules located on the inside surface are not accessible to Tl^+ ions, and their fluorescence would not be quenched.[24] The results of the steady-state quenching experiments are shown in Figure 4, plotted as I_0/I versus the quencher

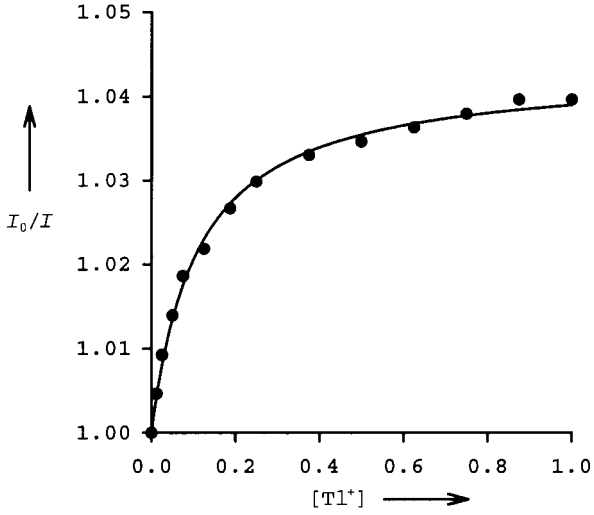

Figure 4. Steady-state fluorescence quenching by Tl^+ ions for PS_{300}-*b*-PAA_{11}/PS_{295}-Py-*b*-PAA_{12}/PS_{310}-*b*-$P(4\text{-}VP)_{33}$ (molar ratio: 7/1/12) vesicles.

concentration. I_0 is the fluorescence intensity without quencher, while I is the steady-state fluorescence in the presence of quencher. The modified Stern–Volmer equation [Eq. (1)] was used to fit the data.[24, 25, 32]

$$\frac{I_0}{I} = 1 + \frac{\phi K[Tl^+]}{1 + (1 - \phi)K[Tl^+]} \quad (1)$$

K is the Stern–Volmer constant and ϕ is the fraction of accessible chromophores. The best-fit ϕ and K values are 0.042 ± 0.001 and 9.5 ± 0.5 mM^{-1}, respectively; the line was, in turn, calculated from these numbers. The results suggest that 4.2% of the pyrene molecules are accessible to the Tl^+ ions in the solution, which means that approximately 96% of the molecules are inaccessible because they are located on the inside of the vesicles. Therefore, it can be concluded that the PAA chains are mainly segregated on the inside of the PS_{300}-*b*-PAA_{11}/PS_{295}-Py-*b*-PAA_{12}/PS_{310}-*b*-$P(4\text{-}VP)_{33}$ vesicles.

In conclusion, we have shown that polymeric vesicles can be prepared from a diblock copolymer mixture of PS_{300}-*b*-PAA_{11}/PS_{310}-*b*-$P(4\text{-}VP)_{33}$. The PAA block chains in PS_{300}-*b*-PAA_{11} are segregated into the inside of the vesicles, while the outside corona of the vesicles consist of P(4-VP) chains. This segregation occurs because the PAA chains are much shorter than the P(4-VP) chains and stabilize the curvature. Another factor which contributes to the curvature stabilization is that the P(4-VP) chains are positively charged (which implies a repulsive interaction in solution), while PAA chains are neutral under the experimental conditions. The one-step assembly of vesicles in which one species is attached to the inside wall and another to the outside, as demonstrated here, may have useful applications.

Experimental Section

Micellization: A mixture of PS_{300}-*b*-PAA_{11}/PS_{310}-*b*-$P(4\text{-}VP)_{33}$ was dissolved in DMF (polymer weight: 0.49/0.81%, w/w; molar ratio: 2/3). The pH value was adjusted to 3 using 4M HCl to protonate the vinylpyridine units in order to avoid formation of complexes between PAA and P(4-VP). To induce micellization, water was added at a rate of 0.1% per minute to the solution until a water content of 50% was reached. The colloid solution was then quenched by excess water and dialyzed against water. As controls, the micellization of PS_{300}-*b*-PAA_{11} and PS_{310}-*b*-$P(4\text{-}VP)_{33}$ was also preformed under the same conditions and following the same procedure. Furthermore, a diblock copolymer mixture of PS_{300}-*b*-PAA_{11}/PS_{295}-Py-*b*-PAA_{12}/PS_{310}-*b*-$P(4\text{-}VP)_{33}$ (polymer weight %: 0.43/0.06/0.81, w/w/w ; molar ratio: 7/1/12) was used to prepare fluorescently labeled aggregates.

Transmission electron microscopy was performed on a JEOL microscope with a CCD camera operating at an acceleration voltage of 80 kV. Copper EM grids were precoated with a thin film of Formvar and then coated with carbon. A drop of solution containing 0.05 wt% of polymer was deposited on the resulting grids. Samples were dried in air overnight.

The mobility of the vesicles was determined in aqueous 7.5 mM NaCl solutions at 25°C over a pH range of 3–9 on a MKII Microelectrophoresis Instrument to obtain the ζ potential of the samples. The pH value of the solutions was altered by adding 7.5 mM HCl or NaOH solutions.

For the turbidity measurements, the PS_{300}-*b*-PAA_{11}/PS_{310}-*b*-$P(4\text{-}VP)_{33}$ and PS_{310}-*b*-$P(4\text{-}VP)_{33}$ vesicles were dispersed at pH 3.0 in a 7.5 mM NaCl solution. The pH value was adjusted to pH 7.0 by adding a 7.5 mM NaOH solution. The turbidity of solutions was monitored at a wavelength of 650 nm.

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A Method To Identify and Screen Libraries of Guests That Complex to a Synthetic Host**

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In supramolecular host–guest chemistry, the de novo design of a host molecule often does not lead to selectivity for the desired guest.[1] Alternatively, host–guest recognition can be reformulated from the perspective of a known host molecule that requires the identification of suitable guest molecules. This would allow the application of existing host molecules in other fields, for example, for sensing other guest molecules, or for carrying other drugs in artificial drug-carrier systems. The identification of guests is a well-known problem in medicinal chemistry, where lead discovery aims at the identification of possible binders to an enzyme, for example. In this field, one approach to overcome the limitations of de novo design is the development of rapid (virtual) screening techniques.

Docking is a computational method often used to identify new leads or suggest possible binding modes of known guests.[2] When used for the identification of leads, docking starts from a simplified representation of the binding pocket of a protein or receptor, for example, one derived from a crystal structure. Subsequently, a large number of potential ligands are fitted into this binding site and the docking algorithm finds guests that yield a favorable interaction energy with the host. The success of this approach in identifying potential binders for a receptor inspired us to investigate whether it would also allow the rapid screening of large numbers of guests for synthetic receptors.

In supramolecular chemistry, cyclodextrins (Figure 1a) are often used because of their unique ability to complex a variety of small organic guests in water.[3] Previously, we reported the binding properties of cyclodextrin dimer **1** (Figure 1b) with cholates and the fluorescence-signaling behavior of a closely related dansyl-appended dimer.[4] Recently, a number of cyclodextrin dimers have been reported and these often exhibit enhanced binding with suitable guests,[5] some of them as stable as enzyme–ligand interactions. This renders these

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