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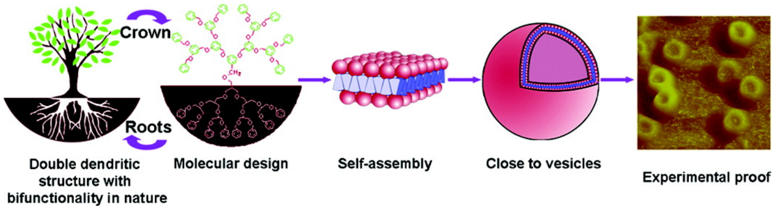

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Soft Vesicles Formed by Diblock Codendrimers of Poly(benzyl ether) and Poly(methallyl dichloride)

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Abstract: The synthesis of a block codendrimer (*g*3-PBE-*b*-*g*3-PMDC), composed of a third-generation poly(benzyl ether) (PBE) monodendron and an aliphatic polyether (PMDC) monodendron is reported. In THF/diisopropyl ether (1:1) the PMDC block functions as a "hydrophilic" block, while the PBE acts as a "hydrophobic" block. The codendrimer can form interdigitated layers leading to vesicle formation. Tapping mode atomic force microscopy (AFM), dynamic light scattering (DLS), and transmission electron microscopy (TEM) were used to characterize the vesicles. The effect of molecular architecture on the formation of the interdigitated layers and vesicles was studied.

Introduction

In selective solvents, amphiphilic block copolymers form bilayers that close to form vesicles.[1−14] The length and composition of the hydrophobic and hydrophilic blocks determine the vesicle size. Various vesicular morphologies[1b,e,8] have been found simply by manipulating the degree of polymerization of the two blocks. The stiffness of the blocks plays an important role in controlling the vesicle size.[6,11,13] Giant vesicles were formed in rod−coil diblock copolymers due to the high bending modulus of the bilayers.[1d,15] Vesicle formation was also observed for block copolymers with blocks having different molecular architectures, such as dendritic−linear hybrid block copolymers.[2] Changes in the hydrophobic volume and constraints in the hydrophobic−hydrophilic interfacial area occupied by the blocks are the driving force for vesicle formation.[1d,15]

Monodendrons and dendrimers are novel macromolecules with well-defined architectures,[16] which can function as a class of fundamental building blocks. These building blocks can self-organize into spherical or cylindrical supramolecular objects,[17] which can lead to the formation of giant crystals.[18] The concept of a codendrimer was established by Hawker and Fréchet in 1992 by synthesizing segmented and layered codendrimers based on ester and ether monodendrons.[19a] Recently, two kinds of amphiphilic diblock codendrimers have been synthesized.[19b−d] To date, the formation of self-assembled supramolecular structures from diblock codendrimers has not been reported in the literature.

In this work, the synthesis of a block codendrimer composed of two monodendrons is reported. One block is the third-

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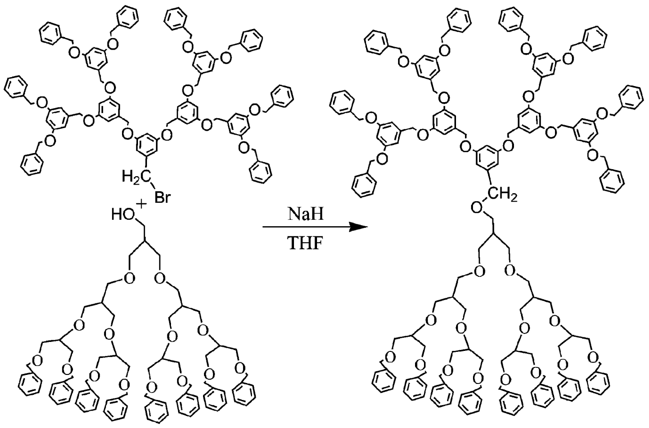
Scheme 1. Synthetic Route to the *g*3-PBE-*b*-*g*3-PMDC Block Codendrimer



generation Fréchet-type poly(benzyl ether) (*g*3-PBE) monodendron based on 3,5-dihydroxybenzyl alcohol,[20] while the other block is the third-generation aliphatic polyether monodendron based on methallyl dichloride (*g*3-PMDC).[21] The dendritic architecture of these monodendrons is different from that of conventional linear polymers. The shape of the codendrimer molecules may be like two inverted umbrellas linked chemically at the handles. This unique molecular architecture was the inspiration to explore the effects of the molecular architecture on the interfacial area occupied by the monodendron blocks. The key aim was to understand the aggregation behavior of the codendrimer when the two blocks have different solubilities in organic solvents. It was hypothesized that the diblock codendrimers could function as polymeric amphiphiles which have the advantages of linear−linear amphiphilic block copolymers, like high stability, but form vesicles having some features more closely related to cells, such as membrane thickness.

Results and Discussion

Synthesis and Properties of the Codendrimer. The *g*3-PBE and the *g*3-PMDC monodendrons were synthesized according to convergent growth approaches using literature procedures.[20,21] The *g*3-PBE dendrons have a bromide group at the focal point, while the *g*3-PMDC dendrons contain a hydroxy-functionalized focal point. Subsequently, the two dendrons were coupled together by performing a Williamson ether synthesis in anhydrous THF using NaH as the base (Scheme 1). This typical ether synthesis has the advantages of high yield and few side reactions. The total yield of the coupling reaction was 85%. This is acceptable because the folding back of PBE and PMDC dendrons could obscure the reactive groups causing a reduction in the reactivity.[22] The formation of *g*3-PBE-*b*-*g*3-PMDC was verified by NMR spectroscopy (Figure 1 in the Supporting Information) and MALDI-TOF mass spectrometry as shown in Figure 1. The MALDI-TOF MS spectrum clearly shows a strong peak corresponding to a codendrimer plus a potassium ion at 2913 g/mol. The calculated molecular mass is 2874 g/mol, which was in agreement with the theoretical molecular mass of the *g*3-PBE-*b*-*g*3-PMDC. This illustrates that the codendrimer had high purity and a mono distribution. This is different from most linear−linear block copolymers that normally possess a molecular weight distribution.

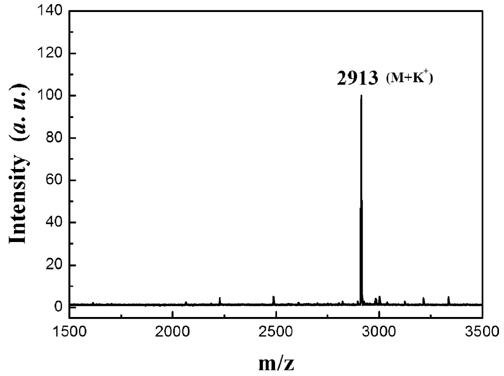


Figure 1. MALDI-TOF mass spectrum of the codendrimer.

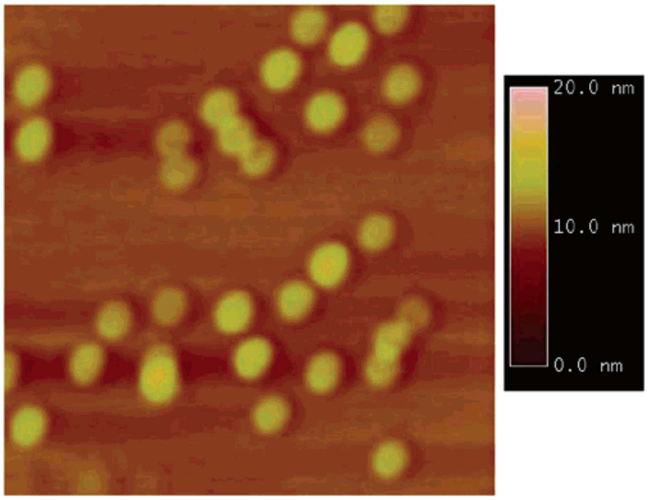


Figure 2. Tapping mode AFM image, 2 μm × 2 μm, showing the aggregates of *g*3-PBE-*b*-*g*3-PMDC.

At room temperature the block codendrimer was a sticky and transparent liquid. The DSC measurement showed a single glass transition temperature at −3.6 °C (Figure 2 in the Supporting Information), indicating that this block codendrimer was of a homogeneous, amorphous nature at room temperature.

Characterization of the Codendrimer Aggregates. THF (tetrahydrofuran) is a good solvent for the monodendrons and the codendrimer. DIE (diisopropylether) is a good solvent for the PMDC dendrons but is a nonsolvent for the PBE dendrons. Dilute THF solutions of the codendrimer ($\sim 1 \times 10^{-4}$ g/mL) were clear. Upon the dropwise addition of DIE to reach a critical value of THF/DIE (1:1); no clear changes in turbidity were observed. The solution was dropped on the surface of a freshly cleaved mica substrate and then the solvent was rapidly removed using a piece of filter paper. Spherical aggregates were observed with tapping mode AFM. The height image in Figure 2 illustrates the typical aggregates in the THF/DIE solvent. The images obtained at a lower magnification (see the images in Figure 3 in the Supporting Information) exhibit several hundred objects. Figure 3 shows a Gaussian size distribution with an average size of 150 nm and fwhm (full width at half-maximum) of 15 nm. It is significant to point out that the height of these aggregates was only in the range of 4−8 nm, much smaller than the average diameter.

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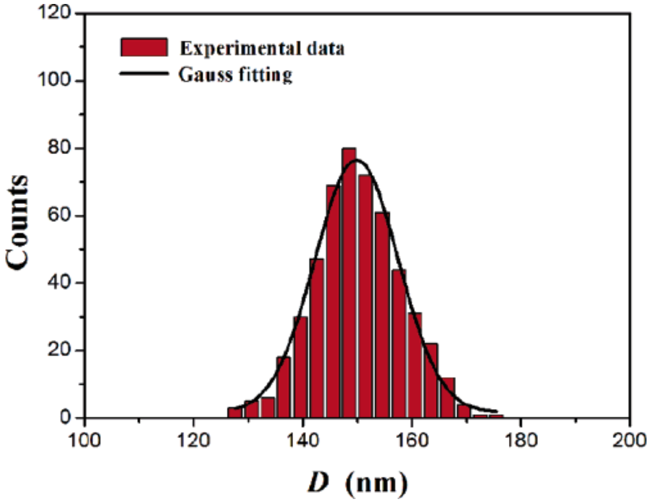

Figure 3. Size distribution obtained from 508 aggregates observed by AFM.

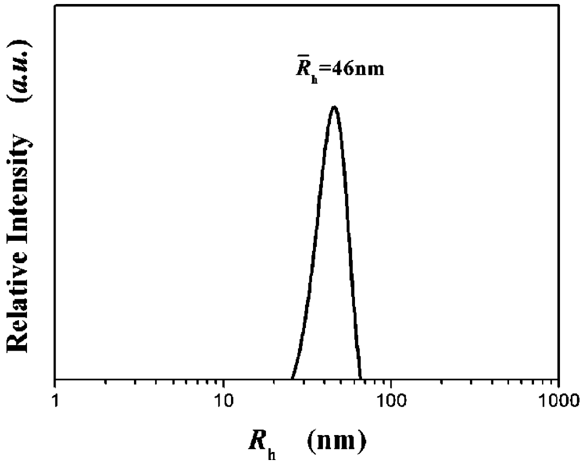

Figure 4. The intensity-weighted distribution of the aggregates obtained from the DLS measurements at 25 °C.

DLS was used to confirm the existence of the aggregates in solution. The observation of scattering signals indicates the presence of aggregates. Therefore, the aggregates were not formed during solvent evaporation. The hydrodynamic radius, R_h, of the aggregates in the THF/DIE solvent mixture was determined to be 46 nm (see Figure 4).

Vesicular Aggregates. The nature of the aggregates is the major concern of this study. The literature value for the mean-square radius of gyration of the *g*3-PBE is 0.99−1.10 nm in THF or deuterated THF.[23] The diameter of the *g*3-PMDC is known to be ca. 1 nm.[24] In the mixed solvent, the solubility would be worse than in THF. The diameter of the codendrimer is about 3 nm, much smaller than the aggregate diameter measured by DLS. If these codendrimer molecules could form micelle-like aggregates, the diameter would be twice that of the molecular diameter. The aggregates observed are much larger than the expected 6 nm and, therefore, are believed to be of a vesicular nature.

Assuming that the codendrimers form vesicles in the mixed solvent, the difference in the values of diameters found by AFM and DSL can be easily explained. The vesicles adsorbed on the mica surface would be expected to become deformed when the solvent is removed. The force of the AFM probe at room temperature (above its T_g) can also cause deformation of the vesicles. This deformation causes the vesicles to appear as circular plates on the mica surface as observed by AFM. Here $S_{\mathrm{nondef}} = \pi d_{\mathrm{nondef}}^2$, where S_{nondef} and d_{nondef} are the surface area and diameter of the nondeformed vesicles suspended in the solvent mixture, while $S_{\mathrm{def}} = \pi d_{\mathrm{def}}^2/2$, where S_{def} and d_{def} are the surface area and diameter of deformed vesicles on the mica surface. Assuming that $S_{\mathrm{def}} = S_{\mathrm{nondef}}$, then

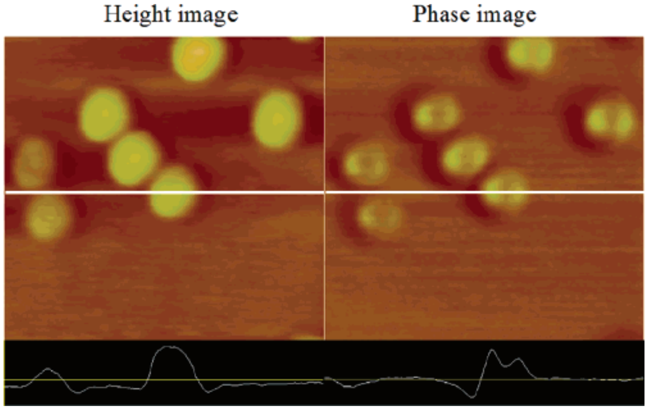

Figure 5. Height and phase images (800 nm × 800 nm) with the surface profile curves showing the features of the deformed and hollow vesicles.

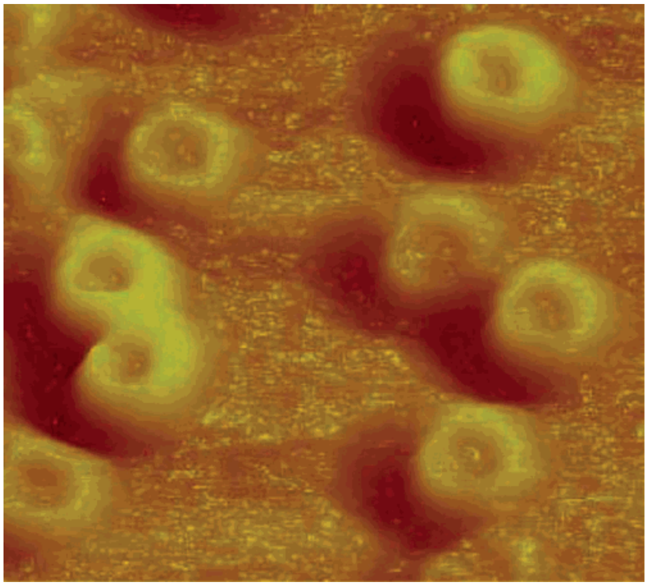

Figure 6. Phase image (670 nm × 670 nm) showing the features of the deformed hollow vesicles.

$$\pi d_{\mathrm{nondef}}^{\ 2} = \pi d_{\mathrm{def}}^{\ 2}/2 \tag{1}$$

and

$$d_{\mathrm{nondef}} = d_{\mathrm{def}}/\sqrt{2}. \tag{1'}$$

The diameter of the deformed vesicles measured by AFM was $d_{\mathrm{def}} = 150$ nm. The corrected diameter (d_{nondef}) was found to be 105 nm, which is in agreement with the 92 nm measured by DLS for the aggregates suspended in THF/DIE.

The AFM images shown in Figures 5 and 6 further support the formation of the vesicles. Figure 5 shows the height and phase

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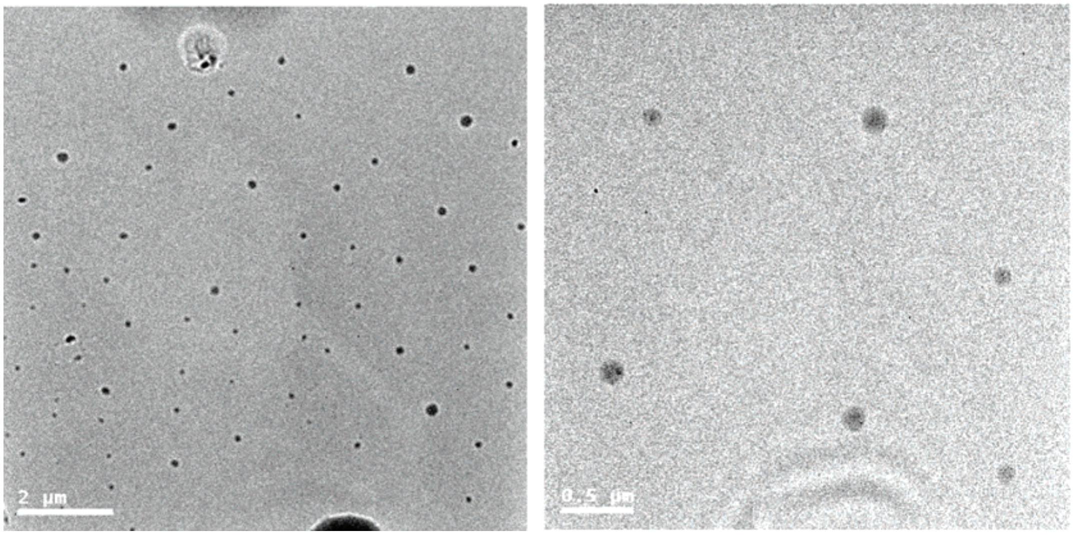

Figure 7. TEM images of the vesicles with at different magnifications.

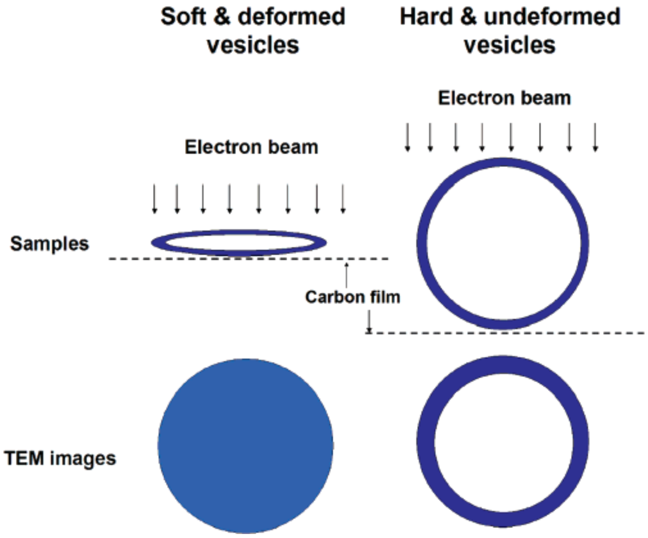

Figure 8. Schematic explanation of the difference between soft and hard vesicles when viewed under TEM.

images with their surface profiles of the same area. The surface profile of the vesicle in the height images display a relatively smooth surface, while the profile of the same vesicle in the phase image shows a high periphery and a lower center. This indicates that the periphery and center of the deformed vesicles have different responses to the force of the AFM probe. The phase image in Figure 6 illustrates the features of several deformed vesicles, which are similar to the features observed in a previous study.[25] Such features may be observed because the center of the vesicle is expected to be softer than the periphery due to the existence of a small hollow volume under the curved membrane of the deformed vesicle. The formation of the hollow volume is due to the lack of interpenetration and entanglement of the participating dendritic fragments in the middle of the aggregates.

TEM Evidence. TEM can provide direct evidence to indicate the formation of vesicular aggregates.[1−8,12,13] The two TEM images in Figure 7 show circular plates having an average diameter of ca. 150 nm. These images were taken from the same sample at different magnifications. In comparison to TEM images of vesicles formed by linear−linear block copolymers, the electron contrast is relatively weak, indicating that the membranes are quite thin. Importantly, the thickness of the vesicle membranes could not be seen. This is a typical feature of soft (or rubber) vesicles when observed under TEM. Figure 8 is a schematic explanation of the difference between soft and hard vesicles when viewed under TEM. Due to the rubber-like membrane, the deformed vesicles have an almost constant thickness from the edge to the center and do not show any electron contrast, but hard (or plastic) vesicles do.

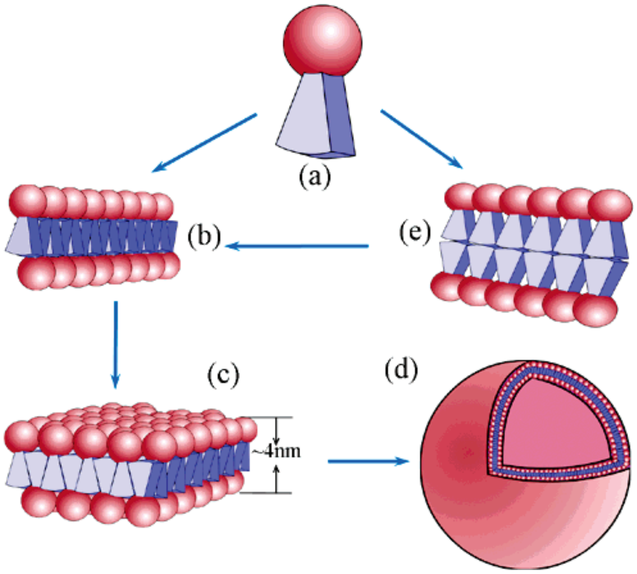

Figure 9. Schematic illustration depicting the formation of a vesicle with interdigitated layer of *g*3-PBE-*b*-*g*3-PMDC. The pink spheres are the PMDC blocks, while the blue fans represent the PBE blocks.

Membrane Feature. The PBE and PMDC blocks have different flexibilities. Computer simulations show that the PBE block is taper-shaped and the PMDC block is spherical. (See Figure 5 in the Supporting Information.) Because of this unique architecture, an interdigitated layer model is suggested (Figure 9) to describe the layered structure that may be formed by the codendrimer. A molecular organization of dense packing and low interfacial free energy can be achieved in this way (Figure 9b). If the double dendritic amphiphiles self-organize into a

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[25] Regenbrecht, M.; Akari, S.; Förster, S.; Möhwald, H. *Surf. Interface Anal.* **1999**, *27*, 418−421.

bilayer structure (as represented in Figure 9e), the resulting unstable membrane would contain many holes due to the shape of the codendrimer.

The disadvantage of using tapping mode AFM with soft materials is that the measured heights do not exactly correspond to the true heights.[26] The measured heights may be lower than the true heights due to the deformation of the soft surface by the AFM tip. Experimentally, the heights of the deformed vesicles were found to be between 4 and 8 nm with an average height 6 nm. The estimated thickness of the hypothetical membrane is about 4 nm according to the interdigitated layer model and about 6 nm according to the bilayer model. The thickness of the deformed vesicles corresponds to two layers. The measured value (ca. 6 nm) is 2 nm smaller than the estimated value (ca. ∼8 nm), supporting an interdigitated layer model.

Solubility. In selective solvents, block copolymer systems forming micellar or vesicular supramolecular structures normally belong to the superstrong segregation limit (SSSL) mainly due to different solubilities of the blocks.[1d] The two blocks should completely segregate in the membrane. For the block codendrimer studied here, the mixed solvent is a good solvent for the PMDC block but is a nonsolvent for the PBE block. The block codendrimer becomes an "amphiphilic" codendrimer. This behavior is similar to amphiphilic block copolymers or liposomes dissolved in selective solvents. The codendrimer molecules assemble into layered structures and then close to form vesicles. The layer composition is expected to be two hydrophilic PMDC layers sandwiching one hydrophobic PBE layer.

Conclusion

In summary, an amphiphilic diblock codendrimer composed of a third-generation poly(benzyl ether) dendron and a third-generation methallyl dichloride monodendron has been synthesized. Characterization by TM-AFM, DLS, and TEM show that this codendrimer forms vesicles with a diameter of 100 nm in THF/DIE. The different solubility of the PBE and PMDC blocks in the mixed solvent is the driving force for the formation of vesicles. In consideration of the molecular size and architecture it is believed that the PBE blocks are interdigitated to give rise to the most dense packing possible.

Because of the special architecture of the codendrimers, the membrane thickness is less than the thickness of the membranes formed by linear−linear block copolymers with the same molecular weight. The current work is underway to study the effect of changes in molecular shape achieved by manipulating the generation of the dendritic blocks and functionalization of the surface groups on the periphery of the dendrons.

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Supporting Information Available: Experimental details, ^{1}H NMR data, DSC thermograms, AFM images, and computer simulation models. This material is available free of charge via the Internet at http://pubs.acs.org.

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