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Well-Defined Polyisoprene-*b*-Poly(acrylic acid)/Polystyrene-*b*-Polyisoprene-*b*-Poly(acrylic acid) Block Copolymers: Synthesis and Their Self-Assembled Hierarchical Structures in Aqueous Media

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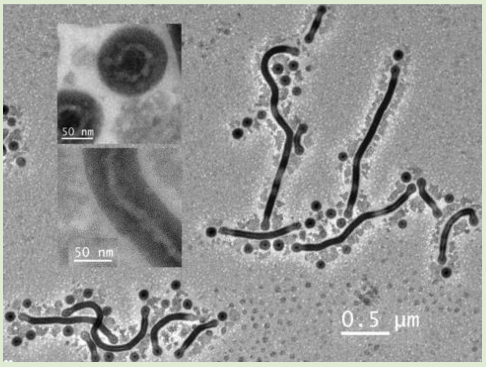
S *Supporting Information*

ABSTRACT: The synthesis and characterization of well-defined polyacid based block copolymers containing polyisoprene (PI) are reported. The challenge of maintaining the integrity of the polydiene while producing polyacid from the *tert*-butyl ester precursor is addressed in this communication. A general purification method was also developed, taking advantage of the different polarities of each block. The polystyrene-*b*-polyisoprene-*b*-poly(acrylic acid) (PS-*b*-PI-*b*-PAA) triblock terpolymers form multicompartmental micelles via aqueous self-assembly. Our work reveals the morphological consequences of unique balances among global and local interactions.



Amphiphilic block copolymers hold great potential for applications in the biomedicine and nanotechnology fields owing to their surfactant behavior, that is, self-assembly into micelles in a selective solvent.[1] Such micelles can exhibit an array of morphologies dictated by multiple interactions among the hydrophilic, hydrophobic segments, and solvent (typically water).[1,2] Although much progress has been made over the past two decades,[2−7] it is still challenging to predict structure−property relationships for many block copolymer-based micelles, which is critical in utilizing their characteristic properties in various applications.

When amphiphilic block copolymer micelles are employed as a delivery vehicle, the core of the micelle should provide a suitable microenvironment for the incorporation of hydrophobic ingredients, while the corona stabilizes this hydrophobic core. Due to the potential differences in solubility of these ingredients, it may be advantageous to use micellar cores with multiple compartments, which can solubilize different ingredients. Such "multi-compartment micelles" may be formed through self-assembly of block copolymers containing multiple immiscible hydrophobic components.[8−10] The majority of studies to date have focused on glassy materials such as polystyrene (PS) as the hydrophobic constituents in block copolymer-based micelles. Poly(acrylic acid) (PAA), a commonly used hydrophilic block, conjugated with a PS block, has been well-studied.[11,12] In contrast, PAA-based diblock copolymers containing polydienes (polyisoprene (PI) or polybutadiene (PBD)), which can self-assemble to create micelles having hydrophobic soft cores, are rarely studied, mainly due to challenges in synthesis and purification of such block copolymers.[13−16] Well-defined polydienes are readily obtained using anionic polymerization, but this method is not applicable directly to acrylic acid. Synthetic difficulties in creating well-defined PI-*b*-PAA and PBD-*b*-PAA block copolymers center around the intrinsically unstable nature of polydienes under strongly acidic conditions (40% loss of double bonds was reported when HCl catalyzed hydrolysis was carried out[17]), which are necessary for hydrolysis of poly(*tert*-butyl acrylate) (P*t*BuA), the commonly used anionically polymerizable precursor to PAA. No spectroscopic evidence for the structural integrity of these polydiene components in block copolymers with P*t*BuA (or poly(*tert*-butyl methacrylate), P*t*BuMA) after converting to PAA through hydrolysis has been furnished.[13−17] It is critical to ascertain that the polydiene remain intact after the ester hydrolysis, since retention of the residual double bonds of the polydienes in the self-assembled structures will provide further opportunities for functionalization and chemical modification. For example, cross-linking can be carried out to stabilize the as-formed structures,[8] or sacrificial degradation (e.g., by ozonolysis) can be employed to create cavities for bioactive reagent encapsulation.[17,18]

Here, we report the synthesis of well-defined block copolymers of isoprene and acrylic acid with the carbon−carbon double bonds in the PI block remaining intact after

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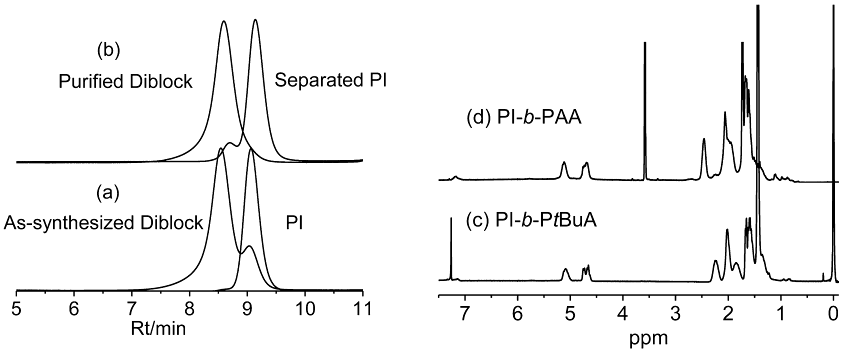

Figure 1. Left: GPC traces of PI and diblock copolymers (normalized) (a) as-synthesized diblock (PI-*b*-P*t*BuA) and polyisoprene (PI) which was sampled before addition of *t*BuA monomer; (b) purified diblock copolymers and PI separated using a neutral alumina column. Right: (c) ^{1}H NMR of purified PI-*b*-P*t*BuA in $CDCl_3$; (d) ^{1}H NMR of PI-*b*-PAA in *d*-THF.

complete hydrolysis of P*t*BuA. We also describe a simple and scalable purification method for PI-*b*-P*t*BuA containing PI homopolymer contaminants, where traditional solvent/nonsolvent fractionation methods fail. We then extend this method to the synthesis of PS-*b*-PI-*b*-PAA triblock terpolymers. Morphological studies reveal distinct multicompartment phase separation in the core of micelles formed by these triblock terpolymers.

Well-defined precursors PI-*b*-P*t*BuA and PS-*b*-PI-*b*-P*t*BuA were synthesized by anionic polymerization employing high vacuum techniques and sequential polymerization of styrene (in the case of triblock terpolymers), isoprene, and *tert*-butylacrylate according to standard protocol.[19] The microstructure of PI can be controlled by adding an appropriate dose of tetrahydrofuran (THF) as an additive with hexanes or benzene as the primary solvent. A solvent switching process was necessary to remove hexanes and introduce pure THF for polymerization of *tert*-butylacrylate at a reduced temperature. Due to multiple steps of introducing additives and reagents, including solvent switching, the addition of 1,1-diphenylethylene, LiCl, and monomers, some PI anions were inevitably terminated during these processes. Purification was thus required to remove residual PI homopolymer. Gel permeation chromatograms (GPC) of as-synthesized PI and PI-*b*-P*t*BuA are shown in Figure 1a. A shift to lower retention time (R_t) demonstrates the successful growth of the P*t*BuA block, while the minor peak in the chromatogram is assigned to PI homopolymer (Figure 1a).

Substantial difficulties were encountered in the purification of diblock copolymers containing PI contaminants. Classical solvent/nonsolvent fractionation and Soxhlet extraction, often used to purify block copolymers,[20−22] failed to remove the PI homopolymer. This is due to the intrinsic solubility characteristics of PI and P*t*BuA, which cause any common solvent selective for one of the blocks to be a nonsolvent for the other one, leading to micelles forming in the fractionation medium. While water is the only common nonsolvent identified for both PI and P*t*BuA, in a trial of THF/water as a solvent/nonsolvent fractionation medium, phase separation slowly occurred (>2 weeks) to form droplets of one phase suspended in another, which makes separation impossible. Thus a different approach for the separation was developed. Upon considering the difference in polarity of PI and P*t*BuA and their molecular interactions with aluminum oxide (neutral, activated, ∼150 mesh), we found that a column separation using toluene as eluent gave highly efficient purification in high yields, as demonstrated in Figure 1b. The purified diblocks are free of PI homopolymer, and the yield of diblock was quantitative. The high purity and high yield of this process can be inferred from Figure 1b, where purified diblock shows a symmetrical peak and the minor peak in the as-synthesized diblock is completely gone. The separated PI chromatogram is identical to that of PI sampled from the polymerization and terminated with methanol before addition of the second monomer. The minor peak in the GPC trace of the isolated PI (Figure 1b) at shorter Rt is PI-*b*-P*t*BuA with lower P*t*BuA content, which was eluted with PI due to its low adsorption to the column. The purification of triblock copolymers was accomplished in the same way, where low levels of PS homopolymer and PS-*b*-PI contaminants were easily removed in one step.

As noted above, although there are several reports regarding synthesis of block copolymers of butadiene and acrylic acid,[13−16] no detailed ^{1}H NMR characterization has been presented before and after the production of the acrylic acid (or methacrylic acid) block. The absence of published data suggests difficulties in obtaining a well-defined polyacid block while retaining a well-defined polydiene block due to the instability of the diene double bonds in strong acid environment and at high temperatures, which are usually utilized during hydrolysis of *tert*-butyl esters. Indeed, Wooley et al., working with PI, reported that ∼40% of the PI double bonds reacted under such conditions.[17]

We executed a number of attempts to cleave the *tert*-butyl groups of P*t*BuA, without jeopardizing the double bonds of PI, under both acid and base conditions. All attempts were monitored by ^{1}H NMR as a function of time. Hydrolysis by methanol/NaOH or KOH/dioxane/methanol, with or without 18-crown-6, took place extremely slowly.[23] A system of *t*BuOK (potassium *tert*-butoxide)/THF/H_2O (H_2O in stoichiometric amounts) was efficiently used to cleave the *tert*-butyl group within 1 week at room temperature;[24,25] however, macro-phase separation occurred during purification by dialysis, with precipitation of polymers (^{1}H NMR showed PI profiles for the precipitants) due to unknown events during the hydrolysis process. Trifluoroacetic acid and iodotrimethylsilane[26] rapidly cleaved the *tert*-butyl group under mild reaction conditions at room temperature over ∼1−2 h, but the double bonds of PI were significantly diminished due to addition reactions between reagents.[27] These methods fail to yield the desired di/triblock copolymers by compromising the well-defined structure of PI.

Usually refluxing the polymer in HCl/dioxane solution is applied for the hydrolysis of P*t*BuA, but it is known that

Table 1. Molecular Characteristics of Diblock and Triblock Copolymers[a]

	PI			PI-*b*-P*t*BuA			
no.	$M_{n,LLS}$	$M_{n,SEC}$	PDI	M_n	PDI	I/*t*BuA[b] (*t*-butyl[c], C*H*[d])	I/AA[b] (C*H*[d])
1	8.6×10^3	1.2×10^4	1.04	2.4×10^4	1.15	0.95:1, 0.98:1	N/A
2				1.9×10^4	1.09	1.36:1, 1.43:1	N/A
3	1.2×10^4	1.6×10^4	1.05	2.3×10^4	1.19	1.58:1, 1.50:1	1.45:1
4				2.2×10^4	1.12	1.99:1, 1.75:1	1.99:1
5	7.0×10^3	9.6×10^3	1.06	1.9×10^4	1.28	0.95:1, 1.01:1	0.99:1
6				1.6×10^4	1.19	1:0.73, 1:0.76	1:0.72
	PS		PS-*b*-PI		PS-*b*-PI-*b*-P*t*BuA		
triblock	M_n	PDI	M_n	PDI	M_n	PDI	St/I/AA (H NMR)
	8.7×10^3	1.06	4.3×10^4	1.05	9.5×10^4	1.08	1:4:4

[a] M_n in units of g/mol. [b] Compositions by ^{1}H NMR in units of mol/mol. N/A stands for not applicable. [c] I/*t*BuA determined by vinyl and *tert*-butyl protons in ^{1}H NMR. [d] I/*t*BuA(AA) determined by vinyl and methine protons of P*t*BuA(PAA) backbone in ^{1}H NMR.

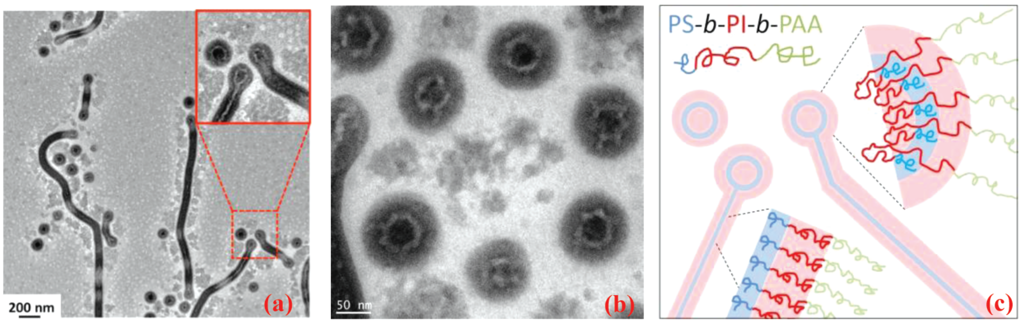

Figure 2. TEM of self-assembled structures of PS-*b*-PI-*b*-PAA in aqueous media. (a) Coexistence of spherical micelles and cylinders with core−shell structures (shown in inset, PS domain in the core center surrounded by PI domain). (b) Details of spherical cores showing "flower-like" structures. (c) A schematic illustration of the formation of micelles.

hydrochlorination occurs under these conditions.[17] However, by carefully controlling the molar ratio of HCl to *t*BuA (mol/mol, 4−6), reaction time (2−3 h), and polymer concentration (∼2% w/v of P*t*BuA), we obtained PI-*b*-PAA with complete hydrolysis and with the PI blocks almost retaining all of their double bonds (no changes for PI in ^{1}H NMR, though traces of chlorine were found in samples by elemental analysis). As shown in Figure 1c,d, the characteristic peak of the *tert*-butyl group at 1.44 ppm disappeared after hydrolysis. The integration of vinyl peaks of PI relative to backbone methine proton (C*H*) of P*t*BuA (at 2.24 ppm in $CDCl_3$)/PAA (at 2.50 ppm in *d*-THF) proves that the double bonds of PI remain intact within experimental error of ^{1}H NMR detection. The same strategy was applied to hydrolyze P*t*BuA in triblock copolymers, and for these materials ^{1}H NMR showed the same peak ratios of aromatic, vinyl, and methine protons of PS, PI, P*t*BuA/PAA, respectively, before and after hydrolysis and purification. The molecular characteristics of precursors and hydrolyzed products are summarized in Table 1. Molecular weights were determined by GPC equipped with light scattering detectors and by ^{1}H NMR through the calculation of component ratios.

PI-*b*-PAA diblock copolymers and PS-*b*-PI-*b*-PAA triblock copolymers dissolved in THF self-assembled into micelles upon the addition of water. Spherical micelles formed for diblock copolymers, as expected. For triblock copolymers, one of the objectives was to explore microphase separation behavior of PS-*b*-PI in the core and its impact on the global aggregates (e.g., spheres, cylinders, etc.) and vice versa.

Structures formed by aqueous self-assembly of triblocks are shown in Figure 2a,b, observed via transmission electronic microscopy (TEM). The samples were stained by exposure to OsO_4 vapor for two hours; thus the PI phase appears dark, and the PS phase appears white, while the PAA corona are invisible.[28,29] Two types of global morphologies are observed, worm-like cylinders, both short and long, and spheres. It can be seen that at the ends of the cylinders, spheres are being separated from or fused into cylinders (inset in Figure 2a). In these cylinders and spheres, multicompartment structures exist in the cores. Similar observations were reported previously for linear and miktoarm star triblock terpolymers.[10,30−34] The worm-like cylinders exhibit core−shell structures with the PS phase residing in the core center surrounded by the dark PI phase (Figure 2a, inset), which is consistent with the sequence of PAA-PI-PS in the triblock terpolymer, where PAA corona chains stabilize the hydrophobic "PI-PS" cores in water (Figure 2c). Surprisingly, for spheres and the ends of the cylinders the phase-separated morphology observed is a dark shell-"white ring"-dark center structure (from outside to inside) corresponding to a PI/PS/PI content sequence (Figure 2), which is literally different from the molecular sequence of PAA-PI-PS (Figure 2c). Furthermore, high magnification TEM shows that the PS "ring" is not smooth. Instead it has a complicated structure with "flower-like" contour (Figure 2b). The presence of diblock copolymer (PS-*b*-PI) contaminants in our triblock copolymer could account for such a morphology. However, according to our careful GPC analysis there can be very little of such material present in the triblock copolymer (Figure S2, Supporting Information). Nevertheless, some very low level of PS-*b*-PI diblock copolymer cannot be ruled out. In future work we will explore the effect of intentionally added diblock copolymer on the morphology of such micelles.

At present, in light of the GPC results we do not have a definitive explanation for the "PI inside" behavior. Figure 2c is a cartoon that shows how the individual chains are arranged into the spheres and how they could possibly form the type of phase separated spherical structures clearly seen in TEM. This would require the PI chains at some point to penetrate the PS "ring" as depicted in the upper right of Figure 2c. This could account for the flower-like appearance of the rings. Clearly, based on TEM with staining, the arrangement of the PS-PI components of the triblocks is organized differently in the spherical structures versus the cylindrical structures, a main point of this paper. Although there is an energy penalty for such penetration, the morphology is controlled by the "minimum energy" of the entire system. To reach minimum energy, the curvature of the global structures plays an important role. We believe the phase separation of the PS-*b*-PI blocks in the confined interior of the micelles significantly affects the global micellar structure and vice versa. It should be noted that whether or not our system is at thermodynamic equilibrium is unclear, as is usually the case for copolymer micelles.

The unique phenomenon observed here is the distinct local morphological structures (formed by the "PS-*b*-PI block") in the cores of both cylindrical and spherical micelles, which coexist. Well-defined narrowly dispersed block copolymers usually form a single morphology. In our case, chains have sufficient mobility to form different local structures in the spherical and cylindrical cores due to the low glass transition temperature of the PI block. We believe such characteristic self-assembled structures reflect the subtle balance between global and local interactions. To the best of our knowledge, such intriguing phase separation behavior has not been reported before in similar systems. Our work clearly demonstrates direct communication and a spontaneous competition between global and local self-assembly in a single system without any external influence (such as change of composition, macromolecular structure, or pH). Detailed investigations to attempt to more fully understand self-assembly of these materials are underway.

In summary, optimal conditions for hydrolyzing tertiary ester groups to convert them to acid functionalities in the presence of PI were established. An efficient and scalable purification method for purifying the resulting PI-*b*-P*t*BuA and PS-*b*-PI-*b*-P*t*BuA block copolymers is presented. In principle, based on the separation mechanism, this method could be applied to many nonpolar-*b*-polar block copolymers. Discoveries were made regarding microphase separation in the confined spaces of micelles in aqueous media. Cylindrical and spherical micelles having different ultrafine structures in micellar cores consisting of PS-*b*-PI were observed.

■ ASSOCIATED CONTENT

Ⓢ Supporting Information

Detailed procedures for purification, hydrolysis, and self-assembly of block copolymers. This material is available free of charge via the Internet at http://pubs.acs.org.

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Notes

The authors declare no competing financial interest.

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