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Thermally Induced Changes in Amphiphilicity Drive Reversible Restructuring of Assemblies of ABC Triblock Copolymers with Statistical Polyether Blocks

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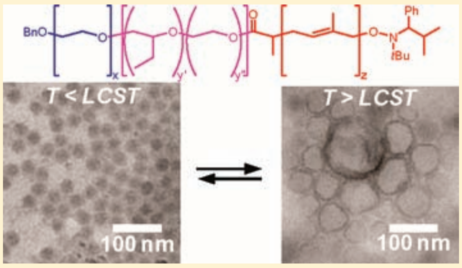
Ⓢ *Supporting Information*



ABSTRACT: ABC triblock copolymers in which a block with stimulus-dependent solvophilicity resides between solvophilic and solvophobic end blocks can undergo reversible transitions between different thermodynamically stable assemblies in the presence or absence of stimulus. As a new example of such a copolymer system, thermoresponsive poly(ethylene oxide)-*b*-poly(ethylene oxide-*stat*-butylene oxide)-*b*-poly(isoprene) (E−BE−I) triblock copolymers with narrow molecular weight distributions (M_w/M_n: 1.05−1.18) were prepared by sequential living anionic and nitroxide-mediated radical polymerizations. The specific copolymers examined ($9.0 \leq M_n \leq 14.4$ kg/mol, 14% ≤ wt % isoprene ≤35%) form near-spherical aggregates with narrow size distributions at 25 °C. The thermoresponsive behavior of these polymers was studied by applying cloud point, DLS, and TEM measurements to a representative polymer, $E_{2.3}BE_{5.3}I_{2.3}$. The transformation of polymer aggregates from spherical micelles to vesicles (polymersomes) at elevated temperatures was detected by DLS and TEM studies, both with and without cross-linking of polymer assemblies. The rate of transformation with E−BE−I systems is more rapid than that observed for poly(ethylene oxide)-*b*-poly(*N*-isopropylacrylamide)-*b*-poly(isoprene) assemblies, suggesting that interchain hydrogen bonding of responsive blocks after dehydration plays an important role in the kinetics of aggregate rearrangement.

INTRODUCTION

Most natural processes can be understood at some level to arise from responses to a range of stimuli. Controllably mimicking this behavior in synthetic constructs has been a long-term goal in many subdisciplines of chemistry. A great deal of this effort has been put toward the design and preparation of materials that exhibit a detectable response to specific external stimulus because of their great potential in applications such as scaffolds for tissue growth,[1] self-healing materials,[2] responsive textiles,[3] and electro-optical devices.[4]Stimuli-responsive materials have been designed to respond to a number of external parameters, including temperature,[5−13] pH,[6,10−15] light,[16−18] magnetic field strength,[19] oxidation potential,[13,20,21] ionic interactions,[22] supramolecular interactions,[23,24] and enzyme activity.[25,26]

The continuing refinement of methods for the synthesis of polymers with tailored structures has led to the development of synthetic polymer-based stimulus-responsive materials.[27] Thermoresponsive polymers undergo a sharp coil−globule transition in a specific solvent at a critical temperature. For example, poly(*N*-isopropylacrylamide) (PNIPA) shows a lower critical solution temperature (LCST) of approximately 32 °C in water, above which the loss of polymer−solvent hydrogen bonds results in desolvation of the polymer.[28] Thermoresponsive polymers have been incorporated into a range of more complex materials including micellar assemblies,[5,6,9,11,13,14,29−33] hydrogels,[34] surface-bound brushes,[35] and bioconjugates;[36] such materials have in turn been used in a range of applications, including drug delivery,[33,37,38] catalysis,[39,40] chromatography,[41] and DNA sequencing.[42]

Responsive assemblies of amphiphilic copolymers, especially thermally responsive and/or pH-responsive micelles, have been extensively investigated,[5,6,9,11,13−15,29−33] as they are of particular interest for their potential use in drug delivery systems due to their biocompatible size and ability to encapsulate hydrophobic drugs.[33,37,38] Previous studies have largely focused on the assembly of soluble block copolymer chains into aggregates upon the stimulus-induced increase in the hydrophobicity of one of the blocks.[6,43−48] Much less is known about transitions in stimulus-responsive block copolymer systems that form assembled structures both in the presence and in the absence of a stimulus.[14,49−55]

The structures formed by responsive amphiphiles in solution are to a large extent dictated by the size of the hydrophilic portion relative to that of the hydrophobic portion and the effect of this ratio on interfacial curvature in the assemblies.[56−58] From this simple model, it follows that a triblock copolymer composed of terminal hydrophilic and hydrophobic blocks and a thermoresponsive central block should exhibit a different amphiphilic

Received: October 14, 2010
Published: December 23, 2010

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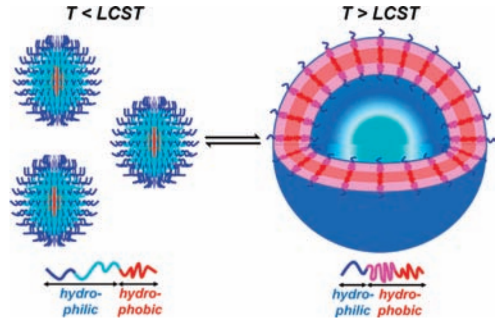

Figure 1. Schematic illustration of the thermally induced size change of assemblies of copolymers containing a thermoresponsive block. Below the LCST, the central block (cyan) is hydrophilic; above the LCST, the central block (pink) becomes hydrophobic.

balance above and below the critical temperature of the central block. For example, for a copolymer containing a block with an LCST in water, heating an aqueous solution of the copolymer above the central block's LCST should result in dehydration of the thermoresponsive block and therefore increase the relative hydrophobic volume of the amphiphilic chain. Such change in amphiphilicity should drive formation of assemblies with less interfacial curvature and should thus be capable of inducing significant changes in the morphology of the resulting polymer assemblies (Figure 1).

As an example of such a system, our group has demonstrated the synthesis of poly(ethylene oxide)-*b*-poly(*N*-isopropylacrylamide)-*b*-poly(isoprene) (PEO−PNIPA−PI) triblock copolymers that reversibly form spherical micelles in aqueous solution at temperatures below the PNIPA LCST and larger vesicles (polymersomes) above the PNIPA LCST.[50] The potential utility of these systems in many applications is hampered by the slow rate of transformation (∼4 weeks) from micelles to vesicles.

One potential reason for the slow rearrangement kinetics is that the dehydration of PNIPA-containing micelles most likely results in interchain hydrogen bonding between PNIPA amide groups that would slow further rearrangement; this phenomenon results in a high glass-transition temperature (T_g) for bulk PNIPA (145 °C).[59] To test this hypothesis, we have prepared similar copolymers in which the stimulus responsive block is a statistical copolymer of ethylene oxide (EO) and butylene oxide (BO), which cannot form strong interchain hydrogen bonds, as reflected in the low T_g values reported for PEO (−67 °C) and poly(butylene oxide) (PBO) (−88 °C).[60] Such copolymers are related to commercially available and widely studied Pluronic or Poloxamer copolymers of poly(ethylene oxide) (PEO) and poly(propylene oxide) (PPO).[61−67] Copolymers of PEO and PPO are especially interesting in responsive systems as the LCST can be tuned by changing the ratio of the two monomers in the copolymer.[68,69]

The anionic polymerization of propylene oxide (PO), however, is complicated by a chain transfer reaction between the living chains and the PO monomer, which makes the precise synthesis of PO-based copolymers difficult.[70] By contrast, this side reaction is not as significant in the polymerization of 1,2-butylene oxide (BO).[71] In addition, statistical copolymers of BO and EO are similar to PO/EO copolymers in that they also show a composition-dependent LCST.[72] While a number of block copolymers and statistical copolymers of EO and BO have been prepared and their solution behavior studied,[72−74] copolymers of EO and BO have not previously been incorporated as one thermoresponsive block of a more complicated block copolymer structure.

To confirm that EO/BO-based responsive copolymers undergo thermally reversible transitions similar to those observed for PNIPA copolymers and to explore the role that interchain interactions play in assembly transformation rate, we have synthesized ABC PEO-*b*-poly(EO-*stat*-BO)-*b*-poly(isoprene) (E−BE−I) triblock copolymers by sequential living anionic and nitroxide-mediated free radical polymerizations (NMRP). In these copolymers, PEO serves as the hydrophilic block; the EO/BO statistical copolymer forms the central responsive block, with a thermal-transition temperature that can be tuned by altering the relative amounts of the two comonomers; and poly(isoprene) (PI), which has a glass transition temperature (∼ −58 °C) lower than the LCST of the thermosensitive block, is the hydrophobic block to ensure that the polymer assemblies have a "soft" cross-linkable core to facilitate structural transitions and to allow trapping of assemblies.

■ RESULTS AND DISCUSSION

Preparation of Triblock Copolymers . *PEO Synthesis.* The preparation of E−BE−I triblock copolymers began with the synthesis of the hydrophilic PEO block (target number-average molecular weight, M_n = 2.2 kg/mol) by living anionic polymerization of ethylene oxide (47 equivalents) from potassium benzyl oxide as previously described.[75,76] Growth of PEO chains from a monofunctional alcohol under anhydrous conditions minimizes the contamination of the resulting polymers with dihydroxyl chains, which are commonly seen in commercially available products such as PEO monomethyl ether.[77,78] After 3 days at room temperature, the polymer chains were terminated by adding acidic methanol to give rise to monohydroxyl-functional PEO homopolymers with an M_n of ∼2.3 kg/mol (^{1}H NMR) and a polydispersity index (M_w/M_n) of 1.08 (SEC). The M_n calculated from NMR integration implies that the polymerization proceeded to nearly full conversion.

Diblock Copolymer Synthesis. The monohydroxyl PEO **1** was subsequently converted to the potassium alkoxide by treatment with trityl potassium to initiate the statistical copolymerization of ethylene oxide and butylene oxide to give the diblock copolymer PEO-*b*-P(EO-*stat*-BO) (E−BE) (Scheme 1, **2**). Because EO is much more reactive than is BO toward alkoxide chain ends,[79] copolymerization to high conversions would lead to tapered statistical copolymers with block-like character. Thus, the conversion of the monomers was kept low (<15%) to prevent the composition from drifting too far from that of a statistical polymer.[72] The living polymer solution was again quenched by acidic methanol to form monohydroxyl E−BE diblock copolymers (**2**).

Two E−BE diblock copolymers were prepared, one with a BE-block M_n (NMR) of 5.3 kg/mol ($E_{2.3}BE_{5.3}$) and the other with a BE-block M_n (NMR) of 7.0 kg/mol ($E_{2.3}BE_{7.0}$) (Table 1). Both diblock copolymers had narrow molecular weight distributions (M_w/M_n < 1.1) as confirmed by SEC. Comparison of ^{1}H NMR integration values for diblock copolymers **2** to homopolymer **1** allowed the molecular weights and compositions of the copolymers to be determined (see Supporting Information, Figure S1 for details). The mole fraction of EO (F_{EO}) in the BE blocks was determined to be 0.79 for $E_{2.3}BE_{5.3}$ and 0.88 for $E_{2.3}BE_{7.0}$. These

Scheme 1

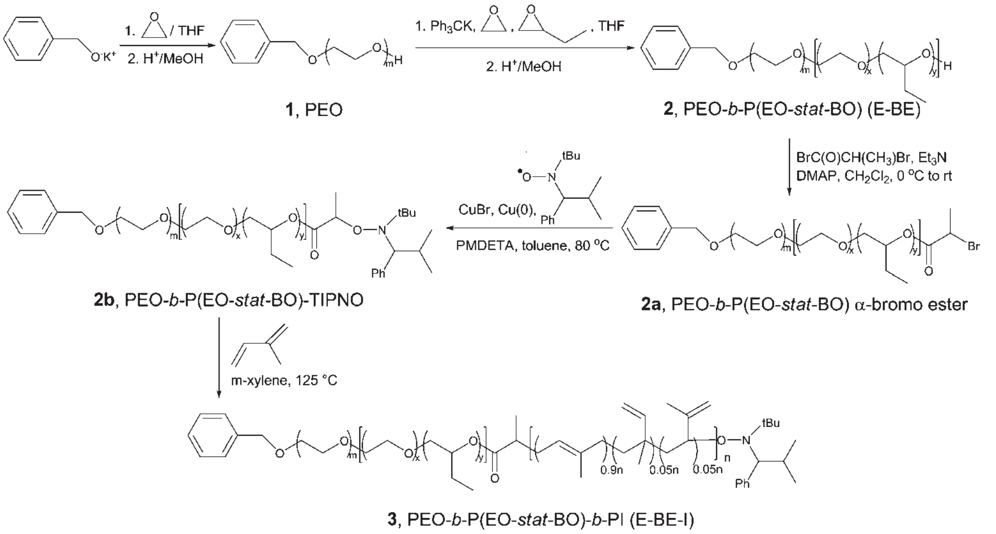

Table 1. Characterization of Poly(ethylene oxide)-*b*-poly(ethylene oxide-*stat*-butylene oxide) (E−BE, 2) Diblock Copolymers

		NMR		SEC		
	monomer feed ratio [EO]:[BO]	M_n (g/mol)[a]	F_{EO}[b]	M_n (g/mol)[a,c]	M_w/M_n[a,c]	cloud point (°C)[d]
$E_{2.3}BE_{5.3}$[e]	3:4	7600	0.79	6800	1.07	52
$E_{2.3}BE_{7.0}$[e]	3:2	9300	0.88	8800	1.07	62

[a] M_n, M_w values for diblock copolymers. [b] Calculated mole fraction of EO in the P(EO-*stat*-BO) block by NMR integration. [c] Conventional calibration versus polystyrene standards. [d] Measured by UV−vis turbidimetry at a concentration of 1 mg polymer/mL H_2O. [e] Diblock copolymers are given notation E_x−BE_y. The subscripts denote the NMR-calculated value of M_n in kg/mol. This notation is used throughout the text.

values of F_{EO} were close to those predicted by the Mayo−Lewis equation:[80,81] 0.770 for $E_{2.3}BE_{5.3}$ and 0.865 for $E_{2.3}BE_{7.0}$ (calculated using values of r_{EO} = 4.1 and r_{BO} = 0.17[79]and the monomer feed ratios given in Table 1).

Thermoresponsive Behavior of E−BE Diblock Copolymers. Both E−BE diblock copolymers displayed LCSTs in water (1 mg polymer/mL H_2O) as evidenced by the observation of cloud points by UV−vis turbidimetry at 52 °C for $E_{2.3}BE_{5.3}$ and 62 °C for $E_{2.3}BE_{7.0}$ (Figure S3). These results agree reasonably well with those reported for a previously studied EO/BO statistical copolymer, $BE_{7.1}$ (M_n = 7100 g/mol, 78 mol % EO), which is directly comparable to $E_{2.3}BE_{5.3}$ (79 mol % EO). $BE_{7.1}$ showed a cloud point between 40 and 50 °C (1 mg $BE_{7.1}$/mL H_2O).[72] The presence of the hydrophilic PEO block in $E_{2.3}BE_{5.3}$ is expected to result in a higher cloud point temperature than that observed for $BE_{7.1}$. Copolymer $E_{2.3}BE_{7.0}$ has a higher EO mole fraction (88 mol % EO in BE block) than does $E_{2.3}BE_{5.3}$ and shows a correspondingly higher cloud point temperature.

The thermoresponsive behavior of the diblock copolymers was also studied by dynamic light scattering (DLS). Copolymer solutions (1 mg/mL H_2O) were heated from 25 to 50 °C (for $E_{2.3}BE_{5.3}$) or 65 °C (for $E_{2.3}BE_{7.0}$) with diameters measured at 5 °C intervals after equilibration at each temperature for at least 0.5 h. Both copolymer solutions showed a significant increase in average diameter near the measured cloud point temperatures. The hydrodynamic diameter (D_h) of $E_{2.3}BE_{5.3}$ was measured to be 3.8 nm at 25 °C but grew to 33 nm at 50 °C. $E_{2.3}BE_{7.0}$ exhibited an analogous size transition from a D_h of 4.8 nm at 25 °C to a D_h of 56 nm at 65 °C (Figure 2). The observed temperature-induced increase in D_h confirms the formation of diblock copolymer aggregates when the thermoresponsive block becomes more hydrophobic above its LCST.

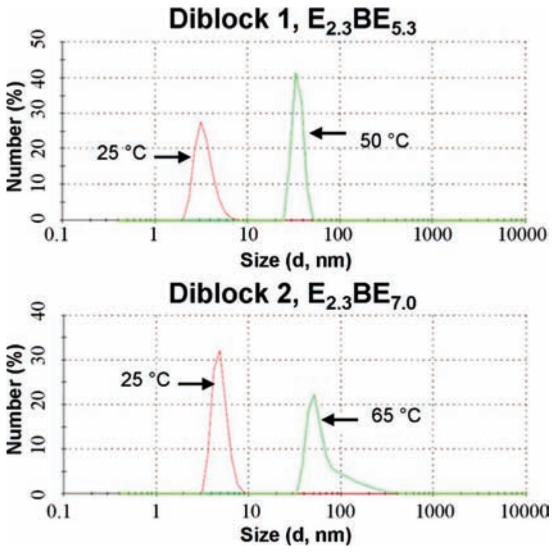

Figure 2. DLS size distributions of diblock copolymers $E_{2.3}BE_{5.3}$ (at 25 and 50 °C) and $E_{2.3}BE_{7.0}$ (at 25 and 65 °C). Size distributions were recorded after each sample was held at a temperature for at least 0.5 h.

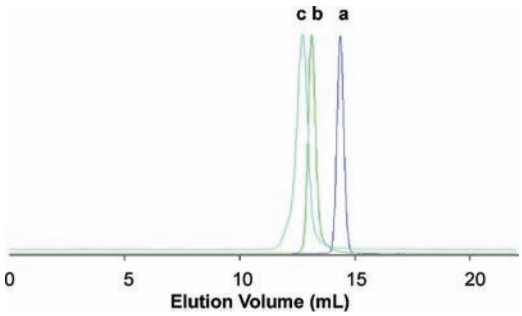

Figure 3. Representative SEC traces of (a) PEO ($E_{2.3}$), (b) $E_{2.3}BE_{5.3}$, and (c) $E_{2.3}BE_{5.3}I_{2.3}$. SEC eluent: THF.

Triblock Copolymer Synthesis. The hydrophobic PI block was added to E−BE diblock copolymers by NMRP. Previously, our group reported the controlled growth of a poly(isoprene) block from a PEO macroinitiator by NMRP.[82] Here, the same strategy was used to convert the monohydroxyl E−BE diblock copolymers **2** (Scheme 1) to the corresponding alkoxyamine macroinitiators **2b** (Scheme 1), which were then used to initiate the NMRP of isoprene. First, the hydroxyl group of **2** was converted to an α-bromo ester by reacting the diblock copolymer with 2-bromopropionyl bromide, using a modified literature approach (Scheme 1).[82,83] During initial attempts, conversion of the end group was found to be incomplete when a slight excess of 2-bromopropionyl bromide was used. It was found that a larger excess (close to 2 equiv) of the acid bromide allowed the reaction to proceed to completion. The α-bromo ester **2a** was then converted to the E−BE alkoxyamine macroinitiator **2b** through radical halogen abstraction and trapping with 2,2,5-trimethyl-4-phenyl-3-azahexane-3-nitroxide (TIPNO)[84] by a known method (Scheme 1).[85]

The polymerization of isoprene was carried out in *m*-xylene from diblock macroinitiator **2b** at 125 °C. The polymerizations were normally allowed to proceed to less than 10% conversion to avoid problems with side reactions observed at high conversions.[82] A comparison of SEC traces for PEO **1**, $E_{2.3}BE_{5.3}$, and the corresponding triblock copolymer $PEO_{2300}PEOBO_{5300}$-PI_{2300} ($E_{2.3}BE_{5.3}I_{2.3}$) suggests that polymerization occurred in a controlled fashion (Figure 3). Additionally, the absence of a significant low molecular weight shoulder in the SEC trace for the triblock copolymers shows that diblock copolymers **2** were efficiently converted to alkoxyamine macroinitiators **2b**.

^{1}H NMR spectra of the triblock copolymers show the isoprene blocks to contain roughly 90% 1,4-, 5% 1,2-, and 5% 3,4-repeating units, which is typical for radical polymerizations of isoprene (Figure S2).[86] Isoprene conversion was calculated by comparing the degree of isoprene polymerization calculated by ^{1}H NMR (from integrals of all isoprene isomers and the benzyloxy methylene moiety) to the theoretical maximum degree of polymerization calculated from the starting monomer/macroinitiator ratio. Conversion values calculated by this method usually agreed well with the conversion calculated by gravimetry. A range of E−BE−I triblock copolymers (Scheme 1, **3**) with controlled molecular weights ($1.4 \leq M_n \leq 5.1$ kg/mol) and narrow molecular weight distributions ($1.05 \leq M_w/M_n \leq 1.20$) were prepared by this method (Table 2).

Table 2. Polymerization Conditions and Characterization of PEO-*b*-P(EO-*stat*-BO)-*b*-PIs (E−BE−I) Copolymers[a]

	[I]/[**2b**][b]	time (h)	% conv.[c]	PI M_n (kg/mol)[d]	M_w/M_n[e]	identifier[f]
1	530	3.0	3.9	1.4	1.07	$E_{2.3}BE_{5.3}I_{1.4}$
2	522	5.5	6.1	2.2	1.08	$E_{2.3}BE_{5.3}I_{2.2}$
3	655	3.5	5.2	2.3	1.10	$E_{2.3}BE_{5.3}I_{2.3}$
4	645	6.0	6.8	3.0	1.15	$E_{2.3}BE_{5.3}I_{3.0}$
5	545	8.5	8.4	3.1	1.11	$E_{2.3}BE_{5.3}I_{3.1}$
6	618	3.0	3.6	1.5	1.05	$E_{2.3}BE_{7.0}I_{1.5}$
7	623	6.0	7.1	3.0	1.08	$E_{2.3}BE_{7.0}I_{3.0}$
8	504	11.0	10.5	3.6	1.07	$E_{2.3}BE_{7.0}I_{3.6}$
9	692	10.0	10.8	5.1	1.18	$E_{2.3}BE_{7.0}I_{5.1}$

[a] For all entries, wt % **2b** = 9−10%, wt % xylene = 39−53%. For full details, see Table S2. [b] Entries 1−5, **2b** = $PEO_{2300}PEO$-BO_{5300}−TIPNO ($E_{2.3}BE_{5.3}$−TIPNO); entries 6−9, **2b** = PEO_{2300}-$PEOBO_{7000}$−TIPNO ($E_{2.3}BE_{7.0}$−TIPNO); [I] = isoprene concentration. [c] Percent conversion calculated from ^{1}H NMR ($CDCl_3$). [d] Number-average molecular weight of PI block calculated by ^{1}H NMR. [e] Determined by SEC (THF) versus polystyrene standards. [f] Triblock copolymers are given notation E_x−BE_y−I_z. The subscripts denote the NMR-calculated value of M_n in kg/mol. This notation is used throughout the text.

Formation and Stabilization of Triblock Copolymer Assemblies in Water. Triblock copolymer micelle solutions were prepared by dissolving a given triblock copolymer (10 mg) in water (10 mL). The solutions were stirred for at least 2 weeks before any measurements on the aqueous polymer solutions were performed. In a few initial attempts, micelle solutions were also prepared by dissolving polymer (5 mg) in THF (2 mL) followed by extensive dialysis against water. DLS studies disclosed that the dialysis method yielded solutions containing polymer assemblies with size distributions similar to those prepared by direct dissolution. Therefore, further studies focused on micellar solutions made by the more straightforward direct dissolution method.

Sizes (D_h) of triblock copolymer assemblies were measured by DLS (Table 3). Longer isoprene blocks resulted in larger polymer aggregates within each polymer series ($E_{2.3}BE_{5.3}I_a$ and $E_{2.3}BE_{7.0}I_b$). The number-average D_h increased from 21 to 32 nm as the M_n of the PI block (a) increased from 1.4 to 3.1 kg/mol within the $E_{2.3}BE_{5.3}I_a$ series. Likewise, D_h increased from 22 to 44 nm as M_n of the PI block (b) increased from 1.5 to 5.1 kg/mol within the $E_{2.3}BE_{7.0}I_b$ series.

To stabilize the assembled structures and to enable their imaging in the dehydrated state by transmission electron microscopy (TEM), the PI cores of the polymer assemblies were cross-linked with potassium persulfate according to a literature method.[87] Cross-linking at room temperature resulted in slightly larger polymer assemblies with D_h increases up to 18% (Table 3).

To test the effectiveness of chemical cross-linking on stabilization of polymer aggregates, a solution of cross-linked $E_{2.3}$-$BE_{5.3}I_{3.1}$ (triblock 5, Table 3) was heated at 60 °C for 3 h. DLS measurements showed that cross-linked $E_{2.3}BE_{5.3}I_{3.1}$ at 60 °C formed slightly smaller aggregates (D_h = 32 nm) than their room temperature counterparts (D_h = 38 nm) as a result of dehydration of the BE block (Figure S4). By comparison, assemblies of noncross-linked $E_{2.3}BE_{5.3}I_{3.1}$ expanded from 38 nm at room temperature to much larger aggregates (DLS showed a bimodal distribution with peaks at 270 and 1050 nm) when heated at 60 °C for 3 h (Figure S4). The apparent difference in

Table 3. Sizes of E−BE−I Copolymer Aggregates at 25 °C

	DLS		TEM
polymer	D_h (nm)[a]	D_h (nm) XL[b]	D_{ave} (nm) XL[c]
$E_{2.3}BE_{5.3}I_{1.4}$	21	21	16 ± 2.5
$E_{2.3}BE_{5.3}I_{2.2}$	24	28	18 ± 1.9
$E_{2.3}BE_{5.3}I_{2.3}$	25	28	22 ± 2.8
$E_{2.3}BE_{5.3}I_{3.0}$	28	33	26 ± 3.2
$E_{2.3}BE_{5.3}I_{3.1}$	32	38	27 ± 2.5
$E_{2.3}BE_{7.0}I_{1.5}$	22	25	19 ± 2.0
$E_{2.3}BE_{7.0}I_{3.0}$	30	35	25 ± 2.3
$E_{2.3}BE_{7.0}I_{3.6}$	38	39	36 ± 2.8
$E_{2.3}BE_{7.0}I_{5.1}$	44	51	55 ± 4.5

[a] Number-average D_h of uncross-linked aggregates measured by DLS (1 mg/mL aqueous polymer solutions). Values are averaged over three runs, each of which included 12 measurements. Standard deviations for all values are smaller than ±2 nm. [b] Number-average D_h of cross-linked aggregates measured by DLS (1 mg/mL aqueous polymer solutions). Values are averaged over three runs, each of which included 12 measurements. Standard deviations for all values are smaller than ±2 nm. [c] Average apparent assembly diameter and standard deviations obtained from TEM particle analysis. More than 40 particles were included in each calculation.

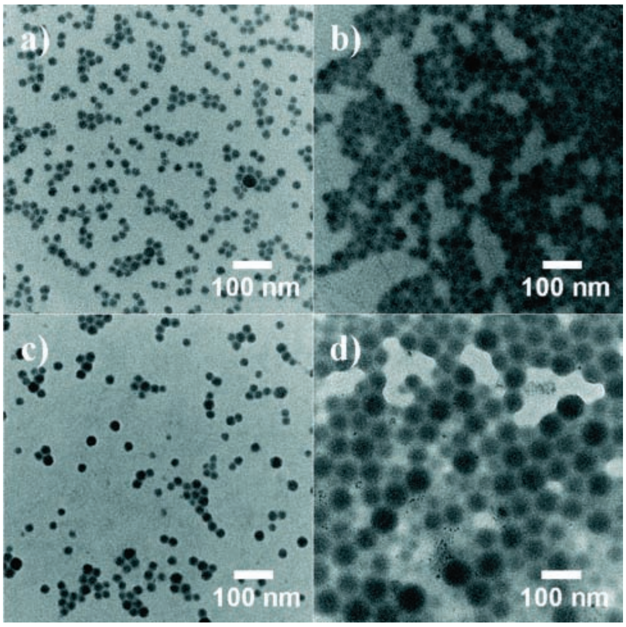

Figure 4. Representative TEM images for cross-linked E−BE−I triblock copolymer aggregates at 25 °C (0.3 mg/mL aqueous solution; stained with OsO_4 vapor). (a) $E_{2.3}BE_{5.3}I_{1.4}$; (b) $E_{2.3}BE_{5.3}I_{3.0}$; (c) $E_{2.3}BE_{7.0}I_{3.0}$; (d) $E_{2.3}BE_{7.0}I_{5.1}$. All micrographs have been normalized to the same magnification. See Figure S5 for TEM images in their original magnification for all nine E−BE−I copolymers.

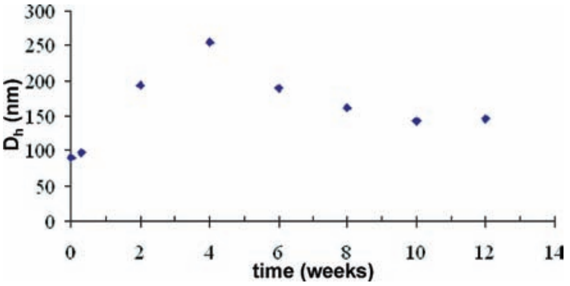

Figure 5. Size evolution of $E_{2.3}BE_{5.3}I_{2.3}$ copolymer aggregates at 70 °C measured by DLS during a 3 month period.

heating profiles of $E_{2.3}BE_{5.3}I_{3.1}$ aggregates before and after chemical fixation confirmed the successful stabilization of copolymer assemblies via double bond cross-linking.

To image copolymer assemblies by TEM, polymer solutions were stained by OsO_4 vapor, which reacts with double bonds in poly(isoprene) blocks so that the polymer aggregates become more electron-dense and appear as dark regions in TEM images. The staining process might also help stabilize the assemblies by forming cross-links through osmate diesters.[88] The resulting TEM micrographs showed that all nine polymers formed aggregates in aqueous solutions, with greater assembly sizes corresponding with longer isoprene blocks within each polymer series. These aggregates have nearly spherical micellar shapes and relatively narrow size distributions, as evidenced by representative TEM micrographs (Figure 4).

Temperature-Dependent Size Changes of Triblock Copolymer Assemblies. The thermoresponsive behavior of representative triblock copolymers was studied. For example, the cloud point of $E_{2.3}BE_{5.3}I_{2.3}$ (entry 3, Table 3) was found to be 49 °C, slightly lower than the value of 52 °C observed for the parent diblock $E_{2.3}BE_{5.3}$, by visual observation or by UV−vis turbidimetric measurements, as polymer solutions (1 mg/mL) were slowly heated to 65 °C at a rate of roughly 0.2 °C/min.

The thermal response of $E_{2.3}BE_{5.3}I_{2.3}$ assemblies was also evidenced by DLS measurements (Figure S6). DLS of an aqueous solution (1 mg/mL) of $E_{2.3}BE_{5.3}I_{2.3}$ at 25 °C showed a D_h of 25 nm. When the solution was slowly heated up from 25 to 70 °C, D_h initially decreased to 21 nm between 25 and 50 °C, which suggests the dehydration of the central thermo-sensitive BE block. As compared to its parent diblock polymer $E_{2.3}BE_{5.3}$, which grew rapidly around 50 °C, $E_{2.3}BE_{5.3}I_{2.3}$ only exhibited a limited increase in D_h to 24 nm between 50 and 65 °C.

This comparison reflects the fact that these are two different reorganization processes. Diblock copolymers, such as $E_{2.3}BE_{5.3}$, form intermolecular assemblies directly from molecularly dissolved polymer chains as the temperature is increased above the cloud point, while triblock copolymers, such as $E_{2.3}BE_{5.3}I_{2.3}$, must restructure from small assemblies to larger ones, which can be a significantly slower process.[50] $E_{2.3}BE_{5.3}I_{2.3}$ assemblies with greater apparent sizes (D_h = 93 nm) were detected at 70 °C. It was found, however, that the correlation functions obtained at 70 °C within the experimental time frame (2 h) varied from test to test and that the assemblies typically had a broad size distribution (polydispersity index (PDI) > 0.4, as calculated by cumulant analysis). These findings suggest that large assemblies (vesicles, see below) form relatively rapidly at 70 °C, but their size distributions evolve over time.

The size distributions of the assemblies at 70 °C were followed by DLS for the next few months, and it was found that the sizes of the assemblies grew for the first 4 weeks, then shrank before eventually stabilizing and becoming more monodisperse after 9 weeks, with a narrower size distribution (PDI = 0.2) and a peak D_h at 143 nm after 12 weeks (Figure 5, Table S1). Although our studies have not yet focused on the mechanism of how these changes in observed size distribution occur, it is quite obvious

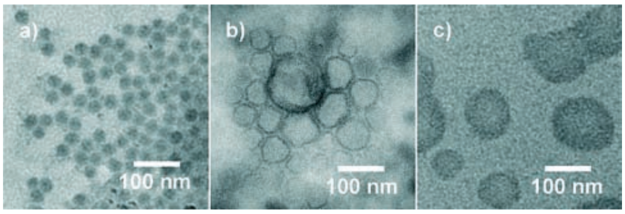

Figure 6. TEM images of $E_{2.3}BE_{5.3}I_{2.3}$ assemblies. (a) Cross-linked $E_{2.3}BE_{5.3}I_{2.3}$ aggregates at 25 °C, D_{ave} = 22 nm (0.3 mg/mL, stained by OsO_4 vapor); (b) $E_{2.3}BE_{5.3}I_{2.3}$ aggregates cross-linked after 2 days at 70 °C, D_{ave} = 58 nm (0.5 mg/mL, stained by OsO_4 vapor); and (c) $E_{2.3}BE_{5.3}I_{2.3}$ aggregates cross-linked after 2 weeks at 70 °C, D_{ave} = 106 nm (0.5 mg/mL, stained by OsO_4 vapor and then uranyl acetate solution). Micrographs have been rescaled so that they are displayed at the same magnification. Images (a) and (c) are smaller sections of the original micrographs (see Figure S7 for unprocessed micrographs).

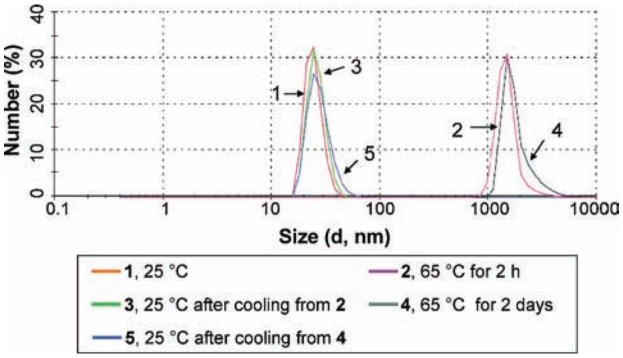

Figure 7. DLS measurements of D_h of $E_{2.3}BE_{7.0}I_{1.5}$ aggregates over two heating−cooling cycles. See Scheme S1 for a flowchart illustrating the process.

that the evolution of these polymers into stable structures at high temperature is slow, as the eight other polymer solutions examined required more than 2 weeks to reach a stable size distribution (Table S3). Such slow evolution in size distribution was also witnessed with related block copolymers having PNIPA as thermoresponsive block,[50,51] although the initial size expansion of $E_{2.3}BE_{5.3}I_{2.3}$ assemblies at elevated temperatures appears to occur more rapidly than what was observed with the PNIPA copolymers. DLS study confirmed that all of the block copolymers found in Table 3 underwent size expansion upon heating, forming vesicles with sizes of 110−220 nm (Table S3). However, the size expansion profiles were quite different from one polymer to another, and comparison of size distributions of different polymers within the initial 2 months revealed no obvious relationship between vesicle sizes and polymer compositions. It was not until ∼10 weeks of heating that a trend that longer PI blocks resulted in larger assemblies within both $E_{2.3}BE_{5.3}I_x$ and $E_{2.3}BE_{7.0}I_y$ series became clear (Table S3).

The temperature-dependent size changes of $E_{2.3}BE_{5.3}I_{2.3}$ assemblies were also observed by TEM. As the persulfate redox cross-linking protocol was useful in allowing visualization of assemblies formed at room temperature, we investigated the same cross-linking procedure with the polymer assemblies formed at higher temperatures to fix the assemblies for room temperature TEM analysis. After 48 h of heating at 70 °C, $E_{2.3}BE_{5.3}I_{2.3}$ was cross-linked in aqueous solution using the same method that was used for room temperature cross-linking. TEM images of these samples show vesicular assemblies with an average diameter (D_{ave} = 58 nm) larger than those formed at 25 °C (D_{ave} = 22 nm) (Figure 6a,b). When $E_{2.3}BE_{5.3}I_{2.3}$ solutions were cross-linked after 2 weeks at 70 °C, even larger vesicles (D_{ave} = 106 nm) were observed by TEM (Figure 6c). The chemical cross-linking process obviously affects the size distribution of copolymer assemblies, but the formation of larger vesicles above the LCST clearly indicates that change in amphiphilic balance of the block copolymers drives the formation of structures with less interfacial curvature.

The expanded assemblies of copolymers formed at high temperatures can be restored to smaller aggregates upon cooling, as evidenced by studies on $E_{2.3}BE_{7.0}I_{1.5}$ (Figure 7 and Scheme S1). Heating of an aqueous solution of $E_{2.3}BE_{7.0}I_{1.5}$ at 25 °C (Figure 7, distribution 1) to 65 °C for 2 h led to larger aggregates (Figure 7, distribution 2). Cooling the solution back to 25 °C and allowing it to sit for 12 h resulted in a restoration of the previous size distribution (Figure 7, distribution 3). Structures with slightly larger sizes than the initial size were obtained when the polymer solution was cooled back to 25 °C and measured immediately. Cooling the polymer solution to an even lower temperature, for example, by chilling the solution in an ice−water bath, and then gradually increasing the temperature to 25 °C resulted in a more rapid return to the original size distribution. The same solution was reheated to 65 °C for 2 days to again produce larger assemblies (Figure 7, distribution 4), and the reconstitution of smaller assemblies (Figure 7, distribution 5) was again observed after the solution was allowed to cool. This study demonstrated that the size expansion of the polymer aggregates can be turned "on" and "off" through several cycles by simply altering the temperature.

The stability of these block copolymers in aqueous solutions at elevated temperatures is a major concern, as the observed size change and therefore any potential applications reliant upon the response require lengthy exposure of the polymers to high temperatures. To probe the stability of these polymers under elevated thermal conditions, an aqueous solution of $E_{2.3}BE_{5.3}I_{3.0}$ (entry 4, Table 3) (5 mg/mL) was heated at 75 °C for 25 days. No precipitate was observed during this period. The solution was then cooled to room temperature and concentrated. The dried polymer was dissolved in THF for SEC study. Comparison of the SEC traces for the polymer before and after heating reveals no apparent difference in elution volume (Figure S8). The SEC trace showed no apparent small molecular weight peak or shoulder for the polymer with a history of heating, suggesting that the copolymers do not undergo significant degradation over 3−4 weeks in water at elevated temperatures.

■ CONCLUSIONS

We have prepared a library of amphiphilic ABC triblock poly(ethylene oxide)-*b*-poly(ethylene oxide-*stat*-butylene oxide)-*b*-poly(isoprene) copolymers with narrow molecular weight distributions by the combination of sequential living anionic and controlled nitroxide-mediated radical polymerizations. The polymers examined form spherical micelles in water at room temperature with sizes and shapes dictated by each polymer's molecular weight and amphiphilic balance. Reversible heating-induced size changes in the triblock copolymer assemblies were confirmed by DLS and TEM studies on representative polymers. In comparison to previously reported thermally driven size changes of PNIPA-containing block copolymer assemblies,[50,51] $E_{2.3}BE_{5.3}I_{2.3}$ aggregates underwent faster initial size expansion into vesicles at temperatures above the LCST of the responsive block. The seemingly faster initial response to heating is likely due to the absence of strong interchain hydrogen bonding in the alkylene oxide copolymers. Additional studies with other responsive blocks that are incapable of strong interchain interactions, such as poly(*N*,*N*-dialkylacrylamides),[9,89] will allow us to further probe this hypothesis.

Further studies are in progress to allow more insight into the relationship between the molecular weights and amphiphilic balance of polymers and the mechanism and rate for thermally triggered size change of polymer assemblies. In addition, compositions of the random BE block of the triblock copolymers can be adjusted through synthesis so that the size transition occurs at lower temperatures that are biomedically relevant. Recently, O'Reilly and co-workers have reported a similar micelle—vesicle transition upon crossing the LCST of PNIPA in assemblies of a poly(*N*-isopropylacrylamide)-*b*-poly(*t*-butylacrylate) (PNIPA-*b*-PTBA) block copolymer with a hydrophilic tetraalkylammonium group at the PNIPA terminus of the polymer, so it appears likely that the size and/or degree of hydration of the water-miscible component of the polymer also play an important role in governing the transition rate.[51] When better understood, the reversible size expansion among these polymer aggregates may be applied in designing thermally triggered encapsulant release devices.

ASSOCIATED CONTENT

Ⓢ Supporting Information. Experimental procedures, DLS data, TEM micrographs, and polymer stability study data. This material is available free of charge via the Internet at http://pubs.acs.org.

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ACKNOWLEDGMENT

The anionic polymerizations were carried out at the Silvio O. Conte National Center for Polymer Research at the University of Massachusetts Amherst. All other experimental work was carried out at the Department of Chemistry at Dartmouth College (DC) and Dartmouth-Hitchcock Medical Center (DHMC). We thank Profs E. Bryan Coughlin and Todd Emrick for kindly lending us their lab space and Mr. Chris Scilla and Dr. Kurt Breitenkamp for help in preparing E—BE. We thank Dr. Charles P. Daghlian at the Rippel Electron Microscopy facility (DC) for assistance with the acquisition of TEM images and Dr. Mark Savellano at DHMC for his assistance with the Malvern Zetasizer, which was made available through the Cancer Nanotechnology Working Group (CNWG) at Dartmouth College. The NSF (DMR-0239697, DMR-0804792) and the CNWG are acknowledged for partial financial support of this work.

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